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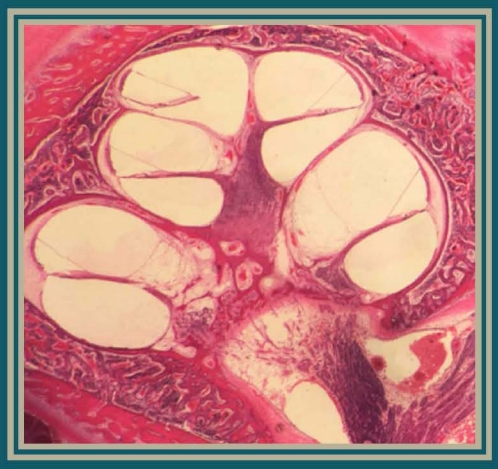
Scott-Brown's Otorhinolaryngology Head & Neck Surgery



VOLUME 2

Paediatrics
The Ear
Skull Base

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John C Watkinson
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Scott-Brown's

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Otorhinolaryngology Head and Neck Surgery

VOLUME 1

Basic Sciences, Head and Neck Endocrine Surgery, Rhinology

VOLUME 2

Paediatrics, The Ear, Skull Base

VOLUME 3

Head and Neck Surgery, Plastic Surgery

Scott-Brown's Otorhinolaryngology Head and Neck Surgery

EIGHTH EDITION

VOLUME 2

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Foreword

The eighth edition of *Scott-Brown* signals the beginning of a new and exciting era for ear, nose and throat surgeons, and also the end of 10 years of very hard work undertaken by John Watkinson and Ray Clarke, the Editors-in-Chief, their team of subeditors and, not least, the publishers. Whatever subspeciality the current generation of trainees decides to follow, they will all have to read and refer to *Scott-Brown* in order to complete their education and gain accreditation. It will be a constant companion and guide throughout their professional lives.

When asked to write the foreword for this edition, I was immediately reminded that I had read John Ballantyne and John Groves's third edition as a trainee, bought the fourth edition as a senior registrar, written chapters for Alan Kerr and Philip Stell in the fifth edition, edited the *Basic science* volume of the fifth edition and was ultimately Editor-in-Chief of the seventh edition. As each edition takes about 10 years to produce, that makes me very old indeed. John and Ray have one final task as Editors-in-Chief: to recommend their successors to the publishers. That was made easy for me as both of them had proved themselves more than capable with the previous edition, and the eighth edition is now their masterpiece. They can enjoy the next 10 years as thousands of surgeons worldwide recognize and thank them for their industry.

This edition reflects the continued expansion of our speciality into fields that Scott-Brown himself could never have imagined. It lays the groundwork for the current generation to make their contribution that will, no doubt, be prompted by technological developments, an evidence base of what is wise and what is not, together with the experience gained by teamwork with other clinicians in today's multidisciplinary approach to patient care.

Simply looking at the table of contents it is clear to see that our role in endocrine surgery has increased dramatically over the last 10 years. The thyroid and parathyroids now account for 30 chapters. How would Scott-Brown have viewed that when the tonsils and adenoids justify just one chapter each, and the sore throat has a mere passing reference? Times have certainly changed and ENT surgery has grown up. We have reflected on our past practices, and the evidence base for our management protocols that was emphasized in the previous edition of *Scott-Brown* has been taken to heart.

I hope that this edition will find its way into every medical library in the world and onto every ENT surgeon's bookshelf. It will serve and guide surgeons throughout the English-speaking world, whether they live in high- or low-income countries. It is said that the tragedy of getting old is that we feel young. Reading these volumes makes me wish that I had my time all over again.

Michael Gleeson

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Preface

When we were asked to head up the editorial team for this, the eighth edition of *Scott-Brown*, we were mindful of Michael Gleeson's towering achievement in bringing the seventh edition to fruition. Michael delivered a much-loved text – conceived in the early post-war years when antimicrobials, the operating microscope and the National Health Service were all in their infancy – in an entirely new format that befitted modern surgical scholarship. Authors, editors and readers alike had become acutely conscious of the need to quote high-quality evidence to guide clinical decisions; the concept of grading clinical recommendations – and, by implication, acknowledging gaps in the evidence base of our practice – was born. Recognizing the enormity of Michael's contribution led us into the trap that has befallen every editor who has come before us; we grossly underestimated the task ahead. We had misjudged the pace of change. What began as an 'update' of some outdated chapters became a complete rewrite to reflect the advances that marked the decade between editions, but we were determined to keep the text to a manageable size. In the end, we have 330 chapters, but with a slightly smaller page count than the seventh edition.

The basic science knowledge that underpins our clinical practice is no longer focused just on anatomy and physiology; genetics, molecular biology, new techniques for auditory implantation, information technology, new medical therapies for many old disorders together with seismic changes in endoscopic technology and in medical imaging have transformed our specialty. Today's head and neck surgery would have been unrecognizable to the early authors and editors. Surgical oncologists have recourse to completely different treatment strategies than did their predecessors and now work as part of multidisciplinary teams. They deal with different disease patterns and vastly changed patient expectations. Thyroid and parathyroid surgery has become almost exclusively the domain of the otolaryngologist. Surgery of the pituitary fossa has come within our ambit, as has plastic and reconstructive surgery of the head and neck as well as aesthetic facial surgery. Neurotology, audio-vestibular medicine, rhinology and paediatric otolaryngology are accepted subspecialties, each with its own corpus of knowledge and skills and each warranting a sizeable section of this text. Contemporary otolaryngology is now a collection of subspecialty interests linked by common 'stem' training and a shared passion for looking after patients with disorders of the upper respiratory tract and the head and neck.

There is a view that a single text – even a multivolume tome of this size – cannot cover the entire knowledge base of modern clinical practice. The subspecialist will, of course, need recourse to supplementary reading. The pace of change shows no sign of slowing down, but there is still a need for a comprehensive working text embracing the whole spectrum of our workload. That was the task we set our authors and section editors; we think they have done our specialty proud.

In the new 'digital' editorial world authors create manuscripts on personal computers. They transmit chapters, figures, amendments and revisions across continents and time zones with a few keystrokes. The bulky packages containing grainy photographic prints and the reams of paper with closely-typed and heavily scored text that accumulated on authors' and editors' desks are a distant memory. References, guidelines and systematic reviews are all available online; the editorial 'red pen' has been replaced by a cursor on the screen. This 'new age' has enabled us to look ever further for expertise. We are proud to have enlisted the support of authors from more than 20 countries for this edition. *Scott-Brown* always enjoyed particular affection and respect in Asia, Australia, Africa and the Middle East. It has been a joy to welcome authors in increasing numbers from many of these parts of the world. We are now a truly global specialty and the eighth edition fully reflects this.

What has not changed is the huge time commitment authors and editors need to make. That time now has to be fitted into an increasingly pressurized work environment. Revalidation, mandatory training, more intense regulatory scrutiny, expanding administrative burdens and ever-expanding clinical commitments leave little time for scholarship. Our section editors are all busy clinicians. They have generously given their time, first instructing authors, cajoling them and then editing their chapters, virtually all of which have been completely rewritten since the last edition. Each author was chosen because of his or her specific clinical and scientific expertise and none has disappointed. Authors and section editors receive no reward other than the satisfaction of knowing that they have made a contribution to teaching and learning in a specialty that has given us all so much professional satisfaction. We are profoundly grateful to them and hope that their endeavours spur the next generation of otolaryngologists to carry on this noble tradition. *Scott-Brown* simply wouldn't happen without this generous and dedicated commitment, unstintingly and graciously given.

It is impossible to produce a book like *Scott-Brown* without the contribution of many individuals working behind the scenes. We would like to express our gratitude to our Publishers, Taylor and Francis, and to the staff who have worked on this project from its early days in 2011 to publication in 2018. In particular we would like to mention Cheryl Brandt who with good humour and patience helped to reel in many of the 330 chapters. Miranda Bromage joined the team in 2016 and her publishing experience and enthusiasm for medical education have helped guide this new edition through its final phases to publication. Finally, we are indebted to Nora Naughton who has dedicated so much more than just her extensive publishing skills to this project. Nora's meticulous attention to detail, combined with her warmth and wisdom have encouraged us all at the end of this endeavour.

We are truly 'passing on the torch' of a huge amount of accumulated knowledge and wisdom; it is this that gives us, the Editors-in-Chief, the greatest pleasure.

Read on and enjoy, our thoughts are yours.

RWC
JCW

I wish to acknowledge the love, happiness and inspiration that have been passed on to me by both my parents and grandparents. I recognise and value the friendship of my dear friend Ray Clarke who has been with me all the way on this rewarding and worthwhile endeavour. I would specifically like to thank Esme, Helen and William, without whom none of this would have been achievable. Their love and support has helped guide me through the years leading up to the publication of this tome, and my final thanks go to Angela Roberts and Sally Holden for their typing and editing skills.

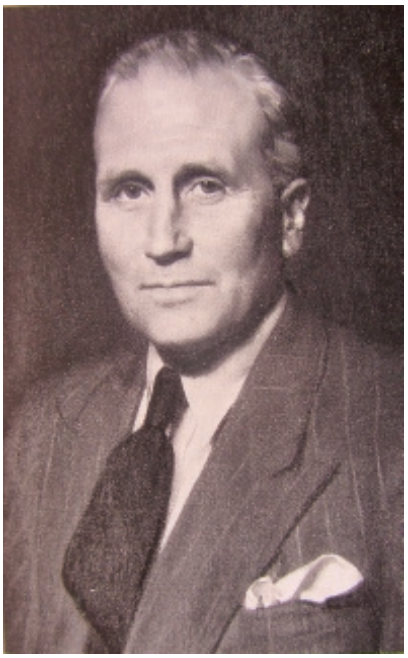
JCW 2018

Thanks to my wife Mary for her patience and support. My parents, Emmet and Doreen Clarke, both sadly died during the preparation of this book. They would have been proud to have played a part in such a scholarly enterprise.

RWC 2018

Black Hut on the River Test – Pastel by W G Scott-Brown – circa 1970. Reproduced by kind permission of Mr Neil Weir, who was presented with the original by the artist.

A Tribute to Bill Scott-Brown



Walter Graham ('Bill') Scott Brown. 1897–1987

Walter Graham ('Bill') Scott-Brown was twenty-three when he arrived at Corpus Christi College Cambridge in 1919. One of the generation of young men whose entry to university and the professions was delayed by their participation in the First World War, he had joined the Gunners in 1915 as an 18-year-old. He considered himself blessed to have survived – although wounded – when so many of his contemporaries never returned from the Front. In those early post-WW1 years the medical school at St Bartholomew's ('Barts') in London was keen to attract 'gentlemen'. To this end a series of scholarships – 'Shuter's scholarships' – was established to lure those with humanities degrees from Oxford and Cambridge into medicine. It was via this scheme that the young Scott-Brown qualified MB, BCh in 1925. By now married to Margaret Bannerman, one of the very few women medical graduates of her generation, the two established a general practice in Sevenoaks, Kent. His work here involved looking after children with poliomyelitis, which was then commonplace, and his MD thesis was on polio-related bulbar palsy. It earned him the Copeman Medal for research from the University of Cambridge. While working in general practice, Bill pursued his interest in the then fledgling specialty of otolaryngology, securing fellowships from London and Edinburgh. Postgraduate training was haphazard; there were no structured programmes or even junior posts, so the young Scott-Brown was fortunate to be awarded a Dorothy Temple Cross Travelling Fellowship. Mrs Florence Temple Cross had set up these awards (now administered by the Medical Research Council) in memory of her daughter, who died in 1927 aged thirty-two. They were made available to young physicians to help them travel to overseas centres specifically to study tuberculosis, then rampant and one of the commonest causes of death in young adults. The young Scott-Brown visited the leading pioneers of the day in Berlin, Vienna, Budapest, Stockholm, Copenhagen, Madrid and Venice. Here he developed his considerable endoscopy skills. He reported that his first bronchoscopies were done on a Venetian street entertainer who, for a few coins, would inhale sundry objects that the doctors would then dexterously retrieve from his main stem and segmental bronchi – without of course any anaesthesia!

Times were lean on Scott-Brown's return. Margaret ('Peggy') was now a popular and well-established GP who supported him as his private practice developed. Eventually he secured appointments at East Grinstead, the Royal National and Royal Free Hospitals. He had a thriving Harley Street practice and was the favoured otolaryngologist of the aristocracy. His reputation was such that he become laryngologist to the Royal family, was appointed Commander of the Victorian Order and was a particular favourite of the then Princess Royal, HRH Mary the Countess of Harewood.

By 1938 he was wealthy enough to purchase a farm in Buckinghamshire where he bred prize-winning shorthorn cattle. Ironmongery and blacksmith work were hard to come by during the war years, so Scott-Brown prided himself on his ability to make his own agricultural implements, cartwheels and farm wagons in a makeshift forge he himself established on the farm. He would while away endless hours here at weekends following a busy week in London. An accomplished fly fisherman, he was part of the exclusive Houghton Club whose members fished the River Test in Hampshire, where he numbered aristocrats including the Prince of Wales among his circle.

Scott-Brown's celebrated textbook came about in the early 1950s, when he became ill with jaundice and heart trouble. He was advised to rest, and took 6 months off work. Not satisfied with editing what has become the standard UK textbook, he took up painting as well. He became a celebrated artist whose work is still prized in many private collections. One of his pastels is reproduced on the preceding page.

Bill Scott-Brown lived to be 90. He died in July 1987, six weeks after his beloved Peggy and just as the fifth edition of the celebrated textbook that still bears his name was going to press. His legacy lives on in the pages of this book, and we are proud to continue the tradition of scholarship and learning which he established all those years ago.

We would like to thank Martin Scott-Brown for his help in compiling the biography above.

John C. Watkinson and Raymond W. Clarke
London, 2018

Acknowledgements

We acknowledge our debt of gratitude to the many authors who have contributed to previous editions of Scott-Brown's Otorhinolaryngology, and in particular to authors from the seventh edition, published in 2008. We are also grateful to Neil Bateman who helped with the initial planning of the Paediatrics section.

Chapter 10, **Management of the hearing impaired child,** contains some material from 'Investigation management of deaf child' by Sujata De, Sue Archbold and Ray Clarke. The material has been revised and updated by the current author.

Chapter 28, **Stridor,** contains some material from 'Acute laryngeal infections' by Susanna Leighton. The material has been revised and updated by the current author.

Chapter 31, **Acquired laryngotracheal stenosis,** contains some material from 'Jugular foramen lesions and their management' by Kees Graamans. The material has been revised and updated by the current author.

Chapter 97, **Imaging of the temporal bone,** contains some material from 'Anatomy of the skull base and infratemporal fossa' by Charlie Huins. The material has been revised and updated by the current author.

Chapter 106, **Non-vestibular schwannoma tumours of the cerebellopontine angle,** contains some material from 'Evaluation of the skull base patient' by Ranit De and Richard M Irving. The material has been revised and updated by the current author.

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Volume 3 – Table of Contents

Section 1 Head and Neck

Section 2 Plastic Surgery

Abbreviations

2D	two-dimensional
3D	three-dimensional
4D	four-dimensional
5-HT	5-hydroxytryptamine
A	adenine; *or* anterior
AABR	automated auditory brainstem response
AAHL	age-associated hearing loss
AAOHNS	American Academy of Otolaryngologists/ Head and Neck Surgeons
ABC	aspiration biopsy cytology
ABCDE	airway, breathing, circulation, disability and exposure
ABG	air–bone gap
ABI	auditory brainstem implant
ABR	auditory brainstem response; *or* acoustic brainstem-evoked response
ABRS	acute bacterial rhinosinusitis
AC	air conduction; *or* alternating coupled; *or* auditory cortex; *or* acquired cholesteatoma
ACC	adenoid cystic carcinoma; *or* American College of Cardiology
ACD	acoustic hearing devices
ACE	angiotensin-converting enzyme
aCGH	array comparative genomic hybridization
ACh	acetylcholine
ACHD	acoustic hearing devices
AchR	acetylcholine receptor
ACT	Aid for Children with Tracheostomies; *or* acceptance and commitment therapy
ACTH	adrenocorticotrophic hormone
AD	Alzheimer's disease; *or* autosomal dominant
ADD	attention deficit disorder
ADH	antidiuretic hormone
ADHD	attention deficit hyperactivity disorder
AEP	auditory evoked potentials
AF	atrial fibrillation; *or* anterior fontanelle
AFP	alphafetoprotein
AFRS	allergic fungal rhinosinusitis
AHI	apnoea/hypopnoea index
AI	apoptotic index
AICA	anterior inferior cerebellar artery
AIDS	acquired immunodeficiency syndrome
AIED	autoimmune ear disorders
AJCC	American Joint Committee on Cancer
ALD	assistive listening device
ALPS	autoimmune lymphoproliferative syndrome
ALR	auditory late responses
ALS	advanced life support; *or* amyotrophic lateral sclerosis
ALSPAC	Avon Longitudinal Study of Parents and Children
ALTB	acute laryngotracheobronchitis
ALTE	apparent life-threatening event
AMA	American Medical Association
AMEI	active middle ear implant
AML	acute myeloid leukaemia; *or* anterior malleal ligament
AN	acoustic neuroma; *or* auditory neuropathy; *or* audiovestibular nerve
AN/AD	auditory neuropathy/auditory dyssynchrony
ANCA	antineutrophil cytoplasmic antibody
ANSD	auditory neuropathy spectrum disorder
AOAE	automated otoacoustic emission
AOM	acute otitis media
AP	anteroposterior; *or* action potential
APD	auditory processing disorder
APHAB	Abbreviated Profile of Hearing Aid Benefit
APLS	Advanced Paediatric Life Support
APMET	aggressive papillary middle ear tumour
APTT	activated partial thromboplastin time
APUD	amine precursor uptake and decarboxylation
AQP2	aquaporin 2
ARHL	age-related hearing loss
ARNSHL	autosomal recessive non-syndromic hearing loss
ARS	acute rhinosinusitis
ARSAC	Administration of Radioactive Substances Advisory Committee
ART	acoustic reflex threshold; *or* advanced rotating tomograph; *or* antiretroviral therapy
a-SCC	anterior semicircular canal
ASD	autistic spectrum disorders
ASHA	American Speech-Language-Hearing Association
ASPO	American Society of Pediatric Otolaryngologists
ASSR	auditory steady state response
AT	ataxia telangiectasia; *or* auditory therapy *or* training; *or* autotransplantation

ATD ascending tract of Deiters
ATN auriculotemporal nerve
ATP adenosine triphosphate
AV apical vesicles; *or* arteriovenous
AVF arteriovenous fistula
AVM arteriovenous malformation
AVP Amplatzer vascular plug; *or* arginine vasopressin
AVPU alert, voice, pain, unresponsive
aVOR angular VOR

BAAP bone-anchored auricular prosthesis
BAC bacterial artificial chromosome
BAHA bone-anchored hearing aid
BAO-HNS British Association of Otorhinolaryngologists – Head and Neck Surgeons
BAPO British Association for Paediatric Otolaryngology
BC bone conduction
BC-FMT bone conduction floating mass transducer
BCG Bacillus Calmette–Guérin
BCHA bone conductor hearing aid
BCHD bone conduction hearing device
BCHI bone conducting hearing implants
BCI bone conduction implant
BET balloon Eustachian tuboplasty
BiPAP bilevel positive airway pressure
BKB Bamford-Kowal-Bench
BLEC benign lymphoepithelial cysts
BLEL benign lymphoepithelial lesions
BLS Basic Life Support
BM basilar membrane
BMI body mass index
BMP bone morphogenetic protein; *or* bone morphogenic protein
BNOE benign necrotizing otitis externa
BOA behavioural observation audiometry
BOR brachio-oto-renal
BP blood pressure
BPPV benign paroxysmal positional vertigo
BPV benign paroxysmal vertigo; *or* benign positional vertigo
BRBNS blue rubber bleb naevus syndrome
BRUE brief resolved unexplained event
BS Behcet's syndrome; *or* brain stem
BSA British Society of Audiology
BTE behind the ear
BTK B-cell antigen receptor; *or* Bruton's tyrosine kinase
BTO balloon test occlusion

CAD caspase-activated DNase
CAGE cerebral air gas embolism
CAM2 a prescription rule for amplification. It is the second version of a rule devised by Dr Moore and colleagues at Cambridge University
CAMHS child and adolescent mental health service
cAMP 3',5'-monophosphate; *or* Cyclic AMP
CAMREST Cambridge method for loudness restoration
CANS central auditory nervous system
CANVAS cerebellar atrophy, neuropathy, vestibular arreflexia syndrome
CAP compound action potential; *or* category of auditory performance; *or* College of American Pathologists
CAPD central auditory processing disorder
CAT combined approach tympanoplasty
CBCT cone beam CT
CBNS congenital bony nasal stenosis
CBT cognitive-behavioural therapy
CC congenital cholesteatoma
CCA common carotid artery; *or* congenital canal atresia
CCD charge-coupled device
CCR chemokine receptor
CCSS Childhood Cancer Survivor Study
CCT Consonant Confusion Task
CCW counter-clockwise
CDC Centers for Disease Control and Prevention
CDP computerized dynamic posturography
CEA carcinoembryonic antigen
CERA cortical evoked response audiometry
CF cystic fibrosis; *or* characteristic frequency
CFRT conformal radiotherapy
CFTR cystic fibrosis transmembrane conductance regulator
CFU colony-forming unit
CGH comparative genomic hybridization
CH congenital haemangiomas
CHA conventional hearing aids
CHABA Committee on Hearing, Bioacoustics, and Biomechanics
CHAMP cochlear hydrops analysis masking procedure
CHAOS congenital high airway obstruction syndrome
CHARGE coloboma, heart defects, atresia choanae, retardation of growth, genital anomalies and ear abnormalities
CHAT Childhood Adenotonsillectomy Trial
CHD congenital heart disease
CHL conductive hearing loss
CI cochlear implantation; *or* cardiac index; *or* confidence interval; *or* concha inferior

CIC completely in canal
***cis*-DPP** cis-dichlorodiammine platinum II
CISS constructive interference in steady state
CJD Creutzfeldt–Jakob disease
CL cleft lip
CM capillary malformation; *or* concha media; *or* cochlear microphonic; *or* cricothyroid muscle
CMAP compound muscle action potential
CMCC congenital midline cervical cord/cleft
CMT Charcot–Marie–Tooth; *or* combined modality therapy
CMV cytomegalovirus
CN cranial nerve; *or* cochlear nuclei; *or* cochlear nerve; *or* congenital nystagmus
CNAP cochlear nerve action potential
CNLDO congenital nasolacrimal duct obstruction
CNS central nervous system
CNV copy number variations
CO_2 carbon dioxide
COM chronic otitis media
COMT catechol-O-methyltransferase
COR conditioned orientation reflex
COSI Client Oriented Scale of Improvement
COWS cold-opposite-warm-same
COX-2 cyclo-oxygenase 2
CP cleft palate; *or* cuticular plate
CPA cerebellopontine angle
CPAP continuous positive airway pressure
CPO cleft palate only
CRH corticotrophin-releasing hormone
CRIDE Collaboration for Research in Deaf Education
CRM canalith repositioning manoeuvre
CROS contralateral routing of signal *or* sound
CRP C-reactive protein; *or* canalith repositioning procedure
CRS chronic rhinosinusitis; *or* congenital rubella syndrome
CS corticosteroid
CSD chronic subjective dizziness
CSDD cervical spine degenerative disease
CSF cerebrospinal fluid
CSOM chronic suppurative otitis media
CT computed tomography; *or* conventional thyroidectomy
CSSD cervical spine degenerative disease
CTME carcinoid tumour of the middle ear
CTR cricotracheal resection
CTSIB Clinical Test of Sensory Integration and Balance
CUSA cavitational ultrasonic surgical aspirator
CVA cerebrovascular accident
CVID common variable immune deficiency
CW clockwise
CWD canal wall down
CWU canal wall up

DACI direct acoustic cochlear implant
DACS direct acoustic cochlear stimulation
dB decibel
dBEML decibel effective masking level
dBHL decibel hearing level
dB SPL decibel sound pressure level
DCR dacryocystorhinostomy
DDHS Direct Drive Hearing System
DFO deferoxamine mesylate
DHE dihaematoporphyrinether
DHI dizziness handicap inventory
DM diabetes mellitus
DNA deoxyribonucleic acid
DNSI deep neck space infection
DO distraction osteogenesis
DoH Department of Health
DP directional preponderance
DPOAE distortion product otoacoustic emission
DPTA diethylenetriamine penta-acetic acid
DQ drooling quotient
DSA digital subtraction angiography
DSFS Drooling Severity and Frequency Scale
DSL desired sensation level
DSS disease-specific survival; *or* Department of Social Security
DTI diffusor tensor imaging
DTPA diethylene triamine pentacetic acid
DVN descending vestibular nuclei
DWI diffusion-weighted image
DW-MRI diffusion-weighted magnetic resonance imaging

E exposure
EA episodic ataxia; *or* early antigen
EABR electrical auditory brainstem
EAC external auditory canal; *or* external acoustic canal
EAM external auditory meatus
EANONO European Academy of Otology and Neurotology
EAS electric acoustic stimulation
EBV Epstein–Barr virus
ECA external carotid artery
ECAP electrically evoked compound action potential
$ECCO_2R$ extracorporeal carbon dioxide removal

ECG	electrocardiogram
ECLA	extracorporeal lung-assisted
ECLS	extracorporeal life support
ECM	extracellular matrix
ECMO	extracorporeal membrane oxygenation
ECog	electrocochleography
ECPR	extracorporeal cardiopulmonary resuscitation
EE	external frontoethmoidectomy; *or* excitation–excitation
EEA	endoscopic endonasal approach
EEG	electroencephalography; *or* electroencephalogram
EES	endoscopic ear surgery
EFS	event-free survival
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EI	excitation–inhibition
ELISA	enzyme-linked immunosorbent assay
ELS	European Laryngological Societies
ELST	endolymphatic sac tumour
EMFA	extended middle fossa approach
EMG	electromyography
EML	effective masking level
ENG	electronystagmography
ENoG	electroneurography
ENT	ear, nose and throat
EO	eosinophilic oesophagitis
EOR	extra-oesophageal reflux
EORD	extra-oesophageal reflux disease
EORTC	European Organisation for Research and Treatment of Cancer
EP	endolymphatic potential
ES	embryonic stem; *or* endolymphatic sac
ESID	European Society for Immunodeficiencies
ESPO	European Society of Pediatric Otorhinolaryngology
ESR	erythrocyte sedimentation rate
ESS	endoscopic sinus surgery; *or* Epworth Sleepiness Scale; *or* empty sella syndrome
ET	essential thrombocytosis; *or* endotracheal tube; *or* Eustachian tube
ETD	Eustachian tube dysfunction
ETT	endotracheal tube
ETV	endoscopic third ventriculostomy
EU	European Union
EUA	examination under anaesthesia
EVAS	enlarged vestibular aqueduct syndrome
EXIT	extrauterine intrapartum treatment
F0	fundamental frequency
FAO	far advanced otosclerosis
FAAF	four alternative auditory feature
FBC	full blood count
FDA	Food and Drug Administration (USA)
FDG	fluorodeoxyglucose; *or* 2-[18F] fluoro-2-deoxy-D-glucose; *or* F18-fluoro-2-deoxy-D-glucose
FDG-PET	2-[18F] fluoro-2-deoxy-D-glucose–positron emission tomography; *or* fluorine-18-labelled deoxyglucose positron emission tomography
FDT	fluorescein disappearance test
FEES	fibreoptic endoscopic evaluation of swallowing
FESS	functional endoscopic sinus surgery
FGF	fibroblast growth factor
FIESTA	fast imaging employing steady-state acquisition
FIG6	a prescription rule for amplification, named after the figure in an article on which it was based
FiO_2	fraction of inspired oxygen
FLAIR	fluid attenuated inversion recovery
fMRI	functional magnetic resonance imaging
FMT	floating mass transducer
FN	facial nerve
FNA	fine-needle aspiration/aspirate
FNAC	fine-needle aspiration cytology
FNS	facial nerve schwannoma
FOAR	fronto-orbital advancement and remodelling
FT	fibrous tissue
FTA-ABS	fluorescent treponemal antibody test
GABA	gamma-aminobutyric acid
GABHS	group A beta-haemolytic streptococcus
GAS	Goal Attainment Scaling
GCS	Glasgow Coma Scale
G-CSF	granulocyte-colony stimulating factor
GDNF	glial cell-derived neurotrophic factor
GERD	gastrooesophageal reflux disease
GGF	geniculate ganglion fossa
GHABP	Glasgow Hearing Aid Benefit Profile
GI	gastrointestinal
GLUT-1	glucose transporter-1
GMC	ganglion mother cell; *or* General Medical Council (UK)
GN	glossopharyngeal nerve
GOR	gastro-oesophageal reflux
GORD	gastro-oesophageal reflux disease
GP	general practitioner
GRADE	Grading of Evidence, Assessment, Development and Evaluation

GSA general sensory afferent
GSPN greater superficial petrosal nerve
GVA general visceral afferent
GVE general visceral efferent

H2 histamine receptor type 2
HA hydroxyapatite
HAART highly active antiretroviral therapy
HADS Hospital Anxiety Depression Scale
HAPI Hearing Aid Performance Inventory
HAT hearing assistance technology
HB House–Brackmann
HBOT hyperbaric oxygen therapy
HCG human chorionic gonadotrophin
HDU high dependency unit
HES Hospital Episode Statistics
HHIE Hearing Handicap Inventory for the Elderly
HHT hereditary haemorrhagic telangiectasia
HI hearing impaired
Hib Haemophilus influenzae type b
HIF hypoxia inducible factor
HINTS head impulse, nystagmus characteristics, test for skew
HIT heparin-induced thrombocytopenia; *or* head-impulse test
HIV human immunodeficiency virus
HJB high jugular bulb
HL hearing loss; *or* hearing level; *or* hairy leukoplakia; *or* Hodgkin lymphoma
HLA human leukocyte antigen
HM history of migraine; *or* hemifacial microsomia
HME heat and moisture exchanger
HPV human papillomavirus; *or* human herpes virus 8
HR hazard ratio
HRCT high-resolution computed tomography
h-SCC horizontal semicircular canal
HSF heat shock factors
HSMN hereditary sensory-motor neuropathy
HSP heat shock protein
HSV herpes simplex virus
HSV-1 herpes simplex virus type 1
HSV-2 herpes simplex virus type 2
HT hydroxytryptamine
HTA hyalinizing trabecular adenoma; *or* Health Technology Assessment
HVDT health visitor distraction test
Hz hertz

IAC internal auditory canal
IAM internal auditory meatus
IC inferior colliculus; *or* immunochemistry
ICA internal carotid artery
ICAM-1 intercellular adhesion molecule 1
ICD International Classification of Disease
ICHD International Classification of Headache Disorders
ICP intracranial pressure
ICTD intracranial tumour diameter
ICU intensive care unit
ICVD international classification of vestibular disorders
IDT infant distraction test
IFN interferon
Ig immunoglobulin
IgA immunoglobulin A
IgE immunoglobulin E
IGF-1 insulin-like growth factor 1
IgG immunoglobulin G
IgM immunoglobulin M
IHAFF International Hearing Aid Fitting Forum
IHC immunohistochemistry; *or* inner hair cell
IHS International Headache Society
IJV internal jugular vein
IL-1 interleukin-1
ILD inter-ear latency difference; *or* interaural intensity level difference
IMRT intensity-modulated radiation therapy
IMSPAC imitative test of speech pattern contrast perception
INC interstitial nucleus of Cajal
INO internuclear ophthalmoplegia
iNOS inducible nitric oxide synthase
INR international normalized ratio; *or* interventional neuroradiology
IPD invasive pneumococcal disease
IQ intelligence quotient
IRS insulin receptor substrate; *or* Intergroup Rhabdomyosarcoma Study
ISJ incudostapedial joint
ISMAR Innsbruck Sensory Motor Activator and Regulator
ISO International Standards Organization
ISSNHL idiopathic sudden sensorineural hearing loss
ISSVA International Society for the Study of Vascular Anomalies
IT inferior turbinate; *or* intratympanic
ITDs interaural time differences
ITE in the ear
ITT intention to treat analysis

IUCC International Union against Cancer
i.v. intravenous

JB jugular bulb
JCIH Joint Committee on Infant Hearing
JNA juvenile nasopharyngeal angiofibroma
JOF juvenile ossifying fibroma
JORRP juvenile recurrent respiratory papillomatosis

KADS keratinocyte attachment destroying substance
KO keratosis obturans; *or* keratizing obturans
KMS Kasabach–Merritt syndrome
KTP potassium titanyl phosphate

LA lymphangioma; *or* left anterior
LADD Lacrimo-auriculo-dento-digital
LARP left anterior–right posterior
LCH Langerhans' cell histiocytosis
LDH lactic dehydrogenase
LDL low-density lipoprotein; *or* loudness discomfort level
LED light-emitting diode
LGOB loudness growth in octave bands
LI language impairment
LINAC linear accelerator
LMA laryngeal mask airway
LOCHI long-term outcomes from childhood hearing impairment
LOH loss of heterozygosity
LP lamina papyracea; *or* lichen planus; *or* lymphocyte predominant; *or* left posterior; *or* levator palatini
LPI long process of incus
LPR laryngopharyngeal reflux
LRST lateral reticulospinal tracts
LSCC lateral semicircular canal
LSP language service professional
LTB laryngotracheobronchitis; *or* laryngotracheobronchoscopy
LTR laryngotracheal reconstruction
LTV long-term ventilation
LVA large vestibular aqueduct
LVAS large vestibular aqueduct syndrome
LVN lateral vestibular nuclei
LVOR linear vestibulo–ocular reflex
LVST lateral vestibulospinal tract

M metastases; *or* microphone; *or* mastoid
MAF minimum audible field
MAIS Meaningful Auditory Integration Scale
MAP minimum audible pressure
MAPK mitogen-activated protein kinase
MARD migraine anxiety-related dizziness
MBCT mindfulness-based cognitive therapy
MBL mannose-binding lectin
MCF middle cranial fossa
MCL maximum comfortable level
MCP-1 monocyte chemotactic protein-1
MDCT Multidetector computed tomography
MDT multidisciplinary team
ME middle ear
MEA middle ear adenoma
MEG magnetoencephalography
MEI middle ear implants
MEK MAPK/extracellular signal related kinase
MELAS mitochondrial encephalopathy, lactic acidosis and stroke-like episode
MEN multiple endocrine neoplasia
Men C Meningococcus C
MERI Middle Ear Risk Index
MET middle ear transducer; *or* mechanoelectrical transduction
MF middle fossa
MGB medial geniculate body
MHC major histocompatibility complex
MIBG metaiodobenzylguanidine; *or* iodine-123-metaiodobenzylguanidine
MIP-1a macrophage inflammatory protein-1a
MLC multi-leaf collimator
MLF medial longitudinal fascicle *or* fasciculus
MLR middle latency response
MLTB microlaryngotracheobronchoscopy
MMP-2 metalloproteinase-2
MMP-9 metalloproteinase-9
MMA middle meningeal artery
MMR measles, mumps and rubella
MOTT mycobacteria other than tuberculosis
MPS mucopolysaccharoidoses; *or* massive parallel sequencing
MR magnetic resonance
MRA magnetic resonance angiography
MRC Medical Research Council (UK)
MRI magnetic resonance imaging
MRL minimal response level
mRNA messenger ribonucleic acid
MRS Melkersson–Rosenthal syndrome; *or* magnetic resonance sialography
MRSA methicillin-resistant *Staphylococcus aureus*
MRST medial reticulospinal tracts

MRV migraine-related vestibulopathy
MS multiple sclerosis
MST maximal stimulation test
MTC medullary thyroid carcinoma
mtDNA mitochondrial DNA
mTHPC meso-tetra (hydroxyphenyl) chlorin
MVN medial vestibular nuclei
MVST medial vestibulospinal tract

N nodal
NADP nicotinamide adenine dinucleotide phosphate
NADPH reduced form of nicotinamide adenine dinucleotide phosphate
NAI non-accidental injury
NAL National Acoustic Laboratories (Australia)
NAM nasoalveolar moulding
NBN narrow-band noise
NBCA n-butyl-2-cyanoacrylate; *or* N-butylcyanoacrylate
NEAME neuroendocrine adenoma of the middle ear
NESSTAC North of England and Scotland Study on Tonsillectomy and Adenoidectomy in Children
NET nerve excitability test; *or* neuroendocrine tumour
NFκB nuclear factor kappa B
NF1 neurofibromatosis type 1
NF2 neurofibromatosis type 2
NFA non-functional adenoma; *or* nasofrontal approach
NG nasogastric
NH normal hearing; *or* neurophypophysis
NHL non-Hodgkin lymphoma
NHS National Health Service (UK)
NHSP Newborn Hearing Screening Programme
NI nervus intermedius
NICE National Institute for Health and Care Excellence (UK)
NICH non-involuting congenital haemangiomas
NICU nonimmunological contact urticaria; *or* neonatal intensive care unit
NIH National Institutes of Health (USA)
NIHL noise-induced hearing loss
NIL noise immision level
NMDA N-methyl-d-aspartate; *or* National Minimum Data Set (UK)
NNT number needed to treat
NO nitric oxide
NO_2 nitric dioxide
NOD-2 nucleotide-binding oligomerization domain-containing protein 2
NOE naso-orbito-ethmoid
NP nasopharynx; *or* nasopharyngeal
NPA nasopharyngeal airway
NPC nasopharyngeal cancer; *or* nasopharyngeal carcinoma
NPH nucleus prepositus hypoglossus
NPTA National Prospective Tonsillectomy Audit (UK)
NPV negative predictive value
NRT neural response telemetry
NSAID non-steroidal anti-inflammatory drug
NSC National Screening Committee
NSRAN nonsyndromic recessive auditory neuropathy
NTHi non-typeable *Haemophilus influenzae*
NTM non-tuberculous mycobacteria
NU-CHIPS Northwestern University Children's Perception of Speech

OAE otoacoustic emission
OAVS oculoauriculovertebral spectrum
OCS otic capsule sparing
OCT optical coherence tomography
OCV otic capsule violating
OHC outer hair cell
OKN optokinetic nystagmus
OM occipitomental; *or* otitis media
OMC osteomeatal complex
OME otitis media with effusion
OMENS orbit, mandible, ears, nerves and soft tissue
OMIM Online Mendelian Inheritance in Man
ONSM optic nerve sheath meningiomas
OOPS Ossiculoplasty Outcome Parameter Staging
OPG orthopantomogram; *or* osteoprotegerin
OR occupational rhinitis
ORL otorhinolaryngology
OSA obstructive sleep apnoea
OSAS obstructive sleep apnoea syndrome
OSPL output sound pressure level
OTOF otoferlin
OVAR off-vertical axis rotation
oVEMP ocular vestibular evoked myogenic potentials
OWN oval window niche

P phosphate; *or* posterior; *or* promontory
PACU post-anaesthesia care unit
PAIG Paediatric Audiology Interest Group
PAM postauricular muscle artefact
PAMR postauricular myogenic response

PANQOL Penn Acoustic Neuroma Quality of Life
PaNSTaR Paediatric and Neonatal Safe Transfer and Retrieval (PaNSTaR)
PBI primary blast injury
p-BPPV persistent benign paroxysmal positional vertigo
PBT proton beam therapy
PC Paediatric cholesteatoma; *or* processus cochleariformis
PCA patient-controlled analgesia
PCD primary ciliary dyskinesia
PCHI permanent childhood hearing impairment
PCP planar cell polarity
PCR polymerase chain reaction
PCTR partial cricotracheal resection
PCV7 heptavalent pneumococcal conjugate vaccine
PD Parkinson's disease
PDB Paget's disease of bone
PDH prevention to deafness and hearing impairment
PDL pulsed dye laser; *or* paediatric long
PDS polydimethylsiloxane
PDT photodynamic therapy
PEACH Parents' Evaluation of Aural/Oral Performance in Children
PEG percutaneous endoscopic gastrostomy
PET polyethylene terephthalate; *or* positron emission tomography; *or* patulous (branching) Eustachian tube
PEWS paediatric early warning scores
PFAPA periodic fever, aphthous stomatitis, pharyngitis and cervical adenitis
PFS progression-free survival
PI pulsatility index; *or* performance-intensity
PI3K phosphotidyinositol 3
PICA posterior inferior cerebellar artery
PICANet Paediatric Intensive Care Audit Network
PICS Paediatric Intensive Care Society
PICU paediatric intensive care unit
PID primary immunodeficiency
PIHA partially implantable hearing aid
PIP peak inspiratory pressure
PIVC parietoinsular vestibular cortex
PLF congenital perilymphatic fistula
p.o. by mouth
POGO prescription of gain and output
PORP partial ossicular replacement prosthesis
POSTA Preschool Obstructive Sleep Apnoea Tonsillectomy Adenoidectomy
PP palatopharyngeus
ppeSPL peak-to-peak equivalent sound pressure
PPG pterygoplatine ganglion
PPI proton pump inhibitor; *or* patient and public involvement
PPPD persistent postural-perceptual dizziness
PPRF parapontine reticular formation; *or* paramedian pontine reticular formation
PPV phobic positional vertigo; *or* positive predictive value; *or* pneumococcal polysaccharide vaccine
PROM patient-reported outcome measure
PRRs pattern recognition receptors
PRS persistent rhinosinusitis; *or* Pierre Robin sequence
PSA prostate-specific antigen; *or* pleomorphic salivary adenoma; *or* persistent stapedial artery
p-SCC posterior semicircular canal
PSG polysomnography
Psol parasolitary nucleus
PSP progressive supranuclear palsy
pSPL peak Sound Pressure Level
PT prothrombin time
PTA pure tone audiometry; *or* peritonsillar abscess
PTS permanent threshold shift
PTSD post-traumatic stress disorder
PVA polyvinyl alcohol
PVC polyvinyl chloride
PVP pause vestibular position; *or* position vestibular pause
PVRQOL Paediatric Voice-related Quality of Life

QOL quality of life
QTF Quebec Task Force

RA retinoic acid; *or* right anterior
RAAS renin-angiotensin-aldosterone system
RALP right anterior–left posterior
RANKL regulation of nuclear factor κB ligand
RAST radioallergosorbent test
RCPCH Royal College of Paediatrics and Child Health
RCS Royal College of Surgeons of England
RCT randomized controlled trial
RDI respiratory disturbance index
REAG real-ear aided gain
REAL Revised European American Lymphoma
RECD real ear to coupler difference
RED rigid external distractor
REFTL reference equivalent force threshold level
REIG real-ear insertion gain
REM rapid eye movement
RET rearranged during transfection

RETSPLs reference equivalent sound pressure levels
REZ root entry/exit zones
RI resistance index; *or* reflux index
RICH rapidly involuting congenital haemangiomas
RIMLF rostral interstitial nucleus of the medial longitudinal faciculus
RION radiation induced optic neuropathy
RIP raphe interpositus
RMS root mean square; *or* rhabdomyosarcoma
RMHA remote microphone hearing aids
RNA ribonucleic acid
RNP ribonucleoprotein
RNS reative nitrogen species
ROS reactive oxygen species
RP rapid prototyping; *or* right posterior
RPR rapid plasma regain
RR relative risk; *or* respiratory rate
RRI relative risk of improvement
rRNA Ribosomal ribonucleic acid
RRP recurrent respiratory papillomatosis
RS retrosigmoid
RSV respiratory syncytial virus
rTMS repetitive low-frequency transcranial magnetic stimulation
RW round window

SAD supraglottic airway device; *or* specific antibody deficiency
SAL sensorineural acuity level
SALT speech and language therapist
SCA superior cerebellar artery
SCBU special care baby unit
SCC squamous cell carcinoma *or* cancer; *or* semicircular canal
SCDS superior canal dehiscence syndrome
SCID severe combined immunodeficiency
SCM sternocleidomastoid
SCN severe congenital neutropenia; *or* solid cell nests; *or* Suprachiasmatic Nucleus
SCUBA self-contained underwater breathing apparatus
SEM scanning electron microscopy
SENTAC Society for Ear, Nose and Throat Advances in Children
SF-36 Medical Outcome Study Short-Form 36-Item Health Survey
SGS subglottic stenosis
SHML sinus histiocytosis with massive lymphadenopathy
SIDS sudden infant death syndrome
SIGN Scottish Intercollegiate Guidelines Network
SIMEHD semi-implantable middle ear electromagnetic hearing device
SiN speech reception in noise
SISI short increment sensitivity index
SL sensation level
SLE systemic lupus erythematosus
SLP superficial lamina propria
SLT speech and language therapist
SMD space and motion discomfort
SMHL sinus histiocytosis with massive lymphadenopathy
SNHL sensorineural hearing loss
SNP single-nucleotide polymorphism
SNR signal-to-noise ratio
SNRI serotonin–noradrenaline (norepinephrine) reuptake inhibitors
SNVs single nucleotide variants
SP substance P; *or* summating potential
SPD spatial processing disorder
SPECT single photon emission computed tomography
SPITE surgical, prosthetic, infection, tissue, Eustachian
SPL sound pressure level
SqCC squamous cell carcinoma
SR stereotactic radiation
SRS subacute rhinosinusitis; *or* stereotactic radiosurgery
SRT speech recognition threshold; *or* speech reception threshold; *or* stereotactic radiotherapy
SSC superior semicircular canal
SSCD superior semi-circular canal dehiscence
SSD single-sided deafness
SSEP somato sensory evoked potential
SSG split skin graft
SSNHL sudden sensorineural hearing loss
SSP steady state potential
SSPL saturation sound pressure level
SSRI selective serotonin reuptake inhibitor
ST superior turbinate; *or* subtotal thyroidectomy; *or* sinus tympani
SUV standardized uptake value
SVA special visceral afferent
SVE special visceral efferent
SVN superior vestibular nuclei; *or* superior vestibular nerve
SVS selective venous sampling
SVV subjective visual vertical

T thymine; *or* tumour; *or* telecoil
T3 triiodothyronine

T4 thyroxine
TARGET Trials of Alternative Regimens in Glue Ear Treatment
TB tuberculosis; *or Mycobacterium tuberculosis*
TBI traumatic brain injury
^{99m}Tc technetium-99m
TCF tracheocutaneous fistula
TDT tone decay test
TEOAE transient evoked otoacoustic emission
TFI Tinnitus Functional Index
TGF transforming growth factor
TGF-α transforming growth factor alpha
TGF-β transforming growth factor beta
TGF-β1 transforming growth factor beta 1
Th T helper
THI transient hypogammaglobulinaemia of infancy; *or* tinnitus handicap inventory
TIA transient ischaemic attack
TICA totally implantable cochlear amplifier
TIVA total intravenous anaesthesia
TLR toll-like receptors
TM transmastoid; *or* tympanic membrane; *or* tectorial membrane
TMC1 transmembrane channel-like gene 1
TMJ temporomandibular joint
TMM test and tubomanometry
TN trigeminal neuralgia; *or* trigeminal nerve
TNF tumour necrosis factor
TNF-α tumour necrosis factor alpha
TNM tumour, node, metastasis
TOAE transient evoked otoacoustic emission
ToD teachers of the deaf
TOE transoesophageal echocardiography; *or Trichophyton*, *Oidiomycetes* and *Epidermophyton*
TOF tracheo-oesophageal fistula
TORCH toxoplasmosis; other (such as syphilis, varicella, mumps, parvovirus and HIV); rubella; cytomegalovirus; herpes simplex
TORP total ossicular replacement prosthesis
TORS transoral robotic surgery
TP tensor palatine
TPHA *Treponema pallidum* haemagglutination assay; *or* treponemal haemagglutination
TPMT thiopurine-5-methyltransferase
TPN total parenteral nutrition
TRH thyrotrophin-releasing hormone
TRT tinnitus retraining therapy
TSH thyroid-stimulating hormone; *or* thyrotrophin
TSS transitional space surgery
TT thrombin time; *or* total thyroidectomy; *or* tensor tympani
TTEABR transtympanic electrical auditorybrainstem
TTS temporary 'threshold shift'

UICC International Union Against Cancer
UHL unilateral hearing loss
UNHS universal newborn hearing screening
UNICEF United Nations Children's Fund
URTI upper respiratory tract infection
US ultrasound; *or* ultrasonography
uVD unilateral vestibular deafferentiation

VACTERL vertebral defects, anal atresia, cardiac defects, tracheo-oesophageal fistula, renal anomalies and limb abnormalities
VAS visual analogue scale; *or* visual analogue score
VATS video-assisted thoracoscopic surgery
VBRT Vestibular balance rehabilitation therapy
VCA viral capsid antigen; *or* vestibulocochlear artery
VCR vestibulocollic reflex
VDRL Venereal Disease Research Laboratory
VEGF vascular endothelial growth factor
VEGFA vascular endothelial growth factor A
VEMP vestibular-evoked myogenic potential
VFSS videofluoroscopic swallowing study
VHI Voice Handicap Index
VHIT video head impulse test
VHL Von Hippel–Lindau
VM venous malformations; *or* vestibular migraine
VMA vanillylmandelic acid
VN vestibular nuclei; *or* vagus nerve
VNG videonystagmography
VOG video-oculography
VOR vestibulo-ocular reflex
VORP vibrating ossicular prosthesis
VORS vestibulo-ocular reflex suppression
VP ventriculoperitoneal
VPI velopharyngeal insufficiency
VR vestibular rehabilitation
VRA visual reinforcement audiometry
V-RQOL voice-related quality of life; *or* Voice-related Quality of Life Questionnaire
VS vestibular schwannoma; *or* vibrant soundbridge
VSB vibrant soundbridge
VSM velocity storage mechanism
VSR vestibulospinal reflex

VT	ventilation tubes
VV	visual vertigo
vWD	von Willebrand disease
VZV	varicella zoster virus
WAD	whiplash-associated disorder
WBC	white blood cell
WDT	word discrimination threshold
WES	whole exome sequencing
WGS	whole genome sequencing
WHO	World Health Organization
WIPI	Word Intelligibility by Picture Identification test
WRS	world recognition scoring
WVA	wide vestibular aqueduct

Section 1
Paediatrics

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CHAPTER 1

INTRODUCTION TO PAEDIATRIC OTORHINOLARYNGOLOGY

Raymond W. Clarke

SEARCH STRATEGY

The author's personal bibliography formed the basis for this chapter. Some material is reproduced from '*Clarke's Paediatric otolaryngology – practical clinical management*'.[1]

HISTORY OF PAEDIATRIC OTORHINOLARYNGOLOGY

Laryngology

Otorhinolaryngologists have been caring for children since the specialty began. Diphtheria, epiglottitis and laryngeal tuberculosis were commonplace in children throughout the 19th and early 20th centuries. Victorian and Edwardian laryngologists such as Morell Mackenzie and Sir Felix Semon in London had large paediatric practices and dealt with these often-fatal upper respiratory tract pathologies. Semon was laryngologist to the British Royal family and undertook tonsillectomy on the grandchildren of Queen Victoria, making tonsillectomy a fashionable intervention in the drawing rooms of the aristocracy.[2–4]

Gustav Killian pioneered suspension laryngoscopy in Freiburgim Breisgau at the beginning of the 20th century and the technique was soon taken up for children. Chevalier Jackson (**Figure 1.1**) in Philadelphia established a reputation throughout the United States and beyond for his skills at tracheobronchoscopy. A brilliant teacher, he illustrated his work in his own hand and was probably the single most important figure to popularize airway endoscopy in children on both sides of the Atlantic.[5–7]

Sophisticated diagnostic and therapeutic procedures in children are only possible because of the huge advances made in improving the survival and care of small babies. Joseph O'Dwyer (New York) is credited with the first successful emergency endotracheal intubation in a child in 1884 (**Figure 1.2**), but the technique was associated with a high mortality. Long-term nasal endotracheal intubation as an alternative to tracheotomy was popularized only from the 1960s onwards; paediatric otolaryngologists are acutely aware of the debt they owe to paediatricians and anaesthesiologists. Wilson published the first English-language textbook of paediatric otorhinolaryngology (ORL) in 1955 (**Figure 1.3**) and wrote of emergency tracheotomy in children: 'these are desperate cases at best, and it may be a comfort to remember that the worst thing which can happen is that the patient will die. This is unfortunately a likely event in any case.'[8]

The pioneering work of British physicist Harold Hopkins in the design of 'rod-lens' telescopes (**Figure 1.4**)

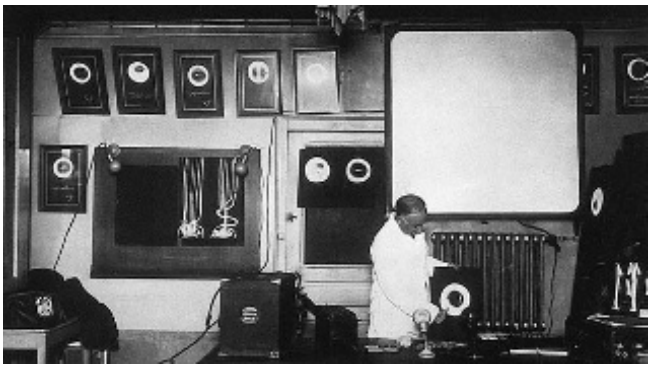
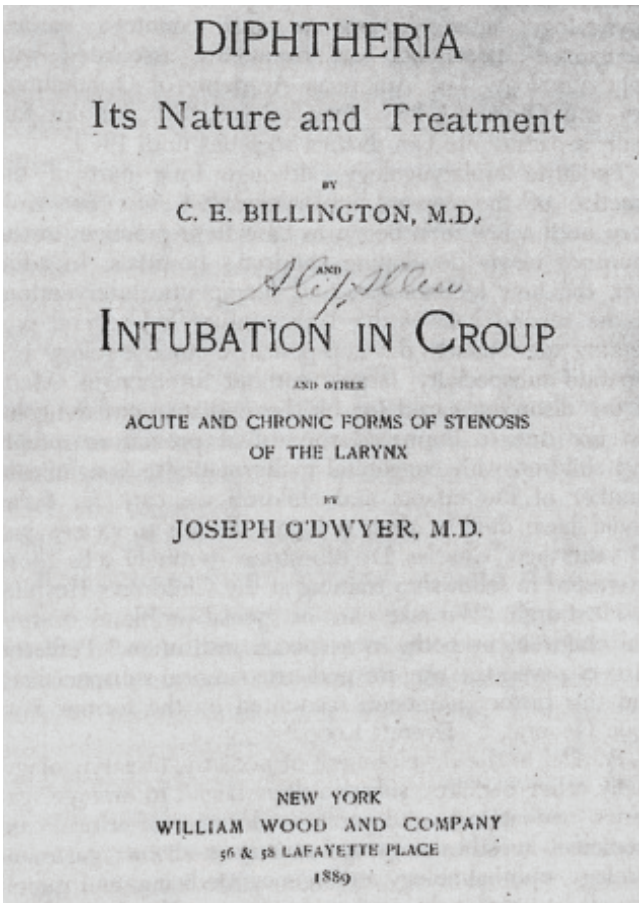


Figure 1.1 Chevalier Jackson. Reproduced by kind permission of the John Q. Adams Center for the History of Otolaryngology – Head and Neck Surgery, American Academy of Otolaryngology – Head and Neck Surgery Foundation, 2007. All rights reserved.


DIPHTHERIA

Its Nature and Treatment

BY

C. E. BILLINGTON, M.D.

AND

INTUBATION IN CROUP

AND OTHER

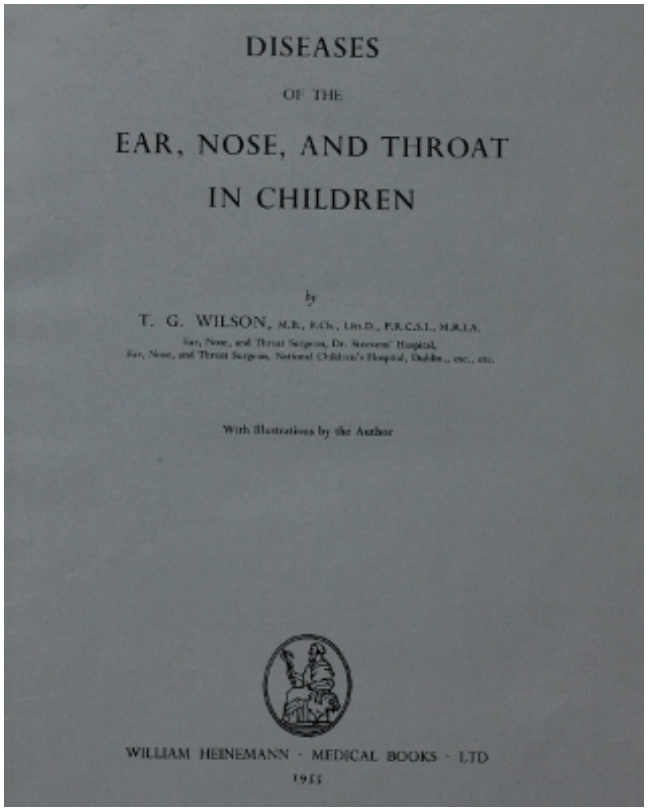
ACUTE AND CHRONIC FORMS OF STENOSIS OF THE LARYNX

BY

JOSEPH O'DWYER, M.D.

NEW YORK
WILLIAM WOOD AND COMPANY
56 & 58 LAFAYETTE PLACE
1889

Figure 1.2 Joseph O'Dwyer paper 1865.


DISEASES

OF THE

EAR, NOSE, AND THROAT

IN CHILDREN

by

T. G. WILSON, M.B., F.C.S., L.M.D., F.R.C.S.I., M.R.I.A.

With Illustrations by the Author

WILLIAM HEINEMANN · MEDICAL BOOKS · LTD

1955

Figure 1.3 Frontispiece of Wilson's textbook (1853).[8]

Figure 1.4 Paediatric airway endoscopy using Hopkins rod lens.

moved paediatric airway surgery to new levels.[9] Modern-day airway endoscopy in children is a highly skilled – and safe – undertaking and the fear and trepidation that surrounded tracheostomy in children is a distant memory.

Otology and audiology

Mastoid surgery in children was popularized by Sir William Wilde (1815–1878). Wilde described otitis media with effusion – 'strumous otitis', recognizing its association with Eustachian tubal dysfunction.[10, 11] He advocated tympanocentesis as a treatment and pioneered the use of the myringotome (**Figure 1.5**). He was an early advocate for the recognition and education of the deaf child, but the profession of audiology really began in the 1920s when audiometers became available. Edith Whetnall in London established a network of clinics which became a model for the assessment and treatment of hearing-impaired children; her 1964 textbook *The Deaf Child* was the standard work for many years.[4]

Cochlear implantation, developed in the 1970s and refined and improved upon throughout the next 30 years, has transformed the lives of hearing-impaired children and their families in the developed world.

The assessment and rehabilitation of the hearing-impaired child has advanced greatly in recent years, and paediatric audiology is an important and growing medical specialty.

Societies and associations

Gatherings of otolaryngologists with an interest in ORL in children took place in Eastern Europe from the beginning of the 20th century. In the United States the Society for Ear, Nose and Throat Advances in Children (SENTAC) (https://sentac.org/) met in 1973. The American Society of Pediatric Otolaryngology (ASPO) (htpp://aspo.us/) was founded in 1985. The European Working Group in Pediatric ENT was founded in 1977 and later became the European Society of Pediatric Otorhinolaryngology (ESPO) (http://www.espo.eu.com/), a forum for discussion and advances in paediatric ORL through international

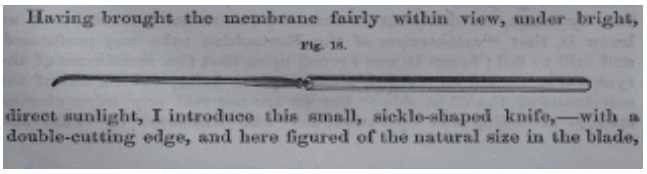

Having brought the membrane fairly within view, under bright,
Fig. 18.
direct sunlight, I introduce this small, sickle-shaped knife,—with a double-cutting edge, and here figured of the natural size in the blade,

Figure 1.5 Wilde's myringotomy knife as illustrated by Wilde in *Practical observations on aural surgery: and the nature and treatment of diseases of the ear.*[10]

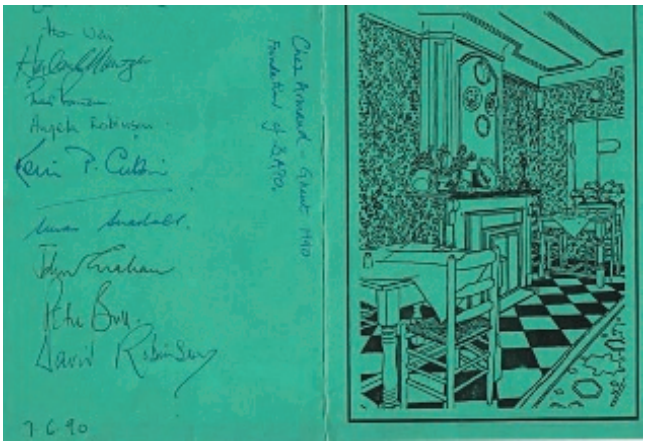


Figure 1.6 Menu from Ghent 1990, foundation of BAPO.

meetings and via its journal the *International Journal of Pediatric Otolaryngology*. The British Association for Paediatric Otolaryngology (BAPO) (https://www.bapo.co.uk/) was formed in 1991. The idea for a British society came about at a meeting of colleagues attending the international congress at Ghent in 1990. Surviving mementos include a signed menu from the Chez Armand restaurant (**Figure 1.6**) (John Graham FRCS, personal communication)!

DEVELOPING ENT SERVICES FOR CHILDREN

Advocating for children

ORL is the specialty with the biggest paediatric surgical workload. It is important that ORL clinicians are to the fore in driving service changes forward to best serve children, families and the next generation of specialists. Up to 30–50% of our workload involves the care of children. Otolaryngologists have, and must maintain, an important role as strong advocates for children.

The philosophy and thinking that influences how we care for children has undergone a radical transformation in recent years. Doctors are no longer seen as infallible. Parents are well informed and expect full participation in decision-making. They expect that their child will be treated in an environment that serves the needs of the child and family and that carers and other staff are fully trained not only in delivering health care, but also in the principles of looking after children and families. There is a growing expectation that service organization should be driven not by the needs of professionals but by the needs of children and families. These legitimate expectations put an onus on us as doctors and planners when setting up services for children. Despite the desirability of treating children close to home, children with unusual or complex conditions or who are in need of highly specialized intervention will have their care best delivered in one of a small number of more specialized settings, where resources and skills are concentrated.

Hospitals that undertake the care of children need to commit to exemplary standards, with the involvement of senior staff in ensuring that the specific requirements of children are met.[12] In a hospital with several otolaryngologists on staff, one should ideally be designated as lead for paediatrics so that he/she can advocate for children at the highest level and can coordinate management, transfer and referral of children with complex needs who may need treatment in a specialized centre. Well-established liaison networks and good communication with specialist centres, paediatricians, community paediatric services, social services, parents and advocacy groups are a cornerstone of good paediatric practice.

Organizing clinics and theatre

Children are best seen in a designated children's clinic rather than in a mixed adult and children's setting.

The clinic setting should be 'child-friendly' with suitable toys, papers and pens and facilities for parents and siblings (see Chapter 2, The paediatric consultation). Similarly, it is nowadays accepted best practice that surgical lists should be planned so as to permit 'children only' lists rather than mixed adult and child surgery.[12]

Theatre staff looking after children need to be suitably trained and in particular the anaesthesiologist should be competent in paediatric anaesthesia with a sufficient workload and throughput to maintain his/her skills in the peri-operative care of children. Children under the age of 3 years will usually require more specialized anaesthetic care. The professional associations that govern anaesthesia in different jurisdictions have their own recommendations with which anaesthesiologists will generally be familiar. If at all possible and provided it is safe, children should be admitted and discharged on the same day ('day' surgery or 'ambulatory care').

Children are best looked after in a children's ward rather than in a mixed ward with adults, again with appropriately trained and accredited nursing staff. Provision should be made for parents, who will usually wish to stay with the child overnight.

If children require overnight nursing care – for example, following adenotonsillectomy for obstructive sleep apnoea (OSA) – experienced paediatric ear, nose and throat (ENT) nurses are usually best placed to look after them. A small number of children will need more thorough monitoring and supervision, perhaps with one-to-one nursing care, or admission to a high dependency unit (HDU) or, exceptionally, to a paediatric intensive care unit (PICU).

TRAINING THE OTORHINOLARYNGOLOGISTS OF THE FUTURE

The diagnosis and management of ORL conditions in children forms an essential part of the syllabus for all ENT surgeons in training. Examinations in ORL – including the European Board Examination[13] – put much emphasis on this, and in general otolaryngologists are well trained in the principles of looking after children with common disorders of the upper respiratory tract.

Although subspecialization in ORL is largely 'system' (otology, head and neck surgery, rhinology) rather than age-based, a growing number of otolaryngologists now choose to undertake advanced training in a fellowship programme in one of the major children's hospitals with a view to taking a special clinical interest in the care of children. In addition to basic and fellowship training, all of us who care for children need to have up-to-date knowledge and skills in topics such as child protection, prescribing for children, analgesia and paediatric resuscitation, and continue to maintain and refresh our knowledge and skills.

BEST CLINICAL PRACTICE

- ✓ Clinicians caring for children and young people should undertake a level of paediatric clinical activity that is enough to maintain minimum competencies.
- ✓ Children should be treated safely, as close to home as possible, in an environment that is suited to their needs, with their parents' involvement in decisions, and with the optimal quality of care.
- ✓ Where theatre scheduling permits, children should have their surgery performed on a dedicated children's operating list.

FUTURE RESEARCH

- ➤ There is an increasing trend to centralize children's surgery. Otolaryngologists must ensure they are to the fore in local service planning.
- ➤ ENT surgeons need to take a strong advocacy role to make for better services for children.
- ➤ Training in the generic skills required to care for children is essential to ORL practice.
- ➤ Training in paediatric emergencies should be encouraged for all ORL practitioners who look after children.

KEY POINTS

- Paediatric otorhinolaryngology is as old as the specialty of otolaryngology itself.
- The pathophysiology and natural history of disease may be very different in children.
- Looking after children is an integral part of the work of an ORL specialist.
- Developments in medicine, anaesthesia and intensive care have brought about a need for increasingly specialist care for children with ORL disorders.
- The improvements in endoscopy brought about by the discoveries of Harold Hopkins transformed paediatric airway care.

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13. European Board Examination in Otolaryngology – Head and Neck Surgery. http://ebeorl-hns.org

FURTHER INFORMATION

American Society of Pediatric Otolaryngology (ASPO): htpp://aspo.us/

British Association for Paediatric Otolaryngology (BAPO): https://www.bapo.co.uk/

European Society of Pediatric Otorhinolaryngology (ESPO): http://www.espo.eu.com/

Society for Ear, Nose and Throat Advances in Children (SENTAC): https://sentac.org/

CHAPTER 2

THE PAEDIATRIC CONSULTATION

Raymond W. Clarke

SEARCH STRATEGY

Data for this chapter are mainly drawn from the author's personal bibliography. The websites of the General Medical Council (GMC) (http://www.gmc-uk.org/), the Royal College of Surgeons of England (RCS) (https://www.rcseng.ac.uk/), the Department of Health (DoH) (https://www.gov.uk/government/organisations/department-of-health), General Medical Council: http://www.gmc-uk.org and the National Institute for Health and Care Excellence (NICE) (https://www.nice.org.uk/) were also consulted.

INTRODUCTION

Children and their parents will often vividly remember their encounters with a doctor. The child's first contact with medical staff and hospitals sets the scene for subsequent visits. A good paediatric consultation is more than a forum for making a diagnosis and planning management; it is an opportunity to familiarize the child and family with the hospital, the clinic, and the members of the team who will look after them during one or more admissions and outpatient visits. For the doctor, it is often the beginning of a rapport with a family who may need to see you many times over the ensuing years. Attention to a few details makes for a far better experience. It is worth putting time, effort and preparation into making the exchange as pleasant and productive as possible for the child and family.[1–4]

The principles that make for a satisfactory and worthwhile visit to the otorhinolaryngology (ORL) department apply to both adults and children, but some features of the children's clinic are unique. The decision to seek advice will have been made not by the patient but by the parent(s) or carer. The older child will express her views; with babies and young children you are essentially looking after a family rather than a patient. The history, the diagnosis, the discussion of management options, and the decision-making are 'by proxy' and will usually involve the parents – sometimes alone, and sometimes in consultation with the child.

BUILDINGS AND FACILITIES

The clinic experience for the family starts well before they see you. Easy road access, car parking, a bright friendly environment with adequate outlets for food and drinks, baby-feeding facilities, wheelchair-friendly access and an environment where children and parents feel safe and welcome contribute greatly to parental and child satisfaction with their visit. Planning modern children's hospitals and facilities is a highly skilled and complex endeavour. It requires close liaison between the architects and their design team, clinicians, hospital staff, children and their advocates, and planning authorities (**Figure 2.1**).

Despite their small size, children need proportionately more space than adults. Seating has to be comfortable and suitable for all ages. Wheelchair access is essential as are spaces for breastfeeding, well-equipped bathrooms and facilities for changing of babies' clothes. A bright spacious waiting room well stocked with toys, pens, paper, crayons and computer games and able to

Figure 2.1 Foyer of Royal Liverpool Children's Hospital.

Figure 2.2 Waiting room with toys.

withstand the rough and tumble that is inevitable in a group of children will make for a far happier experience than a cramped facility (Figure 2.2).[5] Children become bored and fractious if they wait too long or have not got enough space.

Play therapists are invaluable and, if the hospital authorities can be persuaded to hire a professional entertainer, better still.

An examining room should be able to accommodate not just the patient, doctor and nurse but two parents, one or more siblings, sometimes in 'Moses baskets' or pushchairs, and often a grandparent. In the case of many of the children with special needs who make up a sizeable proportion of referrals to an ORL service, there may be a need to accommodate a wheelchair, oxygen cylinders and the various bits and pieces the parents carry for tracheotomy care and gastrostomy management. Ideally, an examining room should have a small play area as well where the child and siblings can occupy themselves while the mother gives the history and the doctor can quietly observe the child. The physical environment must be safe for the child, with no spirit lamps, sharp instruments or corners. Discreetly put away instruments other than those in frequent use. Small children will be frightened at the sight of an array of picks and hooks. Handwashing facilities are mandatory. An operating microscope is nowadays essential, either in the room or nearby. Endoscopy – both flexible and rigid – is now so frequently performed in an outpatient setting in children that it can be regarded as a standard requirement in a paediatric ORL clinic. A range of scopes – with facilities for safe storage – and ideally a monitor and a high-specification image capture system with a printer are nowadays mandatory.

Audiological testing rooms should be adjacent to the clinic so that the child can easily move from one to the other.

STAFFING CHILDREN'S CLINICS

Paediatric clinics need more nursing support than general ENT clinics.[6] Reception staff and care assistants with the training and expertise needed to deal with parents and children make for a far better clinic experience. Best practice is that a registered children's nurse should be available 'to assist, supervise, support and chaperone children'[1, 2] but arrangements will vary in different jurisdictions and in different healthcare settings. Staff numbers need to be sufficient not only to support the working of the clinic, but also to ensure the safe supervision of patients and their siblings while parents are preoccupied.

Audiological professionals are an integral part of paediatric ENT practice; a fully registered audiology technician with facilities for audiometry and tympanometry should be available for all children's ENT clinics.

Other professionals may be needed depending on the nature of the clinic: a speech and language therapist (SALT) for voice disorders or cleft palate, or specialist audiological personnel for children with bone-anchored hearing aids (BAHAs) or cochlear implants (CIs).

Trained specialist nurses who liaise with families in the community – for example in supporting home tracheostomy care – greatly enhance the clinical experience for parent and child. Some units arrange a 'preadmission' clinic so that when a child is scheduled for surgery she can

have her pre-op checks in advance of the day of admission. A dedicated nurse usually runs these clinics, and it can be useful for the family to meet her/him at the first clinic visit so that they can plan ahead.

PREPARING FOR THE CONSULTATION

Ideally, the children's clinic must be separate from the adult clinic. If it is not possible to have a clinical area and a set of consulting rooms that are used exclusively for children throughout the working week, they should be scheduled for a dedicated paediatric session; children should no longer be seen in a 'mixed' adult and paediatric setting. It can be very uncomfortable for children and families if they are allocated the same clinic and have to share a waiting room with a group of adult patients.

Adolescents may feel uncomfortable surrounded by hordes of small children and need to have their particular needs catered for. Some hospitals have separate clinics for adolescents planned for after school times, and teenagers usually appreciate a separate ward or section of a ward if they need inpatient care.

There is much to be said for running separate clinics for some categories of patients. These may include 'special needs' clinics and clinics where multidisciplinary input is required, for example audiology, cleft palate and plastic surgery. Plan the optimum organization of time and space in such clinics to strike a balance between making the most efficient use of time by all concerned and the need to ensure you do not overtire or overwhelm the child by asking her to see too many adults in one room at one time.

A visit to the hospital is a routine event for the doctor. It is a major episode in the life of the child and parent.

Remember that the parent/carer is likely to have had to make arrangements in advance of their visit. They may have had to book time off work, childcare for siblings, a day off school for the child, and transport for the trip.

Take time to read the case-notes – often electronic nowadays – including the results of investigations if applicable, and learn the child's name before the consultation starts. If the child has a chronic medical condition or a syndrome, read up on it in advance if you can. This is relatively easy nowadays as so much information is available online. Parent and child will appreciate continuity and, if a child needs to be seen for repeat visits, it is ideal if the same doctor sees them each time.

Make sure parents or children do not feel rushed in clinic; if you have to hurry them along, the clinic has not been properly planned. If family members do not speak the same language as the doctor and clinic staff, an interpreter will be needed, and this should be arranged well in advance of the visit.

It is not the author's place to advise on dress code; suffice to say that your best tailored suit and crisp, freshly pressed shirt will neither impress the average 8-year-old nor continue to look crisp at the end of a busy morning with a succession of spirited children!

THE HISTORY

Welcome the family and greet the child by name. Make eye contact and start by introducing yourself. Introductions should include others in the room; ask permission for medical/nursing students to be present and for them to examine the child. Multidisciplinary clinics can be particularly intimidating as several specialists are present. It is good practice for all to wear a name badge and many hospitals will demand this. Establish who is with the child – it may be a parent, a carer or a grandparent. Be clear on who is going to give you the history and make sure the child gets an opportunity to speak if she is old enough. Doctors are taught to take very focused histories, but in a paediatric setting it is often better to ask an open question, such as 'What are your worries about Kirsten?', than to steer the parent down a particular set of symptoms.

Good consultation skills can be taught, learnt and improved upon with constructive feedback and should be an important part of training and assessing surgeons as they progress towards independent practice.

Many doctors regard themselves as good communicators because they can explain illnesses and procedures in easy-to-follow terms, but of course communication is a two-way street. Listening – without interruption – can be more useful than talking. It is essential that the parent – usually the mother – feels that her account has been carefully listened to and understood before you probe with more direct questions. Watch the child, look at the mother's facial expressions, note how she interacts with the child and pick up as much information as you can from both verbal and non-verbal clues.

Listen well and talk less until it is clear that the parent feels you have the full picture.

If the parents offer to show you the child's growth chart, a record of their visits to the doctor, diary entries, photographs or short video clips, make sure you look at them. The parents will feel any record of their child's health is important and they may give you much information, for example about the child's overall development or, in the case of video clips, the child's sleep pattern. The birth and perinatal history may be important, and particularly with airway pathology it is helpful to ask the mother about the delivery, whether the baby was term or premature, whether there were any concerns about breathing and feeding as a newborn and in particular

whether there was any airway intervention such as an endotracheal tube or a period in the special care baby unit (SCBU).

EXAMINATION

Begin the examination as soon as the child comes into the room. Note the child's gait, breathing pattern and state of alertness. Once they have had a chance to settle in the clinic room, young children are usually happy to be examined. Smaller children are best examined sitting on their mother's knee.

For the ENT examination explain in an age-appropriate way what is going to happen; don't persist if the child is fractious or struggling.

It is not appropriate to restrain an older child for the purpose of an elective clinical examination, but the mother/father can gently but firmly hold a baby or toddler to facilitate otoscopy, examination of the nose and examination of the neck (Figure 2.3).

Most children will tolerate otoscopy; if there is wax or debris, it is usually possible to remove it by suction to get a better view. Use the biggest speculum that will comfortably fit in the ear canal. If you need a better view, use the microscope, which should be as well tolerated as a standard otoscope. Thin otoendoscopes with high-quality cameras and viewing monitors are becoming more widely available and represent a good opportunity to record findings, to facilitate better explanations of pathology to parents and to use as an aid to teaching.

A good way to start a nasal examination is to assess the nasal airway using a cold metal spatula to look for the pattern of condensation (Figure 2.4). Children do not like the Thudicum's speculum; you can get a good view of the nasal cavities by elevating the tip of the nose and looking with a good light source (Figure 2.5) but high-quality modern endoscopes have made rhinoscopy far easier and better tolerated. Although some surgeons like to use a local anaesthetic spray, the author has not found this useful and in general, if a child will not tolerate a nasendoscope, she will tolerate a spray even less; get the best view you can using a headlight.

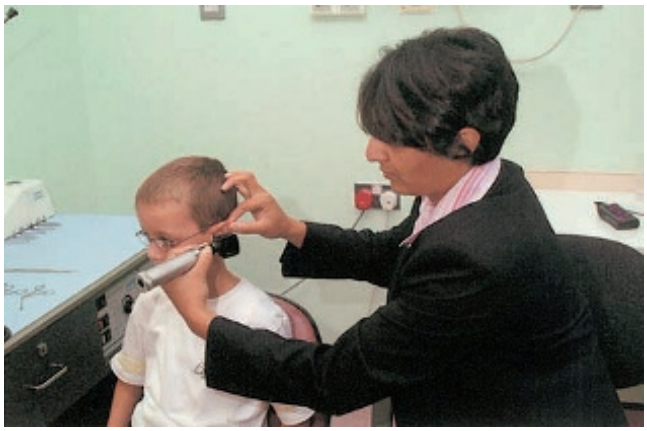

Figure 2.3 Examining a child.

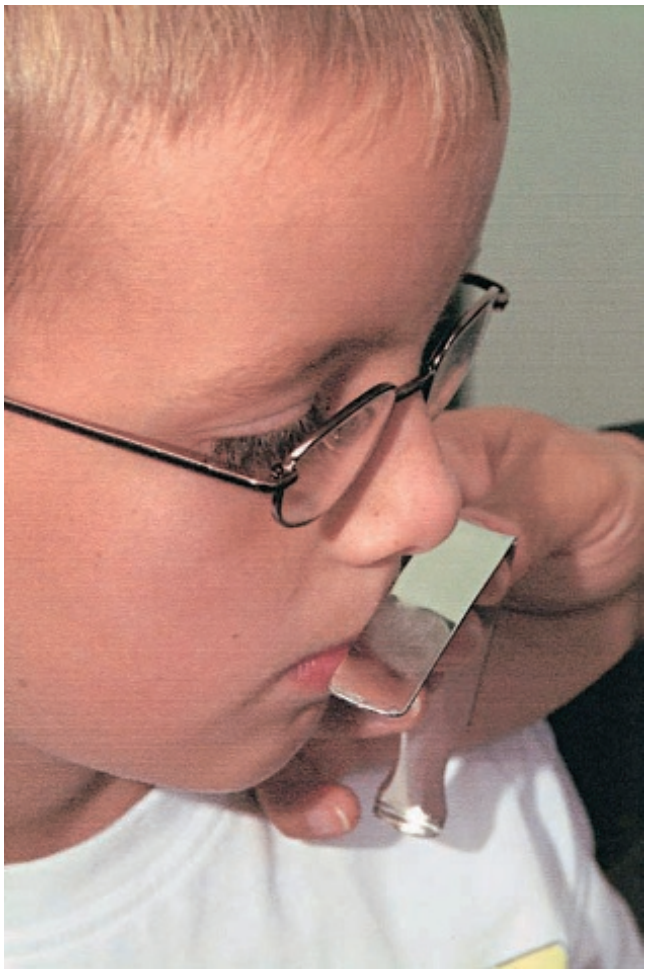

Figure 2.4 The spatula test.

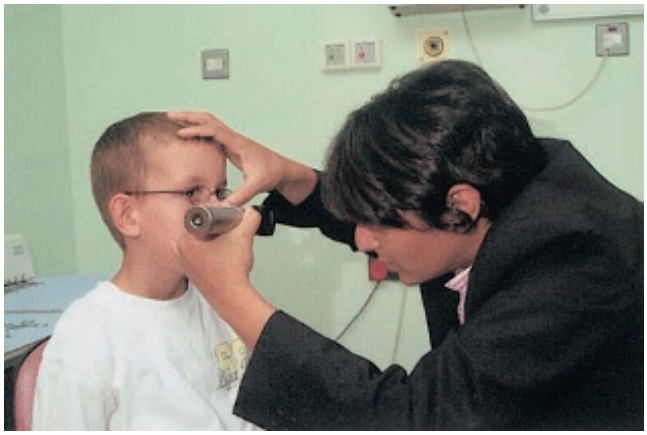

Figure 2.5 Nasal examination.

Examine the pharynx with a standard headlight. Children dislike tongue depressors; the author very rarely uses one. You can get a good view of the nasopharynx using a telescope with an angled lens carefully placed between the tonsils.

Examining the larynx can be difficult, but flexible transnasal endoscopy will give you a very good view in a

cooperative older child, or in the case of a baby who is gently but firmly held by the mother. As with nasendoscopy, the author has not found local anaesthesia very helpful. You may be able to see the vocal cords with an angled-lens rigid telescope but, if a child is anxious or distressed and you have to get a view of the larynx, then arrange admission for a general anaesthetic.

Neck examination should focus on observation for lumps, bumps, sinuses and asymmetry, gently palpating to assess for lymph nodes. 'Lymphadenopathy' is probably a misnomer in children as some degree of lymph node enlargement is physiological and should cause no alarm.

INVESTIGATIONS

Few if any investigations are needed for most common ENT presentations in children.

Pure-tone audiometry (provided the child is old enough) and tympanometry are essential components of a full ENT examination. Radiological imaging may be needed depending on the pathology, and ultrasonography is increasingly used to quickly assess neck swellings. Some ENT surgeons are now skilled at getting good ultrasound images in clinic. If the child needs blood tests, then she should have local anaesthetic cream (e.g. EMLA™ cream, an emulsion containing lidocaine and prilocaine) before being sent for phlebotomy. Photography can be useful – for example, for facial and neck lesions – and close liaison with a skilled medical photography department will make for a better paediatric ENT service.

MANAGEMENT PLAN

The parents have come to see you to hear your opinion on their child's condition and to discuss a management plan with you. This part of the consultation is vital and must never be rushed. Explanations should be straightforward and easy to understand, involving the child where appropriate. Models, diagrams, printed and audiovisual material can aid this process greatly. For many interventions, such as tonsillectomy, adenoidectomy and insertion of tympanostomy tubes, there will be more than one management option and it is important that each is discussed in an open and honest way. This sometimes means doctors have to admit doubts and uncertainties and these are best explained without embarrassment so that a way forward can be agreed by consensus. The treatment will be a matter for negotiation between the otolaryngologist and the mother and/or child and questions should be encouraged. Some parents see the ORL consultation as a means to confirm a treatment option they have already decided on with their family doctor (e.g. tonsillectomy for recurrent sore throats). Others are reluctant to consider any surgery, but all will greatly appreciate an informed discussion and an honest presentation of the evidence for current practice focused on the specific needs of their child. In general, parents appreciate a discussion with the senior clinician, but this needs to be balanced with the need for residents and juniors to see patients and improve their diagnostic and consultation skills.

PAEDIATRIC MEDICAL ASSESSMENT

ENT surgeons are not typically trained medical paediatricians; if you are seeing a significant number of children, you will come across conditions that are best diagnosed and dealt with by paediatrician colleagues. Some knowledge of these conditions can help early detection and referral so that parents and children are offered skilled support as soon as is practicable. Attention deficit hyperactivity disorders (ADHD), autistic spectrum disorders (ASD), and a variety of 'functional' disorders may well present first to the otolaryngologist.

ADHD

Every clinician will be familiar with the child who fidgets, won't sit still, and seems to have a poor attention span. Parents will often volunteer that the child is 'hyperactive' or disruptive. In extreme cases this may constitute a behavioural syndrome termed attention deficit hyperactivity disorder (ADHD). This condition is now thought to affect 3–4% of children worldwide. They occasionally present with suspected hearing loss or poor sleep patterns.

The defining features of ADHD are hyperactivity, impulsivity and inattention, but these characteristics are distributed in varying degrees throughout the population.

ADHD diagnostic criteria vary somewhat, but the core feature of the diagnosis is that symptoms are associated with 'at least a moderate degree of psychological, social and/or educational or occupational impairment'. ADHD is not a categorical diagnosis; it should only be made with great care following a thorough assessment by a skilled and experienced paediatric team.[7] A diagnosis of ADHD has serious potential implications; it is generally a persisting disorder. Most affected children will go on to have significant difficulties in adulthood, including continuing ADHD, personality disorders, emotional and social difficulties, substance misuse, unemployment and involvement in crime. Management can be very taxing, involving social and educational services, the family doctor and his/her team, specialist paediatricians and, of course, the child's family.

Autistic spectrum disorders

Autism was once thought to be an uncommon developmental disorder but is now estimated to occur in at least 1% of children. Healthcare personnel need to be aware of some of the features so as to facilitate early diagnosis and intervention. The characteristic features are impairment in reciprocal social interaction and social communication,

TABLE 2.1 Some features of autistic spectrum disorders (ASD) in preschool children

Aspect	Examples
Language	Delayed speech development Frequent repetition of set words and phrases
Responding	Not responding to their name being called Rejecting cuddles
Interacting	Unaware of other people's personal space Intolerant of people entering their personal space Avoiding eye contact
Behaviour	Repetitive movements Playing with toys in a repetitive way Getting upset if there are changes to normal routine

combined with restricted interests and rigid and repetitive behaviours. In recognition of the great heterogeneity of autism, the term 'autistic spectrum disorder' (ASD) is now more commonly used. The list of possible symptoms is very large but some key features are shown in Table 2.1.

Otolaryngologists may suspect that a child referred for a hearing or speech assessment has an ASD. The diagnosis needs to be made with great care and warrants a full assessment by an experienced team.[8] If ASD is confirmed, families and the child or young person themselves can experience a variety of emotions, including shock and worry about the implications for the future. Some have a profound sense of relief that others agree with their concerns. Skilled diagnosis is important: it can offer an understanding of why a child or young person is different from their peers, open doors to support and services in education, health and social care, and provide a route into voluntary organizations and contact with other children and families with similar experiences. All of these can improve the lives of the child or young person and their family.

Children with ASD may present to the ENT clinic with language delay or suspected hearing loss.

Given the frequency of the condition, many children who present to the ENT clinic will have a background history of ASD and it is important to be aware of the diagnosis because of its very common association with comorbidity. ASD is strongly associated with a number of coexisting conditions. Approximately 70% of people with autism also meet diagnostic criteria for at least one other (often unrecognized) psychiatric disorder that further impairs their psychosocial functioning. Intellectual disability (intelligence quotient [IQ] below 70) occurs in approximately 50% of young people with autism. Deafness and other sensory impairments are more common and may be difficult to recognize.

Children with ASD need particularly sensitive care and attention if they are admitted for surgery.

Some children with ASD find the company of other children distressing and they are especially likely to become upset if they have to wait too long. In general they should be assessed early by the anaesthesiologist, considered for a sedative – 'pre-med' – scheduled early on the operating list, and discharged as soon as they are fit. Day surgery is preferable unless there are very good medical reasons to keep the child in overnight.

Functional disorders

Just as in adult medicine, children present to the ENT clinic with symptoms for which no organic pathophysiological explanation can be found despite a thorough examination and in some cases extensive investigation. The term 'functional disorders' is often used to emphasize that, although no structural or anatomical abnormality can be demonstrated for example on imaging, endoscopy or microscopy, there may be physiological dysfunction.

ENT symptoms in children may include:

- earache
- tinnitus
- hearing loss
- dysphagia
- neck pain
- balance disorders
- dysphonia
- stridor (very occasionally).

Terms such as 'medically unexplained', 'psychogenic', 'stress-related', 'psychosomatic' and 'hysterical' were used in the past but have been abandoned as they were unhelpful, became derogatory and implied a certain amount of 'blame' on the part of the patient.

Functional disorders are not the same as factitious or feigned illness; it is hugely counterproductive to make the child or parent feel that they are not believed.

The symptoms are very real to the patient and can cause great distress, which can be exacerbated if they are treated in an insensitive or judgmental way.

Take a full history, examine the child thoroughly, arrange investigations as needed – including audiometry, imaging and endoscopy – and formulate a diagnosis. If you suspect a functional basis for the symptoms, enquire into issues such as school, relationships with siblings, friends and family and whether there has been any change in home circumstances. Parental disharmony, bullying at school and the trauma of the physiological and psychological changes of puberty and adolescence can all have an impact on health and well-being, with somatic symptoms coming to the fore. An experienced clinician will need to strike a balance between a thorough investigation to rule out an organic aetiology and a more minimal approach focusing on history, examination and reassurance. A sensitive and thoughtful explanation of the findings to parent and child will allay fears and make for a good rapport for follow-up visits.

There is often a background history of environmental or psychological stress, but dealing with a certain amount of anxiety, uncertainty and insecurity is all part of

growing up. Children can – consciously or unconsciously – describe symptoms that bring about some 'secondary gain' for them, such as time off school, increased parental attention in the event of a new sibling, and the benefits associated with being perceived as 'sick'. Functional disorders are distinct from true malingering or feigned symptoms, although these do very occasionally present as well. It is difficult to know on the basis of a single consultation whether there is any significant psychological morbidity; too-early referral to a psychological support service can be counterproductive.

Many functional disorders are short-lived and should not be 'over-medicalized.'

It is the author's practice in most circumstances to reassure the family that the majority of these symptoms are transient and rarely need intensive intervention. Bear in mind that depression, pathological anxiety and rarely overt psychosis do occur in children, and skilled psychiatric help will be needed in some circumstances. Referral protocols vary but most children's hospitals will have a child and adolescent mental health service (CAMHS) team, who will see and assess children at short notice. Many hospitals will have specific policies covering this type of scenario; clinicians should ensure they have the appropriate training for the setting in which they work. Management must be tailored to the individual child and family and prognosis varies greatly.

CONSENT AND PARENTAL RESPONSIBILITY

It goes without saying that every medical intervention requires the informed consent of the patient. What is different in the case of young children is that they may not have the capacity and understanding ('competence') to weigh the benefits and risks of an intervention, and consent will usually need to be given on their behalf. It is wise to involve the child whenever possible. The interests of the child must, of course, take precedence over the wishes of others, even parents, and the law in almost all jurisdictions recognizes this, but clinicians will want to respect the legitimate concerns of parents, carers or legal guardians. The legalities that govern these processes vary in different jurisdictions and healthcare settings but the principles are broadly similar.

Once children reach the age of 16 years they are deemed legally 'competent' in the UK.

Reaching the age of legal competence means children are responsible for decisions relating to consent themselves, but it is of course wise to involve parents if at all possible in major decisions in the young. If a young person up to the age of 18 years is not 'competent' – for example, due to learning disability, reduced consciousness, or severe illness – then a parent or person with 'parental responsibility' (see below) can give consent for them, but over the age of 18 years in UK law a parent cannot give consent on behalf of a young person. This causes difficulties in the case of young adults with learning disabilities, many of whom remain under the care of children's hospitals. In these cases the clinician must make the decision on the young person's behalf, ideally with the written agreement of another senior clinician and with the full approval of the parent.

A child under the age of 16 years may well be able to understand the implications of a treatment strategy. In UK law such a child who has 'sufficient understanding and intelligence' to enable him or her to understand fully what is proposed is deemed 'Gillick competent' or as it is sometimes known 'Fraser competent'.[9] The decision as to whether a child fulfils the criteria for 'Gillick competence' rests with the clinician, hence teenagers undergoing, for example, tonsillectomy may give their own consent. The issues around consent in children can cause great sensitivity and are fraught with medicolegal pitfalls. If in any doubt, seek the advice of one or more senior clinicians.

In the case of a child who is not 'competent', consent has to be sought from and given by a person with 'parental responsibility.'

'Parental responsibility' is usually held by one or both of the parents. The situation varies in different jurisdictions but in England and Wales 'parental responsibility' is automatically given to the mother, and to most fathers. A father will have parental responsibility if he is married to the child's mother or listed on the child's birth certificate (after a certain date, which varies in jurisdictions). Fathers who do not have parental responsibility can get it via an agreement with the mother or they can apply for it through the courts. Grandparents, foster parents and others who look after children do not have parental responsibility unless special legal arrangements have been made. Consent from one parent is legally valid but it is best to obtain consent where applicable from both. A written record of consent, signed by the doctor and the parent, is an important document and, although not legally mandatory, in general an invasive intervention should not proceed without it. Verbal consent for surgery is possible – and in many circumstances entirely reasonable. If, for example, a newborn baby needs urgent surgery, very often the mother will be recovering in the maternity unit. The surgeon should speak to her by telephone, explain the natural history of the condition, the implications of treatment, the consequences of not treating, and the timing of treatment. It is good practice to get another healthcare professional (e.g. a nurse) to confirm with the mother that she understands and agrees with what is being proposed and to record the exchanges in the case notes.

It may be necessary in emergency scenarios to proceed without consent – for example when a child needs urgent

intervention following an accident and the person with parental responsibility is not immediately available.[10–13]

A recent UK legal judgement – the 'Montgomery' case – has moved the focus of consent more towards the specific needs of the individual patient. This follows the guidance of the General Medical Council[11, 12] but makes even more explicit the need for doctors to take reasonable steps to ensure that **patients are aware of any risks that are material to them.** This puts a greater onus on us as surgeons not only to communicate the benefits and risks of interventions but to judge the individual needs and perceptions of our patients/parents and to customize our discussion of management options to those varying patient/parent views.[14, 15]

Consent in children causes great sensitivity. Make sure you are familiar with the Department of Health guidelines,[10] the findings of the 'Montgomery' case,[14] the advice of the General Medical Council[11–13] and the guidance of the surgical Royal colleges.[15] Trainee surgeons in particular are advised to seek the advice of senior colleagues in the event of any uncertainties.

FUTURE RESEARCH

- Department of Health (DoH): https://www.gov.uk/government/organisations/department-of-health
- General Medical Council (GMC): http://www.gmc-uk.org/
- National Institute for Health and Care Excellence NICE): https://www.nice.org.uk/
- Royal College of Surgeons of England (RCS): https://www.rcseng.ac.uk/

KEY POINTS

- A visit to the hospital is a routine event for the doctor. It is a major episode in the life of the child and parent.
- Children should be seen in appropriately staffed, dedicated children-only 'child-friendly' clinics.
- Audiological professionals and audiological testing facilities are an integral part of children's ENT clinics.
- Autistic spectrum disorders (ASD) are increasingly common and may present to the otolaryngologist.
- Make sure you are familiar with the procedures governing consent in children in your healthcare setting.

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CHAPTER 3

RECOGNITION AND MANAGEMENT OF THE SICK CHILD

Julian Gaskin, Raymond W. Clarke and Claire Westrope

SEARCH STRATEGY

Data in this chapter are taken from the Advanced Paediatric Life Support (APLS) manual and the websites and publications of the General Medical Council, the National Institute for Health and Care Excellence (NICE), and the Paediatric Intensive Care Society (PICS), supplemented by the authors' personal bibliographies and their experiences as clinicians and teachers.

INTRODUCTION

Children under the care of otolaryngologists are mostly looked after in an outpatient or planned inpatient setting, and are in good general health. Very ill children – sometimes with complex and multisystem diseases – are typically cared for by paediatricians and their teams, but the otolaryngologist will often participate in shared care. Every doctor who looks after children will, from time to time, be presented with an emergency situation; children who are apparently well can deteriorate very quickly.

Doctors who deal with children also need to be aware that children are vulnerable to harm and abuse and that we have a duty of care to recognize and act if we have any concerns about such abuse or maltreatment.

This chapter outlines some of the general principles that underpin the care of the very sick child, and highlights some of the features of child abuse that may present in an ORL clinic.

A short book chapter is, of course, no substitute for structured learning and experience. ORL training programmes now recognize this and both otolaryngologists-in-training and established practitioners will need to complete formal 'hands-on' training courses in the principles of resuscitation and in 'child protection'.

THE 'NORMAL' CHILD

The aphorism that 'children are not small adults' conveys important lessons, not least that the physiology of the child and their responses to illness may be very different from those in adults. Children have lower physiological reserves; they can deteriorate with alarming rapidity. Doctors who work largely with adults may not always appreciate, for example, the widely varying baseline observations in children, and their changes with age (**Table 3.1**). Fluid requirements are, of course, also very different in children (**Table 3.2**).

An awareness of the normal parameters is essential, as deviations away from these allow the clinician to recognize them at the earliest opportunity. Ongoing assessment and monitoring can facilitate early detection of change and prompt life-saving intervention.

RECOGNIZING THE SICK CHILD

The way we approach recognizing and managing seriously ill patients nowadays has largely been shaped by the principles developed in Basic and Advanced Life Support courses (BLS and ALS).[1, 2] Courses and teaching modules

TABLE 3.1 Normal range at different ages for children's weight, respiratory rate, pulse rate and systolic blood pressure (adapted from APLS manual[1])

Age	Weight (kg)	Respiratory rate (RR) (breaths/minute)	Pulse/minute	Systolic blood pressure (mmHg)
Birth	3.5	25–50	120–170	65–105
1 year	9.0	20–40	110–160	70–95
4 years	16.0	20–30	80–135	70–110
10 years	32.0	15–25	70–120	80–120

TABLE 3.2 Fluid requirements in normal healthy children (adapted from APLS manual[1])

Body weight	Fluid per day (mL/kg)
First 10 kg	100
Second 10 kg	50
Each subsequent kg	20

focused on the needs of healthcare personnel looking after sick children developed from the early 1990s as the Advanced Paediatric Life Support (APLS) system, which teaches a structured and reproducible set of skills applicable across specialty, language, cultural and geographical boundaries.[1] APLS teaching materials are produced and regularly updated by a multidisciplinary team of paediatric emergency physicians, anaesthetists, surgeons and paediatricians. Much emphasis is given to the care within the first hour, the so-called 'golden hour', which governs the trajectory of subsequent management. With important, easy-to-remember initial steps, the right order of resuscitation can begin to help avert a sick child deteriorating, or even worse, dying.

Prioritizing bodily systems has helped clinicians and those first on the scene to deal with complex situations in the best possible way. A structured approach concentrates on different systems of the body in an order that generally allows the most important problems to be assessed and dealt with first before moving on. These systems include the **respiratory**, **circulatory** and **central neurological** systems. They can be remembered as:

A – Airway
B – Breathing
C – Circulation
D – Disability (central neurological system)
E – Exposure (temperature, rash, bruising).

The respiratory system – airway and breathing

In the initial assessment of a sick child, the airway and breathing must be considered first. A blocked or reduced airway has to be addressed as a matter of extreme urgency as this impacts quickly on all of the organ systems. Signs to be observed include **apnoea**, **stertor** and **stridor**. As the child's ribcage is soft and pliable, sternal and intercostal **recession** and **'tracheal tug'** (indrawing of the suprasternal tissues) can often be seen if a child is working hard to breathe.

The respiratory rate must be measured. This will vary according to the child's age (see Table 3.1). If a child is tachypnoeic, this may be due to airway or lung pathology, or a metabolic acidosis (trying to 'blow off' carbon dioxide). A slowing respiratory rate is not always a comfort; it may be due to fatigue or cerebral depression and can be a preterminal sign.

Respiratory noises can help to define the level of airway narrowing, but this is not specific enough to make a definite diagnosis. If the noise is a low-pitched, snoring-type sound ('stertor'), then obstruction is usually at the level of the nasopharynx or oropharynx. 'Stridor' – generally a higher-pitched noise, (although the two terms are used imprecisely) – is often inspiratory but can also be biphasic (inspiratory and expiratory), and is classically brought about by obstruction in the larynx. This can be the supraglottis, glottis or subglottis but stridor can also be due to narrowing of the trachea or even the main bronchi. Biphasic stridor is particularly ominous and suggests severe airway compromise. Obstruction in the lower airway or in the distal bronchial tree will usually produce **wheeze**, which is more pronounced on expiration. All these respiratory noises are normally more pronounced in the presence of good airflow. In a preterminal state when the airflow is reduced, there may not be an obvious respiratory noise, despite significant obstruction within the airway. Beware the stridulous child who becomes quiet. Gasping is almost invariably a late sign of a severely hypoxic, exhausted child.

A child with severe airway obstruction will often adopt a position – usually when lying down – with the neck extended. This is called an 'opisthotonic' position and is aimed at trying to open the upper airway maximally due to obstruction. Other signs to look for in the assessment of airway compromise include flaring of the nostrils as an infant tries to increase the intake of air during inspiration.

Inspection, palpation and auscultation of the chest can reveal important signs too. Chest expansion can be a very sensitive sign when making an assessment of the amount of air passed during inspiration and expiration. The same goes for auscultation, where reduced air entry can be evaluated. If air entry is unequal across the lungs, this may point to pathology affecting one lung, such as a pneumothorax or a bronchial foreign body. A 'silent chest' is another late sign in a child that may be about to have a cardiopulmonary arrest.

Simple measurement of the pulse can inform the clinician of the presence of tachycardia associated with hypoxia. However, this is also likely if the child is anxious or pyrexial. Bradycardia is an ominous preterminal sign.

Monitoring equipment such as a pulse oximeter may be of additional support as it can help give a measure of the arterial oxygen saturation. Pulse oximetry should be used as an adjunct; guard against false reassurance if other clinical signs do not support a good read-out from the pulse oximeter. It is important to realize that there is often a time delay of a few seconds before the oxygen saturation registers; the true oxygen saturation in the patient's arterial blood may be lower than the reading suggests. Conversely, a low reading may relate not only to a patient's low oxygen levels but can occur in hypothermia, severe shock or if there is poor contact with or interference from the sensor.

In severe hypoxia, expect to see skin pallor due to vasoconstriction. Cyanosis is a late and highly ominous sign. In a child without an underlying cardiac condition it is extremely serious, suggestive of severe respiratory compromise; if due to hypoxia it suggests that the child is close to a respiratory arrest.

The circulatory system (C)

After airway and breathing, circulation needs to be assessed next. One of the first signs is the pulse rate, measured either by palpation (better centrally via a larger artery such as one of the carotid or femoral arteries) or with pulse oximetry (again, bearing in mind its limitations). Normal ranges of pulse rate can be seen in Table 3.1, varying with age. Tachycardia will often be seen in shock, where a decreased stroke volume (amount of blood pumped from the left ventricle in a beat) leads to release of catecholamines such as adrenaline. Bradycardia is a late sign of impending cardiac arrest. Weak pulses, particularly centrally, can be a sign of very poor perfusion as blood pressure is usually maintained until severe shock develops. Blood pressure readings are not as useful because systolic blood pressure is usually well maintained in a shocked child. Once hypotension has supervened, a cardiac arrest is highly likely.

Capillary refill is a much earlier sign of circulatory compromise. This should be assessed centrally, ideally on the sternum, where digital pressure is applied to the skin for 5 seconds and then released. The resultant blanched skin colour change should usually return to normal within 2 seconds. If this is prolonged, it is a sign of poor skin perfusion but is also suggestive of potential underlying poor perfusion to other organs. Although fever does not affect this sign (which is therefore very useful in assessing a child with septic shock), a cold environment does, so the ambient temperature needs to be taken into account.

Other signs of poor circulation relate to the effects on other organs. The skin can show obvious changes such as cold peripheries but also mottling. Poor perfusion will affect the conscious state and cause reduced urinary output and increased respiratory rate.

The central neurological system – disability (D)

A formal assessment using the Glasgow Coma Scale (GCS) used in adult patients is often very difficult to transfer over to a child. A quick way of assessing the conscious level in a child is using the acronym AVPU to signal progressively decreasing conscious level:

- **A**lert
- responds to **V**oice
- responds to **P**ain
- **U**nresponsive.

If the child in unresponsive to verbal stimulus but does respond to painful stimulus, this would equate to a GCS of 8 or less. Ways to measure response to painful stimuli can be to exert pressure over key points of the body, such as the sternum or supraorbital ridge. Subsequent sounds, localization to the painful stimulus or seeing if the eyes open can then be recorded.

Observing the posture of the child can be helpful. Often, hypotonia ('floppy' child) is present if the child has had a significant neurological insult. Sometimes there are specific positions a child will adopt depending on the location of intracranial pathology. Flexed arms and legs is known as a decorticate posture and extended arms and legs is known as a decerebrate posture, which is usually in keeping with a more severe injury. With meningitis, there may be neck stiffness.

The reaction of the pupils to a light stimulus can reveal important information related to the function of the central neurological system. Dilated pupils, or pupils that are unequal or unresponsive to light, may point toward serious neuropathology.

There may also be signs of abnormal central neurological function in the respiratory and circulatory systems, with altered breathing patterns, hyperventilation or apnoea. Brain herniation can cause a vasopressure response with hypertension and bradycardia.

Exposure (E)

A full assessment of the sick child involves stripping the patient down to look at the skin for bruising related to injury or rashes related to infection or allergy, which may dictate the need for investigations such as blood cultures, CT imaging and lumbar puncture (provided there is no evidence of raised intracranial pressure). It is also important to check the temperature and reassess all the signs again such as respiratory rate, pulse rate and so on.

With this simple but highly effective order of assessment, using airway, breathing, circulation, disability and exposure (ABCDE), the correct priorities are set to ensure that important features in the recognition of the sick child are not missed.

EARLY MANAGEMENT

Following the structured approach of assessing a seriously ill child, resuscitation and treatment is required. This follows the same systematic format.

Airway

Suctioning of secretions, removal of intra-oral foreign bodies or debris, a chin lift and jaw thrust are the immediate measures to free the airway. This is likely to overcome any oropharygeal obstruction. If the airway obstruction is not resolved by such simple manoeuvres, an **adjunctive airway** may be required. This may be in the form of a nasopharyngeal airway (NPA), an oropharyngeal or 'Guedel' airway or a laryngeal mask airway (LMA). If the airway cannot be maintained by one of these measures, endotracheal (ET) intubation will be needed. This could be via the nose (nasotracheal) or mouth (orotracheal). Externally, a tracheostomy can be formed, or in a dire emergency situation a cricothyroid puncture.

Nebulized adrenaline and intravenous steroids such as dexamethasone may all help to improve upper airway obstruction (see Chapter 28, Stridor).

If an airway foreign body is likely and the child is *in extremis,* then immediate transfer to an operating theatre for removal of the object using a ventilating bronchoscope can be life-saving. An oropharyngeal foreign body may need to be immediately engaged and removed with Magill forceps.

Breathing

Once the airway is secured, breathing needs to be efficacious. This requires there to be no intra-cerebral compromise of the respiratory centre and no abnormality of the lungs or musculature surrounding the lungs. Emergency treatment to aid breathing would be by applying high-flow oxygen via a facemask with a reservoir bag, or direct attachment to an endotracheal tube if the child has been intubated. Bag-valve ventilation ('bagging') can also be performed and works by introducing positive pressure. Investigations may include a chest radiograph, arterial blood gases or blood cultures, but stabilizing the airway and ensuring the child is breathing safely is by far the highest priority.

Circulation

Supporting and reversing inadequate circulation requires intravenous cannulation and administration of intravenous fluids in the first instance. However, if intravenous cannulation is not readily achievable, particularly in hypovolaemic shock where peripheral venous access may be difficult due to vasoconstriction, intra-osseous access will be required. Intra-osseous fluids can be infused effectively to reverse a circulatory deficit in children. Replacement of blood in the presence of significant blood loss may also be needed. Primary investigations are blood tests in the form of a full blood count, urea and electrolytes, clotting screen and a group and save/cross match. An electrocardiogram is also needed. If septic shock is suspected, blood cultures and intravenous antibiotics are required.

Disability

Rapid assessment using the AVPU stimulus test above will help ascertain if intubation is necessary to protect the airway. A child with responses only to painful stimulus or a child who is unresponsive (**P,U**) meets this criterion. Any patient with a neurological deficit must have their glucose level checked (don't ever forget glucose – **DEFG**). If blood glucose levels are found to be abnormal, they can be reversed with intravenous treatments. Seizures or convulsions can be treated with benzodiazepines. Signs of raised intracranial pressure are likely to require CT scanning and specialist input from neurology or neurosurgical teams.

Adequate analgesia – including the use of opioids where safe and appropriate – is an important part of the early management of the sick child.

Exposure

Septicaemia may cause a purpuric rash. Meningitis may cause a non-blanching purpuric rash, along with other signs of meningism. Intravenous antibiotics are then needed immediately. Anaphylaxis may cause an urticarial rash and angio-oedema, particularly around the lips and oropharynx. In such cases, adrenaline given via nebulizer and intra-muscularly is often immediately helpful, with intravenous steroids and intra-muscular antihistamines later on in the resuscitation period.

SAFE TRANSFER

Once the seriously ill or injured child has been appropriately resuscitated and stabilized, the next step in their care may involve some form of transfer to another hospital unit. Inter-hospital transfer will be needed if the level of care or expertise cannot be delivered at the first location where the child is seen. Reasons for this may include the need for specialist teams such as neurosurgery for intra-cerebral complications, paediatric ENT surgery for complex airway issues such as foreign body inhalation or laryngeal stenosis or even because of a lack of available facilities and staff within that hospital's intensive care unit. Wherever the destination or whatever the indication, the principles remain the same.

Resuscitation as described earlier needs to have taken place prior to transfer. It is essential to have good teamworking and communication throughout the whole process. From an ENT viewpoint this may require securing the airway jointly with the anaesthetist and could even mean a tracheostomy or cricothyroidotomy in an extreme airway emergency, although nowadays this is very rarely needed. Urgent treatment should not be delayed waiting for transfer or for a retrieval team to arrive. If endotracheal intubation is required and achieved, one of the

greatest concerns would be accidental displacement or dislodgement and it is essential that endotracheal tubes and tracheostomy tubes are carefully secured.

The principles of safe transfer have been refined by guidance from the Paediatric and Neonatal Safe Transfer and Retrieval (PaNSTaR) group[3] who, following the lead of APLS, have created the acronym **ACCEPT** to help focus thinking around safe transfer:

- **Assessment:** Before making a transfer a formal assessment needs to be undertaken by the transfer team. Continuous monitoring and reassessment will also be required.
- **Control:** The one in overall charge of the transfer needs to take control of identifying and allocating key tasks.
- **Communication:** Good communication between the current, transfer and receiving teams needs to take place, along with the child's family.
- **Evaluation:** Ensure that the transfer is appropriate.
- **Preparation and packaging:** Ensure appropriate preparation of the child, equipment and personnel has taken place, mindful of the limitations when providing medical care in a mobile setting.
- **Transportation:** The mode (road or air) and effects of that mode of transport to medical care need to be fully considered.

'Retrieval' teams are an increasingly important part of networked care for children. Teams may include paediatricians, anaesthetists, intensive care physicians, nurses and paramedics and a paediatric otolaryngologist. These teams have particular training needs including ongoing attention to maintaining their skills, and the otolaryngologist will often have a key role in the team.

PAEDIATRIC INTENSIVE CARE

Paediatric critical care describes the care of children who need an enhanced level of observation, monitoring or intervention which cannot safely be delivered in general wards.[4] Paediatric intensive care unit (PICU) staff look after children and young people whose conditions are life-threatening and who need constant close monitoring and support from equipment and medication to restore/maintain normal body functions. This includes care of children requiring intubation and ventilation, single- or multiple-organ support and continuous or intensive medical and nursing supervision. This also includes routine planned post-operative care for surgical procedures and during some planned medical admissions.

Three levels of such care are now widely accepted:

- **Level 1 Basic critical care:** A child, for example, with mild upper airway obstruction needing nebulized adrenaline would be managed here.
- **Level 2 Intermediate critical care:** This includes care of a child with an NPA, and early care of children with a newly fashioned tracheostomy. A level 2 unit (often referred to as a high dependency unit or HDU) would usually manage a child needing non-invasive ventilation such as CPAP.
- **Level 3 Advanced critical care:** This is often referred to as a paediatric intensive care unit (PICU). Such a unit would have a high ratio of nurses to children and be able to provide mechanical ventilation, in addition to other forms of organ support.

Cross-specialty working between ENT surgeons and PICU is essential in the care of critically ill children. Examples include post-operative management of a child after upper airway surgery, acute management of the difficult airway, acute upper airway obstruction, diagnosis and management of upper or lower airway malacia and multispecialty working for establishing and maintaining long-term ventilation (LTV) in patients with severe respiratory disease.

Strategies used in PICU are aimed at restoring and maintaining normal body functions. In essence, this is done by providing adequate oxygen and energy supplies to all organs and tissues to maintain their function. Oxygen is delivered to the body via respiration and delivered to the tissues by being carried in the blood (mostly via haemoglobin) and so normal tissue function is dependent on adequate oxygen supply to the lungs (ventilation) and adequate blood supply to the tissues (cardiac output and circulation). The principles of ventilation are largely generic, regardless of the large variety of underlying pathologies leading to the child needing ventilation. Ventilation ensures adequate pulmonary oxygen supply and carbon dioxide removal, but it may cause injury to the lungs by barotrauma/volutrauma and alveolar collapse, or by direct oxygen toxicity. Regardless of whether the lungs are normal or diseased, a 'lung-protective' ventilator strategy should be used. Pressure, volume and oxygen settings can be minimized and mild or 'permissive' hypercapnia and hypoxia is now accepted. In PICU PIP (peak inspiratory pressures) ≥30 cm H_20, expiratory tidal volumes ≥10 mL/kg and inspired oxygen concentration (FiO_2) ≥60% are all associated with ventilator-induced lung injury.

PICANet (Paediatric Intensive Care Audit Network) reports indicate that around 40% of admissions in the UK are planned (34% post-surgery) and 60% are for unplanned emergency care. The top three indications for admission to PICU are cardiovascular (28.6%), respiratory (26%) and neurological (11%). Around 65% of admissions require invasive ventilation and 15% non-invasive ventilation. PICU mortality rates remain low (<4%).[5]

If a child in PICU has signs of inadequate cardiac output (e.g. low blood pressure, evidence of poor perfusion, decreased urine output), this can be supported in a number of ways. It may simply involve restoration of intravascular volume (either with i.v. fluids or blood/blood products) or additional support with drugs that increase cardiac output. Inotropes (e.g. adrenaline) increase myocardiac contractility and heart rate; vasopressors (e.g. noradrenaline/vasopressin) increase systemic vascular resistance (e.g. in vasodilatory shock). Lusitropes (e.g. milrinone) aid diastolic relaxation of the heart so that it will contract better (Starling's law) and cause peripheral vasodilation increasing blood supply to the tissues.

Other therapies available in PICU replace the function of acutely injured organs in the short term until they recover or in the longer term until a more definite therapy option is found. Examples of this are total parental nutrition (TPN) and continuous renal replacement therapies (dialysis).

While maintaining/restoring normal function using the above strategies it is important to treat the underlying condition (e.g. antibiotics for infection, surgical intervention), keep the patient comfortable using sedation and analgesia if required, and ensure the patient's safety by preventing hospital-acquired harm and delivering high-quality care at all times.

For the very seriously injured/ill child in whom usual PICU therapies are not restoring or maintaining normal cardiac or respiratory function, but in whom the underlying condition is considered to be reversible, the use of extracorporeal life support (ECLS) strategies should be considered. Extracorporeal life support is a general term to describe prolonged but temporary support of heart and lung function using mechanical devices. Device applications require a combination of vascular access catheters, connecting tubing, a blood pump, a gas exchange device (oxygenator), a heat exchanger, measuring and monitoring devices, and systemic anticoagulation.

There are various subtypes of ECLS (with varying degrees of overlap) including:

- ECLA – extracorporeal lung-assisted systems
- ECMO – extracorporeal membrane oxygenation: a high-flow ECLS to replace lung and/or heart function, the term used synonymously with ECLS
- $ECCO_2R$ – extracorporeal carbon dioxide removal
- ECPR – extracorporeal cardiopulmonary resuscitation (emergency cardiac support in cardiac arrest).

The principle of these techniques is that blood is drained from the circulation and reinfused back after passing through the extracorporeal circuit where it is oxygenated and carbon dioxide is removed.

These are highly specialized techniques available only in a few designated centres.

MONITORING AND RECORDING

A child's medical condition can change very quickly; a previously 'well' child can become very ill in a short space of time. Careful monitoring and recording of simple physiological measurements such as pulse and temperature can alert staff early that a child is becoming dangerously ill, and may prompt early life-saving intervention. If parents or nursing staff feel a child has deteriorated, that in itself should be enough to prompt a careful medical review. There has been increasing emphasis on 'paediatric early warning scores' (PEWS) in recent years[6, 7] and most hospitals now have policies and protocols that guide staff on the need for a rapid response. There is no universally agreed PEWS system, so for now clinicians will need to familiarize themselves with the system in use in the setting in which they work. The important issue for doctors looking after children – particularly doctors who are less familiar with paediatric practice – is to be aware of the need to seek specialist advice if in any doubt.

RECOGNIZING 'SEPSIS'

Children may develop a life-threatening, rapidly progressive, exaggerated inflammatory response to infection, leading to impaired organ function. This has come to be known as 'sepsis' and has been the subject of much attention in recent years.[8, 9] There is a significant mortality (25%). Children at particular risk are the very young (infants under 1 year), those with a history of recent trauma including surgery, children with immune dysfunction and children with indwelling medical devices such as lines and catheters.

Whenever a patient presents with symptoms or signs raising the possibility of infection, sepsis should be considered. It is a time-critical emergency and warrants immediate intervention with completion of the 'sepsis six' within an hour, shown in **Box 3.1**.

BOX 3.1 The 'sepsis six' (NICE guidelines)[9]

1. High-flow **oxygen** via facemask
2. Blood **investigations** including blood culture (ideally before antibiotics) and blood gas
3. **Antibiotics** – broad-spectrum, intravenous (or parenteral) according to local guidance and taking account of patient's microbiology, given at maximum recommended dose within an hour of recognition of sepsis
4. **I.V. fluid** bolus – if signs of fluid depletion (including raised lactate)
5. **Lactate** measurement – repeated regularly if raised (>2 mmol/L)
6. **Fluid balance** monitoring

CHILD PROTECTION

Every professional involved in the care of children needs to be aware of the potential for children to be subject to abuse or neglect.

This can take the form of physical, emotional, or sexual abuse and may be perpetrated by family members, by friends and acquaintances or by professionals who come in contact with the child. Professional regulatory bodies – e.g. the General Medical Council (GMC) in the UK – expect doctors working with children and young people to be especially conversant with the features of abuse and neglect and to act upon any concerns they have.[10] Arrangements for raising such concerns vary in different healthcare settings and in different jurisdictions but the principles are essentially the same.

You should be familiar with the main presentations in your area of practice that can be caused by abuse and with the strategy for seeking appropriate advice and support.

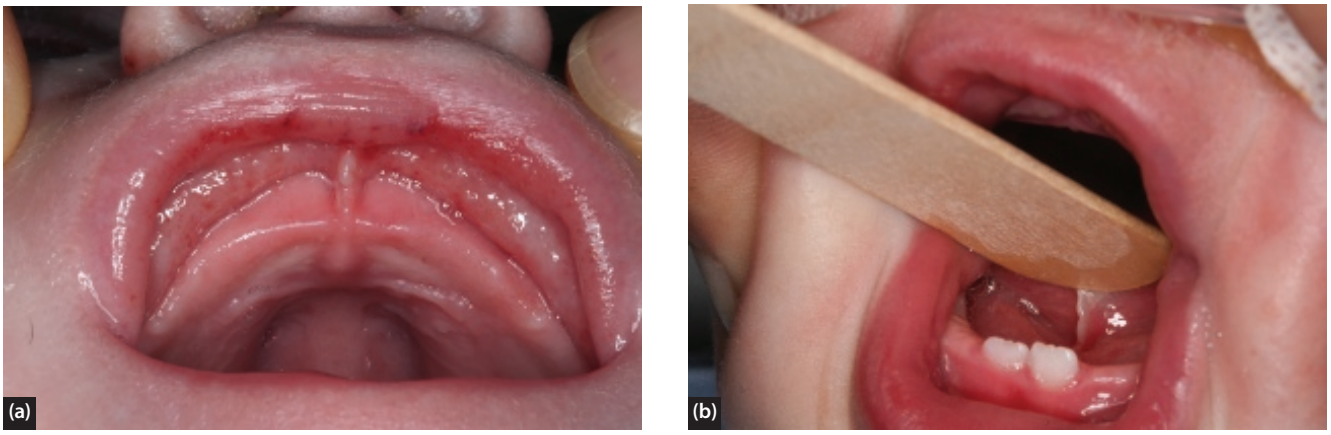

Figure 3.1(a) Tear of the labial frenulum with ulceration of the labial mucosa, **(b)** healing tear of the lingual frenulum.

Most children's hospitals will have a 'child protection' team who can be contacted for advice in confidence. Anecdotal evidence would suggest that few ENT surgeons make a diagnosis of child abuse, but it is essential that they are aware of it as a possible explanation for some unusual presentations. Up to 75% of children who suffer physical abuse have injuries to the head and neck (**Figures 3.1a, b and 3.2**). Some ENT presentations that may be linked with child abuse are shown in **Box 3.2**. If you suspect that a child's symptoms may be due to abuse or neglect, seek advice from an experienced colleague. Most children's hospitals have a designated team headed up by a paediatrician 'child protection lead' who has the expertise and sensitivity to give advice and support to you as a concerned clinician, and where necessary to explore the issue with the parents. This is clearly an area where great sensitivity and delicacy are needed. An accusation of abuse or neglect can have devastating consequences for the child and family.

BOX 3.2 Some possible non-accidental injuries in the head and neck

Tears to the lingual frenulum
Bruises to the cheeks, lips, gums
Nasal injuries
Injuries to the pinna, especially 'pinch' marks (**Figure 3.2**)
Auricular haematomas
Traumatic perforation of the eardrum
Maxillofacial fractures
Dental trauma
Injuries to the palate, e.g. due to forceful feeding
Bruising to the neck

A very small number of parents deliberately bring about symptoms and signs of disease in their child in an attempt to gain attention from healthcare personnel. ENT examples include ear injuries, blocked tracheostomy tubes and deliberate smothering. This is a serious psychiatric condition (Munchausen Syndrome by Proxy) and needs urgent and expert management.

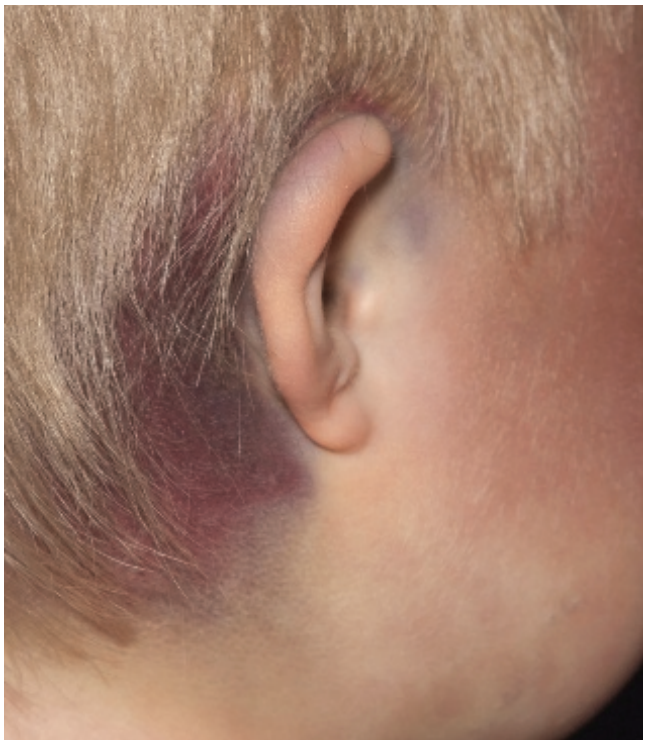

Figure 3.2 Bruising of the ear. 'Pinch' marks as seen on the upper aspect of the pinna are said to be pathognomonic of non-accidental injury.

A small number of children may, for various reasons, be best looked after outside their family setting, for instance by social services or the local authority. They may be placed in a designated care setting or with an alternative family (foster family). Arrangements will vary in different healthcare settings, but in general these children ('looked-after children', or 'children in care') need particularly vigilant medical attention. They will usually have a named social worker and close liaison with her/him is important in ensuring continuity of medical management, especially if they require surgery, investigations or repeat follow-up visits.

BEST CLINICAL PRACTICE

- Retrieval teams are increasingly important in paediatric care, and otolaryngologists may be key members of the team.
- Beware impending 'sepsis' in a child. It warrants immediate intervention.
- Be aware of the potential for children to be subject to abuse or neglect.

FUTURE RESEARCH

- ➤ Paediatric critical care is a recognized and expanding medical specialty, with the potential for ever better care and outcomes for very seriously ill children.
- ➤ Early warning scores for sick children are being harmonized with the potential for more widely accepted guidelines on early intervention for the sick child.
- ➤ 'Retrieval' of sick children and transfer to PICU is an increasingly important part of the work of specialized children's hospitals.

KEY POINTS

- Children who are apparently well can deteriorate very quickly.
- Biphasic stridor suggests severe airway obstruction.
- Bradycardia and cyanosis are ominous signs in a child with airway obstruction.
- Beware the stridulous child whose breathing becomes quiet – she may be close to cardiac arrest.
- Cross-specialty working between ENT surgeons and PICU is essential in the care of critically ill children.

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CHAPTER 4

ANAESTHESIA FOR PAEDIATRIC OTORHINOLARYNGOLOGY PROCEDURES

Crispin Best

SEARCH STRATEGY

Data in this chapter are based on the author's personal bibliography of key papers on paediatric anaesthesia and on his extensive experience in clinical practice. The website of the Association of Paediatric Anaesthetists of Great Britain and Ireland (APA) http://www.apagbi.org.uk is a good source of information on guidelines and current best practice relating to anaesthesia in children.

INTRODUCTION

The purpose of this review of anaesthesia for paediatric otorhinolaryngology (ORL) procedures is not to produce a definitive text for the expert anaesthetist working in a tertiary centre; rather it is to give a flavour of the techniques and pitfalls associated with the specialty. Guidance on patient selection and pre-operative preparation is discussed and some aspects are considered in greater detail.

Paediatric ORL surgery covers a whole range of conditions from the apparently simple such as the insertion of grommets to complex airway reconstruction. Even simple cases need advance planning. Any treatment episode for a patient is a cooperative effort between all the professionals involved. Only if the team works together will optimum conditions be provided to treat each condition quickly and effectively. From the moment the patient presents, no matter how 'routine' the case may be, this principle must be foremost in the minds of all. In the case of the shared airway (vide infra), this is even more critical.

Once the patient has been diagnosed, assessed for surgery and anaesthesia and their procedure scheduled, there must be a briefing of all staff at the beginning of the session to ensure that all are fully informed of what is proposed, and that everything is required for full pre-, peri- and post-operative care. More complex cases may require detailed advanced planning.

If in doubt, discuss the case with the anaesthetists well in advance of the day of surgery.

PATIENT SELECTION

The reason why families attend an ENT clinic is to seek an opinion for treatment for their child. If surgery is planned, anaesthesia and peri-operative care is a vital part of this process. It is important that whoever sees the patient in clinic is aware of what aspects of the medical history the anaesthetist needs to know. This can be broadly broken down into problems resulting from the condition itself, and associated conditions – both congenital and acquired. These need to be considered in the light of what treatment is proposed.

ORL conditions of anaesthetic relevance

Patients with obstructive sleep apnoea may need special nursing care and present challenges for post-operative management (see Chapter 27, Paediatric obstructive sleep apnoea).[1]

Any patient presenting with stridor or other symptoms of airway obstruction will be a source of particular concern to an anaesthetist. These patients can cause huge problems on induction of anaesthesia and can potentially lead to that most acute of emergencies the

'can't intubate, can't ventilate' scenario. Preparation and planning will prevent most of these dramas.

Associated conditions

CONGENITAL

There are many congenital conditions that may need special consideration in a child undergoing a general anaesthetic. These range from the obvious ones affecting the airway directly, such as laryngotracheal obstruction, to conditions affecting the child's general health, such as myotonic, neurological or cardiac conditions. Sometimes more than one condition coexists, for example Down syndrome in which patients have abnormal tissues, neck instability with cardiac anomalies such as atrial or ventricular septal defects. Some conditions improve with age, for example Pierre Robin sequence or Goldenhar syndrome, as the micrognathia associated with both improves with age. Some get worse, for example Treacher Collins syndrome and the mucopolysaccharidoses such as Hurler syndrome.[2]

It is also useful to know in advance if the patient has any conditions such as attention deficit hyperactivity disorder (ADHD) that may influence behaviour (see Chapter 5, The child with special needs). Children with autistic spectrum disorders (ASD) need to be identified well in advance of surgery. Many struggle with disturbance of their routine and are best having surgery on a day admission basis, preferably first on the list and with early discharge so that they can get back to their normal surroundings as soon as possible.

ACQUIRED

These conditions will be what patients usually present with, for example subglottic stenosis after prolonged endotracheal intubation, laryngeal webs and recurrent respiratory papillomatosis. Knowledge of what caused the problem and what has been done previously makes anaesthesia less of a challenge.

Drug history

Children fortunately do not tend to be the victims of the polypharmacy that afflicts the modern elderly adult. It is useful to document drugs that affect the heart, lungs and nervous system so that we can ensure that long-term conditions continue to be treated. Several of these may directly affect the conduct of the anaesthetic, including beta-blockers, vasodilators and diuretics.

Nature of procedure

Many ENT operations are considered 'routine'. Procedures such as adenotonsillectomy and insertion of drainage tubes into the middle ear are the bulk of the operative work of a department and children undergoing this type of surgery will not ordinarily need any special anaesthetic considerations unless the patient has any of the associated factors outlined above, or unless they have significant obstructive sleep apnoea (OSA). Other procedures (e.g. microlaryngoscopy and bronchoscopy) may be considered 'routine' in a tertiary referral centre. Which children need to be discussed individually in advance of surgery will depend on the experience of the surgeon and anaesthetist and on what is done in that particular unit.

Where do we operate?

The surgeon assessing the patient needs to consider where the procedure should be carried out. This depends on the nature of the case, the experience and practice of the team and the peri-operative facilities available on site, including nursing care and the availability of ventilatory support. Some cases are best suited to a tertiary referral centre and, if in any doubt, the staff at these institutions will be pleased to discuss the case with any referring clinician.

More detailed planning

It may be necessary to involve other disciplines in the care of cases which are difficult in themselves (e.g. major airway reconstructions) or where the patient has significant comorbidities. It is the practice in our institution to have a multidisciplinary meeting once a month where surgeons, anaesthetists, intensivists, specialist nurses and any other disciplines necessary meet and discuss forthcoming cases in detail. In this way PICU and HDU beds can be booked in advance, and ward and anaesthetic staffing rosters can be planned.

If in doubt, discuss the case with the anaesthetists.

PRE-OPERATIVE ASSESSMENT

It is becoming common practice for children and their parents or carers to attend a pre-operative assessment clinic before any operative procedure. It should be borne in mind that attending hospital with a child is in itself disruptive for both child and family, so ideally the patient should attend the pre-operative assessment clinic on the same day that they are seen by the surgeon.

Pre-op clinics are typically conducted by an experienced and suitably trained children's nurse. At this clinic the staff can take a history, examine the child and help prepare them for the procedure. This may include the provision of written and illustrated materials, which the family can peruse at home. It should be emphasized that, useful though these leaflets can be, they are no substitute for a proper interview with the anaesthetist. Any material used should also be prepared in conjunction with the anaesthetic department in order to reflect current practices and guidelines. If any problems are detected at this clinic, there should be a prompt communication with both surgeon and anaesthetist to aid planning. It is pointless for a patient to attend such a clinic if they then present on the day with something which should have been dealt with earlier.

ADMISSION

Whether a patient is admitted on a day-case basis (ambulatory care) or for overnight stay depends on local policies, geography and the nature of the operation. Many hospitals now carry out tonsillectomy, adenoidectomy, microlaryngoscopy and bronchoscopy and other similar procedures on a day-case or '23-hour' basis.[3] Irrespective of the time the patient stays in hospital, several things must happen before the operation commences.

PREPARATION AND ANAESTHETIST'S VISIT

The patient's weight and temperature must be checked. This allows the calculation of drug doses and early warning of any infections that may be present. The operating surgeon must see the patient, obtain consent for the procedure if this has not already been done, and mark the site of the operation if appropriate. The anaesthetist will see the patient, check the patient's general condition and confirm their suitability for anaesthetic. Careful note will be taken of any infection, especially of the respiratory tract. An active symptomatic respiratory tract infection causes a large increase in anaesthetic problems and these children should have their procedures delayed for 2 weeks until they have recovered. The anaesthetist will also explain the induction of anaesthesia to the patient and family and deal with any concerns they may have. In addition, they will discuss the post-operative period, especially with regard to analgesia.[4]

Fasting guidelines

It is very important that the patient is adequately fasted for the procedure (Table 4.1). Nothing ruins the anaesthetist's day like the appearance of a wave of vomit coming towards the airway on induction of anaesthesia. Compliance with guidelines can be patchy; parents sometimes misunderstand instructions or for one reason or another do not give accurate information, so detailed questioning may be necessary.[5]

Premedication

Some patients may require 'premedication' to reduce anxiety. As all the commonly used agents are sedative, they are almost always contraindicated in any patient who has an obstructed airway for any reason. If one is to be used, it must be **only** on the expressed instructions of the anaesthetist performing the procedure. Anticholinergics are sometimes given to dry up secretions and militate against the bradycardic effects of volatile anaesthesia. It is not our practice to use them as we find that we have more problems post-operatively with patients being unable to clear sticky secretions. They are, however, always drawn up ready for use in an emergency. Local practices will vary according to anaesthetic preference.

As always, if in doubt, discuss the case with the anaesthetists.

TABLE 4.1 Fasting guidelines

Food/drink	Fasting time (hours)
Clear fluids*	2
Breast milk	4
Formula or cow's milk	6
Pastes and solids	6

* Clear fluids include diluting juice but NOT natural fruit juices.

ANAESTHESIA

Briefing

Any operation is a cooperative venture. Before any operating list is started, the full team must assemble and there must be a thorough briefing given where all members can discuss the cases of the day. This will ensure that the list is correct, treatment plans can be finalized and the availability and operability of any specialized equipment that may be necessary can be checked. This is in line with the WHO recommendations on surgical safety, which also include a checklist to be completed before every individual case is started (Figure 4.1).[6]

Basic principles

There are few occasions in anaesthesia and surgery where the surgeon and anaesthetist work so closely together as in paediatric ENT procedures. Many of these involve a shared airway, and it must be accepted that, in the case of any deterioration in the condition of the patient, the anaesthetist must be allowed instant and full access to the patient to deal with the immediate problem. The surgeon's role in this circumstance is to provide assistance to the anaesthetist, which may extend in life-threatening circumstances to the provision of an emergency surgical airway. It therefore follows that any surgeon undertaking an operating list that includes patients likely to need emergency care **must** be capable of performing such a procedure. Unlike the adult situation, cricothyroid membrane puncture on children is difficult and has a high failure rate irrespective of how it is done, so *in extremis* a surgical cricothyrotomy or tracheostomy may need to be carried out urgently.[7]

Technique

The choice of anaesthetic technique will be largely dependent upon the type of operation being performed, the nature of the patient and any specific requests from the surgeon to assist with the operation. The well-known anaesthetic triad of 'anaesthesia, analgesia and relaxation' can be obtained in a number of different ways. Similarly, whether the patient should breathe spontaneously or be ventilated and whether they should be intubated or not will be covered in 'Spontaneous respiration vs endotracheal intubation and paralysis' below.

World Health Organization

SURGICAL SAFETY CHECKLIST (FIRST EDITION)

Before induction of anaesthesia ▶▶▶▶▶▶▶▶▶ Before skin incision ▶▶▶▶▶▶▶▶▶▶▶▶▶ Before patient leaves operating room

SIGN IN

☐ **PATIENT HAS CONFIRMED**
- IDENTITY
- SITE
- PROCEDURE
- CONSENT

☐ **SITE MARKED/NOT APPLICABLE**

☐ **ANAESTHESIA SAFETY CHECK COMPLETED**

☐ **PULSE OXIMETER ON PATIENT AND FUNCTIONING**

DOES PATIENT HAVE A:

KNOWN ALLERGY?
☐ NO
☐ YES

DIFFICULT AIRWAY/ASPIRATION RISK?
☐ NO
☐ YES, AND EQUIPMENT/ASSISTANCE AVAILABLE

RISK OF >500 ML BLOOD LOSS (7 ML/KG IN CHILDREN)?
☐ NO
☐ YES, AND ADEQUATE INTRAVENOUS ACCESS AND FLUIDS PLANNED

TIME OUT

☐ **CONFIRM ALL TEAM MEMBERS HAVE INTRODUCED THEMSELVES BY NAME AND ROLE**

☐ **SURGEON, ANAESTHESIA PROFESSIONAL AND NURSE VERBALLY CONFIRM**
- PATIENT
- SITE
- PROCEDURE

ANTICIPATED CRITICAL EVENTS

☐ **SURGEON REVIEWS:** WHAT ARE THE CRITICAL OR UNEXPECTED STEPS, OPERATIVE DURATION, ANTICIPATED BLOOD LOSS?

☐ **ANAESTHESIA TEAM REVIEWS:** ARE THERE ANY PATIENT-SPECIFIC CONCERNS?

☐ **NURSING TEAM REVIEWS:** HAS STERILITY (INCLUDING INDICATOR RESULTS) BEEN CONFIRMED? ARE THERE EQUIPMENT ISSUES OR ANY CONCERNS?

HAS ANTIBIOTIC PROPHYLAXIS BEEN GIVEN WITHIN THE LAST 60 MINUTES?
☐ YES
☐ NOT APPLICABLE

IS ESSENTIAL IMAGING DISPLAYED?
☐ YES
☐ NOT APPLICABLE

SIGN OUT

NURSE VERBALLY CONFIRMS WITH THE TEAM:

☐ **THE NAME OF THE PROCEDURE RECORDED**

☐ **THAT INSTRUMENT, SPONGE AND NEEDLE COUNTS ARE CORRECT** (OR NOT APPLICABLE)

☐ **HOW THE SPECIMEN IS LABELLED** (INCLUDING PATIENT NAME)

☐ **WHETHER THERE ARE ANY EQUIPMENT PROBLEMS TO BE ADDRESSED**

☐ **SURGEON, ANAESTHESIA PROFESSIONAL AND NURSE REVIEW THE KEY CONCERNS FOR RECOVERY AND MANAGEMENT OF THIS PATIENT**

THIS CHECKLIST IS NOT INTENDED TO BE COMPREHENSIVE. ADDITIONS AND MODIFICATIONS TO FIT LOCAL PRACTICE ARE ENCOURAGED.

Figure 4.1 WHO Surgical Safety Checklist (from http://whqlibdoc.who.int/publications/2009/9789241598590_eng_Checklist.pdf6).

Equipment

In addition to the full range of anaesthetic equipment that should be present in all locations where anaesthetics are given, there are several features that should receive extra attention (**Figure 4.2**). Although any child when anaesthetized may have a 'difficult' airway, this is much more likely in a situation where the patient is being anaesthetized for the investigation of just such a condition. Although every theatre suite should have a difficult intubation trolley containing emergency equipment, there is a case for duplication of this provision where elective airway work is being done. Specific items may be a matter for personal choice, especially with regard to equipment such as types of laryngoscope blade, for example. Recent reviews[8, 9] have emphasized the need for training and a common approach to any problems.

As well as the more traditional endotracheal tubes and face masks, the use of the laryngeal mask has proved invaluable in some cases of the difficult airway. Once one of these is in place, if the airway needs to be secured further, a fibre-optic intubation can be performed through the mask using a guide wire and airway exchange catheter, and the laryngeal mask removed.[10] This kind of procedure is complex and ideally should be planned in advance.

In addition to the traditional range of anaesthetic laryngoscopes, the anaesthetist may also have recourse to a number of newer video and fibre-optic devices (**Figure 4.3**).[11, 12] To a large extent, which is to be used is a matter of personal preference, however it is important for every unit to choose only one, and become expert in its use during routine cases. An emergency is no time to learn how to use an unfamiliar piece of equipment.

'Can't intubate, can't ventilate'

This is a situation every anaesthetist dreads and, as mentioned above, the surgeon may be called upon to assist in obtaining an airway. **NEVER FORGET the option of waking the patient up. The case can then be planned for another time in the light of what has happened.**

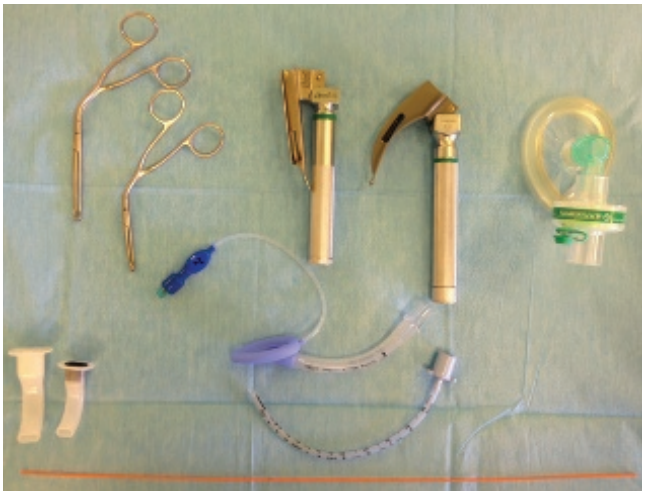

Figure 4.2 Basic set of equipment for paediatric airway anaesthesia. Included are face mask with a soft seal, different types of anaesthetic laryngoscope, endotracheal tube and laryngeal mask, Guedel airways, Magill forceps and an intubating bougie.

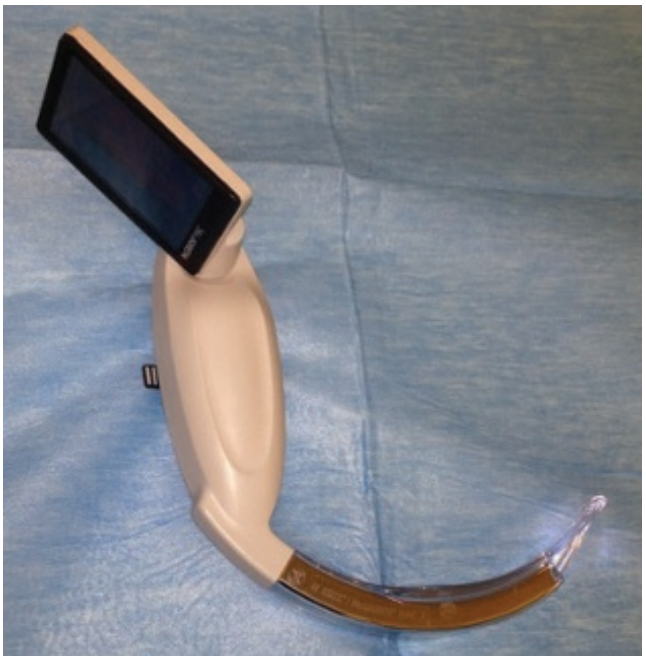

Figure 4.3 McGrath videolaryngoscope. This is one of the more effective types of videolaryngoscope, enabling a view of the larynx when conventional methods may not be adequate.

Assistance

The anaesthetist must have a trained assistant. This may be an experienced operating department assistant or nurse or another anaesthetist. Irrespective of who this person is, they must be familiar with local policies and guidelines, have a good knowledge of the available equipment and how it is used, and have taken part in the pre-operative briefing.

POST-OPERATIVE CARE

There is little point in proceeding with complex anaesthesia and surgery if facilities do not exist to care for the patients post-operatively. The post-anaesthesia care unit (PACU) must be staffed to a defined level of competence, and there must be equipment available in the unit to deal with any emergency, including emergency drugs and an anaesthetic machine. More complex cases may require the services of a high dependency or intensive care unit. The basic rule is never to start a case unless you have the facilities to finish it. The Association of Anaesthetists of Great Britain and Ireland has published general recommendations for organization and staffing.[13] If an emergency case has to be done where appropriate facilities do not exist, the anaesthetic team must recover the patient. Patients should not be discharged from the PACU until the anaesthetist/recovery staff are sure that the patient is fully conscious, is appropriately hydrated, is not in pain and has had appropriate analgesia prescribed as well as full instructions to

the ward on post-operative care. A handover sheet, which can be filled out by staff, is very useful for this purpose.

When patients are discharged, they should be provided with information sheets particular to their procedure, containing contact details for the institution should they have any problems.[14]

NEVER start a new case until the last patient is safe.

SPECIFIC OPERATIONS

Tonsillectomy and adenoidectomy

This is probably the commonest operation performed by the ENT surgeon. Surgical options are 'cold steel' dissection, or the use of the coblator or harmonic scalpel systems. Anaesthetically, the choice of airway management is to use either an endotracheal tube (ETT) or a laryngeal mask airway (LMA). The ETT is more secure than an LMA and is easier for the surgeon to keep out of the way in placing a Boyle Davis gag. However, the LMA is quicker and easier for the anaesthetist to place. The choice will depend ultimately upon surgical and anaesthetic preference. It important never to compromise an airway merely for convenience's sake.

Another discussion is whether to admit these patients as day cases (by which is meant early morning admission and evening discharge) or for an overnight stay. This will depend upon local facilities, patient population and patient preference, among other things. Analgesia must be effective no matter what system is chosen. A useful review covers this subject in more detail.[15]

Antiemesis can be helped with dexamethasone,[16] ondansetron or a combination of the two. Remember that patients can swallow a little blood during the operation, which can often lead to a vomit afterwards. This is of no consequence if small and not repeated.

Post-operative analgesia in our institution is provided by regular oral ibuprofen, with paracetomol as required. We do not give any form of oral opiate as a take-home drug; instead, patients are asked to contact us if they have any problems.

Airway examination and treatment

There is no doubt that the treatment of a compromised paediatric airway is one of the most challenging procedures to face any operative team, particularly for the anaesthetist. Not only will the patient have to be kept safe, but also there is little point in the child having an anaesthetic unless the surgeon is able to do the procedure. Safety is paramount. Surgery will not proceed until the anaesthetist is satisfied that the patient is in a fit state for that to happen. It **must** be remembered that waking the patient up again if the airway cannot be adequately secured is always an option. Recent reviews have emphasized the importance of training and a considered approach.[17, 18]

Patients will present with a variety of conditions, both congenital and acquired, which will be covered in other chapters of this book.

SPONTANEOUS RESPIRATION VS ENDOTRACHEAL INTUBATION AND PARALYSIS

The basic principle of paediatric airway anaesthesia is to keep the patient breathing. This sounds almost too obvious to state, but it must be remembered that all anaesthetic agents of whatever type depress respiration and reduce muscle tone such that a patient who, when awake, is capable of maintaining their own airway promptly loses it when anaesthetized. Additionally, in some cases such as mediastinal tumours the patient may be impossible to intubate in an emergency, making rescue very difficult if they have a respiratory arrest. A careful gas induction using sevoflurane in oxygen is the preferred method for anaesthetizing these patients. The airway is being constantly observed as the patient becomes anaesthetized and the process is gradual and controllable. Intravenous access, if not gained beforehand to avoid upsetting the patient, can be gained as soon as possible and the airway is under constant control.

Unlike the adult situation where the bulk of examination is for tumour or infection, the majority of paediatric patients present with disorders of breathing requiring further investigation. If they are intubated and paralysed, tracheo- or laryngomalacia may not be seen due to the pressure effects of insufflated gas. Similarly, if the patient is intubated for ventilation, the pressure of the endotracheal tube may squash pathology such as tracheal haemangiomata, making them impossible to see.

The ideal situation for both diagnosis and treatment of airway problems is the spontaneously breathing patient maintaining their own airway. This can be achieved either by using a volatile anaesthetic agent in oxygen or by the use of total intravenous anaesthesia (TIVA). Whichever method is used depends upon anaesthetic and institutional preference.

The use of a volatile agent has the benefit of simplicity in that the patients control their own depth of anaesthesia. If they become 'light', they breathe up and get deeper; if 'deep', the respiratory rate slows down, thereby lightening the anaesthetic. TIVA can be quite labour-intensive, as the rates of the infusions may have to be constantly adjusted according to circumstance. This takes the anaesthetist's attention away from the airway at what may be a crucial time.

The larynx is also sprayed with lidocaine to decrease the response to instrumentation, although care must be taken to ensure the patient is anaesthetized deeply enough to avoid temporary laryngospasm when this is done. Oxygenation can be obtained by means of a nasal airway attached to an Ayres 'T' piece anaesthetic circuit. If the patient is to be ventilated, they are better intubated. Jet ventilation, frequently used in adults, carries significant risk of barotrauma in small children although some centres use it successfully.[19] This is not our practice, as we believe the disadvantages far outweigh any benefits. Finally, a dose of dexamethasone is given to patients to try to reduce any oedema that may affect the airway post-operatively. The evidence for this is scanty but most experienced airway anaesthetists feel that this is of value.[20]

In summary, a logical approach with a high degree of safety is a gas induction of anaesthesia with sevoflurane or halothane (if available) in oxygen, the establishment of intravenous access if not already present, getting the patient deep enough to spray the larynx with lidocaine and the nose with xylometazaline, and maintenance of anaesthesia with spontaneous respiration using insufflated volatile with oxygen via a nasal airway. This has the added benefit of leaving instrumentation of the airway to the surgeon, as the anaesthetic has not affected the airway appearance.

Once the patient is stable on the operating table, any surgical examination and intervention can take place.

Micro-laryngoscopy and bronchoscopy

Examination of the airway is essential to diagnosis and treatment. There are a variety of methods including suspension laryngoscopy, examination with a Hopkins rod and bronchoscopy.

Suspension laryngoscopy is used for detailed examination of the larynx and associated structures (**Figure 4.4**). Great care must be taken not to overextend the neck, especially with conditions such as Down syndrome where there is a pre-existing instability. The mechanical advantage of the wheel used to adjust the suspension is enormous; the anaesthetist must watch this closely and stop the surgeon if the neck is moved too far.

The bronchoscope has a side arm for the attachment of the anaesthetic circuit and the delivery of gases (**Figure 4.5**). It also has side holes along the shaft to allow ventilation of both lungs when the instrument has been passed down one bronchus. When the surgeon first places the instrument, it must be passed down to the carina or these side holes may still be in the pharynx, preventing proper ventilation and control of the airway.

At every stage of the examination the surgeon must check with the anaesthetist that the patient is stable and well oxygenated. Communication is key; there must be a constant dialogue between the two. During any examination the anaesthetist must ensure that, when the surgeon is assessing the airway, the patient is not subjected to any degree of positive pressure from the anaesthetic circuit. This may distend the trachea or bronchi and make airway collapse much less apparent. However, positive pressure can be applied on demand to assess how much a collapsed airway can open.

Removal of airway foreign body

The approach here is the same as above, except that grasping forceps may be used either on their own with the aid of a Hopkins rod or through a bronchoscope. The preferred method is to have the patient breathing spontaneously as some feel that positive-pressure ventilation may force bits of the object further into the respiratory tree and the paralysed patient will, by definition, have periods of apnoea when examination and retrieval are taking place. However, jet ventilation can be used as long as the astute anaesthetist is aware of potential problems.[21]

Laser surgery

Laser surgery is covered in more detail in a review.[22] Safety is the prime consideration, and the laser must never be used unless staff are properly trained in its use and all appropriate precautions are taken.

Reconstruction of the airway

There are a large number of procedures that can be carried out for reconstruction of the airway, ranging from a cricoid split to full tracheal reconstruction under cardiopulmonary bypass. The principles, however, are exactly the same as above, i.e. scrupulous attention to the airway and good communication with the surgeon. If we take the example of an anterior laryngotracheal graft, the procedure may be as follows.

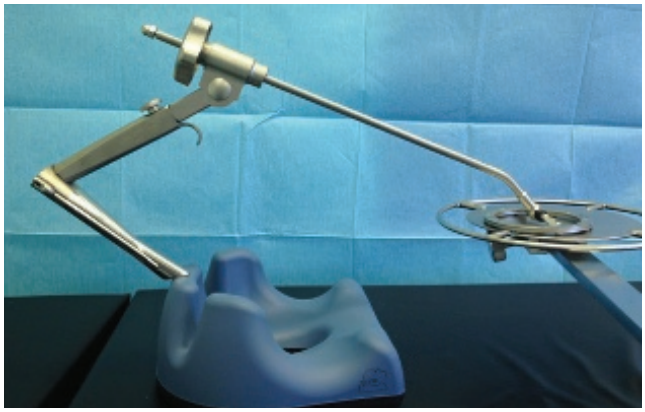

Figure 4.4 Laryngoscope and suspension. This illustrates the lever formed by the laryngoscope with the arm of the suspension system. The wheel at the top, which is used for adjusting the extension and flexion of the head on the neck, has a considerable mechanical advantage and damaging overextension could result.

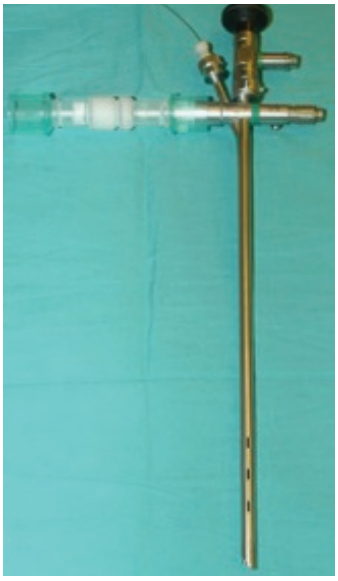

Figure 4.5 Bronchoscope. Note the side holes towards the end of the 'scope, and the plastic mount for attaching the anaesthetic 'T' piece. This one is prepared for laser surgery, with a Hopkins rod and YAG laser fibre *in situ*, which reduces the bore of the system considerably, making it even more important to keep gas leakage as low as possible.

Pre-operatively the patient is breathing normally, albeit partially obstructed. In this case the patient will be orally intubated with a smaller than normal-sized ETT. The surgeon will then make a tracheostome for the duration of the operation through which the anaesthetist will ventilate the patient, and the patient will then have a nasal ETT placed at the end of the procedure. The tip of the ETT can be positioned under direct vision by the surgeon before the tracheal incision is closed. The patient remains intubated for some days post-operatively, with the head in a neutral position to allow time for the trachea to heal.

Tracheostomy

A paediatric tracheostomy differs from the adult in technique, as a vertical slit is made in the trachea after placing two lateral support sutures. Anaesthetic technique will depend upon why the patient is having the procedure. A stoma for a patient who requires one for chronic ventilation is very different from one who is undergoing the procedure for an acute airway problem. The anaesthetist, who may have to sit at the head of the patient manually supporting the airway, must guide the surgeon. Once the surgeon has identified the trachea and made a vertical slit, the endotracheal tube will be slowly withdrawn under direct vision until the tracheostomy tube can be inserted.

Post-operative care is key; the stay sutures remain in place and are stuck to the chest with tape while a track forms. This will enable a replacement tube to be placed in the event of the first one being displaced or falling out.

Ear operations

GROMMETS

The commonest operation and one of the simplest. Beware this illusion. The patient is still fully anaesthetized and asleep is asleep. The anaesthetist will probably use a laryngeal mask airway. The surgeon must check that the patient is fully prepared before starting: a myringotomy is highly stimulating and the patient suddenly moving as the incision is made could be disastrous.

MIDDLE AND MAJOR EAR OPERATIONS

The requirement seen in adult surgery for induced hypotension during the procedure is not necessary in children. Children have a lower resting blood pressure than adults, and modern anaesthetic agents can produce a good operating field for the surgeon without recourse to beta-blockers or vasodilators. Placing the patient a little 'head up' to reduce venous pressure and ventilating the patient to normocapnia is often all that is necessary. The use of nitrous oxide is a little more controversial: some believe it increases the pressure in the middle ear, some that it makes no difference, and evidence can be found in the literature for both positions. Ultimately, this is a question of operator preference and should be discussed with the anaesthetist beforehand.

Nasal surgery

ADENOIDECTOMY

Adenoidectomy is either a single procedure or carried out in conjunction with the placement of grommets and/or tonsillectomy. Again, the choice of how to maintain the airway is a matter of discussion between surgeon and anaesthetist.

REDUCTION OF NASAL FRACTURE

This ostensibly simple operation can be fraught with danger: the nasal bone may have to be refractured in order to get a good result and this can occasionally result in a torrential haemorrhage. The anaesthetist is best advised to use a laryngeal mask airway and place a throat pack before the surgeon proceeds. No one wants to have to deal with an unprotected airway rapidly filling up with blood.

Head and neck

This can range from a 'lumpectomy' to the excision of branchial or thyroglossal cysts. Operations common in adults, such as total laryngectomy, are fortunately extremely unusual in children. The anaesthetist will ensure that the airway is protected by placing an endotracheal tube. A laryngeal mask airway is not secure enough when the head is fully draped, as the head position may be changed during the procedure to improve surgical access.

KEY POINTS

- The airway must be protected at all times. If there is any problem whatsoever, the anaesthetist must instantly be given as much access as required.
- Good communication is crucial. Never start a procedure until there has been a full briefing of all involved staff. This is the time to plan for any problems, not when they occur.
- Never forget that the patient can always be woken up again, to come back another day. Do not persist in the face of adversity.
- Finally, if in any doubt, discuss the case with the anaesthetist.

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CHAPTER 5

THE CHILD WITH SPECIAL NEEDS

Kate Blackmore and Derek Bosman

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: special needs, cerebral palsy, disability, prematurity, neurodisability, Down syndrome, hearing loss, cochlear implant, obstructive sleep apnoea, laryngomalacia, tonsillectomy/adenoidectomy and aryepiglottoplasty.

INTRODUCTION

While the majority of paediatric otolaryngology deals with routine work in the well child, there is a significant part of the workload for the paediatric otolaryngologist that deals with children with special needs. The incidence and survival of very preterm infants has increased dramatically over the last few decades and with this comes increased morbidity.[1, 2] Children with special needs are prone to the usual childhood otolaryngological problems but they are also predisposed to specific problems mainly related to airway difficulties and hearing loss. The whole approach to treating a child with special needs is different and requires special consideration.

TERMINOLOGY

An **impairment** describes a pathological process (e.g. cerebral palsy) and a **disability** is the consequence of an impairment. A **handicap** is a disability of body or mind which interferes with the ability to lead a normal life or to benefit from a normal education.[3] Although terms such as handicap and disability are used commonly in the medical literature, they can be upsetting to parents, and doctors should be sensitive to this.

Special needs is an umbrella underneath which a diverse range of needs often caused by a medical, physical, mental or developmental condition or disability can be categorized. It can include cognitive difficulties, physical or sensory difficulties, emotional and behavioural difficulties, and difficulties with speech and language. This term seems to be more commonly acceptable to parents.

GENERAL CONSIDERATIONS

Hospital appointments

The clinical environment in which children with special needs are seen is important. The consulting room needs to be large enough to accommodate wheelchairs and equipment along with room for the carers.

It is paramount that these families are not kept waiting for long periods in the outpatient department as this can cause great difficulties and distress for the child. Child-friendly waiting areas and the presence of play therapists can help minimize distress and upset during outpatient consultations.

Ideally, hospital appointments should be kept to a minimum. Children with multiple comorbidities will see many different specialties, resulting in frequent trips to the hospital. The disruption to the child's routine can be significant. Specialist clinics that bring clinicians and allied healthcare workers together offer a great advantage to both the clinicians and the family, for example a tracheostomy clinic

bringing together ENT, respiratory paediatricians and speech and language therapists.

Clinicians should also not forget the cost implications of multiple hospital appointments. A recent cross-sectional study in the UK revealed that children with multiple comorbidities are more commonly born to families in the lower socioeconomic groups so that economic challenges may compound the difficulties of looking after a child with complex needs.[4]

Whether within a specialist clinic or not, the time required for an adequate consultation is significantly longer than for typically developing children without complex needs and multiple morbidities and this should be acknowledged when planning clinics and operating lists. Histories are more complex, examination is more challenging and discussions regarding treatment, particularly potential surgery, require more detailed explanation and planning.

Communication

Good doctor patient/parent communication has been shown to result in improved patient knowledge, better adherence to treatment, decreased surgical morbidity and greater satisfaction with care.[5, 6] This is especially true when treating children with special needs. Good, clear communication with the parents/carers, the child and any healthcare professionals involved with the child is paramount.

PARENTS/CARERS

In assessing children with complex problems it is often tempting to used closed questioning to control the duration of the consultation. Parents perceive this approach as showing a lack of interpersonal interest and ultimately it will result in a suboptimal consultation. Parents have greater trust in doctors who allow them to tell their whole story, express their concerns and listen to their ideas.[5, 6]

Parents of children with multiple comorbidities or complex problems will be 'experts' in their children and want, rightly, their views and concerns to be addressed in any decision-making. Decisions about care and management should be part of a family-centred process in the majority of cases.

It is also important to recognize that the parents' priorities for their child may not reflect your own. For example, parents of a child with a tracheostomy may be keen for early decannulation, or conversely may be reluctant to consider decannulation as they are nervous about losing the security of what they perceive as a 'safe' airway.

Parents commonly report that doctors do not give enough information with regard to their child's surgery or health status, particularly in the context of chronic or terminal illness.[5, 6] While we may feel that we have covered all the essential information in explaining, for example, a surgical procedure, its complications and recovery time, it is some of the more minor points that can be important to the parents: how much hair will be removed, the site of the intravenous cannula, how long until their child can eat. In children with special needs these seemingly minor issues can be particularly important and it is essential that the doctor takes the time to answer all the parents' questions.

PATIENT/CHILD

Children should be involved in as much of the consultation as possible. They should be given information in a way they can understand it, given choices about their care and asked their opinion. Children will often understand more than has been assumed.[6] This was shown in Bluebond-Langner's study of terminally ill children in which children as young as 3 years were aware of their diagnosis and prognosis despite not being told by an adult.[7]

While involving the patient may be more difficult in a child with special needs, it is important that any child who has the ability to understand and process the information is given the opportunity to do so. Increased understanding will heighten confidence, decrease fear and improve the level of trust between the child and their parent/doctor. However, this has to be undertaken with the agreement of the parents – giving too much information may be severely detrimental to a child with special needs.

Again, where possible, understanding the child's priorities regarding their health care and what they deem to be important for improving their quality of life should not be underestimated.

COLLEAGUES

Children with special needs will often be under the care of many different specialties and it is vital that there is clear communication between everyone in the healthcare setting. All involved clinicians and allied healthcare workers should be copied in to letters from outpatient consultations and inpatient attendances. This clear communication ensures that everyone involved is aware of the child's current health status and treatment plans. It also allows for the potential coordination of multiple procedures under a single general anaesthetic (e.g. blood tests and tooth extraction), which will decrease the amount of undue stress on the child.

PROGNOSIS, PALLIATION AND QUALITY OF LIFE

Full discussion of this issue is beyond the scope of this chapter but it is important that we take time to consider some areas that we will have to address during our work with children.

The significant advances in neonatology over recent years have dramatically increased the survival of extremely premature babies.[8–11] There was a 44% increase in the number of extremely premature babies admitted to the neonatal intensive care units in the UK over the 10-year period from 1995 to 2006,[10] although evidence suggests that the long-term morbidity, particularly neurodisability,[9] of the survivors has remained unchanged.[10]

Because of the advances we have seen in neonatology, doctors are increasingly likely to have to make difficult decisions about whether to start or continue invasive life-sustaining treatment with the known risk of a poor long-term prognosis. Withholding or withdrawing life-sustaining treatment in a neonate, or indeed a child of any age, is extremely difficult and often highly charged and emotive. While advances in technology make it increasingly possible to sustain life, this may only increase pain and suffering to the child and their family. It is essential that the healthcare team has allowed enough time to gather information about the child's condition and other relevant problems before any discussions or decisions on whether further treatment is appropriate can be made.[3] Decisions should never be rushed.

The Royal College of Paediatrics and Child Health document *Withholding or withdrawing life sustaining treatment*[3] gives guidance on the circumstances when withholding or withdrawing treatment should be considered. The guidelines advise that, if the future life of the child will be 'impossibly poor', then it would be reasonable to withhold treatment. In a child whose life is already 'impossibly poor' and there is no sign that this will improve in the foreseeable future, then it would be reasonable to consider withdrawing treatment.

In situations where withholding or withdrawing treatment is deemed the most appropriate course of action, this should be discussed with the family at an early stage. The family must be given all the information they require, along with enough time to be able to understand and process it. They should also be given the opportunity to seek a second opinion if they wish. The consent of the parents is important for the final decision to be made, but the ultimate responsibility lies with the healthcare team. This may help lessen the guilt that some parents/carers feel following decisions in these situations.[3]

Reaching a decision to withdraw or withhold treatment does not mean cessation of care. The provision of palliative care to provide pain relief, alleviation of other symptoms (e.g. airway distress) and also support the emotional, social and spiritual needs of the child and their family is paramount.[3]

In situations where withdrawal of treatment is not appropriate but there is an expected progressive morbidity, communication with the family, and the child if appropriate, is again extremely important. When discussing prognosis and long-term morbidity, doctors have a tendency to 'medicalize' outcomes and list potential complications and morbidities with percentages of likelihood. While this is obviously an important area, it is imperative that the quality of life the child and family may have is discussed, including the capacity for happiness, and the good and the bad that go along with caring for a child with multiple comorbidities. The positive aspects of what life ahead may look like need to be considered; do not simply dwell on the potential problems.[12]

What makes a 'good quality of life' is a difficult philosophical question to which there would be no unanimous answer. Many people with severe functional limitations consider they have a life of high quality and are happy to be living it while an observer may not rate it so highly. Do those living with disabilities have a more positive view of their life because they have never known an alternative?[13] Do they find more value in things that able-bodied individuals value less?[14] Whatever the answer, it is important that we do not judge the quality of life of those with several functional limitations on the same basis as we view our own lives. Our priority should be to provide a high quality of care to children with disabilities and provide support for their families.

THE EAR AND HEARING LOSS

Hearing loss

Children with hearing loss who have additional disabilities make up a significant proportion of the hearing-impaired paediatric population and they can be a challenging group to manage. It is estimated that 2–4% of neonates in the neonatal intensive care unit will have a significant bilateral hearing loss.[15] The underlying cause for sensorineural loss is probably multifactorial, with risk factors such as low birthweight, low Apgar score, hyperbilirubinaemia, ototoxic medication and mechanical ventilation all being well documented.[16] It has also been reported that low birthweight babies often have central auditory processing problems, with difficulty discriminating speech and poorer auditory recognition than that of term neonates.[17, 18]

Hearing loss may also be conductive or have a conductive element to it. This is often seen in children with Down syndrome or craniofacial abnormalities, and it has been associated with ventilator-dependent children.[19]

Hearing loss is associated with delayed speech development and learning at school[20] so it is imperative that these children are picked up by audiological services at the earliest opportunity. In the past, children with multiple comorbidities have been overlooked with regard to improving their hearing simply because of the difficulty in obtaining accurate audiometry. Testing using auditory brainstem responses (ABRs) has allowed detection of hearing loss to be more accurately assessed in children with multiple problems.

Fitting of hearing aids at an early stage, regardless of neurological or mental status, has been shown to improve auditory behaviours in a significant proportion of children with multiple disabilities.[21] However, there will be a number that do not improve or simply cannot tolerate wearing the aids. There may also be difficulties fitting the aid in a congenitally narrow external meatus, or increased problems with wax impaction or recurrent otitis externa as a result of the mould.

Cochlear implantation in children with profound hearing loss and other disabilities was a controversial issue in the earlier days of implantation. There is increasing evidence that children with additional disabilities can benefit greatly from a cochlear implant.[22–26] This group of children may not achieve the same outcomes with regard to open set speech recognition as those with no other disabilities

but in the majority of cases they have improved speech perception and communication abilities.[22] Being able to predict the outcomes of surgery in children with additional disabilities is obviously much more difficult and parents must have realistic expectations of surgery.

Middle ear disease

OTITIS MEDIA WITH EFFUSION

Otitis media with effusion (OME) is common in the paediatric population and the associations with speech and language delay in early childhood and poor behaviour have been well reported.[27–29] Children with multiple disabilities are often already predisposed to language deficits and behavioural and learning difficulties.

Children with craniofacial abnormalities are more susceptible to OME due to the presence of a small nasopharynx and Eustachian tube anomalies, and there should be a heightened awareness when seeing these children.

Diagnosis can be difficult as examination is often challenging, particularly in the presence of wax impaction or anatomical changes such as narrow external canals in children with Down syndrome. If obtaining hearing thresholds with age-appropriate audiometry and tympanometry is not possible, it may be necessary to undertake ABR under a general anaesthetic. This would also allow any necessary ear toilet and thorough examination of the tympanic membrane/attic plus the insertion of ventilation tube if appropriate. Controversies regarding ventilation tube insertion in children with Down syndrome will be discussed in Chapters 6, The child with a syndrome and 13, Otitis media with effusion.

CHOLESTEATOMA

Cholesteatoma in a child with special needs is a difficult situation often requiring a general anaesthetic to confirm the diagnosis. Computed tomography (CT) of the temporal bone will aid planning of the surgical approach and identify and any anatomical variants. There is no single correct approach to surgery and each case has to be assessed individually. Open mastoid surgery has the advantage that, hopefully, only one surgical procedure is required and any residual disease will be visible on examination. However, open cavities often require regular aural toilet, particularly in the early post-operative period, and the child may not tolerate this. The family may also find keeping the ear dry difficult to achieve, and swimming may be an important part of the child's therapy.

Undertaking a combined approach tympanoplasty would avoid these problems but may require multiple surgeries to exclude recurrence, particularly as audiometric testing may not be possible as an observation tool. The associated comorbidities of the child, however, may make multiple general anaesthetics unviable.

Recent studies reveal that diffusion-weighted magnetic resonance imaging (MRI) of the temporal bones is becoming a useful tool for detecting residual and/or recurrent cholesteatoma. This technique is increasingly showing a high positive predictive value for detection of cholesteatoma and may reduce the number of second-look procedures in canal wall-up surgery.[30, 31] One drawback in paediatric patients with special needs is that it will almost certainly have to be undertaken under general anaesthetic.

THE UPPER AERODIGESTIVE TRACT

Children with complex physical comorbidities, particularly neurological, will frequently have respiratory problems and feeding difficulties. There may be a number of contributory factors which may have an overall cumulative effect.

Feeding, aspiration and gastro-oesophageal reflux

Oromotor skills are often dysfunctional in those with neuromuscular pathologies.[32–34] Children with cerebral palsy in particular may have difficulty coordinating swallowing with ventilation. The resultant 'turn taking', alternating between breathing and swallowing, can lead to aspiration of solids and fluids at mealtimes.[33]

Gastro-oesophageal reflux is also more common, and often more severe, in children with cerebral palsy or other neuromuscular disorders. The reason for this is unknown but it is hypothesized that it may be due to increased intra-abdominal pressure caused by the spasticity of the abdominal muscles. Altered peristalsis combined with dysfunctional oesophageal sphincters can then result in aspiration of refluxed material.[33]

Coughing and choking during feeding will draw attention to the possibility of aspiration, particularly when associated with recurrent lower respiratory tract infections, but often in children with comorbidities aspiration is silent.[33–35] While these children may struggle during mealtimes, they rarely show signs of aspirating.

The consequences of aspiration are also varied, with some children tolerating recurrent episodes with no sequelae. More commonly, recurrent aspiration results in lower respiratory tract infections, which may ultimately lead to lung fibrosis in severe and unrecognized cases. Diagnosing silent aspirators is more difficult and they often go unrecognized until malnutrition or respiratory complications occur.[34]

Treatment of aspiration ranges from positional/postural feeding positions and feed thickeners to tube feeding via a nasogastric tube or gastrostomy. Tube feeding has been associated with a higher mortality than in those fed orally but whether this is a result of the parenteral feeding rather than a reflection of the underlying comorbidities is not known.[36, 37] Tube-fed children are still at risk of reflux and aspiration even in those who have had a fundoplication at the time of gastrostomy.[38] Children with a tracheostomy appear to have some protection from the complications of tube feeding and this may be due to the ability to undertake regular suctioning, application of oxygen and nebulizer and positive-pressure ventilation.[39]

Obstructive sleep apnoea (OSA)

Children with craniofacial anomalies, Down syndrome and neuromuscular disorders are all at increased risk of obstructive sleep apnoea (OSA). With the multitude of other problems that this population of children may have, OSA is often overlooked or simply felt to be 'normal for him/her' by their parents/carers. Given the association with disrupted sleep, irritability and behavioural problems, failure to thrive and at the severe end of the spectrum pulmonary hypertension and right heart failure, it is vital that there is a high index of suspicion.

Predisposing factors may relate to anatomical abnormalities such as midface hypoplasia in the craniofacial disorders and hypotonia of the pharyngeal musculature in the neuromuscular disorders. In some cases (e.g. Down syndrome) it may be a combination of both. Other documented associations are seizure disorders, gastro-oesophageal reflux, increased oral secretions and obesity.[40, 41]

Management of OSA in children with complex problems should be undertaken in a multidisciplinary approach. Sleep disorder problems are common in this group of children and it is difficult to be assured of a correct diagnosis of OSA from clinical examination alone. Polysomnography is the gold standard for diagnosis and will aid in selection of children who are appropriate for surgical intervention.

Management should be undertaken in a stepwise approach, eliminating simple factors like bacterial or allergic rhinitis as a first line. Although in the general paediatric population over 80% of cases of OSA will be effectively treated by adenotonsillectomy alone,[42] the same cannot be said for those with additional comorbidities, particularly if there is a neuromuscular element.

Most would agree that the aim is to avoid a tracheostomy where possible and first-line surgical management of removal of the tonsils and adenoids, even if only mildly enlarged, is the general approach. Whilet adenotonsillectomy may not completely resolve the obstructive symptoms, it may allow the consequent use of a nasopharyngeal airway or continuous positive airway pressure (CPAP) to maintain an adequate airway.

The implications of anaesthesia in children with other comorbidities and the increased risks of complications following surgery need to be considered and any decision to proceed with surgery made within the multidisciplinary team. Parents should be counselled accordingly.

Other surgical approaches that have been shown to improve OSA in some circumstances but are rarely helpful in routine practice include uvulopharyngopalatoplasty,[43–45] mandibular advancement,[46] tongue base reduction and hyoid suspension.[44] Distraction osteogenesis may have a role in some children with craniofacial anomalies (see Chapter 19, Craniofacial anomalies).

The management of OSA in children with complex problems should not be rushed but it is also imperative in some circumstances to act early, for example if there is concern about impending pulmonary hypertension. Some disorders, such as the mucopolysaccharidoses, are progressive and delaying intervention may result in a lost opportunity.

Laryngotracheal disease

Stridor in children with multiple comorbidities may be multifactorial and/or multilevel. It is often simply, but incorrectly, attributed to the underlying neuromuscular problems associated with the child's diagnosis. Where possible, a flexible nasolaryngoscopy in the clinic will allow a dynamic assessment of the upper airway to the level of the vocal cords. There should be a high index of suspicion of multilevel disease, and a full airway assessment under general anaesthetic may be required.

When underlying airway pathology is found it must be remembered that children with complex comorbidities, particularly neuromuscular, often do not respond as well to treatment as an otherwise well child would be expected to. Laryngomalacia is a good example of this. While most cases of laryngomalacia do not require surgical intervention, for those that do supraglottoplasty has a high success rate.[47] Patients with comorbidities, however, tend to have a worse outcome.[48] Children with cardiac abnormalities have been found to have a significantly higher failure rate following supraglottoplasty, which may be related to respiratory rate, an increased work of breathing or associated developmental problems.[49] However, it is children with neurological comorbidities who do particularly badly with laryngomalacia, many requiring revision surgery[49–51] and a significant proportion requiring tracheostomy.[49, 52] This may be due to a difference in underlying pathophysiology in laryngomalacia associated with neuromuscular disorders. Rather than being due to overly pliable cartilage, the underlying problem is more likely due to laxity of the soft tissue of the supraglottis. This results in an excess of redundant soft tissue, which prolapses into the airway, and ultimately the underlying cartilage will also be involved.[53]

SURGERY IN THE CHILD WITH SPECIAL NEEDS

Undertaking surgery in a child with special needs requires careful consideration and planning. Multiple comorbidities may affect decision-making and sometimes a more conservative or aggressive approach is undertaken compared with what would be required in an otherwise well child. In some cases it may not be possible to undertake a full assessment of the child other than under a general anaesthetic. While it is certainly not a standard approach, in these cases decisions as to the surgical procedure may need to be made 'on the table'. This has implications for consent and often requires the surgeon to speak to the family while the child is under anaesthetic.

It is essential that there is a dedicated pathway for children admitted for surgery with special needs and that all involved specialties are aware of the impending surgery and admission.

Hospital admission and surgery in children with complex medical problems or learning disabilities are often associated with high levels of anxiety in both the patient and parent. In order to minimize distress it is imperative that communication, planning with the family and pain management are undertaken on an individual basis.

Children with special needs often have a very strict daily routine and alterations to this can cause significant distress. Trying to accommodate the child in a side room where possible will help avoid excessive noise disturbance and will make it easier for the parent to care for their child.[54] Where possible, having the child first on the theatre list will help reduce fasting time and the anxious wait for surgery.

Surgical pre-assessments enable the child and parent/carer to visit the ward and theatre complex prior to surgery and allow the family to familiarize themselves with the department. This may help decrease anxiety on the day of surgery and help highlight any potential problems prior to admission.

Anaesthetics can be challenging but assessment by the anaesthetist prior to admission will help prepare for a smooth patient journey. Sedative premedication may help settle the child prior to the anaesthetic and may aid with cooperation. It may not be possible to insert cannulae until the child is anaesthetized and these may need to be removed as early as possible after the procedure.

Pain management in children who are unable to express pain through the usual verbal or behavioural routes can be difficult, and standard approaches are often unhelpful. Parents often recognize specific signs when their child is in pain, such as change in vocalization, altered facial expression, change in usual posture and reduced responsiveness to stimuli.[55] These can often be very subtle findings that would be apparent only to the parent/carer who knows the child well. Health professionals need to work closely with the parents in assessing pain levels in order to be able to manage the child's pain appropriately.

Many of these children require a 'step up' of services when surgical procedures are undertaken, such as a high dependency unit bed post-tonsillectomy in a child with OSA and spastic cerebral palsy. It is also important, however, to try to discharge them home as soon as it is safe to do so. This will allow them to be in a more familiar environment and to return to their usual routine. In some situations it is preferable to discharge before all the usual criteria have been met (e.g. passing urine, eating).[56]

BEST CLINICAL PRACTICE

- ✓ Examination of a child with special needs can be difficult and it may be necessary to proceed to examination under general anaesthetic in order to gain a diagnosis.
- ✓ There is increasing evidence that children with additional disabilities can benefit greatly from cochlear implantation.
- ✓ Stridor in children with complex comorbidities may be multilevel and multifactorial.
- ✓ Obstructive sleep apnoea is often overlooked in children with complex comorbidities. Management should not be undertaken without careful consideration and planning, but some disorders are progressive and treatment needs to be undertaken without untimely delay.

KEY POINTS

- The survival of preterm babies has dramatically increased over recent years but the long-term morbidity has remained unchanged.
- Children with special needs require a more detailed evaluation which takes longer.
- Specialist clinics that bring together health professionals offer a great advantage to both the clinicians and the family.
- It is essential to ensure good communication with all the health professionals involved in the care of a child with special needs.
- Surgical outcomes are often less successful in the child with special needs than for other children.

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CHAPTER 6

THE CHILD WITH A SYNDROME

Thushitha Kunanandam and Haytham Kubba

SEARCH STRATEGY

Data in this chapter may be updated by an OVID search using the keywords: Trisomy 21 (Down syndrome), Turner's syndrome, 22q11 deletion (velocardiofacial syndrome and Di George sequence), mucopolysaccharidosis, CHARGE and Pierre Robin, each of which was cross referenced with search term such as otolaryngology, airway, otology, larynx and nose.

INTRODUCTION

The subject of syndromes can be a confusing mess of eponyms, acronyms and gene deletions. In this chapter, we will try to get to grips with the terminology, what to do when faced with a child who is known to have a particular syndrome, when to suspect a syndrome that has not been diagnosed yet, and finally what the general otolaryngologist needs to know about some of the commoner syndromes in paediatric otolaryngology practice. Many of the syndromes will be covered in other chapters.

DEFINITIONS

A **syndrome** is a well-characterized constellation of major and minor anomalies that occur together in a predictable fashion, and for which a single underlying cause is known or suspected. The syndrome is a descriptive term for the collection of clinical features and often carries the name of the person who first described it (such as Down syndrome) or a description of the clinical features themselves (often as an acronym, such as CHARGE, or a simple list, such as velocardiofacial syndrome) while the **disease** is a way to describe the same entity in terms of its underlying cause (such as trisomy 21, which is the cause of Down syndrome, or 22q11 deletion, which is the cause of velocardiofacial syndrome).

A **sequence** occurs when a single developmental anomaly causes a chain of effects on nearby or related structures. For example, in the Pierre Robin sequence, the small mandible causes the tongue to fall back obstructing the pharynx (glossoptosis) and also to sit high in the oral cavity, preventing the palatal shelves from fusing, leading to a U-shaped cleft palate. These features are all directly related and can be considered as one. Thus, the Pierre Robin sequence may be found as one feature of Treacher Collins syndrome. Another example of a sequence would be an absent thymus leading to impaired T-cell immunity with recurrent ear infections (Di George sequence, which often occurs as a part of velocardiofacial syndrome).

In an **association**, a number of clinical anomalies appear together more often than would be expected by chance alone but no underlying genetic cause has been identified. An example would be the VACTERL association (vertebral defects, anal atresia, cardiac defects, tracheo-oesophageal fistula, renal anomalies and limb abnormalities). Once the genetic cause is known, the association becomes a syndrome. CHARGE is one such example, where what used to be known as CHARGE association is now more properly referred to as CHARGE syndrome since the cause has been identified as a mutation in the gene *CHD7*.[1]

GENERAL APPROACH TO THE CHILD WITH A SYNDROME

There are a few syndromes that occur commonly enough in otolaryngology practice that the otolaryngologist should probably know something about them. There are considerably more syndromes, many thousands in fact, that are so rare that the otolaryngologist may see them once in a lifetime. When faced with a syndrome you have never heard of, there is no shame in admitting the fact and no need to panic. Two minutes with any internet search engine will usually fill in most of the blanks. A more detailed literature search can be done at leisure for selected complex patients if required.

The best source of information, however, is usually the parents. For the rare syndromes they are usually the most experienced people in the room and you should not be afraid to use their expertise. In order to establish a good rapport with parents, it is not necessary to pretend to be the world's greatest expert in some rare syndrome that you looked up on the internet two minutes before; it is very important, though, to handle the family with sensitivity and respect. They will often be frequent hospital attenders who are under the care of many specialists and are therefore very 'medicalized'. They can be exquisitely sensitive to language so always remember that the child comes first and the syndrome second: you are dealing with 'a child who has Down syndrome', not 'a Down's kid', and certainly not 'a Down's'. Thankfully, old-fashioned terms like 'mongol' are long gone.

Parents can be very sensitive to any suggestion that their child is being treated less well than others because of their syndrome. A common cause of misunderstanding is in saying that a certain treatment 'is not worthwhile' because you think it is unlikely to work, which the parents hear as 'because the child is not worth treating'.

Ultimately, the syndrome is only ever of secondary importance. You are there to treat the child and to manage the same conditions that you always do. Whatever the syndrome, you are going to look at ear health and hearing, airway problems and recurrent infections, and you are going to be very careful with the cervical spine if the child is having an operation.

A child can present to the ENT clinic in one of two ways. Many children with enter the clinic with an underlying diagnosis of a syndrome already established, likely to be common in those with a characteristic phenotype. There are, however, a group of children who will present through ENT clinics with what would be considered common presentations and where there is a 'hidden syndrome'. In these cases the ENT surgeon is quite often an early opportunity to aid diagnosis. Naturally, this pathway can be more complicated and will also have to be handled incredibly sensitively.

Common presentations to ENT clinics include ear infections, hearing concerns and airway issues. These three presentations are often very common in children with syndromes as much as with the otherwise typically developing population of children. Coupled with an index of suspicion and additional features, this can be the path to early diagnosis.

SYSTEMATIC APPROACH TO THE CHILD WITH A SYNDROME

As some of the common ENT conditions can be associated with certain syndromes, this is a good basis upon which to assess and manage children with any syndrome. The approach can then be adapted to each specific syndrome and child.

Systematic management mainly involves assessment of otological manifestations and airway manifestations.

Otological manifestations

A history of recurrent acute otitis media (AOM) can be common in children with syndromes. Of course, ear infections are extremely common in all children. About half of all children have had an episode of AOM before their first birthday, increasing to 80% by their third birthday.[2] Most are managed in the community without seeing an otolaryngologist. In the UK, specialist referral is usually only requested for those with recurrent episodes of infection. During the consultation, the question inevitably arises as to whether the repeated infections are due to some underlying cause. Parents very often suspect some kind of systemic immune problem and for most the answer is 'no'. However, the otolaryngologist should be aware that among these many children with ear infections are a small number with specific syndromes that might not yet have been diagnosed.[2] In particular, a female child of short stature with a history of ear infections should make one alert to the possibility of Turner syndrome.

As well as infective problems, there are several types of hearing problem noted in children with syndromes. It is important to recognize these issues early and give consideration to the management options. Children with syndromes may have learning difficulties and additional support needs and addressing any hearing difficulties early on will help to reduce any potential handicap. Audiological screening can be a useful means of identifying problems and intervening early, although testing in this population can have its own challenges.

Conductive hearing loss can be common, particularly otitis media with effusion (OME). Although the management of this condition can mirror that in the typical childhood population, occasionally adjustments should be made for the underlying syndrome. For example, in children with Down syndrome, hearing aids are recommended in preference to ventilation tube insertion. However, in children with a cleft palate and a middle ear effusion, ventilation tube insertion is highly recommended. The high incidence of middle ear problems can lead to the development of cholesteatoma in these children and this should be kept in mind.

Sensorineural hearing loss should also be diagnosed early and treated appropriately. Hearing amplification options should be fully considered for each case, including standard hearing aids through to cochlear implantation. Children with craniofacial syndromes may present

some practical difficulties due to their head shape and/or behaviour, for example with respect to the wearing of hearing aids. Soft band and bone-anchored hearing aids may be more suitable options. In terms of cochlear implantation, again the anatomy may make surgery more tricky and there are naturally additional anaesthetic considerations to deal with for many of these children. Both these factors require surgery of this nature to be performed in specialist implant centres in tertiary level paediatric hospitals.

One should also remember to consider the cosmetic aspect under 'otology' management in terms of microtia. Again, these children should be managed in a multidisciplinary setting taking into account the hearing and cosmetic components. These settings should allow for an informed discussion on the merits of surgery in terms of auricular prostheses or auricular reconstruction.

Airway manifestations

Airway management in children with syndromes can be exceptionally challenging. Craniofacial abnormalities in particular can lead to great anxiety regarding airway management when the children present to other services for elective or 'routine' surgery: the anaesthetist may have to deal with a difficult intubation scenario in addition to a potentially more complicated peri-operative and post-operative period. Airway manifestations can also present as neonatal emergencies at birth, such as in bilateral choanal atresia or severe micrognathia.

In managing the airway, the level of obstruction should be considered with an awareness that this could be at the nasal level, nasopharynx, tongue base or at the level of the larynx/trachea/bronchi. Formal airway endoscopy (MLB) will allow for complete assessment of the level(s) of obstruction and exclude any other airway anomalies.

Adenotonsillar surgery can often be undertaken to help alleviate obstruction at the naso- and oropharyngeal level. The degree of adenotonsillar hypertrophy is not always clearly related to the degree of obstruction and no doubt the situation is much more complex with neurological and muscular tone often confounding the situation. Pre-operative assessment by means of sleep studies can be useful in assessing obstruction and certainly useful in guiding post-operative recovery.

Nasopharyngeal airways can be extremely useful airway adjuncts. Their use is indicated where the pathology relates to tongue-base collapse and micro/retrognathia as, for example, seen in Pierre Robin sequence (PRS). Often there can be symptomatic improvement as the child grows and a nasopharyngeal airway is a successful temporizing measure. However, in some situations formal surgery is required in the form of mandibular distraction or midface advancement.

Finally, tracheostomy may be required in some children with significant airway obstruction. The implications of a tracheostomy must be carefully considered for the child and the family. The procedure itself may also be more complex due to unusual airway anatomy, such as a tracheal sleeve.

WHEN TO SUSPECT THERE MAY BE A SYNDROME

Among the many children presenting on a daily basis to the otolaryngology clinic, there are a few whose symptoms are due to an underlying genetic condition. In most cases the underlying syndrome is obvious and has already been diagnosed, such as the child with Down syndrome. There are some syndromes, however, whose features may be subtler and easily missed. For some, the first presenting features may be in the ears, nose or throat and the otolaryngologist may be the first doctor to see the child and therefore the first to have the opportunity to spot the underlying diagnosis. This is an important opportunity to make potentially a huge difference to the child and family as making the correct diagnosis can affect not only the management of the otolaryngological condition but also of many other body systems.

The commonest clinical situation where this chance to make an early diagnosis occurs is in the child with recurrent AOM. It is very worthwhile looking out for a few underlying syndromes that might not have been diagnosed yet, specifically common variable immunodeficiency, Turner syndrome, mucopolysaccharoidosis and 22q11 deletion. The latter three have characteristic facies (which are often subtle) and mucopolysaccharoidosis and Turner also have short stature as a feature. All are discussed further below. Immunodeficiency is discussed in Chapter 7, Management of the immunodeficient child.

It is important that the ENT surgeon has knowledge of some of the less common genetic disorders in order that appropriate and timely referral for specialist management can be made.

SPECIFIC SYNDROMES

Down syndrome

Down syndrome is a common and easily recognizable disorder with familiar phenotype and genotype (trisomy of all or a critical portion of chromosome 21). This syndrome easily demonstrates the ear, nose and throat problems that can need to be considered in managing a child with any syndrome.[3]

The most common ENT reasons for referral in children with Down syndrome are OME, sleep-disordered breathing and laryngomalacia. The possibility of atlantoaxial subluxation in this group of children should mean that any surgical procedure involves very careful handling of the neck. Immunological aspects of the disease can lead to ventilator tube otorrhoea, persistent rhinorrhoea and recurrent upper respiratory tract infections. Endotracheal intubation can be difficult and often the child will need a smaller diameter ET tube than her age would suggest. There is an increased mortality in this group of children (×6 throughout infancy and ×17 until age 9 years) compared to age-matched controls.[4]

Otological aspects of the disease include the following:

- persistent otitis media with effusion – hearing aids should normally be offered to children with Down syndrome who have hearing loss due to OME[5]
- narrow and waxy ear canals – ventilator tube otorrhoea and early extrusion can be more common
- conductive hearing loss secondary to ossicular anomalies
- sensorineural hearing loss with increased labyrinthine dysplasia – inner ear dysplasia is common in children with Down syndrome
- increased incidence of cholesteatoma
- anatomical abnormalities of the facial nerve – tympanomastoid surgery can be especially challenging.

Hearing screening with behavioural testing throughout early childhood should be carried out to establish near-normal hearing with the use of amplification or ventilation tube insertion. Cholesteatoma should be suspected in continuously discharging ears.

Airway aspects of the disease include:

- obstructive sleep apnoea – relative adenotonsillar hypertrophy, upper airway obstruction as part of craniofacial condition including hypoplasia of pharynx and maxillary arch with nasal obstruction, sometimes generalized muscle hypotonia ('floppy baby')
- tracheobronchomalacia – increased incidence in this population and there may be a need for ventilation with/without tracheostomy and continuous positive airway pressure (CPAP)
- synchronous airway anomalies can be seen including a tracheal bronchus, subglottic stenosis and tracheo-esophageal fistula.

Annual screening for OSA until age 3–5 years is recommended. It is important to realize that, even after adenotonsillar surgery, there is a greater than 50% finding of residual OSA that will likely need medical intervention (e.g. CPAP). These children are unsuitable for day-case adenotonsillectomy and they will often require high-dependency care post-operatively.[6, 7]

Turner syndrome

Turner syndrome (TS) is characterized by the complete or partial loss of one X chromosome. TS is surprisingly common, affecting 1 in 2000 females, although perhaps only half have been formally diagnosed and are known to medical services. Some are diagnosed at birth due to characteristic features such as oedematous feet, while others are diagnosed in adolescence due to growth failure and delayed puberty. The vast majority of girls with TS present to otolaryngologists in their early years with recurrent AOM and OME, and for many this occurs long before the diagnosis of TS has been made.[8] Progressive mid-to-high tone sensorineural hearing loss is common in school years and early adulthood. Cholesteatoma is also not infrequent.[9] Early diagnosis can make a huge difference to these patients as it enables the detection of heart anomalies, which are commonly present, as well as growth hormone treatment for short stature. Suspicion is key: consider TS in any girl with ear problems and short stature, and refer on to an endocrinologist if concerned. If she is the shortest girl in her school class, think, 'could this be Turner syndrome?'

22q11 deletion syndrome

22q11 deletion syndrome encompasses the clinical conditions previously termed velocardiofacial syndrome and Di George syndrome which are now known to be different manifestations of the same genetic defect. A variety of clinical features can occur but not in every child.[10] Common features include submucous cleft palate, congenital heart anomalies, absent thymus with impairment of T-cell immunity (Di George sequence) and characteristic facial features. The ENT clinical features result from abnormal development of structures derived from the third and fourth pharyngeal pouches. The first presentation to medical services may well be with recurrent episodes of AOM due to the impaired T-cell immunity. Another presentation to the otolaryngologist is with a congenital glottic web which is almost always diagnostic of 22q11 deletion (see Chapter 30, Congenital disorders of the larynx, trachea and bronchi).[11, 12] Again, the phenotypic profile is highly variable and awareness and suspicion are key. If there is suspicion of 22q11, full ENT assessment including laryngoscopy should be performed and referral to a geneticist and cardiologist initiated.[13]

Mucopolysaccharoidoses

The mucopolysaccharoidoses (MPS) comprise a group of conditions that result from the deficiency of lysosomal enzymes causing the accumulation of glycosaminoglycans in tissues. Head and neck structures are frequently involved early and the otolaryngologist may see children before the onset of systemic disease.[14] Features commonly include recurrent otitis media, mixed hearing loss, upper airway obstruction +/– obstructive sleep apnoea and coarse facial features. Due to the non-specific clinical features, diagnosis is frequently delayed but early diagnosis is essential, particularly in Hunter syndrome, where enzyme replacement therapy is now available.[15] MPS is also associated with intubation difficulties and may pose a significant anaesthetic risk. OSA is extremely common, with a prevalence of up to 90%, and patients may benefit from adenotonsillectomy.[16] Suspicion of MPS should prompt specialist referral, and confirmation is with urinary glycosaminoglycan measurement and enzyme assays.[14]

CHARGE syndrome

CHARGE syndrome is an autosomal dominant genetic disorder typically caused by mutations in the chromodomain helicase DNA-binding protein-7 (*CHD7*) gene.[1, 17, 18] The acronym 'CHARGE' denotes the non-random

association of coloboma, heart anomalies, choanal atresia, retardation of growth and development, and genital and ear anomalies, which are frequently present in various combinations and to varying degrees in individuals with CHARGE syndrome.[19]

Neonatal presentation:

- small for gestational age
- dysmorphic features
- respiratory distress/cyanosis
- swallowing/feeding difficulty
- failed newborn hearing screen
- inability to pass nasogastric tube.

Choanal atresia is membranous or bony, and bilateral in over 50% of cases, usually presenting in the newborn period with a cyclical pattern of respiratory distress. This can be a threat to life because infants cannot establish mouth breathing. Of all features of CHARGE syndrome, choanal atresia (when bilateral) is the most easily ascertained and requires early surgical correction. When associated with other anomalies (e.g. cyanotic heart disease, tracheoesophageal fistula and/or atresia), prognosis is poor. Unilateral atresia may present as persistent nasal discharge in early childhood.

External ear malformations are seen in 90–100% of patients. Ears may be small, simple, low-set, and/or cup-shaped; a protruding helix may be unravelled.

Vestibular or cochlear defect leads to sensorineural deafness. Middle ear problems cause conductive hearing loss and are commonly due to ossicular malformations, stapedius tendon abnormality, or serous effusion. CT scan of the temporal bone demonstrates partial or complete semicircular canal hypoplasia.

Syndromes discussed elsewhere

Syndromic craniosynostosis (Pfeiffer, Apert, Crouzon and Saethre–Chotzen syndromes) are discussed in Chapter 19, Craniofacial surgery.

Syndromes causing deafness (such as Pendred, Waardenburg and Usher, as well as many others) are discussed in Chapter 10, Management of the hearing impaired child.

KEY POINTS

- Far too many syndromes have been described for anyone to be familiar with them all, but a few common ones should be well-known to any paediatric otolaryngologist.
- Be careful with the words you use in front of parents as they are often very sensitive to anything that sounds like a lack of respect for the child.
- Regardless of the nature of the syndrome, the role of the otolaryngologist will most often be to address issues of hearing, recurrent infections and airway obstruction, whilst always being careful with the cervical spine.
- Some children presenting with common otolaryngological problems may have an underlying syndrome that has not yet been diagnosed. Be alert to any features that may allow you to make the diagnosis.

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CHAPTER 7

MANAGEMENT OF THE IMMUNODEFICIENT CHILD

Fiona Shackley

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: immunodeficiency, otitis media, sinusitis, mastoiditis, otolaryngological disease, ENT, nasopharyngeal colonization, hypogammaglobulinaemia and HIV.

INTRODUCTION

The infant nasopharynx becomes colonized with microorganisms from shortly after birth.[1] There is a consequent constant balance of host, microbial and environmental factors that allow individuals to be colonized with potentially infectious organisms or allow microorganisms to breach host defence to cause local or systemic disease.[2] In the young child with an immature immune system, recurrent respiratory tract infection, particularly otitis media, is common. Studies carried out prior to the widespread introduction of pneumococcal conjugate vaccines indicate that 83% of children will have suffered one episode of otitis media by 3 years of age and 46% will have had at least three episodes.[3] Recurrent infections of the upper respiratory tract are also common in children with primary immunodeficiency (PID). ENT specialists may be the first clinicians to see a child with an immune defect and have a key role in identifying these children. This is also the case for children with HIV infection who may present to an ENT specialist before their diagnosis has been confirmed. Early diagnosis and commencement of treatment for both primary and acquired immune deficiency improves long-term outcome.[4, 5] Unfortunately, identifying the children who need further investigation can be difficult, although other features including failure to thrive, absence of or excessive lymphadenopathy, dysmorphic features and skin problems should raise concerns.[6] Some children with minor immune defects may only become symptomatic because of other associated features including allergic tendency, GOR and Eustachian tube dysfunction.[7, 8]

PRIMARY IMMUNODEFICIENCY

Children born with a reduced immune system, or the tendency to develop a reduced immune system over time, are classified as having PID.[9] Ascertainment of the true incidence of these conditions is difficult. An estimate from a US telephone survey indicated a prevalence of PID in the US of 1:2000.[10] Over 60% of these immune problems relate to antibody production.[10, 11] Antibody plays an essential role in the process of opsinophagocytosis,[12] destroying common organisms in ear and sinus disease including *Streptococcus pneumoniae*, non-typable *Haemophilus influenzae* and *Moraxella catarrhalis*. These are clearly children or adults who may have seen an otolaryngologist before the diagnosis is considered.

Identifying children with immune deficiency

Several guidelines are available to help clinicians identify children with immune deficiency. The Jeffrey Modell '10 warning signs of infection'[13] indicate that immunodeficiency should be considered in any child with more than four new ear infections in one year; more than two episodes of severe sinusitis pneumonia, infections that do

not respond to routine antibiotics, failure to thrive or a family history of immunodeficiency. Consequent studies using these risk indicators have shown that, particularly for antibody deficiency, it can be very difficult to differentiate the immunologically normal and abnormal child in the absence of features such as poor growth or family history.[14] The current ESID guidelines, while not giving a threshold for ENT infections that might indicate the need to investigate, do give clear pathways for appropriate investigations.[6]

Transient hypogammaglobulinaemia of infancy

All children rely on transplacental transfer of maternal antibodies during the last trimester of pregnancy, which helps protect them over the first 6 months of life while the infant's antibody production becomes adequate.

In some children, there appears to be a delay in this maturational process resulting in low IgG, which can be associated with a reduced IgA and IgM. Transient hypogammaglobulinaemia of infancy (THI) is a diagnosis of exclusion and a definitive diagnosis is only possible over time when the problem resolves. In paediatric series this is the commonest form of symptomatic antibody deficiency.[15, 16] The pathogenic process behind THI is not understood. A small number of children continue to have problems with infections and persist in having low antibody levels or fail to make adequate response to their routine immunizations. The majority are reported to improve by the age of 4 years although in some children the IgG remains low into late childhood.[16, 17]

Hypogammaglobulinaemia is common in preterm infants who may not be symptomatic although routine prophylactic immunoglobulin is not recommended.[18] Also, high levels of cord blood pneumococcal-specific antibodies did not seem to provide sufficient protection for Aboriginal infants who are known to be at increased risk of early otitis media illustrating the fact that low antibody levels alone may not be the sole explanation for recurrent ENT infections in early infancy.[19]

If low immunoglobulin levels are identified, it is important to be sure that there is not a more significant underlying immune defect present.[6]

IgA deficiency/ IgG subclass deficiency and specific antibody deficiency

IgA deficiency is present in around 1 in 600 blood donors.[20] Most individuals with IgA deficiency are completely well and, in many children, the deficiency is transient. Some people do suffer more frequent infections including ear and sinus disease and occasionally develop progressive antibody deficiency.[21] This is more likely if they have an associated IgG subclass deficiency, particularly IgG2, or specific antibody deficiency (SAD). Activity against pneumococcal capsular polysaccharide appears best mediated by the IgG2 subclass which young children may be poor at generating. IgG2 deficiency is commoner in some series of children with recurrent otitis media.[22] However, asymptomatic IgG2 deficiency is also well documented.[23] Quality of antibody production can be assessed by looking at protective levels of antibody following immunizations. A group of individuals has been described who have reduced ability to make antibodies to polysaccharides, a key component of the capsular wall in some organisms. Poor polysaccharide responses are normal in children under 2 years but are also seen in some older children and adults where it will be labelled as SAD. While definitions of this condition are available,[24–26] the introduction of routine pneumococcal conjugate vaccine immunizations and lack of access to standardized assays to assess response adds controversy to diagnosis of this condition.[27, 28]

Common variable immune deficiency

In combined adult and paediatric data common variable immune deficiency (CVID) is the commonest symptomatic antibody deficiency[29] defined by a reduced IgG (beyond the age of 4 years), a history of infections and often inadequate response to immunizations.[9] A proportion of children with CVID may initially have been labelled as THI but continue to be symptomatic and have low IgG levels in later chidlhood. In a recent paediatric series, 88% of children with CVID had recurrent respiratory tract infections, 78% otitis media and 78% sinusitis.[30] Around 10% of individuals with CVID[31] have an identifiable gene defect but the cause for the majority of CVID remains unclear. There are two peaks of onset, in mid-childhood and early adulthood. Delay from symptoms to diagnosis and treatment is usually around 4–5 years.[30, 32] These are clearly the type of children who may have seen an otolanyngologist before the diagnosis is considered.

X-linked agammaglobulinaemia

A small group of children, predominantly boys, who present with severe infection and a paucity of lymphoid tissue will have X-linked agammaglobulinaemia. Due to defects in the *BTK* gene, affected boys fail to manufacture mature B-cells and consequently make no or very little IgG. While some of these children suffer serious life-threatening infections, recurrent otitis is the commonest infection identified prior to diagnosis.[33] In a small number of patients, deletions in the terminal portion of the *BTK* gene may extend to involve the deafness dystonia protein gene resulting in sensorineural deafness.[34] These children are differentiated from THI and CVID patients initially on the basis of extremely low IgG, IgA and IgM or absent B-cell numbers. Consequent protein and molecular studies confirm a *BTK* defect in most children. In a small number of individuals there are autosomal recessive conditions that result in a similar phenotypes affecting both boys and girls.[35] Boys with X-linked agammaglobulinaemia usually present at 6–18 months of age but diagnosis may be delayed till

later in childhood in 10–15%, unfortunately sometimes after children have already sustained lung and ear damage. Bruton's use of regular immunoglobulin infusions was the start of what is a key treatment for children with antibody deficiency.[36]

Other conditions that may mimic antibody deficiency

X-linked hyper IgM syndrome may present like CVID with absent or low IgG and IgA but normal or elevated IgM.[37] The defect in CD40 ligand results in T- and B-cell functional problems. Hyper IgE syndrome[38] and DOK 8 deficiency[39] are both associated with eczematous skin problems, raised IgE and recurrent infections, again particularly otitis media. Wiscott–Aldrich syndrome, due to mutations in the WASP cytoskeletal protein, also often presents with severe eczema, thrombocytopaenia and ear infections.[40] These children are at increased risk of opportunistic infection and may require bone marrow transplant in addition to immunoglobulin replacement.

TREATMENT OF ANTIBODY DEFICIENCY

Children with antibody deficiency, THI and SAD with mild infections may be managed with prophylactic antibiotics including amoxicillin, azithromycin and cotrimoxazole.[41, 42] There is very little trial evidence to support this but practice has been based on studies from otitis media.[43] For more severe immunodeficiency, and certainly X-linked agammaglobulinaemia, or in children where antibiotic prophylaxis alone does not control infections, immunoglobulin replacement can be given either as an intravenous infusions 0.4–0.6 g/kg every 3–4 weeks or a weekly subcutaneous infusion which can be easily given at home and is well tolerated by children. There is good evidence that adequate immunoglobulin replacement improves long-term outcome.[44, 45]

Phagocyte abnormalities

Due to the key role of neutrophils in phagocytosis, ENT infections are also frequently seen in children with reduced neutrophil numbers and function. In infancy, neutropaenia may be consequent to a number of known molecular defects but is also seen in conjunction with some metabolic conditions including glycogen storage disease. These children can be at risk of life-threatening sepsis but otitis media, oral ulceration and abscesses are also common.[46, 47] The commonest cause of neutropaenia in our practice in young children is benign autoimmune neutropaenia or alloimmune neutropaenia. Recurrent otitis media can be a frequent problem in these children and severe mastoiditis or adenitis may be a presenting feature.[48] A blood count will identify children with persistent neutropaenia who can then have consequent genetic or autoimmune studies to define the cause. Congenital neutropaenia usually requires treatment with granulocyte-colony stimulating factor (G-CSF) to increase neutrophil numbers but may require bone marrow transplant. Autoimmune neutropaenias can often be managed with antibiotic prophylaxis and prompt treatment of infections.[47]

Defects in the neutrophil oxidative burst pathway are well described, resulting in chronic granulomatous disease. These children can develop deep-seated infections, sometimes with unusual organisms including *Serratia species, Burgholdheria cepacia* and fungal infections.[49] These may cause severe adenitis, mastoiditis or sinusitis.[50] This should always be considered in children with particularly severe disease who may present to ENT teams for acute surgical intervention. Unlike with many other immune defects, these children may not have problems early in infancy and can present in late childhood with an unusual infection. Management is with long-term prophylactic antibiotics and antifungals and, with an appropriate donor, bone marrow transplant has been very successful. Most cases are X-linked but AR forms also occur.

Children with defects in leucocyte adhesion molecules may also present in infancy with severe otitis and mastoiditis.[51] One of the key laboratory findings that may alert an ENT surgeon to this defect is the presence of a very high WBC. Consequent questioning may reveal a history of delayed cord separation.

Other innate immune system defects

Deficiencies in the compliment system are more likely to present with septicaemia than recurrent ear or sinus infections.[52] However, deficiency in mannose-binding lectin (MBL), which facilitates complement activation, is relatively common in the population[53] and may, particularly in conjunction with other immune system abnormalities or Eustachian tube dysfunction, contribute to recurrent ear and sinusitis infections.[54, 55] No specific treatment options are available apart from prompt antibiotic treatment.

IMMUNE DEFICIENCY IN OTHER PAEDIATRIC SYNDROMES

Di George or velocardiofacial syndrome,[56] CHARGE (coloboma, heart defects, atresia choanae, retardation of growth, genital anomalies and ear abnormalities)[57] and Down syndrome[58] are all linked to an increased risk of ear infections through facial structure and palatal abnormalities but are also at risk of immune deficiency which, in the case of 22q deletions, may be quite severe. Clinicians should have a lower threshold for considering immune deficiency in children with dysmorphic syndromes. Children with developmental delay and associated microcephaly may have a defect in DNA repair or chromosome stability. Immune deficiency is a recognized complication of many

of these conditions,[59] the most notable being ataxia telangiectasia where recurrent otitis media is a well-recognized common complication.[60]

Autoimmune lymphoproliferative syndrome

Autoimmune lymphoproliferative syndrome (ALPS) is an uncommon group of conditions associated with defects in the apoptosis pathway. The degree of immune deficiency associated with this condition is variable but children can present in infancy and early childhood with persistent, sometimes, massive cervical adenopathy.[61]

MHC Class 1 deficiency

Rarely older children may present with sinusitis, nasal polyposis and bronchiectasis due to MHC Class 1 deficiency.[62]

Severe combined immune deficiency

Children with these severe immune defects will not usually present to the ENT team at diagnosis, as the majority will suffer severe generalized infections in early life.

INVESTIGATIONS FOR PID

The European Society for Immunodeficiencies (ESID) guidelines provide a helpful pathway indicating initial screening test for children with recurrent ENT infections should include FBC, and measurements of IgG, IgA and IgM.[6, 9] Perisistent or recurrent neutropaenia may indicate a congenital or autoimmune neutropaenia requiring further genetic and autoantibody testing. If low immunoglobulins are identified, lymphocyte subsets should be carried out particularly to ensure the child has adequate B-cell numbers. Responses to routine immunizations should also be evaluated including Hib, tetanus and *Pneumococcus*. For children who have had pneumococcal conjugate vaccine, measurement of pneumococcal serotypes if available should be carried out rather than total pneumococcal antibodies. Children with low vaccine responses should be offered booster immunizations and the response reassessed in 4–6 weeks. Looking at children's response to Pneumovax is recommended by some guidelines but lack of access to standardized tests to assess the response can limit the clinical utility of this. If symptoms are persistent, IgG subclasses, MBL and complement studies CH50 APCH50 are recommended. Children with other features to suggest a more fundamental immune defect including failure to thrive, family history, severe eczema, abnormal lymphadenopathy or dysmorphic features should be discussed with the local immunology service as further investigation is likely to be indicated. In the context of features suggesting SCID, including lymphopaenia, the local paediatric team should be urgently alerted.

IMPACT AND USE OF IMMUNIZATIONS

The introduction of routine infant immunization with pneumococcal conjugate vaccines in many developed countries since 2000 has had a significant impact on invasive pneumococcal disease[63] but has also reduced otitis media[64] and the need for surgical intervention with tympanostomy tubes.[65] There is evidence that pneumococcal strains present in the older pneumococcal polysaccharide vaccine (PPV) but not current conjugate vaccines are now causing more otitis media[66] but there is no evidence unfortunately that giving additional doses of either conjugate or PPV to children with recurrent otitis media reduces infections.[67, 68] There is also some concern that repeated doses of PPV may result in blunting of the immune response.[28]

HIV/ACQUIRED IMMUNE DEFICIENCY

HIV is estimated to affect 3.4 million children worldwide.[69] Rates of new infections in children have dramatically reduced worldwide through treatment interventions that prevent mother-to-child transmission. The majority of children with HIV acquire infection from their mothers before birth, during delivery or during breastfeeding. Without control of maternal infections with highly active antiretroviral therapy (HAART), and infant prophylaxis, mother-to-child transmission was around 25%.[70] With appropriate maternal and infant medication, advice against breastfeeding or control of maternal virus while breastfeeding and, where indicated, Caesarean section, it is anticipated that transmission can be reduced to less than 2% worldwide and is already less than 1% in some developed countries.[71]

ENT complications

Many children become symptomatic over the first 2 years of life but others may be well into late adolescence.[72] In this group of children parotid enlargement may be a common feature and may be the initial presentation to ENT services. Otitis media and chronic suppurative complications are common, with a trend to increasing ear infections over time as the child's immune system fails.[73]

Conductive hearing loss as a consequence of ear infections can have significant impact on a child's well-being and development. In addition, HIV-infected children appear to be at increased risk of sensorineural deafness, tinnitus and vestibular symptoms, highlighting the importance of audiological assessment in all HIV-infected children.[74] Access to HAART has had a significant impact on children's survival and may have led to a decrease in the number of children with ENT manifestations of HIV.[75, 76] HIV-infected children will still, however, suffer from ENT-related problems and potentially require surgical intervention including tympanostomy tubes

and myringoplasty. Infectious cervical lymphadenitis with common and opportunistic organisms including tuberculosis and atypical mycobacteria may also present neck swelling to ENT specialists.

Who and how to test

UK national guidelines for HIV testing list recurrent and troublesome ear infections and chronic parotitis as clinical indicators for HIV testing in children.[77] While routine testing of all children with recurrent ear infections may not be indicated, HIV testing in children with chronic parotitis is recommended irrespective of there being no other apparent risk factors. HIV should also be considered if a child is found to have significantly raised immunoglobulins when being investigated for a PID.[6] Unexplained lymphadenopathy is an indication in adult but not paediatric UK guidance but is a well-described feature, though the clinical appearance may be difficult to differentiate in infected and uninfected children.[78]

Any trained heath professional should be able to obtain consent for HIV testing.[77] However, HIV testing a child adds the additional complexity of the implications the test result may have for the family, particularly if the parents themselves are unaware of their own underlying diagnosis. Usually local paediatric or infectious disease colleagues are happy to be involved. The significant stigma, guilt and concern around disclosure can make it extremely difficult for parents to agree to testing. Parental refusal to have HIV testing may then become a child protection issue requiring involvement from social care and the court system.[79] Wherever possible, however, healthcare staff should work with families to encourage them to have testing carried out and engage with ongoing clinical input voluntarily.

Initial screening for children over 18 months of age is by HIV serology and p24Ag, which should then be repeated and include a DNA PCR and RNA viral load. Children under 18 months of age require testing using DNA or RNA PCR.[80] A CD4 count may be arranged with the confirmatory testing but CD4 count alone should not be used as a surrogate for HIV testing in families who will not consent to testing.

TABLE 7.1 ENT features and staging (adapted from PENTA)[80]

Clinical stage WHO or CDC	ENT features in children
Mildly symptomatic WHO 1 and 2; CDC A	Recurrent otitis media +/– chronic otorrhoea Recurrent sinusitis Chronic parotitis
Moderate to severe symptoms WHO 3 and 4; CDC B and C	Oral candidiasis Oesophageal candidiasis Extrapulmonary TB Atypical mycobacterial disease Necrotizing gingivitis Recurrent oral HSV Oral hairy leukoplakia Lymphoma/Kaposi sarcoma

When to treat

A variety of guidelines is available to indicate when it is appropriate to commence children on antiretroviral treatment based on a combination of symptoms and CD4 count. A number of common ENT presentations are seen in the relatively well HIV-infected child who may not yet need to be on medication unless associated with a low CD4 count. Other conditions that may present to ENT are key indicators themselves of the need to start treatment (**Tables 7.1** and **7.2**).

Families need significant support with compliance with HAART. Most children show rapid improvement in their CD4 count and immune reconstitution over the first few months of treatment. However, for some children the residual damage caused by recurrent ear and chest infections may mean they continue to have problems that need ongoing input from the ENT team.

TABLE 7.2 Age-specific thresholds to start treatment (adapted from PENTA)[80]

	Under 12 months	1–3 years	3–5 years	Over 5 years
Clinical stage	Start all	CDC B or C WHO 3 and 4	CDC B or C WHO 3 and 4	CDC B or C WHO 3 and 4
CD4 count	Start all	CD4 < 1000 (25%)	CD4 < 500 (20%)	CD4 < 350

KEY POINTS

- Children with primary or acquired immunodeficiency will commonly present with ENT problems.
- Clinical features may not differentiate immune-deficient children from normal children.
- Simple baseline investigation can screen out a number of severe immune defects.
- Close working between ENT teams and the local paediatric immunology/infectious disease services should be encouraged.

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CHAPTER 8

HEARING SCREENING AND SURVEILLANCE

Sally A. Wood

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search for relevant articles published in English, using the following keywords: infant or newborn and hearing screening and hearing impairment.

INTRODUCTION

Any discussion of screening must be grounded in an understanding of the principles of screening as a public health exercise and an understanding of the epidemiology of the condition of interest, in this case moderate–profound permanent childhood hearing impairment (PCHI). This chapter starts with an outline of the key definitions and principles of screening, before proceeding to review evidence on the epidemiology of permanent childhood hearing impairment. The case for newborn screening and the current performance of the newborn hearing screening programme in England is summarized. The need for surveillance in the preschool years is reviewed and the school entry screen is briefly discussed.

PRINCIPLES AND DEFINITIONS

Screening

Screening is a public health service in which members of a defined population who do not necessarily perceive they are at risk of or already affected by a disease or complications are asked a question or offered a test, to identify those individuals who are more likely to be helped than harmed by further tests or treatments to reduce the risk of a disease or its complications.[1] In the UK the National Screening Committee (NSC) assesses the evidence for the introduction of national screening programmes and monitors the effectiveness and quality of these programmes in the English NHS.

Screening is ethically different from clinical practice; in screening the individual has not presented with a symptom or concern but is offered a test. When you treat an ill person, they have the possibility of benefit as well as the risk of harm. In screening some people who do not have the condition may experience the harm but have no benefit. Screening is not an infallible process and in all screening programmes there are inevitably individuals who fail the screen but do not have the condition (**false positives**), and individuals who pass the screen but do have the condition (**false negatives**). Thus there is an added ethical imperative to ensure that the screening programme does more good than harm.[2] The most likely potential harms from newborn hearing screening are related to parental anxiety for the parents of babies who fail the screen but do not have an impairment (false positives) and the ability of audiology services to make a correct and timely assessment in screen positives.

The principles that a screening programme should satisfy have been identified by Wilson and Junger[3] (1–10 below) and expanded by Haggard and Hughes[4] (11–14) in their review of screening for hearing impairment in children.

1. The condition (hearing impairment) should be an important health problem.

2. There should be an accepted treatment, i.e. an acceptable means of habilitation for those identified by the screen.
3. Facilities for assessment, diagnosis and treatment should be available.
4. The hearing impairment should be recognizable at an early stage.
5. There should be a suitable test for use as the screen.
6. The test should be acceptable to the parents and to the child.
7. The natural history of the condition should be known and understood.
8. There should be an agreed policy on who to treat.
9. The cost of case finding (including all consequential costs of the screening programme) should not be disproportionate to overall healthcare costs of care for the hearing-impaired child.
10. Case finding should be seen as a continuing process.
11. The incidental harm should be small compared to the overall benefits.
12. There should be guidelines on how to explain results to parents with appropriate support.
13. All hearing screening arrangements should be reviewed in the light of changes in demography, epidemiology and other factors.
14. Cost and effectiveness of hearing screening should be examined on a case-type basis to maximize the effectiveness and benefit for each type before considering overall costs, effectiveness and benefits.

There are a number of key definitions relevant to screening programmes which should be used in the quality assurance and audit of any screening programme. These measures are defined in Table 8.1 and described below.

Coverage is the proportion of the eligible population who complete the screen.

Screen positive/fail (A+B) is a screening result that is greater than or equal to a specified cut-off level. True positives (A) are those who fail the screen and have the condition. False positives (B) are those who fail the screen and do not have the condition.

Screen negative/pass (C+D) is a screening result that is less than the specified cut-off level. True negatives (D) are those who pass the screen and do not have the condition. False negatives (C) are those who pass the screen and have the condition. Screening programmes attempt to reduce false negatives to a minimum, while keeping false positives within manageable service levels. The aim of a screen is to refer on a manageable proportion of the population for further (diagnostic) tests, that proportion being likely to contain as many of the true cases in the population as possible.

Sensitivity (A/(A+C)) is the proportion of individuals with the target condition in the population who are correctly identified by the screen. The term can be applied to a screening test, or to the screen as a whole (if, as is the case with newborn hearing screening, the screen consists of more than one test) or to the screening programme as a whole. **Programme sensitivity** is the proportion of the subjects in the whole population with the specified condition (impairment) who are detected by the screening programme. It is a function of the screen sensitivity and the coverage achieved by the screen programme.

Specificity (D/(B+D)) is the proportion of individuals without the target condition in the population who are correctly identified as such by the screen. As with sensitivity, the term specificity may be applied at the level of test, the screen or the programme. **Programme specificity** is a function of specificity and coverage.

Positive predictive value (PPV) (A/(A+B)) is the proportion of individuals with a positive test result who have the target condition.

Yield is the number of cases identified by a screen. The yield is sometimes expressed as the number of cases identified via the screen per 1000 individuals screened, thus allowing comparison with published prevalence figures, and acting as a surrogate for sensitivity (since sensitivity can only be established in retrospect, once all false negative and missed cases have been found). The yield of a screen is affected by coverage and sensitivity, and affects the cost per case identified. The **incremental yield** is the number of true cases referred by a screen when any true cases that would have been or were identified by preceding screening, surveillance programmes or responsive services are excluded.

Incidence is the number of new instances of the condition (impairment) occurring during a certain period (e.g. a year) in a specified population. Thus, in an average-sized health community with 5000 births per year, an incidence of between five and ten cases of congenital permanent childhood hearing impairment of moderate or greater degree might be expected.

Prevalence is the total number of individuals who have a given disease or condition (impairment) at a given point in time per population figure (e.g. per 1000 live births). Davis et al.[5] have suggested a figure of 1.12 per 1000 for congenital permanent bilateral hearing impairment of moderate or greater degree.

Haggard and Hughes extended the screening criteria to include costs and cost-effectiveness as

TABLE 8.1 Measurement of screen performance

Screen outcome	Condition present	Condition absent	Total
Fail (positive)	A: true positive	B: false positive	A+B
Pass (negative)	C: false negative	D: true negative	C+D
Total	A+C	B+D	A+B+C+D

important issues for screening programmes (points 9 and 14 above). **Cost-effectiveness** analysis measures costs per unit of health gain.

Lost to follow-up is a measure of the percentage of screen positives that fail to enter follow-up. This is usually measured at a specific point in time.

Surveillance

The concept and practice of child health surveillance has been extensively discussed in the literature.[6,7] It is generally recognized to include a partnership between parents, children and health professionals in which parents are empowered to make use of services and expertise according to their needs. Ongoing surveillance for childhood hearing impairment is of considerable importance:

- Newborn hearing screens will not find all those with permanent hearing loss, because of late onset and progressive hearing loss.
- Any screening programme will miss some true cases.
- Mild permanent hearing loss will not be identified by the screen.
- Surveillance is a more justifiable approach to identification of children with persistent otitis media with effusion (OME) than a screening programme.

EPIDEMIOLOGY: PREVALENCE AND RISK FACTORS

Terminology and definitions

In the sections that follow, hearing impairment is categorized as mild, moderate, severe or profound on the basis of hearing threshold in dB HL (hearing level) averaged over the frequencies 0.5, 1.0, 2.0 and 4.0 kHz for the better hearing ear as follows:

- Mild 21–39 dB
- Moderate 40–69 dB
- Severe 70–95 dB
- Profound >95 dB.

This categorization is widely used in the literature.[5] It is slightly different from that adopted by the British Society of Audiology.[8] The World Health Organization has recently defined an alternative classification.[9]

Permanent childhood hearing impairment (PCHI) includes hearing impairment that results from a structural abnormality in the outer ear, middle ear as well as sensorineural hearing loss. The term congenital is used to denote hearing impairment that is present at, or very soon after, birth. While this is not a strictly accurate use of the term, it has been commonly used as a functional definition. Acquired hearing impairments are considered to be (i) postnatally acquired PCHI (e.g. as a sequela of meningitis or head injury); (ii) progressive hearing impairments usually diagnosed following ongoing progression of the impairment post diagnosis; (iii) impairments that are considered to be late-onset, with no evidence of progression but with some evidence of previously normal hearing.

Congenital permanent bilateral hearing impairment

The quality of published studies on the prevalence of PCHI is variable, with many studies marred by lack of clarity on case definition, uncertain methodology and incomplete case ascertainment. Of the better studies, those of Fortnum and Davis[10] and Fortnum et al.[11] are probably the most extensive and reliable. Fortnum and Davis report the results of a retrospective ascertainment of all cases of permanent bilateral hearing loss of moderate or greater degree in children born in the UK's Trent health region between 1985 and 1993. Based on the birth cohorts for 1985–1990, the prevalence of moderate to profound congenital permanent bilateral hearing impairment was 1.12 (95% CI 1.01–1.23) per 1000 live births as shown in Table 8.2. Acquired impairment was estimated at 0.21 per 1000. Prevalence is presented per 100 000 for ease of interpretation.

In a later study Fortnum and colleagues[11] reported prevalence rises from 0.91 per 1000 (95% CI 0.85–0.98) for the 3-year-old cohort to 1.65 per 1000 (95% CI 1.62–1.68) for the 9-year-old cohort, where it levelled off. The authors conclude that there are more late-onset and progressive permanent childhood hearing impairments than previously suspected. However, this prevalence was arrived at by including an adjustment for under-reporting based on data for the relatively small subgroup that had received cochlear implants. To date there are no longitudinal population studies that confirm this rise in prevalence. More recently Watkin and Baldwin[12] have shown a prevalence of 1.51 (95% CI 1.11–1.92)/1000 at the end of the first year in primary school (i.e. at age 6 years). Some of the children in their study had moved from countries outside the UK without newborn hearing screening and four had acquired a PCHI following meningitis. For Australian children Ching et al.[13] reported a similar prevalence of 1.57/1000 at age 16 years.

Irrespective of the true increase in prevalence over childhood these data support the use of newborn hearing

TABLE 8.2 Prevalence of PCHI[10]

	Severity (dB HL)	Prevalence per 100 000	95% CI
Congenital	40–69 (moderate)	64	56–73
	70–94 (severe)	23	19–29
	≥95 (profound)	24	20–30
Acquired	40–69 (moderate)	9	7–12
	70–94 (severe)	5	3–8
	≥95 (profound)	7	5–10

screening for the identification of the 1.12 (or thereabouts) congenital cases per 1000 births.

Risk factors

Risk factors for permanent congenital hearing loss are well established (Joint Committee on Infant Hearing, JCIH).[14] Davis and Wood[15] showed that babies admitted to a neonatal intensive care unit for more than 48 hours were 10.2 (95% CI 4.4–23.7) times more likely to have a permanent hearing loss (greater than 50 dBHL in this study) than those who did not undergo intensive care. Fortnum and Davis[10] showed that prevalence was increased 14-fold for children with a family history of early permanent childhood deafness. Babies with craniofacial anomalies associated with hearing impairment (e.g. cleft palate) are also at high risk for hearing loss. The large-scale Wessex study[16] reported that, of 25 000 newborns screened, 8.1% fulfilled high-risk criteria. The three major risk factors are:

- history of treatment in a neonatal intensive care unit (NICU) or special care baby unit (SCBU) for more than 48 hours
- family history of early childhood deafness
- craniofacial anomaly (e.g. cleft palate) associated with hearing impairment.

About 60% of congenital bilateral permanent hearing impairment of moderate degree or greater is associated with one or more of these three risk factors, in the proportions 29.3% NICU, 26.7% family history and 3.9% craniofacial anomaly.

Acquired and late-onset permanent bilateral hearing impairment

Acquired hearing impairment is one which, on the basis of case history, was not considered to be present and detectable using appropriate tests at or very soon after birth. Meningitis is the most common causes of acquired hearing impairment in children.[5] There remains a lack of evidence about the prevalence of progressive or late-onset impairments. Any newborn hearing screening programme will, of course, not identify these cases; other means of finding them are required.

Unilateral permanent hearing loss

Previous studies have suggested a prevalence of around 1 per 1000 in school-age children for unilateral impairment although prior to newborn hearing screening it was difficult to estimate how much of this was congenital. In the Newborn Hearing Screening Programme (NHSP) in England all babies that are screen positive, whether unilaterally or bilaterally, are referred for immediate follow-up. The rationale for this is to increase the sensitivity for bilateral PCHI rather than to identify unilateral PCHI per se. However, this has provided data on the prevalence of unilateral PCHI at 0.61 per 1000 screened.[17, 18] Such early identification does lead to issues about optimal management of unilateral PCHI.[19]

Mild hearing loss

Prevalence of mild hearing loss has been difficult to ascertain. Estimates based on clinical populations are biased as those with difficulties arising from a mild loss present to clinical services whereas those not experiencing difficulty do not. Hence population data are needed to estimate prevalence. Hall et al.[20] assessed hearing in children at age 7, 9 and 11 years as part of the ALSPAC (Avon Longitudinal Study of Parents and Children) study. They reported on prevalence of mild PCHI on the basis of consistent findings at all three test occasions. This methodology reduced the likelihood of a one-off assessment in a child with normal hearing but poor concentration being recorded as a case of mild PCHI. They found a prevalence of 0.4% for mild bilateral sensorineural hearing loss and 0.1% for bilateral high-frequency hearing loss giving an overall prevalence of 0.5% (CI 0.4, 0.8) at age 11 years. This is lower than commonly reported estimates from the USA[21] but similar to estimates from Australia.[22]

Auditory neuropathy spectrum disorder

Auditory neuropathy spectrum disorder (ANSD) is the label applied to clinical audiological test findings that indicate normal outer hair cell function as evidenced by the presence of otoacoustic emissions (OAEs) and/or the cochlear microphonic response and absent or severely abnormal auditory brainstem response (ABR). In earlier literature this was termed auditory neuropathy (AN); the new terminology was adopted in 2008.[23] This combination of test results suggests relatively normal activity in the outer hair cells but disruption of transmission at some point from the inner hair cells along the neural pathway to the brainstem. In some cases, neural firing may be occurring but with a lack of synchrony, so that no clear ABR is recordable. In some cases dys-synchrony may arise due to delayed maturation or myelination of the auditory pathway. The true prevalence of ANSD is not yet determined. It has been reported that up to 10% of all children with confirmed PCHI have auditory neuropathy. It is a condition found predominantly in the NICU population and it is considered relatively rare in the well-baby population.[23]

Temporary childhood hearing impairment

Temporary childhood hearing impairment due to otitis media with effusion (OME) is extremely common, with a point prevalence of 20% and a period prevalence in the under 5-year-olds of 80%.[4] The major risk factors are season, passive smoking, bottle-feeding, upper respiratory tract infections, admission to NICU as a newborn, day care and siblings having had OME. Refinement of risk factor analyses has indicated season, passive smoking, siblings having had OME and snoring and

mouth-breathing as the best indicators for persistence.[24] The TARGET (Trials of Alternative Regimens in Glue Ear Treatment) studies indicate effects of persistent OME on hearing difficulties, speech/language delay, disturbed sleep patterns, behaviour and (consequent on these) parental and child quality of life (see Chapter 13, Otitis media with effusion).[24]

THE RATIONALE POSITIVE FOR NEWBORN HEARING SCREENING

In this section, we will consider newborn screening mainly with respect to PCHI of moderate to profound degree.

The critical review (1997) of newborn hearing screening carried out as part of the UK's Health Technology Assessment programme[5] reviewed the evidence on the epidemiology, age at identification and intervention for PCHI, the performance of screens and services that were in place at the time and views of parents and appraised the options for detection of PCHI. The review concluded by recommending the introduction of universal newborn hearing screening for PCHI of moderate or worse degree in the better ear. Below is a brief summary of some of the evidence.

Outcomes

There is good evidence that outcomes in a number of domains are affected by bilateral moderate to profound PCHI. In most cases this is a severity-dependent effect, with greater effects for more severe impairments; there are, however, very great individual differences, with some children performing at levels appropriate to their age and others performing very poorly. These differences are not always a function of severity but will be a result of a range of intrinsic and extrinsic factors. One such factor is the age at identification, as well as habilitative support provided. The evidence of compromised outcomes associated with congenital PCHI comes from studies looking at communication skills,[25] literacy,[26] behaviour,[27] educational achievement,[28] mental health, [29] family dynamics[30] and quality of life.[27]

Age of identification

Prior to the introduction of universal newborn hearing screening the UK had a universal 8-month screen for childhood hearing impairment carried out by health visitors in community clinic settings and known as the health visitor distraction test (HVDT). With the introduction of newborn hearing screening this has been phased out; there is good evidence that it had poor sensitivity, poor specificity, high refer rate, low yield and was not cost-effective in terms of cost per case found.[5] The retrospective study of permanent childhood hearing impairment greater than or equal to 40 dBHL in children born between 1985 and 1993 and resident in Trent health region showed that the median ages at referral, confirmation of the impairment, prescription of hearing aids and fitting of hearing aids were, respectively, 10.4, 18.1, 24.4 and 26.3 months.[10] While much of the delay was clearly due to delays in the assessment process after referral, nonetheless the median age of screen referral for children with congenital hearing loss was little short of 1 year.

Benefits of early identification and intervention

There have been many observational studies that have reported benefits from earlier identification and intervention for PCHI[31, 32] but no true RCTs that address the question of whether universal newborn hearing screening (UNHS) results in earlier identification of PCHI, earlier intervention and improved outcomes. The only quasi RCT of the effect of newborn hearing screening on age at identification of PCHI and outcomes is the Wessex trial.[33] This study showed that birth during periods of UNHS was associated with confirmation of PCHI by 9 months of age and in turn this was associated with better receptive language scores but not with better speech at age 8 years.[33, 34] In 2008 the UNHS Task Force concluded that infants identified with PCHI through universal newborn screening have earlier referral, diagnosis and treatment than those identified by other means.[35] They concluded that the data from studies on language outcomes at school age strengthen the case for newborn screening but caution that effective methods of referral, follow-up and treatment are needed to maximize the effectiveness of newborn screening. Since then two population studies have confirmed that UNHS results in earlier identification and intervention and improved outcomes at age 3–5 years[36] and 7–8 years.[37] A further study found outcomes at age 3 years to be only weakly related to age at hearing aid fitting but for cochlear implant users the age at switch-on was significantly associated with better outcomes.[38]

The evidence around mild PCHI is equivocal. In a population study to determine the prevalence and effects of slight/mild sensorineural hearing loss in school children Wake et al.[22] concluded there was no strong evidence for adverse effects on language, reading, behaviour or health-related quality of life in children who are otherwise healthy and of normal intelligence. They did caution that further research is necessary to determine whether children with bilateral PCHI at the upper end of the slight/mild range experience adverse effects at the population level and, if so, whether they might gain more benefit than harm from systematic intervention. However, the optimal form of systematic intervention, including the role and benefits of amplification, remains to be determined.

Assessment and management

Some aspects of audiological assessment are easier in the first few months of life: for example, electrophysiological tests such as the auditory brainstem response, and habilitative procedures such as real ear measurements for hearing aid fittings can more readily be carried out during periods

of natural sleep. Perhaps more importantly, the earlier that parents and services know about the child's hearing impairment, the earlier decisions can be made about management including fitting of appropriate hearing aids, referral for cochlear implant, choice of communication methodology and provision of family support. In order to realize these advantages, screening and assessment must be viewed as the initial steps in a seamless family- and child-centred service with a multidisciplinary focus.

Costs

Bamford et al.[17] compared the NHS costs of NHSP (newborn) and HVDT (at 8 months of age) and concluded that NHSP appears to be a cost-effective strategy for hearing screening when compared to HVDT screening.

Cost-effectiveness

It has been argued that UNHS will have paid for itself within 10 years in terms of the long-term savings made in special education and social interventions. However, in a systematic review of cost-effectiveness Colgan et al.[39] identified only one study that found that UNHS could be cost-effective if early intervention leads to a substantial reduction in future treatment costs and productivity losses. Longitudinal data do not yet exist.

Parental wishes

Parents' views on the desirability and timing of newborn hearing screening received some attention in the literature prior to the widespread introduction of newborn hearing screening. Surveys show that around 80–90% of parents of children with permanent hearing impairment would have wanted it for their children if it had been available to them when their child was born.[40] It is also known that early identification tends to avoid the parental anxiety and anger that may be associated with delayed detection.[40, 41] Newborn hearing screening is widely accepted; data for the English programme show that less than 0.1% of families decline the screen.[18]

NEWBORN HEARING SCREENING

Case definition

While many North American screening programmes[42, 43] include babies with permanent mild and unilateral hearing impairments in their target group, the Newborn Hearing Screening Programme in England aims to identify all children with a moderate–profound PCHI in the better hearing ear.[17] As a by-product, the screen will also identify a number of babies who have unilateral and in some cases mild permanent hearing impairments, as well as temporary hearing impairments. The consequences of delay in identification are not well established in these infants, and optimal management is not clearly known. However, this is lack of evidence for effects rather than evidence of no effects, and research is needed to identify best practice for the early management of congenital permanent mild and unilateral hearing impairment as well as early management for temporary hearing impairments.

Current screening tests

The tests available for newborn hearing screening are automated otoacoustic emissions (AOAEs) using either transient or distortion product otoacoustic emissions or automated auditory brainstem response (AABR). Otoacoustic emissions reflect the activity in the outer hair cells of the cochlea, while AABR measures the neural response from the brainstem. Both types of test are available in portable hand-held screening instruments that employ automated detection algorithms to determine the presence or absence of a response and thus screening staff are not required to make any judgements about the response. Most screening programmes use a two-stage protocol (either OAE followed by AABR if required or two-stage AABR). The OAE is quick, minimally invasive and consumable costs are relatively low compared with AABR. The disadvantages are that it can be affected by the presence of fluid/debris in the outer or middle ear and will also miss neonates with auditory neuropathy. However, auditory neuropathy is predominantly found in the NICU/SCBU population and thus AABR is the method of choice in the NICU/SCBU population.

In the English NHSP screening is carried out using standard techniques and protocols[44, 45] and with equipment that has been approved for use within the programme. There are separate protocols for well babies and babies who have spent 48 hours or more in NICU/SCBU.

Well babies follow a two-stage two-technology protocol; the first stage is a transient AOAE screen, with a maximum of two attempts, followed by an AABR screen if required. A pass in both ears using AOAE, or a pass in both ears on AABR, constitutes an overall screen pass. **Babies cared for in NICU or SCBU for more than 48 hours** undergo a transient AOAE screen and an AABR screen. Those that fail the AABR screen in one or both ears are considered to be screen referrals and are referred for audiological assessment. Babies that pass the AABR screen in both ears and fail the AOAE screen in both ears are included in the risk-factor group and receive a follow-up at 8 months.

The most commonly used model in the English NHSP is a hospital-based screen employing a team of dedicated screeners performing the screening tests on newborns in the maternity unit before discharge. This is backed up by a recall clinic for the babies missed by the initial screen. In some areas a community-based screening model is used for well babies, with screening performed in the home or at local clinics.

Newborn hearing screening is also implemented in Wales, Scotland and Northern Ireland. These programmes also fall under the remit of the UK NSC. The details of their implementations differ in some respects from the English programme. Details can be found via the NSC website.[1]

High-risk screening

The high proportion of cases with risk factors led, in the early 1990s, to the widespread introduction of high-risk or targeted newborn screening in which attempts were made to screen all those babies (around 10% of the birth cohort) with risk factors, in order to achieve early identification for the 60% of true cases of congenital permanent impairment. However, in practice there are a number of difficulties with high-risk newborn hearing screening. The use of the family history risk factor is difficult to implement effectively[46] and thus the proportion of the target population identified by at risk screening was rarely above 40%.[5] Barker et al.[47] carried out a population audit of the effectiveness of stand-alone NICU screening compared with NICU screening as part of a universal screen and showed better performance in the latter case as measured by screening coverage, age of detection, loss to follow-up and positive predictive value of a refer result. More importantly, some 40–50% of babies born with permanent hearing loss demonstrate no risk factors. Numerous studies agree that around half of all affected infants have no risk factors at birth and thus would be missed by even the best-performing high-risk newborn hearing screening.[5]

Performance of universal newborn hearing screening

The NHSP in England was fully implemented in April 2006. Since then coverage has gradually improved and for the 2015/16 birth cohort 98.1% of babies completed screening by 4 weeks corrected age and 99.2% by 3 months. The refer rate has been relatively constant at 2.5% with 0.5% referring bilaterally. The yield for bilateral PCHI has been shown to be 1.01/1000 and the median age of identification for those screened by the programme is currently around 7 weeks.[18]

Parental anxiety

The prospect of the parental anxiety that might be engendered as a result of newborn hearing screening and in particular around false-positive results had been a cause for concern prior to the implementation of the screen. During implementation the NHSP in England developed a number of processes for ensuring high levels of information for mothers/parents, including a national screener-training programme, training and information sessions for other professionals, plain English information leaflets and DVDs for parents and informed parental consent to the screen. The detailed evaluation of Phase One of the English programme[17] indicated that, although referral for diagnostic tests has a small but significant effect on mothers' emotional well-being in the first 3 weeks after screening, the effect is below the cut-off for clinical concern. This small but significant emotional distress following recall for diagnostic tests after the screening is no longer evident at 6 months. The evaluation further concluded that ensuring good knowledge of possible reasons for referral seems to be protective against anxiety and newborn hearing screening does not cause more emotional distress than a test conducted some months later in infancy.[17] In the years since full implementation of the newborn screen in England parental anxiety has not emerged as a significant cause for concern.

Lost to follow-up

Lost to follow-up is an important consideration; there is little point in running a screening programme if the families of screen-positive babies are not willing to engage with diagnostic services and early intervention programmes. In the United States only slightly more than half of the infants who refer on newborn hearing screening receive follow-up.[48] In the English screening programme follow-up rates are much better; 87% of screen referrals have entered follow-up by 4 weeks and 95% by 6 months of age.[18, 49] Clearly there is a different context with services free at the point of use and a national programme and information system to track babies through screening and follow-up and record audiology results.

Quality assurance

There is an ethical duty within a screening programme to ensure not only a good quality screening service but also that good quality follow-up services are in place. The NHSP in England developed quality standards that include the screening pathway but also the follow-on diagnostic, medical, habilitation, early intervention and family support services.[50] These standards have been used as the basis for a national quality assurance programme. The quality and effectiveness of audiology services responsible for the electrophysiological assessment for babies that refer from newborn screening is pivotal to achieving early identification and intervention. Rigorous protocols and guidelines for these early assessments have been extensively developed alongside the implementation of the screening programme.[44]

THE SCHOOL-ENTRY SCREEN

Although there is a long history of school-entry hearing screening in the UK dating back to the 1950s, there has been little systematic evaluation of the benefits and there remains confusion about its aims and definition of the target condition. Apart from referring children with progressive and acquired permanent hearing loss that have not been picked up by parental observation and responsive services, the school-entry screen also has the potential to identify children with mild and unilateral hearing loss, as well as high-frequency hearing loss and other hearing losses with unusual configurations.

A Health Technology Assessment (HTA) review in 2007[51] found that a school-entry hearing screening is widely implemented, coverage is around 90% (in state schools), referral rates are high (8%), methods and referral criteria are highly variable and there is poor recording of data and little audit or quality assurance. The review concluded that, while screening for PCHI at school entry meets all but three of the requirements for

a screening programme, screening for temporary hearing impairment fails to meet at least six.

The current NSC policy acknowledges that, with the introduction of newborn screening, most cases will be identified before school entry; however, there will be some cases that were missed or have developed after the test. The current recommendation is that screening for hearing impairment in school-age children should continue while further research is undertaken.[1]

SURVEILLANCE

Surveillance for childhood hearing impairment is of considerable importance:

1. Newborn hearing screens will not find all those with preschool permanent hearing loss because of acquired, late-onset and progressive hearing impairment.
2. Any screening programme will miss some true cases.
3. Children with mild hearing loss and some with high-frequency hearing loss will not be identified by the screen.
4. Infants and children move in from countries where newborn hearing screening is not available.
5. Surveillance is a more justifiable approach to identification of children with persistent OME than a screening programme.

In an effort to identify children in category 1 above, many newborn hearing screening programmes have historically adopted regimes of targeted surveillance for babies who pass the screen and have certain risk factors. More recently, some programmes have questioned whether this is a useful service model.[52, 53] A recent analysis of data from English NHSP[54] showed that much of this risk factor-based surveillance is not effective and is now only recommended for babies that pass the screen with the following risk factors:

- syndrome (other than Down) associated with a hearing loss
- NICU with refer in both ears at OAE and pass in both ears at AABR
- craniofacial anomaly
- Down syndrome
- congenital infection.

Audiological assessment should always be carried out following recovery from meningitis, extracorporeal membrane oxygenation (ECMO), skull fracture and hyperbilirubinaemia.[55] Routine audiological monitoring should be offered to specific groups of children with a high risk of otitis media with effusion including children with Down syndrome and cleft lip and palate.[56, 57] Surveillance policies should encourage services to be highly responsive to parental or professional concern about a child's hearing or their development of auditory, vocal or communicative behaviour; where concern is identified, an age-appropriate audiological assessment should be carried out. The importance of ongoing surveillance by health visitors, family doctors, community health teams, as well as parents (reinforced by appropriate checklists such as those given to parents shortly after the birth of their child), should not be underestimated.

Otitis media with effusion has a high prevalence between 1 and 7 years of age. Screening for either the pathology or the consequent hearing impairment fails to meet the criteria for screening programmes outlined above because of its fluctuating nature, high remission rate and uncertainties over treatment.[58, 59] However, it can have an important impact on children's lives and development in persistent cases. Some sort of surveillance system needs therefore to be in place for identifying and intervening with those 5–10% of cases that have OME with a persistence or severity likely to interfere with development. It has been shown that the use by family doctors of a simple checklist and a training video significantly improves the positive predictive value of their referrals.[24]

FUTURE RESEARCH

- More evidence is needed on the medium- and long-term outcomes for children identified with PCHI and on the predictors for better outcomes.
- Further research is needed concerning the prevalence, aetiology, outcomes, diagnostic and habilitative options for children with auditory neuropathy spectrum disorder.
- Currently, some children with mild and unilateral hearing impairment will be identified as a by-product of newborn hearing screening for permanent bilateral hearing impairment of ≥40 dB HL. More research is needed about the prevalence, effects, outcomes and habilitative options for these children.
- There is evidence to show that progressive and acquired permanent childhood hearing impairment is more prevalent than previously thought. Confirmatory population-based prevalence data are needed together with continued assessment of the evidence on the risk factors to inform surveillance programmes.
- The school-entry screen requires a more extensive evidence base to enable evaluation of its effectiveness.

KEY EVIDENCE

- At least 1 in 1000 children is born with permanent bilateral hearing impairment ≥40 dB HL.
- If permanent bilateral congenital hearing impairment is identified before 6 months of age and habilitation started soon thereafter, the adverse effects are lessened.
- The prevalence of permanent bilateral hearing impairment ≥40 dB HL increases through childhood although the final prevalence figure is not yet certain; parents and professionals must continue to be appraised of this and surveillance systems and responsive services must be in place.
- Newborn hearing screening of all babies is the most cost-effective method of delivering early identification of congenital permanent hearing impairment of at least moderate or greater degree.
- More evidence is required on the outcomes for children with permanent mild or unilateral hearing impairment, and on alternative approaches to management.
- The evidence for school-entry screening is equivocal.
- Identification of persistent OME cases depends upon good surveillance systems in primary care and responsive services.

KEY POINTS

- Newborn hearing screening of all babies is the most effective and cost-effective way to identify congenital hearing loss.
- Audiology and screening services must work together to ensure rapid follow-up of screen referrals. This facilitates accurate audiological assessment. Such rapid follow-up, together with good-quality information, minimizes family anxiety.
- Audiology services must maintain and develop expertise in early audiological assessment techniques to enable early confirmation (or otherwise) of PCHI in babies referred from newborn hearing screening.
- Good quality services for true-positive cases based upon informed choices for parents are central to screening programmes at any age, but particularly for newborn screening.
- Management of true-positive cases involves close cooperation between health, education and social services.
- A surveillance programme must be in place to help identify late-onset and acquired hearing losses, backed up by fast responsive services.
- Parents and professionals in primary care need to be alert to the presence of persistent OME in some children.

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CHAPTER 9

HEARING TESTS IN CHILDREN

Glynnis Parker

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: audiometry/child and hearing test/child. Further information was accessed on the websites of the British Society of Audiology (BSA) (http://www.thebsa.org.uk/) and the American Speech-Language-Hearing Association (ASHA) (http://www.asha.org/).

INTRODUCTION

It is essential that suspected hearing loss in young children is promptly investigated. Accurate assessment of hearing is fundamental to diagnosis, investigation and rehabilitation. The techniques applicable to adults and older children are often inappropriate for the young child and for the older child or adult with special needs, particularly learning disability. Skilled testing by trained personnel in a suitable test environment is essential. The focus of this chapter is on those tests that require skilled observation and recording of the child's 'functional' responses to speech or 'non-speech' sound stimuli – often referred to as behavioural hearing assessments. The more complex evaluations utilized for pre- and post-assessment of children undergoing cochlear implantation are explored elsewhere (Chapter 11).

Effective assessment includes involving the family in a culturally and linguistically appropriate manner, providing a clear, sensitive explanation of the procedures and outcomes, supported by written information as available. A thorough assessment may require multiple sessions.

ELECTROPHYSIOLOGICAL TESTING

Key developmental age: 0–6 months, up to adult if appropriate

Electrophysiological techniques including otoacoustic emission (OAE), auditory brainstem response (ABR) and cortical evoked response audiometry (CERA) are discussed in Chapter 8, Hearing screening and surveillance, and Chapter 52, Evoked measurement of auditory sensitivity. These methods are mainly employed in newborn screening (see Chapter 8) and diagnostic testing of infants in the first 6 months.[1–4] They can also prove of value in children of any age when behavioural testing has failed to produce reliable results, in particular those with severe learning or communication difficulties.[5] Accurate assessment may require sedation or general anaesthesia. Electrophysiological techniques are also used to confirm hearing thresholds, for example, prior to cochlear implantation or where non-organic factors are suspected. While electrophysiological testing has the advantage of being objective in terms of the child's response, behavioural and

speech discrimination testing remain the only functional measures for assessing the complete auditory system.

BEHAVIOURAL OBSERVATION AUDIOMETRY

Key developmental age: 0–6 months

In behavioural observation audiometry (BOA), changes in activity are observed in response to a sound stimulus. Response behaviours include eye widening, eye blink (auropalpebral reflex), alteration in sucking response, arousal from sleep, startle or shudder of the body or definite movement of the arms, legs or body. From 4–7 months, lateral inclination of the head towards the sound or a listening attitude or stilling may be observed. The test is usually performed with the child cradled in the parent's lap or in an infant seat. The child's attention may be lightly engaged in front by a distractor. The sound stimulus may be presented for <2 seconds, in a horizontal plane, 15 cm from the child's ear, out of peripheral vision, or delivered via insert earphones. The distractor observes evidence of a response. A range of sound stimuli may be employed, including voice or noisemakers but ideally calibrated narrow-band, warble tones or ling sounds.[6,7]

Reliability as a diagnostic test is obviously a concern. A wide variability in judgement of response between testers due to misinterpretation of random movements and a tendency to underestimate hearing thresholds has been demonstrated.[8] Attempts have been made to reduce observer bias by use of video recording of the procedure and scoring the playback without knowledge of the sound or no sound trials.[9]

The use of BOA in infants under 6 months has been largely superseded by the availability of electrophysiological techniques. However, soundfield BOA may be of particular value in the verification of aided responses in infants, or in infants with a diagnosis of auditory neuropathy spectrum disorder when ABR is a poor indicator of functional hearing levels (see Chapter 69, Auditory neuropathy spectrum disorder and retrocochlear disorders in adults and children). It has the merit of allowing parents to participate in the assessment and witness their child's responses, leading to better understanding and acceptance of their child's hearing loss. BOA may have a continuing role in the assessment of older children with learning disabilities who have not reached an appropriate developmental stage for other means of assessment.

VISUAL REINFORCEMENT AUDIOMETRY

Key developmental age: 5-36 months

Visual reinforcement audiometry (VRA) incorporates the principle that young children can be trained by operant conditioning to produce a localizing turn to a visual stimulus in response to a sound stimulus. A technique of conditioned orientation reflex (COR) audiometry was initially described by Suzuki and Ogiba[10] and was further developed by Liden and Kankkunen[11] who introduced the term 'visual reinforcement audiometry'. Further developments and modifications to the technique have been described.[12,13] VRA is now established as a standard technique within the test battery for hearing assessment in preschool children and is generally suitable for infants once they have reached the developmental stage of being able to sit unsupported or with minimal support, i.e. at 5–7 months. VRA has largely replaced the use of the infant distraction test (see below) as it has become more widely available and has been demonstrated to generate more auditory-evoked head turns than an unrewarded sound stimulus and delays habituation so that the assessment is more likely to be completed.[14] The method is described with reference to the British Society of Audiology: Recommended procedure – Visual Reinforcement Audiology[15] and Widen et al.[16]

Test arrangement

The test room should be sound-treated to ensure low levels of ambient noise (ISO 8253),[17] which should be verified using a sound level meter. It should be adequately sized (recommended minimum of 6 m × 4 m), ideally with the ability to dim the lighting to permit enhancement of the illuminated vision reward. It may be partitioned to provide an observation area with a one-way window, with access to a communication system between the rooms, such as a radio link. A suitable arrangement is shown in **Figure 9.1**. If, however, this facility is not available, it is still possible to perform the test within one room, provided the tester operating the audiometer minimizes the distraction to the child and does not provide any additional clues. The child is seated on the parent's lap or on an infant seat or chair in front of a low table, with the parent seated slightly behind. A second tester may sit on the other side of the table or adjacent to the child to provide low-level play activity. For soundfield testing, the loudspeakers should be placed at 90° from the child and at the same height as the child's head at a distance of at least 1 m from the ear. Frequency-specific calibration of the sound signal from a test point equivalent to the child's head position is essential. Alternatively, a calibrated signal may be presented via insert earphones using foam tips or the child's own ear moulds, if available. This has the advantage of potentially providing more precise ear-specific response thresholds and even offers an opportunity to introduce masking by appropriate presentation of narrow-band noise in the contralateral ear. This is particularly valuable in amplification selection and setting.[18] A standard bone conductor may also be used in conjunction with VRA to differentiate between a conductive and sensorineural hearing loss.

Visual reinforcers are generally placed adjacent to or above each speaker. Facility should exist to move the reinforcer closer to the child to enhance reinforcement if indicated by visual ability or developmental status.

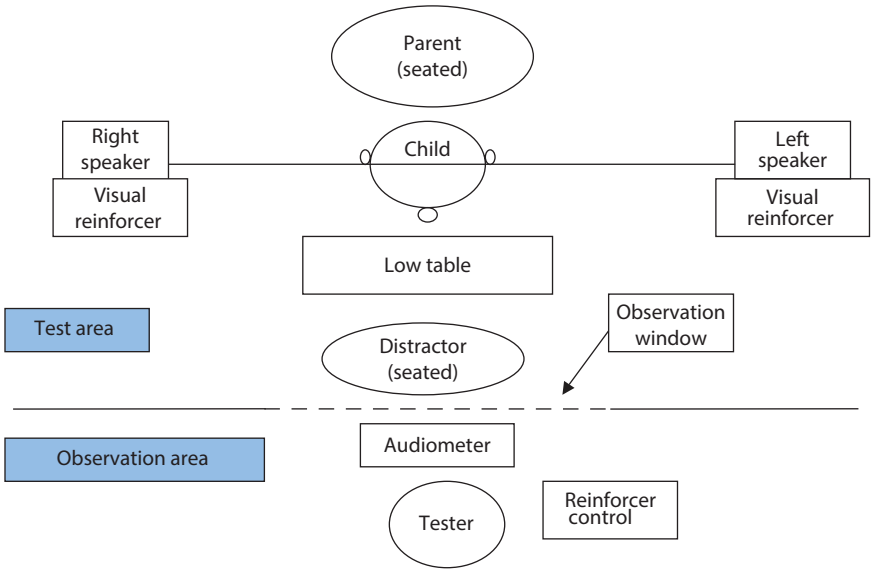

Figure 9.1 Test arrangement for visual reinforcement audiometry.

The reinforcer acts as a reward and therefore increasing the attractiveness or appeal to the child and introducing variety is likely to sustain interest and reduce habituation. Commercially available reinforcers include toys with eyes that light up and puppets in darkened glass cabinets which illuminate and dance. Monitors showing appropriate video displays can also be effective.[19, 20] The reinforcer is generally remotely activated by the tester as required.

Test method

Using the arrangement as described above, the first task must be to establish the conditioned response. Having drawn the child's attention to the front by gentle play activity on the table, a suprathreshold auditory signal should be presented concurrently with the visual reward. Appropriately calibrated frequency modulated (warble) tones, ling sounds or narrow-band noise (NBN) stimuli may be employed via soundfield, insert earphone, headphone or bone conductor, according to the clinical priority. For example, for a child with probable near-normal hearing, one might start with a 2 kHz warble tone at 60–70 dBHL, presented for 2–3 seconds. The child may turn to locate the sound (orientation response) and thereby view the activated reinforcer but, if necessary, the child's attention should be directed towards it. This sequence is repeated several times. The sound stimulus should then be presented alone and the reinforcer only activated after the child has produced an appropriate turning response. Praising the child and making it a game will further help to reinforce the response. If this can be reliably repeated two or three times, operant conditioning has been established. Children under 1 year or those with learning difficulties may take longer to successfully condition. If it appears that the initial auditory stimulus may be inadequate, this can be cautiously increased or a different frequency or vibrotactile stimulus used. NBN stimuli may be more effective in initially establishing the conditioned response,[21] but Thompson and Folsom[22] demonstrated that in VRA, unlike distraction testing, the complexity of the signal, including the bandwidth, had no effect on response rate once the child had been correctly conditioned.

Once the child has demonstrated successful conditioning, the aim is to establish the minimal response level (MRL) for each frequency, as prioritized by the clinical situation, bearing in mind that the child's cooperation may fail at any time. A typical order of stimulus presentation could be: 2 kHz – 500 Hz – 4 kHz – 1 kHz or 1 kHz – 4 kHz – 500 Hz – 2 kHz. Additional frequencies may be included if clinically relevant, for example 0.25 kHz, 3 kHz, 6 kHz, 8 kHz. A flexible descending/ascending (10 dB down, 5 dB up) principle, similar to that used in pure tone or play audiometry (see below), should be applied, although the increments and decrements in intensity (i.e. the steps up and down) may be increased to hone in on the response threshold. The duration of the signal is usually 2–3 seconds. One reliably obtained MRL is more valuable than a number of 'maybes'. Variable inter-trial intervals and 'no sound' control trials should be included to verify a true response and particular scrutiny is required in the event of frequent 'checking behaviour'.[23] If the child becomes bored and less responsive, it may be appropriate to recondition the child using suprathreshold stimuli and/or change the stimulus type or visual reward or, indeed, have a short break. Children generally respond well to praise and encouragement – the assessment should be a fun and enjoyable experience for the child and parent while maintaining objective accuracy. The outcome of each valid presentation and 'no sound' trial should be recorded in chart form, specifying the sound source, frequency range and intensity. A tick or a cross may be used to indicate whether a response was observed The MRL is regarded as the quietest level at which two out of three clear responses were recorded for each particular sound stimulus. The ability to localize the sound source correctly may be assessed, for example using a soundfield high- and low-frequency NBN

stimulus 30 dB above the MRL: difficulty with localization may indicate an asymmetric hearing loss although the converse does not necessarily apply.

Relevant observations which may affect the test reliability, such as alertness or cooperation of the child or subject-generated noise, should be recorded and taken into consideration when interpreting the results of the assessment. Responses recorded on soundfield testing are approximately +10 dB relative to adult thresholds and MRLs down to at least 25 dBHL on soundfield testing are generally regarded as compatible with satisfactory binaural hearing.[24, 25] Correction factors using insert earphones have been estimated for infants with normal hearing assessed by VRA relative to adult thresholds and are currently recommended as +15 dB at 0.5 kHz and 1 kHz and +5 dB at 2 kHz and 4 kHz.[15] Primus[26] found test–retest reliability to be good with 50% repeatability within 10 dB. Widen et al.[16] demonstrated that MRL for at least four frequencies were successfully recorded in more than 90% of over 3000 infants aged 8–12 months, tested using VRA.

THE DISTRACTION TEST

Key developmental age: 6–18 months

The test is based on the principle that the normal response observed when sound is presented to an infant is a head turn to locate the source of sound. The test is suitable at 6–18 months, corresponding to the stage when the child can sit erect unsupported and perform head turns in a horizontal plane. An appropriate allowance should be made for prematurity. Habituation is increasingly likely to occur after 12 months, although the technique may prove to be useful in older children with learning or communication difficulties where other methods have been unsuccessful.

The infant distraction test was first described by Ewing and Ewing in 1944,[27] but was subsequently modified by McCormick[28] who placed particular emphasis on the use of frequency-specific, calibrated sound stimuli. For many years the distraction test was used as a tool for screening for hearing impairment in infants around 7–9 months, but such programmes have generally been withdrawn in favour of electrophysiological screening in the newborn period[1, 2] (Chapter 8, Hearing screening and surveillance). The use of distraction testing by audiologists has also been largely discontinued in favour of VRA.[14] Nevertheless, it remains a valuable diagnostic technique when used by trained, experienced testers in appropriate settings when other methods are unavailable, unsuitable or unsuccessful. The test is described with reference to McCormick[29] and guidelines published by the British Society of Audiology.[30]

Test method

The test environment is similar to that used for VRA. Two testers are required, one to present the sound stimuli out of vision and the other to control the infant or child's attention in the forward direction (the distractor). The latter should be responsible for directing the test. The arrangement is shown in **Figure 9.2**. The child sits on the parent's knee, facing forward and erect, lightly supported around the waist. The distractor directs the attention of the child to a simple activity usually performed on a low table. Suitable examples include spinning a brightly coloured object, showing a small toy or blowing bubbles. In the classic distraction test described by McCormick,[29] the item is covered by the hands which maintain a fine attention control by moving the fingers slightly. The sound stimulus is presented by the second tester, half a second after the item is covered. The distractor observes the child's response.

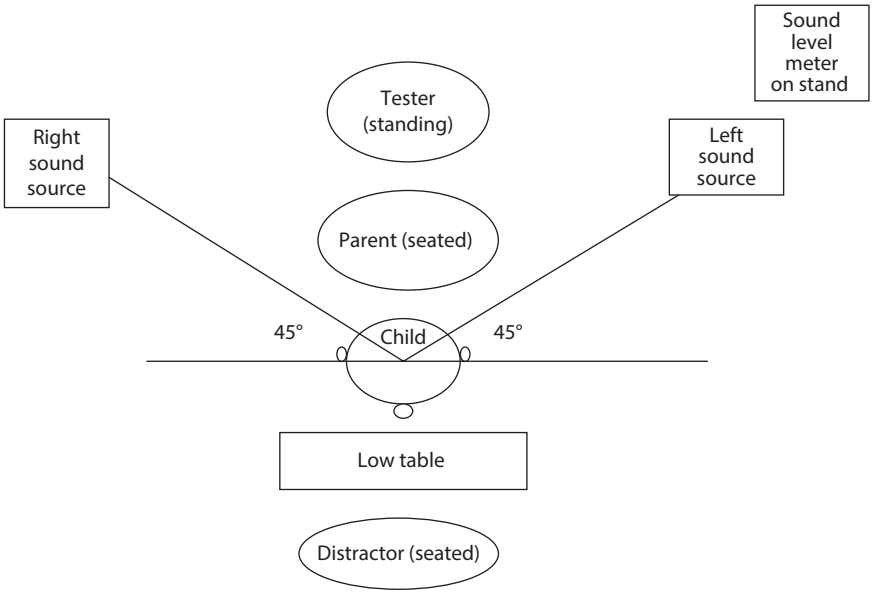

Figure 9.2 Test arrangement for the distraction test.

The second tester should be positioned strictly out of the child's visual field, which can be assumed to extend at least 90° to either side of the child's midline. The sound stimulus should be presented in the horizontal plane to the ears at an angle, set back 45° between 1 m and 15 cm from the child's ear. The shorter distance increases the head shadow effect, thereby increasing the sound stimulus on one side relative to the other. Evidence of asymmetric hearing levels may be indicated by a difference in response thresholds or difficulty in localizing the sound source. Particular care must be taken when presenting the sound close to the ear to avoid visual or tactile clues. The sound stimulus should continue up to 10 seconds if there is not an immediate response. During this interval, the distractor should maintain the fine attention control at the front until a response is observed.

The normal response expected is a full head turn in the direction of the sound. This may be rewarded by a smile or vocal praise or gentle touch from the second tester. Some warble tone generators incorporate a flashing light, which can be activated in response to the turn, providing an incentive to the child and thereby acting as a 'response reinforcer'. The child's attention should then be brought back to the front by the distractor.

A wide range of sound stimuli can be used to elicit a response, including voice (e.g. unforced 'S' = high frequency, or hum = low frequency), musical toys, calibrated high-frequency rattle, NBN or warble tones. Pure tones should be avoided due to the potential creation of standing waves, resulting in unpredictable sound levels. Responses to any sound stimulus may be valid, provided the intensity and the frequency spectrum, as delivered at the level of the ear, can be established. A sound level meter should be employed to check the intensity of the stimulus by accurately reproducing the sound and the distance from the ear. Although it has been demonstrated that infants are more likely to respond to wide-band sounds, this will inevitably provide less information regarding frequency-specific hearing as required for diagnosis and possible amplification prescription. Sound generators delivering calibrated narrow-band and frequency-modulated warble tones have been demonstrated to be effective at eliciting a response and are therefore generally preferred.[22]

Initially, a sound stimulus is presented which is anticipated to be likely to be suprathreshold, for example at 70 dB(A) in a child with probable normal hearing. A sound is then presented at the anticipated minimal response threshold, for example 30 dB(A). The intensity for sound-field testing is generally measured on the dB(A) scale, but this can be converted to dBHL if required, particularly for hearing aid prescription fitting – in practice the only correction factor required to the nearest 5 dB is +5 dB at 4 kHz.[17, 30]

There is no prescribed order for frequency and intensity of sound presentations. The number of reliable responses elicited by distraction testing may be limited, particularly in children over 12 months who may habituate to the test. It is therefore important to prioritize and focus on those thresholds which would be most valuable for each clinical situation but normally aim to include high-, mid- and low-frequency information. This, however, may need to be balanced against the benefit of varying the order and side of presentation simply to sustain the child's interest.

Variable intervals between presentations and control 'no sound' trials are essential for the validation of response thresholds in a distraction test and a scoring system should be employed in the same manner as for VRA (see above). Tactics such as increasing the interest of the distracting activity and/or maintaining that activity while the sound/no sound is presented may avoid 'clueing in' the child. This may be particularly helpful in children over 1 year. Evidence of visual, tactile or even olfactory clues must also be considered and addressed. The MRL is regarded as the quietest level at which two out of three clear responses are recorded for each particular sound stimulus. The MRL for distraction testing may be worse than for VRA and clinical judgement is required in interpreting the results.[14] Other observations such as the ability to localize the sound source correctly or any concerns about the test reliability should also be recorded.

TEST METHOD PITFALLS IN BOA, VRA AND DISTRACTION TESTING

Table 9.1 lists the most commonly encountered pitfalls in BOA, VRA and distraction testing and possible measures to avoid them.

PERFORMANCE TESTING (PLAY AUDIOMETRY)

Key developmental age: 2–5 years

The performance test was first described by Ewing and Ewing[27] as a transitional technique suitable for children from 2.5 years and in some cases younger, until cooperation with pure tone audiometry can be achieved. It follows the simple principle that the child is conditioned to wait for a sound and then to respond with a play activity. The test method is described with reference to McCormick.[29]

Test method

The child should be seated on a low chair adjacent to the parent in an uncluttered room with low levels of ambient noise.[17] A toy is placed on a low table in front of the child (Figure 9.3). Toys which involve a simple repetitive activity are most suitable, such as the classic 'men in a boat', balls on sticks, or pegs in a board. The conditioning sequence starts with the tester engaging the child's attention by holding the response item (e.g. the wooden man) poised waiting in front of the child. After a few seconds, a suprathreshold sound stimulus is presented and the tester responds by an appropriate activity, such as placing the man in the boat. This sequence is repeated several times,

TABLE 9.1 Pitfalls encountered in behavioural observation audiometry, visual reinforcement audiometry and distraction testing

Pitfalls	Avoidance measures
Attempting conditioning to sub threshold stimuli	Cautiously increase intensity of stimulus until a response is elicited
Visual, tactile, olfactory clues from parent, distractor or second tester	Critical observation of all parties 'No sound' control trials
'Checking' responses by child	Critical assessment of responses 'No sound' trials, if necessary take a break, or sustain distraction activity
Loss of interest in test, suprathreshold responses	Vary the sound stimulus Exchange roles of distractor or second tester Use broader band or more interesting sounds
Inaccurate estimation of frequency and intensity of stimulus	Use calibrated sound sources Measure accurately with sound level meter, trying to reproduce conditions
Extraneous noise, leading to false responses or only suprathreshold response	Use a sound-treated room with ambient noise <30 dB(A) Observe other auditory clues, e.g. clicking switch on warbler 'No sound' control trials

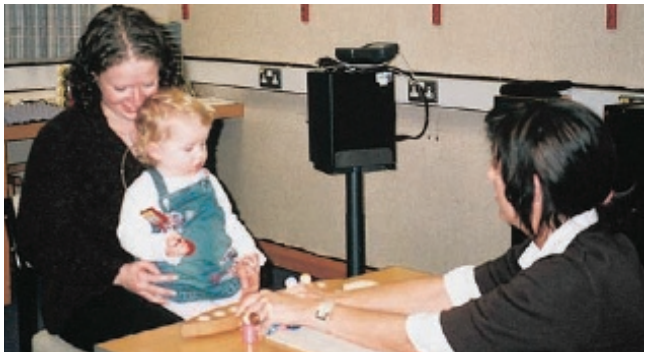

Figure 9.3 The performance test.

often supported by gestures such as a stop sign using the palm of the hand and a cupped hand to the ear to indicate listening. This has the advantage of avoiding dependence on spoken language. The child is then offered the response item and guided to wait and perform the task as shown. Vocal praise and possibly clapping should be used to reinforce a correct response. The number of repetitions required to successfully condition the child will depend on their age, developmental status and willingness to cooperate and in particular their ability to inhibit the response until the signal is detected. It may be necessary to increase the intensity of the signal or initiate conditioning using a vibrotactile stimulus.

Once the child has been successfully conditioned to perform the test without guidance, a flexible descending/ascending technique as described for pure tone audiometry (see Chapter 51, Psychoacoustic audiometry) can be applied to determine the MRL. While the MRL should be determined by a two correct responses out of three method, using the 10 dB down, 5 dB up technique, it may be appropriate to ascend and descend in larger steps to hone in on the threshold, as described for VRA (see above). The interval between presentations must be randomly varied to avoid a predictable rhythm. 'No sound' trials should be included. It may be necessary to reinstruct the child by guiding a few responses when the stimulus is changed or if the child appears to have lost concentration. It may also be necessary to introduce several changes of activity to sustain interest. This provides the tester with an opportunity to be adaptable and inventive and is part of the joy of audiology! Examples might include knocking the man off the table, flicking a small ball into a 'goal', or banging a drum. The aim is to be fun enough to motivate the child while being accurate enough to provide valid responses.

In the original description of the performance test, the signal used was a voiced 'go' (low frequency), or a sibilant 's' (high frequency).[27] When using voiced signals, it is essential that the face is totally outside the child's visual field and the mouth is shielded to prevent any awareness of air movement. The tester should therefore adopt a position similar to that described for distraction testing. Frequency-modulated warble tones with stimulus duration of 1–3 seconds are now the preferred option, providing low-, mid- and high-frequency-specific signals delivered by means of portable soundfield noise generators, loudspeakers, insert earphones (using the child's own ear moulds if available) or bone conductor, used in a similar arrangement to that described for VRA. The technique is particularly useful for recording aided soundfield responses. Whatever the signal, it is essential that the test conditions are reproduced accurately to calibrate the intensity delivered to the child's ear. The sequence of presentation should be determined by the clinical priority but would typically be 1 kHz–2 kHz–4 kHz–0.5 kHz then possibly 8 kHz, 0.25 kHz, 3 kHz and 6 kHz as indicated.

PURE TONE AUDIOMETRY

Key developmental age: 3 years onwards

The techniques employed in performance testing (play audiometry) naturally lead into pure tone audiometry as the child matures. This progression should be adapted to the individual child's ability and cooperation and to

the clinical priority. It may be possible, for example, to introduce a bone conductor before a child will tolerate headphones or, alternatively, a child who is accustomed to wearing hearing aids may comply with insert earphone audiometry via their ear moulds, as a progression from VRA. Insert earphones have the advantage of increasing transcranial attenuation reducing 'crossover' and of reducing the effect of ear canal collapse which may occur with supra-aural headphones. Again, it is important to sustain interest and concentration by the appropriate use of toys and praise.

The recommended procedures for pure tone audiometry[31] based on the Hughson and Westlake descending/ascending technique using 10/5 dB steps should be flexibility adapted (see Chapter 51, Psychoacoustic audiometry). There is no standard for the interpretation of results in children. Nielsen and Olsen[32] reported that it was possible to obtain at least six ear-specific air conduction thresholds from virtually 75% of 3-year-olds. An MRC multicentre otitis media study which examined a cohort of over 15 00 children found that there was only an improvement of 0.1 dB for bone conduction thresholds for each month of increase in age between 3 and 6 years. It was concluded that, by the age of 3 years, it should be possible to record hearing thresholds close to adult levels, if the child has conditioned adequately to the test.[33] The introduction of standard masking techniques, where appropriate, will depend on the child's cognitive developmental level and cooperation, but these may not be reliable until the age of 7 years.

AUDITORY SPEECH PERCEPTION TESTS

The ability to discriminate speech signals may be a valuable measure of functional hearing in children with normal to moderate degrees of impairment and is also increasingly used in the evaluation of more severely affected children supplied with hearing aids or cochlear implants. The test batteries developed for use in these latter situations are discussed elsewhere (see Chapter 51, Psychoacoustic audiometry). The tests described below represent a selection from a wide range available and are for use in more general clinical situations.

THE COOPERATIVE TEST

Linguistic developmental level: 18–30 months

The cooperative test is another test originally described by Ewing and Ewing[27] and requires the child to discriminate three different simple instructions, for instance having been handed a small toy, asked to 'give it to Mummy' or 'give it to teddy' or 'give it to baby'. Starting at a suprathreshold level, the voice is then dropped and visual clues removed by covering the mouth. A child with normal hearing may discriminate the instruction at 35–40 dB(A). This technique has been largely superseded by the more effective methods of assessing behavioural hearing thresholds such as VRA and by the more complex speech discrimination tests described below, but it may have some value if equipment and facilities are limited. It can obviously be adapted to suit different cultures and languages.

SPEECH DISCRIMINATION TESTS

Linguistic developmental level: 30 months onwards

A wide range of speech discrimination assessments are available and may be valuable in verifying hearing thresholds and in assessing the effectiveness of hearing aids or auditory implants.[34, 35] The choice of test will depend on the child's age, stage of linguistic development and home language and may be influenced by non-auditory factors such as access to language, specific language impairment and cognitive level.[36, 37] Several generations of toy and picture tests have been progressively developed and refined for the younger child including the Stycar test,[38] the Word Intelligibility by Picture Identification test (WIPI),[39] Northwestern University Children's Perception of Speech test (NU-CHIPS),[40] the Manchester picture test,[41] and the McCormick toy test,[42] which is widely used in the UK. This employs seven pairs of similar sounding nouns such as spoon/shoe or cup/duck, each represented by a small easily recognizable toy, placed on a table in front of the child in a quiet room, i.e. a closed-set assessment. Using live voice, the child is asked to 'show me the … spoon', etc. Having established an understanding, the voice level is dropped and visual clues removed by covering the mouth. The word discrimination threshold (WDT) is taken as the quietest level at which the child correctly identifies 80% of the toys including the paired consonants. For a child with normal hearing, this would be expected to occur at ≤40 dB(A). A digitized recorded version of the test is available which utilizes a small loudspeaker to deliver the instruction at variable intensities and this has been further developed to incorporate a scoring system using the ascending and descending principle to calculate the WDT, both in quiet and in the presence of a broadband noise signal. For children aged 2-5 years, a WDT at or less than 35 dB(A) in quiet is regarded as satisfactory, based on 71% correct responses for six reversals. The choice of words can be adapted for English as an additional language.[43, 44]

Further closed-set or 'forced-choice' speech test packages are available which examine more specific elements of consonant or vowel discrimination in quiet or in noise. In the Consonant Confusion Task (CCT)™, for example, the child is presented with nine sets of cards, each showing four pictures representing monosyllabic words containing the same vowel but different consonants such as cow/house/owl/mouse. The child is asked to point to the target word that they hear, presented at a calibrated level. Two of the four words in each set are repeated to reduce predictability. The percentage of correct responses can be calculated for each level and may be particularly valuable in verifying the effectiveness of a hearing aid programme.[45, 46] Other examples include the four alternative auditory feature (FAAF) test,[47] the imitative

test of speech pattern contrast perception (IMSPAC),[48] and the 'plurals test' which specifically assesses the ability to detect the word-final fricatives /s/ or /z/.[49]

Similar assessment tools are available in alternative languages.[50, 51]

Older children who have acquired appropriate linguistic skills, generally from around the age of 6–8 years may be compliant with formal speech audiometry, using open set tasks whereby they listen and repeat a word or sentence presented at a calibrated level in quiet or in noise to a single ear or binaurally. Original examples include the AB word list described by Arthur Boothroyd in 1968[52] and the BKB (Bamford-Kowal-Bench)[53] sentence list, which are widely used in children and adults and are described in Chapter 51, Psychoacoustic audiometry.

Monitoring tools using parental observation of auditory behaviour and language development are increasingly used to assess progress in children supplied with hearing aids and cochlear implants. Examples include LittlEARS® Auditory Questionnaire[54] for children under developmental age of 2 years and subsequently the Parents' Evaluation of Aural/Oral Performance in Children (PEACH)™ questionnaire.[55, 56]

HEARING ASSESSMENT IN CHILDREN WITH COMPLEX NEEDS

Approximately 30% of hearing-impaired children have an additional disability.[57] Children with global developmental delay have a particularly increased risk of hearing impairment and hearing assessment is therefore advocated for this group of children in addition to routine hearing screening.[58] However, this may be challenging and techniques must be appropriately adapted. For a child with complex needs, the test most suited to their developmental level rather than chronological age should be selected. Clear, simple demonstrations of conditioning tasks may require multiple repetitions to achieve understanding. In children with motor delay or physical disabilities, such as cerebral palsy, the required response must be tailored to the child's capability. In VRA, for example, it may be necessary to bring the visual reward closer and to accept an eye glance response. In distraction testing, a partial head turn, eye glide or stilling may be judged as an acceptable response provided it is reproducible and validated by 'no sound' trials. For performance testing and pure tone audiometry, the conditioning task may need to be modified, such as knocking a toy brick off a table with hands or feet, hitting a drum or observation of a reproducible body movement such as wriggling toes.

Visually impaired children are more likely to respond to familiar sounds or if the response is reinforced by a tactile reward such as puffs of air on the cheek.[59] The use of brightly illuminated reinforcers in a darkened room may facilitate VRA in the partially sighted.[15] Assessment of hearing in a child with autistic spectrum disorder may present a particular challenge, due to the characteristic self-directed behaviour and lack of shared attention, making interaction with the tester difficult, although the repetitive nature of performance testing may particularly appeal to some. Fear of the unfamiliar test room and staff may be addressed by building confidence over a number of visits. Pre-preparing the child by explanatory booklets or a personalized 'social story' may reduce the anxiety.[60, 61] Many children with autistic spectrum disorder have sensory processing issues resulting in sound sensitivity and care must be taken to provide reassurance and avoid distress.[62]

If the outcome of behavioural hearing assessment for a child with complex needs proves to be inconclusive, consideration should be given to objective electrophysiological measurement, which may require sedation or anaesthesia.[5]

BEST CLINICAL PRACTICE

- ✓ Be age-appropriate: use the test technique that is most suited to the child's age, developmental status and willingness or ability to cooperate.
- ✓ Be specific: know what you are testing. Calibrate the frequency and intensity of the sound stimulus.
- ✓ Be valid: reproducibility and use of 'no sound' trials are essential. Avoid other clues. Children can make good cheats.
- ✓ Be adaptable: non-standard techniques may be best in non-standard children.
- ✓ Be fun: children easily get bored and frightened. Their cooperation is required. Use toys and smiles – make it a game.

FUTURE RESEARCH

The only level 1 evidence and grade A recommendations cited in this chapter relate to the use of electrophysiological testing (ABR, OAE) for screening and diagnostic assessment in infants under 6 months of age.[1] Other test methods are essentially descriptive, having been progressively modified, based on expert experience and summarized in guidelines.[7, 15, 16, 30, 31, 35] While specific elements of the test protocols have been subjected to small-scale controlled studies,[12, 19–22, 43] the only large-scale studies available examine the feasibility of obtaining response thresholds using a test protocol, rather than its sensitivity or specificity.[16, 33] There is clearly a difficulty in performing blind controlled trials of obviously differing techniques. There are also no subject-specific definitive response thresholds available for comparison. Reliance is placed on intra- and inter-test/retest reproducibility, as an indication of accuracy.[8, 14, 16, 18, 23–26, 32, 36, 43, 54] Comparison of behavioural test response thresholds with subsequent pure tone audiometry thresholds cannot take account of fluctuating hearing levels during the intervening months or years.

There are therefore inherent challenges in conducting large-scale controlled trials. In the UK, emphasis has more recently been placed on establishing guidelines for good practice, promoting training and availability of equipment with the aim of improving equity of service.

KEY POINTS

- Accurate testing of hearing is essential in the diagnosis and management of childhood hearing loss.
- Testing and accurate assessment of the test results requires considerable skill and expertise.
- A 'menu' of tests is available depending on the child's age, the availability of expertise and the purpose of the test.
- More than one test method may be needed.
- Testing children with complex needs can be particularly challenging.

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FURTHER INFORMATION

American Speech-Language-Hearing Association (ASHA): http://www.asha.org/.
British Society of Audiology (BSA): http://www.thebsa.org.uk/.

CHAPTER 10

MANAGEMENT OF THE HEARING IMPAIRED CHILD

Chris H. Raine, Sue Archbold, Tony Sirimanna and Soumit Dasgupta

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: aetiology, deafness, hearing loss or hearing impairment, and child. The websites of the various associations shown in Box 10.1 are useful sources of information in this rapidly changing field.

INTRODUCTION

This chapter focuses on the general principles of the management of a child with stable or progressive sensorineural hearing loss including auditory neuropathy spectrum disorder (ANSD) (see Chapter 69, Auditory neuropathy spectrum disorder and retrocochlear disorders in adults and children).

Permanent childhood hearing impairment (PCHI) is defined as a confirmed permanent bilateral hearing impairment ≥40 dBHL (hearing level) averaged over the frequencies of 0.5, 1, 2 and 4 kHz in the better hearing ear. A PCHI can be conductive, sensorineural or mixed. The onset of hearing loss may be pre-natal, peri-natal or post-natal. The aetiology may be congenital or acquired.

The hearing loss may occur before (pre-lingual deafness) or after the child has acquired the ability to speak (post-lingual deafness). This distinction has important implications for education and management. Early identification and appropriate audiological, medical and educational intervention will help maximize the child's potential. Identifying and understanding the consequences of associated medical conditions, impairments and disabilities is also extremely important to provide the best opportunity for the child and the parents to make informed choices and plans for the future.

Earlier identification with universal newborn hearing screening (Chapter 8, Hearing screening and surveillance) is now practised in many developing -and most developed- countries. Improved audiological assessment techniques have provided a unique opportunity to confirm the exact nature and extent of the hearing loss within 8 weeks of birth, leading to very early habilitation with precise amplification and with diagnostic verification using well-developed and internationally

BOX 10.1

British Association of Paediatricians in Audiology www.bapa.uk.com[1]
British Association of Audiovestibular Physicians www.baap.org.uk[2]
British Society of Audiology http://www.thebsa.org.uk[3]
Genetics home reference http://ghr.nlm.nih.gov[4]
Hereditary hearing loss homepage http://hereditaryhearingloss.org[5]
NHS Modernising Children's Hearing Aid Service www.psych-sci.manchester.ac.uk/mchas[6]
NHS Newborn Hearing Screening Programme http://hearing.screening.nhs.uk[7]
The World Health Organization (WHO) www.who.int[8]
National Deaf Children's Society www.ndcs.org.uk[9]
British Association of Teachers of the Deaf www.batod.org.uk[10]

agreed techniques. Improved knowledge and understanding of aetiologies has made it possible to provide better information on the nature of the hearing loss, preventing deterioration in some cases and aiding identification of other system involvement, for example, retinitis pigmentosa in Usher syndrome and enlarged vestibular aqueduct in Pendred syndrome. Early confirmation of hearing loss, early amplification, early assessment of benefit from hearing aids, early understanding of important medical and aetiological factors, and early cochlear implantation have all led to much better audiological, educational and longer-term outcomes. This progress depends on multidisciplinary working, agreed professional guidelines, and the involvement of families and those with a hearing loss themselves.

The terms 'deafness' and 'deaf' are used in this chapter to cover moderate, severe and profound hearing loss. This is not to imply that mild hearing losses should be ignored. The severity of hearing loss or deafness may not necessarily have a direct relationship with disability (see WHO definition of impairments, activity limitations, and participation restrictions). These terms are discussed in a chapter on the special needs child (Chapter 5, The child with special needs).

According to the WHO[11] there are 466 million people worldwide with disabling hearing loss, i.e. hearing loss greater than 40 dB in the better hearing ear in adults (432 million) and a hearing loss greater than 30 dB in the better hearing ear in children (34 million). The majority live in the middle- and low-income countries of South Asia, Asian Pacific and sub-Saharan Africa.

CLASSIFICATION AND MEASURES OF HEARING LOSS

Although dBHL is an internationally agreed measure, there are differences in the classification and categorization of hearing loss between various organizations. It is important to describe which classification is employed and the frequencies used to average so that comparison can be made.[12–16] Classification of hearing losses by hearing thresholds is shown in **Table 10.1**.

TABLE 10.1 Four commonly used systems

dB HL	WHO	NHSP	BSA[13]	ASHA[12]
Normal	≤25	≤20	<20	–10 to 15
Slight	26 to 40			16 to 25
Mild		21 to 39	20 to 40	26 to 40
Moderate	41 to 60	40 to 69	41 to 70	41 to 55
Moderately severe				56 to 70
Severe	61 to 80	70 to 94	71 to 95	71 to 90
Profound	≥81	≥95	>95	>90

WHO World Health Organisation; NHSP Newborn Hearing Screening Programme; BSA British Society Audiology; ASHA American Speech-Language Hearing Association.

EPIDEMIOLOGY

The incidence of a child born with a PCHI is typically quoted as 1 per 1000 births. Fortnum et al.[17] reported an adjusted prevalence of 1.07/1000 and this may rise to 2.05/1000 amongst children 9 years or older,[17] as PCHI may present well after birth as a result of late onset congenital progressive or non-progressive hearing loss, either conductive or sensorineural. According to the NHS Newborn Hearing Screening Program (UK) from December 2012 to December 2013, the incidence of confirmed *bilateral* PCHI was 0.76%, while the figure for *unilateral* loss was 0.46%. About one third of all children with PCHI have severe to profound sensorineural hearing loss (SNHL). About one third of children with sensorineural PCHI will have a simultaneous vestibular weakness. Figures are considerably higher in developing countries.

AETIOLOGY

Hearing loss in a child may be present at birth ('congenital') or may develop after birth ('acquired'). Management of a child with confirmed PCHI requires a holistic approach for optimal audiological care with supporting services for the child and the family and also appropriate medical management, which includes offering and arranging necessary investigations to determine the aetiology. Most children with a PCHI have a SNHL. Those children who have a purely conductive hearing loss may have some congenital conditions, such as ossicular abnormalities and bilateral aural atresia. (Chapter 12, Congenital middle ear abnormalities) Some may have a mixed hearing loss, many have a fixed loss but others have a progressive hearing loss. In children, especially during the first 5–6 years of life, acute otitis media (AOM) and middle ear effusions ('glue ear') are common with a much greater prevalence than PCHI. Children with PCHI especially with craniofacial abnormalities are also vulnerable to AOM and to middle ear effusions, making their hearing loss temporarily worse. This is even more important in those who have unilateral hearing loss as their ability to hear is significantly compromised during such episodes (see Chapter 13, Otitis media with effusion and Chapter 14, Acute otitis media).

Infections causing a hearing loss include congenital conditions such as rubella and cytomegalovirus (CMV), and acquired childhood infections such as mumps, measles, meningitis and chronic otitis media. In the developed world, deafness from meningitis is declining because of HiB and Meningitis C vaccination and over half of children with PCHI have a genetic cause for their deafness.[18]

The causes of PCHI are shown in **Table 10.2**.

Genetic causes

Hereditary or genetic hearing loss results from aberrations in the coding function or processing of human DNA. In the Western world genetic factors are now thought to be responsible for over half the cases of congenital SNHL but with more genetic tests becoming available, and the pressure to perform them, this proportion is expected to

TABLE 10.2 Causes of permanent childhood hearing impairment

Causes of hearing impairment		
Congenital disorders		
Genetic	Syndromic	Autosomal recessive
		Autosomal dominant
		X-linked
		Mitochondrial
	Non-syndromic	Autosomal recessive
		Autosomal dominant
		X-linked
		Mitochondrial
Non-genetic	Congenital rubella syndrome	
	Cytomegalovirus First-trimester maternal infections (viral or bacterial)	
	Congenital syphilis Toxoplasmosis Hyperbilirubinemia Low birth weight Birth asphyxia Drugs during pregnancy, such as aminoglycosides, some antibiotics, anti-epilleptic drugs, cytotoxic drugs, antimalarial drugs, and diuretics. Maternal substance abuse e.g. alcohol, recreational drugs Maternal endocrine disorders e.g. diabetes mellitus, thyroid dysfunction 'Third window' disorders (see text, aetiology often unknown, may be congenital or acquired)	
Acquired causes		
Perinatal	Hypoxia	
	Hyperbilirubinemia	
Postnatal	Infections	Chronic otitis media
		Herpes Meningitis
		Mumps
		Measles Toxoplasmosis Varicella
		HIV
	Ototoxic drugs	
	Trauma / noise exposure	
	Neoplastic disease Foreign bodies in ear canal Immune system disorders	
Idiopathic		

rise significantly.[8, 19, 20, 21] About 70% of children with PCHI are considered to be non-syndromic (**Figure 10.1**) and the remaining 30% have one of a large variety of syndromic conditions.[22] Genetic hearing loss is mainly of monogenic phenotype. The majority ≈80% are autosomal recessive typically presenting pre-lingually, and some 20% are autosomal dominant, more typically presenting as progressive or post-lingual[23] with about 1% with X-linked or mitochondrial inheritance in which the trait is passed through the maternal lineage (see Volume 1, Chapter 2, Genetics in otology and neurotology).[24]

The gene mutations related to non-syndromic hearing loss are currently reported on web pages such as http://hereditaryhearingloss.org[5] and http://ghr/nlm.nih.gov.[4] Identification is labour intensive and expensive but with advancement in techniques new platforms are being applied.[25] Screening with Sanger sequencing for *GJB2* mutations is commonly performed, as they account for about 20% of autosomal recessive non-syndromic hearing loss (ARNSHL) for families in Northern Europe. Mutations in the pendrin gene *SLC26A4* are the next most frequent cause of ARNSHL.[21] The carrier

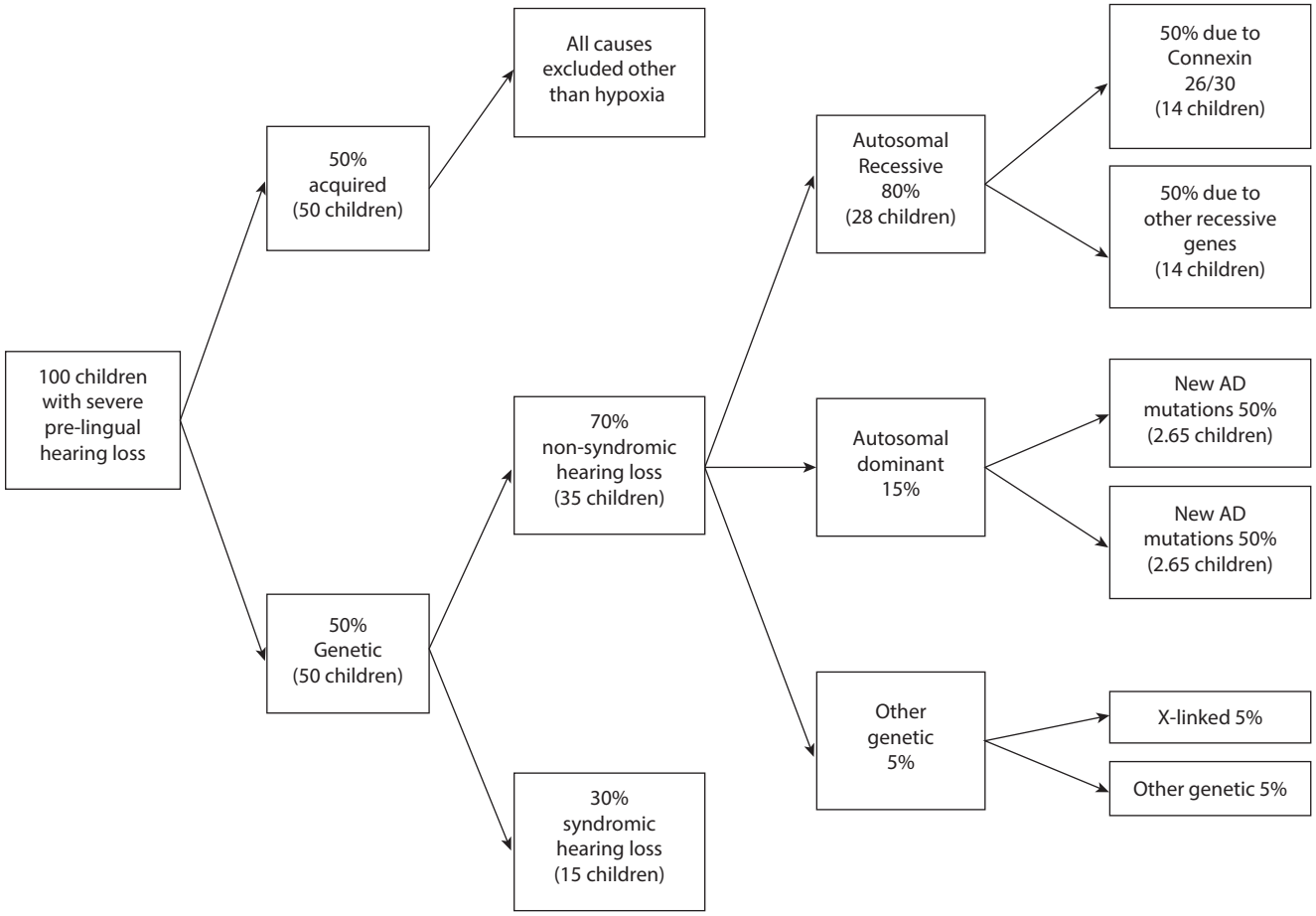

Figure 10.1 Aetiology of hearing loss in children.

rate in the general population for a recessive deafness-causing *GJB2* mutation is about one in 33.[26] Syndromic SNHL is found in conditions such as Pendred syndrome, Branchio-oto-renal syndrome, Usher syndrome and Waardenburg syndrome, amongst others.[19, 20] Conductive hearing loss is commonly encountered in Down syndrome and Treacher Collins syndrome likely to be due to the craniofacial abnormality encountered in these syndromes.

Congenital infection causing hearing loss

Maternal infections are still responsible for a significant proportion of acquired hearing loss, especially in developing countries, although vaccination has greatly reduced the incidence. The distribution of genetic hearing losses are shown in **Figure 10.1**.

Cytomegalovirus (CMV)

Congenital CMV, a herpes virus, is now the most common cause of non-hereditary SNHL in the developed world.[27, 28] CMV infection occurs in about 1% of pregnancies and 40% of affected mothers pass the virus on to the baby. In the UK congenital CMV affects 0.3–0.5% live births, but the incidence varies from 0.2% to 2.2% in other parts of the world.[28–30] Maternal infection within the first trimester is associated with greatest risk.[31] The hearing loss can be of delayed onset giving challenges in predicting which children with congenital CMV infection will develop hearing loss and whether or not the loss will continue to deteriorate.[32] About 30–50% have a unilateral hearing loss that may progress to a bilateral SNHL, so audiological monitoring is important.

Congenital rubella syndrome (CRS)

CRS is probably the most important cause of congenitally acquired hearing loss in countries with no rubella vaccination programme. CRS occurs when there is maternal infection with the rubella virus in the first trimester of pregnancy. It leads to a number of abnormalities in the child including deafness, ocular defects (cataracts, glaucoma), cardiovascular anomalies (patent ductus arteriosus, pulmonary artery stenosis and ventricular septal defects), central nervous system problems (microcephaly, global retardation) and characteristic skin changes (**Figure 10.2**).[33]

The WHO has recommended vaccination against rubella.[34] Two approaches have been suggested: prevention of CRS only, through immunization of adolescent girls and/or women of childbearing age; and elimination of rubella, as well as CRS through universal vaccination

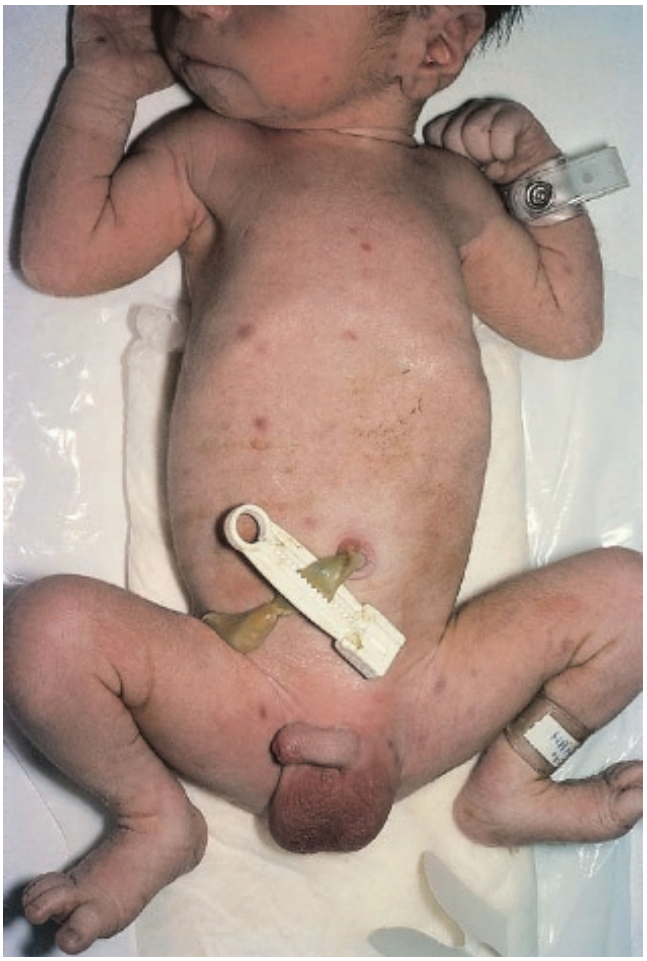

Figure 10.2 Congenital rubella with characteristic skin rash. The child was profoundly deaf. Courtesy of J Verbov, Emeritus Professor of Paediatric Dermatology, Royal Liverpool Children's Hospital, Alder Hey.

of infants and young children.[35, 36] This latter is the norm in most developed countries where CRS deafness is almost unknown.[37]

Syphilis

Syphilis is caused by the bacterium *Treponema pallidum*. It is a common infection in much of the developing world and has recently re-emerged in parts of the developed world. The main route of transmission is sexual contact, but syphilis can also be transmitted from an infected mother to her baby (congenital syphilis). Congenital infection can occur at any stage during pregnancy, but the highest likelihood of damage to the fetus is when infection occurs and is untreated during the first or second trimesters. During primary syphilis, the rate of vertical transmission in untreated women is 70–100%; this drops to 10–40% in the latent stage of the disease. The poorest prognosis is for an infant infected during the first or second trimester by a mother in the primary or secondary stages of disease. Hearing loss is a late feature of congenital syphilis and often appears as one of a group of signs known as 'Hutchinson's triad'. These include inflammation of the cornea giving it an opaque appearance, which leads to loss of vision, peg-shaped upper incisors (Hutchinson's teeth) and VIIIth cranial nerve deafness. Hearing loss is the least common component of Hutchinson's triad and occurs in around 3% of children with late congenital syphilis. It typically appears when the child is 8–10 years of age, although occasionally it may be delayed until adulthood. Onset is sudden and damage to the cranial nerve is thought to result from a persistent and ongoing inflammatory response to the infection. Loss of hearing may be unilateral or bilateral and initially involves higher frequencies, with normal conversational tones affected later.[38] Syphilitic hearing loss is uncommon.[39] Congenital syphilis can be treated with high-dose penicillin, but is best prevented by identification and eradication of the infection in the mother. Pre-natal screening for syphilis is commonplace in developed countries and is the main priority for prevention of the disease in developing countries.[38]

Toxoplasmosis

A systematic review on neonatal toxoplasmosis showed that the use of anti-parasitical therapy initiated early showed very encouraging results in preventing SNHL. Children with congenital toxoplasmosis that had no treatment, partial treatment, delayed onset of treatment, or compliance issues should undergo annual audiological monitoring until able to reliably self-report hearing loss.[40]

ACQUIRED CAUSES

While the frequency of infections has dropped with the introduction of vaccines, a concomitant improvement in the survival rates of pre-term babies has increased the proportion of babies with hearing loss related to perinatal events, including stays in the neonatal intensive care unit (NICU). Pre-term and low-birth-weight infants are particularly susceptible to factors such as hypoxia and hyperbilirubinaemia. Davis and Wood[41] showed that babies admitted to a NICU for more than 48 hours were 10.2 (95%, confidence interval 4.4–23.7) times more likely to have a permanent hearing loss (greater than 50 dBHL in this study) than those who did not undergo intensive care.

Hypoxia is associated with apnoea, difficult delivery, low Apgar scores and use of ventilation. It is known to be associated with neurodevelopmental deficits, but the exact mechanism of hypoxia-related hearing loss is unclear. Although most believe that brain cells are more susceptible to hypoxia than the hair cells in the inner ear, there is some emerging evidence that apoptosis of hearing cells can occur without any injury to brain cells.[42]

Hyperbilirubinemia is an independent risk factor for SNHL in infants. High levels of unconjugated bilirubin have been associated with neuronal damage. The auditory brain nuclei and the inferior colliculi are often the first

part of the brainstem to be involved, often leading to hearing abnormalities.[43] These infants are more often than not nursed on a NICU, where they may receive ototoxic drugs, such as aminoglycoside antibiotics (e.g. gentamicin, tobramycin and amikacin) and diuretics (e.g. furosemide). Aminoglycoside-induced and non-syndromic deafness have been shown to have a genetic susceptibility and the pathogenic mitochondrial 12S rRNA. A1555G mutation was identified as the primary factor underlying the hearing loss in many familial as well as in genetically unrelated cases; also see ototoxicity in acquired causes of hearing loss.[44, 45]

Other causes of permanent acquired hearing loss include bacterial meningitis, chronic otitis media, mumps, measles, trauma, ototoxic drugs and head injury.

Meningitis

The most common cause of acquired PCHI is childhood bacterial meningitis. The risk of developing significant sensorineural impairment after bacterial meningitis has been estimated at approximately 10%.[46–49] but this varies depending on the organism. In the developed world Haemophilus influenza B (HiB) and Meningococcus C (Men C) vaccinations have led to significant reduction in these infections.

All patients should have early audiological assessment after an episode of meningitis. Patients identified with severe to profound loss should be 'fast tracked' for an assessment by a cochlear implant centre to minimize delay as ossification of the cochlear duct can make implantation difficult or even impossible (see Chapter 94, Cochlear implants).

Measles

Measles is a highly infectious viral illness, which presents acutely with high fever, running nose, characteristic Koplik's spots on the buccal mucosa and a distinctive generalized maculopapular rash (**Figure 10.3**). It occurs worldwide but its incidence has reduced significantly in developed countries since the introduction of an effective vaccine in 1968. It is predominantly a disease of infants and young children and occurs mostly after the age of 6 months. Globally, measles is the leading cause of vaccine-preventable child deaths.

Measles has been reported as a major aetiological factor for mild to moderate bilateral hearing loss in deaf children. As it was known that mucous membranes all over the body were affected, the observed hearing loss was previously thought to be conductive and attributable to suppurative otitis media, chronic perforation and mastoiditis, but SNHL occurs as well.

The WHO and United Nations Children's Fund (UNICEF) have emphasized primary prevention of measles in its global campaign against the prevailing childhood illnesses in the developing world for several decades. Immunization for measles can be administered as a single vaccine or as the triple MMR (measles, mumps and rubella) vaccine.

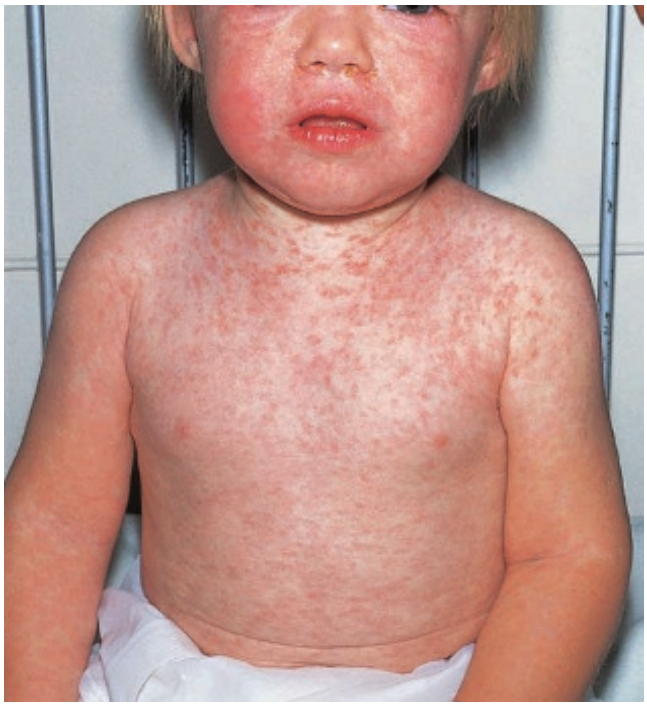

Figure 10.3 Child with maculopapular rash characteristic of measles. Courtesy of J Verbov, Emeritus Professor of Paediatric Dermatology, Royal Liverpool Children's Hospital, Alder Hey.

Mumps

Mumps, caused by infection with the mumps virus, is a non-suppurative enlargement of the salivary glands, particularly the parotids (see Chapter 39, Salivary glands). The infection may be subclinical in up to one third of the cases and in these the first presentation may be the appearance of complications. SNHL as a result of mumps is mostly unilateral and severe to profound, although bilateral loss has been described. The incidence of mumps-related SNHL has been reported as 0.5–5/100,000.[50]

Ototoxicity

'Otoxicity' refers to pharmacological agents that can cause a hearing loss with or without a vestibular loss usually at the cochlear level. The mechanism of action is by their action on the apoptotic pathway of cochleovestibular hair cells where generation of reactive oxygen species is a rate limiting step. The agents implicated are the aminoglycoside group especially gentamicin and tobramycin, chemotherapeutic agents especially the platinum derivatives cisplatin and carboplatin, vinca alkaloids, cyclophosphamide and methotrexate, anti-malarials including chloroquine, diuretics especially frusemide and ethacrynic acid, and iron chelators like desferrioxamine. These agents are not infrequently used in the paediatric population especially in cystic fibrosis, cancers and in paediatric haematological conditions. Chemotherapy ototoxicity monitoring protocols with subjective and objective assessment of hearing and vestibular function is required

to adjust therapeutic dosage. Genetic susceptibilities are reported with both gentamycin and cisplatin ototoxicity.[51]

Autoimmune ear disorders (AIED)

Autoimmune ear disorders can either be primary or secondary. Primary AIED affects only the cochleovestibular apparatus and the hearing loss is non-syndromic with autoantibodies directed only against the inner ear whilst secondary AIED affects multiple organs being part of the wider connective tissue disorder spectrum including rheumatoid and juvenile arthritis, the inflammatory bowel disorder group and for that matter any autoimmunity disorder.[52] The exact prevalence or incidence of AIED in children is unknown. The hallmark of this condition is a sudden SNHL with variable vestibular involvement which is responsive to steroids. Hearing can be salvaged during the acute phase within a critical time frame of 72 hours but in many presentations, this time period may be exceeded leading to a permanent irreversible hearing loss. Diagnosis is still a matter of controversy and inflammatory markers may not be raised especially in primary AIED. Therefore, all children presenting with sudden SNHL should receive a diagnostic and therapeutic steroid administration and a full workup of autoimmune markers.

Third window disorders

A condition involving the bony labyrinth may lead to a mixed hearing loss and can mimic other conditions. These conditions are called third windows and examples include semicircular anal dehiscences, enlarged vestibular aqueducts, X-linked gusher syndromes and dilated internal auditory meati (see Chapter 48, Physiology of hearing). Usually the vestibular system is also affected; therefore, a full vestibular quantification is necessary. In the paediatric population, this is not well researched but is now recognized as a condition which can often be missed.[53]

NEWBORN HEARING SCREENING

It has been shown that early diagnosis of PCHI has an important bearing on outcome. Several studies have demonstrated that children whose hearing losses were identified by 6 months of age demonstrated significantly better receptive and expressive language skills than did children whose hearing losses were identified after the age of 6 months.[54–56]

Prior to introduction of the newborn hearing screen in England and other countries within the UK, infant distraction test (IDT), first used in 1960s, was used as a hearing screening test until early 1990s. It was usually carried out by health visitors at the age of nine months within the community. IDT had neither high sensitivity nor specificity. As a result, a large number of children with normal hearing were referred for further investigations. More worryingly, almost one quarter of children born deaf were not identified until they were over 3.5 years of age.[57, 58] These concerns led to a Health Technology Assessment[59] of hearing screening in England and subsequently setting up of a newborn hearing screening programme (NHSP). As a result of universal neonatal screening in England, the median age of detection of PCHI is now 10 weeks.[60]

Currently, in England, all children are screened with automated otoacoustic emissions (AOAE) as close to the time of birth as possible by a trained operator with over 95% of babies having the hearing screen completed by 4 weeks of birth in hospital hearing screening programmes and within 5 weeks of birth in community newborn hearing screening programmes. AOAE screen is sensitive to hearing losses from 1 to 4 kHz while automated auditory brainstem response (AABR) detects hearing loss in the 2–4 kHz frequencies of more than 40 dBHL. The result of the screen is either a 'pass' or 'refer'. In addition, all NICU babies have AABR screen in addition to AOAE screen. This is because there is a higher incidence of children with permanent hearing loss (including auditory neuropathy, the latter estimated to be 0.9%) whose AOAE test would give a 'pass' result. Normally, a 'well' baby who passes the AOAE screen in both ears would be discharged so anyone in this group with ANSD(see Chapter 69, Auditory neuropathy spectrum disorder and retrocochlear disorders in adults and children) will be missed at this stage. Fortunately only 5–7% of all ANSD patients come from the 'well baby' population. On the other hand babies from NICU will have both AOAE and AABR screening tests and therefore anyone with a moderate or greater cochlear or neural hearing loss (up to the brainstem) should be identified by the NICU screen protocol.

In some babies the hearing loss could be progressive, and may develop after birth. As passing a hearing screen at or soon after birth can give a false sense of security to parents and professionals alike, it is extremely important to be vigilant so that any future suspicion of hearing loss is investigated promptly. In most countries there is some form of targeted follow-up of the babies with a risk factor, who passed the neonatal hearing screen.

More information on screening can be found in Chapter 8, Hearing screening and surveillance.

Unilateral hearing loss (single-sided deafness)

Screening has also resulted in early detection of unilateral permanent hearing loss. In the past, unilateral hearing loss (UHL) was considered to have little impact on speech and language development; this is not the case.[61] The yield for permanent unilateral moderate or greater hearing loss in the NHSP in England is 0.64 (95%, CI 0.37–0.91) per 1000 screened.[60] UHL can also be acquired as a result of trauma, infection, ototoxicity, metabolic disorders and surgery. UHL results in an inability to hear binaurally (from both sides), leading to difficulty in hearing speech in noise and poor localization of sound. Further, with frequent middle ear infections or effusions in the early years, those with a UHL may be at a greater risk of suffering with periods of significant hearing difficulties. School children with UHL may have increased rates of grade failures, need additional educational assistance and may

show behavioural issues in the classroom.[61] A unilateral conductive loss arising from atresia (absence of the external ear canal) has also been shown to have an impact on academic performance.[62]

It is unclear if children always 'catch up' as they grow older.[61, 63]The impact of UHL on language development and educational performance varies considerably but it needs to be kept in mind.[64] It is important to assess these children on an individual basis and make available appropriate support if needed, but many children can be managed expectantly.

Current practice is that UHL is investigated to identify progressive pathology or conditions that might affect the other ear, e.g. dilated vestibular aqueducts. Audiological management of children with UHL includes regular monitoring of their educational performance and maintenance of their technology by their teachers supported by specialist advisory teachers of the deaf (ToD), and environmental modifications including minimizing background noise and reverberation in the classroom and preferential seating nearer the teacher. More recently an increasing number of children with UHL have been fitted with and benefited from various hearing devices including contralateral routing of signal (CROS) hearing aids, bone conducting hearing implants (BCHI)) and FM devices such as iSense (see Chapter 93, Bone conduction hearing aids).[64–67]

Progressive hearing loss

Some children have normal hearing or only a mild loss at birth, but develop progressive hearing loss with time. Prevalence of permanent SNHL almost doubles by the second decade of life.[17] This group includes those with progressive as well as post-natally acquired hearing loss, highlighting the importance of continuing vigilance.

In countries where universal neonatal hearing screening has not yet been established, identification of children with PCHI is still dependent on parental or teacher suspicion, locally arranged behavioural screening programmes or questionnaires and preschool screening. In a questionnaire-based study in Nigeria, only 12% of parents of a child with hearing loss suspected hearing difficulty by the age of 6 months. Parental suspicion occurred mostly at 12–24 months, compared with 8–14 months in developed countries. The most common mode of detection was a child's failure to respond to sound (49%).[68] Since this study Nigeria has started a newborn hearing screening programme leading to early detection of hearing loss in that country.[69]

Progressive hearing loss may be due to genetic or environmental causes. In some syndromes such as Pendred syndrome, the hearing loss is typically progressive. Non-syndromic hearing loss related to a variety of known and unknown mutations can also be fluctuant or progressive.[70] Some infections such as congenital CMV and occasionally congenital syphilis can cause late-onset or progressive hearing loss. Similarly, children who contract bacterial meningitis, viral infections such as mumps and measles, chronic otitis media, suffer trauma including noise exposure or ototoxicity (e.g. aminoglycosides, platinum drugs) require audiological assessments. Early detection of hearing loss in these groups is based upon surveillance of at-risk groups (e.g. children undergoing chemotherapy) and parent/teacher/medical staff suspicion.

This group poses a challenge, as neonatal screening will not identify them and school entry screening no longer takes place in the UK. Identification of these cases therefore is dependent upon a high degree of suspicion in children with known associated syndromes, careful surveillance and prompt assessment in response to parent or teacher concern regarding hearing or speech and language development.

THE NEWLY DIAGNOSED DEAF CHILD AND FAMILY

For the majority of parents, having a child with hearing loss is completely unexpected; about 95% of deaf babies are born to hearing families.[71]

Parents remember with clarity the day they were told their baby was deaf, and cumbersome inexpert handling of this scenario can have profound adverse long-term effects. An experienced empathic team that works in a coordinated way with the family and can present a knowledgeable and non-partisan approach to the various options and resources available makes for the best outcome for parents and child. Now the diagnosis is likely to take place very early in the child's life while parents are adjusting to being parents and it is even more important that time is made available for them and that they are supported in the early days.

Parents may experience a range of emotions following diagnosis of hearing loss, including shock, confusion, depression, anger and guilt.[72] The presence of a child with hearing loss has often been linked with psychosocial stress in the parents and other family members,[73] but better information regarding screening and rehabilitation help families to deal with the trauma. The degree of hearing loss does not seem to influence the parents' reactions. In fact, stress levels were found to be higher in the parents of children with less severe hearing loss.[74] This might be because the child with a less severe hearing loss may at least sometimes respond to some sounds, which can delay the parents' adjustment to the hearing loss and confuse the diagnosis. Parents and healthcare professionals are faced with a series of dilemmas and challenges when it is established that a child is deaf. Parents will have questions regarding the reason for the hearing loss, prospects for development of the child – especially speech and future communication – and educational needs. Many of these questions cannot be answered straight away but parents are often required to make decisions without having time to take in the information they have been given before they have been able to adjust to having a child with hearing loss. Ensuring that parents and child develop effective early communication skills is vital to support language development.

The impact of the diagnosis on parents and family can remain in the long term when the further implications on education, social life and self-esteem become apparent. It is therefore vital that the process of screening and diagnosis is carried out by experienced multi-professional teams and that parents and family have continuing support.

Meeting other families has been found to be useful and the National Deaf Children's Society[9] provides helpful services and resources, as does SoundSpace.[75]

Medical management

While appropriate and optimum amplification along with early support is essential to achieve the best audiological outcome, deafness is a symptom rather than a definitive diagnosis, and it is important to identify the underlying cause and associated conditions, if any, as these may need their own management. A holistic approach often leads to better overall outcomes. for the child and family.

Medical management consists of a developmental assessment and identifying coexisting medical conditions as well as carrying out an extensive investigation into finding the cause of the deafness. It is therefore essential for every audiology team to have an appropriately trained medical practitioner, preferably at consultant level, to provide this aspect of care and support for children diagnosed with a hearing loss, and for their families. Investigating aetiology is an important and integral part of the management of a child with hearing loss at any age primarily to answer two questions:

1. How might the hearing loss evolve? This, in turn, alleviates uncertainty.
2. Is there a genetic factor for patients and parents/carers? They can be counselled from a genetic point of view.

In the UK, national guidelines for investigating the aetiology of PCHI were developed by the British Association of Audiological Physicians[2] in conjunction with the British Association of Paediatricians in Audiology[1] and are available on those two websites. It is recommended that core investigations are offered to the parents of all children with a newly diagnosed SNHL, while 'additional' investigations are dictated by individual circumstances and the findings of core investigations (Table 10.2). Parents may not wish to pursue investigations at such an early stage, the results of which in many cases may have no immediate impact on the management of the child and the family, but it is essential that healthcare professionals are aware of the baseline investigations and can discuss the rationale behind various tests so parents can make an informed choice.[2] These guidelines are not always fully implemented.

The aims of aetiological investigations are:

- to try to provide reasons for the deafness for parents
- to identify conditions that may affect audiological and medical management
- to provide better advice to parents with regard to best management of associated conditions
- to assist the family in making educational and management decisions for the child
- to inform genetic counselling
- to inform epidemiological research.

The recommendation is that patients should undergo core investigations with additional investigations as dictated by the clinical scenario.

History

A detailed and careful history of the pregnancy, perinatal period and birth and the post-natal period including

TABLE 10.2 Core investigations for all cases of bilateral severe to profound sensorineural hearing loss

Investigation	
Paediatric history	Detailed history of pregnancy delivery and postnatal period. Developmental milestones including speech and language and motor milestones, pre- and postnatal noise exposure, history of ototoxic medications, head injuries, ear disease, meningitis, viral illness and immunization status
Family history	Deafness or risk factors associated with hearing loss in first- and second-degree relatives
Clinical examination	Inspection and physical measurement of craniofacial region, assessment of the neck, skin and nails, limbs, chest and abdomen. Developmental examination
Audiology	Age-appropriate assessment including tympanometry. Audiometry on first-degree relatives
Imaging	Magnetic resonance imaging of inner ears and/or computed tomography of petrous temporal bones.
Electrocardiograph	
Urine for microscopic haematuria and for CMV DNA PCR in neonatal congenital hearing losses	
Connexin 26 and 30 mutations testing with access to clinical genetics service for counselling	
Ophthalmic assessment	
Referral to clinical geneticist	
Vestibular investigations	
CMV serology	

infections and medication is invaluable. Wherever possible, maternity and birth-related notes should be examined. Note details of drugs used, if appropriate with doses, duration and the blood levels of any potentiating medication. If jaundiced, blood levels of unconjugated bilirubin levels and the baby's condition at the time e.g. acidosis etc. should be noted. A history of hypoxia should be explored in great detail including length of ventilation, blood gases, metabolic evidence of hypoxia and evidence of any other neurological effects including memory and learning difficulties. It is important to note that, although hypoxia alone does not cause isolated sensorineural loss, there is recent evidence that cochlear cell death can occur without evidence of hypoxic brain injury.[42] Family history of hearing loss, speech and language delay and medical conditions should be explored.

Clinical examination

All children with hearing loss of unknown cause should be evaluated for features associated with syndromic deafness. Important features include branchial cysts, sinuses, fistulae and pits, pre-auricular appendages and pits, telecanthus, heterochromia iridis, white forelock, pigmentary anomalies, high myopia, pigmentary retinopathy, goitre and other craniofacial anomalies, palatal abnormalities e.g. cleft palate, submucus cleft, high-arched palate and abnormalities of teeth etc. It is also useful to look for any dysmorphism in the immediate family.

Audiology

Skilled audiological testing must be performed to assess the severity of the hearing loss and to determine whether it is conductive, sensorineural or mixed. This is discussed in detail in Chapter 9, Hearing tests in children. This should include ear specific hearing thresholds with ear and bone conduction as appropriate and testing for neural involvement e.g. ANSD where appropriate as per NHSP) protocols.[76, 77]

Imaging

The aetiology of profound hearing loss in children is multifactorial. Cross-sectional imaging is extremely useful in the detection and management of congenital abnormalities. Generally computed tomography (CT) including 3D reconstruction would be useful for exploring conductive hearing losses, inner ear bony dysplasia and large vestibular aqueduct syndrome. It is also of use to define facial nerve anatomy, integrity of the ossicular chain and dimensions of the internal auditory canal. MRI scans are more likely to detect abnormalities primarily involving the membranous labyrinth, and lesions of the central auditory pathway in the internal auditory canal, cerebellopontine angle, brainstem and cerebral cortex.[78–80] Bamiou et al. reported that about 28% of children with profound and/or progressive hearing loss and/or craniofacial abnormalities have an abnormal CT scan whereas, the child's gender, consanguineous parents, or family history of SNHL were far less likely to be associated with CT abnormalities.[81]

Dilated vestibular aqueduct was significantly correlated with the presence of progressive SNHL. At least 40% of children with large vestibular aqueduct (LVA) will develop profound SNHL. An interesting meta-analysis by Spencer et al.[82] reported on the linear relationship of hearing loss to LVA duct diameter. The identification of LVA should raise the suspicion of Pendred syndrome and thyroid abnormality but it also occurs in Branchio-oto-renal syndrome (BOR).[19, 20, 83] Patients with LVA are at risk of progressive deafness after minor head trauma. Identifying this anomaly influences management as it prompts a search for treatable thyroid function anomalies and parents can be counselled with respect to the dangers of incidental head trauma.[73]

Imaging can highlight characteristics of congenital syndromes such as BOR, CHARGE, X-linked and Waardenburg syndromes. In later life, inner ear infections, inflammatory conditions, trauma and tumours come to the fore.[8]

Studies of unilateral SNHL strongly support the need for imaging. Abnormalities on CT imaging have been detected in between 28% and 66% of sequential observations (**Figure 10.4**). There is a slightly higher yield of radiological abnormalities with increasing severity of hearing loss and a significantly higher imaging yield with unilateral than with bilateral SNHL.[81, 85–87]

Imaging modalities and techniques are discussed in Volume 1, Chapter 57, Imaging in head and neck endocrine disease and Volume 2, Chapter 97, Imaging of the temporal bone.

Blood tests

Although routine blood tests such as full blood count (FBC), thyroid function tests, erythrocyte sedimentation rate (ESR), syphilitic blood tests, cholesterol and triglyceride levels, urea and electrolytes are carried out, abnormalities are rarely related to the cause of the hearing loss.[85] The use of these blood tests is dependent on clinical suspicion of various conditions although some tests may be used as generalized screening tests e.g. inflammatory markers. **Table 10.3** lists these tests.

URINALYSIS

Simple testing for proteinuria and haematuria can identify renal disease and can be found in Alport syndrome.

TABLE 10.3 Additional investigations

Investigations
Haematological and biochemical tests
Serological test for congenital rubella and other infections e.g. syphilis, toxoplasma etc.
Thyroid tests
Immunology tests
Metabolic screen blood and urinalysis
Renal ultrasound
Chromosomal analysis

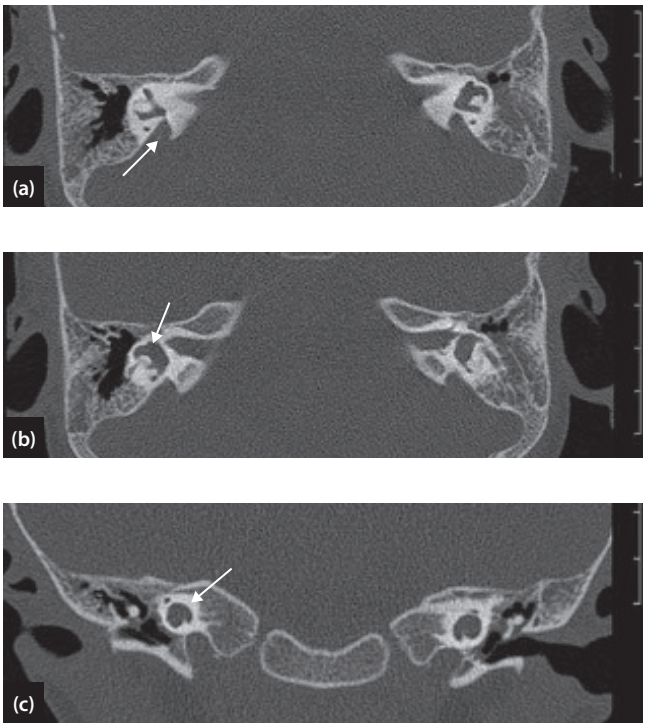

Figure 10.4 Typical appearances of a Mondini deformity in a child with bilateral severe sensorineural deafness. Axial high resolution CT scan through **(a)** dilated vestibular aqueducts and **(b)** a more inferior slice that shows bilateral dysplastic vestibules. **(c)** Coronal image through the abnormal cochlea showing typical Mondini abnormality with incomplete formation of the apical and middle turns of the cochlea. Images kindly supplied by D Saunders, Consultant Neuroradiologist, Great Ormond Street Hospital, London, UK.

SEROLOGY

Universal neonatal screening will detect less than half of all SNHL caused by congenital CMV infection[88] as the hearing loss in a large proportion of children with congenital CMV is progressive.[89] Laboratory testing has to be carried out in neonatal samples within 3 weeks of life for diagnosing congenital CMV. This presents difficulties as after 3 weeks of age, virus isolation could be due to acquired infection, which is not usually associated with adverse outcomes although there are a few publications suggesting extremely pre-term and immunocompromised babies can be susceptible to hearing loss from post-natally acquired CMV.[90, 91] Previous studies[28, 92, 93] have shown that dried blood spots on Guthrie cards collected at birth for the screening of metabolic disorders have proved a valuable tool for retrospective demonstration of CMV DNA for diagnosing congenital infection after months or even years of life. However, as the sensitivity of this test in symptomatic babies is around 90%, absence of CMV DNA in the dried blood spot does not necessarily exclude congenital infection. Infants who are born to sero-immune mothers are not completely protected from SNHL, although their hearing loss is often milder than that seen in CMV-infected infants following primary maternal infections. Late-onset and progressive hearing losses occur following congenital CMV infection and CMV-infected infants should be evaluated regularly to provide for early detection of hearing loss and appropriate intervention. Fluctuating hearing loss that is not explained by concurrent middle ear infections is another characteristic of CMV-related hearing loss in children.[32] Consideration for targeted screening and appropriate early treatment to reduce long-term morbidity is a potential option.[94, 95]

Rubella-specific IgG and IgM synthesized by the fetus are detectable at birth in CRS. However, since maternally derived rubella-specific IgG is also present in infants' sera, laboratory diagnosis of CRS is almost invariably made by detection of rubella-specific IgM responses. This response is detectable in almost 100% of CRS cases up to age 3 months with the most sensitive antibody-capture assays. The response declines progressively to less than 50% at 12 months and is rarely detectable after 18 months. It is therefore suggested that there is value in testing for CRS only if the deafness is identified within the first 6 months of life.[96]

OPHTHALMOLOGICAL ASSESSMENT

A comprehensive ophthalmic assessment is required as deaf children are heavily reliant on the sense of vision in order to develop efficient communication skills and explore the world around them. Any ophthalmic disorder needs to be recognized as soon as possible to optimize language development (spoken or sign, or both). These disorders may be correctable (such as myopia) or treatable (such as cataract). Those children with non-correctable and non-treatable visual disorders, like retinitis pigmentosa in Usher syndrome, require multiple environmental adaptations and appropriate support services and information.[97]

ELECTROCARDIOGRAM (ECG)

Deafness and electrocardiographic changes (prolongation of the Q-T interval and inversion of the T wave) with a clinical picture of syncopal attacks and sudden death, were described as a distinct syndrome by Jervell and Lange-Nielsen in 1957.[98] The syndrome is inherited as an autosomal recessive trait. This syndrome should be sought in children with syncope or a family history of it, especially those with congenital deafness.[99] Cardiologic control is required. The auditory and language outcomes after cochlear implantation in this syndrome are no worse than those in patients with non-syndromic sensorineural deafness.[100]

GENETIC SCREENING

The disorder DFNB1, caused by mutations in the *GJB2* gene (which encodes the protein connexin 26) and the *GJB6* gene (which encodes the protein connexin 30), accounts for about 50% of ARNSHL. The carrier rate in the general population for a recessive deafness-causing *GJB2* mutation is about one in 33 although this can vary according to racial background.[101] It is current practice

that the families of all children with bilateral PCHI are offered genetic screening for these two mutations. Establishing a molecular diagnosis of *GJB2*-related deafness is important clinically since these children can avoid some of the other aetiological investigations (although it must be remembered that dual pathology could exist) and usually are not at increased risk for medical comorbidity. In general, bony abnormalities of the cochlea are not part of the deafness phenotype and developmental motor milestones and vestibular function are normal.[102] The hearing loss associated with *GJB2*-related deafness can vary from mild to profound although most have a symmetrical severe to profound SNHL.[103] The diagnostic yield of *GJB2* screening is significantly higher in patients with severe to profound SNHL than in all other groups.[85]

There have been significant developments in genetic screening. Screening for the mitochondrial gene mutation *A1555G* (that makes individuals susceptible to aminoglycoside ototoxicity) is offered to patients who have developed hearing loss following exposure or to those individuals who are more likely to have repeated exposure to such antibiotics. If the gene is identified and subsequent administration of aminoglycosides restricted, then the severity of aminoglycoside-induced hearing loss can be limited. Also, as the gene is inherited from the mother, genetic screening to those members of the family and also restricting the use of aminoglycosides in maternal relatives will also limit the likelihood of hearing loss caused by these drugs. Hereditary Hearing loss[5] aims to give an up-to-date overview of the genetics of hereditary hearing impairment for researchers and clinicians working in the field.

SUPPORT AND EDUCATION

With the introduction of newborn hearing screening, the development of more effective hearing technologies including digital aids, implantable devices and wireless technology, and greater understanding of the implications of hearing loss on the development of communication, language and cognition, the opportunities and expectations for deaf children have changed dramatically. New communication technologies such as remote captioning, Skype and Facetime enable deaf young people to be supported in education in new ways. This has had great implications for all those involved with deaf infants, children and young people and their families, including audiologists, medical practitioners, speech and language therapists, teachers of the deaf and educational psychologists.

Early intervention

Following the introduction of newborn hearing screening, and the routine fitting of hearing aids in the first few months of life, and implantable devices in the first year of life, speech and language therapists and teachers of the deaf are involved with deaf infants and their families providing early intervention services at a very early stage. At this time the family may be faced with coming to terms with the diagnosis and new terminology and technology, while dealing with a young baby in their family. The consensus statement for Family Centred Early Intervention[104] provides useful guidelines, recommending the provision of:

- early timely and equitable intervention
- family provider partnerships
- informed choice and decision making
- family, social and emotional support
- family infant interaction
- use of assistive technology and supporting means of communication
- qualified providers
- collaborative teamwork
- progress monitoring
- programme monitoring

They provide guidance under each section and helpful resources, with the emphasis on family-centred services. These requirements place a great responsibility on the team providing the early intervention, particularly as we know its effectiveness has a positive long-term impact on outcomes in terms of language and education for the deaf infant. Early intervention is a strong predictor of later outcomes.[105, 106]

Hearing technology

See Chapters 54, Hearing aids, 55, Beyond hearing aids: An overview of audiological rehabilitation, 93, Bone-conduction hearing aids and 94, Cochlear implants for a comprehensive description of the rapidly changing available technology. Interventions include digital hearing aids, implantable devices (cochlear implants, bone-conduction hearing implants on softband for young children, middle ear implants), and assistive technologies such as FM systems and wireless technology.

The earlier that hearing aids or implantable devices are provided for a deaf child, the more effective they are known to be in the long term.[106] The early intervention team is key to their acceptance and use on a daily basis. For the family of a young deaf infant, adapting to the use of this technology can be challenging when coming to terms with the diagnosis and the implications of hearing loss. The technology itself may be complex to deal with in a family setting with a young baby and it is important that the audiology service liaises closely with those working with the family to ensure that there is a shared understanding of the implications of the hearing loss and expectations of the technology. The technology is changing constantly including sophisticated programmable hearing aids, electro-acoustic implants for those with high-frequency losses, middle ear and brainstem implants and developing techniques. Much information is available on websites and it is essential that all in a position of advising families keep up to date with current practice. Meeting other families and young people using the technology is helpful, and useful resources, including DVDs, are available from www.ndcs.org.uk[9] and from www.earfoundation.org.uk.[107]

The education of deaf children

The impact of childhood hearing loss on communication and language development and hence on educational outcomes and educational decisions has long been recognized as significant, and how to overcome it the source of much controversy with little in the way of evidence.[108] The seminal work of Conrad[109] showed that half of deaf children leaving school had speech that was 'difficult to understand' and had a median reading age of 9 years. Little changed with regard to educational outcomes until comparatively recently. With the rapid growth of hearing technologies, their earlier use, and more sophisticated assistive devices to address the problems of listening in noise and over distance, the impact of hearing loss on language and education has changed considerably in recent years.

Deaf children and young people represent challenges for researchers: they are a particularly heterogenous population with many variables to account for, including aetiology, age at diagnosis and amplification, cognitive ability, socioeconomic status, parental support, communication preference and educational management. Cochlear implantation has added more variables, including device used, age at implantation, surgical technique, generation of device and programming strategy. The impact of profound deafness on communication is readily apparent, but even a mild or moderate, or unilateral hearing loss which may not be so apparent can have an educational impact, with delayed language and a disadvantage in the classroom.[61, 110–113] A mild—moderate hearing loss impacts on the development of language and reading skills and hearing in one ear makes listening in noise and the localization of sound challenging, impacting on the ability to participate in the classroom.[113] A conductive, long-lasting hearing loss can also have a significant impact on access to the curriculum in the classroom; its fluctuating nature can exacerbate the difficulties it causes in listening in the classroom. In spite of this, the impact is often not recognized or addressed: for example, only 68% of deaf educational services are reported to support children with a conductive loss.[112]

Early identification, followed by early amplification has been shown to improve auditory abilities and hence language outcomes,[115] and the comprehensive LOCHI (Long-term outcomes from childhood hearing impairment) in Australia has demonstrated the benefits of early amplification.[116] The study showed that early intervention, maternal education, the absence of additional difficulties and oral communication in early intervention were linked to higher language scores. Early cochlear implantation has long been shown to be a predictor in producing language growth comparable to hearing peers[116–118] and is linked to improved spoken language acquisition, speech intelligibility, educational outcomes and greater participation in mainstream education.[119, 120]

More recent studies of educational outcomes show the positive impact of early cochlear implantation on educational outcomes including literacy; the study of Mayer et al.[121] found that of 33 young people aged 9–16, 75% were within the normal range for reading comprehension, when compared with hearing peers. Mayer and Trezek[122] reviewed the literacy outcomes for deaf students with cochlear implants with encouraging results.

However the picture remains complex. The National Deaf Children's Society, commenting on the Department of Education's report on children's grade attainment in 2015, pointed out that in spite of an increase in the numbers of deaf children achieving five GCSEs (41.1%), almost two thirds (58.9%) were failing to achieve the government's expected benchmark of five GCSEs at grade A*–C (including English and Maths), compared to just 35.8% of other children with no identified special educational need (from www.ndcs.org.uk).[9]

In spite of the progress made following early detection and intervention, hearing loss still has an educational impact. It impacts negatively on the more subtle areas of language development such as pragmatic skills.[105, 123, 124] Together with challenges in acquiring world knowledge, there remain challenges for deaf children in some higher order reading skills, such as inferencing skills, impacting on later educational attainments.

Schools and language teaching

Specialist education for deaf children was established long ago, with large schools for deaf children in many countries in the latter half of the nineteenth century and children taught according to the prevailing philosophy in the school, whether orally or using sign language. During the second half of the twentieth century more deaf children were educated in integrated settings, with their hearing peers, supported by improved technology, such as the fitting of FM systems which enabled teachers to use a microphone to aid communication with the deaf child (**Figure 10.5**) (Chapter 54, Hearing aids) and overcome the issues of background noise and distance, coupled with the political will to include more children with disabilities in mainstream education. Now the terms 'inclusive education' and 'least restrictive environment' are used internationally and supported by the legal requirement in most developed countries for deaf children to have an individual education programme with their needs identified.

Figure 10.5 A teacher of the deaf using an FM microphone.

More information on the history of deaf education can be found at www.batod.org.uk.[10]

Children with hearing loss may be educated in mainstream schools with or without support, in a special class or resource base in a mainstream school, in a specialist school for the deaf, or in a school which specializes in children with other difficulties, such as visual impairment, or language difficulties. The majority of deaf children are now in mainstream schools, where there may be challenges for access to the expertise and management necessary to overcome the impact of deafness and to fully utilize the technological and communication support available today.

The comprehensive CRIDE (Collaboration for Research in Deaf Education) 2015 report for the UK, available from www.batod.org.uk)[125] reveals that:

- 65% of deaf children are in mainstream provision
- 6% are in resource bases in mainstream
- 2% are in schools for the deaf
- 10% are in other special schools
- 15% are educated at home.

Whether to use a signed or oral approach has long been contentious. The Milan conference of 1880 concluded that the deaf were to be taught by oral means with the 'uncontestable superiority of speech over sign' and thus began 100 years of the dominance of oral education over sign – at a time when useful hearing could not be provided. The 'oral' view was challenged strongly by the reports of poor linguistic and educational outcomes[125] and by the increasing voice of the deaf community, promoting its own culture and language. Sign language is silent, with a grammar of its own and cannot be used with spoken language, and an interest in sign bilingual programmes where sign language is used independently of spoken language grew. To summarize, communication choices used with deaf children can be categorized in three major groups:

- oral/aural alone;
- those approaches using speech and sign (total or simultaneous communication);
- sign bilingualism.

There is increasing evidence that the new technologies of implantation and of earlier identification are changing some of these educational decisions.[126] There appears to be an increasing percentage of deaf children in the UK using spoken language. The CRIDE[125] shows that 87% of deaf children use spoken English or Welsh, with 2% using British or Welsh Sign Language and 8% using spoken English with signed support. The lack of empirical evidence for sign bilingualism and the better outcomes in terms of spoken language from early diagnosis and cochlear implantation than were predicted have been recognized.[126] While the evidence for the best method to support the development of improved educational outcomes remains contentious, an oral input, rather than a sign bilingual one, is most effective in producing spoken language outcomes.[116, 129] This may be provided with signed support for spoken language, for those who may need some visual support, either prior to implantation or in specific situations.[130]

Whatever the educational placement of the child it is important to ensure that the child's educational and social needs are met. Medical and audiological services have the goal of improving hearing and general health; for the educator there may be differing goals – those of literacy and numeracy and of social and emotional wellbeing. With regard to social and emotional wellbeing, there is no evidence to show that the advent of cochlear implantation has had an adverse effect on young people's wellbeing. Several studies show that young people with implants have a flexible view of their identity, as being both deaf and hearing, and have mental health status on a par with their hearing peers[131] and most do not relate to deaf culture as in the past.[132]

With the huge impact of today's technology on educational outcomes and management by providing useful hearing from an early age, it is vital that the technology supporting the child's access to the curriculum is used effectively; the acoustics in schools are often poor, the technology can be difficult to manage, particularly in a mainstream setting, and there may be considerable discrepancy between the child's functioning in the clinic and in school. Much of classroom learning takes place in group settings, which can be challenging for hearing aid or implant users, and the problem of signal to noise ratio (SNR) can be difficult to overcome. The acoustics of the educational setting need careful consideration, and a clinician involved in the fitting of hearing aids or implants should ensure that the child's teacher or classroom assistant understands the technology, can carry out simple trouble-shooting and has access to spares to ensure that the child is not without their amplification during the day. Accessories such as radio hearing aid systems (or FM), or the developing wireless, streaming systems or sound field systems are increasingly common, but need to be managed in the classroom rather than in the clinic. Children and young people are unlikely to use their equipment if it is not functioning properly, and the growing complexity of the technology demands increasing competence from teachers and increasing liaison with the audiology clinic. Communication technology is increasing in effectiveness too — remote captioning on tablets is available for use in school, college and work, and communication systems such as Skype and Facetime make lectures and meetings more widely accessible to deaf children and young people.

An additional challenge for deaf education in today's technological era is the growing number of deaf children with additional difficulties, and often very complex needs. CRIDE[125] reports that 21% of deaf children have an additional difficulty. Vestibular dysfunction is also very common in this group of children, and often overlooked. For these children it is even more important to ensure that today's audiological and communication technologies are available. It has been shown that they may not be referred for cochlear implantation in a timely fashion[133, 134] and parents reveal that education and the management of

audiology technology in schools which are not specialist schools for the deaf is a particular issue.[133] These are children for whom access to hearing can be particularly important, although the outcomes may not include the acquisition of spoken language and ones who present challenges for cochlear implant teams.[134]

Educational services for deaf children have a particular responsibility in times of challenging financial constraints and also of developing and changing technologies to ensure that children are monitored for changing hearing needs. For example, those with progressive hearing loss, and those for whom their hearing aids may not be sufficient and who should be referred for cochlear implant or bone-conduction hearing system. This responsibility involves training mainstream teachers in the monitoring of children and young people in the classroom and providing them with information about what changes in behaviour may be significant and where and how referrals should be made.

Support into further education and the world of work

Teachers of the deaf are now responsible for young people with hearing loss until the age of 25, and therefore now working in further and higher education settings and supporting young people into the workplace. The transition to further education and into the workplace is challenging, but it is essential that support is continued there and that young people learn to advocate for themselves and ensure whatever communication and hearing technology they require.

A report by Ng[135] revealed that these young adults have little or no communication or technology support as they enter work, and little knowledge of what is available to them. The continued positive impact of early diagnosis, intervention and today's technology require support into adulthood, to ensure long-term benefit.

Worldwide, the role of the teacher of the deaf is being challenged in these changing times. Teachers are likely to be involved with deaf children early in infancy and with their families, and require quite a discrete set of skills to effectively support parents and child at this vital time. With today's technologies, the educational needs of deaf children and young people are more subtle than they were previously, when they were more obvious. Teachers of the deaf work in a greater range of educational settings, with a greater range of deaf children than before, at a time where services are financially challenged. New ways of working enable education and audiology to be linked efficiently via Skype sessions, with the programming of cochlear implant systems in schools, and data logging on hearing aids and implants providing information to the clinic about what is happening in everyday life. There is a greater than ever need for collaboration between education and ENT and audiology departments to ensure that the benefits of today's technologies can be realized in education.

BEST CLINICAL PRACTICE

- ✓ All children with PCHI should have a full history and clinical examination, with audiological testing as appropriate to the child's age. Families should be offered aetiologiocal investigations to include imaging, genetic testing and other investigations as per published guidelines, followed by appropriate management of associated conditions and skilled genetic counselling.
- ✓ Optimum initial management is with early fitting of binaural hearing aids.
- ✓ If hearing aids are not appropriate early referral should be made for assessmnt of otological implants including cochlear implantation.
- ✓ Clinicians involved in the fitting of hearing aids or implants should ensure that the child's teacher of the deaf understands the technology, can carry out simple trouble-shooting and has access to spares to ensure that the child is not without their amplification during the day.
- ✓ Although the optimum management strategy for single-sided deafness is unknown, the child's teachers should be made aware of this condition.

FUTURE RESEARCH

- ➤ Vaccination programmes, particularly for measles and rubella, will have an important influence on reducing the incidence of PCHI in the developing world.
- ➤ Hearing aid technology continues to improve. These technological improvements need to be accompanied by wider worldwide distribution and availability of hearing aids.
- ➤ Establishing techniques for making a precise diagnosis in genetic deafness, with research into analysis of identified genetic abnormalities to inform focused genetic counselling and may ultimately facilitate therapeutic interventions.
- ➤ Imaging techniques continue to improve and are helping to facilitate more precise anatomical diagnosis.
- ➤ There is a need for further population studies on the effect of single-sided deafness and for a rational approach to management and surveillance for these children.
- ➤ Implementation of the 2016 WHO resolution[136] by governments and international public health legislators would greatly improve detection, prevention and treatment of childhood hearing loss.

KEY POINTS

- One infant per thousand is born with permanent deafness or hearing impairment that significantly affects language and social development. a further one per 1000 develops permanent deafness during childhood.
- Early identification and habilitation and optimal audiological and medical management leads to better life chances for the child.
- The benefits of universal screening are now widely accepted as best practice.
- Approximately half of permanent childhood hearing impairment is caused by genetic factors.
- Neonatal screening programmes have brought about earlier diagnosis, but some children with progressive hearing loss will not be detected unless surveillance is carried out during childhood.
- Unilateral hearing loss is detected much earlier as a result of universal screening.
- There is better understanding of optimum management of unilateral hearing loss to include active classroom management and amplification.
- Improved imaging and advances in genetic testing have meant that a precise aetiological diagnosis can be made in an increasing proportion of deaf children.
- A diagnosis of deafness has profound psychological and social implications for both the parents and the child.
- Patients who have had meningitis should have early audiology assessment.
- Initial management is usually with hearing aids but early referral for otological implants should be considered.
- Educational support is an essential part of the management of a deaf child and his/her family.
- Liaison between audiology and educational services is vital to ensure the technology is fully utilized in school.

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CHAPTER 11

PAEDIATRIC IMPLANTATION OTOLOGY

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: paediatric, cochlear implant, middle ear implant, auditory brainstem implant, bone conducting implant, BAHA and focusing on diagnosis, surgery and management. The evidence in this chapter is mainly levels 3/4. The clinical recommendations are predominantly B and C.

INTRODUCTION

Paediatric hearing implants have become a routine part of the rehabilitation of deaf children. Cochlear implantation is one of the most dramatic and life-changing medical innovations of the 20th century. Bone-conducting hearing aids are an important tool for restoring hearing to deaf children if conventional hearing aids are ineffective, and middle ear implants are now starting to be used in specific indications in children. Developments in the field are driven by three main forces: technological progress, greater surgical confidence, and psychophysiological understanding of early language development. This chapter reviews the current boundaries for the clinical use of auditory stimulators to establish hearing in deaf children.

The auditory rehabilitation of prelingually deaf children has been revolutionized by cochlear implantation.[1] To date, more than 150 000 children have received cochlear implants, with often spectacular results. Cochlear implants provide access to sound that enables development of speech, language and literacy as well as attendance in mainstream education for many deaf children and is established as an effective and cost-effective intervention.[2]

Implantable hearing aids for children include two broad groups: 'electric hearing' with cochlear implants, and 'acoustic hearing' with bone-conduction implants (of which there are several types). For the great majority of children with profound sensorineural hearing loss (SNHL), the implant of choice is a cochlear implant.

COCHLEAR IMPLANTS

Cochlear implants are auditory implantable prostheses that electrically stimulate the spiral ganglion cells of the cochlear nerve directly in circumstances when the cochlear hair cells themselves do not function effectively to give adequate speech intelligibility. An implant consists of an external device with a microphone/processor and an internal device to stimulate the cochlear nerve. With improving technology, the indications for cochlear implantation are continually widening (see Chapter 94, Cochlear implants).

The first attempt to implant a cochlear implant (CI) was made in 1957 by Djourno and Eyries in Paris using a single-channel device.[3] These devices established that hearing could be achieved, but these early recipients used their implants largely in concert with lip-reading. In 1961, William House (otologist), John Doyle (neurosurgeon) and James Doyle (physicist) began work to implant a single-channel device. House's work continued into the 1970s, leading to the production of a 3M manufactured single channel device which was the first US Food and Drug Administration (FDA) approved model in 1984, and eventually to the Nucleus 22, which was the world's first commercial multi-channel CI with FDA approval.

The technology continued to improve with more widespread application of the product and greater confidence in its use. It was finally FDA approved for use in children in 1990. At this stage it was only approved for use for children above 2 years of age, but the age limit

was reduced to 18 months in 1998 and then further to 12 months in 2000. Since then, CIs have been routinely placed in children as young as 6 months, although in an anomaly the licence has never been amended to children below 12 months.

Design of implants

Although there are differences between devices, a basic arrangement is common with all the main manufacturers. There are four parts to the internal component: a magnet, a receiving induction coil (placed together to locate the outer transmitting coil by magnetic attraction), a processor and an electrode (**Figure 11.1**). A return electrode is also present, although this is usually incorporated in the housing of the processor unit.

An external processor is worn which communicates by induction with the internal receiver and also transmits power to activate the internal unit. There are various designs of the external processor to accommodate the different needs of users, but all have a microphone (or often two), and a speech processor, which employs a coding strategy to convert sound into electrical stimulation by the electrode. Various filters and coding strategies are used to give a variety of programs, optimized for speech, direction, music and so on. There is a magnet which holds the processor to the internal magnet, and a transmitter to send the signal by induction across the skin.

The number of active stimulating positions on the intracochlear electrodes varies from 12 to 22 according to the design of the implant. There are common themes to the types of intracochlear electrodes, although this is a field with relatively rapid development.

Figure 11.1 Internal part of cochlear implant (Cochlear N512).

POSITION WITHIN THE SCALA TYMPANI

The ideal position of the electrode is within the scala tympani where it sits close to the neural elements. Disruption of the basilar membrane by traumatic insertion or displacement into the scala vestibuli causes complete loss of residual hearing and may lead to worse outcomes.[4] Electrodes can be modiolar hugging (e.g. Cochlear Contour), Midscala (e.g. Advanced Bionics Midscala electrode) or lateral wall (e.g. MED-EL FLEX electrode).

SIZE

The cross-sectional size of the electrodes is reducing, mainly to improve the ease of insertion and to avoid trauma to the inner ear structures. The current electrodes allow preservation of residual hearing in many cases and may improve long-term cochlear health.

PLUGS, WINGS AND EXTRAS

MED-EL form electrodes have plugs to sit in the cochleostomy to help seal the cochleostomy and prevent cerebrospinal fluid (CSF) escape in abnormal anatomy with CSF 'gushers'. Other electrodes have wings to help positioning of the device (e.g. Cochlear Hybrid and EAS electrodes). Intracochlear positioners were tried in early devices, but these appeared to cause increased rates of bacterial meningitis and are no longer used.[5]

Custom-made electrodes for abnormal cochlear anatomy such as common cavities as well as split arrays used for ossified cochleas are also available.

Guidelines and funding

Prior to 2009, public funding in the UK allowed access for children to unilateral CI. However, in 2009, NICE published new guidelines which established that all eligible children were to receive bilateral simultaneous CI.[6] These guidelines were reviewed in 2011 after a multicentre audit and left unchanged.[2]

Given that binaural hearing skills are acquired early, there has been a preference for early implantation. This allows children rapid development of hearing and speech understanding by reducing deafness duration, maximizing the opportunity of early plasticity of the auditory system.[7] Children receiving a second implant several years after their first have demonstrated more significant asymmetries in brainstem and cortical function than those with a delay of less than 1 year or those implanted simultaneously.[8] These children have demonstrated poorer speech scores in the second ear compared to the first, stronger ear.

With the recognition of the benefits of bilateral and simultaneous cochlear implantation for children, a consensus was reached in 2010 by the Working group of European CI surgeons who released the European Bilateral Paediatric Cochlear Implant consensus statement. This stated that any infant or child who is an unambiguous CI candidate should receive bilateral simultaneous CI as soon as possible after the definitive

diagnosis is made and that surgery should be atraumatic to preserve cochlear function. Currently, more than 25% of children implanted before the age of 3 years have received bilateral implants worldwide whereas in children older than 3 years it is most likely that bilateral implants are inserted in a sequential manner.[7]

Prelingual deafness

Prelingually deafened children have not had the opportunity to organize the same cortical pathways as hearing children. Such deficits in maturation of the auditory cortex of prelingually deafened infants can be counterbalanced if hearing is introduced early. Animal models demonstrate a sensitive period of adaptation within the second to sixth months of life.[9] Similar outcomes have been noted in CI candidates in children. Prelingually deafened children implanted just prior to their teens show a delay in the development of normal morphology of cochlear-evoked potentials and prelingually deafened adults with CI do not achieve open-set speech discrimination.[10]

Thus there is a window or critical period of development during which it is important for these children to function at the same level as their hearing counterparts. With the introduction of newborn hearing screening (see Chapter 10, Management of the hearing impaired child), there has been an increased opportunity to diagnose these children early and therefore to implant them before 12 months of age. Parallelling this, there has also been an increased development of clinical and surgical skill, improved technology and a wider awareness of the benefit of speech understanding of implanted children, which have led to an increase in the number of children undergoing implantation prior to 12 months of age.[11]

Children implanted earlier have quicker language acquisition, earlier binaural skills, better language skills and can even develop along the normal path for language development.[12] Furthermore, data exist that early implantation increases the proportion of children in mainstream school and increases the cost utility of CIs significantly.[13]

Surgery in these young children is safe,[14–16] but barriers exist to early implantation. These include delays in scanning children, protracted behavioural audiology, parental concerns and waiting for surgery, but usually the greatest delay is referral from audiology/paediatric services for cochlear implantation. Newborn hearing screening, which exists in the majority of developed countries, identifies almost all of the children with congenital severe/profound hearing loss, but there is sometimes a reluctance to refer to cochlear implant centres without extended hearing aid trials and reassessment, which causes significant delays.[17]

Evidence does not yet exist that implantation below 6 months of age continues to improve outcomes further, and there is surgical concern that simultaneous implantation in very young infants carries a risk of bleeding which may be significant. Very early implantation (less than 6 months of age) is not yet a standard in paediatric implant surgery.

Postlingual deafness

Postlingual deafness in children is often due to meningitis or head injury. The outcome depends on the duration of deafness but most children who have had a period of hearing do well with CI. Recent changes in candidacy, however, have allowed other groups of postlingually deaf patients to benefit from CI. Children with auditory neuropathy spectrum disorder (ANSD) fall into this category and there is extensive ongoing work to understand this disorder better.[18, 19]

Partial deafness

An increasing number of studies have confirmed that partial deafness, most commonly high-frequency hearing loss with residual low-frequency natural hearing, is effectively treated in children with cochlear implantation.[20, 21] These children are hard to aid with conventional hearing aids because of the 'ski-slope' nature of the hearing loss. They may have limited ability to hear consonants and fricative sounds[20] though they have good low-tone hearing, which is important to appreciate music.[22] It is possible to implant with an approximately 90% chance of preserving useful hearing using a variety of electrodes.[23] Soft atraumatic electrode arrays and careful surgery are required to preserve the hearing.[24] There is an incidence of late loss of hearing a few months after the surgery, and it is usual to lose around 10–20 dB of hearing. There are speech processors that are designed to stimulate the high-frequency hearing using the electrical implant, and low-frequency hearing can be boosted with an acoustic hearing aid – combined in a single processor. This approach still allows access to interaural level and timing differences which facilitates localization of sound and binaural effects to increase speech understanding in background noise, compared to a conventional CI without low-frequency residual hearing. Once the residual hearing is below 80 dB this approach is ineffective as the residual hearing is no longer aidable – so, assuming a hearing loss due to the implant, it means that this 'hybrid' strategy is usually not attempted if the pre-operative low-frequency hearing is less than 60 dB HL.

A concern in children is that they will lose the residual hearing eventually during the natural process of ageing in the cochlear, a process which often occurs early in individuals with hearing loss. However, the modern hearing preservation electrodes are full or near full length and will function well even if the residual hearing is lost.

Single-sided deafness

Although the concept of cochlear implantation to restore bilateral hearing in adults is quite well established,[25] the value of using CROS (contralateral routing of sound) aids, bone-conducting aids or CIs is much less clear in children. Unilateral hearing loss in children results in educational deficits. Children with unilateral hearing loss are at increased risk of grade failures (24–35% vs

3% in normal-hearing children) and are more likely to require educational assistance (12–41%). Compared to normal-hearing siblings, these children have lower oral language scores, a 4.4 times risk of requiring an educational plan and a 2.5 times risk of having speech therapy.[26] Functional MRI scans have demonstrated neuroanatomical differences in auditory regions between single-sided deaf children and normal-hearing controls, but also in attention and executive control areas, and these children have a much higher incidence of behavioural problems[27] see Chapter 10, Management of the hearing impaired child.

CROS hearing aids are very poorly tolerated in children. Bone-conducting hearing aids (BCHAs) are more accepted, but the majority of children with single-sided deafness do not use them. A bone-conducting aid corrects the head shadow effect but does not give interaural level or timing differences to allow binaural hearing. Consequently, there are only modest improvements with a BCHA in localization or speech-in-noise comprehension. A CI will allow access to interaural level differences and will improve localization and speech in noise compared with BCHA, especially in situations where noise is presented to the normal-hearing ear and speech to the implanted ear. Interestingly, adults with unilateral CIs report a reduction in tinnitus; in children with hearing loss, tinnitus is often present but is rarely a major clinical problem.

There are only a few published reports of cochlear implantation in children with unilateral hearing loss.[28] However, it appears that this is as well tolerated by children as by adults who have had a sudden SNHL,[25, 29] and studies of prelingually unilaterally deaf children are underway. Early results are promising and this may be a viable treatment in the very near future. However, there may be additional issues to consider when treating congenital profound hearing loss in one ear. Animal studies indicate that, if unilateral deafness develops early and especially if it is congenital, then a period of time exists after which there is a shift in the cortical processing in preference of the hearing ear, which will influence the outcome of the second deaf ear if implanted.[30] The recommendation therefore from the animal work is to minimize the period of monaural stimulation as much as possible. Further data are necessary, investigating both short- and long-term implications of CI in single-sided hearing in children.

There will be additional prognostic factors to consider in children in addition to those in adults, such as whether the ear has ever heard, the presence of any malformations in the cochlea, the status of the nerve, the optimal window of time to implant, other comorbidities and their influence and so forth. As with bilaterally deaf children, minimizing the duration of deafness and early implantation will probably be very important in achieving good outcomes. However, significant questions remain about the cost-effectiveness of this treatment, and about the acceptability of a unilateral CI in older children and teenagers who may not wish to wear a hearing device for a unilateral disability.

Bilateral implantation

Bilateral CIs improve hearing for children with bilateral deafness beyond that which can be realized with a unilateral CI.[31] The aim in children is to promote important auditory processing that normally occurs when listening with two ears. Binaural hearing skills are normally acquired very early on; by 6 months of age, children with normal hearing show consistent lateralization of sounds by turning their heads. This means that small differences in interaural timing and level differences are detected and perceived by the auditory pathways. Speech comprehension in noise and localization are compromised when sound is heard from only one side or through only one CI but can be improved with bilateral CIs in both adults and children.[32]

Children receiving a sequential bilateral implant with an interval of several years have demonstrated significant asymmetries in brainstem and cortical function compared with those with a delay of less than 1 year or simultaneous implantation.[7] These children have demonstrated poorer speech scores in the second ear compared to the first, stronger ear.[33]

A most telling outcome of bilateral cochlear implantation is that children with two implants almost universally wear both devices and demand to have any equipment breakdowns (depleted batteries, broken components or device failures) repaired. Children and families also report improved hearing in the 'real world' even when outcomes measured in the audiological sound booth are minimal, which probably reflects the increased complexity of most listening situations beyond the quiet test environment.[34, 35]

Nevertheless, there are still many children around the world who receive a single implant or sequential implants. The main reason for this is financial. A number of children have residual hearing in the unimplanted ear and can benefit from bimodal (CI + hearing aid) amplification. There are also surgical concerns about bilateral simultaneous implantation (although there is no evidence to suggest a higher complication rate)[14, 36] and about possible vestibular dysfunction.

Assessment

Assessment for candidacy needs to be conducted in a specialized multidisciplinary team. In the UK the audiological guidelines for implant candidacy as per guidelines set by NICE[6] include severe to profound deafness (defined by thresholds of 90 dB or worse at frequencies of 2 kHz and 4 kHz without amplification) that preclude the child from attaining adequate speech, language and listening skills appropriate to age, developmental stage and cognitive ability with optimal acoustic amplification.

As with adults, assessment in children involves a battery of sound detection and speech perception tests, though the latter are somewhat limited in infants and in prelingual profound deafness. Preceding implantation, children undergo electrophysiological testing in the form of an auditory brainstem response (ABR) to obtain the true thresholds of the child. This may be acoustic and, if necessary, also

electric. In cases of auditory neuropathy, children may have an absent or abnormal ABR and thus otoacoustic emissions. Electrocochleography (ECoG) or eABR may also form part of the general battery of investigation for assessing candidacy for a CI. Aided thresholds and behavioural tests are important as well as speech perception tests but are conducted in an age- and disability-appropriate manner. Similarly, a hearing aid trial is offered to those children who may benefit from a trial or whose candidacy may be ambiguous, such as in the setting of ANSD.

In addition to the audiological factors that play a central role in candidacy, many other factors influence the outcome of children and thus a multidisciplinary assessment is very important.

Screening

Newborn hearing screening is now the accepted standard of care in most countries.[37] The National Health Service (NHS) Newborn Hearing Screening Programme (NHSP) was commissioned by the Department of Health in 1997 following a National Institute for Health Research (NIHR) Health Technology Assessment report which showed that a large number of deaf children were not being identified. Between 2001 and 2006 universal newborn hearing screening (UNHS) was implemented in England, Scotland, Wales and Northern Ireland and it is now estimated that, between 2006 and 2011, 74% of eligible children between 0 and 3 years had been implanted and 94% by age of 17.[38]

Medical assessment and imaging

A detailed history and examination should be conducted to evaluate the cause of the hearing loss, including prenatal and perinatal history to assess for risk factors some of which include TORCH infections (toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], rubella, cytomegalovirus [CMV] and herpes infections), teratogens, prematurity, low birthweight, low APGAR scores, hyperbilirubinaemia, sepsis, meningitis and the administration of ototoxic medications. Other aspects of medical evaluation include a detailed family history, assessment for the presence of syndromes, immunization status and the presence of other otological disease which also involves the use of dedicated imaging of the temporal bone and knowledge of the status of the cochlear nerve.

Genetic hearing loss

The incidence of congenital hearing loss in the UK equal to or worse than 40 dBHL is somewhere in the order of 1 in 1000 children, with nearly 60% of these children having a genetic cause of deafness. It is estimated that 70% of genetic causes of hearing loss is non-syndromic and of these nearly 80% are inherited in an autosomal recessive manner.[39] The other 20% constitutes autosomal dominant, X-linked and mitochondrial DNA variant abnormalities. Although numerous loci of abnormalities have been characterized, the most common defect – constituting nearly 50% of all non-syndromic hearing loss – is a mutation in connexin 26 which codes for a gap junction protein beta 2.[40]

Syndromal deafness is less common and, although there are over 400 syndromes associated with hearing loss,[41] some common ones include Pendred, Usher syndrome and Jervell and Lange-Nielsen which are inherited in an autosomal recessive manner. Autosomal dominant syndromes include Stickler, branchio-oto-renal and Waardenburg syndrome.

Neurofibromatosis type 2, which can present later in childhood, is characterized by bilateral vestibular schwannomas (VS). Until recently, the presence of a schwannoma was considered a contraindication for CI. However, recent studies have reported successful outcomes of CI in untreated but stable VS, or in VS that has been stable following radiotherapy. When the tumour is growing and/or cochlear nerve preservation in not possible, an auditory brainstem implant (ABI) is another option.[42] (See Chapter 102, Surgical management of vestibular schwannoma, for more information).

Acquired hearing loss

Some of the causes of acquired hearing loss are outlined above. Although many such forms cannot be distinguished from genetic causes in young children, a thorough history may help provide helpful information, such as a history of prenatal infection with toxoplasmosis, syphilis, rubella, cytomegalovirus or herpes (TORCH microorganisms), and/or a perinatal history of prematurity, low birthweight, low Apgar scores and hyperbilirubinaemia.

Cytomegalovirus (CMV) is particularly interesting as early treatment with valganciclovir can prevent further hearing loss, or in a few cases bring about recovery in hearing. The optimum duration of treatment is not yet known, although 6-week to 6-month courses have been used. Early treatment appears to be more effective than later treatment.[43]

Meningitis, temporal bone trauma and rarely autoimmune inner ear disease may cause profound hearing loss and subsequent cochlear ossification. There have been reports of strategies that may be utilized to overcome partial and total ossification of the cochlea, including drilling out the basal turn, scalae vestibuli insertion and even the insertion of short or split electrodes. These procedures are, however, uncommon and therefore not well trialled and may risk damaging the neural elements. Nevertheless, they help emphasize the importance of a thorough medical and radiological evaluation in a multidisciplinary setting to inform the patient of the likelihood of success of implantation and also of the medical and psychosocial hurdles that lie in the path of postoperative rehabilitation.

Congenital malformations

About 20% of congenital SNHL can be attributable to inner ear malformations. Development in modern imaging and clinical experience has led to improved diagnosis and management of these disorders with respect to

cochlear implantation. The two main difficulties in surgery with malformations are CSF gusher and facial nerve abnormalities. Balanced with these is also a higher risk of meningitis with inner ear malformations with or without cochlear implantation.[44] Malformations were first divided into five main abnormalities: Michel deformity (labyrinthine aplasia), cochlear aplasia, common cavity, cochlear hypoplasia and incomplete partition. Minor adjustments have been recommended based on radiological differences of these abnormalities, subclassifying incomplete partition into three further categories depending on degree of severity. Type 2 incomplete partition, first described by Carlo Mondini, consists of a normal size cochlea with deficiency of the apical part of the modiolus and the corresponding interscalar septum. Together with a minimally dilated vestibule and a large vestibular aqueduct, a Type 2 incomplete partition forms the triad called the Mondini deformity. Incomplete partition Type 3 was reported in X-linked deafness.[45] In cochlear hypoplasia the normal cochlea turns do not form fully.

Pre-operative imaging therefore plays a very important role. An MRI not only is important in confirming the presence of a cochlear nerve in the presence of pre-lingual deafness, but will also show the turns of the cochlea and the anatomy of the vestibule. Furthermore, in cases where a CT scan may identify a narrow internal auditory canal, an MRI is also important to confirm that the nerve is present and not hypoplastic, especially when associated with certain syndromes such as CHARGE (coloboma, heart defects, atresia choanae, retardation of growth, genital anomalies and ear abnormalities). An absent cochlear nerve is a contraindication for CI. A finding of a hypoplastic cochlear nerve needs to be assessed individually, which may involve further imaging or an electrically evoked ABR.

High-resolution computed tomography (HRCT) helps to display the anatomy of the mastoid and the facial nerve as well as identify any malformations in the cochlea, the internal acoustic canal and other ear malformations. Altered facial nerve course is seen particularly in cochlear hypoplasia and common cavity. A hypoplastic cochlea may make for a difficult electrode insertion through a facial recess, as the round window may not be found in the usual area or the flatter profile of the promontory may mislead the surgeon. In these cases, alternate approaches such as a transmastoid labyrinthotomy, canal wall-down with a blind sac closure of the external ear canal or even a transcanal approach or insertion through the oval window may need to be employed.[46] Identifying the malformations also helps with the choice of electrode. Where the exact location of the neural tissue is not known, for example in a common cavity, an electrode with complete contact rings is likely to be more beneficial whereas in a hypoplastic cochlea, a shorter electrode may need to be used. Alternatively, in incomplete partition Type 2 all types of electrodes may be used.

Although there has been debate over which modality (MRI or CT) is more important in children, most implant teams utilize both CT and an MRI in the pre-operative planning of a CI as they each have their advantage and in the setting of malformations provide complementary information. It is important that these take place early in the workup of these patients to help guide them towards appropriate rehabilitation.

Auditory neuropathy spectrum disorder

First described in the mid-1990s,[47] auditory neuropathy is a hearing disorder characterized by the presence of outer hair cell function (evidenced by the presence of intact evoked otoacoustic emissions and/or cochlear microphonics) but abnormal or absent auditory brainstem response. However, due to the multifaceted nature of the aetiology of this condition and the recognition that the abnormality is not localized to the cochlear nerve, but may involve other defects such as inner hair cell/synapse or a synchronization of the signals being transmitted, the terminology was expanded to auditory neuropathy spectrum disorder (ANSD).[48]

Although the prevalence varies between studies and is difficult to quantify accurately, it has been estimated to be present in up to 1 in 10 children with permanent hearing loss.[49] The manifestation of this disorder involves difficulty hearing in noise, fluctuating sensitivity and speech perception scores not consistent with the level of residual hearing on the audiogram.

The aetiology can be multifactorial including genetic, congenital and acquired causes. Risk factors for ANSD include extreme prematurity (<28 weeks gestation), hyperbilirubinaemia reaching exchange transfusion levels, low birthweight or intrauterine growth restriction, and other neurological conditions such as hypoxic ischaemic encephalopathy and intraventricular haemorrhage (likely to occur in prolonged ventilation and sepsis). Genetic causes include Freidrich's ataxia, Charcot–Marie–Tooth disease and non-syndromic conditions such as DFNB9/*OTOF*.[50]

The electrophysiological tests constitute definitive diagnosis but, due to the heterogeneous manifestations of the ANSD, the recommended habilitation approach and choice of assisting device (whether it be a hearing aid or CI) remains controversial. The approach in children suffering with ANSD therefore has been to address patients on their own individual needs. Children with ANSD with cochlear nerve hypoplasia on MRI have worse CI outcomes and those with an absent cochlear nerve are unsuitable for CI.[51] Similarly, children who exhibit an atypical or absent ECAPs (electrically evoked compound action potentials) during implantation are also associated with poor outcomes.[52] Therefore, though a significant proportion of children will benefit from CI, some will benefit from amplification and some others who have bilateral cochlear nerve deficiency will not benefit from either intervention. Reasons for this heterogeneity with CI may be associated with their other comorbidities or with the failure of the electrical stimulus from CI to create adequate neural synchronization of signals. Thus a stepwise approach in a specialized multidisciplinary team is crucial to help guide the habilitation of these complex patients.

Chronic suppurative otitis media

Chronic suppurative otitis media (CSOM) was previously considered a contraindication to cochlear implantation. More recently, surgeons have applied a staged technique, in clearing the disease in the first stage and then performing an implant a few months later when the ear is dry. It is important to eradicate the source of any biofilms prior to the insertion of the CI. Some surgeons prefer to obliterate the mastoid cavity at the same time as the first operation, but the risk of future development of cholesteatoma remains and follow-up is made difficult due to the artefact created by a CI while using a diffusion-weighted MRI scan. In the presence of a dry, stable cavity, a blind sac closure and CI may be undertaken as a single stage.

Surgery

In most cases, cochlear implantation may be safely performed as a day-case[16] although in infants it is often sensible to admit overnight, especially if the surgery is in the afternoon.

INCISION

A postauricular approach with a small incision is preferable. The optimal incision for access has evolved over time. The general principles of the incision, irrespective of individual preferences, are that the incision should not be placed near the receiver/stimulator, to prevent skin breakdown and extrusion and also to ensure that blood supply to the region is not compromised. More complications relating to the skin are associated with a history of previous radiotherapy to the area.

APPROACH

Subperiostial flaps are raised and the mastoid exposed. A small cortical mastoidectomy is performed with a posterior tympanotomy. The round window should be identified and the surgically important landmarks include the incus short process, the facial nerve, chorda tympani nerve, incudostapedial joint and round window membrane.

RECEIVER/STIMULATOR PACKAGE

A bony recess which is specific to the device intended is drilled. The cortical bone is very thin in young children and at times the entire thickness of the cortical bone may be removed to the level of the dura to accommodate the receiver/stimulator and minimize skin complications. There are various ways to secure the electrode to prevent electrode migration, including drilling holes and tying sutures over the electrode or securing it with bone wax.

ROUND WINDOW VERSUS COCHLEOSTOMY

With the advent of electroacoustic stimulation in patients with residual low-frequency hearing there has been much interest in examining whether a round window perforation or cochleostomy is preferable. The advantage of a round window approach is that a small perforation can be made by a needle in the round window which helps seal the entry site of the electrode into the cochlea. Furthermore, there is no need for intracochlear drilling. A cochleostomy should be placed inferior to the round window. This involves meticulous drilling with exposure of the endosteum, which needs to be removed with a small hook thereby minimizing the trauma to the cochlea and preventing the entry of bone dust or blood into the cochlea. Both techniques have been shown to preserve low-tone hearing, and to minimize cochlear trauma. 'Soft surgery' may also minimize scar formation within the cochlea if the child needs revision surgery in the future.

Once the electrode has been inserted, the electrode entry is packed with fascia or periosteum at the site of entry to prevent leak of perilymph. In the case of residual hearing it is important not to overpack the middle ear as it may cause a degree of conductive hearing loss of the residual hearing frequencies.

NEURAL RESPONSE TESTING

Most units in the UK perform intra-operative testing to confirm electrode integrity and measure impedance.

BILATERAL SURGERY

This requires bilateral facial nerve monitoring. Care must be taken to plan the placement of the devices at the same level behind the ear so there is symmetry when the patient wears the external device.

POST-OPERATIVE RADIOGRAPH

A post-operative X-ray (Stenver's view) helps to confirm electrode insertion, identify potential tip foldover, and give a reference for the correct placement of the electrode in the cochlea should there be future problems. If required, radiographs, fluoroscopy and/or image guidance may also be used intra-operatively in cases of expected difficulty such as revision cases or congenital malformations.

Complications

Complication rates in paediatric cochlear implantation are in the order of 10% with major complications constituting < 3%. Malformations of the cochlea make for a higher incidence of complications.[14, 36, 53]

INFECTIONS

Wound infections constitute nearly half of all complications in children and a course of peri-operative antibiotics is important to minimize this.

FACIAL NERVE INJURY

With the use of facial nerve monitoring facial nerve paresis in a paediatric population is rare, though a rate of chorda tympani nerve injury between 5% and 20% has been reported.[54]

CSF FISTULA

This is rare and can occur early or late with an incidence of 1%. Secondary meningitis may occur but is extremely rare. It is important to pack the cochleostomy adequately to prevent this, especially in the presence of an enlarged vestibular aqueduct.

DEVICE FAILURE

The rate of device failure of contemporary CIs has been reported as <1%. Late device failure is difficult to predict and may even be difficult to diagnose in the setting of a developmentally delayed child or one with numerous comorbidities.

CHOLESTEATOMA

Secondary cholesteatomas, though rare, have been reported. It is important to stabilize any ear disease prior to embarking on cochlear implantation. Early retraction pockets may be repaired by cartilage tympanoplasty. Secondary cholesteatomas may need a radical mastoidectomy with blind sac closure and removal of all squamous epithelium but the inability to monitor the cavity for recurrence is a drawback.

POST-OPERATIVE MRI

If necessary for the patient, an MRI can be conducted in the presence of CI using a 1.5 Tesla MRI scanner. If the magnet of the receiver stimulator is left *in situ*, an ovoid void is created of approximately 60 mm × 100 mm in size compared to 35 mm × 55 mm size if the magnet is removed. The image quality is inferior in the immediate region of the void surrounding the receiver/stimulator but the rest of the image is of high quality. Tight head bandaging is recommended to avoid movement of the receiver/stimulator. Pain and discomfort during scanning can be alleviated by the injection of local anaesthetic to the area of the receiver/stimulator prior to head bandaging. Occasionally, movement of the internal magnet occurs, but this can usually be corrected by replacement of the magnet at a later stage.

MED-EL now have a rotating magnet design which allows the magnet to move within the implant to align with the magnetic field. This allows use of a 3T MRI and reduces the risk of discomfort and dislodgement of the magnet. However, the artefactual degradation of the image on the ipsilateral head is still present.

Post-operative rehabilitation

Specialist multidisciplinary support including audiologists, speech therapists and educators is crucial to the successful rehabilitation of implantation. Patients are typically seen at 2–4 weeks for 'switch on' and ongoing follow-up and support are required to enable optimal use of the implant and for acquiring appropriate speech and language development.

There is no doubt that there are multiple benefits from CI in children. After only 1–4 years of implantation, paediatric patients can demonstrate speech and language skills equivalent to their hearing counterparts. Prognostic factors influencing outcome include age at implantation, age of onset, residual hearing, use of hearing aids, other comorbidities, family support, post-operative rehabilitation and consistent use of the implant. Despite the best support and rehabilitation, in certain children, especially those with complex needs, it is more important to measure outcome with a quality-of-life measure than with traditional measures of outcome. In these children, it may be unrealistic to expect the development of oral language and therefore it will not accurately reflect the benefit that CI can give in providing the awareness of sound in the life of a child who is already deprived of many other psychological, sensory and social inputs.[55]

Extended candidacy

Different criteria for candidacy have been adopted in different health economies. In the UK the NICE (National Institute for Health and Care Excellence) guidelines determine candidacy: for children this is 90 dB hearing loss at 2 kHz and 4 kHz, with evidence of delayed speech and language development. However, children with hearing above these thresholds benefit from cochlear implantation in certain circumstances. There are numerous reports of children with asymmetric hearing loss benefiting more from the implanted side than the hearing aid side.[55] Furthermore, the outcomes after cochlear implantation in around 80% of children with hearing thresholds of 80–90 dB are better than can be achieved with hearing aids. This raises the possibility that current guidelines are too restrictive, and that a wider range of severely deaf children could be offered CIs, especially as residual hearing can usually be preserved allowing hybrid electroacoustic stimulation in both ears.[56]

Future technologies

The technological advancement of auditory implants continues apace and, in fact, it is likely that any report on this will be out of date within a few months, and certainly within several years. The following current areas of development look to be fruitful.

ELECTRODE DESIGN AND INSERTION

There are a number of electrodes developed by commercial implant companies which allow hearing preservation and deep insertion into the cochlea for 'complete cochlea coverage', and custom electrodes for anomalies in cochlea anatomy. Insertion forces appear to be crucial to maintain a healthy cochlea for long-term health of the inner ear, as well as hearing preservation. Robotic insertion to reduce these forces further is an active area of research interest with promising early studies.

NEUROTROPHINS AND GENE THERAPY

A CI is a promising conduit for delivering growth factors directly or by gene therapy techniques, as well as electrical stimulation to prolong and increase neural response. Recent animal studies have shown great promise in animal models, but these have not yet been translated to human trials.[57]

TOTALLY IMPLANTABLE IMPLANTS

Adults implanted with totally implantable devices have found outcomes limited by the subcutaneous microphone.[58] Newer devices may use the ossicular chain as a microphone for middle ear stimulation, and the translation of this technology to CIs is inevitable.[59] However, at this point, no totally implantable CIs have been used in children.

IMPROVED PROCESSING STRATEGIES

Sound processing strategies to improve the appreciation of music and to allow speech discrimination in background noise are actively being developed and released. Bidirectional microphones to determine sound direction, and communication between bilateral cochlea implants, along with automatic programmes that especially suit children, give better outcomes and are often retrospectively available to previous versions of CIs.

IMPROVED USER EXPERIENCE

Already, CI processors are routinely available which are compatible with add-on devices by Bluetooth™, or Wi-Fi signals. The processors are water-resistant, and in some cases waterproof, to allow swimming and showering while hearing. Off-the-ear solutions to minimize the visibility and improve the comfort of the processors are also helpful to some patients, although CIs still use significant power and so battery size can limit the size of devices. Finally, data logging and feedback to audiologists to help with tuning and remote management of devices to save on clinic visits can make life easier for patients and their families.

AUDITORY BRAINSTEM IMPLANTS

Auditory brainstem implants (ABI) are auditory prostheses designed to provide electrical stimulation directly to the cochlear nucleus in the absence of a functional cochlear nerve (**Figure 11.2**). First used in 1979 by William House and William Hitselberger after removal of an acoustic neuroma, their use has been mainly reserved in the setting of NF2.[60] Colletti et al first reported their use in a paediatric setting.[61] Use in prelingually deaf children remains primarily in those children in whom CI is contraindicated, for example in complete labyrinthine aplasia or congenital malformations with cochlear nerve hypoplasia or aplasia. In postlingual deafness, an ABI may be indicated in tumour or non-tumour patients. Tumour patients include patients affected with NF2 or bilateral VS whereas non-tumour patients include those with bilateral severe cochlear ossification (which may be secondary to meningitis), gross cochlear destruction from otosclerosis, other surgical conditions precluding CI, and fractures through the IAC causing cochlear nerve avulsion or unmanageable facial nerve stimulation post CI.[62]

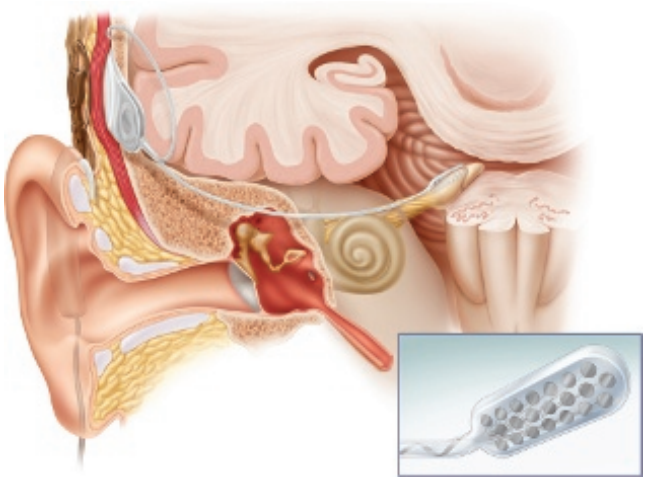

Figure 11.2 Schematic diagram of ABI placement on auditory nuclei. The insert shows the panel of electrodes.

Long-term results are still pending but audiological outcomes are not seen to parallel CI. Open-set speech discrimination only occurs in occasional cases and therefore a CI where possible should always be the first option. Furthermore, a CI is easier and safer to implant, with a much lower risk of life-threatening complications. Prior to considering a paediatric ABI, therefore, very careful radiological assessment and electrophysiological testing (e.g. eABR) is crucial. In the setting of prelingual deafness, outcome will depend on early intervention and therefore it is important to identify candidates through newborn screening and subsequent medical and radiological assessment.

The optimal age for elective intracranial surgery is 18–24 months, but in some experienced centres the minimum age for an ABI can be regarded as low as 1 year. Earlier intervention carries the risk of hypovolaemia through CSF and blood loss, poorly formed lateral recess size and higher risk of brain swelling post-op but delayed intervention loses the benefit of cortical plasticity. Parents and carers need to be counselled prior to embarking on surgery that for prelingual recipients programming and rehabilitation is a lot more intensive that for CI and the results are not as good.

BONE-CONDUCTION HEARING IMPLANTS

Children with malformations of the external and middle ear or children who cannot use air-conduction hearing aids may be aided by bone-conduction hearing implants

(BCHIs). Surgical reconstruction of congenitally abnormal ears is performed in some centres but even in successful cases an air–bone gap of 20–30 dB may remain. Consequently, bone-conduction hearing aids have become widely used and with time, the indications, surgical techniques and number of available devices have continued to evolve.

Indications

Current indications for use of bone conduction devices in a paediatric setting include:

- conductive hearing loss
- congenital causes such as atresia or microtia
- acquired causes such as chronic otitis media or ossicular pathology
- chronic discharging ear (such as CSOM or recurrent otitis externa)
- unilateral mixed or profound hearing loss
- failure of the child to tolerate a conventional hearing aid.

Bone-anchored hearing aids

The first bone-anchored hearing aid (BAHA) was implanted in Sweden in 1977[63] and became commercially available in 1987. These hearing aids function by transmitting sound through bone via an osseointegrated abutment (Figure 11.3).

AGE OF IMPLANTATION

The US Food and Drug Administration have set a minimum age for paediatric use at 5 years. However, the minimum age for implantation is debated and there is no fixed worldwide guideline. In 2005 an international consensus was issued regarding bone-conduction hearing aids which recommended that surgery should not be undertaken prior to the age of 2–3 years. This was to allow the skull thickness and conditions to reach a minimum thickness to fit the fixture and allow osseointegration.[64]

Though successful implantation has been reported in a child as young as 14 months, the complication rate is inversely proportional to the age of implantation.[65] It is important to stimulate hearing as early as possible, and therefore in children too young for implantation the use of a bone-conduction hearing aid via a Softband™, which holds the hearing aid to the skin of the scalp via a metal or elastic headband, is advocated from about the age of 3 months.

Figure 11.3 Diagram of percutaneous bone-anchored hearing aid with titanium fixture in the bone (1), abutment (2) attaching to the fixture and hearing aid (3) (placed later and removable by patient).

SURGICAL CONSIDERATIONS

In the past BAHA surgery on children was staged, but tissue-preserving single-stage implants mean this is no longer necessary. The linear insertion technique eliminates the need for a skin flap. More recently, changes in device design have enabled preservation of soft tissue which both decreases the complication rates and also significantly reduces surgical time. However, in children a longer time to osseointegrate is recommended to compensate for the thinner calvarium.

COMPLICATIONS

Despite the advantage of the bone-conduction hearing technology, major short- and long-term complications of the percutanous implants in children include soft-tissue complications and fixture loss. Classification of soft-tissue complications are staged by Holger, ranging from 0 to 4, with 0 being reaction free skin around the implant and 4 being overt infection requiring implant removal. These complications seem to affect children more than adults and are associated with a higher rate of fixture rate loss (up to 14% over 15 years) in the paediatric population.[66] A much higher rate of fixture loss occurs when the shorter 3 mm fixture is placed, and so a 4 mm fixture should always be used. This involves depressing the dura during the implantation in all but the largest children.

CURRENT DEVICES AND RECENT MODIFICATIONS

Cochlear

In 2010, Cochlear introduced changes to the osseointegrated titanium fixture which included a wider base (4.5 mm versus 3.75 mm) for increased stability, smaller treads at the implant neck to improve load distribution and a Tioblast™ coating for faster osseointegration to the BI300 system. In 2012, it further modified the abutment with a hydroxyapatite coating (BA400) which

eliminated the need for soft-tissue reduction. The abutment sizes became longer to adapt to the thickness of the skin. Challenges in a paediatric setting include accommodating for growth and increases in soft-tissue thickness especially during puberty. The abutment is available in various lengths and may be changed to adapt to the child's growing needs.

A new transcutaneous system, the BAHA Attract, uses a magnet to secure the BAHA. While a major advantage in a paediatric setting is eliminating the soft-tissue complications of a BAHA, disadvantages include problems with future MRI scans and possible dampening of the signal through the skin.

Ponto

Oticon Medical introduced the Ponto in 2009, which is another bone-anchored hearing system. Similar to the Cochlear BAHA system, it comprises an implant, percutaneous abutment and external processor and – similar to the Cochlear BA400 system – has long abutments available which enable tissue-preservation surgery. The results are comparable and it is a well accepted option for a bone-conduction hearing device.

Middle ear implants

Middle ear implants, in selected patients, offer an option of hearing rehabilitation in conductive, mixed or SNHL. A worldwide consensus regarding the application of the vibrant soundbridge (VSB) found it is viable for use in children and adolescents if they have adequate anatomy to place the VSB, but each case and each treatment option should be weighed on its individual advantages and disadvantages.[67] The floating mass transducer may be connected to the incus long process, stapes remnant or round or oval window.[68, 69] The patient should be counselled about surgical issues and MRI compatibility and the risk of dislocation of the device with future MRI.

Bone Bridge

A transcutaneous bone-conduction hearing aid, which is indicated in conductive or mixed hearing loss as well as single-sided hearing – the Bone Bridge – was released by MED-EL corporation in September 2012. The device consists of an external audio processor and an internal bone-conduction implant. The internal component has an internal receiver coil, a magnet, a demodulator and a bone-conduction floating mass transducer (FMT) that is secured to the bone by two titanium screws. The power to drive the FMT and sound energy are transmitted transcutaneously via an inductive link to the internal coil, processed by the demodulator and then relayed to the BC-FMT, which then tranduces the signals into mechnanical energy. Osseointegration of the titanium screws is not thought to be crucial.

CONCLUSION

New devices continue to be introduced and current technology continues to evolve. With time, new indications continue to arise in the treatment of paediatric deafness. Despite the rapid introduction of new technology, it is important that the introduction and application of this into patient care be conducted in a rigorous evidence-based manner. To achieve this, it is essential that good collaboration continues between clinicians and industry and, most importantly, that regular and thorough feedback is obtained from patients and caregivers regarding the influence of new developments on their quality of life.

FUTURE RESEARCH

- ➤ Current areas of development in cochlear implant technology are discussed above.
- ➤ Fully implantable bone conducting devices will avoid skin complications in future but must increase gain to be suitable for all patients.
- ➤ The optimum rehabilitation of the child with single-sided deafness is still in evolution and awaits stronger evidence of benefit.

KEY POINTS

- Auditory implants can rehabilitate children with conductive and sensorineural hearing loss.
- Early, preferably bilateral, rehabilitation improves outcomes.
- Identification and rapid assessment of deaf children is essential.
- The technology is advancing quickly and should result in better outcomes in the future.

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CHAPTER 12

CONGENITAL MIDDLE EAR ABNORMALITIES

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SEARCH STRATEGY

Data in this chapter may be updated by a search of the Guidelines databases on www.library.nhs.uk, the Cochrane library and TRIP databases using the keywords: congenital, middle ear and ossicle. This was supplemented by a PubMed search using the keywords: congenital and middle ear or ear, ossicle.

INTRODUCTION

Conductive hearing loss in children is usually acquired. The most common aetiology is otitis media with effusion (OME) but it may be the result of chronic otitis media (mucosal or squamous). In the presence of severe congenital deformity of the external ear, associated abnormalities of the ossicular chain are common but in isolation they are rare and often have a delayed diagnosis, particularly if unilateral.

A variety of non-ossicular congenital middle ear abnormalities may also be associated with ossicular deformities. They may be symptomatic in themselves or be important aspects of other middle ear conditions and surgery. They include:

- persistent stapedial artery
- anomalous course of the facial nerve
- congenital perilymphatic fistula
- high jugular bulb
- aberrant internal carotid artery.

Definition of congenital ossicular abnormalities

Congenital ossicular fixation and defect is defined as a malformation affecting the ossicular chain, present at birth, which leads to a dysfunction of the ossicular mechanism due to immobility or discontinuity of the ossicular chain.

Major malformations involve both the tympanic cavity and the external ear (ear canal and pinna) and are described as congenital aural atresia or microtia. In association with these conditions, in either sporadic cases or as part of a syndrome such as Treacher Collins or Goldenhar, there may be a variable degree of ossicular abnormality and there may also be associated inner ear dysplasia.

Minor malformations affect the ossicular chain alone and the tympanic membrane and ear canal are normal.

CLASSIFICATION OF CONGENITAL OSSICULAR ABNORMALITIES

There have been many published classifications based on individual surgeons' series.[1] Cremers' classification describes the largest published series of operated minor congenital ear anomalies (104 cases).[2] It has been modified by Tos[3] and seems to be the most inclusive and descriptive of all the published schemes (**Table 12.1**).

Minor malformations are divided into four main groups, each of which may be subdivided: isolated stapes ankylosis, ankylosis with other ossicular anomaly, isolated ossicular anomaly, and aplasia or severe dysplasia of the oval or round windows.

TABLE 12.1 Cremers' classification of minor congenital anomalies of the ossicular chain in 144 operated ears (modified by Tos) (reproduced from Tos,[3] with permission)

Class	Main anomaly	Subclassification	% ears operated (*n* = 144)
1	Isolated congenital stapes ankylosis (or fixation)	1. Footplate fixation a. Normal stapedial arch b. Monopodial stapedial arch c. Monocrural stapedial arch 2. Stapes suprastructure fixation a. Elongation of the pyramidal eminence b. Stapes - pyramidal process bony bar c. Stapes - facial canal bony bar d. Stapes - promontory wall bony bar e. More than one bony bar	30.6
2	Stapes ankylosis associated with another congenital ossicular chain anomaly	1. Incus and/or malleus deformation or aplasia of the long process of the incus 2. Bony fixations of the malleus and/or incus	38.2
3	Congenital anomaly of the ossicular chain but mobile stapes footplate	**Discontinuity of the ossicular chain** Aplasia of the long process of the incus Dysplasia of the long process of the incus	15.3
		Epitympanic fixation Malleus Anterior Superior Lateral Incus body Superior Lateral Medial Short process of the incus In incudal fossa **Tympanic fixation** Of the malleus handle Of the long process of the incus	6.3
4	Congenital aplasia or severe dysplasia of the oval or round window	**Aplasia**	6.9
		Dysplasia	
		Crossing (prolapsed) facial nerve Persistent stapedial artery	2.1 0.7

INCIDENCE OF CONGENITAL OSSICULAR ABNORMALITIES

Bergstrøm[4] reported that out of a group of 687 children with congenital hearing loss, only eight (1.2%) were found to have isolated middle ear anomalies. There is no systematic report of absolute incidence though Thringer et al.[5] reported the incidence of conductive hearing loss, severe enough to require amplification, to be 0.6:1000. These cases were all bilateral. The incidence of unilateral cases is unclear.

Cremers and Teunissen's series[2] does provide a relative incidence with stapes ankylosis with another associated ossicular chain anomaly being the most common finding (38%) with isolated stapes ankylosis being the other largest group (30%). Isolated anomaly of the ossicular chain was found in 22% and aplasia or severe dysplasia of the oval or round windows in 10%.

In a Japanese surgical series, Hashimoto et al.[6] reported a much higher rate of incudostapedial joint defects, either in isolation or with stapes fixation, making up nearly 50% of cases.

The majority of Cremers' cases were sporadic although in 25% they were part of a recognizable congenital syndrome including branchio-oto-renal, hemifacial microsomia, Klippel–Feil, Crouzon and Pfeiffer syndromes.

CLINICAL PRESENTATION OF CONGENITAL OSSICULAR ABNORMALITIES

Children with bilateral ossicular abnormalities will often present at a similar age to children with OME because of poor hearing performance and speech delay. It is not unusual that the children are managed with one or more sets of ventilation tubes before the diagnosis is made. The observation of a conductive hearing loss, normal tympanic membrane and normal middle ear pressure should lead to the general diagnosis.

INVESTIGATION OF CONGENITAL OSSICULAR ABNORMALITIES

Audiometry

There is an average threshold of approximately 50 dB, producing a flat air conduction line, with no low-frequency bias as with otitis media. There is an average air-bone gap (ABG) of 35 dB at 0.5-2 kHz, either due to Carhart's effect or because of the presence of an underlying sensorineural hearing loss. Tympanometry usually demonstrates a normal middle ear pressure with reduced compliance due to fixation of the ossicular chain.

Imaging

High resolution computed tomography (CT) scanning remains the primary imaging modality though complementary magnetic resonance imaging (MRI) studies may demonstrate associated labyrinthine and internal auditory meatal abnormalities. CT virtual endoscopy may offer a further mode of presenting the images for pre-operative surgical planning although currently it fails to image satisfactorily the stapes suprastructure.[7]

Exploratory surgery

The diagnosis may only be made during a tympanotomy, but an interesting alternative to lifting the tympanic membrane is to attempt to visualize the ossicles via Eustachian tube and middle ear endoscopy.[8] The innate risk of damage to the ossicles and extent of view with this technique is not yet well defined.

PRINCIPLES OF MANAGEMENT

As with all cases of hearing loss, children and adults with congenital ossicular abnormalities need to be managed with thought to their overall hearing performance and requirements.

In the presence of a bilateral moderate hearing loss due to a maximal or near-maximal conductive hearing loss, some form of auditory rehabilitation should be recommended. For the majority, this will mean a conventional unilateral or bilateral air conduction hearing aid. With minor malformations there should be a stable external ear canal as a platform for amplification. If the patient develops local complications in the external ear canal, such as recurrent or chronic otitis externa, a bone-anchored hearing aid (BAHA) would be a suitable alternative.

Unilateral cases are less well defined in terms of best management. In the presence of ipsilateral tinnitus, amplification may act as a tinnitus masker. A hearing aid may improve the patient's hearing performance in background noise and optimize sound localization. The positive benefits need to be weighed against the potential morbidity of a conventional hearing aid, which includes the occlusion effect, otitis externa and the body image issues involved in wearing hearing aids, particularly among children and adolescents.

Surgery for congenital ossicular abnormalities should only be undertaken by dedicated otologists with experience of complex middle ear reconstruction. When the diagnosis has been made in childhood, consideration for surgery should be preceded by an adequate trial of amplification. Whatever middle ear surgery is contemplated, but particularly with stapedotomy, there is a significantly higher risk of delayed sensorineural hearing loss due to sporadic episodes of acute otitis media in children under 10 years of age. By this time it may be appropriate to involve the child in the decision-making process or to wait until adolescence or adulthood to allow the patient to come to their own decision regarding surgical treatment.

A pre-operative CT scan would be a mandatory investigation to attempt to identify the ossicular abnormality, but also to visualize any other middle or inner ear abnormality such as an anomalous facial nerve, congenital cholesteatoma, aberrant vascular structures or labyrinthine dysplasia.

MANAGEMENT OF SPECIFIC CONGENITAL OSSICULAR ABNORMALITIES

Isolated stapes ankylosis

Tos[3] subdivided Cremers' basic classification to separate stapes ankylosis into two main groups, depending on whether the footplate or suprastructure is fixed (see **Table 12.1**). In 20% of cases the suprastructure may be abnormal, with one crus being absent (monocrural) or there being no recognizable crura but instead a single strut (monopodial).[9]

Congenital stapes ankylosis at the level of the footplate was first described by Shambaugh[10] in 1952. He emphasized the clinical contrast to otosclerosis, in particular that the margins of the congenitally fixed footplate and the annular ligament are difficult to visualize since the footplate bone blends into the bone of the surrounding otic capsule.

The pathological processes leading to stapes footplate fixation are unclear. Lindsey et al.[11] concluded from a temporal bone study that fixation occurs due to failure of the annular ligament to differentiate from the lamina stapedialis. This leads to continuous ossification from the otic capsule to the footplate. Nandapalan and Tos[12] argue, however, that the cause is a subsequent ossification of the already-formed annular ligament, around 16 weeks of gestational age, because any arrest of development at this stage would be likely to cause a more widespread inner ear abnormality.

An ossified stapedial tendon may develop because of a failure of its precursor to form a tendon and instead become cartilaginous like the neighbouring precursor of the pyramidal eminence.[12] This subsequently becomes ossified, fixing the stapes. The other rare forms of fixation of the stapes suprastructure are probably caused by the

persistence of the contact between the developing stapes and Reichert's cartilage, which is usually lost as the stapes forms.

Surgery for congenital stapes footplate fixation

Pre-operative scanning may demonstrate labyrinthine dysplasia, any degree of which should alert the surgeon to an increased risk of inner ear damage. In particular, a dilated fundus of the internal auditory meatus (IAM) should be sought. This is a feature of X-chromosome-linked progressive mixed deafness with perilymphatic gusher.[13] The dilation of the IAM is associated with a defect allowing communication of cerebrospinal fluid (CSF) with the labyrinthine, which is released through a stapedotomy and leads to a high rate of sensorineural hearing loss. The high perilymph pressure may be the cause of the apparent conductive element of the hearing loss, which may mask the principal sensorineural nature of the raised air conduction thresholds. A previously reported association with a 'patent cochlear aqueduct' has been shown to have no histological basis in temporal bone studies.[14] The aqueduct is normally patent and cases of so-called 'widely patent' ducts seem to relate to a flaring on the medial aspect of the duct as it enters the jugular foramen. There is little variation in the duct as it passes through the otic capsule.

The surgical technique is similar to otosclerotic stapes ankylosis. A common feature of congenital fixation is the presence of thick anterior and posterior crura. To reduce the risk of inner ear damage these may be vaporized with a KTP laser.[15] This may also be used to aid the formation of a stapedotomy as the footplate is often thick.

Reported outcomes of surgery from specialist centres for isolated congenital fixation of the stapes nearly match the outcomes in the literature for adult series for otosclerosis, with more than 70% closure of the ABG to 20 dB or less.[6, 16] However, excellent results, with an ABG of less than 10 dB, seem less common than with surgery for otosclerosis.[17] Rates of inner ear damage are also comparable.

Surgery for stapes suprastructure fixations

In the very rare cases where the footplate is mobile but the suprastructure is fixed, removal of the bony bar can be achieved using a CO_2, argon, potassium titanyl phosphate (KTP) or erbium laser or with a microdrill. Traditionally, this has been achieved with a curette or by fracturing with good results.[12]

Isolated non-stapes middle ear anomalies

There is a large variety of described anomalies among case reports in the literature and these represent the different subclasses in Table 11.1. In addition, the stapes itself, though mobile, may be dysplastic.

The surgical management is by appropriate tympanoplasty. If there is attic fixation, then a separate atticotomy is necessary to expose the problem and allow surgical treatment. If there is a bony bar, this can be relieved by laser, microdrill or curette. A similar approach is used with fixation of the malleus handle by an atretic plate. With the absence of the long process of the incus, an interposition prosthesis is indicated.

Stapes ankylosis associated with other deformities

The potential anomalies are as described when found in isolation. Stapedotomy is again indicated but it may be necessary to consider a mobilization of the ossicular chain if there is epitympanic fixation or a malleovestibulopexy following removal of the head of the malleus.[6] Though surgery is difficult in cases of a deformed incus or fixations of the incus and malleus in the attic, reported results are good.[17]

Congenital aplasia or severe dysplasia of the oval and round windows

The stapes crura are usually poorly developed and do not reach the region of the footplate and may be embedded in the facial nerve. In such cases the course of the facial canal is often anomalous.

With such a severe abnormality preventing conduction of sound energy into the inner ear and particularly with the risk of a facial palsy with an anomalous facial nerve, auditory rehabilitation with hearing aids or a BAHA may be most appropriate. The potential surgical solutions have significant drawbacks. A fenestration procedure would leave a cavity requiring long-term care. A neo-oval window operation, in which a *de novo* entrance into the labyrinth is either drilled on the promontorial or even on the rostral side of the Fallopian canal, has a high risk of inner ear damage.[2]

NON-OSSICULAR CONGENITAL MIDDLE EAR ABNORMALITIES

Persistent stapedial artery

The stapes forms around the stapedial artery, leading to formation of the obturator foramen. By 10 weeks of development the artery atrophies, leaving a patent foramen underneath the arch of the stapes. If persistent, it arises from the petrous internal carotid artery (ICA), traverses Jacobsen's canal for a short segment, exits at the promontory, passes through the stapes obturator foramen and enters the Fallopian canal close to the cochleariform process. The persistent stapedial artery (PSA) passes anteriorly, exiting the canal at the geniculate ganglion, and passes into the extradural space of the middle cranial fossa, where it gives rise to the middle meningeal artery. In the presence of a PSA, the foramen spinosum is usually

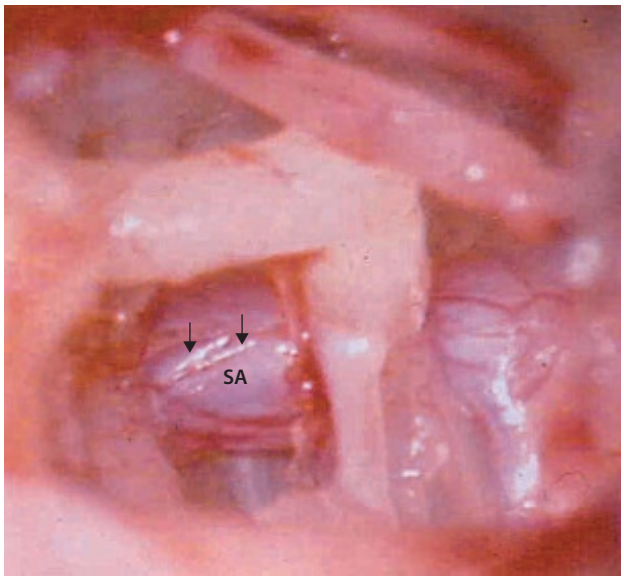

Figure 12.1 Finding during stapes surgery – a persistent stapedial artery (PSA).

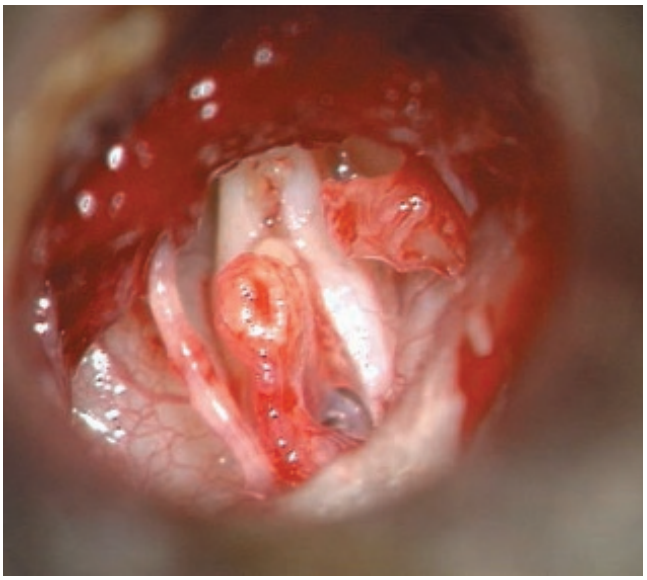

Figure 12.2 Stapes may be normal and mobile, even in the presence of a bifurcated facial nerve.

absent and the ICA may have an aberrant course due to its collateral formation secondary to a segmental agenesis of the ICA.[18]

A PSA may present as a vascular mass within the middle ear,[18] found either during otoscopic examination of the ear or during middle ear exploration, but is often asymptomatic or the cause of pulsatile tinnitus and has no relationship to conductive hearing loss.

It may also present as a chance finding during stapes surgery (Figure 12.1). It is unclear whether the discovery of a PSA during a stapedectomy indicates a congenital fixation or is coincidental in cases of otosclerotic stapes ankylosis.

Traditional teaching has been that the presence of the artery is an absolute contraindication to stapedectomy, partly as it was thought that damage to the artery would lead to ischaemic damage to the facial nerve. Govaerts et al.,[19] however, reported 12 cases, including two of their own, in which the outcome of surgery was satisfactory. In three cases the artery was damaged or clipped without any post-operative complications.

Anomalous course of the facial nerve

The Fallopian canal may show dehiscence or have an anomalous course within any part of its course within the temporal bone. This has great surgical significance and may be a hazard in all forms of tympanomastoid surgery. An abnormal course is particularly common with microtia or with dysplasia of the oval and round windows and there should be a high index of suspicion in any surgery for congenital conductive hearing loss and the use of the facial nerve monitor is highly recommended.

The Fallopian canal arises from the otic capsule and the second branchial arch and a theory of the cause of an anomalous facial nerve is a failure of fusion of the two. As there is a relatively high association with other ossicular abnormalities other than of the stapes, a local teratogenetic effect may also be responsible.

Rohrt and Lorentzen[20] classified facial nerve displacement in the middle ear into four groups:

- facial nerve partially obliterates the stapes footplate
- bifurcation of the facial nerve
- facial nerve rests on the footplate with deformed stapes or oval window
- facial nerve rests on the promontory.

Although these abnormalities are often found in association with stapes fixation, it may be normal and mobile, even in the presence of a bifurcated facial nerve (Figure 12.2).

Congenital perilymphatic fistula

Congenital perilymphatic fistula (PLF) is an abnormal communication between the middle and inner ear. It may be associated with:

- microfissures around the oval and round windows
- labyrinthine or IAM dysplasia.

The diagnosis is controversial as there is no reliable preoperative test which identifies the condition and management is based on the suggestive diagnosis of a child presenting with progressive or fluctuating sensorineural hearing loss, possibly associated with vertigo. Weber et al.[21] define the intra-operative diagnosis as being based on the identification of clear fluid which reaccumulates with anaesthetic Valsalva or Trendelenburg manoeuvre. Beta-transferrin positive samples are consistent with CSF being a constituent of the leak and this will be a feature of some but not all cases of PLF, usually associated with

labyrinthine or IAM dysplasia. This is not a real-time test during the surgical procedure and is very specific but not very sensitive for PLF, which may not contain CSF.[22]

In view of the difficulties of diagnosis, Weber et al.[21] suggest the policy of packing temporalis muscle around the oval and round windows in all suspected cases. This is based on the observation that packing does not seem to cause any significant complications (such as a subsequent conductive hearing loss) and he argues that it may be beneficial despite no confirmation of a PLF. In his series of 160 ears with suspected PLF there was a greater than 90% rate of stabilization or improvement in hearing in both PLF-positive and PLF-negative cases, though he acknowledges that in other series there is a similar outcome in nearly half of cases without packing.

High jugular bulb

A high jugular bulb (HJB) is usually asymptomatic and discovered as an incidental finding on otoscopy or during middle ear surgery. It can cause heavy bleeding from accidental puncture while lifting a tympanomeatal flap or even inserting a ventilation tube.

The jugular bulb can be defined as 'high' if it reaches the level of the inferior bony annulus and is often covered by thin bone or is dehiscent. In the presence of a plethoric mass within the tympanic cavity, the differential diagnosis will include HJB, aberrant ICA, a PSA and a glomus tympanicum tumour.

An HJB can be associated with hearing loss. If it includes a medial portion impinging on the cochlear or vestibular aqueduct, a connection with vestibular symptoms and a sensorineural hearing loss has been suggested. There may be a more direct association with a conductive hearing[23] loss due to interference with the ossicles, contact with the tympanic membrane and obstruction of the round window niche.

Major surgery to occlude or reroute an HJB is unlikely to be justified by symptoms alone, though there are occasional reports of intrusive pulsatile tinnitus associated with an HJB. It is possible to consider endovascular occlusion in the rare case of persistent haemorrhage, when tympanic cavity surgery is contraindicated.[24]

Aberrant internal carotid artery

This may be associated with other vascular abnormalities such as a PSA and likewise present as a vascular middle ear mass. Associated symptoms include pulsatile tinnitus, which may be objective, and hearing loss. In approximately 20% of cases it is bilateral.[25]

An aberrant ICA is an important differential diagnosis of a glomus tympanicum tumour, which can be resolved by CT scanning. Brisk bleeding, hemiparesis, aphasia, deafness, Horner syndrome and intractable vertigo may result if the vessel is unintentionally injured.[25]

BEST CLINICAL PRACTICE

- ✓ Unless deafness is bilateral, management can be conservative.
- ✓ If there is bilateral hearing loss, auditory rehabilitation will be required.
- ✓ Surgery is difficult with uncertain outcomes and best considered only by those with specific training and experience.
- ✓ Surgery may be best deferred until children can participate in the process of informed consent.

FUTURE RESEARCH

- ➤ The incidence, aetiology and pathogenesis of congenital ossicular abnormalities is poorly understood.
- ➤ The role of otoendoscopy in the diagnosis and management of these conditions needs to be better defined.
- ➤ Developments in middle ear implantation may render corrective surgery almost redundant.

KEY POINTS

- Congenital abnormalities of the middle ear may occur in association with major malformations such as microtia.
- Isolated malformations are rare but include anomalies of the ossicular chain and the middle ear vasculature.
- Diagnostic delay is common. Deafness due to ossicular pathology is often misdiagnosed as otitis media with effusion. It is not unusual for children to have repeated ventilation tubes before the correct diagnosis is made.

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CHAPTER 13

OTITIS MEDIA WITH EFFUSION

Peter J. Robb and Ian Williamson

SEARCH STRATEGY

Data in this chapter may be updated by searches in The Cochrane Library, Medline, Google Scholar and PubMed, using the keywords: adenoid, adenoidectomy, biofilm infection, gastro-oesophageal reflux, otitis media, otitis media with effusion, ventilation tubes. References from selected articles were reviewed after reading the abstract and included where relevant.

DEFINITION

Otitis media with effusion (OME) is the accumulation of mucus within the middle ear and sometimes the mastoid air cell system. Persistence of the fluid for the condition to be described as chronic is normally taken as 3 months or longer.[1] In children, OME may present with hearing loss, but also delayed speech and language development, poor social behaviour and, in younger children, difficulties with balance. There is sometimes a clearly defined history of preceding respiratory tract infection and otalgia with an episode of acute otitis media. The condition is widely known among both doctors and the general public as 'glue ear'. Approximately 80% of all children will have had a single episode of OME before the age of 3 years and 40% will have three or more episodes.[2] In the USA, the cost of managing all forms of otitis media is estimated at US$5 billion (£3.2 bn, €3.7 bn) annually.[3]

When childhood OME is preceded by an episode of acute otitis media, however, this typically follows a viral upper respiratory tract infection, associated inflammation and infection of the adenoid, secondary bacterial infection with a cascade of inflammatory mediators,[4] upregulation of mucin genes and effusion from the middle ear mucosa. In many children with OME there is no clear history of acute otitis media. Research currently in progress indicates a genetic inheritance of susceptibility to OME, causing impaired middle ear oxygen metabolism.[5] It is likely that ventilating the middle ear establishes a higher oxygen tension in part, inhibiting bacterial biofilm activity.

AETIOLOGY AND PATHOGENESIS

Histology

The Eustachian tube and anterior mesotympanum are lined by ciliated, pseudostratified columnar respiratory epithelium. The mucosa contains both goblet cells and mucus-secreting glands.[6] Inflammation of the epithelium and production of a serous or mucus effusion results in OME. In established OME, the flat cuboidal middle ear mastoid mucosa may be replaced by thicker pseudostratified mucus-secreting epithelium with varying degrees of specialization, such as the development of cilia. Goblet cells are frequently present and sometimes mucus-secreting glands are formed. The ciliary lining would appear to be less efficient at moving the secretions into the nasopharynx than normal.[7] The submucosa is oedematous and inflamed with dilated blood vessels and an increased number of macrophages, plasma cells and lymphocytes.

CHARACTERISTICS OF THE EFFUSION

The effusion varies in composition but is predominantly made up of the glycoprotein mucin. Also present in the effusion are secretory immunoglobulin A (IgA), lysozyme, interleukins and other inflammatory cytokines. Rheological adhesiveness and poor mucociliary transportability are characteristics of the effusions and the behaviour of the mucosa predicting persistence of the effusion and the need for surgical drainage and middle ear ventilation.[8, 9]

Microbiology

Positive bacteriological cultures of middle ear aspirate of OME fluid in children (more than 2 months' duration) produces the anticipated range of respiratory bacteria, including *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Branhamella* (*Moraxella*) *catarrhalis*.[10] However, 66% of the cultures were negative using traditional culture techniques, and no pathogens were cultured from fluid that had been present for at least 6 months. In contrast, using polymerase chain reaction techniques (PCR), 36% of middle ear mucosal biopsy specimens demonstrated intracellular *Streptococcus pneumoniae*.[11] The authors concluded this as important supporting evidence as a mechanism for bacterial persistence. Biofilms, which are communities of sessile bacteria, resistant to disruption and with a low metabolic rate, are embedded in a matrix of extracellular polymeric substances of their own synthesis. These communities may adhere to a foreign body or a mucosal surface with impaired host defence.[12] They are increasingly implicated in chronic inflammatory conditions such as OME. Biofilms were demonstrated in 92% of middle ear mucosal specimens of patients undergoing ventilation tube surgery for OME.[13] High-grade biofilm formation is also found on adenoid samples removed at surgery, supporting a role for adenoidal biofilm in the aetiology of OME. Adenoidal size is not correlated with biofilm formation, supporting the hypothesis that inflammation associated with the biofilm rather than adenoidal size per se blocking the Eustachian tube is the critical factor.[14] The contribution of biofilm formation in the middle ear and adenoid and the pathogenesis of OME is not yet completely understood, but it is likely that the biofilm is a secondary bacterial effect following viral respiratory tract infection, contributing to inflammation and mucus production. It is possible that those with a genetic defect of middle ear oxygen metabolism are predisposed to persistent OME with all its clinical manifestations.

Craniofacial abnormalities

OME occurs in nearly all infants and children with a cleft palate, and surgical repair of the cleft does not appear to reduce the incidence. The palatine muscles controlling Eustachian tube opening remain deficient through loss of decussating muscle fibres across the midline of the soft palate. In this group, OME has an incidence of at least 20% of 10-year-olds.[15] Children with a bifid uvula do not appear to have a higher incidence of OME[16] although, if adenoidectomy is combined with insertion of ventilation tubes, a sub-total removal should be performed under direct vision to reduce the potentially higher risk of velopharyngeal insufficiency.

It is unlikely that there is any correlation between dental malocclusion and OME.[17] While the incidence and persistence of OME in Down syndrome is well recognized, there is little evidence to clarify the factors contributing to the natural history of OME in those with Down syndrome.

Allergy

There is conflicting evidence on the importance of atopy and allergy in the pathogenesis of OME in childhood. In a validated questionnaire study of 89 children, with OME confirmed at the time of ventilation tube insertion, no difference in prevalence of allergic symptoms was found between the OME and reference group. Symptoms of nasal obstruction were significantly more prevalent, but this might represent adenoidal hyperplasia rather than allergic rhinitis.[18] In contrast, of 209 children with a history of OME extensively assessed in a specialist allergy clinic, 89% had evidence of allergic rhinitis, 36% had asthma and 24% eczema.[19] In addition to clinical history and examination, the assessment was based on nasal smears and skin prick testing, with blood eosinophil count and total immunoglobulin E (IgE) in a randomly selected subset. Such a study setting is subject to referral or spectrum bias. The worldwide prevalence of allergic rhinitis is 20%. The higher 89% figure reported in this study points towards a likely allergic component in many referred children with OME because of the strength of the association.[20] Furthermore, children with OME with a family history of allergy are more likely than controls to have a positive finding of rhinovirus in the middle ear cavity, indicating a link between viral respiratory tract infection and allergy predisposing to middle ear disease.[21]

Gastro-oesophageal reflux

The role of gastro-oesophageal reflux in the pathogenesis of OME in childhood is unclear, although it is known that, during swallowing, fluid can travel from the nasopharynx via the Eustachian tube into the middle ear. Gastro-oesophageal reflux is common in children, occurring in up to two-thirds of infants at 4 months of age, but decreasing thereafter.[22] Pepsin was first identified in middle ear effusions in 2002.[23] (Bile acids have also been identified in samples of middle ear fluid in children with OME.)[24] Biochemical analysis of middle ear fluid in OME suggest that pepsin is present in approximately 80% of samples at a level 1000 times higher than serum levels.[25] Mucosal damage is postulated to be mediated by the proteolytic activity of pepsin.

Pepsinogen immunoreactivity in adenoid tissue of children with OME has been found to be significantly higher than matched controls with no history of OME.[26] In this study, pepsinogen was detected in 84% of middle

ear effusions. *Helicobacter pylori*, confirmed by PCR assay, has been detected in middle ear effusions in 9/55 (16.3%).[27] An animal study concluded *H. pylori* did not per se cause a middle ear effusion, but rather contributed to the inflammatory process in the presence of middle ear fluid.[28] Gastro-oesophageal contamination of the middle ear appears not to correlate with symptomatic gastro-oesophageal reflux disease (GORD).[29]

The evidence in favour of a role for gastro-oesophageal reflux in the cause and/or persistence of OME is accumulating, but the relation between cause and effect, if any, is not fully understood. A systematic review of 242 studies (of which 15 met the inclusion criteria) concluded there is insufficient evidence to recommend antireflux treatment for otitis media with effusion.[30]

EPIDEMIOLOGY

The epidemiology of OME has been extensively studied in many countries. The studies include cohorts of children followed up at regular intervals for periods between birth and approximately 10 years of age. Most such studies are not designed or inadequately control for confounders (risk factors/effect modifiers). The background prevalence of OME is very high, making long-term effects difficult to evaluate with children frequently switching between having the condition and being clear of the condition. The prevalence of a condition is the number of true cases identified in a carefully estimated population (that might become cases) either over a fixed period or at any time point. Case ascertainment can be quite variable so tympanometry is recommended for larger studies (see 'Diagnosis' below for test characteristics). Such prevalence data are useful as an indicator of the potential clinical workload and the scale of the problem to children, their families and society. The incidence and remission rate of a condition measure the chances or rate of developing the condition and its clearance over a defined time frame respectively, which because of the chronic relapsing/remitting nature of the condition adds much value to the picture of the natural history, knowledge of which should help guide management decisions. In childhood OME, the two main determinants of the prevalence and incidence rates are the age of the child and the season of the year. When considering the evidence in this area there are many case-cohort level 2b studies to report from, but most of the larger well-conducted methodological studies are not recent.

Association with age

Zielhius et al.[31] reviewed a total of 23 studies that all used tympanometry as one of the diagnostic instruments to give age-specific prevalence rates up to 10 years of age. The background prevalence is bimodal with the first and largest peak found in approximately 20% of children aged 2 years. This is around the time when many children extend their social contacts, at playgroup or nursery school for example. Thereafter, the prevalence shows a dip with a second peak of approximately 16% in 5-year-olds, when most start attending a primary school. A study using a diagnostic algorithm of tympanometry combined with otoscopy in an attempt to improve precision, suggested that the early peak is most likely occurring around 1 year of age.[32] By the age of 8 years, the background prevalence in UK schoolchildren fell to 0–6% depending on time of year, whereas 5-year-olds had a higher season dependent range of 13–20%, 6-year-olds 8–13% and 7-year-olds 4–10%.[33]

Association with season of the year

In temperate climates, the effect of the season on the prevalence of OME has been recognized for many years, with around twice as many children being diagnosed with OME in the winter as in the summer months.[33–37] The most likely reasons for seasonal variation are the increased frequency of upper respiratory and ear infections in the winter, including the effects of seasonal influenza, and the greater chance of passing on infections between children because of the closer household contact in cold weather. If these factors are controlled for by analysis, however, the effect of season is no longer as evident,[38] but is demonstrated in other studies.[39, 40]

Little data exist for the effect of season from countries in non-temperate climates. The background prevalence of OME in Mediterranean children[41, 42] and subtropical countries[43, 44] does not appear to be very different from those in temperate countries but no independent effects for season are available. One study based in the northern tropical country of Vietnam showed increase in seasonal prevalence of OME from 3% to 11% when comparing the dry April with the December chilly rainy season.[45]

Risk factors for OME

The identification of the clinically most important risk factors is a key aspect of child health and clinical management because of the potential wide-scale benefit if these are able to be addressed, such as by strategic use of vaccines. Any identified risk factors cannot be assumed to apply equally to all age groups, for example breastfeeding effects may be greatest in the youngest cohorts. On *a priori* grounds, the risk factors for persistence of OME may well be different from the risk factors for its actual occurrence (incidence). Also one needs to consider the behavioural and clinical expression of the biological features including hearing impairments such as poor speech, or schoolwork that might be expected to relate more to how long the fluid has been present, and additional risk factors for 'disability' such as poor communicating styles.

When comparing evidence from risk factor studies it should be noted that potential factors are often inconsistently evaluated in the literature and heterogeneous, due to design issues, different populations, lack of agreement about what they are, and how to measure them uniformly and reliably. Often such studies have too few subjects with a particular characteristic to evaluate it reliably: for example, there are not many 5-year-old children who do

not go to school in the UK. A multivariate analysis can control for potential confounding variables. If low socioeconomic group is a mooted factor, for example, is it the small house, the number of siblings, the smoking, the junk food or the lack of a maternal university education and a car that makes the difference? It is unlikely to be all of these. Interim surgery in some risk factor cohort studies may complicate the analysis and interpretation, as it is clearly an important effect modifier of the outcome. It is deemed very likely that the risk factors for the occurrence of unilateral and bilateral OME will be the same. This premise has been experimentally confirmed by Engel et al.[40] That is why, in randomized clinical trials of children with OME, children rather than ears should be the unit of analysis for the primary outcome (because the ears are not independent variables).

Risk factors can be of interest in helping to understand why some individuals are more prone than others to suffer from a condition. Many journals prefer these presented as relative risk (RR) as easier to comprehend, although odds or hazard ratios may be used. In any specific individual, the number of risk factors present can be used as an approximate estimate of the risk of developing the condition. Usually, however, the relative risks for any single factor are only small (around two) and, to date, combinations of risk factors have not provided a sufficiently good or reliable guide for referral or interventions, although some factors may be modified.

Acute otitis media

In the age most studied, i.e. 0–2 years, recurrent episodes of acute otitis media (AOM) are frequent and this is likely to be the largest single group for developing persistent ear effusions. Each acute episode increases the reported odds ratio of developing OME by 12 (95% CI 6, 25) but this risk level no longer remains after 3 months.[46] Hence, the known risk factors for AOM, such as prematurity, frequent upper respiratory infections and non-breastfeeding, will apply in such clinical situations (OME preceded by AOM).[47] Studies of children in this age group that do not report the important frequency of AOM must also be considered less than optimal for clinical use in OME. There is no evidence that any medical management of AOM, including antibiotics, makes any difference to the chances of developing subsequent OME.[48]

Risk factors found in addition to AOM in a multivariate analysis confirm the increasing effect of age up to 2 years but also the effect of having siblings and a family history of them having OME.[38] Another study that otoscopically assessed family members of children with OME rather than just relying on historical reports found that 32% of siblings and 19% of parents were classified as otoscopically affected.[49] Other multivariate studies have suggested that, in addition to the number of siblings, attendance at day care with four or more other children up to 3.5 years of age can approximately double the risk (CI 1, 3).[39, 50] An international systematic review of risk factors found that the main risk factors for otitis media in populations were: attending day care, number of siblings, smoking, not breastfeeding, low birthweight and socioeconomic status.[51] Some of these factors are potentially modifiable (e.g. the number of children in day-care settings could be reduced to lessen this risk), but for most parents availability, convenience and cost are limiting determinants.

Genetic factors

In a same-sex twin/triplet prospective cohort study, Casselbrandt et al.[52] looked at sets where the zygosity was known. In children who had OME during the first 2 years of life, there was greater concordance in monozygotic sets in both the number and duration of OME episodes than in dizygotic sets. The magnitude of the effect of heredity in comparison to other risk factors for OME was not investigated. More recent work in mouse mutant models of chronic otitis media (COM) where hypoxia in microenvironments is known to be aetiologically important has demonstrated upregulation of hypoxia inducible factor (HIF) and vascular endothelial growth factor A (VEGFA).[53] This paves the way for targeted therapeutic interventions in future studies, although transferability of mouse-model findings to humans requires some caution and fuller evaluation.

Race

Whether the prevalence of OME is truly different in different races requires control for many other factors. When factors including socioeconomic group and child contacts are controlled for in a multivariate analysis, the prevalence in black children is no different from white children.[54] Chinese children may have a lower overall prevalence, but a multifactorial analysis has not been reported.[44]

Gender

Some multivariate studies report the risk of developing OME to be no different between boys and girls.[39, 40, 55] Some studies report a higher risk in boys[46, 49] and others a higher risk in girls.[38] It must be concluded that there is likely to be little difference, if any, in the background risk for boys compared to girls, with most epidemiological studies showing comparable base rates.

Smoking

For public health reasons, parental smoking has frequently been reported as a risk factor for the occurrence of OME. However, in one multivariate analysis when other factors had been controlled for, no effect of parental smoking was detected[40] but in another study it was found present for smokers of up to 20 cigarettes per day.[39] A large, more recent epidemiological study noted a temporal decline in consultations for otitis media, which was attributed to an increase in smoke-free households.[56]

Duration and recurrence of episodes

One large study of 1328 children aged 1–2 years showed the duration of episodes in individual ears was very skewed; the median duration of effusions was 3 months

or less, but the 95th percentile was at 12 months. Half of affected ears had resolved after 3 months. However, around 50% of the ears that resolved had a further episode.[57] What happens in individual infants rather than in ears has been well documented by Paradise et al.[54] in a large cohort (n = 2253) followed up from 2 months of age to 6, 12, 24 months of age, who found that 49%, 79% and 91% of infants respectively had had at least one episode of OME.

Hogan et al.[58] followed up 95 full-term infants monthly for 3 years. Overall, infants were twice as likely to develop unilateral as opposed to bilateral OME. One month later, in infants with a unilateral effusion, the majority (50%) had resolved, a minority (20%) had become bilateral and the other 30% remained unilateral. In those with bilateral effusions at the start, the majority (60%) remained bilateral 1 month later. In the others (40%), bilateral resolution was more frequent than unilateral resolution (in a ratio of 3:1).

An older cohort of 856 British children aged 5–8 years was screened three times a year (approximately every 4 months) for 3 successive years.[33] In a subsample of 67 ears with B tympanograms and with three consecutive screens, the resolution rates (to a non-B) at 4, 8 and 12 months were 52%, 78% and 91% respectively. The overall recurrence rate for this community study was quite low at 7%. A more detailed monthly study of 7-year-old Danish pupils (n = 387) reported the mean overall duration of an ear episode to be 1.8 months with 12% lasting more than 6 months.[59] Ears first diagnosed to have OME between September and February persisted longer than those first diagnosed between March and August.

Risk factors for persistence

Three studies have been identified that have followed up children to identify risk factors that might be used to predict those who are more likely to have persistent bilateral OME. One study was carried out in primary care and followed up children of 6 months or older for 3 months.[60] Another study was of children aged between 3 and 7 years referred from primary care with suspected OME and seen at secondary care on average 13 weeks later.[61] The third study was of children of the same age identified at secondary care to have bilateral OME with an associated hearing impairment in both ears of at least 20 dB hearing loss. These children were followed up for 3 months to identify those in whom the OME persisted bilaterally with the same degree of impairment.[62–64]

In these three studies, which all followed up the children for 3 months, the persistence rates of bilateral OME were 56%, 35% and 51% respectively. All studies identified the second half of the year (July–December) as a major risk factor, with odds ratios of between two and three. In primary care, whether a child has frequent or upper respiratory symptoms at the time of assessment is also an important determinant of persistence. In secondary care, the degree of associated hearing impairment predicted persistence. The only factor that might have had an influence and has the potential to be modified was whether the mother smoked, and this was a significant multivariate factor in the secondary care study.[61] In all three studies, the magnitude of the effect of any factor singly or in combination was insufficient to predict with reasonable certainty those likely to persist or resolve.

Clinical summary of best epidemiological evidence

The prevalence of OME in childhood is age-dependent, with two peaks in the distribution, one centred around 1–2 years of age and the other around 3–7 years of age.

In temperate countries, twice as many children have OME in the winter as in the summer. The increased frequency of upper respiratory infections and close contact with other children during the winter months contribute to this association.

Under 3 years of age, episodes of AOM, contact with other children and heredity are factors that increase the risk of occurrence. Unilateral OME is twice as common as bilateral OME. Those with a propensity to develop OME have more frequent episodes rather than longer episodes. Bilateral OME is more likely to persist than unilateral OME. In primary care, children with bilateral OME and a history of upper respiratory infections are more likely to persist. In secondary care, children with bilateral OME seen in the second half of the year (July–December) with a hearing impairment of 30 dB HL in both ears are more likely to persist.

None of the factors for persistence singly or in combination are sufficient to negate a requirement for a 3-month period of active monitoring before considering surgery.[65]

DIAGNOSIS

History

Parental recognition of hearing loss in their child is perhaps surprisingly only poorly correlated with OME. In a population-based study of 117 children with OME and 159 controls, parental suspicion of their child's hearing loss in the affected group was only 19.7%.[66] Furthermore, parents of children with OME tend to underestimate the severity of the hearing loss and overestimate their child's quality of life when assessed with the validated OM-6 questionnaire.[67] When parents were reassessed after surgical treatment of their child's OME, there was a significant response-shift bias for both hearing loss and quality of life. Indeed, many parents report concerns other than hearing loss, including poor speech and language development and signs of difficulties with balance. When balance was formally tested, one study reported improvement in balance with practice, but less so in those children with OME until after ventilation tube insertion.[68] In a case-control study, the post-surgery treatment group had a statistically significant decrease in sway velocity compared to the control group.[69] Children attending day care or nursery also may cause their carers or teachers concern, because of inattention and behavioural problems.[70] Difficulty taking part in group activities due to the hearing loss associated

with OME actually reflects an underlying impaired ability to process speech in noise which is more noticeable in this context than in one-to-one situations with primary carers.[71]

Taking a history, it is important to confirm a normal pregnancy, delivery and neonatal period and that neonatal hearing screening was performed and reported as normal. A very small number of children may pass neonatal hearing screening and have or develop sensorineural hearing loss during early childhood. It is important to be aware of the possibility of OME coexisting with a mixed hearing loss. Children with comorbidities (e.g. Down syndrome, cleft palate) are more commonly affected by OME, and this is usually more persistent.

Examination

OTOSCOPY

In some children, otoscopy may not be possible, either because the child is unable to cooperate or because the view is obscured by wax. In primary care, sodium bicarbonate or olive oil eardrops are often prescribed to soften and encourage dispersal of the wax. In second-tier community clinics and in secondary care, tympanometry and audiometry will usually provide sufficient additional information on the level of hearing loss, with or without wax obscuring the view of the tympanic membrane (**Figure 13.1**).

Otomicroscopy

In a study of 81 children (155 ears) using otomicroscopy with myringotomy under local anaesthesia as the reference standard, otomicroscopy showed better diagnostic agreement with myringotomy than otoscopy or tympanometry.[72] While not applicable to the outpatient clinic setting, intra-operative otomicroscopy performed by a specialist otolaryngologist in the anaesthetized child prior to myringotomy achieves greater diagnostic accuracy than pneumatic otoscopy and tympanometry. The overall accuracy of otomicroscopy was 94.1%.[73]

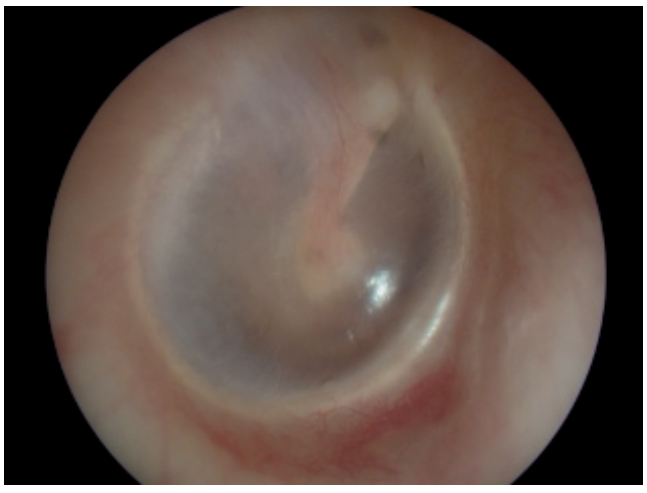

Figure 13.1 Normal right tympanic membrane. (Image courtesy of Mr Michael Saunders.)

Pneumatic otoscopy

When performed by trained specialists, the sensitivity of pneumatic otoscopy ranges from 85% to 93% and its specificity from 71% to 89%. However, these calculations omitted up to 20% of the children in whom pneumatic otoscopy was not possible.[74] Including these children alters the sensitivities and specificities dramatically. The sensitivity and specificity of pneumatic otoscopy, even where practicable, would be markedly poorer in practitioners whose skills have not been validated.[75] In contemporary practice, many clinicians will rely on a combination of otoscopy and tympanometry when assessing small children.

TUNING FORK TESTS

In a study of 58 children, aged between 2 and 11 years, the Rinne and Weber tuning fork tests poorly predicted conductive hearing loss in children with OME compared with pure tone audiometry. The results were independent of the child's age.[76] Tuning for tests should not be relied on to assess conductive hearing loss.[77]

FREE-FIELD VOICE TESTING

In primary care, audiometry is seldom available, particularly for younger children. In children over the age of 3 years, the sensitivity of modifications of the voice test administered by experienced examiners (e.g. use of pictures to point at or two-syllable words) is 80–96% and the specificity is 90–98%.[78] However, these outcomes are unlikely to be achieved when carried out by less experienced examiners in a primary-care setting.

Investigations

TYMPANOMETRY

For more than 30 years, tympanometry using an automated impedance meter (see Chapter 51, Psychoacoustic audiometry) has been widely available as a method of detecting OME. While an acoustic seal is sometimes difficult to achieve, bilateral tympanograms are generally obtainable in 98% of children between the ages of 3.5 and 7 years,[79] in 90–94% of infants 2–11 months of age[80] and 78–88% of infants 12–24 months of age.[81]

A modification of the Jerger classification is the most commonly used in clinical practice.[31, 82] This uses compliance and pressure as the numerical parameters, presented visually as a compliance curve (**Figure 13.2**).

Comparing the finding of middle ear fluid at the time of myringotomy, soon after tympanometry, a type B tympanogram is frequently associated with OME; a type A is infrequently associated with OME and a type C falls in between.[84] This study did not, however, subdivide type C tympanograms as type C_1 or C_2.

Overall, a number of level 1 evidence studies conclude that a type B tympanogram compared with all other types of tympanogram has a sensitivity of between 56% and 73% and a specificity of between 50% and 98% in detecting OME confirmed at the time of myringotomy.[84–86] Compared with

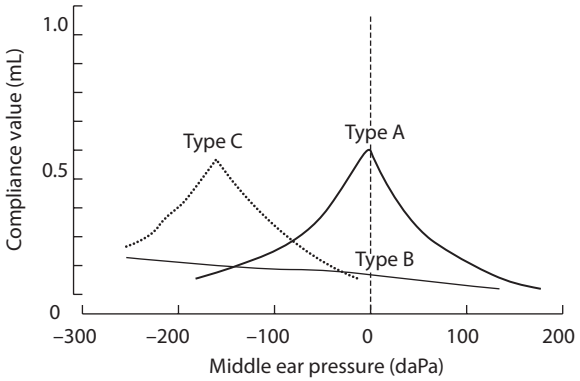

Figure 13.2 Tympanogram trace types.[83] A, peak between +200 and –99daPa; C, peak between -100 and -399daPa (further subdivided into C1, peak between –100 and –199daPa; C2, peak between –200 and –399 daPa); B, no observable peak between +200 and –600 daPa (Image courtesy of Mr Michael Saunders.)

all other types, a type B plus C_2 has a greater sensitivity of between 73% and 99%, and a specificity of between 40% and 74%.[87–90] The reasons for such a wide range of values are unclear and can be only partly explained by the differing proportion of ears with OME (sample bias). When nitrous oxide is omitted from general anaesthesia at the time of myringotomy (excluding the risk of a 'false dry tap'), the sensitivity and specificity of a Jerger type B trace predicting middle ear fluid is 0.73 and 0.84 respectively.[91]

Tympanoscopes

Automated, hand-held tympanoscopes (screening tympanometers) have the advantages of portability and lower cost and are particularly suited for primary care. In a primary care setting, when this equipment is used by trained operators,[92, 93] and a type B tympanogram is classified with a type C_2 tympanogram, the sensitivity and specificity (100% and 75%) is comparable to conventional impedance bridge tympanometry.[94, 95]

TYMPANOMETRY IN COMBINATION WITH OTOSCOPY

The diagnostic predictability of otoscopy and tympanometry, when in agreement, can be referenced against the findings at myringotomy.[96] When otoscopy suggests OME and is associated with a type B tympanogram, the combined sensitivity is 98%. When otoscopy suggests no OME and is combined with a type A tympanogram, the specificity is 98%. However, in this study the findings were in agreement in only 44% of ears. In the 56% where the results were not in agreement, another indicator of OME such as audiometry would be required to confirm the diagnosis. A combined otoscopy and tympanometry sensitivity and specificity were calculated for those otoscopy and tympanometry determinations in agreement, revealing both sensitivity and specificity above 90%.

ACOUSTIC REFLEXES

Measuring the acoustic reflexes in association with classification of tympanometry as peaked/non-peaked substantially lowered its specificity while adding little to the sensitivity, and it is therefore not recommended.[97, 98]

AUDIOMETRY

Audiometric assessment is mandatory for all children referred to secondary care with a suspected hearing impairment. While all children in the UK will have an objective neonatal hearing assessment, this does not guarantee continuing, normal hearing throughout childhood because some will develop sensorineural hearing loss. If a hearing loss is diagnosed in the absence of OME, this should be pursued with further hearing assessment, including bone-conduction thresholds and objective electrical response audiometry. Approximately 1% of children will have a previously undiagnosed congenital, sensorineural hearing loss[97] and a smaller number a postnatal hearing loss from *in utero* infection (e.g. cytomegalovirus).

Conventional air and bone conduction testing is the preferred method as it tests each ear separately and can quantify any conductive component present. In children over 3.5 years of age, air and bone conduction thresholds are obtainable in the majority of children (95% and 92% respectively) on the first occasion. Age, rather than the method of audiometry, is the main determinant of whether thresholds are obtainable. Even if the child's concentration is poor, the results on average are only 5 dB poorer and can still be used to guide management.[99]

Evidence from a small study of 31 children compared high-frequency hearing between 14 who had experienced no more than three episodes of bilateral OME and those who had experienced at least four episodes. There was an increase in hearing thresholds with increasing frequency, higher than those normally clinically tested (9 kHz to 18 kHz) and poorer high-frequency hearing in the group who had a history of four or more episodes of OME.[100]

Air–bone gap

The presence of an air–bone gap of at least 10 dB is a poor predictor of concurrent OME. It was only when the air–bone gap was greater than 30 dB that the dry tap rate reduced to 4% (1 of 27).[101]

Carhart notch in the bone-conduction thresholds

As OME is a conductive hearing loss, it is associated with a Carhart notch in the bone-conduction thresholds around 2 kHz. (By definition, the notch has to be 10 dB or greater between 0.5 kHz and 4 kHz as any lesser dips could be due to test/retest error.) Accurate bone-conduction thresholds are required and, in younger children, this may not be possible. In children older than the typical age group for OME, a Carhart notch was present in 48% of children with OME whose mean age was 9 years.[102] In those able to perform bone-conduction audiometry, the positive predictive value of a Carhart notch in diagnosing fluid at myringotomy was 97% and the negative predictive value was 87%.[103]

Diagnosis and management of OME

Confirmation of the diagnosis of childhood OME is based on a combination of otoscopy, tympanometry and audiometry. Otoscopy should be attempted in all children, not just to diagnose OME but also to confirm or exclude other ear pathology (Figure 13.3). Pneumatic otoscopy may be of added value where there is uncertainty, but it is limited in predictive value by the experience of the examiner and the cooperation of the child.

In a general secondary care setting, where audiological testing of younger children is not available, children under the age of 4 years should be referred to a community paediatric audiology (second tier) clinic for age-appropriate hearing assessment, combined with tympanometry. Children of 4 years of age and above, in the absence of cognitive or behavioural comorbidity, can be assessed in a general hospital paediatric ENT clinic, with both audiometry and clinical assessment on the same visit. When OME is confirmed, active monitoring of hearing over a 3-month period is recommended.[104] The benchmark for hearing loss due to bilateral OME is hearing in the better ear of 25–30 dB HL or worse, averaged at 0.5, 1, 2 and 4 kHz. Tympanometry will typically demonstrate probability of effusion in cases of reduced middle ear compliance, with Jerger type B or C_2 traces.

As well as applying strict audiometric criteria, it is also important to make a child-centred assessment as to how the child's hearing loss may affect their quality of life. Where the impact of the hearing loss, although less than 25–30 dB HL is judged to have a significant impact on the child's development, social skills or educational attainment, more active management is appropriate.

Having excluded a sensorineural hearing loss with audiometry, it is reasonable thereafter to use tympanometry alone to identify those children with persistent hearing impairment due to OME. Taking 25 dB HL in the better-hearing ear as the level requiring detection, limiting audiometry to those with a bilateral type B reduces audiology workload by 50% but detects 90% of such impaired children. Limiting audiometry to those with bilateral type B or C_2 tympanograms reduces the workload to 69% of the sample yet detects 95% of the children with hearing impairment due to OME.[79]

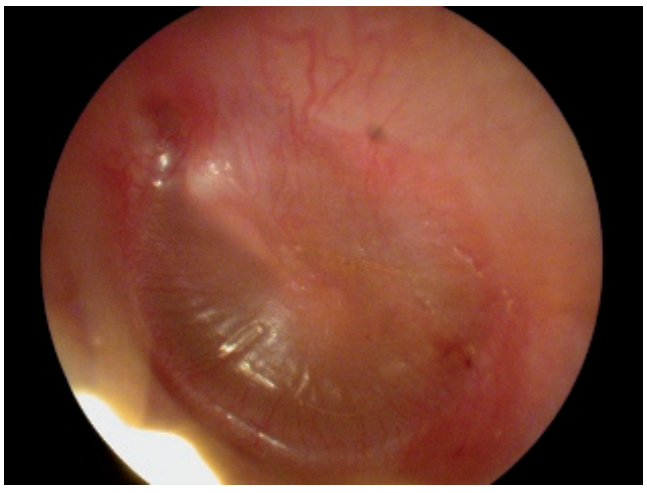

Figure 13.3 Right tympanic membrane: OME fluid and bubbles. (Image courtesy of Mr Michael Saunders.)

OUTCOMES OF CHILDHOOD OME

Natural history

The natural history is very important, as outlined above, and can help guide management in both primary and secondary care. Hogan found that the effusions in children under 3 years of age with a propensity to have bilateral OME lasted on average 10 weeks, albeit the children were likely to have a further episode within 11 weeks.[58]

The UK MRC (Medical Research Council) TARGET (Trial of Alternative Regimens in Glue Ear Treatment) study is also an invaluable source of natural history information in those children referred to secondary care aged between 3 and 7 years of age. A total of 3831 children of this age were referred because of suspected OME. The techniques for correctly diagnosing and detecting OME across primary care are currently less than adequate, with reliance predominantly based on subjective histories. When screened at the trial clinic, only 34% satisfied the criterion for further study of having bilateral OME associated with a hearing impairment of at least 20 dB HL in both ears.[62–64] This cohort underwent a 12-week watchful waiting period, following which 49% of children no longer met the bilateral OME hearing criterion, i.e. only 51% of the hospital cohort persisted. At that stage, children with persistent OME were randomized and, in those who had non-specific medical management, only 49% remained persistent 3 months later.[65] In summary, children referred into the TARGET study waited on average 13 weeks to be seen, underwent a watchful waiting period of 3 months and then waited a further 3 months for surgery, by which time in 92% the hearing impairment associated with their OME had resolved. Thus, even in secondary care, the vast majority of children with bilateral OME resolve spontaneously over a 9-month period, although the OME might recur.

OTOPATHOLOGY

Addressing the natural history of OME and possible progression to cholesteatoma, the best evidence comes from a large study of 964 children, screened for OME every 3 months between the ages of 2 and 4 years. The children were subsequently re-examined with otoscopy at between 7 and 8 years of age.[106]

The findings indicate that attic retractions are a disease effect of OME, with an incidence of approximately 14% in the most severely affected children (Figure 13.4). The proportion of these retractions that progress to cholesteatoma remains unknown. There is no evidence that the risk of attic retraction is altered by the insertion of ventilation tubes. Tympanosclerosis and atrophy of the pars tensa are also disease effects of OME. The risk of these is increased by the insertion of ventilation tubes to more than 45% and approximately 70% respectively. Long-term pars

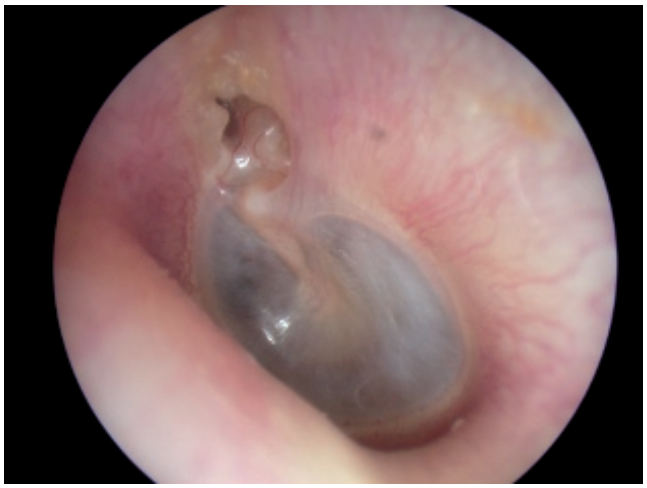

Figure 13.4 Attic retraction. (Image courtesy of Mr Michael Saunders.)

tensa retractions (approximately 15%) are more likely to be due to insertion of ventilation tubes than by the disease process itself.

CONDUCTIVE HEARING IMPAIRMENT

There is a widely variable hearing loss due to OME. In a series of 385 children aged between 2 and 11 years with bilateral OME confirmed by a diagnostic algorithm including pneumatic otoscopy, tympanometry and reflexes, the hearing loss in the better-hearing ear varied from 0–4 dB HL to 50–54 dB HL.[107]

Overall, the mean threshold in the better ear was 21 dB HL (s.d. 10). In 54% of those with bilateral OME the pure-tone average in the better ear was better than 20 dB HL.[107] The mean threshold in the poorer-hearing ears was 31 dB HL (s.d. 13). The speech reception or speech awareness thresholds in infants in this study were of a similar distribution. This might suggest that many children with bilateral OME in this study had an insufficient hearing impairment to cause 'significant' disability warranting such intervention, although significance remains difficult to define. In the same study, the authors describe a group of children with unilateral OME. In these children, the mean threshold in the better ear was 11 dB HL (s.d. 7) and 23 dB HL (s.d. 10) in the poorer ear, indicating these are a potentially significant group who may experience hearing disadvantage on occasions.

While there is no predictable difference in the hearing levels in ears from a serous effusion compared with those with a mucoid effusion,[108] those children with recurrent OME have an effusion with a different rheological profile, with fluid that has higher frictional adhesion.[8]

Sensorineural hearing impairment

There is no high-level evidence indicating that OME is associated with sensorineural hearing impairment in the short term.[109] However, the previously noted study[100] described sensorineural hearing loss above the clinically tested frequency range (>9 kHz) in children with recurrent episodes of OME. High-frequency sensorineural damage above 8 kHz has also been reported in a case series of children with OME who had been operated on and followed up for between 3 and 5 years.[110]

Long-term hearing impairment

In children followed from birth to 18 years of age, those who had otitis media (both acute and OME) produced air-conduction thresholds 4 dB HL poorer on average and bone-conduction thresholds poorer on average by 2 dB than those who had not had otitis media.[111] In this clinically heterogeneous group, it is not possible to know if the poorer thresholds were the result of infection, OME or surgical intervention.

SPEECH AND LANGUAGE

Normal childhood speech and language development is a multifactorial process, dependent on many factors including the age of the child, the ethnic background and verbal communication at home, particularly from the primary carer. Hearing impairment, including that from OME, is likely to impede normal speech and language development. Assessment of speech and language is complicated by it having many components, including speech reception, speech and sound production, expressive language and cognitive understanding.

In comparison to the profound effect on speech and language development a severe sensorineural hearing loss would be expected to produce, the mild to moderate conductive hearing loss associated with OME in the first 2–3 years of life should result in a much smaller effect. In a meta-analysis of 14 studies, the authors concluded that the impact of OME in early childhood on later speech and language development was very small, and of uncertain clinical relevance.[112] However, the authors cautioned generalizing the findings, instead recommending child-centred individual management in the context of other variables, including attention to language skills, development and the general supportiveness of the child's environment. Prospective cohort studies suggest an impact of otitis media, related to the number of days with bilateral fluid during the first 2–3 years of life. However, follow-up of these children when they are 7–8 years of age suggests that, by then, the children have caught up with their non-affected peers.[113] Overall, while the data suggest a mild effect on speech production in early childhood,[114–116] evidence looking at receptive language, using speech reception in noise (SiN) rather than pure tone audiometry, shows that 40% of children with the poorest pre-treatment SiN scores achieved high benefit from insertion of ventilation tubes. The authors concluded that SiN is a better tool than pure tone audiometry to predict benefit from surgical intervention. There appear to be small but significant long-term effects on sound discrimination in children with a history of OME.[117, 118] If there are measurable lasting effects, from current evidence these seem to predominantly affect receptive language. Treating OME in very young children appears to have no significant effect on speech and language development in the short term.[119, 120]

COGNITION

The influence of OME as one of many interrelated variables affecting a child's intellectual development is difficult to determine. Cohorts of children can be grouped as to how much OME they have had and this is correlated to a particular outcome, having controlled for demographic and environmental factors. The effect of OME as an independent factor for academic development is probably small compared with the more influential demographic, social and economic factors. If there is an effect, this has been reported as generally small.[118, 121] While these studies conclude that any negative effect has disappeared by the age of 7–8 years, a birth cohort of 200 was reviewed as older children, during their teens. A history of OME in early childhood was associated with a deleterious effect on reading ability.[122] A further study[123] reviewing a larger cohort of the same group[124] concluded a lower IQ in the OME group, after adjustments for covariates, persisting at least until the age of 13 years.

BEHAVIOUR

Behaviour can be assessed using questionnaire reporting by parents or teachers. These give a global behaviour measure and can also score the various components of behaviour. The widely used Rutter Children's Behaviour Questionnaire[125] is subdivided into antisocial, neurotic, hyperactive and inattentive behaviour scores.

In a randomized, controlled trial, 55% of 3-year-old children with bilateral, 3-month persistent OME had abnormal overall Rutter scores, compared with 10–15% of unselected 3-year-olds.[126] There is also evidence that, even when a child with a history of early OME has reached the age of 13 years, they performed less well than non-OME children for neurotic and inattention traits. By 15 years of age, the OME group scored less well in the total behaviour score and specifically for inattentive and hyperactive behaviour.[122, 123]

BALANCE

While OME is one of the most common causes of balance disturbances in young children,[127] only about 30% of parents of children with OME report that they are concerned about their child's balance. When formally tested, 61% of children with OME have objectively defective motor proficiency; these symptoms resolve following insertion of ventilation tubes.[126, 127]

QUALITY OF LIFE

Quality of life (QOL) is a multidimensional concept reflecting general valuation of health states, also important as a child- or parent-centred measure of outcome in routine contexts. Only relatively recently have specific ear-related QOL measures been developed. The MRC Multi-centre Otitis media Study Group has produced the OM8-30 functional health status measure, which has been impartially evaluated, with favourable recommendation[128] and mapped onto generic QOL.[129] For routine patient-reported outcome measure (PROM) applications emphasizing QOL, a short-form easy-to-use measure, the OMQ-14, has recently been developed from the OM8-30. This uses two databases, from UK secondary[130] and primary[131] care trial cohorts, to define the 14 items from OM8-30 best reflecting QOL. Facets covered by the OMQ-14 questions include four main profile areas: (i) recurrent AOM, (ii) reported hearing difficulties, (iii) behaviour and parental QOL, and (iv) speech and language. Clinical research currently being performed using these measures is suggesting that such estimates of child- and parent-centered outcomes in 'the real world' are of considerable practical use. This is partly because hearing level, although an important assessment and outcome, demonstrates only low correlation with QOL. Short questionnaire measures have great potential to become a useful routine aspect of individual clinical assessment, alongside their current research use as an evaluation of interventions for OME.[132]

MANAGEMENT

Counselling and hearing tactics

Parents of children with OME are often misinformed about many aspects of the condition. In particular, they can have over-pessimistic views about its severity and be over-optimistic about the merits of surgery. At their first visit to the general practitioner or the specialist, time has to be spent explaining that, in general, OME is a benign condition with a high spontaneous recovery rate with no serious long-term sequelae. In most children, the main concern will be the hearing. It should be explained to the parents that the impairment associated with OME is very variable in degree and duration and mild or moderate at most.

It is important that all parents of children with OME receive appropriate general counselling about the natural history and relative benign nature of the condition. Those in contact with the child, including any minder or teacher, should be made aware that hearing-related disability can be minimized by adopting hearing tactics, including the following:

- Get the child's attention before starting to talk.
- Reduce the background noise as much as possible (e.g. turn off the television).
- Face the child so that they can see you talk to encourage lip reading.
- Speak in a normal voice in volume, speed and emphasis, as close as possible to the child.

Leaflets such as *Glue ear: A guide for parents* offered to parents could reinforce the above messages.[133]

Medical management

Medical management would potentially be of greatest benefit if it could speed the resolution of an episode of OME. Hence, randomized controlled trials carried out in

primary care settings would be those most appropriate to consider using resolution of OME as the outcome. Such studies need to define their target populations to exclude non-cases, etc. Some trials followed up children for just 1–2 weeks after therapy. However, if any treatment is effective after 1–2 weeks, then follow-up for the recommended watchful waiting period of 12 weeks is necessary to see if it is of benefit in the longer term, and might be used to reduce the proportion of children being considered for surgery.

NASAL TOPICAL STEROIDS

A Cochrane systematic review[134] identified several studies of topical nasal or oral steroids versus placebo.[131, 135, 136] The review, which included a sizeable UK study of nasal steroids versus placebo from UK primary care, concluded that there is evidence for no benefit from topical intranasal steroids.

SYSTEMIC STEROIDS

Considerable concern has been expressed about the use of oral steroids being given to children for a non-life-threatening and spontaneously resolving condition. Consequently, such treatment would have to be highly effective in the long term before it could be recommended. The review that included 12 studies in total and 945 patients[134] did, however, find some evidence to suggest that oral steroids are effective in the short term (2 weeks), and when combined with antibiotics.[137, 138] Systemic steroids cannot be recommended at present for childhood OME.[139]

ANTIBIOTICS

A Cochrane review based on 23 trials mostly from secondary care and 3027 subjects has suggested that antibiotics are unlikely to be beneficial.[140] There was evidence to show that antibiotics had no statistically significant benefit in the short term. Because trials were very heterogeneous, meta-analysis was not attempted. In the longer term there appeared to be slight benefit from use of antibiotics but there are some concerns about the generalizability of these data, and the disadvantages of antibiotics: rashes, diarrhoea, antibiotic-associated colitis, anaphylaxis, thrush and antibiotic resistance are increasingly well known, making them unsuitable for longer-term use. In particular, the Chief Medical Officer for England and Wales has highlighted antibiotic resistance as a major public threat to health.

NASAL DECONGESTANTS

A systematic review and meta-analysis of four trials (n = 1202) found that antihistamine/decongestants had no significant effect on the resolution rate of OME.[141] Nasal decongestants are not recommended for use in childhood OME.

MUCOLYTICS

A systematic review of six randomized controlled trials of S-carboxymethylcysteine published before 1993 could not demonstrate that they had an effect.[142] A later trial also showed no significant effect.[143] Because of a non-significant trend for increased benefit in these small, biased trials, a larger well-designed study is merited.

Other non-surgical approaches

AUTOINFLATION

A systematic review of autoinflation for the treatment of glue ear in children identified eight studies with 702 participants.[144] Pooled estimates found non-significant improvement in tympanometry at less than 1 month (relative risk of improvement (RRI) 1.47, 95% CI 0.69–3.13) and non-significant improvement at more than 1 month (RRI 1.22, 95% CI 1.00–1.49). A composite measure of tympanometry with audiometry showed a significant improvement at more than 1 month (RRI 1.74, 95% CI 1.22–2.50). Because of the low cost and absence of reported adverse effects, it was concluded that autoinflation was worth considering while awaiting natural resolution, and that primary care was a good setting for further studies. Some concerns have been raised though about the age at which the method can be performed reliably in children, and this also requires further evaluation. Currently autoinflation appears the most promising non-surgical management to augment active monitoring (watchful waiting).

HOMEOPATHY

No randomized controlled trials have been identified. A small, non-blinded study showed homeopathy to be of no benefit.[145]

Surgery

MYRINGOTOMY AND INSERTION OF VENTILATION TUBES

Myringotomy with aspiration of middle ear fluid but without insertion of a ventilation tube (grommet, tympanostomy tube) is ineffective surgical management of OME.[146] The incision closes within a few days and the effusion usually recurs.

Ventilation tubes of different materials are available, although in the UK, Teflon® grommets are typically used. Titanium-, gold- or silver oxide-coated ventilation tubes are intended to inhibit biofilm formation, although *in vitro* evidence indicates this is only the case if the material is coated with antibiotic.[147] Using scanning electron microscopy, some biomaterials, such as ionized, processed silicone, appear more resistant to biofilm formation, reducing the incidence of plugging of the tube and post-operative otorrhoea.[148]

Standard pattern ventilation tubes (e.g. Shepard, Shah – **Figure 13.5**) stay *in situ* for a shorter period than longer-term T-tube designs (**Figure 13.6**), but the longer a tube stays *in situ*, the higher the chance of complications, including plugging of the lumen, infection, thinning and collapse of the tympanic membrane with possible retraction and permanent perforation.[149] Up to 55% of Shepard

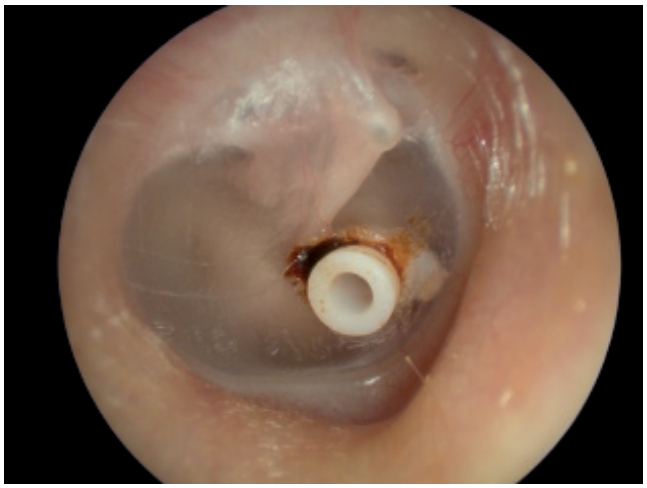

Figure 13.5 Right tympanic membrane Shah grommet *in situ*. (Image courtesy of Mr Michael Saunders.)

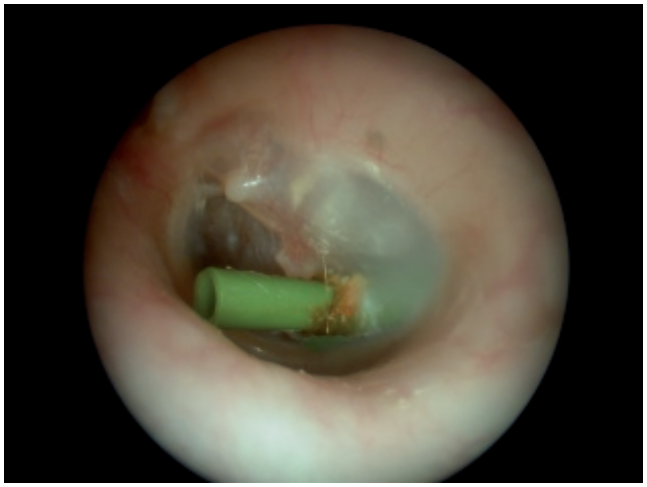

Figure 13.6 Right tympanic membrane T-tube *in situ*. (Image courtesy of Mr Michael Saunders.)

ventilation tubes have extruded within 6 months of insertion;[149, 150] in the same period, approximately 10% of T-tubes will have been extruded.[148]

In the future, both biofilm formation with infective complications and persistent perforation may be reduced or abolished by a currently experimental biodegradable, absorbable ventilation tube manufactured from poly-bis (ethylanate) phosphazene.[151]

Surgical technique

Site To maximize the duration of placement and minimize damage or perforation, the preferred insertion site of the ventilation tube is anteroinferior through a circumferential or radial incision. Insertion of the ventilation tube posterosuperiorly is not recommended because of the risk of damaging the ossicular chain. The ventilation tube inserted via a radial or circumferential incision does not influence the extrusion rate.[152] Placement of the grommet anteroinferiorly compared with placement posteroinferiorly lengthens the time a Shepard ventilation tube remains *in situ* (80% versus 45% at 6 months and 30% versus 15% at 12 months).[153] A tube placed anteriorly is also associated with a reduced but non-significant reduction in persistent perforation compared to a tube placed posteriorly in the tympanic membrane (1.8% versus 3.7%).[153]

Surgical aspiration While usual practice is to aspirate middle ear fluid through the myringotomy prior to insertion of ventilation tubes, there is no evidence to support this. Hearing levels 3 months following insertion of a ventilation tube were the same independent of aspiration.[155, 156] A literature review of the topic concluded aspiration produced increased rates of tympanosclerosis, secondary to trauma and bleeding of the tympanic membrane. Noise from persistent aspiration may lead to permanent noise-induced hearing loss.[157] Aspiration causing bleeding from the tympanic membrane may encourage subsequent biofilm infection of the ventilation tube.[158]

Topical preparations Ear drops can be used at the time of insertion of ventilation tubes to reduce the risk of tube blockage with blood and mucus, and to minimize local infection during the early post-operative period (see 'Complications of ventilation tubes' below).

ADENOIDECTOMY

Surgical techniques

In the UK, blind curettage adenoidectomy continues to be the most used technique. Digital palpation and blind curettage is used in 79.2% of cases, while only 8.1% use suction coagulation under direct vision.[159] It is surprising that curettage remains popular suffering the disadvantages of a blind procedure with unpredictable bleeding, poor access to choanal adenoid and risk of trauma to the Eustachian cushions. In contrast, suction diathermy affords direct vision with minimal blood loss[160] (mean 4 mL versus 50 ml L), haemostasis and negligible risk of post-operative haemorrhage.[161] Suction diathermy is also effective in performing partial adenoidectomy, leaving a ridge of adenoidal tissue at the inferior part of the nasopharynx, reducing the risk of velopharyngeal insufficiency in those children where this is likely after removal of the adenoid.[162] Other direct vision techniques include Coblation® and microdebrider, which have the disadvantage of high unit cost for adenoidectomy alone. KTP laser is associated with a high risk of nasopharyngeal stenosis,[163] which has not been reported using gold laser for adenoidectomy.[164] All single-use instrument techniques have the advantage of abolishing the potential risk of infection transmission[165] (see Chapter 26, The adenoid and adenoidectomy).

SURGICAL OUTCOMES

Hearing outcomes of ventilation tube insertion

The Cochrane systematic review of 'grommets (ventilation tubes) for hearing loss associated with otitis media with effusion in children'[166] concluded that the benefits of

grommets appear small and the effects on hearing diminish during the first year after surgery.

From the trials reviewed, grommets were beneficial in the first 6 months. At 3 months, the mean hearing was 12 dB better in those receiving grommets, falling to 4 dB at 6–9 months. Using pure tone audiometry as a surrogate for disability due to hearing loss fails to address the potentially complex disadvantage the developing child suffers during the period of untreated hearing loss. While the review reports no proven effects on language, speech development, behaviour, cognitive or quality of life, there is some trial evidence to support effects in these domains from published data.[113–123]

Uncertainties remain as the evidence collected in the review cannot entirely resolve discrepancies between analysed trial data on the one hand and parental and clinical observation of a beneficial treatment effect observed in practice on the other. This may be in some part due to a lack of validated and reliable child and parent-centred measures, lacking in many of the trials (with perhaps hitherto some overreliance on hearing level), while also duly acknowledging discrepancies arising from lack of control for placebo effects and other biases inherent in clinical practice.

The remaining challenge is to identify those children for whom intervention is needed and helpful.[167] Does a return to normal pure-tone audiometry after 12 months of hearing loss from OME equate to absence of disability during the same period? In considering data from randomized controlled trials, the effect of intervention may appear reduced in an intention to treat analysis (ITT), when the rate of transfer from control to intervention group is high (contaminates the control group with the intervention effect). However ITT does control for attrition bias and is the most appropriate and robust analysis when evaluating effectiveness and cost-effectiveness in the NHS setting.

The UK MRC TARGET multicentre study looked at the effect of ventilation tubes alone or with adjuvant adenoidectomy on child-centred outcomes. Children aged between 3.5 and 7 years, with bilateral OME, persistent over a 12-week 'watchful waiting' period and associated with a hearing impairment in both ears of 20 dB HL or poorer were eligible for inclusion. They were randomized to one of three arms: no-surgical management, bilateral ventilation tubes (Shepard) or bilateral ventilation tubes with adjuvant adenoidectomy. In the non-surgical group, hearing improved with time, mainly due to the natural resolution of the OME. Children randomized to have ventilation tubes had a marked improvement of 12 dB 3 months following surgery compared with the non-surgical group. In both ventilation tube groups, the hearing at 3 months does not become 'normal' (i.e. 0 dB HL). If one excludes the small number of ears in which the ventilation tube is non-functioning, there is still an air–bone gap of 13 dB.[168] At all other post-operative visits, when a tube was functioning, the air–bone gap was of a similar magnitude and, as the middle ear space was well-ventilated, was considered due to effusion and oedema around the ossicular chain.

The difference in hearing between the two surgical groups and the non-surgical group became almost negligible at 12 months. The reason for the deterioration in the hearing levels over time in those with a ventilation tube was due to a combination of two factors. First, the proportion of tubes that become non-functioning increased with time, though children were eligible to have them reinserted if the hearing entry criteria were satisfied at that time. The other reason was that, in ears where the ventilation tube has extruded and the OME has resolved, there is still a small but material conduction deficit of approximately 14 dB.[168] The reason why those in the non-surgical arm improved over that period was mostly due to the natural spontaneous resolution rate of the OME combined with a much smaller contribution from those who switched management arms to surgery.

TARGET demonstrated the improvement in hearing from ventilation tubes averaged over the first year was 5.7 dB. In the second year, the difference between the two groups became negligible. Hence, when averaged over 2 years, the benefit of ventilation tubes is reduced to 3.1 dB. A more recent individual data meta-analysis of four trials that randomized children to ventilation tubes or watchful waiting confirmed the benefit of short-term ventilation tube at 6 months but not at 12 months, with a magnitude of difference of 4.5 dB.[169]

In this same study, the meta-analysis from seven trials randomized 1232 children with persistent bilateral OME for 12 weeks to ventilation tubes or non-surgical management. The only factor predictive of a better hearing outcome at 6 months was attendance at day care with an impairment of 20–25 dB in both ears. Those not attending day care had no benefit (>1 dB) at 6 months. No effect of age, sex or socioeconomic group was evident. In three trials which randomized children 'by-ear', those with a binaural hearing level of >25 dB HL benefited by 10 dB at 6 months compared with the 4 dB of those with lesser hearing thresholds. These data suggest that, when the aim is improvement in the hearing, then younger children at day care and those with binaural hearing thresholds poorer than 25 dB HL and persistent over at least 12 weeks will benefit most.

Non-hearing outcomes are discussed in 'Outcomes of childhood OME' above.

Outcomes of adenoidectomy

The role of the adenoid in OME has been discussed above. Chronic inflammatory change in the mucosa of the Eustachian tube and middle ear secondary to biofilm infection of the adenoid rather than physical obstruction of the Eustachian tube is the likely cause, and removing this is how adenoidectomy is beneficial in the management of OME. Adenoidectomy reduces the need for reinsertion of ventilation tubes.[170, 171] At the time of writing, UK guidance[104] does not yet include the recommendation for adjuvant adenoidectomy. While clinicians recommended this for the 2011 NICE guideline update, the guideline was not changed. The US guideline does not recommend adjuvant adenoidectomy until the second insertion of ventilation tubes;[171] this might be appropriate guidance for the younger age group, given the role of the adenoid in laying down immune memory, discussed above.

Hearing In the TARGET trial, adenoidectomy at the time of insertion of ventilation tubes doubled the benefit and extended better hearing through the second year following intervention, reducing the need for repeat insertion of ventilation tubes, with an absolute risk reduction of 21%.[130]

Upper respiratory tract symptoms Adjuvant adenoidectomy confers the additional benefit of improved respiratory health over a 2-year period following surgery (Haggard MP, 2005, personal communication).

COMPLICATIONS OF VENTILATION TUBES

Operative

The most common operative complication is displacement of the ventilation tube into the middle ear, in 0.5% of cases. The tube should be retrieved if damage can be avoided. If not, the inert nature of the tube means that significant further problems are unlikely to occur. Efforts should be made to retrieve the tube at the time, but failure to remove it seldom causes problems. Posterosuperior myringotomy must be avoided as this risks damage to the ossicular chain and incudostapedial joint. Very rarely, a high dehiscent jugular bulb may be pierced by an inferiorly placed myringotomy.

Early post-operative

Aspiration at the time of surgery is unlikely to prevent blockage of the lumen of the ventilation tube.[156, 157] Early infection around the ventilation tube occurs in 9% of ears.[172] Topical antibiotic steroid drops at the time of surgery can reduce the incidence to 1%. Although likely to be safe in clinical practice,[173] aminoglycoside drops carry the potential risk of both ototoxicity and vestibulotoxicity and should be avoided. Quinolone antibiotic eardrops are a safer alternative and, although widely used worldwide, are currently unavailable in the UK. Quinolone eye drops (e.g. ofloxacin) are commonly used for this non-licensed indication.

Otorrhoea Otorrhoea in association with a ventilation tube *in situ* may follow an acute upper respiratory tract infection or can be the result of a chronic biofilm infection of the ventilation tube itself. Post-operative otorrhoea is the most common complication with a reported incidence of 10–50% (**Figure 13.7**). A Cochrane review failed to find good quality evidence to support a meta-analysis. While oral amoxicillin clavulanate combined with daily aural toilet was significantly more effective than placebo and daily aural toilet, no significant benefit could be shown for topical aminoglycoside preparations compared with each other or with oral steroids and oral antibiotics.[174] In a randomized, double-blind, controlled trial, topical ciprofloxacin drops were superior to topical saline and systemic antibiotics in managing ventilation tube otorrhoea. Failure rates were 23%, 58% and 70% in the groups treated with topical ciprofloxacin, topical saline and oral amoxicillin respectively.[175] A randomized, blinded parallel group study compared ciprofloxacin–dexamethasone ear drops with no treatment following ventilation tube insertion. In the treatment group, otorrhoea was observed in 4.95% of patients, compared to 39.39% of the untreated group ($p < 0.0001$).[176]

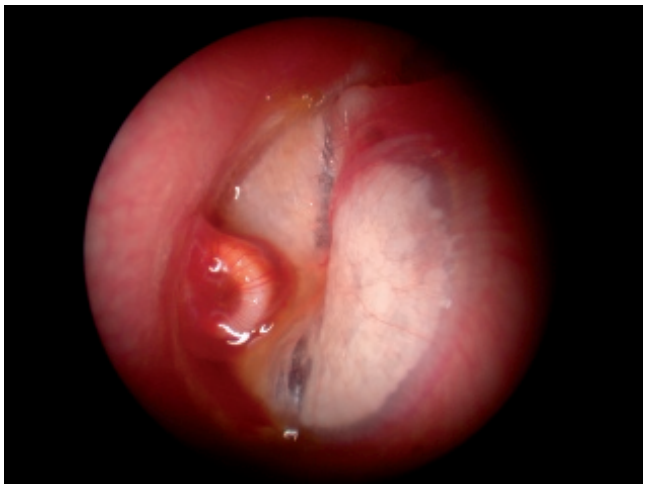

Figure 13.7 Right tympanic membrane with infected grommet. (Image courtesy of Mr Michael Saunders.)

Granulation tissue secondary to infection occurs in approximately 1%, and is similarly managed with topical preparations. Chronic infection of the ventilation tube may require removal of the tube (in approximately 4% of ears).[172] Ofloxacin as a topical antibiotic is preferable to ciprofloxacin, minimizing the risk of antibiotic resistance in a systemically used antibiotic.

Late post-operative

Hearing loss A study of 224 children following grommet insertion concluded that 25 years after surgical treatment for OME hearing was no different to age- and gender-matched controls. Neither myringotomy alone nor insertion of ventilation tubes resulted in a significant difference in long-term hearing level, compared to a gender-matched normative data set. Where myringosclerosis was present in ears following grommet insertion, there was a small associated loss (4–5 dB) in the high-frequency range. Where pars tensa atrophy occurred after grommet surgery, the long-term change in hearing was limited to an overall loss of 3–4 dB.[177]

Myringosclerosis ('tympanosclerosis') The most common structural complication after ventilation tube surgery is myringosclerosis, occurring more often with long-term tubes. Hyaline degeneration of the collagen tissue in the fibrous layer of the pars tensa is visible otoscopically as localized white patches or plaques (**Figure 13.8**). These do not occur in the absence of a history of otitis media. The frequency of myringosclerosis increases with the frequency of OME with an increased risk if a ventilation tube has been inserted.[166] While there was difference between short- and long-term tubes in this review, a later systematic review concluded that myringosclerosis was more common with long-term tubes.[178] This review

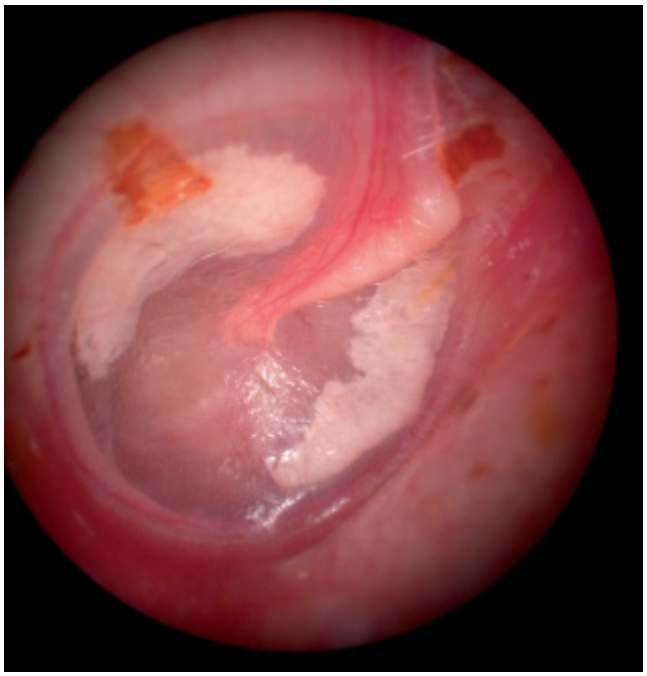

Figure 13.8 Myringosclerosis 'tympanosclerosis'. (Image courtesy of Mr Michael Saunders.)

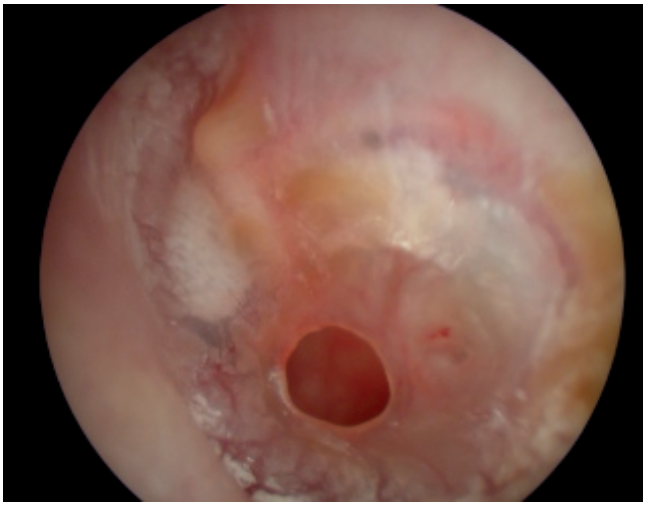

Figure 13.9 Perforation. (Image courtesy of Mr Michael Saunders.)

also concluded no hearing impairment resulted from the presence of myringosclerosis.

Tympanic membrane perforation When a ventilation tube extrudes, the initial pars tensa perforation usually heals. A perforation may then subsequently reoccur at the same site due to a subsequent episode of AOM and, again, will normally heal spontaneously. Perforation is seen in between 1% and 6% of ears that have had a ventilation tube and in 1% of ears that have never had a ventilation tube inserted; perforation occurs more commonly in treated ears, and more often with long-term ventilation tubes (**Figure 13.9**).[179]

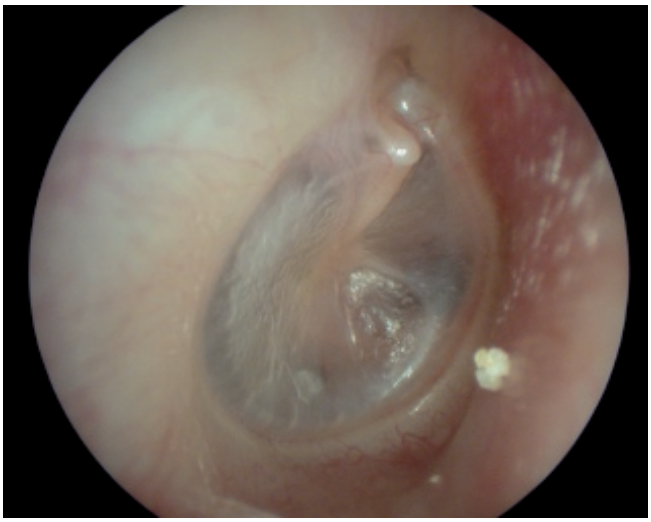

Figure 13.10 Pars tensa atrophy. (Image courtesy of Mr Michael Saunders.)

Pars tensa atrophy and retraction Thinning and retraction of the tympanic membrane are complications of persistent OME. In children initially referred with bilateral OME, pars tensa retraction to the incus or promontory (Sade grade 3/4) occurs in 8% of the better- and 10% of the poorer-hearing ears.[63] These retractions were not associated with a history of longer ear problems. Followed up over a 12-week watchful waiting period, they resolved in 69% of the better and 65% of the poorer ears. The OME had also resolved in 14% of the better and 10% of the poorer ears with a pars tensa retraction, respectively.

Pars tensa atrophy (**Figure 13.10**) also occurs in approximately 3% and retraction to the incus or promontory in 2% of ears in 7–8-year-old children in whom there is no history of OME. This incidence is similar to that in children with transient episodes of OME. However, the incidence of atrophy, but not of retraction, increases to approximately 9% in those with persistent OME. In those who still have a ventilation tube *in situ* for their OME, the incidence of atrophy increases to approximately 68% and retraction to approximately 14%. It could be argued that this increase in ears with a ventilation tube still *in situ* is because these are more persistent cases, rather than because of the ventilation tube itself. This is in part supported by the fact that the incidence is the same with short- and long-term tubes.[173] It can be concluded that ventilation tubes do not prevent the occurrence of atrophy or retraction and should not be inserted for that reason alone. Cholesteatoma is uncommon enough to make it difficult to draw clear conclusions about the effect of ventilation tube insertion on the incidence of this condition.[178]

Swimming and water contamination A meta-analysis concluded that for bathing and swimming, but not diving, ear protection does not or only slightly reduces otorrhoea in children following ventilation tube insertion.[178]

Hearing aids

Hearing aids can be used in children with persistent OME, to avoid repeated surgery, or where parents wish as their preferred initial management. Repeated visits for new ear moulds, maintenance of the aids and replacement of lost aids suggest this option might be time- and cost-intensive for both parents and providers. There is very limited published data on the subject. In a small case series,[179] hearing aids were acceptable to the majority of parents and gave aided thresholds with a mean of 17 dB, in the same range as expected of ventilation tubes. The main concern is potential noise trauma, as up to 13% of children become dependent on the aids and wish to continue to use the aids after the OME has resolved.

The Softband® bone-conduction aid incorporates a bone-anchored hearing aid in a headband. In a small prospective, non-randomized questionnaire study of 11 children aged between 6 and 15 years, half the children found daily listening situations to be mostly easy. All of the children used the Softband® at school. This is an older age group than those typically presenting with OME, but this small study indicates the need for a larger trial to assess the potential benefit of this non-invasive treatment of OME.[180]

Management of OME in children with related comorbidity

Even after surgical repair, children with a cleft palate have a high incidence of OME that in some is a persisting condition. Hearing aids rather than ventilation tubes are usually recommended to maintain near-normal hearing without the complications associated with repeated ventilation tube insertion or long-term tubes.[181] Similar constraints apply to the management of OME in children with Down syndrome, where there might also be a sensorineural component to the hearing loss.[182]

BEST CLINICAL PRACTICE

In primary care

OME should be suspected in children with 'ear-related concerns' who may have recently recovered from an episode of acute otitis media or are suffering from recurrent bouts.

- ✓ All children should have routine otoscopy to help confirm OME and distinguish it from AOM or COM. However, even with good training, otoscopy is unlikely to be sufficiently sensitive or specific to reliably make the diagnosis of OME on its own. Tympanometry with training of staff is likely to be more accurate in diagnosing if effusions are present.
- ✓ Free-field voice testing is a valid assessment of hearing in a primary care setting. Hearing-related QOL can also be estimated using the OMQ-14 (short form) questionnaire.
- ✓ No medical therapy (including antibiotics, topical nasal steroids, systemic steroids, nasal decongestants and mucolytics) has been proven to be clinically effective. Alternative and complementary therapies have not been shown to be effective in the management of OME either. In older children, autoinflation might be beneficial.
- ✓ It is important that all parents of children with OME receive appropriate general counselling about the natural history and nature of the condition. This includes advice regarding hearing tactics.
- ✓ If there is concern regarding the hearing in any child, referral for hearing assessment is indicated. For children under the age of 4 years, initial referral is to community paediatric audiology. In children aged 4 years and older, hearing assessment can be performed in a general paediatric ENT clinic. Active monitoring (watchful waiting) with audiometry can be continued in secondary care.

In secondary care

- ✓ Otoscopy, tympanometry and pure-tone air-conduction thresholds should be assessed in all children referred with suspected hearing impairment at their first clinic visit. Non-masked bone-conduction thresholds are generally obtainable in children over the age of 4 years. This will aid management of those with OME and detect previously undiagnosed sensorineural hearing loss.
- ✓ Primary carers of all children with OME should receive appropriate general counselling about the natural history and nature of OME.
- ✓ The hearing levels associated with the child's OME should be discussed with the parents and advice about hearing tactics given to help the parents mitigate any disability.
- ✓ Children with OME whose hearing thresholds do not satisfy the hearing criterion of 25 dB HL bilaterally should be followed up 12 weeks later with repeat audiometry.
- ✓ Where hearing loss of 25 dB HL or poorer in both ears persists after 12 weeks of active monitoring, discuss options for further management, including insertion of ventilation tubes with adenoidectomy, hearing aids or continued surveillance.
- ✓ While the risk of ototoxicity with topical aminoglycoside preparations is small, for the treatment of infected otorrhoea and where bacterial sensitivities allow, use quinolone ear drops when a grommet is patent or there is a tympanic membrane perforation.

FUTURE RESEARCH

- ➤ Different impact of OME and elevated hearing thresholds in children with different intellectual ability.
- ➤ Possible benefits of surfactant in the management of adenoidal biofilms.

KEY POINTS

- In children, the prevalence of OME is bimodal with the first and largest peak at 2 years of age (~20%) and the second peak at around 5 years of age (~16%).
- For each episode, resolution without treatment of the OME is the most likely outcome.
- The effect of hearing impairment on speech, language, cognition and behaviour may produce measurable changes long after the OME has resolved.
- Attic retractions are an OME disease effect with an incidence of approximately 14% in the most severely affected children. The proportion of these retractions that progress to cholesteatoma is unknown. There is no evidence that the risk of developing an attic retraction and the potential to develop a cholesteatoma is altered by the insertion of ventilation tubes.
- The benefit of ventilation tubes in children under 3 years of age with significant language, development or behaviour problems requires investigation. In children over the age of 3 years, the binaural hearing average is used as a surrogate of behaviour and for impact upon quality of life.
- All children with hearing thresholds of 25 dB or poorer in both ears should have their hearing documented over a 12-week watchful waiting period before any decisions regarding surgery are made.
- If ventilation tubes are to be inserted, adenoidectomy is effective adjuvant treatment, extending the period of benefit to the hearing of short-term ventilation tubes up to 2 years and reducing the proportion of children eligible for reinsertion of short-term tubes from around 50% to 25%. This effect is likely to be greatest in the oldest children. (Adenoidectomy in children under the age of 3 years might impact negatively on immune system development.)

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CHAPTER 14

ACUTE OTITIS MEDIA

Peter A. Rea and Natalie Ronan

SEARCH STRATEGY

Data in this chapter may be updated by searches of Medline and the Cochrane Controlled Trials Register, using the keywords acute otitis media. Reference lists were reviewed for further articles, and authors of recent presentations contacted personally for their reference lists.

INTRODUCTION

For such a common childhood infection, acute otitis media (AOM) remains something of an enigma. It is hard to diagnose accurately and on existing evidence, as opposed to custom and tradition, there is still a high level of uncertainty over how it should best be treated. This is against a background of increasing bacterial resistance to antibiotics. There is plenty of evidence in the literature of the relative frequencies of viral and bacterial pathogens in AOM, but this is often of little help to the clinician on the spot in an individual case. Some of the epidemiological evidence is also relatively 'soft', since it is based on the flawed premise that AOM can accurately be diagnosed from the history and otoscopy alone, unsupported by tympanometry or tympanocentesis. In this chapter the authors have tried to thread their way through the often conflicting evidence about the practical management of AOM at the same time as covering what is known of the pathology, epidemiology and complications of this commonest of childhood illnesses.

Many areas of uncertainty, insufficient evidence and limited information about AOM remain. For this reason we have indicated Level 1 and Grade A evidence in the chapter. Even a meta-analysis, the supposed gold standard of evidence, is only as good as the studies it covers. It must be remembered that the prevalence of otitis media with effusion (OME), 'glue ear', only began to be widely appreciated after the development of the twin tools of universal hearing screening and the tympanometer, in the 1960s and early 1970s respectively. The accuracy of correct reporting of cases of AOM lags behind that of OME mainly because the essential presence of fluid in the middle ear is not confirmed by tympanometry and audiometry in the majority of large population studies of AOM.

DEFINITION

Acute otitis media (AOM) may be defined clinicopathologically as inflammation of the middle ear cleft of rapid onset and infective origin, associated with a middle ear effusion and a varied collection of clinical symptoms and signs. It is synonymous with acute suppurative otitis media. It normally develops behind an intact tympanic membrane but may include acute infections arising in the presence of ventilation tubes or existing tympanic membrane perforations. The requirement to confirm a middle ear effusion, and the nature of the symptoms and signs, vary between authors.[1, 2]

The literature supports four broadly defined subgroups of AOM:

1. **Sporadic** episodes occurring as infrequent isolated events, typically occurring with upper respiratory tract infections (URTIs)

2. **Resistant** AOM: persistence of symptoms and signs of middle ear infection beyond 3–5 days of antibiotic treatment
3. **Persistent** AOM: persistence or recurrence of symptoms and signs of AOM within 6 days of finishing a course of antibiotics
4. **Recurrent** AOM: either 3 or more episodes of AOM occurring within a 6-month period, or at least 4–6 episodes within a 12-month period (no consensus has been reached on the latter).

Groups 2 and 3 appear similar at first glance and this distinction may be questioned. It is included to maintain some consistency with the wider literature.

Grading of the severity of an episode has been attempted and has merit both clinically and for research. Pyrexia from 37.5 °C to 39 °C, vomiting and severity of otalgia have been used.[3, 4]

DIAGNOSIS

Diagnosis is based on the combination of often non-specific symptoms, evidence of inflammation of the middle ear cleft, and by some authors by the additional confirmation of a middle ear effusion. Diagnostic difficulty has affected the quality of research into AOM. There may well not be a clear history of a crescendo of otalgia in a coryzal child, followed by rapid symptomatic relief associated with tympanic membrane perforation and associated blood-stained otorrhoea. The difficulty in establishing clear diagnostic guidelines has been highlighted in an analysis of 80 studies of AOM.[5] In diagnosing AOM only 52.5% of the studies cited middle ear effusions, 32.5% included symptoms and signs of inflammation and 2.5% considered the rapidity of onset. Clinicians recognize this difficulty. A large multinational study rated clinicians' diagnostic certainty in children under 1 year of age at only 58%, rising to 73% in those over 31 months.[6]

Symptoms

Diagnosis by symptomatology alone is inaccurate because of the young age of most patients, and the non-specific nature of the symptoms. One third of children may have no ear-related symptoms. Two-thirds may be apyrexial.[7] Symptoms suggestive of AOM include rapid onset of otalgia, hearing loss, otorrhoea, fever, excessive crying, irritability, coryzal symptoms, vomiting, poor feeding, ear pulling and clumsiness (Table 14.1). AOM most commonly develops 3–4 days after the onset of coryzal symptoms. The otalgia will settle within 24 hours in two-thirds of children without treatment.[9] The otorrhoea, if present, is mucopurulent and may be blood-stained. Symptomatic relief is obtained without treatment in 88% by day 4–7. The hearing loss, caused by the middle ear effusion, occurs early in the illness and may persist at greater than 20 dB for 1 month in over 30%, and 2 months in 20% of children.

Signs

The child may appear unwell, and may rub his or her ear. The diagnosis is often confirmed, rightly or wrongly, by an attempt at otoscopic assessment of the tympanic membrane. However, a poorly functioning otoscope, the moving target of a child's head, the narrow ear canal of an infant, the natural redness of the tympanic membrane of a screaming child, wax, and above all the inaccuracy of an untrained (or even trained) eye straining to interpret a two-dimensional image, all combine to make otoscopy an imprecise art. Since trained observers have been shown to have only an 85% accuracy in otoscopic diagnosis,[10] it would not be surprising for a sensible primary care physician to rely more on history and the general aspect of a child than on otoscopic findings. With these reservations, diagnosis may be supported by otoscopic assessment of tympanic membrane **colour**, **position** and **mobility**. In AOM the tympanic membrane is usually opaque. It is most commonly yellow, or yellowish pink in colour, being red in only 18–19%.[7, 10] The position of the tympanic membrane reliably predicts AOM only when it is bulging. Hypomobility of the drum demonstrated by pneumatic otoscopy has been shown to aid diagnosis[10] and is felt essential in some countries,[1] though others including the Dutch[2] take a more pragmatic view and do not include this in their diagnostic criteria. Should the drum be perforated, or a ventilation tube be *in situ*, mucopurulent otorrhoea will be seen.

Investigations

Tympanometry may be used to establish the presence of a middle ear effusion but is not usually available. Tympanocentesis and culture of middle ear effusion have been used in a number of studies assessing diagnostic

TABLE 14.1 Relation of reported symptoms to presence of AOM in 302 children under 4 years of age (reprinted from Heikkinen and Ruuskanen,[8] with permission)

Symptom	Sensitivity	Specificity	Positive predictive value	Negative predictive value
Earache	60	92	83	78
Restlessness	64	51	46	68
Rhinitis	96	8	41	74
Cough	83	17	40	61
Fever	69	23	38	53

accuracy of clinical signs, and establishing the organisms prevalent in a community. It is rarely required to make the diagnosis, though may be considered in high-risk children such as the immunocompromised, an unwell neonate, those that fail to respond to conventional treatment, and children who are seriously ill or have complications of AOM. Taking a bacterial swab of persistent otorrhoea following perforation is recommended. Nasopharyngeal swabbing for bacterial culture has been assessed but the correlation with middle ear organisms has been too weak to recommend it clinically.[11]

Specific investigation may be prompted by recurrent AOM not responsive to conventional treatment. Both iron-deficiency anaemia and white blood cell disorders have been associated with AOM, so a full blood count is indicated. Immunoglobulin assay may be appropriate: IgA, IgG (with subclasses) and IgM are typically assessed. Children with recurrent infection of ventilation tubes may also merit investigation for primary ciliary dyskinesia, particularly if nasal and pulmonary symptoms coexist.

Differential diagnosis

Pain may be referred from tonsillitis, teething, temporomandibular joint disorders, or simply be the result of an uncomplicated URTI. In a screaming child the tympanic membrane may well appear red. Diagnostic confusion may occur with acute mastoiditis, OME, otitis externa, trauma, Ramsay Hunt syndrome and bullous myringitis. Very rarely AOM may be the first indication of serious underlying disease such as Wegener's granulomatosis or leukaemia.

AETIOLOGY

Microbiological, anatomical and environmental factors combine with altered host defence mechanisms to predispose to infection. Genetic predisposition to recurrent AOM is being cited increasingly in the literature.

Infective agents

AOM results from infection of the middle ear cleft. Both viral and bacterial infections are implicated. These infections may occur in isolation or combination.

VIRUSES

Clinically, it is apparent that AOM is commonly associated with viral upper respiratory tract infections. As our ability to identify these improves, the role of viruses in the aetiology of AOM is becoming clearer. Increasing use of polymerase chain reaction assays for respiratory viruses suggests 60–90% of cases of AOM may be associated with viral infection.[12] In one study a specific viral cause of URTI was shown in 41% of children with AOM.[13] The viruses most commonly associated with AOM vary between studies, but in decreasing frequency include: respiratory syncytial virus (RSV), influenza A virus, parainfluenza viruses, human rhinovirus and adenoviruses. This heterogeneity is important when considering vaccination against viruses as a prophylactic measure.

The mechanism by which they give rise to AOM is likely to vary between viruses.

Viral material has been demonstrated in the middle ear aspirates of children with AOM in 48–71% of cases.[12] The viral material may either arrive passively along the Eustachian tube along with other nasopharyngeal secretions, or actively invade the middle ear cleft possibly by haematogenous spread. These alternative routes of entry are suggested by the wide variation in rates of isolation of specific viral strains in the middle ear during systemic infection, ranging from 4% to 74% of cases dependent upon the specific virus. If all arrived passively, similar rates of isolation would be expected. This implies that some viruses may be actively invading the middle ear cleft, and may be contributing directly to mucosal inflammation. Respiratory syncytial virus invaded the middle ear most frequently.[13] In contrast, those arriving passively appear to cause AOM by virtue of their action on the Eustachian tube, on bacterial adherence and on host immunity.

There is good clinical and animal evidence that viral infection affects Eustachian tube function.[12] At a cellular level there is release of multiple inflammatory mediators from cells within the nasopharynx. Ciliated epithelial cells numbers decline, mucus production increases in the Eustachian tube, and negative middle ear pressure results. This is likely to predispose to AOM.

Alteration of host immunity has been documented after viral infections, increasing susceptibility to bacterial infections. Cell-mediated immunity has been shown to be affected by RSV infection and neutrophil function altered by influenza viruses. In a study of children with bronchiolitis caused by RSV, 62% developed AOM. Bacteria were isolated from the middle ear in all these children.

The ability of bacteria to colonize and adhere to the nasopharyngeal epithelium appears to be increased by certain viral infections. Increased colonization by pathogenic bacteria may predispose to AOM.

Viral and bacterial infections coexist in the middle ear cleft in AOM in as many as two-thirds of cases where viruses have been identified. This is important as clinical studies show that children who have both viruses and bacteria in their middle ear are very much more likely to have a poor response to antibiotics when compared to those with bacteria only (33% versus 3% failure respectively, in one study[14]). Why this should be is unclear, but it may be related to the greater concentrations of inflammatory mediators in ears in which both bacteria and viruses are present.

BACTERIA

Streptococcus pneumoniae (pneumococcus) is the most common bacteria isolated from the middle ear in AOM, and it has been reported in 18–55% of cases. There are, however, some 90 serotypes. *Haemophilus influenzae* has been isolated in 16–37%, and *Moraxella catarrhalis* in 11–23% of cases.[15] Less frequently reported

are *Streptococcus pyogenes* in up to 13% of cases and *Staphylococcus aureus* in up to 5%.[16]

In persistent or recurrent bacterial AOM, repeat culture of middle ear aspirates has failed to grow pathogenic bacteria in 30–50% of patients, implying that inflammation may persist despite the eradication of the infecting organism. The role of biofilms is the subject of intensive study at present. The spectrum of organisms is similar to that in isolated episodes. In the 1980s *H. influenzae* was the most common organism identified in persistent or recurrent AOM, but this has been replaced by drug-resistant pneumococcus. After antibiotic treatment for recurrent AOM it is now estimated that 50% of *H. influenzae* are beta-lactamase producing. A similar proportion of pneumococci are penicillin-resistant.[16] Penicillin resistance in pneumococci results from decreased penicillin-binding protein on the bacterial cell walls so reducing the affinity for penicillin-related drugs, but this means that resistance may often be overcome by increasing drug dosage. This is not the case with beta-lactamase producing organisms. Most *M. catarrhalis* are now beta-lactamase producing.

Studies on HIV-positive children suggest a similar spectrum and prevalence of infecting organisms as occurs in immunocompetent children, except where the child is severely immunosuppressed where a higher percentage of *Staphylococcus aureus* has been reported.

Routes of spread of infection

Three potential routes are described: the Eustachian tube, tympanic membrane perforations or grommets, and haematogenous.

The Eustachian tube is traditionally assumed to be the main route by which organisms reach the middle ear, though there are relatively few studies to confirm this. It is speculated that negative middle ear pressure may facilitate the movement of bacteria up the Eustachian tube.[17] Circumstantial evidence is also gained from similarities in organisms cultured from the postnasal space and the middle ear cleft in AOM. Whether anatomical or physiological differences predispose to AOM is unclear. Studies of American Indians, who are prone to otitis media, suggest their Eustachian tubes are shorter, straighter and more patulous than in whites, but also that they have a low passive tubal resistance.[18] Research has found no difference in tubal dimensions in otitis prone and non-prone children. However, altered tubal function may play a role. Specifically, otitis-prone children have been shown to have significantly poorer active tubal function (muscular opening function).

Pathogen entry through tympanic membrane perforations or ventilation tubes is most commonly associated with water exposure.

Haematogenous spread is inferred from the evidence provided by studies of viral identification in the blood and middle ear described previously. It was shown that the wide variation in rates of identification of specific viral strains from the middle ear could not be explained by passive Eustachian tube transport alone.[12]

Risk factors

GENETIC FACTORS

There is growing evidence that recurrent AOM is largely genetically determined. It is likely that many genes are involved. There are numerous studies suggesting a familial association. A meta-analysis of risk factors has shown that, when one family member had had AOM, the risk increased for other family members (relative risk 2.63).[19] Racial differences are well described, with increases in American Indians, Inuits and Australian Aboriginals. However, environmental factors, such as poor economic status, may contribute to the increased risks in these groups. The most powerful evidence comes from twin studies, in particular comparison of monozygotic and dizygotic twins in whom the occurrence of AOM was compared.[18] Many immune-related mechanisms, which are likely to have a genetic basis, have been proposed. Certain HLA classes have been shown to be significantly associated with increased risk of AOM. Maternal blood group A is reported to an independent risk factor (relative risk 2.82). Atopy has also been associated with increased risk of developing AOM. **[Level 1, 2 and 3 evidence]**

IMMUNE FACTORS

Our understanding of the immune response to AOM remains incomplete. However, a number of specific associations have been identified which suggest that certain defective or immature pathways may predispose to infection. Low levels of IgG2 subclasses have been reported in several studies to be more common in otitis-prone children. Those with IgG2 deficiency were shown to be three times more likely to develop post-ventilation tube insertion otorrhoea, for example. Delayed maturation of anti-pneumococcal antibodies (IgG1 and IgG2 were studied) does appear to predispose to AOM. This may explain in part why children grow out of AOM as immunity matures.

Defective complement-dependent opsonization has been associated with recurrent AOM and diarrhoea in infancy.[18] This is caused in some examples by low concentrations of mannose-binding protein which acts as an opsonin. This appears to be a common defect with over 20% of children with recurrent AOM affected in some studies. This may be particularly important in infancy when the antibody repertoire is limited.

Aberrant expression of critical cytokines such as tumour necrosis factor and interleukins, resulting in suboptimal host defence, has been postulated as a cause for persistent infection. Expression of mucin genes, at least nine of which have been identified, may differ in those predisposed to AOM. Middle ear mucosa expresses specifically the *MUC5B* gene. Mucin genes regulate the production of mucin. Limited evidence is beginning to emerge that overexpression may alter the mucociliary transport system.[18]

A number of studies of children with HIV infection have yielded conflicting results. Advanced disease associated with low CD4 counts does seem to be associated with an increased incidence of AOM.

ENVIRONMENTAL FACTORS

There are many reports on the relative contribution of environmental factors. These are important as it may be possible to modify them. The most important is almost invariably stated to be day-care attendance outside the home. The larger the number of children in the group, the greater the risk. Day care outside the home carries a relative risk (RR) for AOM of 2.45, compared to a risk of 1.59 for children cared for in their own home. The incidence of AOM appears to follow that of seasonal URTIs in the winter months. Breastfeeding for 3 months is protective (RR 0.87). Use of a pacifier (dummy) carries a relative risk of 1.45.[19] Poor socioeconomic status associated with poor housing and overcrowding has been reported to be associated with AOM (e.g. overcrowding: RR 5.55 in a Greenlandic population). Passive smoke exposure from parental smoking is weakly associated (RR 1.0–1.6). There is more limited evidence to support the role of dietary factors, in particular cow's milk allergy, in predisposing to AOM. [Level 1 evidence]

Syndromic associations

Syndromes associated with abnormalities of skull base anatomy are well recognized as being associated with chronic middle ear disease, but less is published on associations with AOM. Children with Turner syndrome do suffer more frequent episodes of AOM. Down syndrome predisposes to middle ear disease including AOM. In cleft palate there is only a minor increase reported. Certainly Eustachian tube dysfunction in these groups predisposes to middle ear effusion, but it is not clear whether it is this dysfunction or an increase in risk secondary to subtle immunological factors that predisposed to infection. No increase is found in children with primary ciliary dyskinesia if grommets are not inserted, or cystic fibrosis.

A direct association between iron-deficiency anaemia, and the degree of anaemia, and frequency of AOM has been reported.

EPIDEMIOLOGY

AOM is one of the commonest illnesses of childhood. It accounts for about 25% of all prescriptions for children under 10 years of age in the USA, for example. Its incidence appears highest in the first year of life, more specifically the second 6 months of life in most studies, and gradually reduces with increasing age. This progression was shown by Strangerup[20] who reported an incidence of a first episode of AOM in 22% in the first year of life, 15% in year 2, and 10% in year 3, falling to 2% by year 8 (**Figure 14.1**). Epidemiological studies have been compromised by difficulty in achieving accuracy in diagnosis when large numbers of children are being assessed, hence there are wide variations in reported numbers. Incidences of over 60% are stated in some reports of infants up to age 1 year. By age 3 years some 50–70% of all children will have had at least one episode of AOM, and at least 75% by age 9 years.

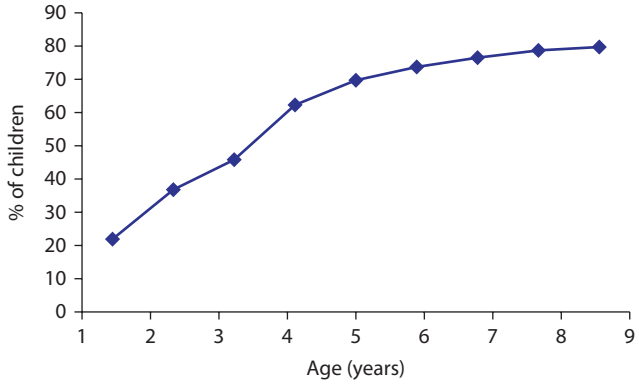

Figure 14.1 Cumulative incidence of acute otitis media (i.e. how many children have had at least one episode in their life). (From Strangerup and Tos,[20] with permission.)

The incidence of AOM certainly varies with the seasonal incidence of viral upper respiratory infections. There are reports that it is increasing over a period of years. Possible reasons include increased day nursery attendance, and changes in diagnostic awareness.

Recurrent AOM has been reported in 5% of children under 2 years of age. Others have reported that by age 3 half of children will have had at least three episodes. An important indicator of future problems is a first episode before 9 months of age: these children have a 1 in 4 risk of developing recurrent AOM.

In the first 2 years of life AOM occurs bilaterally in 80% of cases. After 6 years of age it is unilateral in 86%.[20]

MANAGEMENT OPTIONS

Most children with AOM will get better quickly and without treatment. Some will not. A very small number may develop potentially serious complications. Current debate questions whether and for whom treatment is required, and the role of prophylactic strategies. As serious complications are rare, it can be difficult to obtain high-quality evidence of how effective are prophylaxis and the treatment of episodes of AOM in preventing such complications.

Management of acute episodes

CONSERVATIVE TREATMENT

Most children will benefit from simple analgesics and antipyrexials, in a quiet supportive environment. Paracetamol and ibuprofen are most commonly used in the UK. There is limited experimental animal evidence showing that ibuprofen provides additional benefit by reducing mucosal inflammation when taken in combination with amoxicillin.

MEDICAL TREATMENT

Antibiotics

Uncertainty over the use of antibiotics is reflected in wide variations in usage between countries, ranging from 31%

in the Netherlands to 98% in the USA.[9] There is, however, an increasingly good evidence base for the most appropriate management in children over 2 years of age. In children under 2 the evidence base is weaker.

A recent meta-analysis has addressed the efficacy and safety of antibiotic treatment in children with AOM. Two-thirds of children were shown to recover within 24 hours regardless of treatment. However, antibiotics did have a small beneficial effect on subsequent pain levels, with one third experiencing less pain after 2–3 days and one quarter having reduced pain at 4–7 days. Antibiotics also reduced the number of patients exhibiting abnormal tympanometry at 2 weeks and 2 months, although there was no difference at 3 months. The number of tympanic membrane perforations and contralateral otitis episodes were also reduced in those receiving antibiotics. No effect was demonstrated on late AOM recurrence. However, the occurrence of adverse effects such as vomiting, diarrhoea and rash was significantly increased in the treatment group.[21]

The same review examined the effectiveness and safety of immediate antibiotic treatment against an initial observational approach. No differences were seen between groups in terms of pain, persistence of abnormal tympanometry, tympanic membrane perforations or AOM recurrence, but again the incidence of adverse effects was increased in the immediate treatment group, equating to an adverse event for 1 in every 14 children treated.

Attempts have therefore been made to try to identify a subgroup of children who may benefit from immediate antibiotics. Treatment benefit appears to be most marked in children aged less than 2 years, those with bilateral AOM and those with AOM and otorrhoea. Using short-term symptomatic outcome markers at day 3 has shown that immediate antibiotics may also benefit those children presenting with higher temperatures (>37.5 °C) or vomiting (NNT = 3–6).[4]

The optimum length of a treatment course if commenced has also been addressed in a meta-analysis. Short (less than 7 days) and long (more than 7 days) courses were compared. Risk of treatment failure at 1 month was higher with short courses of antibiotics (absolute difference of 3%) although had no benefit in the longer term. This difference was not observed when using ceftriaxone or azithromycin. In addition, gastrointestinal side effects were reduced when using azithromycin or short-acting antibiotics.[22] In the presence of a tympanic membrane perforation or ventilation tubes, AOM may be treated equally successfully with oral or topical antibiotics. The potential ototoxicity of topical aminoglycoside ear drops in these cases is well recognized and dose-dependent, therefore prolonged topical treatment should be avoided.

Generally, most institutions recommend initial treatment with paracetamol and ibuprofen in uncomplicated cases, with antibiotics to be prescribed if the symptoms worsen or persist for 3–4 days. Immediate antibiotics should, however, be considered if the child is systemically unwell, suffers from significant comorbidities including immunodeficiencies, craniofacial abnormalities or Down syndrome, or if they are under 2 years of age with bilateral AOM, recurrent AOM or tympanic membrane perforation.[2] The usual antibiotic of choice is a 5-day course of amoxicillin, with erythromycin or clarithromycin offered in allergic cases. Guidelines must, however, be adapted to suit local experience, for example in regions of the world with a high incidence of complications of AOM where all patients may be regarded as high risk. **[Level 1 evidence]**

Clinical recommendations for the use of antibiotics in children are summarized in **Box 14.1**.

BOX 14.1 Clinical recommendations for use of antibiotics in children

- Under 6 months of age
- Under 2 years of age with recurrent episodes
- Failure to improve after 2 days of 'watchful waiting'
- More severe symptoms including pyrexia or vomiting, irregular course, or any sign of a complication
- All 'high-risk' children including those with Down syndrome, craniofacial abnormalities, congenital inner ear abnormalities, immunodeficiencies
- Failure to improve after 2–3 days' treatment should lead to change of antibiotic
- Where national guidelines recommend all episodes should be treated

Which antibiotic?

This should be determined by national recommendations. Amoxicillin remains the first choice in most centres, but at higher than previously recommended doses (80 mg/kg/day) if drug-resistant pneumococci are common in a particular country or region, with macrolides for penicillin-sensitive patients. For persistent or resistant episodes, national policies should be sought depending on the prevalence of beta-lactamase producing organisms, and culture results if available. Options include amoxicillin-clavulanate or cefuroxime axetil orally, or intramuscular ceftriaxone (US Centre for Disease Control and Prevention).

Antihistamines and decongestants

A meta-analysis of the use of oral or intranasal antihistamines and/or decongestants concluded that their use could not be supported, and that medication side effects were higher when they were used together. While combining the two treatments was shown to slightly reduce persistent AOM at 2 weeks (NNT = 10.5), the result may have been biased by the design of the studies.[23] **[Level 1 evidence]**

SURGICAL TREATMENT

Surgery has a limited role in the treatment of an uncomplicated episode of AOM. Myringotomy was practised in the pre-antibiotic era, and indeed was continued until the late 1980s in some countries as a first-line treatment for AOM. However, there are now a number of good studies showing that myringotomy plus antibiotics offers no advantage over antibiotics alone. Myringotomy alone has a worse outcome than either of the antibiotic groups.[24]

Myringotomy is reserved for severe cases where complication is present or suspected, to relieve severe pain, or when microbiology is strongly required. [Level 1 evidence]

Management of *recurrent* acute otitis media

ALTERATION OF RISK FACTORS

It may be possible to alter many of the environmental risk factors discussed previously (Box 14.2). Parents should be reassured of the benign natural history of AOM, as these children have been shown to be more demanding than those without recurrent disease, and their mothers more anxious about their care. The most readily modifiable risk factor is exposure to other children. AOM increases with the number of children in day care, the length of time a child spends in day care each week, how young a child is when introduced into day care, the presence of children under 2 years of age in the day-care setting, and having a sibling in day care. Advice should include sitting a child semi-upright if bottle-fed, and avoiding passive smoke inhalation. Restricting the use of pacifiers particularly after infancy should be recommended for otitis-prone children. The mother may be advised to continue breastfeeding for at least 6 months after future pregnancies, and increasing vitamin C intake and avoiding alcohol in the third trimester, both of which have been weakly associated with AOM. The role of food allergies, in particular cow's milk, is still unclear. No effective role has as yet been shown for homeopathic remedies.

BOX 14.2 Modifiable risk factors to discuss with parents

Reduce exposure to other children, e.g. in day-care nursery setting.

Avoid passive smoking.

Sit semi-upright if bottle-feeding.

Avoid the use of pacifiers.

In future pregnancies breastfeed for at least 6 months, and avoid alcohol and increase vitamin C intake in the third trimester.

MEDICAL PROPHYLAXIS

Antibiotics

Antibiotic prophylaxis has the potential to cause problems but can be considered for recurrent AOM. Many organisms need to be covered so a broad spectrum drug is required, although there is no consensus in the literature as to which preparation is superior. Studies of prophylaxis of recurrent AOM invariably treat each individual recurrence with additional antibiotics. Trials therefore compare antibiotic prophylaxis versus placebo between acute episodes. The natural history of recurrent AOM is reassuring. Over 50% of children having no treatment between attacks will not suffer a further episode in the following 6 months. Indeed, only 1 in 8 continues to suffer recurrent AOM (i.e. three or more episodes) during the trials, if treated only for acute episodes. Meta-analysis does, however, show a modest benefit of antibiotic prophylaxis, equating to a reduction of 1.5 episodes per 12 months of antibiotic treatment given, which is about half that expected from the natural history. This suggests that one child would require 8 months of treatment to prevent one episode. However, this effect does not appear to promote longer-lasting benefit after cessation of therapy, and clearly treatment would need to be weighed against the cost of therapy, possible adverse effects and the potential for contribution to bacterial resistance, as well as the potential for masking ongoing active disease.[21]

While the routine administration of prophylactic antibiotics is largely not recommended on the basis of the meta-analysis described above, most trials exclude 'high-risk' children, who are often most in need of treatment. There may therefore be a place for its use in the management of high-risk children with recurrent AOM, despite the absence of specifically targeted studies.

Those studies that assessed the length of time a child has OME in association with AOM showed that, while antibiotic prophylaxis may reduce the incidence of AOM, it does not reduce the length of time with OME. Therefore, ventilation tubes should be considered for those prone to OME. [Level 1 evidence]

Xylitol

Xylitol is a commonly used sweetener that inhibits pneumococcal growth and the attachment of pneumococci and *Haemophilus* to nasopharyngeal cells. As such, it is a recognized prophylaxis for AOM when administered via chewing gum or syrup. A meta-analysis of limited data revealed significant treatment effects, reducing the incidence of AOM in healthy children attending day care by 25% when given at a dose of 8.4 g/day split into five doses,[25] although this effect was lost when the dose was reduced.[26] The very large quantities that must therefore be consumed and associated compliance issues, as well as lack of information with regards to duration of treatment required and long-term effects of consumption, mean that its use cannot yet be recommended.

Zinc

Zinc is a micronutrient found in a variety of foods and is essential for immune function and resistance to infection. It has been demonstrated to have a beneficial effect in the prevention and treatment of pneumonia and other respiratory conditions, and one study has suggested that zinc levels may be lower in children who experience recurrent AOM than in healthy controls. A meta-analysis examining the efficacy of zinc supplementation on frequency of episodes of AOM in children aged 1–5 years living in low- to middle-income countries showed mixed outcomes with no significant overall effect demonstrated.[27] However, there was limited evidence from one small trial that zinc may reduce otitis media in a cohort of infants being treated for malnutrition.

Vaccination

Vaccines have been used effectively against most common childhood infections caused by single specific organisms such as mumps, measles and rubella. The concept of vaccinating against AOM therefore is an attractive one that is being actively explored. Potential obstacles include the wide range of causative organisms, both bacterial and viral, the varied serotypes, technical difficulties in producing an effective immune response, obtaining an immune response before 6 months of age, parental resistance to multiple vaccination, and the possibility that the successfully targeted pathogens will simply be replaced by others.

Vaccination against viruses

Since 60–90% of episodes are initially associated with viral infections (see above), viral vaccination seems the most logical first step. AOM secondary to infection by the measles virus is now relatively uncommon in industrialized countries, for example.

Influenza A vaccination is currently the only commercially available preparation for the prophylaxis of viral upper respiratory tract infections. However, despite early promising results depicting associated reduced episodes of AOM in vaccinated children, a recent meta-analysis suggests that this reduction is small and that the benefits of vaccination for this purpose may not justify the use.[28] In laboratory-confirmed cases of influenza infection, the use of neuroramidase inhibitors such as oseltamivir has been shown to reduce the incidence of AOM in children aged 1–5 years (risk difference -0.14).[29] However, this is at the expense of increased side effects such as vomiting, and the use of oseltamivir for both treatment and prophylaxis should be carefully considered before commencement. **[Level 1 evidence]**

Respiratory syncytial virus vaccines are yet to demonstrate significant protection against lower respiratory tract infection, and currently recombinant monoclonal antibodies such as palivizumab remain the only way to treat severe respiratory disease secondary to RSV infection.[30] No trials are currently underway assessing a role in AOM.

Parainfluenza virus vaccines are not yet commercially available. Results from Phase 1 trials, however, demonstrate relative safety and immunogenicity in adults and seropositive children although proved insufficiently immunogenic in seronegative children,[31] and the impact on AOM has yet to be explored.

Vaccination against bacteria

Vaccination against *Streptococcus pneumoniae*, nontypeable *Haemophilus influenzae* and *Moraxella catarrhalis* is made difficult by the low immunogenicity of the polysaccharide capsule of these bacteria in young children and infants. Success against *Haemophilus influenzae* type b (which causes epiglottitis and meningitis) using a polysaccharide-protein conjugated vaccine provides one potential solution.

Streptococcus pneumoniae vaccination is particularly challenging because of the 90 different serotypes of the bacteria. However, as only a small number of these cause most pneumococcal AOM, and it has been shown that anticapsular antibodies can prevent pneumococcal AOM, progress has been made. Early attempts with unconjugated pneumococcal polysaccharide vaccines proved unsuccessful in children under 2 years of age. However, polysaccharide-protein conjugate vaccines allowed for an improved immunological response (immunogenic as young as 2 months) and a heptavalent pneumococcal conjugate vaccine (PCV7) was introduced in 2001.

Since the introduction of PCV7 into childhood vaccination schedules, the global burden of pneumococcal diseases in children has significantly reduced. The Centers for Disease Control and Prevention (CDC) reported a 77% reduction in overall invasive pneumococcal disease (IPD) rates and a 98% reduction in PCV7 serotype disease in children aged under 5 years compared with the pre-PCV7 era.[31] In addition, rates of outpatient attendance for recurrent AOM in children under 2 years reduced by 43%, with a 42% reduction in AOM-associated prescriptions in studies in the USA, and the insertion of ventilation tubes for AOM reduced by 16% and 23% in two states.[32] Furthermore, a global reduction in microbial resistance in vaccine serotypes, a reduction in nasal carriage of vaccine serotypes and a reduction in antibiotic resistant serotypes has also been noted.[31]

However, following the introduction of PCV7, the overall serotype distribution altered globally with an observed increase in non-vaccine serotypes. Subsequently, higher-valent pneumococcal conjugate vaccines became available and PCV13 (Prevenar 13®) became part of the UK Childhood Vaccination Schedule in 2010, currently administered at 2, 4, 6 and 12–15 months of age. A decline in IPD was consequently noted in the UK in the additional vaccine-related serotypes with a sustained decline in the original serotype related disease.[31] However, vaccines that confer species-wide protection against multiple bacterial pathogens by utilizing an antigen common to all known types of pneumococci would potentially be able to prevent early bacterial colonization and subsequent recurrent AOM and may prove more successful in the future.

These results are encouraging, but a recent meta-analysis demonstrated that, although PCV7 showed modest beneficial effects on recurrent AOM in healthy infants with a low baseline risk, there appeared to be no benefit in preventing further episodes in high-risk infants and older children who already had a history of AOM,[33] suggesting that prevention of early episodes is critical. Further studies assessing the impact of multivalent PCVs on AOM are ongoing, as are trials into maternal immunization strategies with respect to the benefit to the infant. **[Level 1 evidence]**

Since routine immunization against *Haemophilus influenzae* type b (Hib) was introduced, there has been a marked change in the predominant invasive serotype to non-typeable *Haemophilus influenzae* (NTHi), and the intrinsic heterogeneity of NTHi has led to challenges in

the development of a further successful vaccine. Phase 3 trials have now concluded into the efficacy of a 10-valent pneumococcal vaccine utilizing *Haemophilus influenzae* protein D conjugate (PHiD-CV). Protein D is a lipoprotein of *Haemophilus influenzae* and has produced protection against NTHi in rat and chinchilla models. While efficacy was demonstrated against a broad range of pneumococcal diseases including AOM and showed non-inferiority of PHiD-CV in comparison to PCV7, strong evidence of any additional protective efficacy against NTHi otitis was lacking and several other protein antigens remain under investigation.[34] **[Level 1 evidence]**

Moraxella catarrhalis vaccine research is at a preclinical stage, but the possibility of using surface proteins as vaccine candidates is currently being explored.

Special attention should be drawn to children with or awaiting cochlear implants. Concern has been raised about a potential increased risk of pneumococcal meningitis, although whether it is implant-related or reflects inner ear abnormalities in many of these children is unclear. Most children will receive PCV13 through the Childhood Immunisation Schedule, and it is recommended that children with cochlear implants receive an additional single dose of pneumococcal polysaccharide vaccine (PPV23) after they reach 2 years of age. If the vaccines were not received, or the child was treated with PCV7 only, catch-up doses are recommended up to the age of 18 years. Hib conjugate vaccine is also recommended for all children up to the age of 5 years.[35]

Immunoglobulins

The importance of immunological immaturity in the occurrence of recurrent AOM has been emphasized. However, therapeutic administration of immunoglobulin has produced variable results in clinical trials, and more recent data have contraindicated the dogma that otitis-prone children exhibit specific humoral immunodeficiencies.[36] As such, prophylactic treatment with immunoglobulins has failed to gain momentum.

Benign commensals

Previous data considered whether spraying benign commensals (alpha streptococci) into the nose to recolonize the nasopharynx following antibiotics might reduce AOM by inhibiting the growth of pathogenic bacteria. A significant reduction in recurrent disease and subsequent OME was reported, although failure rates remained high in both groups.[37] However, a separate smaller study, which did not pre-treat with antibiotics, showed no difference and no subsequent research has been performed in this area to date.

SURGICAL PROPHYLAXIS

In contrast to the large number of trials comparing antibiotic treatments, there are relatively few addressing surgical prophylaxis. Surgery is potentially attractive, however, in that it may reduce problems of antibiotic resistance and also treat subsequent OME.

Ventilation tubes

A meta-analysis of five trials concluded that the presence of ventilation tubes versus no tubes yielded a relative decrease in episodes of AOM of 56%, equivalent to an absolute reduction of 1.0 episode per child per year.[38] The effect occurred mostly in the first year of follow-up, presumably as this covered the period when the tubes were in place. Of equal importance is the reduction in the prevalence of OME by 115 days per child-year. Overall 79% were reported to have an improved quality of life. Side effects included recurrent otorrhoea in 7% and chronic otorrhoea in 4%. Other studies have shown a higher incidence of tympanosclerosis and focal areas of tympanic membrane atrophy of questionable significance in the ventilation tube groups.

These findings need careful interpretation. One of the studies compares antibiotic prophylaxis with amoxicillin to tubes to placebo.[39] The amoxicillin group had a significant reduction in episodes of AOM; the tube and placebo group did not. However, when AOM occurred in the placebo group, it was more distressing than when otorrhoea occurred with AOM in the group with tubes in place. Also over a 2-year period the surgical group had 26 and 61 days fewer with OME than the antibiotic and placebo groups respectively.

It is difficult to draw conclusions about the role of ventilation tubes. On the evidence available, they may be considered for children with recurrent AOM but no persistent effusion, in whom medical strategies have failed. There may be a greater role for them in preference to, or following failure of, medical prophylaxis in the child with recurrent AOM and persistent OME. **[Level 1 evidence]**

Adenoidectomy and adenotonsillectomy

The limited evidence base for best practice is most striking when considering adenoidectomy. The theoretical advantage of disrupting possibly pathological biofilms is appealing. Two papers are particularly worth discussing, both with a cohort of children from Pittsburgh. Randomization methods have been questioned in these studies, as has follow-up. The first concluded that adenoidectomy may be beneficial in children who had previously had ventilation tube insertion and suffered subsequent AOM. AOM was reduced by 31% relative to the control group in a 2-year follow-up (or 0.32 episodes per child-year), and subjects spent 42% less time with OME. Additionally, the need for further tubes was reduced by 50%.[40]

The second trial was of children who had not previously had ventilation tube insertion. Considering children without overt adenotonsillar disease, a modest reduction in the number of episodes of AOM was recorded in the first year after surgery from 2.1 to 1.4 following adenotonsillectomy, but not adenoidectomy. Similarly, OME was reduced from 30 to 19 days in year 1 in the adenotonsillectomy group, and to 22 days in the adenoidectomy group. The effect was not apparent after the first year. Dropout from the trial was particularly high in the adenoidectomy group, and the results should

be viewed cautiously. For children with adenotonsillar symptoms no AOM benefit was reported from adenotonsillectomy. The authors concluded the risks of surgery were not warranted in children who had not previously had ventilation tube insertion.

In summary, there is little evidence to support adenotonsillectomy. Adenoidectomy may be considered in those children who have failed medical therapy and had further AOM following ventilation tube insertion. The presence of OME increases the benefit of adenoidectomy.

KEY POINTS

Clinical recommendations for prophylaxis of recurrent acute otitis media

- Modify environmental risk factors.
- Consider antibiotic prophylaxis over the winter months, particularly if there is no background middle ear effusion.
- Vaccination against *Streptococcus pneumoniae* is available.
- Immunoglobulins may have a role in specific deficiencies.
- Consider ventilation tube insertion in the presence of persistent middle ear effusions between acute episodes.
- Consider adenoidectomy in children who have previously had ventilation tubes inserted but have further recurrent episodes of AOM.

OUTCOMES

An episode of AOM may:

- resolve rapidly with or without antibiotics
- prove resistant to first-line antibiotics
- persist or recur shortly after a course of antibiotics has finished
- subsequently recur
- progress to tympanic membrane perforation or other complication of infection.

Here we consider the medium- and long-term consequences of infection: the natural history of AOM, middle ear effusions, auditory functioning, and speech and language development.

Natural history

Data come from the control arms of randomized controlled trials, and hence usually exclude high-risk children, complicated cases, and those under 2 years old. Without antibiotic treatment, symptomatic relief from pain and fever occurs in about 60% of children within 24 hours of diagnosis, in over 80% by day 2–3, and 88% by day 4–7.[9, 41] These data do not equate with complete resolution – for example, otorrhoea may still be present without pain or fever – and only 73% reach the stage of complete resolution by day 7–14. In all studies those with resistant or persistent disease will have received antibiotic treatment.

For recurrent AOM the prognosis is also generally favourable. Following study entry, and with only acute episodes treated, recurrence rates fell to 0.13 episodes per child per month in the subsequent 6–24 months – about 1.6 episodes per year. Indeed, over half had no further attack in the following 6 months, and only 1 in 8 continued to satisfy the diagnostic criteria for recurrent AOM.[41] Other work has shown that, even in early recurrences of infection 3–4 weeks after a previous episode, a new organism is usually involved. Caution should be attached to these findings: though pooled numbers are large, high-risk children and those with baseline OME were generally excluded.

MIDDLE EAR EFFUSIONS

Middle ear effusions are an important outcome of AOM. Looking again at those children randomized to placebo, pooled data show rates of OME of 63% 2 weeks after AOM, 40% at 1 month and 26% at 3 months. Antibiotics did not appear to have any effect.[9, 41]

AUDITORY FUNCTIONING

What little work has been done on short-term audiometric outcomes suggests about 1 in 3 children will have an air–bone gap greater than 20 dB at 1 month after infection, and 1 in 5 at 3 months. There is limited evidence to suggest that AOM may reduce long-term audiometric thresholds. Several studies following cohorts of children have reported small but significant loss of very high-frequency hearing (11–16 KHz) in those with many episodes of AOM. There is a suggestion that this may be more a consequence of disturbed middle ear mechanics than cochlear damage. The significance for auditory functioning as the child grows older is not established.

SPEECH AND LANGUAGE DEVELOPMENT

It is difficult to separate the literature on AOM and OME outcomes. Little is written on speech production or reception. In children with OME a significant effect seems to occur in the early years of life on expressive language development but not receptive language. A small number of studies point to persisting effects on expressive language in school-age children. There is little evidence showing different cognitive development in school-age children with a history of otitis media in the first 3 years of life. There are suggestions that poor behavioural traits may be commoner by school age, but more work is required before conclusions are drawn.

COMPLICATIONS

Extracranial complications

TYMPANIC MEMBRANE

Tympanic membrane perforation is considered a complication of AOM. It is the commonest complication of infection

and is reported in 0–10% of episodes. Perforation is associated with a purulent or bloody otorrhoea and immediate relief of pain. It typically occurs in the posterior half of the pars tensa, and is associated with loss of the fibrous middle layer of the drum. This may predispose to future posterior retraction pockets. Four outcomes of perforation may result:

- In most cases the perforation heals spontaneously and the infection resolves.
- The infection may resolve but the perforation may persist. This may predispose the ear to future AOM or chronic suppurative otitis media.
- The perforation and otorrhoea may persist, manifesting as chronic suppurative otitis media. 'Chronicity' is generally deemed to have occurred by 3 months.
- A further complication may arise.

Haemophilus influenzae is the dominant otopathogen cultured in AOM with tympanic membrane perforation (followed by *Streptococcus pneumoniae*, then *Moraxella catarrhalis*). In an animal model, addition of dexamethasone to topical treatment with antibiotic drops significantly impaired short-term healing of perforation (at 4 weeks). The location and size of the perforation correlates to the resulting degree of sound conduction impairment, with larger perforations and those located in the anteroinferior quadrant leading to a larger conductive deficit.[42]

The long-term outcomes were assessed in a cohort of otitis-prone children followed up from 3–14 years of age. By the end of the study 7% had collapse of the posterior superior tympanic membrane, chronic suppurative otitis media, or central perforation.[43] Scarring or tympanosclerosis was present in 27%, though several studies report that ventilation tubes increase this risk.

ACUTE MASTOIDITIS

Four classes of mastoiditis are defined. During episodes of **acute otitis media** infection and inflammation may naturally extend into the mastoid cavity and be visualized radiologically. This is not associated with the typical signs of acute mastoiditis and is not considered a complication of AOM.

Infection may spread to the mastoid periosteum by emissary veins: **acute mastoiditis with periosteitis**. At this stage no abscess is present but the postauricular crease may be full, the pinna may be pushed forward, and there may be mild swelling, erythema and tenderness of the postaural region.

When **acute mastoid osteitis** develops, the infection has begun to destroy the bone of the mastoid air cells, and a subperiosteal abscess may develop. Signs may be similar to those when periosteitis is present. A subperiosteal abscess develops most commonly in the postauricular region. A zygomatic abscess may develop above and in front of the pinna. A Bezold abscess may result from perforation of the medial mastoid cortex, tracking down sternomastoid to the posterior triangle. Pus tracking down peritubal cells may result in a retropharyngeal or parapharyngeal abscess.

A fourth stage may be reached, **subacute ('masked') mastoiditis**, in incompletely treated AOM after 10–14 days of infection. Signs may be absent but otalgia and fever persist. This stage can also progress to serious complications.[3]

In the pre-antibiotic era mastoiditis was a common and serious complication of AOM. In a study in 1954 the control group were reported to have developed mastoiditis in 17% of cases.[9] In some developing countries rates of 5% are still quoted. In the 1970s it was estimated that 0.004% of cases of AOM resulted in surgery for mastoiditis. Many papers reported a drop in the incidence of pneumococcal mastoiditis following the introduction of the pneumococcal conjugate vaccine, however the incidence subsequently rose to parallel pre-PCV7 levels, postulated to be secondary to an increase in replacement serotypes. A recent paper showed, however, that the levels of pneumoccocal mastoiditis did not drop again as expected with the introduction of PCV13.[44] The current incidence is estimated to be around 1.2–6.1 cases per 100 000 inhabitants in developed countries.[45]

Acute mastoiditis is a disease of childhood. A large multicentre study found 28% to be in children less than 1 year of age, 38% 1–4 years, 21% 4–8 years, 8% 8–18 years, and 4% over 18 years old.[46] This higher incidence in younger children reflects the peak ages for AOM. Children under 2 years of age also show more distinct clinical signs of mastoiditis and higher inflammatory markers than older children, but they exhibit a more rapid improvement of symptoms, with lower rates of complications and surgery.[47]

Traditional teaching was that acute mastoiditis is preceded by 10–14 days of middle ear symptoms. However, in many papers the short length of middle ear symptoms prior to presentation is noteworthy. For example, in one large study about 32% had 1–2 days of symptoms, 34% had 3–6 days, 26% 7–14 days, and 8% over 14 days.[46] Prior antibiotic treatment of the infection is common, reported in 22–55% of children. Studies have shown that, despite reducing overall prescription rates for AOM, the incidence of acute mastoiditis has remained stable, with no significant difference demonstrated in prior antibiotic use between those who developed a subperiosteal abscess and those who did not.[48] It is therefore clear that antibiotics do not fully protect against mastoiditis.

Symptoms are of otalgia and irritability in most children. Diagnosis usually rests on the presence of postauricular swelling, present in 80–95% of cases, and protrusion of the pinna, seen in 95–100%.[49] Postauricular erythema and tenderness are also usually present and typically sited over MacEwen's triangle (on palpation through the conchal bowl). Pyrexia is reported in around 81% but is less common in those treated with antibiotics. Otorrhoea is present in only about 30%. Clinically, a red or bulging tympanic membrane will often be seen. A normal drum is reported in a very variable proportion of cases, but certainly does not exclude the diagnosis, and is believed to result from resolution of the mesotympanic infection following antibiotic treatment while the osteitis in the mastoid progresses. Sagging of the posterior wall of the

external auditory canal, resulting from subperiosteal abscess formation, should be looked for but is quoted as an uncommon finding. Few patients will have a 'full house' of the classic signs, and 22% may have no clinical symptoms prior to protrusion of the ear.

A somewhat different incidence of organisms has been identified from those gained from culture in AOM. Around 20% of samples do not grow bacteria. *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most commonly reported in order of decreasing frequency. *Haemophilus influenzae* is less commonly reported, and *Moraxella catarrhalis*, *Proteus mirabilis* and Gram-negative anaerobes rarely. *Fusobacterium necrophorum* is also being increasingly implicated. Clinical features may vary in accordance with the pathogen isolated. *Streptococcus pneumoniae* appears to lead to more severe symptoms and a higher incidence of mastoidectomy, *S. pyogenes* causes less otalgia and *Pseudomonas aeruginosa* particularly affects children with ventilation tubes, with a less aggressive clinical course.[50]

Recommended investigations vary between institutions. A full blood count, CRP and blood cultures are often obtained. A CT scan of the mastoid is recommended when intracranial complications are present or suspected (though MRI may be more helpful in identifying specific intracranial pathology), when mastoidectomy is to be performed, and in those not improving on antibiotic treatment. A CT scan may show evidence of osteitis, abscesses and intracranial complications.

Differential diagnosis includes AOM, otitis externa, furunculosis and reactive lymphadenopathy. Rarely, undiagnosed cholesteatoma, Wegener's granulomatosis, leukaemia and histiocytosis may first present with AOM, hence tissue should be sent for histology if mastoidectomy is performed.

Although simple mastoidectomy represents the most reliable and effective surgical method to treat acute mastoiditis, a more conservative approach consisting of adequate parenteral antibiotic coverage with or without myringotomy is being increasingly adopted for children suffering from uncomplicated acute mastoiditis. The antibiotic of choice is generally a third-generation cephalosporin, or an aminopenicillin combined with a β-lactamase inhibitor. If *Pseudomonas aeruginosa* is suspected, treatment should include ciprofloxacin, piperacillin or fosfomycin.[45] Cases where there is a suspicion of intracranial complication and those not responding to conservative treatment should undergo cortical mastoidectomy. This may be combined with myringotomy with or without ventilation tube placement, and culture of the aspirate. This can be challenging surgery for the less experienced as the mastoid is often full of granulations and the facial nerve superficial in the young child. There is no uniformity in the literature as to the appropriate duration of observation prior to proceeding with surgery, with authors recommending periods in the wide range of 24–72 hours. The presence of a subperiosteal abscess, an unwell child, or a deteriorating clinical picture should prompt more rapid intervention. If in doubt, it is our recommendation to intervene to prevent complication, and sooner rather than later.

A most important message is that intracranial complications from acute mastoiditis develop in 6–17% of cases, and many of these may develop during hospitalization. Although acute mastoiditis may be less common than in the past, its severe complications still occur.

PETROSITIS

Infection may extend to the petrous apex. The classic features of Gradenigo's triad (VI nerve palsy, severe pain in the trigeminal nerve distribution and middle ear infection) are not always present. Patients commonly present with other intracranial complications. Historically, the treatment has been surgical, with a minimum of drainage of the mastoid and, in some centres, decompression of the petrous apex. Resolution of the sixth nerve palsy follows a variable course, from almost instant recovery to taking up to 6 weeks. However, more recently many patients have been successfully managed conservatively with administration of parenteral antibiotics, and most would now reserve surgery for those not responding to conservative management. Sixth nerve palsy resolution with conservative treatment can take up to 3 months.[51]

FACIAL NERVE PALSY

In the pre-antibiotic era it was estimated that acute lower motor neuron facial palsy complicated 0.5% of episodes of AOM. It is now quoted at 0.005%.[52] Most are related to bacterial infection, with one review suggesting the majority are secondary to *Staphylococcus aureus*, but case reports with viral AOM exist. The pathophysiology in most cases is a neuropraxia secondary to oedema or nerve compression, or to bacterial toxic metabolites in the setting of a congenitally dehiscent facial nerve. About four out of five children present with a partial paralysis. The case series in the literature report that about 80% of palsies respond well to ventilation tube insertion and intravenous antibiotics. The remainder undergo cortical mastoidectomy. Corticosteroids are also often used although there is no strong evidence base to support their use. Advice is conflicting about when and in whom mastoidectomy is required and the role of facial nerve decompression, although as recovery is generally so good, a more conservative approach without facial nerve decompression seems appropriate.

Some authors would advocate early electrophysiological testing in all patients with a complete paralysis as recovery in these cases can be more variable, with surgical intervention limited to those who fail conservative treatment or exhibit poor electrophysiological testing.[53] Most children achieve rapid restoration of normal facial function, with a mean time to complete recovery of 4 months. Those with a total paralysis at presentation have a recovery stretching over many months.

Sixth nerve palsy in the absence of petrositis has also been reported. It is speculated this may stem from phlebitis spreading along the inferior petrosal sinus from the lateral sinus.

LABYRINTHITIS

Round window permeability changes during acute infection are important as these may allow entry of bacterial toxins. There is some experimental evidence that permeability can be increased by streptococcal toxins. Preformed channels for bacterial entry may also exist, such as surgical or congenital perilymph fistulae. These may allow infection to spread directly to the subarachnoid space causing meningitis. Particular concern arises in children with congenital inner ear abnormalities, and those with cochlear implants.

Three types of labyrinthitis are recognized. **Perilabyrinthitis** is not associated with AOM. **Serous labyrinthitis** is inflammation of the labyrinth without pus formation, characterized by sensorineural hearing loss and vertigo, usually in a non-toxic patient. There may be an additional conductive loss secondary to the presence of fluid. Typically there is complete and rapid recovery of auditory and vestibular function.

Suppurative labyrinthitis may result from spread of infection from the mastoid or middle ear and may raise the suspicion of an anatomical defect or immune deficiency. Severe vertigo, nausea, vomiting, nystagmus and permanent hearing loss result. The nystagmus may exhibit various patterns, possibly due to differential effects on inner ear function by toxic or inflammatory mediators, however direction-fixed, irritative-type is the most common observed pattern.[54] Suppurative labyrinthitis is rare, and diagnosis is usually made based on clinical and audiometric findings. MRI, if performed, may demonstrate contrast enhancement of the labyrinth and there is some evidence to suggest the degree of enhancement correlates to both subjective symptoms and objective assessment of nystagmus. CT is not helpful in diagnosis but may help to delineate underlying anatomical abnormalities.[53]

The treatment of cases presented in the literature ranges from ventilation tube insertion and aggressive antibiotic use, to tympanomastoidectomy and cochleotomy. Resolution of the vertigo may take weeks to months to occur, demonstrating contralateral vestibular system compensation rather than recovery of function of the affected ear. Longer-term complications of suppurative labyrinthitis may include labyrinthitis ossificans, caused by fibrous or bony replacement of the labyrinth. The administration of steroids during the initial phase of the illness may help prevent the development of this complication.[53]

Intracranial complications

In the pre-antibiotic era intracranial complications of AOM were more common and mortality rates of over 75% are presented. Published mortality rates from intracranial complications now average about 5% in industrialized countries. Estimates of the incidence of intracranial complications vary significantly in the literature, with figures ranging from 0.04% to 17.6%.

The most common symptoms associated with an intracranial complication include fever, otalgia, cephalgia and reduced general condition as well as altered mental status. In other words, do not ignore the child with a headache, pyrexia and ear infection. In half of cases there may be signs only of AOM, and not mastoiditis. Frequently two or more complications coexist. Early diagnosis is important for improving outcomes. As the clinical picture in some cases may not differ from that of acute mastoiditis in terms of signs, symptoms and inflammatory indices, the clinician should always remain alert to the possibility of an otherwise asymptomatic intracranial complication and maintain a low threshold for performing imaging studies. CT with intravenous contrast is the usual imaging technique of choice for patients with acute mastoiditis as this also provides a road map for surgery. MRI is the preferred imaging modality in the presence of suspicion of intracranial complications, as it is superior to CT in the identification of intracranial suppurative lesions, meningeal enhancement and extradural granulation tissue. However, the difficulty in children under 7 years of age is that they are likely to require a general anaesthetic for this so a discussion with the parents regarding the risk and reward of different imaging modalities may be required. MR venography may be utilized to demonstrate the degree of patency of the associated venous sinuses.

Seven classical intracranial suppurative complications of AOM are described:[3] meningitis, extradural abscess, subdural empyema, sinus thrombosis, cerebritis, brain abscess and otitic hydrocephalus.

MENINGITIS

Meningitis is usually cited as the commonest intracranial complication of AOM, accounting for 54–91% of cases. In contrast, studies assessing aetiology of meningitis are conflicting. One of the largest recent studies found no association between bacterial meningitis and AOM, while another found an antecedent history of AOM in 29%,[55] though this does not equate to a causal relationship. The earliest symptoms are headache, fever, vomiting, photophobia, irritability and restlessness, with fullness of the anterior fontanelle in children under 22 months of age. Diagnosis is usually made on the clinical presentation, with a lumbar puncture demonstrating white blood cells and low glucose in the CSF. Special mention has already been made of possible associations between congenital inner ear malformations such as cochlear dysplasia and cochlear implants, and meningitis. Younger children, average age 2 years, are most commonly infected.

Studies focus almost exclusively on bacterial aetiologies. The rate of *Haemophilus influenzae* type b meningitis has dropped dramatically since vaccination was introduced. *Streptococcus pneumoniae* is the causal agent in a greater proportion because of this reduction.[55] A second intracranial complication should be looked for in any infant with meningitis with MRI scanning and the presence of a lung focus has been identified an as independent prognostic factor for an unfavourable outcome.[56] Myringotomy may help establish the infective agent if evidence has not been obtained from lumbar puncture.

Treatment is medical and should comprise a third-generation cephalosporin with consideration given to the

addition of vancomycin to cover for resistant strains. Some papers suggest that addition of dexamethasone may reduce potential neurological sequelae, although this appears to have no effect on audiological outcome which can affect 16% of children.[57] If mastoid surgery is required, it is usual to wait for an improvement in the medical condition of the child first if possible.

EXTRADURAL ABSCESS

This is the next commonest intracranial complication. It is more commonly associated with chronic disease. Pus collects between dura and bone, usually after bone erosion. If this lies in the posterior fossa medial to the sigmoid sinus, it is termed an extradural (epidural) abscess; if it is within the split of dura enclosing the sigmoid sinus, it is called a perisinus abscess. It may be discovered only at mastoidectomy, but may be suspected in the patient with persistent headache and fever, or severe otalgia. Treatment is surgical drainage.

SUBDURAL EMPYEMA

A collection of pus between the dura and arachnoid membranes is termed a subdural empyema. It is rare. It develops by direct extension of infection or thrombophlebitis. In addition to headaches and pyrexia, focal neurological signs, seizures and signs of meningeal irritation may be present. Paranasal sinusitis is reported to be a much commoner cause than AOM. Surgical drainage of the abscess through burr holes or craniectomy may be indicated. Mastoidectomy may sometimes be required, though many cases cited in the literature were treated medically.

SIGMOID SINUS THROMBOSIS

This has an estimated incidence of 0–2.7%[58] and most commonly results from erosion of the bone over the sinus from mastoiditis, and may also be associated with other complications. However, it occurs in association with otitis media alone in 43% of cases. Infected thrombus develops within the sinus and may then extend proximally and distally to the internal jugular vein and superior vena cava, entering the systemic circulation and causing septicaemia. In addition to headache and otorrhoea, a spiking pyrexia may develop. Griesinger's sign is mastoid tenderness and oedema secondary to thrombophlebitis of the mastoid emmisary vein. The presence of specific neurological signs and symptoms is significantly correlated with hypoplasia of the contralateral venous sinus and may be absent in up to 50% of children. The presence of *Fusobacterium necrophorum* dictates a more aggressive and prolonged clinical course. MRI is the imaging of choice showing an acute clot as isodense on T1 and hypodense on T2, with a subacute clot becoming hyperintense on T1. The addition of MR venography will demonstrate lack of flow and increase the sensitivity of the diagnosis especially in the early stage.

Management options described in the literature invariably include the use of systemic broad-spectrum antimicrobials. Non-pneumococcal streptococcal, anaerobic and staphylococcal species are commonly implicated and therefore ceftriaxone, metronidazole or clindamycin are commonly used.[59]

The surgical approach varies dramatically in the literature from myringotomy with ventilation tube placement, to mastoidectomy with or without delamination of the sigmoid sinus, needling of the sinus or thrombectomy. Internal jugular vein ligation and craniotomy have also been described.

The use of post-operative anticoagulation also varies between institutions, with duration ranging from 6 weeks to 6 months. Only one study reported an episode of a subsequent non-life-threatening intracranial haemorrhage, with no other complications related to the treatment identified in any of the other studies, leading to the conclusion that anticoagulation was safe if administered correctly.[60] The current British Society of Haematology guidelines for the management of paediatric cerebral venous sinus thrombosis recommends that anticoagulation should be commenced if there is no associated intracranial haemorrhage. This recommendation is, however, based on a non-significant trend in the anticoagulated group towards better survival and cognitive outcome, and the recommendation is not specific to venous sinus thrombosis of otological origin.[58] At least one series has shown unusually high rates of prothrombotic factors in children with otogenic venous sinus thrombosis, and it has therefore been suggested that anticoagulation may be used selectively in appropriately screened individuals, with a lower threshold for treatment in those in whom there is evidence of thrombus extension, such as Lemierre's syndrome.[59] A multidisciplinary approach with the involvement of paediatricians, haematologists and the infectious diseases team is recommended. In non-anticoagulated cases, it is recommended that further imaging is performed to look for evidence of extension of thrombus.

A recent systematic review into the management of otogenic paediatric cerebral venous sinus thrombosis found that 92% of patients underwent some form of surgery. Just over two-thirds of these patients underwent 'conservative surgery', most commonly mastoidectomy with decompression of the bony covering of the venous sinus. The remainder underwent a more extensive operation, usually mastoidectomy with thrombectomy, with IJV ligation performed in just 6%. Anticoagulation was the treatment for 59%, and a non-life-threatening bleeding-related complication such as post-operative haematoma was reported in 7%. A good outcome was reported in 79%. For those undergoing follow-up scans, complete recanalization was observed in 51% overall occurring up to 5 months later (47% of those who had been anticoagulated and 55% of those who had not).[58] Conservative surgery with anticoagulation is the most common treatment modality administered at present, although the low level of evidence available hinders the development of truly evidence-based guidelines.

FOCAL OTITIC ENCEPHALITIS (CEREBRITIS)

Focal inflammation and oedema of brain tissue may occur independent of or in association with any suppurative complication of AOM. Intensive antibiotic treatment is required.

BRAIN ABSCESS

Brain abscesses are more commonly associated with chronic ear disease but may occur in association with AOM and its complications. They form a larger proportion of complications in developing countries. They develop in both the temporal lobe and cerebellum. In the setting of acute mastoiditis, the most common causative organism is *S. pneumoniae* or other non-pneumococcal *Streptococcus* species.[59] Persistent headaches are the commonest symptom. Initial symptoms may be of encephalitis, but these often settle as the abscess organizes over days or weeks. Eventually, signs of raised intracranial pressure, focal neurology and infection develop. Investigations include CT imaging followed by lumbar puncture if safe.

Patients should undergo treatment with broad-spectrum antibiotics and mastoidectomy to remove the infective foci. In the early stages of cerebritis neurosurgical drainage may be avoided, but it will be required if the abscesses are expanding. Brain abscesses carry a potentially high mortality rate, though in industrialized countries the few large series now quote rates of below 10%. One large review found the mortality from otogenic causes, at 3.8%, was much lower than from other causes. The presence of morbidity such as sensorineural hearing loss, vestibular dysfunction and neurological sequelae varies from 20% to 79% and is reduced with early intervention and treatment.

OTITIC HYDROCEPHALUS

This is a complication of AOM manifesting as raised intracranial pressure in the absence of any space-occupying lesion, and without obstruction to the flow of CSF. Benign intracranial hypertension is a synonym. The aetiology is obscure. Headache is the predominant symptom and may be associated with drowsiness, vomiting, visual disturbance and diplopia, with signs of papilloedema and abducens nerve palsy on examination. It is commonly associated with sigmoid or transverse sinus thrombosis and so MRI/MRV are important investigations. Lumbar puncture will show raised CSF pressure, but normal CSF composition.

A number of medical treatments may be tried such as corticosteroids, mannitol, diuretics and acetazolamide and liaison with a paediatric neurologist is recommended.

CONCLUSION

It can be seen from this chapter that there are deficiencies in our current knowledge of both the diagnosis and aetiology of AOM, and uncertainties in management strategies. We have, however, been able to describe a number of potentially exciting developments that have occurred in the past few years. ‘Future research’ below summarizes what we feel this chapter should be able to report on when the next edition is being prepared.

BEST CLINICAL PRACTICE

- ✓ AOM is one of the commonest illnesses of childhood. Accurate diagnosis is notoriously difficult. A high index of suspicion is required in the unwell child.
- ✓ The clinician should distinguish between sporadic, resistant, persistent or recurrent AOM as management strategies differ. **[Grade A]**
- ✓ Two-thirds of children recover within 24 hours with or without treatment, so a period of watchful waiting may be reasonable in uncomplicated AOM. **[Grade A]**
- ✓ Antibiotics should not be withheld in severe or irregular infections, should be given if a child fails to improve within 2–3 days of the onset of AOM, and should be given in sufficiently high doses. **[Grade A]**
- ✓ Pyrexia (>37.5 °C), severe otalgia, vomiting, age under 2 years, and ‘high-risk’ children have all been used as indicators to use antibiotics sooner rather than later.
- ✓ Practitioners should be aware of local bacterial antibiotic resistance patterns, and prescribing policies. Broad spectrum antibiotics are not generally required as first line therapy. **[Grade A]**
- ✓ In otherwise healthy children over 2 years of age, 5 days antibiotics are usually adequate. **[Grade A]**
- ✓ For persistent or resistant AOM it should be noted that while pneumococcal drug resistance can usually be overcome by increased antibiotic doses, *Haemophilus* may be beta-lactam producing, so broader spectrum antibiotics may be required.
- ✓ Modifiable risk factors should be discussed with parents. These include nursery attendance, parental smoking, breast feeding, and the use of pacifiers.
- ✓ In the management of recurrent AOM, 8 months of antibiotic prophylaxis would on average be needed to prevent one episode of AOM. This strategy may be preferred in the absence of effusions between episodes of AOM. **[Grade A]**
- ✓ Ventilation tube insertion reduces the number of episodes of AOM by over 50%. This option may be preferred when effusions persist between episodes of AOM. **[Grade A]**
- ✓ Additional adenoidectomy may further reduce the number of episodes of AOM. **[Grade A]**
- ✓ The benefits of tonsillectomy on episodes of AOM are not sufficient to warrant its use in the management of recurrent AOM. **[Grade A]**
- ✓ Vigilance should be maintained for complications of AOM, the commonest symptoms being persistent pyrexia and headache.

FUTURE RESEARCH

- Greater standardization and reproducibility of diagnostic criteria is required to compare trials.
- The role of biofilms in the aetiology and treatment of middle ear infection is under intensive study.
- As most children appear to recover without treatment, better characterization of those who may have initial antibiotic treatment withheld is needed.
- Trials should be set up to study high-risk groups of children who are currently excluded from most studies: those with conditions predisposing them to acute otitis media; and children under 18 months of age. These are the children likely to benefit most from our intervention.
- Vaccination has been shown to be beneficial. Broadening the role for vaccination is likely over the next decade.
- The number and quality of trials of surgical intervention do not allow confident guidance to be given as to the long-term benefits, or consequences, of ventilation tube insertion.
- More data are required on the long-term consequences of recurrent infection in terms of altered audiometric thresholds, quality of life, and language and cognitive development.

KEY POINTS

- Acute otitis media is one of the commonest illnesses of childhood.
- Diagnosis can be difficult, particularly in very young children.
- Management recommendations vary widely between countries.
- A range of modifiable risk factors should be addressed.
- Evidence is emerging to support new prophylactic strategies.
- Intracranial complications are still seen despite prior antibiotic treatment.
- Do not ignore the child with AOM, headache and pyrexia.

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CHAPTER 15

CHRONIC OTITIS MEDIA

William P.L. Hellier

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the following keywords: chronic otitis media, chronic suppurative otitis media, cholesteatoma, paediatric, children, residual cholesteatoma and reccurent cholesteatoma.

INTRODUCTION

Traditionally, the term chronic suppurative otitis media (CSOM) describes chronic middle ear (ME) disease and is defined as 'chronic inflammation of the middle ear and mastoid cavity, which presents with recurrent ear discharge or otorrhoea through a tympanic membrane perforation'.[1] Chronic inflammation and changes within the ME cleft are, however, not necessarily associated with a non-intact eardrum. The term chronic otitis media (COM) is a better term to encompass the varied pathology seen as a result of chronic ME inflammation. COM was previously considered a direct result of acute otitis media. It is now suggested that, although COM can certainly be precipitated by an acute infection with or without tympanic membrane perforation, it may occur without episodes of acute otitis media.

Histologically, the findings in COM are similar to the initial changes in acute otitis media (AOM) with mucosal and submucosal inflammation (see Chapter 14, Acute otitis media). Continuing inflammation leads to a submucosal infiltrate with histiocytes, lymphocytes and other mononuclear cells, increasing vascularity, and an increase in mucous-secreting goblet cells. The chronic inflammation can lead to osteitis with bone destruction in or around the ME cleft. The ear responds with attempts at healing and repair. This can lead to the florid vascular granulation tissue that may form aural polyps, and the formation of new bone. Inflammation or infection can spread outside the middle ear or temporal bone leading to the complications of COM.

If the ongoing inflammation does resolve, either due to the body's response or because of medical or surgical intervention, the changes left by the chronic inflammation may persist. Submucosal scarring and fibrosis, increased mucous-producing cells, bony erosion or new bone growth, perforation or thinning of the tympanic membrane and changes in the labyrinth can all be seen. It is useful, therefore, to divide COM into **active COM** (ongoing chronic inflammation) and **inactive or healed COM**, where the chronic inflammation has resolved due to time or medical/surgical intervention but sequelae may still be present.

COM causes a variety of pathological changes that are recognized clinically. Generally, COM can be divided into **COM with cholesteatoma** and **COM without cholesteatoma**.

COM without cholesteatoma includes tympanic membrane changes including perforation, tympanosclerosis, thinning or atrophy of the drum, ossicular changes including erosion or fixation and the mucosal changes as described above. These conditions and their treatment are dealt with in Chapter 83, Chronic otitis media. This chapter will consider COM with cholesteatoma.

COM WITH CHOLESTEATOMA

Muller in 1838 first used the term 'cholesteatoma' describing what he thought was a neoplastic lesion with keratin flakes appearing to look like cholesterol crystals. Despite its 'oma' suffix, cholesteatoma is not a true neoplasm, even taking account of the propensity for the keratin epithelium to accumulate and invade the middle ear and mastoid and to erode the temporal bone. A recent consensus definition is: 'Cholesteatoma is a mass formed by keratinizing squamous epithelium in the middle ear and/or mastoid, subepithelial connective tissue and by the progressive accumulation of keratin debris with/without surrounding inflammatory reaction'.[2]

Paediatric cholesteatoma can be divided into congenital and acquired types.

Congenital cholesteatoma

Congenital cholesteatoma (CC) is 'an expanding cystic mass with keratinizing squamous epithelium located medially to the intact tympanic membrane, assumed to be present at birth but usually diagnosed during infancy or in early childhood in patients with no prior history of otorrhea, perforation, or previous ear surgery'.[2] The most accepted aetiology for the cause of CC is the persistence of epidermoid cell rests found in the anterior part of the epitympanum.[3] These rests are thought to usually regress but, if they persist and grow, squamous epithelium accumulates in the ME space forming a CC. Most CC seems to arise from the anterior ME[4] as a defined sac of epithelium, which would fit with this theory. CC is also found purely arising in the posterior ME or elsewhere in the temporal bone, so there may be other cell rests or there may be another pathogeneses. CC can also be found in the ME as free keratin epithelium with no defined sac.[5]

Petrous apex cholesteatomas, with cholesteatoma in the deep temporal bone with no obvious connection to the ME, are also thought to be caused by congenital rests of epithelium. They represent a different spectrum of disease and are discussed elsewhere (see Chapter 108).

To make a diagnosis of CC most definitions describe that there should be no history of AOM or tympanic membrane perforation, and the drum should be intact. However, AOM is common in the paediatric population, and it has been suggested that infrequent episodes of AOM should not exclude the diagnosis of CC. Late diagnosis of a CC can occur if there are few symptoms in the early stages. An extensive CC can become infected, leading to breakdown of the drum and a perforation, which is seen at the initial presentation. It can therefore be difficult in an older child to be sure whether their cholesteatoma is congenital or acquired.

There have been a number of staging systems suggested for CC, based on the extent of spread of keratin epithelium in the ME. Potsic[6] described a four-point staging system according to the degree of cholesteatoma spread in the ME, from his experience with treatment of 160 CCs:

Stage I	Single quadrant, no ossicular involvement or mastoid extension
Stage II	Multiple quadrants: no ossicular involvement or mastoid extension
Stage III	Ossicular involvement: includes erosion of the ossicles and surgical removal for eradication of disease; no mastoid involvement
Stage IV	Mastoid extension (regardless of findings elsewhere).

The stage of the CC at presentation was directly related to the risk of residual disease post-surgery (see later), and to the degree of initial hearing loss. There are other CC staging systems, such as the one described by Nelson.[4]

Acquired cholesteatoma

Acquired cholesteatoma (AC) in children is similar to adult disease in terms of its definition and aetiology. AC is not present at birth but develops with keratin epithelium invading the middle ear and temporal bone. Acquired cholesteatomas may be classified as being primary or secondary.

Secondary acquired cholesteatoma may develop due to ingrowth of keratin epithelium associated with a tympanic membrane perforation as a result of acute perforation or due to ear trauma of various types. More severe trauma, such as temporal bone fractures, can lead to keratin implantation within the ME or mastoid. Iatrogenic implantation of squamous epithelium can also occur after surgery. Any procedure where the ME is entered, even grommet insertion, can allow keratin epithelium to be left in the ME and the development of cholesteatoma.

The exact pathogenesis of **Primary acquired cholesteatoma** is debated, but four main mechanisms are proposed:

- the metaplasia theory
- the retraction theory
- the immigration theory
- the basal hyperplasia or papillary ingrowth theory.

A number of these factors working together may be responsible for cholesteatoma formation (e.g. retraction and basal hyperplasia).[7] These are discussed in more detail in Chapter 82, Acute otitis media and otitis media with effusion in adults.

The most commonly accepted theory is the retraction theory, which postulates that there is ingrowth of the squamous epithelium of the eardrum into the middle ear due to retraction of either a normal or an atrophic tympanic membrane.

Retraction of either the pars tensa or pars flaccida can occur, and this process is thought to be a sequel of dysfunction of the regulation of middle ear pressure. When the squamous epithelium in the retraction can no longer migrate out and 'self-clean', keratin debris builds up in the middle ear leading to slow invasion.

There are a number of theories regarding failure of the maintenance of normal middle ear pressure. The most widely accepted is that there is dysfunction of the Eustachian tube, leading to hypoventilation of the ME and a negative ME pressure. This negative ME pressure acts on either a normal or, if there has been AOM

or COM, an atrophic or thinned tympanic membrane, causing it to retract and allow cholesteatoma formation. Experimental animal models have shown that obstruction of the Eustachian tube causes drum retractions.[8] Children who have a cleft palate are found to have a higher incidence of cholesteatoma.[9, 10] Children are well recognized to have relatively poor Eustachian tube function, witnessed by their high rates of AOM and OME.

Epidemiology

The exact incidence of cholesteatoma in children is hard to know precisely and may vary between different races. A number of series from a variety of countries give different figures. A Danish study[11] gives the incidence as 8–15 per 100 000 person-years between 1977 and 2010. Earlier studies estimated incidence in the USA as 6 per 100 000 children.[9] Other studies have estimated the incidence as between 3 and 15 cases per 100 000 children.[12–15] Caucasians and African populations seem to have the highest cholesteatoma prevalence of all, with a low rate in non-Indian Asians and the Inuits.[16–18]

In approximately 7–10% of children there may be bilateral cholesteatomas at presentation, or contralateral cholesteatoma may develop during follow-up.[19, 20]

Congenital cholesteatoma has been calculated to make up approximately 10–28% of paediatric cholesteatoma, with 2–3% being bilateral (**Figure 15.1**).[4, 6, 21, 22]

Nelson et al.[4] found that children with CC tend to present earlier (5.6 +/– 2.8 years) than those with acquired cholesteatoma (9.7 +/– 3.3 years). Other authors have found a mean age for surgery for paediatric cholesteatoma to be around 10 years.[23, 24] Most studies on the epidemiology of paediatric cholesteatoma are based on surgical series.

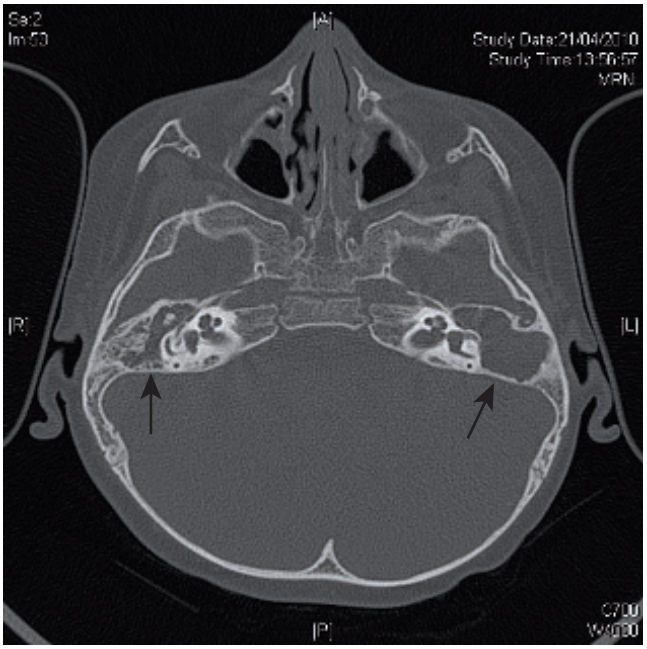

Figure 15.1 Axial CT scan in a 5-year-old child. Arrows show mastoid opacification on both sides due to bilateral cholesteatoma, with erosion of the lateral semicircular canal on the left.

There is some evidence[10, 25] that the use of ventilation tubes may lead to a decrease in the incidence of paediatric cholesteatoma, probably due to the improvement of Eustachian tube dysfunction (ETD) and reducing the negative ME pressure that may cause the tympanic membrane retraction process.

DIFFERENCES BETWEEN PAEDIATRIC AND ADULT CHOLESTEATOMA

There are many similarities between adult and paediatric cholesteatoma: the nature of the disease process, the microscopic pathological findings and certain options for treatment. There are differences in terms of cholesteatoma origin (especially in CC), the areas of the temporal bone affected, temporal bone anatomy, some treatment limitations, the rates of residual and recurrent disease and the extent of ongoing Eustachian tube dysfunction. CC more commonly arises from the anterior middle ear, and therefore will often completely fill the ME cleft, including the Eustachian tube orifice, before spreading to the attic and mastoid. Paediatric cholesteatoma (PC) in general seems to spread more extensively through the temporal bone than in adult disease on average, with more involvement of the peri-labyrinthine cells and petrous apex.

There have been suggestions that PC is more aggressive than adult cholesteatoma, but there is no definitive proof that this is the case. The paediatric temporal bone is often more pneumatized than the adult's, so it is possible that the pathways through which cholesteatoma can invade are more open and the process of spread is easier,[26–29] leading to more extensive disease at presentation. Some studies have reported a greater inflammatory response in PC than in adult cholesteatoma, with an increased expression of various markers including metalloproteinases and certain antibodies.[28, 30–34] Greater inflammation, if present, may well lead to more bone erosion and spread of the squamous epithelium.

When compared to adult cholesteatoma, PC does not seem to invade the petrous labyrinth in as many cases. The rate of lateral semicircular canal (LSCC) fistula is less than in adults, as is erosion of the Fallopian canal and exposure of the facial nerve.[28, 35–39] Ossicular erosion due to cholesteatoma, however, seems to be more common in children.

In the child, the function of the Eustachian tube is often poor. Middle ear disorders such as AOM and OME are far more common in children than adults. The immaturity of the ET and the negative ME pressure it produces is one of the likely aetiological factors for the development of cholesteatoma. In adults, once a cholesteatoma has been surgically treated, aeration of the ME can improve, and this can reduce the potential for further retraction and recurrent cholesteatoma. In the child, however, immaturity of ET function may often continue even after the cholesteatoma has been removed by surgery. This is one of the factors that could explain the continuing ME problems and

greater incidence of recurrent cholesteatoma after surgery in the paediatric population (see below). ETD may slowly improve with age but some children may experience a long period with ME pressure dysfunction. With this in mind, the follow-up of children with cholesteatoma should be for many years, as late recurrence is always a possibility.

One of the most obvious differences between children and adults is their ability to tolerate interventions and procedures. Young children may not allow their ears to be examined under the microscope, or permit aural toilet or post-operative microsuction. Many children, if treated gently and kindly, will allow treatment in the outpatient setting. However, a child does not always understand why they need what is often an uncomfortable treatment and may be unable to tolerate it.

The surgeon treating PC is often working 'against the tide' of Eustachian tube dysfunction in a patient who may not allow easy access to their ear, may not tolerate certain procedures and who may need multiple general anaesthetics. This must be borne in mind when treating PC, and when planning both the surgical approach and the need for long follow-up care. These factors, in many surgeons' opinions, make PC a more difficult condition to treat than adult disease.

Diagnosis

The symptoms and signs of cholesteatoma in an adult are usually straightforward. A history of ear discharge often with hearing loss, and on examination a tympanic membrane retraction filled with keratin debris. In children these symptoms and signs are often present but, especially in younger children or in children with congenital cholesteatoma, these symptoms may not be classic and the ear is often difficult to examine.

Younger children with CC may present with hearing loss alone, which at this age is usually suspected to be OME. Unless the drum is adequately viewed with a modern, well-illuminated otoscope or a microscope, the classic appearance of white keratin behind an intact tympanic membrane may be missed (**Figure 15.2**). If the CC is unilateral, and the other ear has normal hearing, symptoms may not become apparent until quite late, as the ear will be dry and pain-free for some years, and the diagnosis may be made only when the eardrum breaks down and the hearing is assessed and found to be poor on one side, or other complications ensue.

Many children with acquired cholesteatoma (**Figure 15.3**) will present with ear discharge and possible hearing loss. However, as discussed above, it may not be possible to perform microsuction to visualize the drum and make the diagnosis. Discharge from a chronic TM perforation after AOM is more common than cholesteatoma in children, and in both conditions florid granulation tissue and possible aural polyp formation will need treatment before the two can be distinguished. This will usually need aural toilet and antibiotic/steroid eardrops, which the child may not allow.

Making the diagnosis and visualizing the drum can therefore take time and a number of outpatient appointments. Dry mopping of the ear can be used, but with care microsuction even in younger children is possible. The use of antibiotic/steroid ear drops will reduce the inflammatory response and allow a view of the TM. In some children who will not allow access to the ear, however, an examination under general anaesthesia (EUA) is needed to thoroughly toilet the ear, remove an aural polyp if present, and see the exact pathology. In children with congenital cholesteatoma, an EUA is often needed, as it is important to perform a myringotomy to establish if the

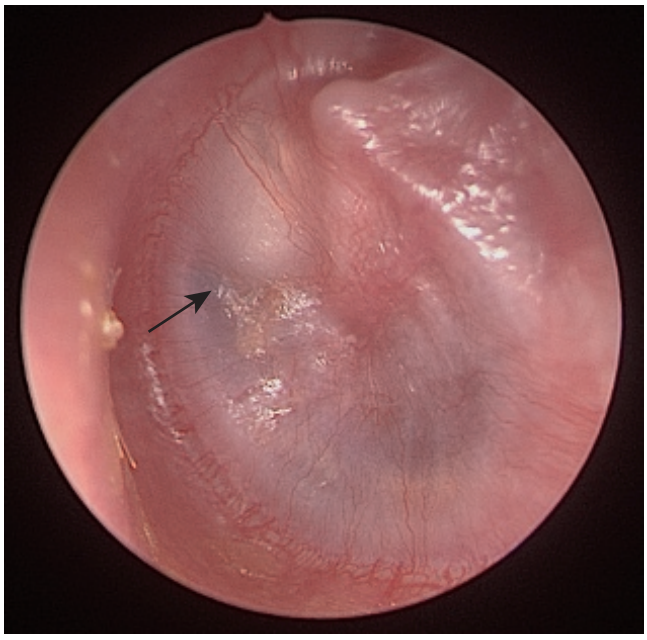

Figure 15.2 Endoscopic photo of a left ear in a 2-year-old child. Arrow indicates white cholesteatoma sac in anterior superior ME behind an intact TM.

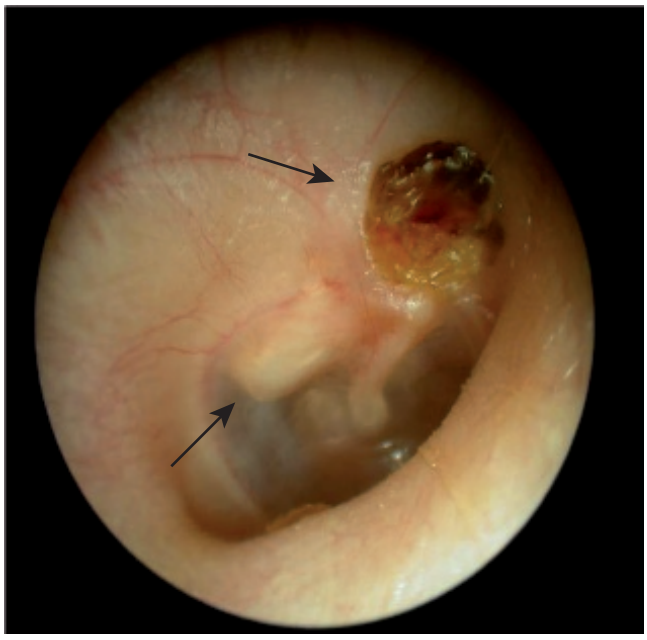

Figure 15.3 Endoscopic photo of the right ear. Thick arrow shows oxidized keratin of the cholesteatoma in the attic. The thin arrow shows the cholesteatoma sac in the posterior ME.

white appearance behind the drum is cholesteatoma, due to an unusually coloured middle ear effusion or another pathology.

MICROBIOLOGY

The bacteria cultured in paediatric COM with cholesteatoma are similar to those in adult disease. Studies show that in children with cholesteatoma *Pseudomonas aeruginosa*, *Proteus mirabilis* and *Staphylococcus aureus* are the most common isolates. Other bacteria can be found but make up a much smaller percentage of the cultures.[40] Any medical treatment used before or after surgery should therefore be targeted to treat these organisms.

IMAGING

Although children can present a difficult problem when it comes to imaging, especially in the under 8–10 years age group, knowledge of the anatomy of a child's temporal bone and the possible extent of the cholesteatoma is vital. Many children will, with the right encouragement, stay still enough for a scan to be performed, but some younger children will need a short general anaesthetic. This should be performed with great care, causing as little distress as possible, particularly as it is likely that the child will need a number of further anaesthetics in the course of their treatment for cholesteatoma, and a good experience at this stage will make the ongoing care far easier for the surgeon.

As discussed above, PC can be extensive at the time of presentation and may have spread around the bony labyrinth (**Figure 15.4**) or into the petrous apex. A computed tomography (CT) scan will give information about cholesteatoma extent but also visualization of any erosion of the bony labyrinth, facial nerve or dural plate that may be incipient or have occurred (**Figure 15.5**). CT scanning allows assessment of the degree of pneumatization of the temporal bone, the height of the middle fossa tegmen and the position of the sigmoid sinus.

Knowledge of the anatomy of the ear and mastoid and the nature of the disease spread allows the surgeon to anticipate potential intra-operative hazards and to plan the exact surgical approach that will be most appropriate to the individual, their temporal bone anatomy and their cholesteatoma.

CT scanning will give good information about the bony anatomy, with an estimation of cholesteatoma extent. This is therefore the main imaging modality. MRI scanning can

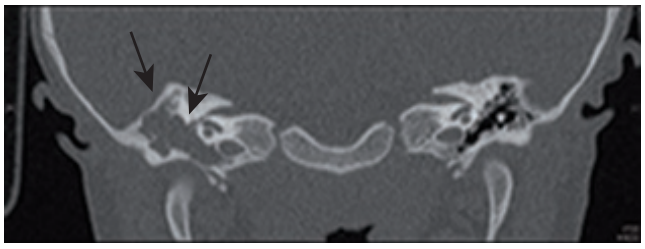

Figure 15.4 Coronal CT scan of a 5-year-old child. The arrow indicates extensive congenital cholesteatoma eroding the anterior attic and the 1st genu of the facial nerve.

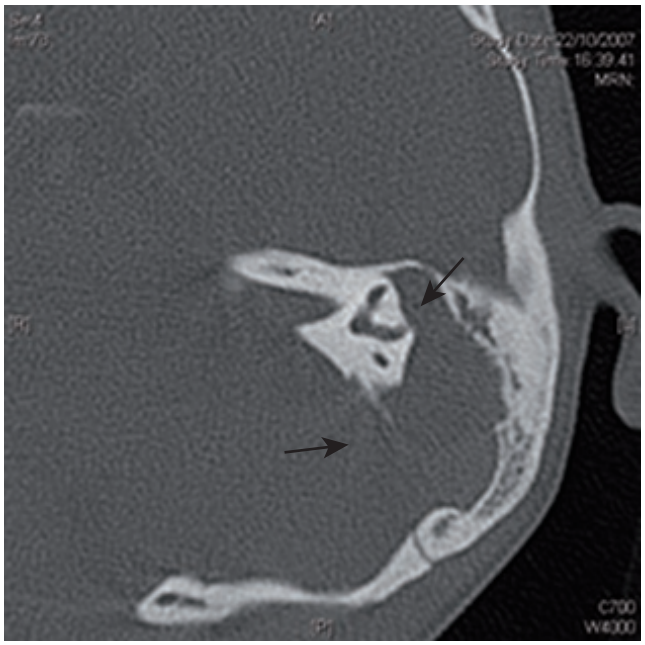

Figure 15.5 Coronal CT of a 5-year-old child. The arrow indicates extensive congenital cholesteatoma eroding the anterior attic and the 1st genu of the facial nerve.

be used but, because it takes longer and as it occurs in a confined space, it is not so well tolerated by children without general anaesthesia. It gives good soft-tissue differentiation so it can be helpful if there has been dural plate erosion to examine for intracranial cholesteatoma spread or complications, but it has a more limited role in the pre-operative workup. The use of MRI is becoming greater in the post-operative stages where it can be used for the assessment of potential residual cholesteatoma after surgery where a canal wall up procedure or a blind sac closure of the external canal has been performed. MRI can be used in the same way as it is for adult cholesteatoma[41] (see Chapter 97, Imaging of the temporal bone).

Treatment

NON-SURGICAL TREATMENT

The risk of an intracranial complication of COM has been estimated to be in the order of 1 in 10 000 every year.[42] In an elderly, medically infirm adult with cholesteatoma there is a case for conservative/medical non-surgical treatment to keep the disease under control, as it may not cause a serious complication in their lifetime. A child who develops cholesteatoma at the age of 10 and who may live to 80 will have a risk of intracranial complications in the region of 1 in 140 per year throughout their lifetime. Surgery is therefore the treatment of choice for children with cholesteatoma. There are some exceptions, including children with other significant pathology who cannot tolerate general anaesthesia such as those with major cardiac disease, but this is very uncommon.

Medical therapy with antibiotic/steroid ear drops, combined with microsuction in those children who will tolerate it, can reduce any infective element of the cholesteatoma

and help to remove accessible keratin epithelium. If there is a waiting list for surgery, medical therapy can be used to help to control the erosive process until surgery occurs.

RATIONALE OF SURGERY IN PAEDIATRIC CHOLESTEATOMA

Parents of children with cholesteatoma usually initially hope that surgery will stop the discharge and smell from the ear, and return the hearing to normal. The paediatric otologist's first job after diagnosis is to help the parents and child understand that the primary role of surgery is to:

- remove all original cholesteatoma squamous epithelial matrix
- prevent further erosion and complications
- give a dry, watertight ear
- give an ear that will be self-cleaning
- prevent the occurrence of recurrent cholesteatoma.

A secondary role of surgery is to improve hearing, but only once the primary aim of a dry, stable, disease-free ear has been achieved. It is important that parents understand that it is not possible to return truly normal hearing, and that the aim is to restore the best possible hearing in an ear that will never be 'normal'.

The parents also need to understand that paediatric cholesteatoma represents a difficult disease process in a patient who is not always cooperative with the treatment. Children do not always understand the rationale for what may be uncomfortable medical and surgical procedures. Rates of both residual and recurrent cholesteatoma are higher in children than in adults, and there is commonly the need for a number of surgeries. Parents should be counselled that the diagnosis of cholesteatoma means not a 'one-stop operation' but rather a number of procedures with a prolonged period of follow-up.

SURGICAL APPROACHES FOR PAEDIATRIC CHOLESTEATOMA

The surgical approaches for PC are no different from those for adult disease. They can broadly be divided into the traditional 'canal wall down (CWD)' surgery – modified radical mastoidectomy or for very extensive disease subtotal petrosectomy, sometimes combined with obliteration or closure of the external ear canal – and the less invasive 'canal wall up (CWU)' approaches as follows, sometimes using endoscopic techniques:

- tympanotomy/tympanoplastic surgery
- atticotomy +/– reconstruction
- canal wall up mastoidectomy/combined approach tympanoplasty.

Many of the factors that influence the surgical technique are the same in children and adults – the extent of the cholesteatoma, whether long-term follow-up can be assured, if any complications have occurred, and the anatomy of the temporal bone. The child's age, their ability to tolerate microsuction or outpatient procedures, and parental choice need also to be considered. The ideal operation for PC is tone that removes all the cholesteatoma, gives a stable self-cleaning ear and heals quickly with minimum post-operative care.

Each surgical technique has pros and cons. The decision on the exact approach must be balanced, taking into account all the factors outlined above. The surgeon who operates upon PC must have the ability to perform a wide range of procedures for cholesteatoma.

Canal wall up versus canal wall down surgery in children

A review by Osborn in 2012 of 542 procedures for paediatric cholesteatoma found 89% of cases underwent CWU surgery and 10% CWD surgery initially.[43] Over the follow-up period, ultimately 14% of the cohort received a CWD procedure. The most common reasons contributing to the decision to perform a CWD operation were disease-related: 56% showed extensive/aggressive disease with erosion of the canal wall (**Figure 15.6**) or the need to remove attic bone. Anatomical reasons accounted for 43% (poor mastoid pneumatization, low tegmen, anterior sigmoid).

CANAL WALL UP SURGERY

Canal wall up (CWU) surgery endeavours to remove all the cholesteatoma but to retain the canal wall and a middle ear closed at the level of the original tympanic membrane. This can be achieved by operating via the canal in the case of localized ME choleasteatoma, with removal of some of the medial canal with an atticotomy or bony marginectomy and then reconstructing the defect and repairing the drum, or by a combined transmastoid and transcanal approach (often called a combined approach tympanoplasty (CAT) or a canal wall up mastoidectomy with tympanoplasty). The philosophy of these approaches is to leave an ear with a normal external canal and a stable reconstructed tympanic membrane.

The benefits and downsides of these CWU approaches in the child, if successful, are given in **Box 15.1**.

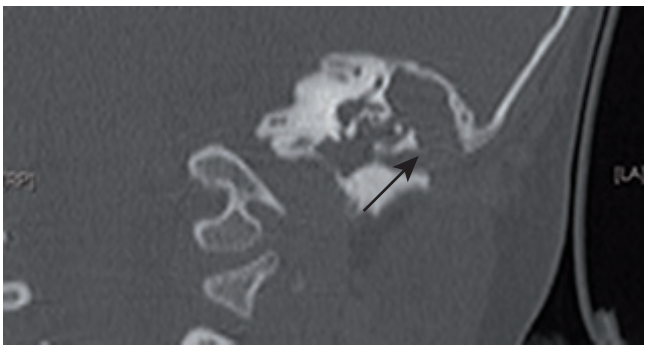

Figure 15.6 Coronal CT scan in an 8-year-old child. Extensive cholesteatoma filling the left mastoid and middle ear, with erosion of the external ear canal (arrow).

BOX 15.1 Benefits and downsides of CWU surgery in children

Benefits	Downsides
Normal ear canal and reconstructed tympanic membrane which does not need to be kept dry	The possible need for a 'second look' operation
Rapid healing as only a small area needs re-epithelialization	The possibility of recurrent cholesteatoma from the reconstructed tympanic membrane
Ear packing usually needed only once after surgery and removed in the outpatient clinic	Technically more demanding surgery
Able to use a normal hearing aid if hearing outcome not satisfactory	
Should not need ongoing microsuction to clean ear	

CANAL WALL DOWN SURGERY

In canal wall down (CWD) mastoidectomy or modified radical mastoidectomy the ear canal wall and the attic scutum are removed to give access to the middle ear, mastoid and attic and to clear the keratin epithelium. CWD surgery gives better intra-operative access to all areas of the ear. The surgical cavity formed is grafted to hopefully allow the migratory epithelium of the tympanic membrane remnant to grow around the cavity. Ideally this creates a bony cavity covered by a dry migratory squamous lining, with the remaining ME and Eustachian tube sealed off from the outside world. However, not every ear heals as well as can be hoped, and a proportion of mastoid cavities may continue to discharge or be wet, for a number of reasons. The 'wet ear' rate may be as low as 5%, but it can be far higher. In the child a wet mastoid cavity that is hard to access and clean presents a very difficult management problem. Males and Gray called this a 'mastoid misery', and many of these discharging cavities will need revision surgery.[44]

The benefits and downsides of the CWD approach in the child are given in Box 15.2.

RESIDUAL AND RECURRENT CHOLESTEATOMA IN CHILDREN

Childhood cholesteatoma has much greater rates of residual and recurrent disease than that seen in adults.[45] **Residual cholesteatoma** is the keratin epithelium that the surgeon failed to remove at the initial operation, so that it grows back (Figure 15.7). **Recurrent cholesteatoma** occurs when squamous epithelium begins to grow again into the middle ear cleft at a new site, either with invagination of the reconstructed tympanic membrane or through a weakness in the reconstruction (Figure 15.8). The term **recidivism** is sometimes used, combining residual and recurrent cholesteatoma. This can confuse as residual cholesteatoma occurs due to inadequate clearance of the initial disease and is therefore purely related to surgical

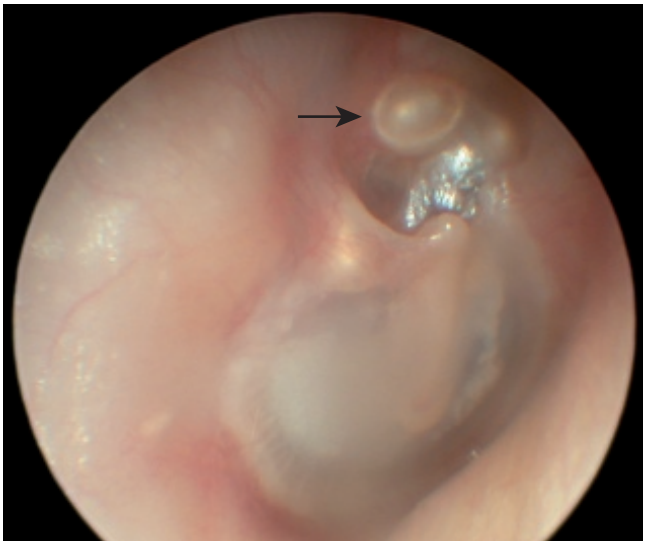

Figure 15.7 Endoscopic photo of a child's left ear, one year after CWU surgery for attic cholesteatoma. Arrow indicates residual cholesteatoma pearls under grafted attic area.

BOX 15.2 Benefits and downsides of CWD surgery in children

Benefits	Downsides
One major operation	A larger mastoid cavity
A cavity that can easily be inspected	If the cavity does not heal well, a discharging ear
Reduction of volume of middle ear and mastoid, so the Eustachian tube has less to ventilate, hopefully leading to a reduction in recurrent cholesteatoma	In an uncooperative child, often several general anaesthetics
	Often the cavity needs to be kept dry, as cold water can stimulate a caloric effect, so swimming may be restricted
	Sometimes difficult to use a hearing aid in a cavity
	After ME inflammation (common in the child) a cavity can be become unstable and discharge

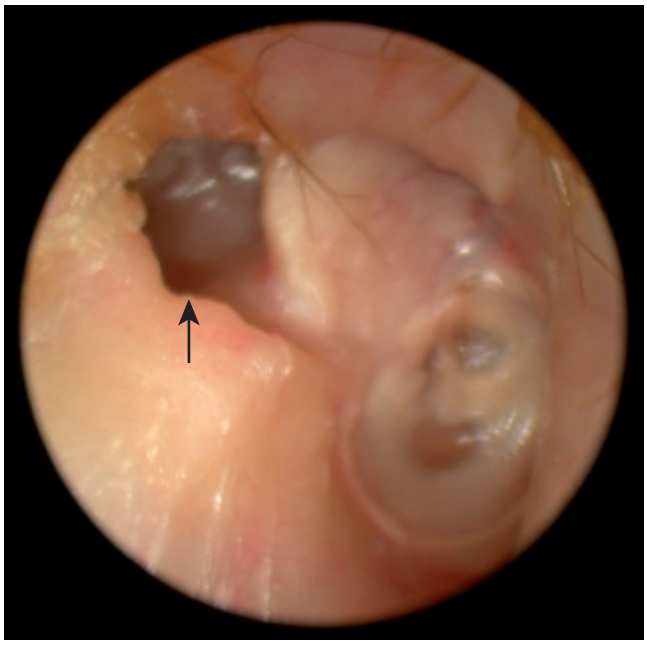

Figure 15.8 Endoscopic photo of right ear some years after CWU surgery for attic cholesteatoma. The attic has been reconstructed with cartilage but there is recurrent retraction cholesteatoma posterior to this (arrow).

technique, whereas recurrent cholesteatoma may occur due to inadequate surgical reconstruction but is caused by the underlying process that drives cholesteatoma formation (such as Eustachian tube dysfunction), which may continue in the child even after surgery.

It would seem logical that, with the challenges of more difficult surgical access, CWU surgery would have a greater incidence of residual disease than CWD. There may be a trend towards this, but in CWD surgery there are still significant rates of residual cholesteatoma in children. These high residual rates are probably related to the greater extent of the initial disease, often in a well-pneumatized temporal bone.

Residual cholesteatoma rates in the literature for children after surgery range from 6% to 43% in CWU surgery[27,43,46–49] and from 6% to 38 % in CWD surgery.[43,50–52] It seems that rates of residual cholesteatoma can be reduced with the use of modern techniques and the increasing use of the laser and otoendoscope[53] (see Chapter 87, Otoendoscopy).

Recurrent cholesteatoma in CWU would be expected to be more common than in CWD, where there is a reconstructed tympanic membrane and larger ME cleft for re-retraction to occur. However, recurrent retraction and cholesteatoma formation does occur with CWD surgery in children, with epithelial pockets insinuating themselves into the temporal bone. This process can occur slowly over many years after both CWU and CWD operations and is probably a reflection of the ongoing Eustachian tube dysfunction in the child. A long period of post-operative follow-up is needed for any child who has had surgery for cholesteatoma.

In CWU surgery, cholesteatoma recurrence in children at 5 years post-operatively has been found by some reviews to be 17–25%.[49,52,54] More recently, techniques of obliteration of the mastoid in CWU surgery have shown lower rates of recurrence (3%),[46] and it is possible that reducing the volume of the middle ear and mastoid that the Eustachian tube has to ventilate may help reduce the recurrence rate. Cartilage reinforcement of the reconstructed drum may also help prevent recurrent cholesteatoma (**Figures 15.9** and **15.10**).

In CWD surgery recurrence rates of 7–25% are described at 5 years[43,51,54,55] but some retraction pockets in a mastoid cavity may form recurrent cholesteatoma up to 13 years after the initial surgery.[51] Other studies have found ongoing recidivism at up to 25 years post-operatively.[56]

Paediatric cholesteatoma represents a difficult disease process with higher rates of post-surgery residual and recurrent disease when compared to adults. This is in a patient who may not tolerate outpatient intervention so well and may not keep their ear dry as requested. There are a number of surgical options but, whichever technique

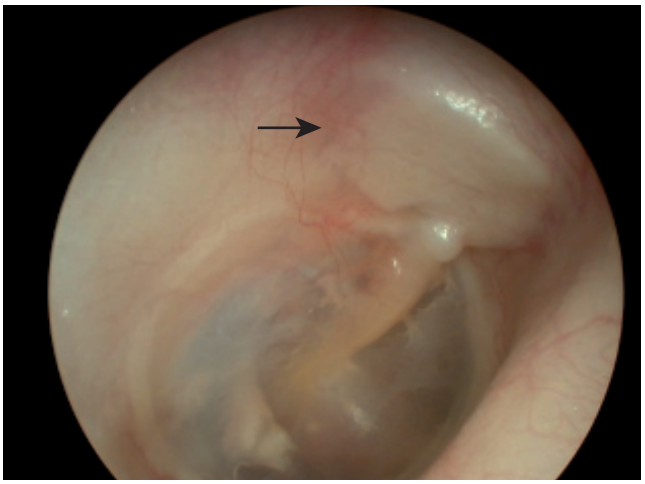

Figure 15.9 Endoscopic photo of a child's right ear. Arrow indicates cartilage reconstruction of the attic defect after CWU surgery for attic cholesteatoma.

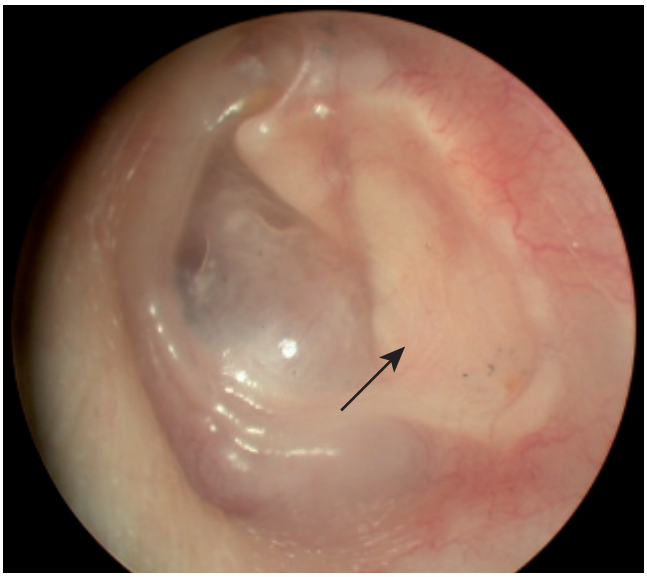

Figure 15.10 Endoscopic photo of the left ear. Posterior tympanic membrane reconstruction with cartilage (arrow) after CWU surgery for posterior pars tensa cholesteatoma.

is chosen, the surgeon will need to use meticulous care to ensure that all the existing cholesteatoma is removed.

In paediatric cholesteatoma over the last 10 years many surgeons have moved away from CWD surgery because of the problems associated with managing a mastoid cavity in children – the potential for 'mastoid misery'.

COM WITH CHOLESTEATOMA IN CHILDREN WITH OTHER SYNDROMES

Children with Down syndrome have an increased incidence of cholesteatoma possibly related to poor Eustachian tube function and midface hypoplasia.[57] Diagnosis of cholesteatoma in this group can be difficult as they often will have small external ear canals and may have learning difficulties. The anatomy of the ear is also challenging with small external canals, poor mastoid pneumatization and often a low mastoid tegmen. Access to the middle ear via the mastoid for a CWU procedure can be very limited and CWD surgery may need to be considered.[58] The facial nerve in children with Down syndrome can run in a more superficial or abnormal course. Care must be taken with mastoid surgery in these children, with the path of the intratemporal bone facial nerve identified on the imaging pre-operatively and the facial nerve monitor used to aid its identification intra-operatively. Careful thought is needed when choosing the operative approach and discussing outcomes with the parents.

Children with craniofacial syndromes, and also di George syndrome (22q11.2 deletion), similarly have a higher risk of cholesteatoma, probably again due to poor palatal and Eustachian tube function. If the child has microtia or a very narrowed external auditory canal with or without these syndromes, it can be difficult to assess the state of the tympanic membrane. An increased suspicion of the presence of COM with or without cholesteatoma should be borne in mind in these cases.

BEST CLINICAL PRACTICE

- ✓ Children with ear disease often need a number of procedures so gentle care is important to prevent a child becoming afraid and adverse to treatment.
- ✓ Imaging of the temporal bone in paediatric cholesteatoma is valuable to gauge disease spread, anatomy and to plan the surgical approach.
- ✓ Cholesteatoma surgery in children requires the surgeon to have the ability to perform a variety of otological approaches.
- ✓ Tympanomastoid surgery can be especially challenging in syndromic children.
- ✓ Residual and recurrent cholesteatoma is greater than in adults and long-term follow up is needed in children.

KEY POINTS

- Paediatric cholesteatoma is thought to be more aggressive than its adult counterpart.
- Children may not tolerate outpatient treatment or microsuction of the ears.
- Paediatric cholesteatoma is a surgical disease. Conservative treatment is very rarely appropriate.
- Canal wall up (CWU) techniques are increasingly preferred in children.
- Endoscopy and use of the laser may reduce the risk of residual cholesteatoma post surgery.

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CHAPTER 16

MICROTIA AND EXTERNAL EAR ABNORMALITIES

Iain Bruce and Jaya Nichani

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: microtia, congenital canal atresia, preauricular sinus, preauricular appendage and unilateral hearing loss.

INTRODUCTION

Abnormal development of the external ear can affect hearing, communication, education, cosmesis and increase the risk of recurrent infections. Our understanding of the consequences of unilateral hearing loss (UHL) upon childhood development continues to expand. While many children with unilateral hearing loss develop normally, some children experience negative effects upon development. The management of the cosmetic consequences of microtia should not occur in isolation, but in combination with the rehabilitation of hearing loss resulting from congenital canal atresia (CCA). Failure to manage cosmesis and hearing loss in combination can result in delayed intervention for hearing loss and/or the compromising of reconstructive options and ultimate outcome.

ANATOMY OF THE EXTERNAL EAR

The pinna, external auditory canal and outer epithelial layer of the tympanic membrane constitute the external ear.

Pinna

The **pinnae** are paired structures with a cartilaginous framework. The inferior part of the pinna (**lobule**) does not have a cartilaginous framework and is only supported by a fibrofatty matrix. The **helix** is the outermost cartilaginous curvature of the pinna. The curve of the **antihelix** runs inside and parallel to the curve of the helix. The antihelix divides superiorly to forms two crura: the **superior crus** and the **inferior crus**. The depression between the two crura is called the **triangular fossa**. Anterior to the antihelix is the concave depression called the **concha**. The conchal bowl is subdivided into the **cymba concha** superiorly and the **concha cavum** inferiorly. The elevation of cartilage anterior to the entrance of the external ear canal is called the **tragus**. The **antitragus** is the inferior-most prominence of the antihelix curvature opposite the tragus, and the gap between the tragus and the antitragus is called the **intertragal notch**. The cartilage of the pinna is continuous with the cartilaginous ear canal, thereby fixing it to the temporal bone along with muscles and ligaments (anterior, posterior and superior ligaments). The intrinsic muscles of the pinna are poorly developed; the extrinsic muscles (anterior, posterior and superior) may be well developed in some individuals.

External auditory canal

The **external auditory canal** (EAC) extends from the concha cavum to the tympanic membrane. It comprises a cartilaginous framework in its outer one-third and a bony canal in the medial two-thirds. The skin and the subcutaneous tissue lining the cartilaginous ear canal contain hair

follicles and glandular structures, whereas the bony canal is covered by a tightly adherent layer of epidermis. The external ear canal is 3–4 cm in length, with the anterior part of the canal being longer and more curved than the posterior canal.

Size and position of the external ear

At birth the anatomical landmarks of the pinna are fully formed. Subsequently, it grows to reach adult size by 8–10 years of age, measuring approximately 60 mm in length. Generally, the superior margin of the pinna lies in line with the eyebrow, and the lower limit of the lobule is in line with the base of the nasal septal columella.[1] It is inclined approximately 15–20° posteriorly and protrudes 15–20 mm from the scalp.

EMBRYOLOGY OF THE EAR

External ear

At 5 weeks of gestation, five paired structures (1, 2, 3, 4 and 6 **pharyngeal arches**) are visible externally, lying close to the developing neural crest. Each pharyngeal arch has an internal endodermal pouch, an external ectodermal cleft and a mesenchymal core which gives rise to an associated named blood vessel, nerve, muscle and cartilage. The external ear develops from the first two pharyngeal arches.[2]

Six nodular swellings called **hillocks of His** develop from the first and second arches, three on either side of the first pharyngeal cleft. Growth, differentiation and fusion of these hillocks result in formation of the pinna. The tragus, helix and cymba concha develop from the hillocks arising from the first arch, while the concha cavum, antihelix and antitragus arise from the hillocks of the second arch. The developing pinna is initially located in the neck and, by 20 weeks of gestation, it ascends to reach its normal location.[3]

The EAC develops from deepening of the first pharyngeal cleft. The first pharyngeal pouch deepens to contact the first cleft. As the embryonic connective tissue proliferates between the first pouch and the first cleft, the contact between the two developing structures is lost and the **meatal plate** develops. The meatal plate starts to canalize between 21 and 28 weeks, forming the inner two-thirds of the EAC. The innermost portion of the meatal plate contributes to the outer layer of the tympanic membrane.

Middle ear

The first and second pharyngeal arches and the first pharyngeal pouch contribute to the development of the middle ear. The middle ear and the inner layer of the tympanic membrane develop from the first pharyngeal pouch. The ossicles develop from the first two pharyngeal arches (malleus and incus from the first arch and the stapes from the second arch).

Inner ear

At week 4 of gestation surface ectodermal cells of the neural plate differentiate into sensory cells and form the **otic placode**. The developing otic placode lies close to the embryonic hindbrain, which contributes to the development of the vestibulo-cochleo-facial ganglion complex. The otic placode invaginates and forms the **otic vesicle**, which gives rise to the membranous labyrinth. The bony labyrinth forms from the periotic mesoderm.

Facial nerve

The facial nerve originates from neural crest cells. The neural crest cells arising from the hindbrain are closely related to the developing pharyngeal arches. The neurons of the first three branchial arches are derived from the neural crest cells (rhombomeres) and form cranial nerves V, VII and IX. The development of these cranial nerve nuclei occurs around the fourth week of embryogenesis and is complete by 16 weeks. Ossification of the Fallopian canal continues into the late foetal period. As the development of the facial nerve and the second arch are closely linked, abnormalities of the facial nerve are often associated with a malformed stapes.

DEVELOPMENTAL ANOMALIES OF THE EXTERNAL EAR

Preauricular sinus

The opening of a preauricular sinus is found in front of the helix, leading into a sinus tract lined with squamous epithelium (Figure 16.1). The tract lies in the subcutaneous tissues lateral to the temporalis fascia superiorly and parotid fascia inferiorly, and with a tortuous and branching course. The terminal portion of the tract is adherent to

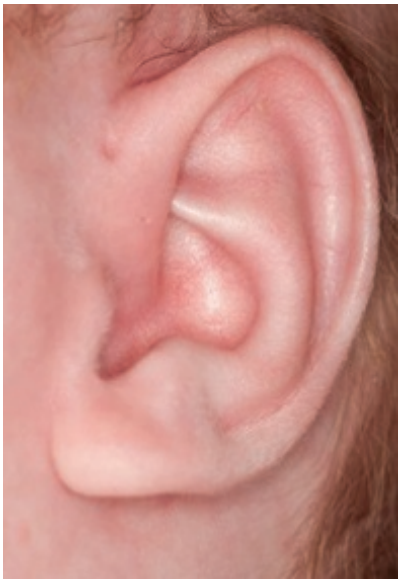

Figure 16.1 Left preauricular sinus.

the cartilage of the helix. Preauricular sinuses are postulated to develop from defective or incomplete fusion of the hillocks of His during auricular embryogenesis. An alternative theory suggests that isolated or localized folding of ectoderm during auricular embryogenesis is the cause of preauricular sinus formation.[4]

Preauricular sinuses occur sporadically or may be inherited. Sporadic abnormalities are generally unilateral and bilateral preauricular sinuses are more likely inherited. Preauricular sinuses may be associated with several syndromes, most notably branchio-oto-renal syndrome. It has been suggested that preauricular sinuses may be linked with anomalies in the region of chromosome 8q11.1-q13.3.[5] Renal anomalies are commonly associated with external ear anomalies, particularly preauricular sinuses, with these patients often investigated using renal ultrasound to detect concurrent renal abnormalities. To aid selection of patients for renal ultrasonography, the following criteria have been suggested:[6]

- maternal history of gestational diabetes
- family history of ear anomalies or hearing loss
- associated craniofacial abnormalities
- associated cardiac abnormalities
- associated gastrointestinal abnormalities
- associated limb abnormalities.

The authors suggest that a preauricular sinus, or any other external ear abnormality, associated with any of the above findings is an indication for a renal ultrasound.

INDICATIONS FOR SURGERY

The decision to operate is usually influenced by the frequency and severity of infective episodes, chronicity of sinus discharge and the development of unsightly overlying skin inflammation (**Figure 16.2**). Incision and drainage should be avoided in acute infections due to the risk of sinus disruption and seeding, and less likely facial nerve injury. Acute infections are best treated with intravenous antibiotics and in severe cases needle aspiration with microbiology culture of the aspirate.[7]

SURGICAL TECHNIQUE

Several techniques have been suggested for excising preauricular sinuses including curettage, microdissection and wide local excision. When selecting a surgical technique, the fact that the sinus may branch extensively and be adherent to the pinna cartilage must be taken into consideration. Curettage is no longer routinely performed due to high recurrence rates and unsightly scarring. Microdissection techniques rely upon identification of the extent of the sinus and its branches, with lacrimal probes and methylene blue being used to delineate the sinus. The 'supra-auricular' approach involves identification of the plane of the temporalis fascia and dissection of the soft tissue between this plane and the helix of the pinna, remaining posterior to the parotid fascia, and without a formal attempt to identify the extent of the sinus and its branches.

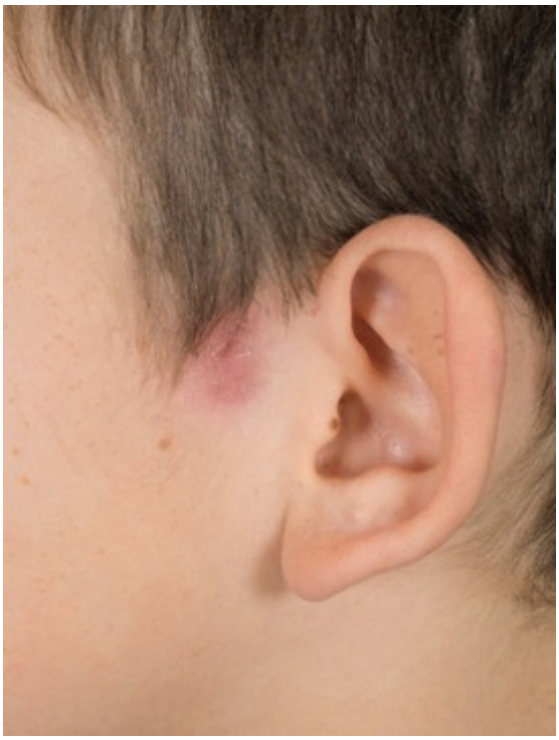

Figure 16.2 Left preauricular sinus with inflammation of the overlying skin.

The resultant wide local excision is considered to give the lowest recurrence rate. Care must be taken to avoid facial nerve injury in revision cases and when skin and soft-tissue inflammation is extensive.[7]

Preauricular appendages

Preauricular appendages result from abnormalities of embryogenesis of the external ear[8] and may be unilateral or bilateral, solitary or multiple. These appendages have a fibrofatty core and often contain a cartilaginous component. They are usually found along a line drawn from the tragus to the angle of the mandible, reflecting origin from the first branchial arch. An increased risk of associated permanent hearing loss has been suggested in infants with preauricular appendages (**Figure 16.3**).[9]

INDICATIONS FOR SURGERY

Operating upon preauricular appendages is undertaken to improve cosmesis and facial symmetry. Surgery is usually undertaken after 1 year of age. Preauricular appendages associated with microtia may be operated upon to improve facial symmetry while waiting for the child to reach an age when ear reconstruction is considered.

SURGICAL TECHNIQUE

Appendages may contain a deeply extending cartilaginous core that may be more extensive than apparent from examination of the external component. Care must therefore be taken when resecting the deep components of

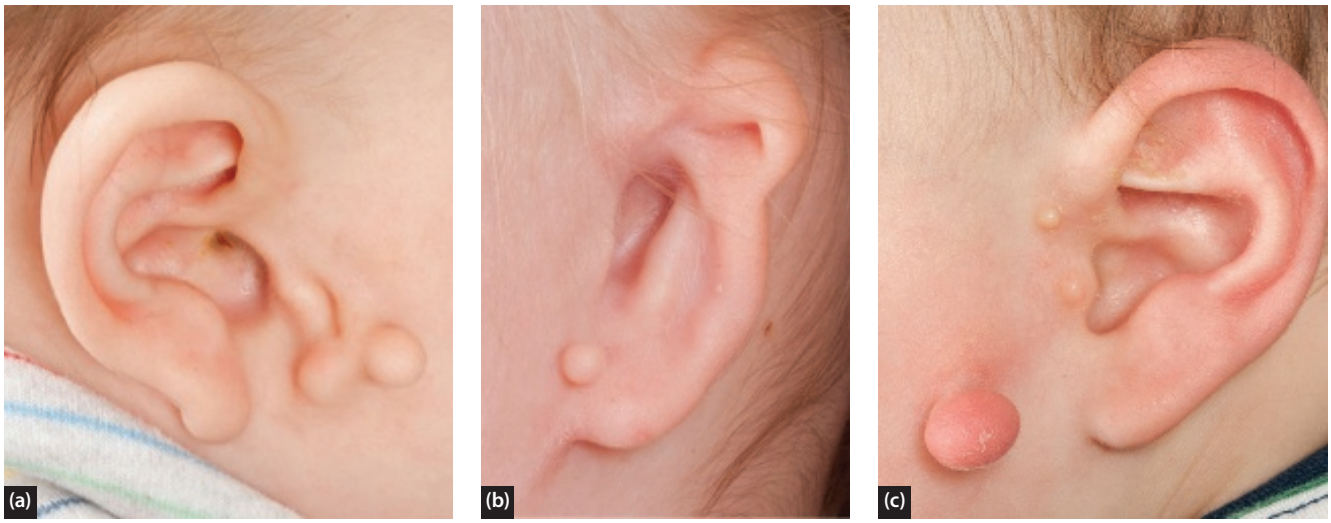

Figure 16.3 Preauricular appendages. **(a)** Associated with a mildly dysplastic right pinna; **(b)** associated with microtia of the left pinna; **(c)** associated with an otherwise normally developed pinna.

the appendage, due to the potential for inadvertent facial nerve injury. Often complete excision of the skin and soft-tissue components is undertaken with partial resection of the superficial part of the cartilaginous core.

MICROTIA

Microtia is a congenital abnormality in which the pinna (auricle) is malformed (see Figure 16.3b). This malformation, or underdevelopment, may be associated with congenital canal atresia or canal stenosis. The incidence of microtia has been reported to be 1 in 10000 and environmental and genetic factors are suggested aetiological factors.[10] CCA often accompanies significant microtia. Results following surgical correction of CCA (canaloplasty) are often disappointing, with a significant risk of chronic discharge and the persisting requirement for amplification. Children with canal stenosis, and those who have undergone canaloplasty, are at risk of developing a canal cholesteatoma and require regular monitoring and interval radiological surveillance.

Grading of microtia and CCA

Several attempts have been made to grade microtia and CCA in a clinically relevant manner, based on clinical, surgical and radiological characteristics (Table 16.1).[11–14] High-quality digital images of the external ear and face often prove more useful as a record of pre-operative appearance and for surgical planning. The pinna malformation may range from mild dysplasia (Figure 16.4) to complete lack of development of the external ear (anotia).

Clinical assessment of children with microtia

A multidisciplinary team is best placed to assess a child with microtia and any associated EAC atresia or stenosis. Attention to the following aspects of clinical and audiological assessment is required.

CLINICAL ASSESSMENT

This involves assessing the general health of the child, with respect to any comorbidity that may affect their management. Some children will also benefit from a psychological assessment, focused on coping with any anxiety associated with their condition and its management. Key points to be considered during assessment are:

- unilateral or bilateral microtia
- size of the microtic ear and its location
- development of the contralateral pinna in unilateral microtia
- hairline
- site and size of a remnant lobule
- presence or absence of normal skin separating the remnants of the microtic ear – this may suggest a superficial course of the facial nerve and caution is exercised during reconstruction to avoid damage to the superficially placed facial nerve
- presence of a stenotic ear canal
- growth and development of the mastoid bone
- space between the temporomandibular joint (TMJ) and the mastoid tip
- presence or absence of facial asymmetry (e.g. hemifacial microsomia in Goldenhar syndrome) (Figure 16.5)
- facial nerve function.

AUDIOLOGICAL ASSESSMENT

Children with microtia and canal stenosis/atresia will usually have a conductive hearing loss (CHL). A small proportion of these children may also have an underlying sensorineural hearing loss (SNHL). It is important to establish ear-specific bone conduction thresholds in early

TABLE 16.1 Examples of grading systems for microtia and congenital canal atresia

	Grading system	Description			
Microtia	Marx[11] *Based on clinical appearance*	**Grade 1** Smaller pinna, but all features of a normal pinna are recognizable	**Grade 2** Some features of a normal pinna are recognizable	**Grade 3** Rudiment of soft tissue and cartilage ('peanut')	**Grade 4** Absent pinna and ear canal
	Weerda[12] *Based on surgical management*	**1st degree dysplasia** Most structures of a normal pinna are recognizable (minor deformities)	**2nd degree dysplasia** Some structures of a normal auricle are recognizable	**3rd degree dysplasia** None of the structures of a normal pinna are recognizable	**Anotia** Absence of external ear
		Surgical definition: Reconstruction does not require the use of additional skin or cartilage	*Surgical definition:* Partial reconstruction requires the use of some additional skin and cartilage	*Surgical definition:* Total reconstruction requires the use of skin and large amounts of cartilage	
CCA	Weerda[13] *Based on clinical appearance*	**Type A** Marked narrowing of EAC with an intact skin layer	**Type B** Partial patency of the lateral EAC with an atretic medial meatal plate		**Type C** Complete atresia of the EAC
	Jahrsdoerfer[14] *Based on radiological appearance*	**Parameter** Stapes present Oval window open Middle ear space Facial nerve normal Malleus/incus complex present Mastoid well-pneumatized Incus/stapes connection Round window normal Appearance of external ear **Rating** 10 9 8 7 6 ≤5			**Points allocated** 2 1 1 1 1 1 1 1 1 **Surgical candidate** Excellent Very good Good Fair Marginal Poor	

infancy to enable appropriate management decisions. Management of bilateral CHL in children with bilateral CCA is of fundamental importance to normal speech and language development. In children with unilateral hearing loss, there is emerging evidence to support early intervention, as discussed below.

Management of significant microtia

The multidisciplinary team delivering care should be able to offer both hearing rehabilitation and all types of pinna reconstruction. Most commonly, children with microtia have three options regarding cosmesis: no intervention, autologous ear reconstruction using cartilage, and bone-anchored auricular prosthesis (BAAP). A proportion of children and young people with significant dysplasia will prefer to keep their 'special ear' and refuse intervention.

AUTOLOGOUS EAR RECONSTRUCTION

This requires two to four surgical procedures dependent upon the technique used (see Vol 3, Chapter 96, Partial and total ear reconstruction). The predominant principles of this procedure include construction of a cartilaginous framework, soft-tissue cover and projection of the reconstructed pinna. Autologous rib cartilage is harvested and used to carve the new cartilage framework. Timing of

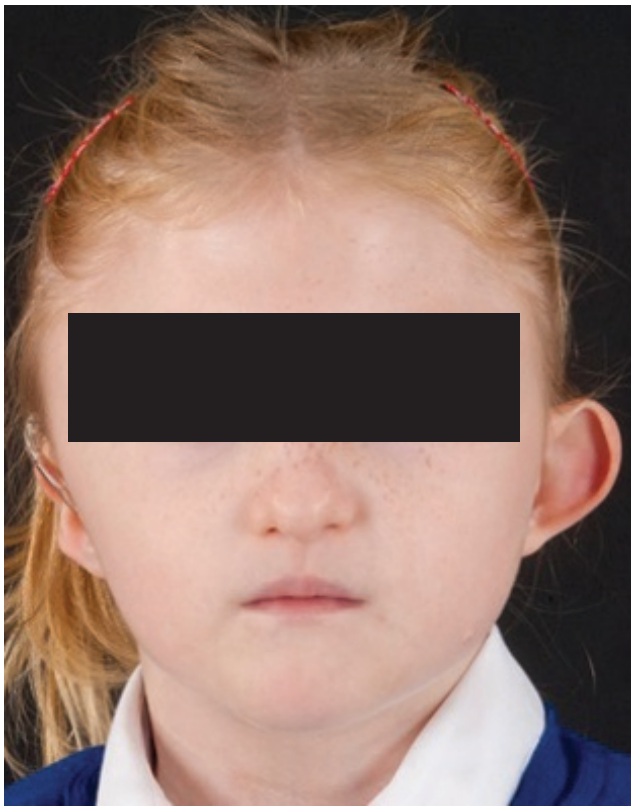

Figure 16.4 Dysplastic left pinna in a girl with CHARGE syndrome.

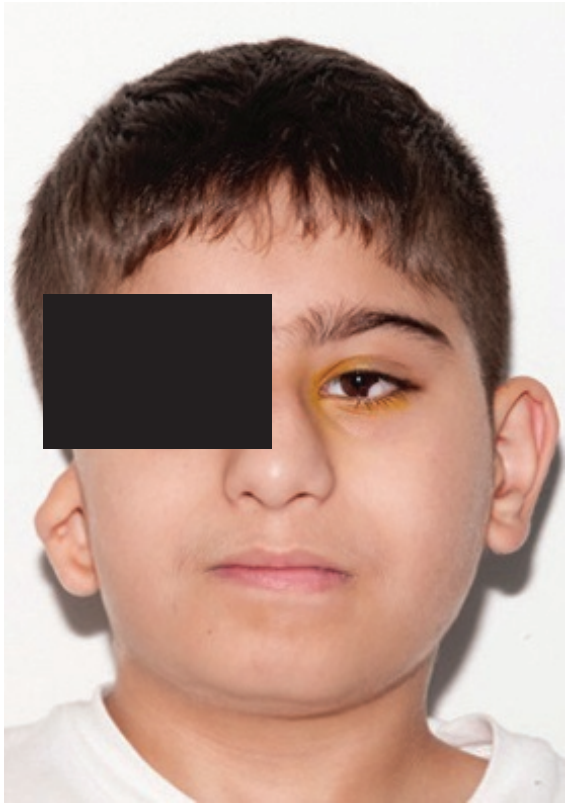

Figure 16.5 Unilateral right microtia in a boy with Goldenhar syndrome. He has right hemifacial microsomia and a left epibulbar dermoid.

surgery will depend on availability of requisite amount of cartilage (8–10 years), and the child's ability to cooperate with the demands of surgery.

The risk of resorption and extrusion of the framework is lower in autologous cartilaginous frameworks as compared to frameworks made from artificial materials.

BONE-ANCHORED AURICULAR PROSTHESIS

A specialist prosthetist is critical in the surgical planning, production of an appropriate prosthesis, and aftercare of older children and young people fitted with bone-anchored auricular prostheses (BAAPs). A BAAP necessitates removal of the vestigial ear (including the lobule), therefore precluding subsequent autologous ear reconstruction if the recipient was dissatisfied with the BAAP. The surgeon and prosthetist must agree the position of the two osseointegrating fixtures. The choice of single- or two-stage surgery is made in the same way as for BAHA insertion. Following osseointegration, a gold retention bar is attached to the abutments, with the prosthetic ear clipping onto this bar. Reasons for opting for a BAAP include patient preference, failed autologous ear reconstruction and significant comorbidities precluding autologous ear reconstruction. The cosmetic outcome of an auricular prosthesis is closely linked to the experience of the prosthetist, with an experienced prosthetist able to add fine contouring and closely match skin colour. However, despite this, some patients prefer a reconstructed pinna that is made from their own tissues. Recurrent soft-tissue inflammation and traumatic fixture loss may complicate the use of percutaneous abutments, as encountered in percutaneous BAHA.

UNILATERAL HEARING LOSS IN CONGENITAL CANAL ATRESIA

Consequences of unilateral hearing loss in children

Traditionally, the presumption has been that UHL would not adversely affect speech and language and academic attainment, if the hearing thresholds in the contralateral ear were within the normal range. However, this assumption is now being challenged, with increasing evidence suggesting that significant numbers of these children could perform better with appropriate management and support.

The work of Lieu and colleagues has described and demonstrated the impact of UHL during childhood, with resultant underperformance in speech, language and cognition in children and young people. Regarding educational performance, a review of UHL (mild to profound severity) in children found a rate of 22–35% for repeating at least one grade and a rate of 12–41% for receiving educational assistance.[15] Lieu also demonstrated in a prospective 3-year longitudinal cohort study of 46 children aged

Figure 16.6 Child with Treacher Collins syndrome and microtia with CCA. The child is wearing a BAHA on a softband and has a tracheostomy *in situ*.

6–12 years with permanent UHL that parents and teachers reported persistent behavioural problems and academic weaknesses or areas of concern in approximately 25% of the cohort.[16] A further case control study of 20 young people (12–17 years) with UHL demonstrated that UHL was associated with a negative effect on standardized language scores and IQ persisting into adolescence. Sibling controls helped to ameliorate any bias resulting from socioeconomic, environmental and genetic factors. The authors also describe children with UHL having difficulty with listening in background noise and sound localization.[17]

Accepting the evidence for the potential negative impact of UHL upon development, the question remains as to the timing of the intervention: before or after the onset of clinically apparent underperformance. Gordon et al. have postulated the existence of aural preference syndrome, in which single-sided deafness in early childhood reorganizes the developing auditory pathways in favour of the hearing ear, and to the detriment of the cortical representation of the deaf ear. They recommend early intervention to secure functioning in the impaired auditory pathway and for restoring (or enabling) binaural hearing.[18] Early intervention would also be supported by the Fischer and Lieu study in which the cohort of young people had not closed the developmental gap with their siblings by adolescence.[17] In broad agreement with the concept of early intervention, the recently developed UK Care Standards for the Management of Patients with Microtia and Atresia[19] advocate the fitting of a bone conduction hearing device (BCHD, e.g. BAHA softband) in infants with microtia and CCA (**Figure 16.6**).

Managing hearing loss in congenital canal atresia

Central to the management of UHL in microtia with CCA is the expectation that in approximately 90% of cases the underlying cochlea function is maintained.[20] Secondly, transcranial attenuation is greater in early infancy, due to the stepwise fusion of the cranial bones during childhood. Therefore, infants and young children will have less transcranial transmission of signal from a BCHD than older children and adults. Also, it is possible to obtain accurate ear-specific bone conduction thresholds in early infancy, despite an inability to mask in a conventional manner in the absence of an external auditory canal.

SYNDROMES ASSOCIATED WITH EXTERNAL EAR ABNORMALITIES

Certain syndromes can be associated with abnormalities of the external ear (**Table 16.2**).[7] Understanding of the manifestations of these conditions is necessary as some may also be associated with other head and neck abnormalities, including abnormalities of the middle and inner ears, and craniofacial abnormalities. Involvement of other body systems (e.g. congenital heart disease (CHD) in a child with Down syndrome) may also be important when planning any surgical intervention under general anaesthesia. Knowledge of cognitive impairment is of critical importance when assessing the likely impact of hearing loss upon development and educational performance.

TABLE 16.2 Syndromes commonly associated with microtia and external ear abnormalities (adapted from Bruce[7])

Syndrome	Description	Chromosomal abnormality	External ear abnormality	Middle and inner ear abnormality
Treacher Collins (Figure 16.6)	Results from abnormal development of structures derived from the first and second pharyngeal complexes	*TCOF1* gene mutations	Bilateral microtia CCA	Ossicular abnormalities
Goldenhar (Figure 16.5)	Heterogeneous disorder associated with hemifacial microsomia, epibulbar dermoid, CHD and vertebral abnormalities	Cause unclear; several chromosomal abnormalities have been described	Unilateral microtia Preauricular appendages	Ossicular abnormalities Abnormal facial nerve anatomy
CHARGE (Figure 16.4)	**C**oloboma, **H**eart defects, **A**tresia choanae, **R**etarded growth and development, **G**enital abnormalities, **E**ar abnormalities	*CHD7* gene mutations	Dysplastic pinnae	Various middle and inner ear abnormalities Facial nerve palsy
Branchio-oto-renal	Branchial cleft abnormalities, ear abnormalities and renal malformations	*EYA1*, *SIX1* and *SIX5* gene mutations	Preauricular sinuses or tags	Ossicular abnormalities WVA Malformed cochlea and vestibular apparatus
Down	Multisystem involvement	Trisomy 21	Small, low-set pinnae Narrow EAC	Hypoplastic mastoid IAC stenosis Vestibular malformations

CCA, congenital canal atresia; CHD, congenital heart disease; WVA, wide vestibular aqueduct; EAC, external auditory canal.

KEY POINTS

- When managing a child with microtia and congenital canal atresia (CCA), consideration should be given to both cosmesis and hearing rehabilitation.
- Cosmesis and hearing should be managed together by a multidisciplinary team.
- In CCA cochlear function is usually normal.
- All children with CCA should undergo regular assessment of hearing, speech and language and educational performance.
- Some children with CAA benefit from a bone conduction hearing device (BCHD).
- Early fitting of BCHD in infants and young children with CCA may be advantageous.
- Bone conduction implants (BCI) should only be inserted in close cooperation with an ear reconstruction service, to prevent inadvertent negative impact upon reconstructive options.

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CHAPTER 17

DISORDERS OF SPEECH AND LANGUAGE

Suzanne Harrigan and Andrew Marshall

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: communication, language, speech, developmental milestones, speech and language therapy.

INTRODUCTION

We live in a world where communication is vital. Modern technologies, including the internet and mobile devices, mean that we can communicate with many more people and across greater distances than at any time in history. In the developed world, jobs that require interaction with others are more prevalent than they were in the last century; the office for national statistics in the UK reports that approximately 71% of men and 92% of women are now employed within service industries, where the skills of interpersonal communication are essential. So, in order to succeed and thrive, both in education and the workplace, the children of the 21st century require a level of spoken language and, in turn, literacy that can be achieved only through exposure to a rich and vibrant language learning environment. For those children who, for whatever reason, fail to develop adequate speech, language and communication skills, the future can be bleak, with a significant percentage of them running the risk of poor attainment levels at school and potentially slipping into antisocial behaviour. Bryan identified high levels of speech, language and communication difficulties within the young offender population.[1] Ironically, however, there appears to be a lack of awareness about the importance of speech and language development in the general population. In a report from the Communication Trust[2] as many as 50% of children were identified as having problems with speech and language on school entry. It is therefore essential that all professionals who come into contact with children are familiar with the developmental milestones for speech and language acquisition in order to intervene both medically and from a multidisciplinary perspective.

This chapter aims to provide the reader with a brief summary of childhood speech and language acquisition, with a particular focus on the first 5 years of life, when the foundations of language for learning and literacy are established. Some of the obstacles that may delay or hinder the developmental process will also be discussed and the 'red flags' that may indicate the presence of speech and language difficulties will be highlighted to ensure that ENT professionals are aware of these warning signs and act in a timely manner, rather than falling into the 'wait and see' trap that often occurs.

A WORD ABOUT TERMINOLOGY

Before looking at the developmental milestones, it is worth considering the terminology used to describe communication, language and speech development.

Pragmatics: using and understanding language in different situations
Verbal skills: understanding and using spoken language
Non-verbal skills: communicating using signs, gestures and body language

Expressive skills: getting a message across, verbally or non-verbally

Comprehension or receptive skills: understanding of language

Voice skills: volume, quality and pitch, which can be used to convey changes in meaning through intonation

Speech: pronouncing sounds and words. Speech and language therapists assess children's speech production in terms of the child's articulation – the physical capability to produce sounds, or phonology, i.e. the child's ability to use a range of sounds contrastively within the rules of the spoken language used.

MILESTONES FOR SPEECH, LANGUAGE AND COMMUNICATION DEVELOPMENT

This section will describe the stages in the development of speech, language and communication over the first 5 years of a child's life (summarized in Table 17.1). However, there is considerable evidence that the process of learning about voices and communication begins before birth, as the mother's speech patterns, particularly prosody (patterns of stress and intonation), are readily available to the baby in the womb. This means that hearing babies arrive in the world with a range of auditory experiences.[3, 4] Babies with hearing losses have therefore already experienced a period of auditory deprivation, despite the earlier identification of hearing problems in babies and management of childhood hearing loss.

Figure 17.1 illustrates the stages in the normal development of speech and communication in the first 5 months.

Birth to 3 months

Babies are born with a desire to communicate and are skilled at getting others to communicate with them. Newborn babies love looking at the human face and will try to copy facial movements. They have different cries for different physical states, so parents quickly begin to differentiate between a hungry cry and a cry of pain. As babies approach the age of 3 months, they are already becoming social beings, with the development of the social smile and laughter. Hearing babies startle to loud sounds and are particularly interested in and calmed by the sound of friendly voices, particularly their parents'. This emphasizes the need for babies with hearing losses to be provided with appropriate amplification as soon as possible, to capitalize on these early listening opportunities.

6 months

As babies grow and start to develop head control, their vocalizations become louder and more purposeful, and babble starts to develop at around the 6-month stage. Babies at 6 months are very sociable and interactive;

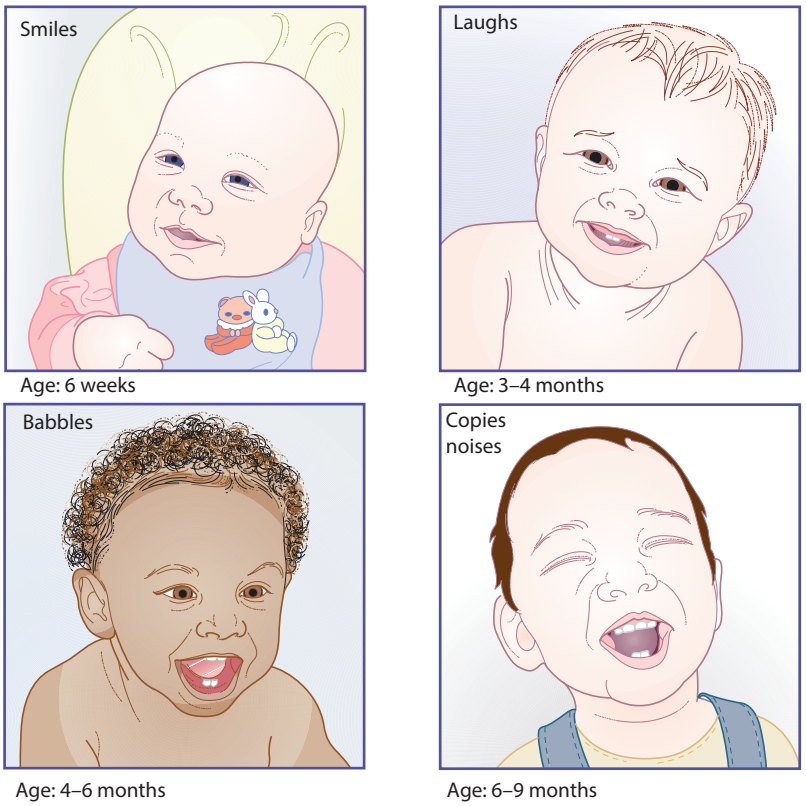

Figure 17.1 Stages in the development of speech and communication in the first 9 months.

TABLE 17.1 Stages of speech and language development in a child up to 5 years of age

Age	Listening and attention	Understanding	Speech sounds and talk	Social skills
Up to 3 months	Turns towards a familiar sound Startled by loud noises	Recognizes parent's voice Often calmed by familiar friendly voice, e.g. parents	Frequently cries, especially when unhappy or uncomfortable Makes vocal sounds, e.g. cooing, gurgling	Gazes at faces and copies facial movements, e.g. sticking out tongue Makes eye contact for fairly long periods
3–6 months	Watches face when someone talks	Shows excitement at sound of approaching voices	Makes vocal noises to get attention Makes sounds back when talked to Laughs during play Babbles to self	Senses different emotions in parent's voice and may respond differently, e.g. smile, quieten, laugh Cries in different ways to express different needs
6–12 months	Locates source of voice with accuracy Focuses on different sounds, e.g. telephone, doorbell, clock	Understands frequently used words such as 'all gone' and 'bye-bye' Stops and looks when hears own name Understands simple instructions when supported by gestures and context	Uses speech sounds (babbling) to communicate with adults; says sounds like 'ba-ba', 'no-no', 'go-go' Stops babbling when hears familiar adult voice Uses gestures such as waving and pointing to help communicate At around 12 months begins to use single words, e.g. 'mummum', 'dada', 'tete' (teddy)	Enjoys action rhymes and songs Tries to copy adult speech and lip movements Takes 'turns' in conversations (using babble)
12–15 months	Attends to music and singing Enjoys sound-making toys/objects	Understands single words in context, e.g. cup, milk, daddy, when the object was there Understands more words than they can say Understands simple instructions, e.g. 'kiss mummy', 'give to daddy', 'stop'	Says around 10 single words, although these may not be clear Reaches or points to something they want while making speech sounds	Likes being with familiar adults Likes watching adults for short periods of time
15–18 months	Listens and responds to simple information/ instructions, e.g. 'Ben, put on shoes', 'Mohammed, give to daddy'	Understands a wide range of single words and some two-word phrases, e.g. 'give me', 'shoe on' Recognizes and points to objects and pictures in books if asked Gives named familiar objects to adult, e.g. coat, car, apple, book	Still babbles but uses at least 20 single words correctly, although may not be clear Copies gestures and words from adults Constant babbling and single words used during play Uses intonation, pitch and changing volume with 'talking'	Simple pretend play Plays alone, although likes to be near familiar adult Although increasingly independent, happiest when near familiar adult
18 months–2 years	Focuses on an activity of their own choice but finds it difficult to be directed by an adult Use of child's name beginning to help them to attend to what the adult says, e.g. 'Sarah, eat sandwiches', 'Ali, put coat on'	Understanding of single words develops rapidly during this stage: between 200 and 500 words are known Understands more simple instructions, e.g. 'get mummy shoes', 'get your bricks', 'tell dad tea's ready'	Uses up to 50 words Begins to put two or three words together Frequently asks questions, e.g. the name of people and objects (towards 2 years of age) Uses speech sounds p, b, m, w	'Pretend' play developing with toys, such as feeding a doll or driving a car Becomes frustrated when unable to make self understood – this may result in tantrums Follows adult body language including pointing, gesture and facial expressions

(Continued)

TABLE 17.1 Stages of speech and language development in a child up to 5 years of age

Age	Listening and attention	Understanding	Speech sounds and talk	Social skills
2–3 years	Beginning to listen to talk with interest, but easily distracted Listens to talk addressed to him/herself, but finds it difficult if prompts are not provided, e.g. use of name, 'stop and listen'	Developing understanding of simple concepts, including in/on/under, big/little Understands phrases like 'put teddy in the box', 'get your book, coat and bag', 'draw a big brown dog' Understands simple 'who', and 'what' and 'where' questions but not 'why' Understands a simple story when supported with pictures	Uses 300 words, including descripting language, time, space, function Links four or five words together May stutter or stammer when thinking what to say Able to use pronouns (me, him, she), plurals and prepositions (in, on, under) Has problems saying speech sounds l/r/w/y, f/th, s/sh/ch/dz/j	Holds a conversation but jumps from topic to topic Interested in other's play and will join in Expresses emotion towards adults and peers using words, not just actions
3–4 years	Enjoys listening to stories Still finds it difficult to attend to more than one thing at a time, so can't easily listen to a speaker while still carrying on an activity; has to switch attention between speaker and task	Understands questions or instruction with two parts: 'get your jumper' and 'stand by the door' Understands 'why' questions Aware of time in relation to past, present and future, e.g. 'Today is sunny, yesterday was rainy. I wonder what the weather will be like tomorrow?' (towards 4 years)	Uses sentences of four to six words, e.g. 'I want to play with cars', 'What is that thingy called?' Uses future and past tense, e.g. 'I am going shopping', 'I walked home' May continue to have problems with irregular words, e.g. 'runned' for 'ran', 'swimmed' for 'swam' Able to remember and enjoys telling long stories or singing songs Has problems saying r, j, th, ch and sh	Understands turn-taking as well as sharing with adults and peers Initiates conversations Enjoys playing with peers Able to argue with adults or peers if they disagree – uses words, not just actions
4–5 years	Attention is now more flexible – the child can understand spoken instructions related to a task without stopping the activity to look at the speaker	Able to follow simple story without pictures Understands instructions containing sequencing words; 'first … after … last' Understands adjectives: soft, hard, smooth, etc. Aware of more complex humour, laughs at jokes that are told	Uses well-formed sentences, e.g. 'I played with Ben at lunchtime' but there may still be some grammatical errors Easily understood by adults and peers, with only a few immaturities in speech sounds, e.g. 'th', 't' and three-consonant combinations 'scribble' Frequently asks the meaning of unfamiliar words and may use them randomly	Chooses own friends Generally cooperates with playmates Able to plan construction and make-believe play activities, e.g. building models from Lego Takes turns in longer conversations Uses language to gain information, negotiate, discuss feelings/ideas and give options

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they can easily express their likes and dislikes through their facial expressions and vocalizations. At around this age, babies begin to understand that they can use their voices to attract the attention of their caregivers and they engage in vocal turn-taking with their carers. Hearing babies are beginning to gain meaning from what they hear at this stage – they can anticipate the arrival of a familiar person from hearing their approaching voice and they can make sense and respond appropriately to different tones of voice – so they can tell the difference between happy and angry voices, for instance. They may also respond to their name being called, and they may start to respond to 'no'.

At 6 months, babies enjoy exploring everything they can lay their hands on and most objects tend to go into the mouth. This is a particularly difficult stage for parents of young hearing-aid users as encouraging 6-month-olds to wear their hearing aids is challenging to say the least. All professionals need to support parents through this stage.

Warning signs are difficult to spot at this early age, but all professionals should be aware of the signs of possible communication difficulties. A baby of 6 months old who does not startle to loud sounds, engage in eye contact or smile back when being spoken to, or seems to lack interest in faces, may need to be seen by a paediatrician for developmental assessment.

9 months

At 9 months a baby's babbling is more advanced, with strings of both canonical babble (where the same consonants and vowels are reduplicated [*bababa*]) and non-canonical or variegated babble (where new and different consonants are introduced to the babble stream [*badabada*]). Babies with hearing are now beginning to understand familiar words and phrases, such as 'wave bye-bye', and they may even be making some early word attempts, where babble patterns such as 'mama' and 'dada' are beginning to be associated with the relevant people.

Babies at this age are starting to point to objects, which draws the adults' attention to the object and makes you name them. This is an important marker for communication development; babies who fail to develop pointing may be at risk of developmental disorders such as autistic spectrum disorder and they need to be carefully monitored.

Other important communication markers to look out for at 9 months are the child's ability to gain your attention and respond to noises. Babies who are failing to do these things, certainly by 12 months of age, may need further investigation.

12 months

Babies become toddlers around their first birthday and are also becoming great communicators! One-year-olds can understand many words and gestures and will respond accordingly. They can also initiate conversations themselves to express their wants and needs. Babies at 12 months will have a small number of words (around ten), although they will not pronounce them clearly and may only be understood by those closest to them. Intelligible speech is not something that should be expected at a year.

18 months

At 18 months toddlers are developing strong personalities and it is at this stage that there is enormous variability in children's language development. Some at this age have an extensive vocabulary and are already stringing words together into short phrases; others will still have only a small handful of words, and yet would still be classed as functioning within normal limits. Crucially, children's understanding of words and phrases is important at this age; 18-month-olds should be able to follow simple requests and point to pictures in a book and to body parts, and children who are not yet able to do this will need careful monitoring and possible referral to speech and language therapy services.

2 years

The 2-year-old's greatest achievement is their language development. A 2-year-old will have an average vocabulary of around 60 words and some two-word combinations, and they will understand many more. They will enjoy naming everything they see, and will repeat everything that they hear. At this time, adults need to focus on the meaning behind the message rather than the children's grammar and speech sounds as there will still be many errors.

It is between the ages of 2 and 3 years that speech, language and communication difficulties become more apparent, and early referral to speech and language therapy services is vital. Children of this age should be referred if:

- the child prefers to point or show what they want rather than to say it
- single words are not yet being combined into phrases or sentences
- they seem slow to follow instructions and prefer to wait to be shown what to do rather than be told
- adults, and particularly close family members, find it hard to understand what they say, either because their speech is unclear, or the language they use is confused.

3 years

A 3-year-old will be developing an understanding of the simple concepts of size, colour and position. They will also enjoy simple stories and be able to answer simple questions such as 'who…?' and 'what…?' They will have a rich and varied vocabulary of approximately 300 words, which they will be linking together into sentences of four or five words. Grammatical development will also be progressing, with children of this age starting to use grammatical markers for plurals, and grammatical words such as pronouns. Three-year-olds often stammer when talking, but this is a developmental stage which passes quickly. Their speech intelligibility is improving, although they will still struggle with certain speech sounds, or blends of sounds.

4 years

At 4 years of age, children use much longer sentences and are beginning to indicate past and future tenses, although they are likely to struggle with irregular tense constructions, so may say 'swimmed' instead of 'swam', for example. They will still have difficulties producing some speech sounds. A 4-year-old will need speech and language therapy assessment if:

- they are struggling to understand and retain language around concepts
- they are finding it difficult to talk in longer sentences, by failing to organize words into the right order or not having the vocabulary to express what they want to
- they miss out words within a sentence, for instance 'boy play ball' rather than 'the boy is playing ball'
- they are not using the right speech sounds or they miss out some sounds altogether
- they seem to have developed a stammer or dysfluent speech has persisted.

5 years

Five-year-olds are confident and competent communicators who use well-formed sentences and are easily understood by others. They are interested in language and words; they will frequently ask what words mean and are developing a verbal sense of humour.

SPEECH, LANGUAGE AND COMMUNICATION DIFFICULTIES: CAUSES AND PREVALENCE

Speech, language and communication needs may be the most common disability in children under the age of 5, with the range of estimates of prevalence across the UK population between 2% and 25%, depending on the data collection methods used and the criteria applied.[6] The speech, language and communication needs of preschool children can be many and varied, ranging from a child who presents with mild speech difficulties, to a child with no communication skills at all. These difficulties may arise as a consequence of other conditions, so children with sensory impairment, learning disabilities, physical needs or developmental disorders are far more likely than their peers to have problems communicating. However, significant numbers of children present with speech and language difficulties where there are no other factors present. Although for the majority of these children their problems may be relatively minor and easily remediated, a proportion of them will experience persistent and complex communication problems which will need specialist support for a prolonged period if they are to progress to their full potential.

An important distinction to make at this point is the difference between a language and/or speech **delay** and a true **disorder**. Speech and/or language delay is defined as 'a delay in speech and/or language development compared with controls matched for age, sex, cultural background and intelligence'.[7] The extent of the delay can vary from being fairly minor to severe and debilitating, particularly if associated with other conditions such as learning disability.

Learning difficulties

Around 2 million people in the UK have a learning disability. Mencap states that 'a learning disability is a reduced intellectual ability and difficulty with everyday activities – for example household tasks, socialising or managing money – which affects someone for their whole life. People with a learning disability tend to take longer to learn and may need support to develop new skills, understand complicated information and interact with other people'.[8]

Speech, language and communication difficulties are found in children and adults with all levels of learning difficulties, from mild through to severe and profound; the more significant and severe the learning disability, then the more likely it is for the communication difficulty to be severe, with approximately 80% of people with severe learning difficulties not acquiring speech.

Physical impairment

Children with physical impairments including cerebral palsy are likely to present with speech, language and communication difficulties. Speech in particular is often affected because of the difficulties in motor control and planning, but individuals with physical disabilities may also present with learning difficulties and sensory impairments, which can further exacerbate their communication difficulties. It is also important to mention that physical impairments of the vocal tract can cause speech difficulties. In particular, cleft palate, which is the most common congenital craniofacial abnormality, affecting about 1 in 600 live births, can cause atypical speech development and problems with resonance that can persist without specialist support and treatment.

Autistic spectrum disorder

Autism is a lifelong condition that affects how a person communicates with, and relates to, other people. It also affects how they make sense of the world around them. Autism is a spectrum disorder, which ranges from mild to profound, and communication difficulties, particularly in the areas of social communication and interaction, are crucial diagnostic indicators. The National Autistic Society suggests that approximately 700 000 people in the UK have ASD, which is 1 in every 100 people.

Sensory impairment

Childhood hearing loss is, of course, familiar to professionals working within ENT and it can have a considerable impact on communication, educational attainment, employment opportunities and quality of life. Deafness may be congenital or acquired, temporary, permanent or fluctuating and may range from a mild difficulty, where individuals may struggle a little to follow speech in noisy environments, through to a profound loss, where speech is inaccessible even with the most powerful hearing aids, and cochlear implantation may be necessary.

Over the past two decades, great advances have been made in hearing technologies, meaning that even profoundly deaf children can access spoken language in ways that were only dreamt of 50 years ago. However, there is certainly no room for complacency. Hearing technologies, although excellent, do have their limitations, especially in less than optimal acoustic conditions, and despite earlier identification of hearing loss thanks to newborn hearing screening programmes both in the UK and worldwide, a significant number of deaf children are still struggling to develop speech and language. The reasons for this are multifaceted and some of these will be beyond the control of professionals; a high percentage

(around 40%) of deaf children will have additional difficulties which may affect their ability to learn.[9] However, the importance of early and appropriate amplification is certainly something that ENT professionals need to consider.

The evidence for the importance of early cochlear implantation for the best spoken language outcomes in profound hearing loss is unequivocal, meaning that early referral to cochlear implant teams should be a priority for all ENT doctors. Many children implanted before 18 months of age show a similar rate of language development as their hearing peers. Those implanted after 3 years of age may struggle to catch up,[10] and it is recognized that a proportion of children will remain language-delayed when compared to hearing peers.[11] It is important to note, however, that children with cochlear implants consistently show a higher level of language attainment than profoundly deaf children using hearing aids (see Chapter 94, for further details).

It is worth noting here that children with visual impairments may also experience difficulties with communication. Children with visual impairments may follow a different developmental path to typically developing children, particularly in the area of social communication, as the early interactive skills of eye contact and shared attention may have been lacking. It is also very common for visual impairments to co-occur with other disabilities, meaning that these children's communication needs can be extremely complex.

Language disorders

Language disorders are identified when a child presents with a language score on standardized tests two standard deviations from the child's age and where there is no neurological, sensory, developmental or physical impairment that could account for the poor performance.[12] Language disorders can therefore be accurately diagnosed only by a process of exclusion and it is vital that thorough and comprehensive assessments are carried out to rule out the presence of other difficulties. This group of children is a significant one, with studies suggesting that 5–7% of children starting school have such a disorder. The most commonly used term to describe this condition is developmental language disorder (DLD), and children with DLD may have difficulty in only one or in a combination of language and speech areas. There is no single known cause of DLD, with both intrinsic and extrinsic factors playing a part.[13] However, genetics are known to have an influence, with evidence of strong family histories for DLD. More boys than girls present with DLD, with studies estimating ratios of around 3:1.

Speech sound disorders are distinguishable from speech delays because the children present with unusual or idiosyncratic patterns of speech production that do not follow normal developmental patterns. Children with speech sound disorders may also continue to use immature patterns for much longer than expected and may be resistant to therapeutic intervention. These children will have restricted and distorted sound systems and will have problems producing connected speech. It is important that any structural factors that may be causing or contributing to speech sound problems are investigated and ENT professionals may be asked to assess these children to check for issues such as palatal function and carry out a thorough examination of the head and neck.

HYPERNASAL SPEECH

In hypernasal speech (rhinolalia aperta) the velopharyngeal sphincter remains open or partly open during speech and air escapes into the nasal cavity. Causes include palatal paralysis (e.g. cerebral palsy), cleft palate, submucous cleft, adenoidectomy, and craniofacial surgery such as midfacial osteotomy. Placing a cold steel spatula under the nostrils and observing the misting pattern as the child speaks is a useful clinical test for the condition. Some nasal escape is normal during 'nasal' sounds such as *mm*, *nn* and *ng*, but misting when the child speaks a phrase with no nasal sounds (e.g. 'Katie's sister was six yesterday') is suggestive of palatal dysfunction. In established cases, there may be compensatory nasal grimacing as the child attempts to correct the nasal escape. Velopharyngeal insufficiency and submucous palatal clefts are discussed in Chapter 18, Cleft lip and palate.

HYPONASAL SPEECH

Hyponasal speech (rhinolalia clausa) can be caused by septal deviation, nasal polyps, gross turbinate hypertrophy, adenoids or a space-occupying nasopharyngeal lesion. The spatula test shows no escape when the child is asked to speak words with 'nasal' sounds; for example, 'Mummy and nanny are mending' will be pronounced 'Bubby and daddy are bedding'.

Tonsils, adenoids and speech

Tonsillectomy may affect the 'timbre' or resonance of the singing voice and, in the case of children who sing, it is wise to inform them and their parents of this. Adenoidectomy causes transient velopharyngeal sphincter dysfunction in about 5% of cases. This can cause troublesome rhinolalia aperta. In a small minority (0.01%) this may be long-standing.[14, 15]

Children with submucous palatal clefting – where the only external sign may be a bifid uvula (**Figure 17.2**) – should have adenoidectomy with extreme caution if at all. Partial adenoidectomy, under direct or endoscopic vision and preserving a buttress of tissue around the lateral margins, may preserve the velopharyngeal closure mechanism.[16]

Hyponasal speech due to large adenoids rarely constitutes an indication for adenoidectomy on its own. Usually there will be an independent indication for surgery, such as airway obstruction. Adenoids regress and parents should be made aware of this when giving informed consent if adenoidectomy is offered to improve the child's speech.

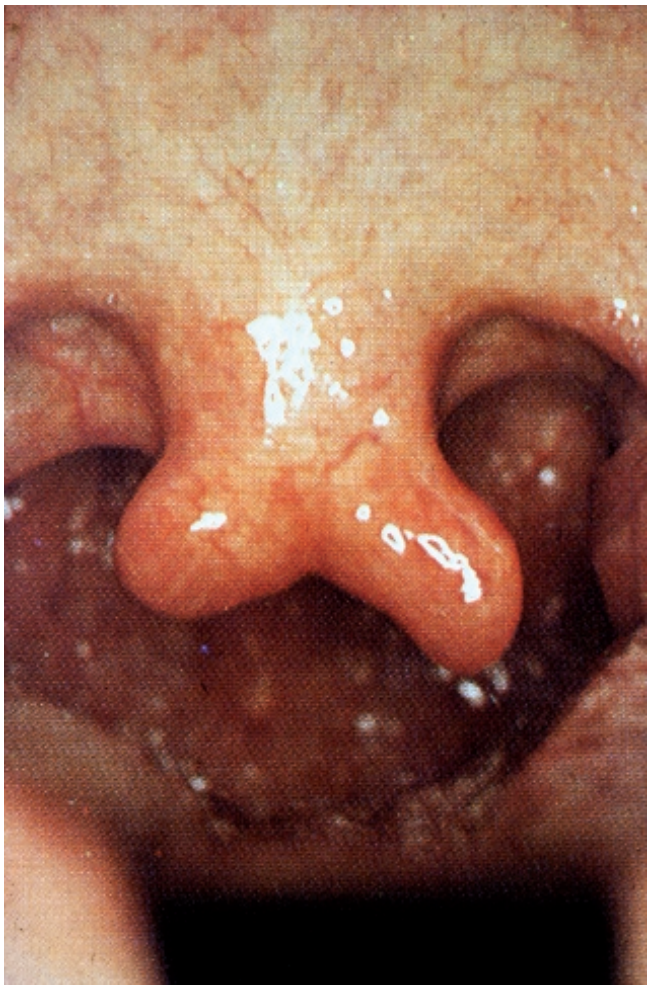

Figure 17.2 Bifid uvula – often associated with submucous cleft palate, causing rhinolalia aperta.

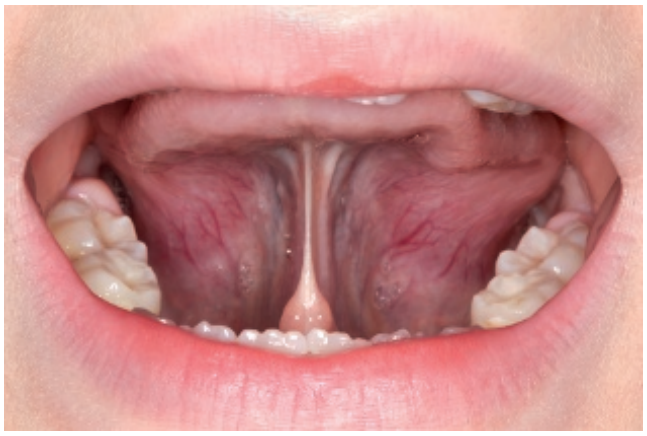

Figure 17.3 Tongue tie.

Tongue tie

Tongue tie (ankyloglossia) is characterized by tethering of the anterior part of the tongue to the floor of the mouth by a short lingual frenulum (Figure 17.3). It is usually asymptomatic but may restrict tongue mobility in the newborn and give rise to difficulties with breastfeeding. Many parents present for treatment as they are concerned about the appearance of the tongue or about the potential for the condition to interfere with activities such as licking the lips and kissing. The condition tends to improve as the child gets older. There is no evidence to link tongue tie with speech and language disorders. Nevertheless, parents often request treatment. If treatment is required, a simple division of the frenulum is adequate. In the newborn, this can be undertaken without anaesthesia but older children require a general anaesthetic.

ROLE OF THE SPEECH AND LANGUAGE THERAPIST

Speech and language therapy aims to help all children and adults to communicate as well as possible. All speech and language therapists (SLTs) practising in the UK are trained to at least graduate level and are registered with the Health Professionals Council. There are around 10 000 speech and language therapists working in the UK. Many of them are employed by the NHS, but some work for education authorities, for charities or in independent practice.

All SLTs understand how children's language, speech and communication develop, the difficulties that can arise, and how to help. Specialist therapists with more knowledge and experience of working with complex cases or specific conditions may also be employed, to help the local therapists plan appropriate interventions for the child and, in some cases, to see the child themselves for therapy. ENT professionals may come into contact with these specialist SLTs in fields such as deafness, where they are mainly involved in supporting children with severe to profound hearing losses, in cleft palate teams and in supporting children with voice problems.

Broadly, SLTs take responsibility for the assessment, diagnosis and treatment of children with speech, language and communication needs, and they may also be responsible for the assessment and treatment of swallowing disorders, if appropriately trained. The type of speech and language therapy a child receives will depend on many factors, including the child's needs and age, and the causes and severity of the problem(s). Therapy packages may include group or individual sessions, or assessment and advisory sessions with programmes of work being carried out by the family or school staff. All speech and language therapists are expected to work closely and collaboratively with other agencies and professionals who support the child, in particular those working in education who see the children frequently and are well placed to support the child's speech, language and communication needs in everyday settings.

For preschool children in particular, the parents will be the main focus of SLT support, as parents are always the child's first teachers, certainly as far as speech and language development is concerned. Research has shown that parents use on average over 12 000 words every day with their normally developing 2-year-olds and that the parents of the best talkers talk significantly more.[17] Interestingly, work carried out by the Lena Research Foundation showed

that the level of parental education does not predict the amount the adult speaks to the child, but gender and birth order does seem to have an effect, with girls being spoken to more than boys and firstborns hearing more talk than their younger siblings.[18] SLTs therefore play a major role in raising awareness of the importance of talking to children, and working with parents of young children with speech, language and communication needs to ensure that true progress happens within the home, not in the clinic.

The easy-to-use 'progress checker' on the Talking Point website[18] is helpful for ENT professionals in the process of deciding when to refer a child to speech and language therapy services. Other useful organizations/websites are listed below in 'References' and 'Further information'.

KEY POINTS

- Communication, speech and language difficulties can occur in isolation, or with associated conditions.
- Left untreated, speech, language and communication difficulties can have pervasive and long-term effects on the individual, including low academic attainment and offending behaviour.
- All ENT professionals should understand developmental milestones for speech and language acquisition, to ensure appropriate and timely referral to Speech and Language Therapy services.

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FURTHER INFORMATION

British Stammering Association: support for people who stammer. https://www.stammering.org/

Cleft Lip & Palate Association: for children affected by cleft lip and palate. https://www.clapa.com/

The Communication Trust: a consortium of over 50 not-for-profit organizations which champion the needs of those with speech, language and communication problems. http://www.thecommunicationtrust.org.uk/

I Can: UK charity for children with speech, language and communication needs. http://www.ican.org.uk/

Mencap: supporting those with a learning disability. https://www.mencap.org.uk/

National Deaf Children's Society: supporting children with all levels of hearing impairment. http://www.ndcs.org.uk/

Talking Point: information about children's communication. http://www.talkingpoint.org.uk/

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Taylor & Francis Group
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CHAPTER 18

CLEFT LIP AND PALATE

David M. Wynne and Louisa Ferguson

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the following keywords: cleft lip, cleft palate, velopharyngeal dysfunction, Pierre Robin sequence, otitis media with effusion and sleep disordered breathing.

INTRODUCTION

Cleft lip and cleft palate are the commonest form of orofacial clefting. Patients with a cleft of the lip or palate have multiple ENT problems and can present to the otolaryngologist with airway, hearing, speech or nasal issues. This chapter aims to describe the epidemiology and aetiology of cleft lip and palate, and the principles of treatment, particularly in regard to ENT-related issues.

CLEFT TYPES AND CLASSIFICATION

Orofacial clefts are generally classified by laterality and extent of the defect. Cleft lip is defined as a cleft of the structures anterior to the incisive foramen, also known as the primary palate (Figure 18.1). Cleft lip can be complete (involving the alveolus), incomplete or microform. It can also be unilateral or bilateral, and may or may not involve the palate. Cleft palate is clefting of the secondary palate and may be incomplete or complete, bilateral or unilateral, or submucous.[1] Cleft lip ± palate (CL±P) and isolated cleft palate/cleft palate only (CPO) are unique in both their aetiology and epidemiology.

Various classification systems have been devised over the years to try to account for the variability in clefting of the lip and palate. Veau's 1931 classification[2] is commonly utilized (Table 18.1), although it is incomplete since it makes no provision for isolated cleft lip.

In the 1950s Kernahan and Stark proposed an embryologically based system centred on clefting in relation to the

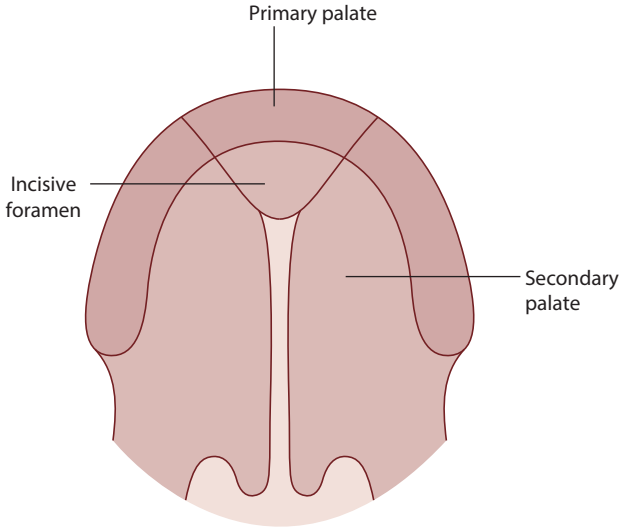

Figure 18.1 Primary palate anterior to the incisive foramen. Secondary palate, posterior to the incisive foramen.

TABLE 18.1 Veau's 1931 classification of cleft lip and palate[2]

Group	Description
Group I (A)	Defects of soft palate only
Group II (B)	Defects involving the hard palate and soft palate, extending not further than the incisive foramen
Group III (C)	Defects from the soft palate to the alveolus (usually involving the lip)
Group IV (D)	Complete bilateral clefts

incisive foramen. This was modified by Kernahan in 1971[3] who proposed a system based on the intraoral view of the palate. A 'Y' diagram representing the cleft is marked from 1 to 9, with the relevant areas marked dependent on the extent of the clefting (Figure 18.2).

The LAHSHAL system is commonly utilized in the UK (Figure 18.3). It involves recording the cleft status starting on the right-hand side and working from the lip back to the soft palate and then forward again on the left and marking each area as complete (C), incomplete (I) or no cleft (X). The areas are subdivided into lip, alveolus, hard palate and soft palate.

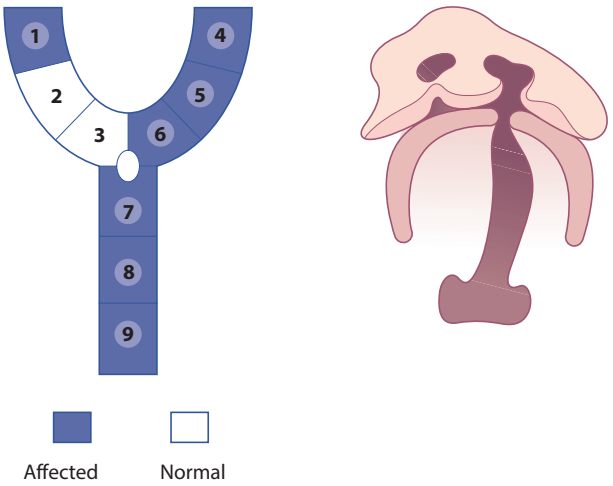

Figure 18.2 Kernahan's striped 'Y' classification. 1, 4, lip; 2, 5, alveolus; 3, 6, hard palate anterior to incisive foramen; 7, 8, hard palate; 9, soft palate; 0, incisive foramen.

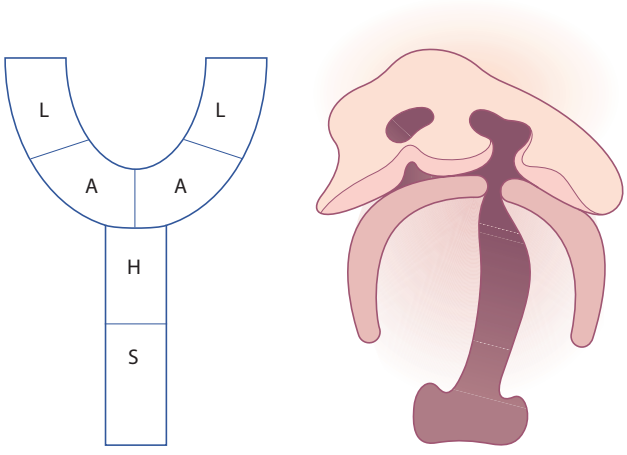

Figure 18.3 LAHSHAL – anatomical paraphrase of cleft lip, alveolus and palate. A, alveolus; H, hard palate; L, lip; S, soft palate.

EPIDEMIOLOGY

Cleft lip and cleft palate are the commonest form of orofacial clefting. CL±P and isolated cleft palate are two separate entities in terms of both aetiology and epidemiology. The overall incidence of orofacial clefting is between 1 in 600 and 1 in 750, which amounts to around 1000 new cases a year in the UK.[1] CL±P incidence varies with ethnicity and race. The Asian population have the highest incidence with approximately 2 per 1000. The white population have an incidence of 1 in 1000 and the lowest incidence is in the Afro-Caribbean population, which has an incidence of 0.3 per 1000 live births.[1,4] CL±P is more common in males and 80% are unilateral, with a left to right ratio of 2:1.[1] Isolated cleft palate is not affected by race and has an overall incidence of 1 in 1500. Cleft palate alone is twice as common in females.[5] The typical distribution of orofacial clefts is cleft lip and palate 46%, cleft palate only 33% and cleft lip alone 21%.[6]

AETIOLOGY AND GENETICS

Orofacial clefts may be syndromic or non-syndromic. Most orofacial clefts are non-syndromic and occur as an isolated anomaly. CPO is more commonly associated with a syndrome than CL±P, with a recent systematic review estimating around 50% for CPO 30% for CL±P.[7] There are now over 400 syndromes associated with CPO and CL±P in the London Dysmorphology Database,[8] with some of the more common syndromes listed in Box 18.1.

The most frequent interstitial deletion in humans is del(22)(q11.2), with an estimated prevalence of 1 per 4000 live births.[9] This deletion is associated with a wide phenotypic spectrum including the Di George and velocardiofacial phenotypes. Approximately half of the cases of 22q deletion will have a palatal abnormality, most commonly submucous cleft palate or CPO. These children can also

BOX 18.1 Common syndromes associated with CPO and CL±P according to the London Dysmorphology Database[8]

Syndromes associated with CPO	Syndromes associated with CL±P
22q deletion syndromes	Van der Woude syndrome
Treacher Collins	Trisomy 21
Stickler syndrome	
Apert syndrome	
Trisomy 21	
Goldenhar	

BOX 18.2 Risk factors associated with CL/P[9]

Maternal age
Maternal smoking
Maternal obesity (BMI>30)*
Prepregnancy diabetes*
First trimester heavy alcohol consumption
Medications (anticonvulsants, folate antagonists, retinoic acid)*
White non-Hispanic race*
Sex*

**Also associated with CPO.* Data from Watkins et al. 2014.[9]

have non-cleft velopharyngeal dysfunction due to a deep post-nasal space secondary to a wide skull base angle. Any patient with a palatal defect, and any other manifestation of 22q11 (cardiac malformation, neurodevelopmental delay, immunodeficiency) should be screened, as prevalence can be as high as 40%.

Non-syndromic clefting is multifactorial and is influenced by both genetic and environmental factors. Non-syndromic clefting may have a known or unknown cause. Variants of the *IRF6* gene (interferon regulatory factor 6) can cause a Mendelian type inheritance, notably Van der Woude syndrome, but variants of *IRF6* have also been implicated in non-syndromic orofacial clefts.[7] Genome-wide association studies have provided insights into the genetic background of non-syndromic CL±P and contributing genes include aberrations in *TGF-b3*, *NAT 1TBX22*, *MSX1* and *FGFR*.[9–12]

Environmental factors which contribute to facial clefting are varied, and many are still under evaluation (**Box 18.2**). Alcohol consumption, particularly in the first trimester, is known to be a risk factor.[13, 14] Maternal smoking also increases the risk of orofacial cleft,[15–19] with a population-attributable risk of up to 20%.[15, 19] Anticonvulsant drugs[20–22] increase risk of cleft palate and positive associations with maternal corticosteroid use in pregnancy have also been reported in the literature, although this is less clear-cut.[23] Low B-complex vitamins, folic acid deficiency[24] and maternal obesity[25] also have some links to clefting, although further research is needed to define these risks more clearly.

If a primary relative has a facial cleft the chances of the child having a cleft, in the absence of a defined syndrome, is 3.5%.[26] This decreases with secondary and tertiary relatives. For parents who already have a child with an orofacial cleft, the risk of a subsequent child having a cleft is around 2–5%.

EMBRYOLOGY

An understanding of the embryology responsible for the development of the cranium and face is important as it allows us to understand why CL±P and CPO are different entities. The five main prominences responsible for development of the face are the frontonasal prominence, the paired right and left maxillary prominences and the right and left mandibular prominences. Incomplete or aberrant timing of fusion of the frontonasal and maxillary prominences results in cleft lip and/or palate (**Figure 18.4**). The frontonasal prominence is split into medial and lateral nasal prominences by development of a nasal pit on the ventrolateral aspect of the frontonasal prominence. Formation of the lip occurs between the fourth and sixth weeks of gestation when the bilateral maxillary prominences fuse with the medial nasal prominence to form the lip and alveolus. The secondary palate begins to form during the sixth week of development as the palatine shelves, which are outgrowths from the maxillary prominences, advance obliquely downward to lie horizontally over the tongue. The palatine shelves fuse with the previously formed primary palate and then from anterior to posterior the palatine shelves fuse in the midline, so that by week 12 the palate is intact. Failure of any of these processes can result in clefting (**Figure 18.5**).

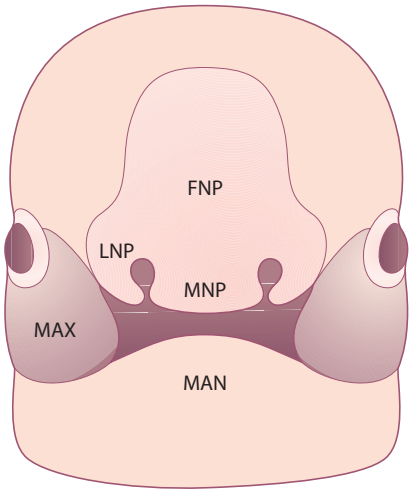

Figure 18.4 Development and fate of the facial processes. Representation of a 30–32-day-old human embryo showing the development of the facial processes. FNP, frontonasal process; MAX, maxillary process; MAN, mandibular process; MNP, medial nasal process; LNP, lateral nasal process.

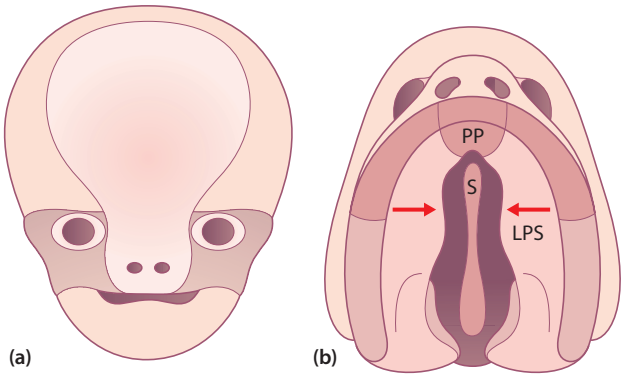

Figure 18.5 Representation of 7-week-old embryo showing the fate of the facial processes. (a) Frontal view; **(b)** ventral view of primary and secondary palate. LPS, lateral palatal shelf; PP, primary palate; S, nasal septum.

FUNCTIONAL ANATOMY

Anatomical anomalies of the lip, palate, septum, external nose and other midline structures can affect patients with a cleft lip and plate.

Lip

Integrity of the lip and oral sphincter is important for normal function of the mouth. A defect in the lip results in abnormal insertion of orbicularis oris and loss of continuity of the vermilion border, both of which have to be addressed in cleft lip repair in order to allow long-term return to form and function. The mucocutaneous area of the lip is well defined into three regions: there is the cutaneous skin of the upper lip and philtrum, an intermediate area of dry mucosa known as the vermilion and an internal area of moist mucosa.[27] The orbicularis oris normally forms a full sling under the mucosal covering, however aberrant muscle due to the cleft results in insertion of the orbicularis oris into the dermis and nasal ala on the cleft side and insertion into the columella on the non-cleft side (Figure 18.6).

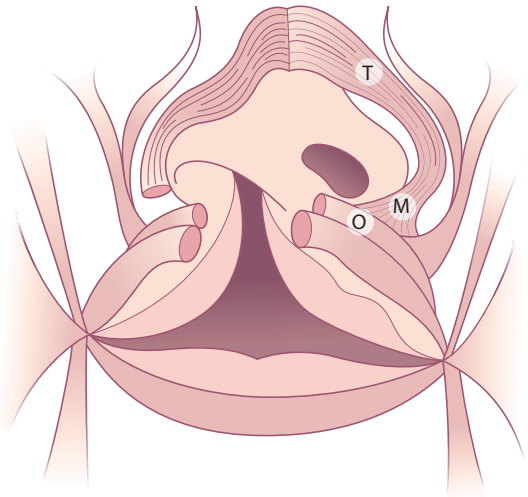

Figure 18.6 Nasolabial muscle ring in unilateral cleft lip. M, myrtiform head of nasalis muscle; O, oblique head of orbicularis oris; T, transverse head of nasalis muscle.

Nose

Abnormality of insertion of the orbicularis oris contributes to the nasal deformity seen as part of cleft lip. By inserting into the nasal alar base there is outward splaying of the lower lateral cartilage, which results in the alar base on the cleft side sitting more lateral and inferior than it should. This results in a differing shape and position of the lower lateral cartilage on the cleft side, with shorter medial crus and longer lateral crus, and a classically flattened and wider dome on the cleft side. The columella is shortened and the anterior cartilaginous septum deviated to the non-cleft side, due to the unopposed pull of the orbicularis oris on the columella. This allows bowing of the septum onto the cleft side more posteriorly and, along with the reduction in the nasal valve area due to lower lateral cartilage abnormalities, the overall nasal airway is restricted. Nasal airflow resistance is known to be higher in patients with CL±P by around 20–30%.[28, 29]

Palate

Clefts of the palate are associated with bony and soft-tissue abnormalities. Adequate closure of the velopharyngeal port for speech and swallowing is the aim of palate repair. The primary velar muscles are the levator veli palatini, palatopharyngeus and palatoglossus (Figure 18.7). The levator

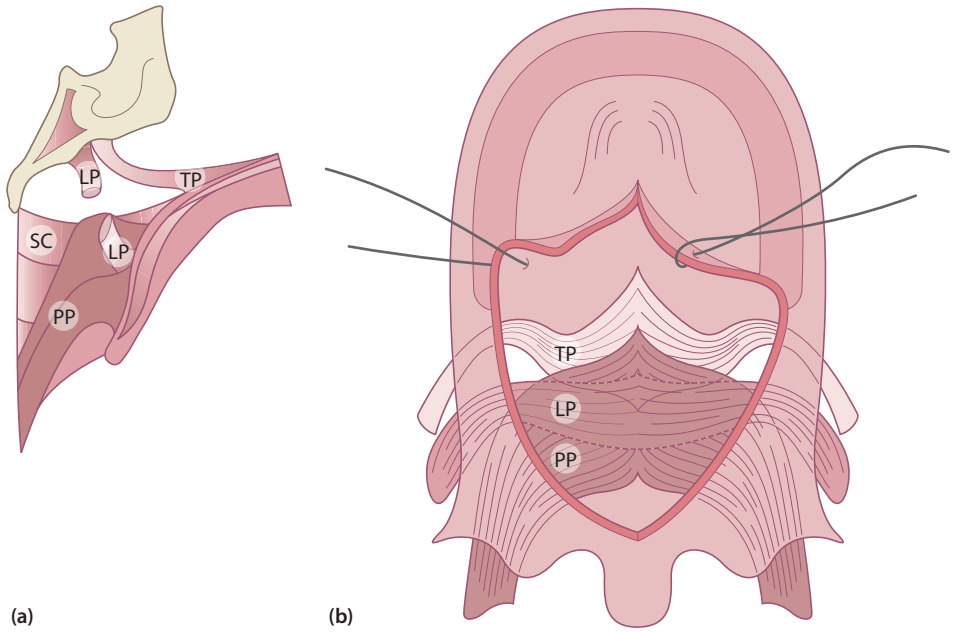

Figure 18.7 Velum muscles. **(a)** Sagittal view from midline; **(b)** inferior view. LP, levator palatini; PP, palatopharyngeus; SP, superior constrictor; TP, tensor palatine.

veli palatini muscle is the primary elevator of the palate. It originates from the medial part of the Eustachian tube and from the petrous temporal bone and runs anteriormedially to enter the middle third of the velum between the two heads of palatopharyngeus to join with its partner from the opposite side, and form the levator sling. In patients with a cleft palate the levator veli palatini no longer has this transverse orientation, but instead the muscle is longitudinally orientated and inserts into the bony cleft margin and posterior palatine bones. The palatoglossus and palatopharyngeus arise from the back of the palatal aponeurosis and maxillary tuberosity. The palatoglossus is a thin sheet of muscle that extends to form the anterior tonsillar pillar. The palatopharyngeus is a more substantial muscle that is split into two heads by the insertion of the levator veli palatini and runs down to form the posterior tonsillar pillar and inserts into the thyroid cartilage and pharyngeal aponeurosis. The palatopharyngeus and palatoglossus act as depressors and, along with the levator veli palatini, these muscles act to lengthen the velum. The final muscle to consider is the tensor veli palatini, whose primary function is opening of the Eustachian tube. Its fibres originate from the sphenoid spine, scaphoid fossa and lateral lamina of the Eustachian tube cartilage,[30] and form a tendon which winds round the pterygoid hamulus and spreads into a fibrous aponeurosis in the anterior third of the soft palate.

ENT ISSUES

Airway

All children are obligate nasal breathers for the first few months of life. This is due to the high position of the infantile larynx that gradually descends. In the neonate the anterior epiglottis can often be easily seen in the oral cavity behind the soft palate. This superior position of the larynx allows the infant to suckle.

There are many congenital anomalies associated with cleft lip and palate, and one of the most commonly seen in ENT is Pierre Robin sequence (PRS). In PRS micrognathia and glossoptopsis may result in upper airway obstruction (Figure 18.8).

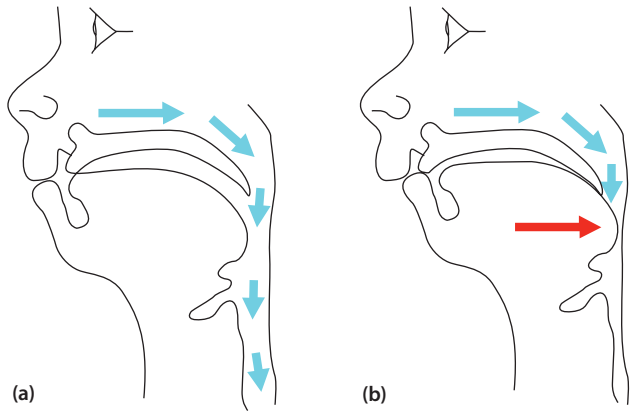

Figure 18.8 Diagrams showing **(a)** normal airway in an infant; **(b)** where retro-position of the mandible has resulted in the tongue blocking the airway.

NEONATAL PERIOD

Upper airway obstruction can happen immediately following delivery or can develop progressively over weeks or months of life. The Royal College of Paediatrics and Child Health (RCPCH) respiratory subgroup recommends that all children with craniofacial disorders including PRS undergo overnight oximetry, preferably in combination with measuring CO_2, within the first 4 weeks of life.[31] Children with PRS may have worsening obstruction between 4 and 8 weeks of age, and reassessment may be required during that time. Otherwise, further studies should be performed at 3–6-monthly intervals during the first year of life, and thereafter according to clinical symptoms. Often children with PRS have their palate surgery delayed until around 18 months of age to allow their airway obstruction to improve.

Treatment options for airway obstruction in these children, depends on the severity of symptoms. The options can be divided into two main subgroups, non-surgical and surgical, as listed in Box 18.3.

POST-OPERATIVE PERIOD

Any airway issues tend to happen within 24–48 hours of surgery. They are usually associated with palatal surgery or pharyngoplasties but on occasion can occur following lip repair or anterior rhinoplasty. Children are often placed in an HDU following primary lip and palatal surgery to allow careful monitoring in the early post-operative period. This allows close monitoring of the child and early intervention if the child develops any signs of respiratory distress.

LONG-TERM SLEEP-DISORDERED BREATHING

All cleft children have the same risk as other children with regard to sleep-disordered breathing and obstructive sleep apnoea (e.g. secondary to adenotonsillar hyperplasia). They may, however, be at higher risk due to their anatomical abnormalities being corrected and narrowing the nasopharynx.

A pharyngoplasty is performed to reduce the nasopharyngeal airway to help prevent nasal escape during speech. This has the potential detrimental effect of increasing the likelihood of apnoeic episodes. Careful pre-operative discussion and patient evaluation within the multidisciplinary team setting should be undertaken to discuss the risks versus benefits of such a procedure. The complications of chronic obstructive sleep apnoea (OSA) include hypoxemia, hypercarbinemia, neuropsychiatric problems and decreased cognitive function. In severe cases the chronic obstruction can result in pulmonary hypertension and cardiac failure. There is also a link between OSA in childhood and adult hypertension.

BOX 18.3 Treatment options for airway obstruction

Non-surgical	Surgical
Nasopharyngeal airway	Tongue–lip adhesion
CPAP	Tracheostomy
	Mandibular distraction

Hearing loss

As in all children, hearing loss in CL±P patients can be conductive, sensorineural or mixed.

Otitis media with effusion (OME) is almost ubiquitous with CL±P. Approximately 97% of cleft children are thought to have had an episode of OME by the age of 2,[32] with the incidence reducing with increasing age.[33] The aetiology behind the increased incidence of OME is thought to be due to Eustachian tube dysfunction secondary to the malposition of the tensor veli palatini muscle, as mentioned previously.

In the recent past this has led to the 'routine' insertion of ventilation tubes at an early age, usually at the time of palatal repair. However, as more data have been collected about the incidence and prevalence of the otological sequelae of OME, a much more selective approach has been introduced. Recent systematic reviews[32, 34] have shown there was insufficient evidence to determine if early ventilation tube placement had any benefit on either hearing or speech development, and that further studies in this area are warranted. Currently in the UK the Cleft Collective research group is undertaking the MOMENT trial (The Management of Otitis Media with Effusion in Children with Cleft Palate) to try to acquire more guidance on the optimum management of OME in CL±P patients.[35] As we know, not all episodes of OME will result in a hearing loss or damage to the middle ear. Current recommendations in the UK are found in NICE60.[36] Essentially, a persistent CHL associated with OME in excess of 25–30 dBHL or OME affecting a child's developmental, social or educational status should be offered treatment. The treatment options should include ventilation tube insertion or provision of hearing aids. Primary ventilation tube insertion is only recommended after careful ENT/audiology assessment in children with a cleft palate.

In the UK cleft care is closely audited and minimal standards of care have been agreed. Routine hearing testing is taken at 6 months, and 1, 2, 3, 4, 5, 10 and 15 years of age. Ensuring adequate hearing thresholds allows normal verbal communication to develop. This is important in the CL±P population as learned 'cleft type' speech cannot be corrected at an older age.

Long-term middle ear disease has also been reported to be higher in the cleft population due to persistence of Eustachian tube dysfunction following palatoplasty. Retraction pockets and subsequent development of cholesteatoma has been found to be higher in the cleft population[37–41] and ongoing otologic assessment in these patients is important.

MANAGEMENT

Care of a child with a cleft lip or palate is a complex, highly specialized and lifelong undertaking. Deficiencies of speech, facial growth, cosmetic appearance, hearing and dental problems require that this care is addressed in a multidisciplinary setting in order to allow adequate attention to all aspects of care and subsequently improve outcomes.[42] Input is needed from a cleft surgeon, otolaryngologist, paediatric dentist, specialist nurse, speech therapist, psychologist, audiologist, orthodontist, geneticist and paediatrician.

During the management of children with a cleft lip and palate, areas to be addressed are:

- speech
- hearing
- appearance
- dental growth and hygiene
- psychosocial health.

Diagnosis

Prenatal diagnosis of cleft lip and palate has allowed around 75% of children to be picked up as early as 13–16 weeks' gestation by ultrasonography.[43] Isolated cleft palate cannot be as easily detected prenatally, but the role of prenatal foetal MRI in further diagnosing palatal clefting may become more frequent in the future.[43] Following diagnosis, the parents should be referred antenatally to the cleft team so that appropriate support can be provided. Advice can be given on feeding, expectations of treatment protocols and details of parental support groups. After birth the specialist cleft nurse will make contact within the first 24 hours to give support and help establish feeding. Children with a cleft lip and palate may be able to breastfeed with help, or the use of specialized bottles (Haberman) may be more helpful, as the ability to create a vacuum to suckle milk is reduced.

Surgical management

Surgical management of cleft lip and plate is complex and tailored to the individual deformity present. There are numerous techniques across the world to deal with orofacial clefts and the detailed surgical steps of each procedure are beyond the scope of this chapter. The principles of surgical management are covered. Table 18.2 summarizes the timings of surgical management options.

TABLE 18.2 Surgical management from birth to adulthood

Age	Procedure
3–6 months	Primary lip ± nose repair ± hard palate
9–12 months	Palate repair ± ventilation tubes
4–5 years	Secondary speech surgery (if required)
8–10 years	Alveolar bone graft (if required)
15–18 years	Secondary rhinoplasty
16 years +	Orthognathic surgery (if required)

PRESURGICAL ORTHOPAEDICS AND NASOALVEOLAR MOULDING

Nasoalveolar moulding (NAM) is a form of presurgical infant orthopaedics designed to reduce the severity of the cleft deformity and move the nasal alar cartilages into a more favourable position. Attempts to reduce the severity of the cleft are not a new phenomenon and various devices have been used in the recent past. NAM involves using an oral plate, which is individually moulded with nasal stents attached, to try to achieve these aims. The device is fitted as soon after birth as feasible and is worn fulltime. It is regularly adjusted to alter the shape and length of the nasal cartilages and columella. The research on whether NAM successfully achieves these outcomes remains inconclusive,[44] although some studies show positive results,[45–47] particularly in improving nasal symmetry in the unilateral cleft lip and palate patients.[48] Randomized controlled trials at a national level are lacking and, although NAM is gaining support particularly in North America, it is yet to be incorporated into routine UK practice.

LIP REPAIR

Repair of the cleft lip aims to address both functional and cosmetic problems. In the UK the lip is generally repaired when the child is 3–6 months of age, along with the hard palate and primary nasal surgery, dependent on requirements. Neonatal lip repair is performed in some centres, although no firm evidence of aesthetic or functional benefit yet exists.[49, 50] The aims in both unilateral and bilateral cleft lip repair are similar: to achieve primary muscle continuity and reconstruct the lip elements to give a symmetrical-appearing Cupid's bow with the minimum of scarring. The importance of reconstructed musculature in achieving optimal results is well reported and should be adequately addressed at the time of lip repair.[51–56]

Bilateral cleft lip is a more severe deformity than unilateral and achieving muscle continuity across the projected premaxilla can be a challenge. The use of lip adhesion (taping of the lateral lip segments to the premaxillary segment) and single-sided staged surgery have been advocated in an attempt to facilitate lip repair, but neither of these approaches is supported in the literature. There are multiple approaches to reconstructing the skin of the lip, the Millard repair and its modifications, and the Fisher repair being the two most commonly practised in the UK.

PALATE REPAIR

Hard palate

Timing of palatal closure is variable between centres, and there is a trade-off between early palatal closure to help speech, and delaying hard palate closure to improve facial growth. In the UK it is common practice to close the hard palate with a vomerine flap at the time of lip repair in a complete cleft lip and palate, or close with the soft palate repair in an isolated cleft palate patient.

Soft palate

The aim of palatoplasty is to reorientate the palatal muscles in order to achieve lengthening and improve movement of the palate in order to create adequate velopharyngeal closure. There are various surgical options available to the cleft surgeon, each of whom will have their preference. The intravelarveloplasty, popularized by Sommerlad, involves radical dissection of the velar muscles and reorientation to a transverse position to recreate the anatomical levator sling.[57] The nasal and oral mucosa are dissected from the muscles and repaired over the newly formed sling to close the cleft (**Figure 18.9**).

The Furlow palatoplasty uses a double opposing Z-plasty technique to lengthen and reorientate the muscles. This method results in posterior repositioning of the velar muscles, albeit with a degree of asymmetry, and results in some degree of palatal lengthening. Both techniques have been shown to have good speech outcomes[58, 59] and there has been no difference found in audiological outcomes between the techniques.[60]

NASAL SURGERY

Nasal surgery in a patient with a cleft lip and palate aims to improve aesthetics and nasal airflow, in a timely fashion but with the minimum of disruption to facial growth. Cleft nose deformity is characterized by an asymmetric nasal tip, deviated septum and asymmetry of the nasal bones. Timing of nasal surgery is somewhat controversial. Given the complexity of cleft nasal deformities, definitive rhinoplasty is often reserved until adolescence and completed facial skeletal growth, however evidence has shown that stable long-term results with limited growth disturbance can be achieved with primary rhinoplasty.[61–64]

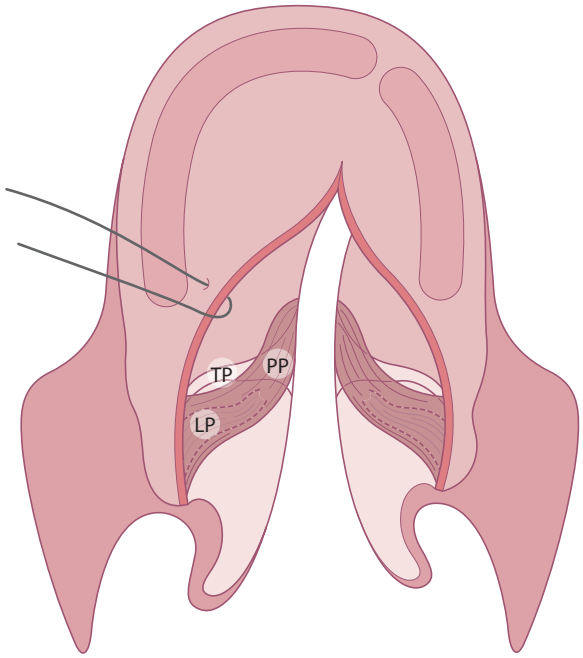

Figure 18.9 Cleft palate muscles. LP, levator palatini; PP, palatopharyngeus; TP, tensor palatini.

ALVEOLAR BONE GRAFTING

Some children will require alveolar bone grafting as a secondary procedure to stabilize the alveolar arch and allow eruption of the lateral incisor and canine into an optimal position. There is good evidence that secondary alveolar bone grafting produces consistently good results.[65, 66] Timing of the bone graft is usually determined by the development of the canine tooth, although earlier bone grafting may be indicated to support the eruption of the lateral incisor. There is no evidence that secondary bone grafting has a detrimental effect on facial growth when performed between 9 and 11 years of age. This is in contrast with primary bone grafting carried out before 2–3 years of age where evidence from retrospective case series suggests that these early bone grafts were associated with significant growth impairment.[67, 68]

SPEECH AND VELOPHARYNGEAL INSUFFICIENCY

Velopharyngeal insufficiency (VPI) can occur in children with a repaired cleft palate, those with a submucous cleft and in children without any obvious palatal abnormalities. It can also occur after adenoidectomy, with a reported clinically significant incidence of between 1 in 1500 and 1 in 3000. Stigmata of a submucous cleft are bifid uvula, zona pellucida and hard palate notch, all of which should be examined for at the time of adenoidectomy. VPI occurring after adenoidectomy will spontaneously resolve in about 50% of cases.[69] In order to achieve intelligible speech, the palate must be able to seal against the posterior pharyngeal wall and close off the nasopharynx. If this is impaired, nasal emissions and hypernasal speech can ensue. Around 20% of cleft palate children have persistent speech disorder following surgery, falling into the worst category of intelligibility.[70]

Treatment for velopharyngeal insufficiency includes speech therapy and palatal or pharyngeal surgery, dependent on the degree of VPI, underlying aetiology and age of the patient. In children with a submucous cleft, management is indicated only if symptoms of VPI occur. Assessment of VPI is best performed in a multidisciplinary environment. Examination of the mouth, concentrating on the integrity and movement of the soft palate and the tonsils, which rarely if hypertrophied may be interfering with palatal closure. Nasal examination and assessment of nasal patency should be performed. Standardized tests to assess articulation and intelligibility are performed by speech and language therapy.[70]

Flexible nasoendoscopy is fast becoming the investigation of choice to assess velopharyngeal port closure objectively. Speech videofluoroscopy is also widely used by many teams and can be an alternative if nasoendoscopy is not tolerated. Both investigations provide information and so far research has not shown superiority of one over the other,[71] although nasoendoscopy may provide a closer correlation with VPI severity.[72]

Management decisions come down to underlying symptoms and the size and location of the velopharyngeal gap. Palatoplasty may be indicated to treat VPI, either as a re-repair where there is evidence of anterior insertion of the levator muscles, or in the case of a submucous cleft. It is mainly used where the velopharyngeal gap is small[73, 74] and has been shown to have a lower morbidity than a pharyngoplasty.[75] Pharyngoplasty involves altering the shape of the velopharyngeal port in order to allow closure on speech. This can be done either by using flaps from the midline of the pharyngeal wall or by employing medial transposition of flaps from the lateral pharyngeal wall. Both types of pharyngoplasty have been shown to improve speech outcomes, with the possibility of achieving normal resonance in up to 85% of cases. The main downside to pharyngoplasty is the associated increased risk of sleep apnoea, and this must be discussed with the patient and their family pre-operatively.

KEY POINTS

- Clefts of the lip and palate are common congenital birth anomalies.
- Aetiology is multifactorial. Known associations are with maternal smoking and alcohol and antenatal anticonvulsants.
- Prenatal screening for cleft lip and palate is now routinely available in many centres.
- Management of patients with cleft lip and palate requires a multidisciplinary approach to ensure the best outcomes.
- Otitis media with effusion is a significant problem in cleft palate children and further research is required to identify best practice for management.

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CHAPTER 19

CRANIOFACIAL SURGERY

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: craniofacial, craniosynostosis, OAVS, Treacher Collins, Apert, Crouzon, Pfeiffer, encephalocele, distraction osteogenesis, facial cleft, scapocephaly, trigonocephaly, brachycephaly and plagliocephaly.

INTRODUCTION

Craniofacial surgery is the medical specialty that diagnoses and manages complex congenital and acquired conditions of the craniofacial skeleton and associated structures. Patients with such conditions vary in their development and phenotypic presentation. Traditionally, these were thought of as congenital conditions but the term can be all-encompassing.

Due to the complexity of patients with craniofacial conditions, their treatment is required to take place in a multidisciplinary unit. Table 19.1 shows the specialties that comprise the multidisciplinary team (MDT) with their roles.

Treatment often lasts from the perinatal period, well into adolescence and often into early adulthood.

Owing to the complexity and heterogeneity of craniofacial anomalies there is no universal classification system. Many classification systems have been proposed, based on embryology, aetiology, anatomical location, morphology and genetics. In England, the National Commissioning Group recognizes six categories of patient:[1]

- craniofacial clefts
- craniofacial dysostosis
- craniosynostosis
- encephalocoele
- overgrowth, undergrowth or dysraphia associated with unilateral or bilateral orbital dystopia or displacement
- any other complex anomaly where referring specialists feel that the expertise present within the service would substantially benefit the treatment of the condition.

There are multiple other conditions of the craniofacial region that, although not specified in this classification, are often treated in these units due to the expertise of the clinicians involved. Currently in England and Wales, there are four units commissioned to treat the above conditions:

- Alder Hey Children's Hospital, Liverpool
- Birmingham Children's Hospital
- Great Ormond Street Hospital, London
- Oxford University Hospital.

The aim of this chapter is to describe the more commonly encountered groups of craniofacial anomalies, to outline the principles of their management and to review the role of the ENT surgeon in managing these patients. The genetic contribution to these conditions will also be discussed.

TABLE 19.1 The craniofacial team

Discipline	Role
Maxillofacial surgery	Surgical correction of deformity
Plastic surgery	Surgical correction of deformity
Neurosurgery	ICP, hydrocephalus, associated abnormalities, combined surgical treatment of the condition
Ophthalmology	ICP, acuity and motility, corneal protection
ENT (+ audiology)	Airway + nasal problems, hearing and middle ear disease
Anaesthetist	Experience of paediatric craniofacial and neurosurgical anaesthesia Access to paediatric intensive care unit (PICU)
Genetics	Diagnosis, associated conditions, risk of future siblings having the condition, risk of patient passing on the condition to his/her children
Speech and language therapist	Speech and language, feeding, general developmental milestones
Psychologist	Parental anxiety, preparation for operations, intervention for older patients, coping strategies, cognitive assessment
Paediatrician	General development, associated abnormalities
Orthodontist	Craniofacial growth and development, dental condition and occlusion
Specialist nurses and coordinators	Coordinating day-to-day activities/ advice/wound management

CRANIOSYNOSTOSIS

Craniosynostosis is the premature fusion of one or more sutures of the skull. This can occur as **primary** or **secondary synostosis**. The differentiation is paramount as treatment options differ greatly. In order to understand the pathophysiology of craniosynostosis, normal skull growth must be considered.

Normal skull growth

The stimulus for growth of the cranium comes from the expanding brain, which grows rapidly in the first 2 years of life, doubling in weight in the first year and achieving 90% of its adult size by the age of 2 years. This rapid brain growth has to be accommodated by a concomitant expansion in volume of the skull. The cranial vault consists of the frontal, parietal, temporal and occipital bones, which are separated from each other by the cranial sutures (metopic, sagittal, coronal and lambdoid). These sutures allow gradual displacement of the individual bones, allowing the brain to expand. In order to avoid large gaps developing between the bones as the expansion proceeds, new bone is deposited at the free margins of the bones adjacent to the sutures. Bone resorption and deposition also take place on the inner and outer surfaces of the calvarial bones to produce changes in their curvature and thickness.

The patent cranial sutures therefore allow for growth to take place in response to the stimulus of the growing brain and, unlike the epiphyseal plates of the long bones, cranial bones do not have intrinsic growth potential. The sutures only remain patent while brain growth is taking place. If brain growth ceases, cranial growth ceases, and the cranial sutures will be replaced by bone, resulting in fusion – a normal phenomenon once growth is complete.

Classification

Premature fusion of calvarial sutures has a variety of underlying causes, broadly divided into primary and secondary craniosynostosis.[2]

Secondary craniosynostosis is uncommon, but may be seen in microcephaly, where there is a lack of underlying brain growth, in some haematologic (polycythaemia, thalassaemia) and metabolic abnormalities (rickets, hyperthyroidism), and may be drug-induced (retinoic acid).

Primary craniosynostosis is much more common than secondary craniosynostosis. It can be classified on the basis of the number of sutures involved (single-suture, multiple or total), the site of the involved suture(s) (metopic, coronal, sagittal, lambdoid) and whether it is an isolated condition (non-syndromic) or associated with other malformations (syndromic). Primary craniosynostosis constitutes a significant workload in craniofacial units.

Incidence

Primary non-syndromic craniosynostosis occurs in approximately 1:2000 live births. Of the non-syndromic craniosynostoses, sagittal synostosis is the most common, accounting for approximately 60% of cases. In cases of non-syndromic craniosynostosis there is a male predominance with male to female ratios of 4:1 in sagittal synostosis and 3:1 in metopic synostosis. Of the syndromic craniosynostoses, Crouzon syndrome has the highest incidence, with 1:25 000 live births[3] and Apert syndrome in 1:60 000 live births.[4]

Aetiology

Craniosynostosis is aetiologically heterogeneous.[4] Both non-syndromic and syndromic craniosynostoses result from an interaction between genetic factors, molecular and cellular events, mechanical and deformational forces and secondary effects of each of these on normal growth and development. Premature fusion of the sutures may take place alone or, in syndromic craniosynostosis, with other anomalies. Most cases of isolated craniosynostosis are sporadic. However, familial cases do occur and a positive family history can be found in 14.4% of coronal, 6% of sagittal and 5.6% of metopic synostosis cases, but very rarely in lambdoid synostosis.[5–9] For isolated, single-suture synostosis with unaffected parents, the recurrence risks range from 1% in sagittal synostosis to 5% in coronal and metopic synostosis.[10]

Chromosomal abnormalities may also cause craniosynostosis, particularly in patients with other anomalies or problems with growth or development. Teratogens may also be causative, as in the case of sodium valproate and trigonocephaly. The syndromic craniosynostoses are usually genetically determined, often occurring as new mutations. There is an increasing recognition that some of the so-called isolated non-syndromic synostoses also have a genetic basis.

Genetics of craniofacial anomalies

The vast array of genetic conditions causing craniofacial anomalies precludes an exhaustive discussion of their genetics in this text. However, it is appropriate to discuss the more common conditions and encourage a low threshold for the involvement of the clinical genetics team in the management of patients with craniofacial anomalies. Clinical geneticists can contribute to both diagnosis and counselling of affected individuals and also their families. Interested readers are encouraged to consult the texts of Gorlin et al.[11] and Cohen and MacLean[4] for more extensive details on craniofacial anomaly syndromes.

When considering the aetiology of craniofacial anomalies, it is helpful to consider their aetiology in terms of **malformations** (e.g. genetic syndromes, teratogens), **deformations** (e.g. positional plagiocephaly) and **disruptions** (e.g. amniotic bands). Some craniofacial anomalies are multifactorial.

Genetic testing is not indicated in patients with isolated sagittal or metopic synostosis in whom there are no associated abnormalities or concerns about growth or development, and no significant family history. However, coronal synostosis, even when isolated, warrants analysis of at least *FGFR3* for the Pro250Arg mutation (see 'Muenke syndrome', or *FGFR3*-associated coronal synostosis syndrome below) and possibly analysis of the *TWIST* gene (see 'Saethre–Chotzen syndrome' below).

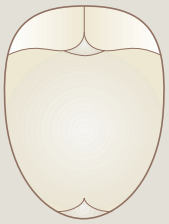
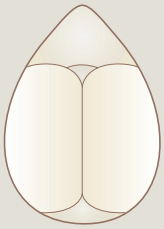
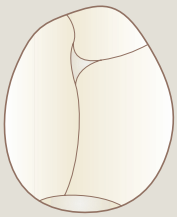
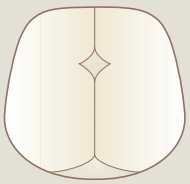
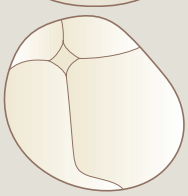
Genetic testing by DNA analysis of specific genes is available only for syndromes where the causative gene has been identified. This facilitates diagnosis and also counselling of family members, particularly when a parent may be a gene carrier with a very mild phenotype. Chromosomal analysis should be considered in any patient with complex or multiple abnormalities, or in whom there are concerns regarding a child's growth or development. Informed consent should be obtained prior to any genetic testing, especially as abnormal results may have implications for other family members as well as the child. Failure to identify a genetic abnormality in a syndromic patient does not, however, rule out a genetic cause for their condition, and involvement of a clinical geneticist is essential.

Prenatal diagnosis by genetic analysis of chorionic villus sample or amniotic fluid may be available for conditions in which the causative genetic abnormality is known. Prenatal ultrasound scanning later in pregnancy may reveal abnormal craniofacial contour or associated skeletal or systemic abnormalities in syndromic conditions; however, the premature sutural fusion of isolated craniosynostosis is much more difficult to detect.

Pathogenesis and consequences

Premature suture fusion results in inhibition of skull growth in a direction perpendicular to the affected suture. Despite this localized failure of skull growth, the brain continues to grow, and expands in different directions, where expansion can be accommodated by normal (patent) sutures, producing compensatory changes at a distance from the abnormal suture and usually parallel to it.[12] In the latter half of the last century, Moss[13] postulated that the cranial base was the site of abnormal physical stresses, and that these could be transmitted to the dura of the cranial vault, resulting in suture fusion. Whatever the underlying mechanism, the restriction of growth perpendicular to the fused suture, and the compensatory changes elsewhere in the cranium, may result in a reduction in cranial volume (and hence raised intracranial pressure (ICP)) and a change in shape (resulting in characteristic changes dependent on the suture or sutures involved) (**Table 19.2**).

TABLE 19.2 The craniosynostoses. Affected sutures and resultant head shapes. The anterior aspect of the skull (the forehead) is towards the top of the table

Shape of skull	Suture affected	Name
	Saggital	Scaphocephaly
	Metopic	Trigonocephaly
	Unilateral coronal	Frontal plagiocephaly
	Bilateral coronal	Brachycephaly
	Unilateral lambdoid	True posterior synostotic plagiocephaly

Clinical assessment and imaging

The history may be of a baby with an abnormal head shape, present at birth, gradually becoming worse. Examination reveals the characteristic head shape with ridging of the affected suture.

Plain films may allow assessment of sutural patency and the overall morphology of the skull. All sutures are usually easily visible in the normal growing skull, with the exception of the metopic suture, which normally fuses early. A prematurely fused suture may be sclerotic or may not be visible at all. The abnormal shape of the head will be apparent, and skull base abnormalities not apparent on clinical examination may be seen (e.g. the 'harlequin eye' appearance of the sphenoid ridge in coronal synostosis). Computed tomography (CT), especially when reconstituted via a 3D format, provides even more detail of the morphology of the skull (**Figure 19.1**). In addition, a CT scan allows evaluation of the intracranial contents although magnetic resonance imaging (MRI) is a more useful modality for assessing intracranial anatomy and pathology.

Raised intracranial pressure

It is logical to think of raised ICP developing as a result of failure of cranial expansion in the presence of continuing pressure from the growing brain. However, the relationship is complex, and other factors have been implicated. Raised ICP is not directly related to a decrease in intracranial volume,[14] and venous hypertension has been identified as a result of a significantly narrower jugular foramen (6.5 mm versus 11.5 mm) in complex and syndromic patients with raised ICP.[15]

The reported incidence of raised ICP in patients with craniosynostosis shows wide variation, and there is variability in the threshold for diagnosis in reported studies, with values of 15 mmHg or 20 mmHg chosen.[16] Reported incidence in mixed cohorts of non-syndromic and syndromic patients vary from 17% to 92%.[14, 17–19] Studies that have compared the incidence of raised ICP in non-syndromic and syndromic patients have shown a higher incidence in syndromic patients (approximately 50%) compared with non-syndromic patients (approximately 25%).[20, 21]

Diagnosis may be difficult because the classic clinical features of raised ICP are often absent. Thus, the child's development, in particular the acquisition of normal developmental milestones, vision, reading and language comprehension, motor skills, and general behaviour are important, and may require detailed specialist investigation, including ophthalmological assessment. Changes in visual-evoked potentials have been shown to be early indicators of raised ICP.[22, 23]

Plain skull films may show the classic 'copper-beaten' appearance of chronically raised ICP (**Figures 19.2**) but the absence of changes does not exclude raised ICP.[24] CT or MRI scanning may be helpful but, in cases where clinical assessment is equivocal, invasive ICP monitoring may be indicated, using either a traditional ICP monitor or, more recently, parenchymal fibre-optic transducers, which have been shown to be reliable as recorders of ICP and are associated with a low rate of complications.[20]

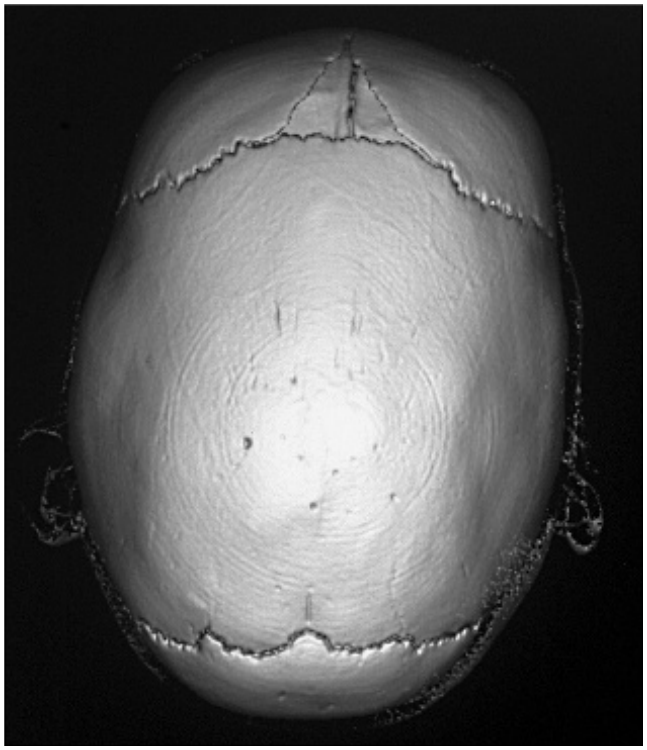


Figure 19.1 3D CT scan of patient with scaphocephaly. Note the absence of sagittal suture.

Hydrocephalus

Hydrocephalus is characterized by enlargement of the cerebral ventricles due to obstructed outflow of cerebrospinal fluid (CSF) somewhere along its path from the lateral ventricles, through the interventricular foramina, third ventricle, cerebral aqueduct, fourth ventricle and subarachnoid space to the sites of absorption. Hydrocephalus can occur in up to 20% of patients with craniosynostosis. It may be associated with chronic venous hypertension and hindbrain herniation, particularly in multisutural synostosis.

Differential diagnosis

Not all abnormal head shapes are due to craniosynostosis, and accurate diagnosis is essential since the management of non-synostotic head shape abnormalities is non-surgical. The bones of the skull in early life are relatively soft and deformable, rendering the head susceptible to alteration in shape for a variety of reasons. Non-synostotic causes of abnormal head shape include intrauterine and birth canal moulding, assisted delivery (e.g. Ventouse), intracranial abnormalities and postnatal deformational forces on the growing skull due to external pressure on the head or to uneven muscle tension in the muscles attached to the skull base.

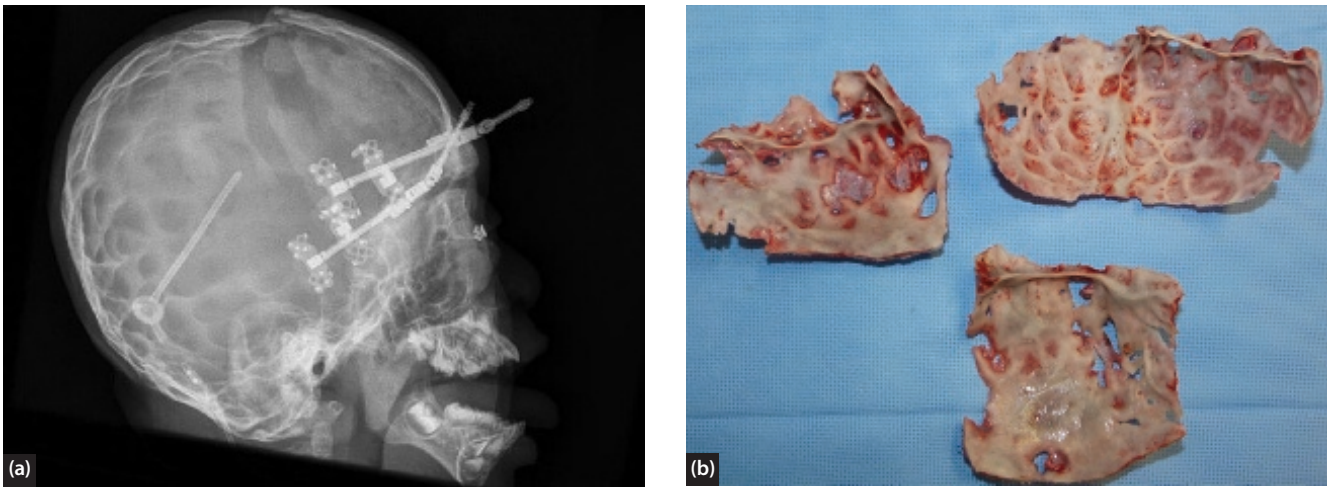


Figure 19.2 **(a)** Skull CT of a patient with raised ICP showing 'copper beating', treated with a shunt and undergoing distraction osteogenesis of the forehead. **(b)** Copper beaten bone shows indentation of underlying brain tissue.

Intrauterine, birth canal and assisted delivery moulding will be present at birth but improve fairly quickly. Intracranial abnormalities will present at birth but persist. Postnatal deformational changes are not present at birth, develop gradually and, if the cause is removed, will improve. This is in contrast to craniosynostosis, which is usually apparent at birth and progresses with growth. Diagnosis is usually possible based on the history and examination alone, but confirmation of the patency of sutures can be confirmed by plain radiographs or CT scan if needed.

The most common presentation of non-synostotic abnormalities of head shape is **occipital plagiocephaly**. This is usually due to deformational or positional plagiocephaly. The incidence of deformational plagiocephaly has significantly increased since 1992 when the National Institute of Child Health and Human Development at the US National Institutes of Health advocated and encouraged infants to sleep on their backs/supine to reduce the risk of sudden infant death syndrome (SIDS). This, combined with prematurity or potentially a delay in the ability to hold one's own head, may predispose a child to either symmetrical or asymmetrical flattening of the occiput. Other causes include abnormal head posture due to torticollis, vertebral abnormalities or ocular squint.

Clinically, there is flattening at the back of the head, often with anterior translocation of the ear on the affected side and an element of frontal bossing. Unfortunately, this condition tends to develop quickly. The natural history of this is that it tends to self-correct but may take a number of years. There is the propensity to have a mild element of asymmetry but with the combination of self-correction and increase in hair length and thickness, it is seldom noticeable. There is no surgical intervention warranted for correction of this. Orthotic firms have advocated the use of corrective helmets but the evidence to support this is currently lacking and thus the costs must be borne by the family.

General principles of surgical management of craniosynostosis

The indications for surgery are prevention and/or treatment of raised ICP, correction of significant cosmetic deformity and prevention of future skull shape deformity (or skull normalization) by allowing normal growth to take place. Essentially this allows the normalization of skull deformities and treats the raised ICP which results from a craniocerebral misproportionation.

The general principles of surgery for the craniosynostoses are to remove the cause by excising the affected suture, correct the existing deformity by reshaping the affected area of the cranium and moving it into the position it would have been in had it grown normally. This leaves an expanded intracranial volume, with a space between the dura and the repositioned bone, into which the brain can expand, thus relieving raised ICP if present. It also corrects the aesthetic deformity. Leaving a gap in the region of the excised suture, which will mimic a normal suture, should allow future growth to take place by movement of the bone in response to continued brain growth.

Timing of surgery is important. Early surgery has the advantage that ICP is normalized without delay, and the deformity may be less severe since it has had less time to develop. However, early surgery may be followed by reossification at the site of the excised suture (restenosis), with a re-emergence of the condition requiring further surgery. The timing of surgery is therefore a balance between operating too early with the risk of restenosis and operating too late when there may be prolonged raised ICP, the deformity is greater and its correction may require more extensive surgery because of lack of future brain growth and, thus, capacity for skull remodelling in response to brain growth. Another factor which must be considered is that surgery results in a significant risk of moderate, and sometimes severe, blood loss. Lastly, consideration should be given to minimizing the potential risks of undertaking a general anaesthetic on the developing brain.[25]

Major craniofacial surgery carries significant risks and complications, and a dedicated team familiar with all aspects of the management of these patients is a prerequisite for surgery to be performed. This will include a dedicated ward and theatre with appropriately trained staff, a paediatric anaesthetist and HDU/PICU facilities.

SINGLE-SUTURE NON-SYNDROMIC CRANIOSYNOSTOSIS

Most commonly, patients present with fusion (or partial fusion) of only one suture. Currently, apart from coronal synostosis, there is little evidence to state that single-suture fusion is commonly due to a Mendelian genetic change.

Sagittal synostosis (scaphocephaly)

With an incidence of approximately 1:4200–8500,[26, 27] sagittal synostosis is the most common form of craniosynostosis. Approximately 6% of cases of sagittal synostosis are familial, mostly transmitted as an autosomal dominant condition.[8] The remaining cases are sporadic and at least a proportion are likely to have multifactorial aetiology, including genetic and environmental factors. The recurrence risk to a couple with a child affected by sagittal synostosis in the absence of a family history of the condition is approximately 2%.[8]

It is usually noted at birth for its elongated skull length but the phenotypical presentation varies depending on the ensuing skull growth in the first 18 months of life. The presentation includes a relatively long, slender skull shape and often a midline sagittal ridge, corresponding to the sagittal fusion. Various or all aspects of the suture may become fused, each giving a different presentation. From a frontal perspective, the child may have significant frontal bossing, an elevated hairline and bitemporal pinching. Posteriorly, an excessive occipital bullet may develop. There may also be a middle 'saddle' deformity.

Various treatment regimes have been advocated and each unit will have their standardized technique. Depending on the age at presentation of the patient, a passive operation (including variations of strip craniectomy/microbarrel staving/spring distraction) may be performed. Older children often undergo a total calvarial vault remodelling (TVR) which addresses all the compensated growth deformities that occur. We advocate a strip craniectomy and microbarrel staving passive procedure if we are able to perform the operation safely prior to 6 months of age. If not, our patients undergo a TVR based on a modified Melbourne protocol at 12–18 months of age.[28]

Unicoronal synostosis (frontal plagiocephaly)

Unilateral/unicoronal or frontal plagiocephaly has an incidence of approximately 1 in 11 000.[4, 29] It has the most varied single-suture variation with both cranial and facial components. Cranially, this often presents with a retruded forehead and brow on the affected side, with a relative orbital dystopia (upwards on the affected side) due to the lack of anteroinferior growth secondary to the fused (or partially fused) coronal suture.

Facially, this then translates into a deviated face, expressed most significantly with a facial and nasal twist towards the affected side. There may also be a maxillary and eventually mandibular cant develop and, probably most functionally importantly, strabismus or a squint may develop. One of the aims of treatment is to obviously minimize these effects.

Bilateral coronal synostosis (brachycephaly)

Bicoronal synostosis is the most likely of all of the single-suture synostoses to have a Mendelian genetic basis.[30] Genetic testing should be offered to all patients with coronal synostosis. Testing can include the mutation hot spots in *FGFR1*, *FGFR2* and *FGFR3*, as well as full analysis of the *TWIST1* and *TCF12* genes.

Approximately 8–15% of patients with non-syndromal coronal synostosis have a family history of the condition. A positive family history is seen more often in patients with bicoronal synostosis.[7, 26] Empiric recurrence risk to a couple with a child with coronal synostosis and no family history of the condition is 5%, although genetic testing should ideally be offered in order to provide a family-specific recurrence risk.[7]

Metopic synostosis (trigonocephaly)

Traditionally thought to be the third most common form of synostosis, metopic suture fusion has over recent years seen a large increase in incidence.[31]

Between 5% and 10% of cases of metopic synostosis have been found to have a positive family history.[9] The incidence of learning disability and other developmental problems (especially expressive speech delay) is higher in patients with metopic synostosis than with other single-suture synostoses. This is at least in part due to the higher incidence of chromosomal copy number variants (CNVs) in patients with metopic synostosis. Suggestive features should therefore prompt detailed chromosomal analysis in patients with metopic synostosis, such as array comparative genomic hybridization (aCGH) studies. Environmental factors, such as exposure to teratogens during pregnancy, are a well-described cause of metopic synostosis.[32] Many cases are thought to be due to a combination of genetic and environmental factors. The empiric recurrence risk to a couple with a child with metopic synostosis with no known cause is 5%.[9]

Clinically, a wedge-shaped forehead typically ensues from premature closure of the frontal bones at the metopic suture. This prevents lateral growth of the frontal bones. This is combined with supraorbital recession and often hypotelorism, decreased interorbital and intercanthal distances. Children will often also develop wider parietal eminences due to compensated growth posterior to the fused frontal bone.

Correction of metopic (trigonocephaly) and coronal (anterior plagiocephaly/brachycephaly) is usually by means of a fronto-orbital advancement and remodelling (FOAR) (**Figure 19.3**). Individual unit protocols vary, but our institution will usually correct this from 12 to 18 months of age.

Tessier[33] originally described this procedure and it is now the mainstay for treatment of these conditions. It allows a conformational change of the forehead (and anterior cranial fossa) to take place, as well as allowing the anterior placement of the neo-forehead in order to increase the skull volume to minimize the risks of raised ICP. At the same time, the bifrontozygomatic width may be altered to correct the relative hypotelorism that ensues secondary to trigonocephaly. Conversely, this can be narrowed for patients with bicoronal synostosis.

The procedure is carried out with the patient supine. A coronal flap is raised. The forehead is then removed. This is designed by selecting bone that may subsequently facilitate a neo-forehead to be created. Techniques vary between institutions but usually this is carried out as a bilateral procedure (even for unicoronal synostosis). This then allows access to the anterior cranial fossa. The supraorbital bar is removed, protecting the frontal lobes of the brain and the eyes and optic nerves. This supraorbital bar is then corrected and remodelled to an ideal shape, allowing the neo-forehead to be attached to this. The construct is then usually replaced in an advanced position (subsequently creating an increased skull volume) and usually attached by resorbable plate fixation.

Lambdoid synostosis

Lambdoid synostosis has an incidence of only about 3% of craniosynostosis. A positive family history is rarely seen in patients with lambdoid synostosis and recurrence risks are low.[5]

The diagnosis of lambdoid synostosis is dependent on history (usually present at birth), examination (a trapezoid head shape when viewed from above compared to a parallelogram in deformational plagiocephaly, an inferiorly and posteriorly situated ear – see **Figure 19.4**) and radiologically (CT scan +/– 3D reconstruction).

Treatment of lambdoid synostosis rarely involves surgery. The risk of raised ICP is low and, once covered by hair, the negative aesthetic element of this is often minimized. If the deformity continues to cause a significant aesthetic concern or raised ICP becomes evident, a vault remodelling is usually undertaken.

SYNDROMIC CRANIOSYNOSTOSIS

It is estimated that there are over 500 different syndromes[35] that have craniofacial anomalies. From a craniosynostosis syndromic point of view, the vast majority of these patients, though, are due to the conditions outlined below. These syndromes are thought to develop through an interaction of genetic factors, molecular and cellular events, mechanical and deformations forces and secondary effects of each of these on normal growth and development.

Crouzon syndrome

Described in 1912 by a French neurosurgeon, this syndrome affects the face and cranium and occurs in 1:25 000 live births. Crouzon syndrome is characterized by craniosynostosis and maxillary hypoplasia with shallow orbits causing ocular proptosis. There is often bicoronal synostosis (brachycephaly) but occasionally the sagittal suture may also be affected. The main abnormality is an underdeveloped midface which results in prolapse of the globes ('exorbitism'), hypoplasia of the malar bones, retromaxillism and a resultant

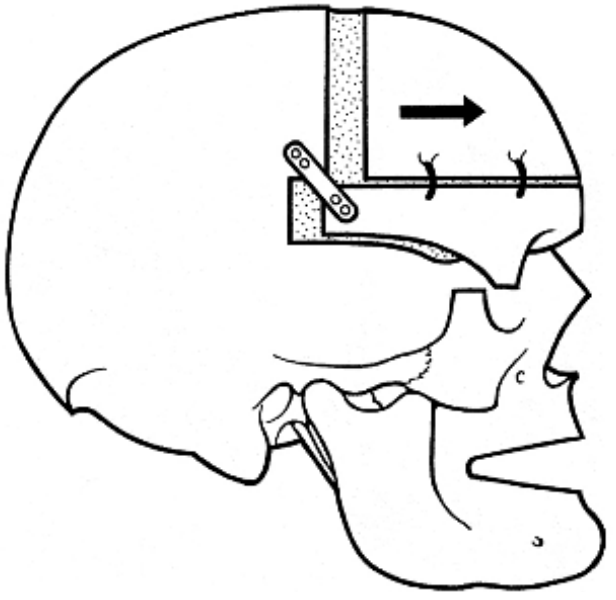


Figure 19.3 Fronto-orbital advancement surgery.

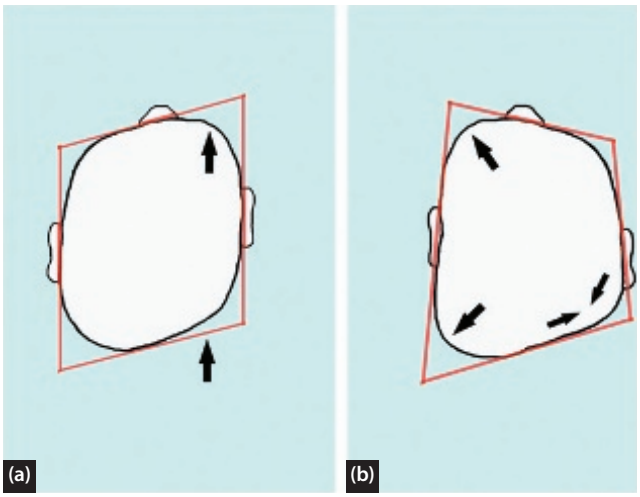


Figure 19.4 Differences between positional and true lambdoid synostosis. Positional moulding **(a)** produces a parallelogram-shaped head and the ear moves anteriorly on the affected side. Unilambdoid synostosis **(b)** produces a trapezoid-shaped head and the ear moves posteriorly towards the affected suture.

malocclusion (Figure 19.5). Anomalies of the middle ear and atresia of the external auditory canal may give rise to a conductive hearing loss. Abnormalities are usually confined to the craniofacial region although there may be systemic anomalies.[4] Intelligence is usually normal. Crouzon syndrome is caused by mutations in *FGFR2* and is autosomal dominant, although new mutations frequently arise.[29] The severity of this condition is extremely variable, even within the same family, and therefore a mildly affected parent may only be diagnosed after the birth of a more severely affected child. Severity may vary from a barely noticeable degree of proptosis and midfacial hypoplasia to, more rarely, cloverleaf skull.

Apert syndrome

Described in 1906 by Apert, this syndrome has an incidence of 1:60 000 live births. Apert syndrome is caused by mutations in *FGFR2*; two-thirds of cases have the mutation Ser252Trp while the remaining one-third have the Pro253Arg mutation.[36] There is an autosomal dominant pattern of inheritance although most cases of Apert syndrome occur without a family history as a result of new mutations and there is a link with advanced paternal age.[37] The main features of this condition include craniosynostosis (usually bicoronal), abnormal midfacial development and fusion of the digits of the hands and feet (syndactyly) (Figure 19.6). Abnormalities of the midface and cranium are evident at birth, with brachycephaly and midface retrusion causing an anterior open bite (malocclusion). Cleft soft palate or bifid uvula is present in 30% of cases. Fixation of the stapes footplate may cause a conductive hearing loss. There may be other associated malformations and intellectual ability may vary from normal to significantly impaired.[38]

Pfeiffer syndrome

First described in 1964, Pfeiffer syndrome is similar to Crouzon syndrome and is characterized by craniosynostosis and midfacial hypoplasia with shallow orbits. Additional features of Pfeiffer syndrome include broad thumbs and broad great toes. Severity of craniofacial anomalies can vary from mild midfacial hypoplasia to a cloverleaf skull (Figure 19.7). Coronal sutures are most commonly affected, with resultant brachycephaly. Other features may include skeletal anomalies such as fusion of the elbow joint, solid cartilaginous trachea and choanal stenosis or atresia. Three clinical or phenotypical subtypes have been suggested depending on the extent of associated features[4] and there is some evidence for a genotype–phenotype correlation for some mutations.[39] Pfeiffer syndrome is caused by mutations in *FGFR1* and *FGFR2*, in some cases the same mutations that can cause Crouzon syndrome.[7, 40, 41] Inheritance is autosomal dominant although many cases arise as a result of new mutations. Intelligence varies from normal to mild learning difficulties, although central nervous system abnormalities may occur in severe cases.[11]

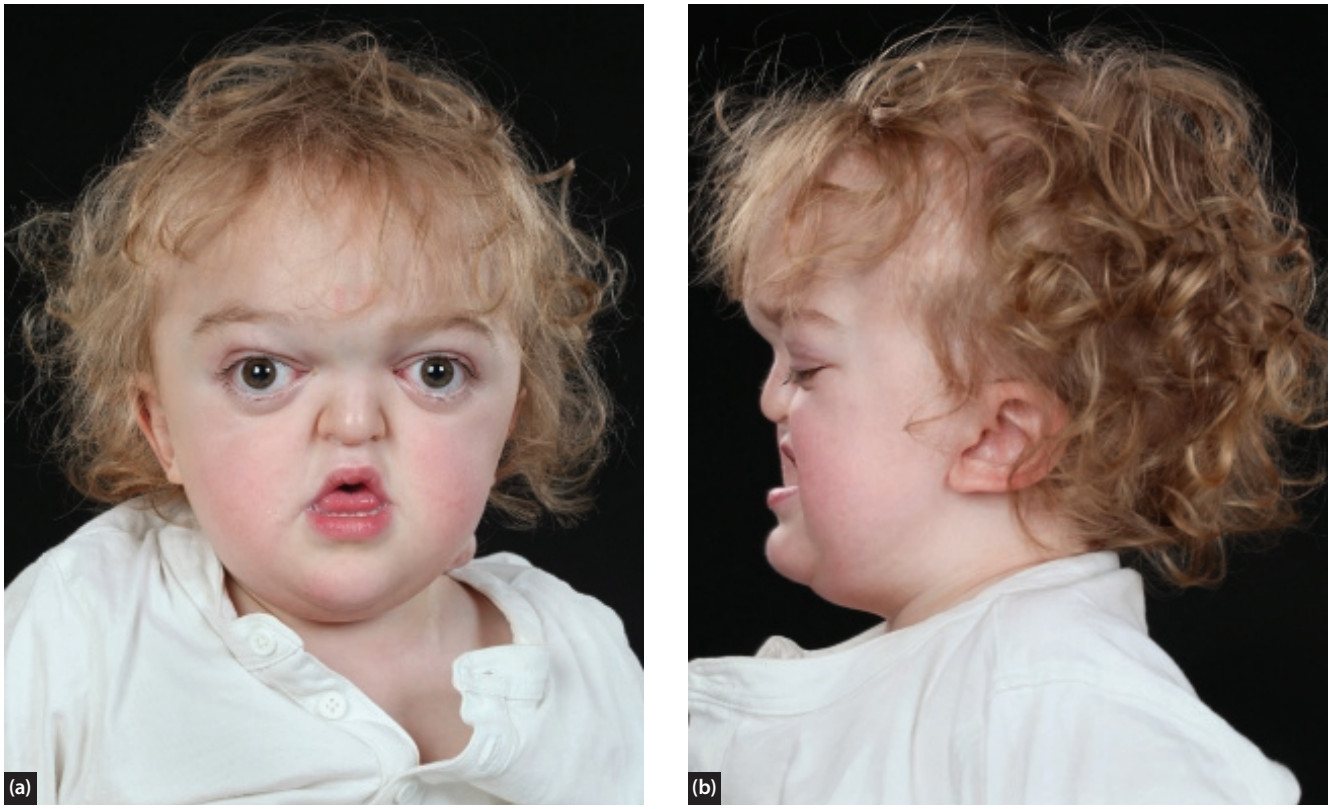


Figure 19.5 Crouzon syndrome.

Figure 19.6 Apert syndrome. Note the brachycephaly and syndactyly.

Muenke syndrome

This autosomal dominant condition is associated with unilateral or bilateral coronal synostosis and a variety of minor anomalies. The cause is a specific mutation of *FGFR3*, the Pro250Arg mutation.[42] The phenotype this causes is extremely variable, even within the same family, and includes coronal synostosis, macrocephaly without synostosis, ptosis and minor anomalies of the hands and feet. Intelligence is usually within normal limits although learning difficulties, usually mild, may be present. The effect of the mutation may be so mild in some family members that they are unaware that they harbour a mutation. Genetic testing can be used to clarify their carrier status.

Saethre–Chotzen syndrome

Saethre–Chotzen syndrome was first described in 1931. This is an extremely variable autosomal dominant condition, although abnormalities may be milder than in other syndromic craniosynostosis conditions. Because of this, a mildly affected parent may not be aware that they also have the condition until after their more obviously affected child is diagnosed. The most commonly affected suture is the coronal suture and the craniofacial abnormalities are frequently asymmetric. Associated features may include ptosis, a low anterior hairline, small ears with a prominent horizontal crus, mild cutaneous syndactyly and broad thumbs and great toes. Mutations in the gene *TWIST1* cause Saethre–Chotzen syndrome but the phenotype has

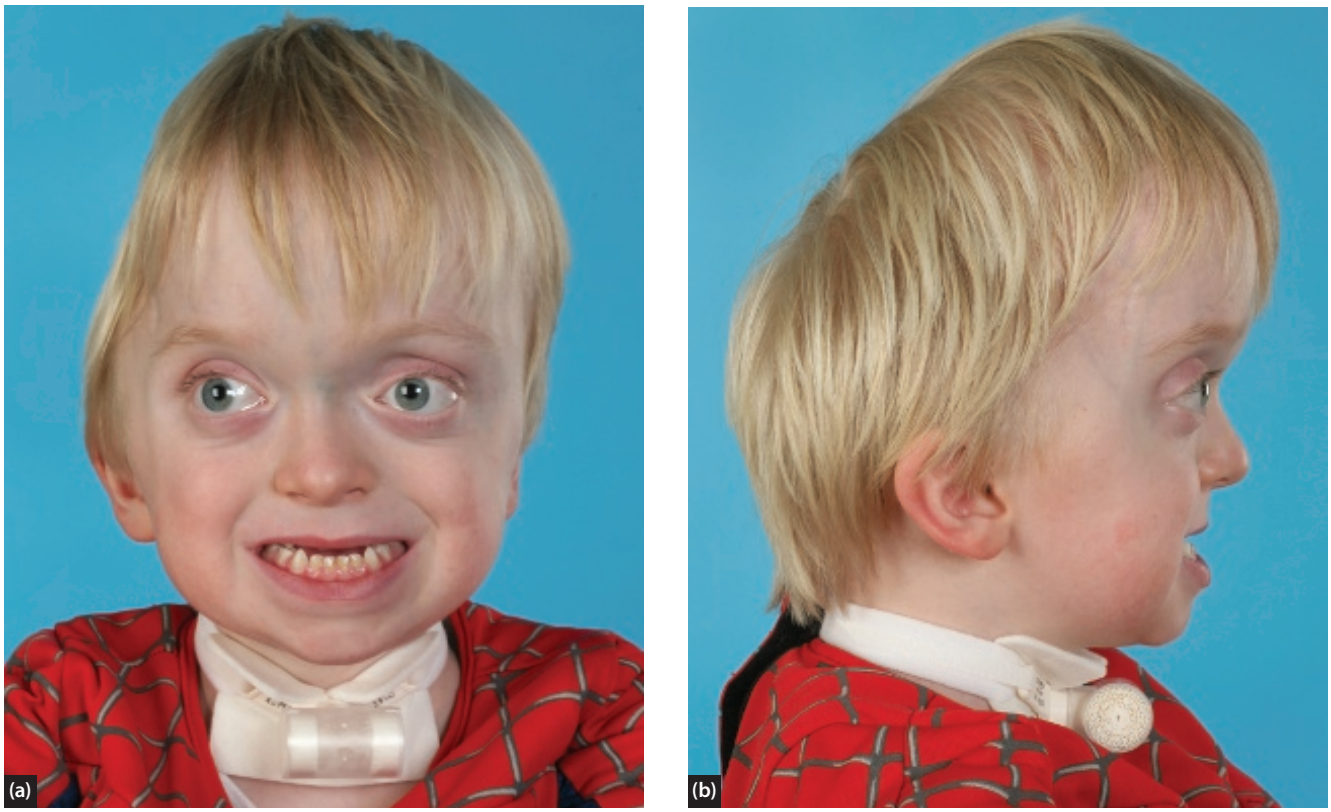


Figure 19.7 Pfeiffer syndrome. Note the bulging temporal region, turricephaly, retruded midface and tracheostomy.

also been seen in association with the Pro250Arg mutation in *FGFR3* and with *TCF12* mutations.[43–45]

TCF12

Mutations in the *TCF12* gene are a recently identified and common cause of coronal synostosis affecting 10% of patients with unicoronal synostosis and 32% of those with bilateral synostosis, occasionally with additional sagittal involvement. Some patients have features consistent with Saethre–Chotzen syndrome, such as syndactyly, but with negative *TWIST1* analysis.[45] This is consistent with the fact that the *TCF12* and *TWIST1* proteins have been shown to interact.[45, 46] Most patients have isolated coronal synostosis with no additional features. A minority of patients with developmental delay, a learning disability or autism have been described but the majority have normal development and educational attainment.[45]

Craniofrontonasal syndrome

This condition is characterized by craniosynostosis which is usually coronal, frontonasal dysplasia, curly or frizzy hair, sloping shoulders and ridged nails. As part of the frontonasal dysplasia there is hypertelorism, a broad nasal bridge and, occasionally, a bifid nasal tip. There may also be skeletal anomalies such as joint hyperextensibilty, scoliosis and broad toes. Mutations in the gene *EFNB1* are causative.[47] The inheritance is X-linked dominant whereby females are more severely affected than males.

Carpenter syndrome

Carpenter syndrome is a very rare autosomal recessive condition characterized by craniosynostosis, which may affect all sutures causing a cloverleaf skull, and also polysyndactyly (accessory digits with fusion of the digits) and brachydactyly (shortened digits). Mixed hearing loss may also occur. Patients may have obesity and may show learning difficulties.[48] The causative gene has been identified as *RAB23*.[49]

Kleeblattschädel anomaly (cloverleaf skull)

This describes a trilobar skull and is usually caused by pansynostosis involving the coronal, lambdoid and metopic sutures, with bulging of the brain through open sagittal and sometimes squamosal sutures. The prognosis is often, but not universally, poor. Cloverleaf skull is a non-specific anomaly and may be an isolated defect or part of wider syndromes. As such, the aetiology of cloverleaf skull is varied. It may be seen in patients with certain chromosomal abnormalities or be a feature of syndromes such as Pfeiffer, Apert, Crouzon and Carpenter.

MANAGEMENT OF SYNDROMIC CRANIOSYNOSTOSIS

The aim of cranial management for syndromic craniosynostosis is similar to non-syndromic craniosynostosis. Primarily, it is to prevent or manage the raised intracranial

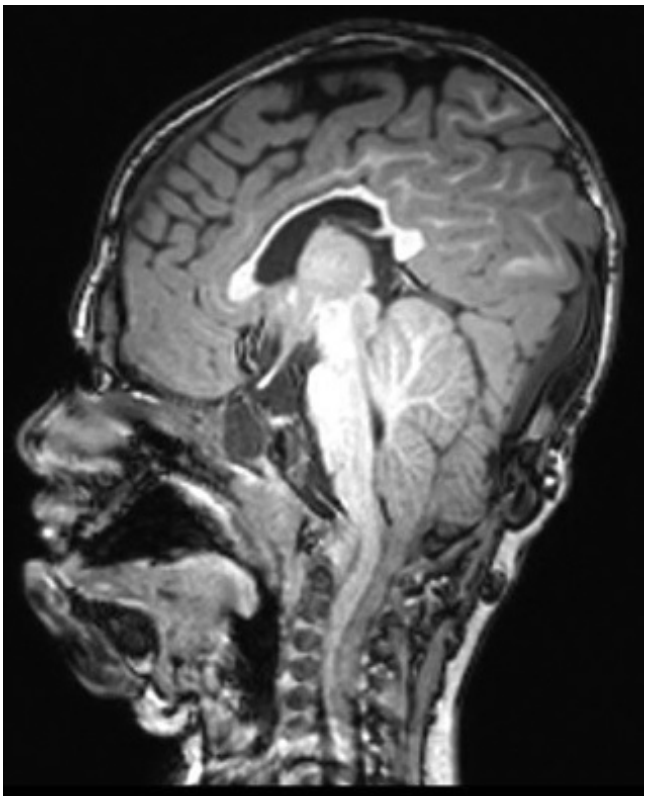


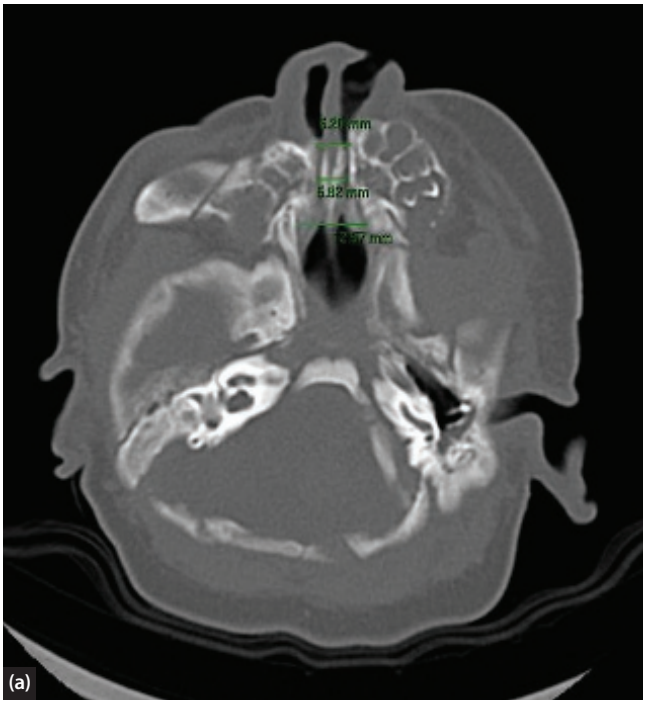
Figure 19.8 MRI scan showing a child with Crouzon syndrome with significant tonsillar herniation below the foramen magnum. Bicoronal synostosis has resulted in a significant brachycephaly deformity resulting in decreased posterior cranial fossa volume and a cramped cerebellum.

pressure that is synonymous with these conditions and to normalize the skull shape and morphology. Prior to this, though, various other factors will need to be addressed. Initially, this will include airway management, feeding and eye protection. Other comorbidities (e.g. cardiac/renal/respiratory systems) may require investigation and correction. Imaging is essential and CT brain and MRI spine and brain scans are routinely performed. In addition, support of feeding, speech and language and psychological needs is ensured by regular surveillance and input as required.

Airway

Respiratory problems may be central or peripheral. Central apnoeas may be related to a Chiari malformation and/or to raised ICP (**Figure 19.8**). An MRI must always be performed as part of a routine imaging series. More commonly, respiratory problems are secondary to obstruction, with reports of 40–83% of children being affected with obstructive sleep apnoea (OSA).[50]

Causes of obstruction in syndromic craniosynostosis are multilevel but include congenital bony nasal stenosis (CBNS) (**Figure 19.9a**), choanal atresia, nasopharyngeal narrowing, a crowded or narrow oropharynx, a thick long soft palate, subglottic stenosis, tracheal stenosis and tracheal cartilage sleeve. CBNS is caused by 3D hypoplasia of the maxilla, leading to narrowing of the nasal passages along their length. In addition, raised ICP can result in compromised neuromuscular control of airway patency.[50]



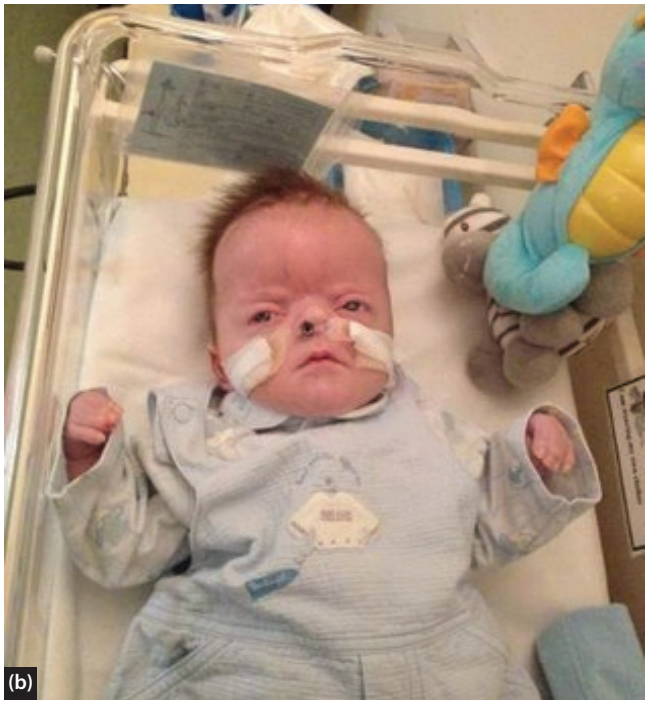


Figure 19.9 (a) CT scan showing congenital bony nasal stenosis (CBNS). **(b)** A child with Apert syndrome and CBNS managed with a nasopharyngeal airway (NPA).

CBNS and choanal atresia, particularly if bilateral, require treatment shortly after birth. Management options include dilatation with or without stenting, nasopharyngeal airways (NPAs), positive pressure ventilation using masks (non-invasive) and tracheostomy. The choice of modality is based upon a number of factors including a full airway assessment, other comorbidities geographical location, and facilities for follow-up and support and parental choice.

Dilatation and NPA insertion has been shown to be a successful first-line management option in the majority of patients (**Figure 19.9b**).[51] An NPA has the advantage over a stent of bypassing the narrow nostril but also the narrow nasopharynx and possibly the long thick soft palate. An NPA is required for 2–48 months. Carers and parents have to undergo training and demonstrate competency in managing the NPA after discharge from hospital.[52] Parents prefer management with an NPA compared to a tracheostomy.[53]

Positive pressure ventilation might be required either instead of or in addition to NPAs and other surgical interventions. Nasal continuous positive airway pressure (CPAP) using a mask has been found to be beneficial in a number of these patients, although fitting of the mask onto a retruded maxilla or a hypoplastic midface can be a challenge.

Adenotonsillar hypertrophy may contribute to ongoing obstructive symptoms and patients should be monitored for this. Although adenotonsillectomy as a treatment modality for OSA is less successful than in the general population, improvements – either symptomatic or on polysomnography (PSG) or both – are seen in up to 60% of patients. Cleft palate is a common finding in patients, particularly with Apert syndrome. A cleft palate or submucous cleft is no longer an absolute contraindication to adenoidectomy. With good visualization techniques, an inferior ridge can be left behind to enable palate–pharyngeal apposition.

Patients should be monitored both clinically and with PSG to detect severity of OSA, and early investigation and intervention is advocated. The frequency of surveillance PSG is to be determined on an individual case-by-case basis. Frequent sleep studies will often be undertaken to determine the level and severity of instruction.

Midface advancement surgery has variable effects upon upper airway obstruction. There are some reports of very successful outcomes of early midface advancement surgery in terms of decannulation or avoiding the need for a tracheostomy[54] while other reports are less positive.[55] In the authors' unit, there is generally an improvement in subjective and objective measures of OSA following midface advancement but not always sufficient to enable decannulation and/or discontinuation of CPAP.

Tracheal anomalies might also contribute towards airway obstruction in syndromic craniofacial patients. *FGFR2* syndromes such as Crouzon, Pfeiffer and Beare–Stevenson syndrome are associated with an abnormality of the trachea known as 'tracheal cartilaginous sleeve'.[56] This is a malformation in which individual tracheal arches are not formed. There is a continuous tracheal cartilaginous piece composed of a vertically fused C- or O-shaped cartilage. This might extend from the level of the subglottis down to the bronchi. When the cartilage is C-shaped, the pars membranacea is often notched posteriorly, giving the appearance of a keyhole.[57] Respiratory problems occur as a result of the reduced calibre and the reduced compliance of the trachea. Premature death occurs in almost all patients with this abnormality but a tracheostomy appears to offer a survival advantage. A tracheostomy will be more challenging to perform. Because of the rigidity of the trachea and the absence of rings, it may be necessary to cut a window rather than a vertical slit as is more common in paediatric tracheostomies. As the sleeve trachea causes narrowing, it might be necessary to select a tracheostomy tube with a smaller diameter than might be expected for age.

Post-operatively, these children are more susceptible to granulations related to trauma from suction (**Figure 19.10**). This is managed by using a shorter tracheostomy tube in order to avoid the end abutting on the abnormal ends of the C-shaped cartilage. In addition, topical application of steroids, regular attention to the 'granulomas' and education of carers with regard to suction help minimize the impact of these 'granulomas'. Nevertheless, they are a cause of significant morbidity and mortality in this group of patients.

Tracheostomy may be required either as a short-term solution, for instance to cover a surgical procedure perioperatively (e.g. midfacial advancement), or as a long-term

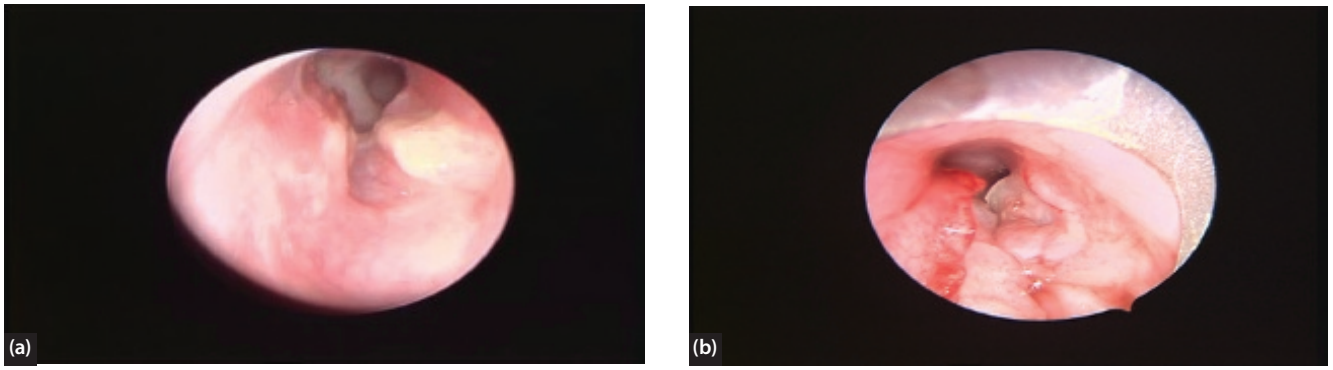


Figure 19.10 **(a)** Keyhole-shaped tracheal abnormality in Pfeiffer syndrome. **(b)** The same trachea with granulation secondary to trauma from suction. (Images courtesy of Ms M. Wyatt, Consultant Paediatric ENT surgeon, Great Ormond Street Hospital, London).

airway solution. Because the airway obstruction in these children is multilevel, a combination of approaches is required to optimize the airway. Ultimately, if these are not successful, a tracheostomy may be the safest approach.

Visual considerations

Due to both restriction of anterior frontal bone growth and midfacial hypoplasia, exorbitism (decreased orbital volume/capacity) often results. This can range from simple exorbitism with complete soft-tissue eye protection to dislocation (with or without reduction) or complete ocular exposure. Corneal abrasions are not uncommon in this situation.

Early ophthalmological assessment is imperative. Education for the family on globe reduction may be required and potentially surgical intervention (tarsorrhaphy) may be indicated.

Regular fundoscopy assessments are also mandatory to establish if raised ICP is present. Papilloedema, optic atrophy and progressive optic nerve dysfunction may accompany raised ICP. Uncorrected refractive effort, strabismus, ptosis and corneal abrasion can lead to amblyopia, potentially causing permanent visual disability if not identified and corrected.

Intracranial pressure

The mainstay of cranial surgery for syndromic craniosynostosis has been in the attempt to increase the intracranial volume, and thus control intracranial hypertension, while at the same time normalizing the head shape and thus improving the patient's overall appearance.[58] Without treatment, both visual and neurological deterioration may result. In addition to craniocerebral disproportionation, raised ICP in syndromic craniosynostosis can be influenced by venous hypertension, OSA and hydrocephalus.

As the most common cause of raised ICP is craniocerebral disproportionation, vault remodelling is intended to address this. Initially, especially for brachycephalic patients or bicoronal synostosis, a suturectomy or posterior vault expansion is advocated.[59]

Role of CSF diversion

Ventricular dilatation is a rare occurrence in non-syndromic craniosynostosis and in such cases hydrocephalus, if noted, is attributable to any coexisting disorder. However, it is a common feature of syndromic craniosynostosis and seen in nearly half the cases.[60] While non-progressive ventriculomegaly is seen commonly in Apert syndrome, it seldom requires CSF diversion. On the contrary, in Crouzon and Pfeiffer syndrome, ventriculomegaly is progressive and requires CSF diversion in most cases, despite early posterior vault expansion procedures. Patients with Saethre–Chotzen and Muenke syndrome are seldom affected by hydrocephalus.

The etiology of hydrocephalus is multifactorial: crowded posterior fossa , venous outlet obstruction and increased CSF outflow resistance are the commonest explanations.[60] The multifactorial nature of the problem is confirmed by the fact that, despite posterior vault expansion, a significant proportion of cases end up needing a shunt placement for progressive ventriculomegaly.

The options in terms of CSF diversion are limited to insertion of a ventriculoperitoneal (VP) shunt. Special precautions have to be taken to avoid shunt overdrainage as excess CSF shunting will lead to worsening of pre-existing venous hypertension (pseudotumour state). The authors recommend the use of a programmable shunt valve with inbuilt antisiphon device to obviate this problem. In the authors' experience, there is a very limited role for endoscopic third ventriculostomy (ETV) for CSF diversion. We have carried out ETV in a small number of cases with moderate ventriculomegaly post posterior vault expansion procedures in patients with subtle clinical and ophthalmological symptoms and signs of raised ICP. However, the default option for CSF diversion for hydrocephalus in syndromic craniosynostosis is insertion of a VP shunt with a programmable shunt valve with an inbuilt antisiphon device.

In our experience, the incidence of shunt infection and ventricular catheter blockage are higher in syndromic craniosynostosis, as are other shunt-related complications because of the associated problems of feeding, airway obstruction, frequent chest infections and progressive craniocerebral disproportion in these cases.

Cranial surgery for syndromic craniosynostosis

If the posterior vault size and shape is satisfactory, a fronto-orbital advancement and remodelling (FOAR) is performed[61] which both increases the volume of the skull and allows a conformational change or normalization of skull shape. Timing of this procedure varies depending on the individual institution's protocol. We will usually operate when the child is 12–18 months of age. This balances the risk of developing raised ICP if surgery is performed at a delayed stage against the risk of restenosis if the procedure is performed too early. Unfortunately, this is seldom the case and most patients will undergo a number of procedures. In our institution, depending on the severity of the craniosynostosis, a suturectomy will usually be performed. This allows continual skull growth and expansion with minimal shape deformities. This is usually only a short term measure, however, as most syndromic patients have a 'pro-ossification' genetic change and, as a consequence, the sutures will often re-fuse. Therefore, a posterior vault expansion is usually undertaken. This utilizes internal distraction devices to increase the posterior vault. It is only after the posterior vault is corrected/normalized that we address the forehead.

Midface advancement surgery for syndromic craniosynostosis

Midface advancement surgery is indicated to attempt to improve the airway in order either to avoid the need for non-invasive ventilation or a tracheostomy or to remove

dependence upon such a modality. However, outcomes of this procedure in terms of the airway are somewhat variable and unpredictable. Apart from the airway, the main indication for midface advancement surgery is to normalize appearance.

Timing of surgery to the midface is a matter of debate. In the UK, surgery is usually delayed until the age of 5–6 years, or older, prior to the child starting secondary education. This delay is intended to allow growth of the child so that their weight increases, as does the circulating blood volume. Midface surgery often results in significant loss of blood volume, with much of the haemorrhage not directly amenable to local control.

The type of surgery is dictated by the pattern of the deformity. There are three basic operations available.

1. The **Le Fort III osteotomy** involves advancement of all midfacial structures inferior to the frontal bone, i.e. nose, zygomas and maxilla en bloc. This requires a bicoronal flap for access to the nasal root, orbits and zygomatic bones and osteotomies of the nasal root, medial orbital walls, orbital floor, lateral orbital wall, frontozygomatic suture and pterygomaxillary complex. This allows mobilization of the midface. Internal fixation and bone grafts may be used to ensure satisfactory healing and stability. Due to the potential issues with achieving adequate advancement, however, this procedure is usually performed by distraction osteogenesis and a rigid external distractor (RED) frame now (see below).
2. Where midface hypoplasia is associated with hypertelorism, a **facial bipartition** may be carried out. It essentially involves a Le Fort III osteotomy to advance the midface and excision of a V-shaped segment of bone from the midline, creating two independent hemifacial segments, which can then be brought together to reduce the interorbital distance.
3. A **monobloc procedure** involves advancement of the forehead and midface at the same time by combining a Le Fort III procedure with FOAR.

See also 'Distraction osteogenesis', below.

Distraction osteogenesis

Conventional surgery involves osteotomy, mobilization and bone movement at one operation. Bone grafting and internal fixation are required to ensure healing and stability and to prevent relapse. This has the advantage of completing treatment at one operation. However, where the required bone movement is large (e.g. greater than 10 mm in the midface) or there is significant scarring of surrounding soft tissues (e.g. cleft or multiply operated patients), the desired movement may be difficult or impossible to achieve. There is also the risk of infected dead spaces (between the neoforehead and dura) in monobloc procedures due to the communication between the intracranial contents and the nasal commensal flora. The alternative of using distraction osteogenesis can be utilized to overcome these difficulties.

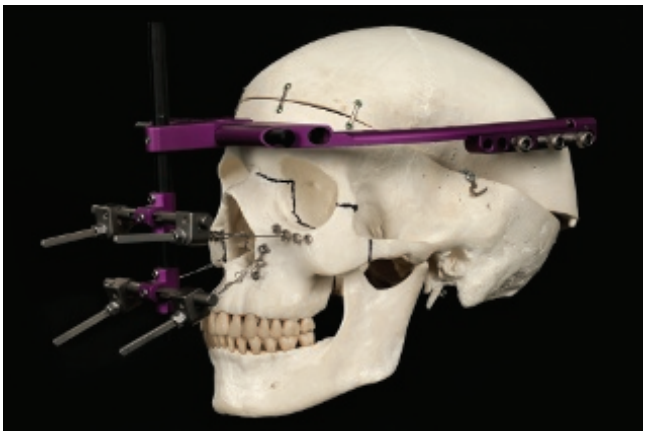


Figure 19.11 Distraction osteogenesis with a RED frame (KLS Martin RED Frame). The procedure is a craniofacial disjunction. The base of the skull is separated from the orbits/nasal bones/maxilla and underlying structures. After ensuring mobilization of these structures, titanium plates are usually secured to the nasal piriform and infraorbital region and percutaneous wires are secured to the RED frame. Progressive distraction is then commenced over the next week. The benefit of this procedure is that it allows growth of the bone as well as allowing soft-tissue expansion.

Distraction osteogenesis (DO) involves initial osteotomy, ensuring complete separation of bony segments, without mobilization or advancement, and application of an internal or external distraction device (e.g. RED frame), which is activated after a 1-week latent period and produces a movement of 1 mm per day. This allows gradual adaptation of a surrounding soft-tissue envelope, as well as osteogenesis within the osteotomy gap, allowing for greater movements without the need for bone grafting or internal fixation. Once the desired movement has been achieved, the distractors are left *in situ* for a further a period of two to three times the activation phase to allow consolidation of the newly formed bone.

Distraction therefore has the advantage of being able to produce larger movements without the requirement for bone grafts or internal fixation. The disadvantages are that the treatment is prolonged, the patient has to tolerate the distraction devices, and a second operation is often required for distractor removal. In most craniofacial patients, the advantages of distraction outweigh the disadvantages compared with conventional surgery and therefore the majority of midface advancements are now carried out using distraction (see **Figure 19.11**).

COMPLICATIONS OF CRANIOFACIAL SURGERY

Blood loss

Infants have a small absolute blood volume and there may be appreciable sudden haemorrhage, in particular from the cerebral sinuses. Blood loss varies with the timing and extent of the surgery. In a simple suture release, blood loss is in the region of 100 mL. Blood transfusion is not uncommon for

infants undergoing this surgery and for older children having more extensive procedures. Risk of viral or bacterial transmission is low but the consequences are potentially devastating. Avoiding transfusion is not always possible but, provided the intravascular volume is maintained, then patients can tolerate low haemoglobin levels.[62, 63]

The combined data of the NHS Designated Craniofacial Units reports approximately 75–85% of patients will require a blood transfusion per fronto-orbital advancement. Usually, this is due not to torrential bleeding but to the accumulation of mild ongoing losses from a prolonged procedure. Routinely, autologous blood recovery systems are used to minimize this, along with the use of relative hypotensive anaesthesia and utilization of tranexamic acid.

Air embolism

A major danger in craniofacial surgery is ingress and embolization of air through the circulation. This can occur at any stage during surgery, from inserting large-calibre central lines, raising a scalp flap or opening into the major sinuses. In anticipation of blood loss and air embolization, arterial and central venous lines are routinely used with a number of peripheral lines. A significant air embolism may result in hypotension, bradycardia and cardiac arrest. The highest risk occurs during elevation of the bone off the dura and preventative strategies are used to minimize this.

Cerebral oedema

All measures should be taken to avoid cerebral oedema. Positioning the patient correctly, ensuring correct endotracheal tube positioning and maintaining the correct intravascular fluid replacement are all vital. There should be minimal brain retraction and handling, particularly in cases of pre-existing raised ICP as this predisposes the patient to developing cerebral oedema. In many cases the use of systemic steroids (e.g. dexamethasone) may be useful in minimizing cerebral oedema.

Dural tear

Craniofacial operations such as suturectomy and vault expansion are essentially extradural procedures. In certain circumstances, for example repeat surgery or when 'copper beating' of the inner table of the skull is present, it may be impossible to avoid tears of the dura mater. The distorted anatomy must also be kept in mind and revision of pre-operative scans is imperative. Usually, small incidental tears are simply sutured closed and reinforced with fibrin glue. Larger tears may require dural grafting or formal repairs with the use of a patch.

CSF fistula

Cerebrospinal fluid leak is uncommon but will take place if a dural tear is not either recognized or adequately repaired. CSF can then leak through the scalp wound or, perhaps more commonly, leak into the nose and present as CSF rhinorrhoea. Often this is transient, lasting a few days and sealing spontaneously. Intra-operatively, it may be beneficial to perform a brief Valsalva manoeuvre in the attempt to identify any CSF (or blood) leaks. Obvious fistulae that fail to resolve must be treated. Of more concern are those that persist unnoticed and lead to infection or meningitis at a later date.

Infection

Infection can occur, particularly in cases involving communication with the paranasal sinuses, and result in meningitis, intracerebral abscess or subdural empyema. Chronic infection can also manifest as lost bone graft or implants. Post-operative infections are treated aggressively with systemic antibiotics and local debridement, with the attempt to preserve the bone flaps at all costs.

Intracerebral/subdural haematoma

Haematoma can present in the early post-operative phase with unexpected signs of raised ICP or 'lateralizing' signs.

Blindness

Surgery around the optic apex and skull base has the potential to damage the optic nerves or tracts. In particular, hypertelorism procedures and monobloc midfacial advancement carry a risk to these structures but all patients (and parents) must be informed and consented on this. Post-operative strabismus may also occur and regular ophthalmological assessments must be performed.

Restenosis

The aim of much cranial vault surgery is to release the prematurely fused sutures, thereby allowing unimpeded brain growth. The gaps created gradually ossify. Occasionally, premature restenosis takes place, and with continued brain growth there is a rise in ICP. This tends to happen more commonly in syndromic craniosynostosis than in non-syndromic cases. Saethre–Chotzen patients have a high incidence of reoperation for craniocerebral disproportionation.[64]

The potential for reossification declines with increasing age of the child (as rapid cerebral growth minimizes). In children over 1–2 years of age large bony defects of the skull vault may not close entirely. In some cases it is necessary to repair these defects using a split calvarial bone switch procedure at a later time.

HEMIFACIAL MICROSOMIA/OAVS

Gorlin et al.[65] and Beleza-Meireles et al.[66] suggested the term oculoauriculovertebral spectrum (OAVS) as a combined definition encompassing the overlapping diagnoses of hemifacial microsomia, first and second branchial arch syndrome, otomandibular dysostosis, facioauriculovertebral syndrome and Goldenhar syndrome.

TABLE 19.3 Vento's 1991 OMENS classification of oculoauriculovertebral spectrum (OAVS)

Aspect	Involvement
Orbit	
O_0	Normal orbit and position
O_1	Abnormal orbital size
O_2	Abnormal orbital position
O_3	Abnormal orbital size and position
Mandible	
M_0	Normal mandible
M_1	The mandible and glenoid fossa are small with a short ramus
M_2	The mandibular ramus is short and abnormally shaped
M_{2A}	Glenoid fossa is in anatomically acceptable position with reference to the opposite TMJ
M_{2B}	TMJ is inferiorly, medially and anteriorly displaced, with severely hypoplastic condyle
M_3	Complete absence of ramus, glenoid fossa and TMJ
Ear	
E_0	Normal ear
E_1	Mild hypoplasia and cupping with all structures present
E_2	Absence of external auditory canal with variable hypoplasia of the concha
E_3	Malpositioned lobule with absent auricle; lobular remnant usually inferiorly and anteriorly displaced
Facial nerve	
N_0	No facial nerve involvement
N_1	Upper facial nerve involvement (temporal and zygomatic branches)
N_2	Lower facial nerve involvement (buccal, mandibular and cervical branches)
N_3	All branches of the facial nerve affected. Other cranial nerves included
Soft tissue	
S_0	No obvious soft tissue or muscle deficiency
S_1	Minimal subcutaneous / muscle deficiency
S_2	Moderate – between the two extremes – S1 and S3
S_3	Severe soft tissue deficiency due to subcutaneous and muscular hypoplasia

OAVS is usually a sporadic condition. Multiple theories have been put forward to try to explain the aetiology but it is likely to be a multifactorial condition due to varying combinations of genetic and environmental (including teratogenic) factors. Rare cases (fewer than 1%) may be due to a mutation in the recently identified *MYT1* gene.[67]

Traditionally thought to have only a unilateral involvement, there is a small subset of those (around 10–25%) who are affected bilaterally. The phenotypical presentation, however, is usually different from left to right when this occurs.

Boys are three times more commonly affected than girls.[11]

Classification

Vento et al.[68] proposed the classification 'OMENS' (and OMENS-plus) to address the craniofacial aspects of OAVS (**Table 19.3**).

O – Orbit/orbitozygomatic[69]
M – Mandible – Kaban-modified,[70] Pruzansky classification[71]
E – Ear – Meurman,[72] modified Marx classification
N – Nerve (specifically facial nerve CN VII)
S – Soft tissue

Clinical diagnosis

The most striking feature of OAVS is the facial asymmetry that ensues from the involvement of the first and second branchial arches. This will usually be portrayed by a deviated chin point and subsequent dental malocclusion and/or orbital malpositioning (**Figure 19.12**).

As OAVS (or 'OMENS-plus'), has extracranial features, these should be investigated to rule out any other associated conditions. Vertebral anomalies should be looked for and investigated. A renal ultrasound and echocardiogram should also be performed to rule out renal and cardiac (e.g. tetralogy/ventricular septal defect or atrial septal defect/patent ductus arteriosus) concerns.

Orbit and orbitozygomatic involvement may vary from orbital and zygomatic malpositioning, micro- or anophthalmia, and epibulbar dermoids.

Ear deformity occurs in up to 95% of affected individuals.[73] Half of these will usually present with microtia. Associated hearing loss depends upon the development of the external auditory meatus and the middle ear. Hypoplasia of the middle ear with fusion or absence of the ossicles may occur (see Chapter 12, Congenital middle ear

Figure 19.12 Child with OAVS. Note the asymmetry and abnormal pinna.

abnormalities and Chapter 16, Microtia and external ear abnormalities).

A. N. Samadpour and H. Merrikh

Neuromuscular deficiencies involve the facial and trigeminal nerves, with hypoplasia or absence of masticatory muscles and/or muscles of facial expression. There is facial weakness in approximately 12% of patients[50] and, more rarely, other cranial nerves may be involved. Soft-tissue asymmetries are partly related to hypoplasia of the masticatory and facial muscles, but other tissues such as salivary glands may be absent.

Management

Management is aimed at addressing each individual component of the classification. This will obviously involve a MDT for the extracranial components. Treatment regimes are similar to all syndromic craniofacial patients with airway protection or establishment, eye protection and feeding as the initial priorities. Hearing assessment soon follows. After this, assessment of mandibular function and the establishment of a ramal–condyle unit will take place. Ear deformities may be corrected by prostheses or autologous reconstruction. Facial nerve procedures will vary depending on the extent of the involvement. Eventually, corrective orthognathic surgery and soft-tissue balancing procedures may be undertaken to minimize the stigmata of the condition. This may be in the patient's late teenage years. Throughout the entire treatment period, regular ophthalmological assessments are required.

TREACHER COLLINS SYNDROME (MANDIBULOFACIAL DYSOSTOSIS)

Treacher Collins syndrome (otherwise known as mandibulofacial dysostosis) is characterized by the absence or hypoplasia of the zygomatic bones, eyelid abnormalities and mandibular hypoplasia and microtia (see Chapter 16).

Aetiology

Unlike hemifacial microsomia, Treacher Collins syndrome is an autosomal dominant condition, although approximately 50% of cases have no family history and therefore represent new mutations. Its incidence is approximately 1:50 000 live births.[74] Severity is very variable and other family members may be very mildly affected. Intelligence is usually normal. Treacher Collins syndrome is caused by mutations in the gene *TCOF1*.[75]

Clinical manifestations

The palpebral fissures may be down-slanting, with colobomas of the lower eyelid and eyelash/follicle malformations being common. A hypoplastic midface with poorly developed or absent zygomas, associated with mandibular hypoplasia, results in a very characteristic facial appearance (**Figure 19.13**). The mandibular hypoplasia might be severe enough to cause significant upper airway obstruction. Features are bilateral and often symmetrical. The difficulties in both intubation and treatment that arise are due to a steep occlusal plane angle (of both the maxilla and the mandible), often dental crowding, and significant retrognthaia of the mandible. Therefore the chin point is rotated in a clockwise direction towards the larynx/trachea (**Figure 19.14**).

Bilateral ear abnormalities including hypoplasia, microtia or anotia, hypoplasia or atresia of the external auditory meatus, middle ear anomalies and associated hearing defects are common. Inner ear function is usually unaffected leading to a conductive hearing loss. There is cleft palate in 35% of cases.

Management

Management of the airway in the neonate is required to overcome respiratory obstruction associated with

Figure 19.13 Treacher Collins. Abnormalities of zygomatic bones, ears, eyelids and mandible. Note the tracheostomy.

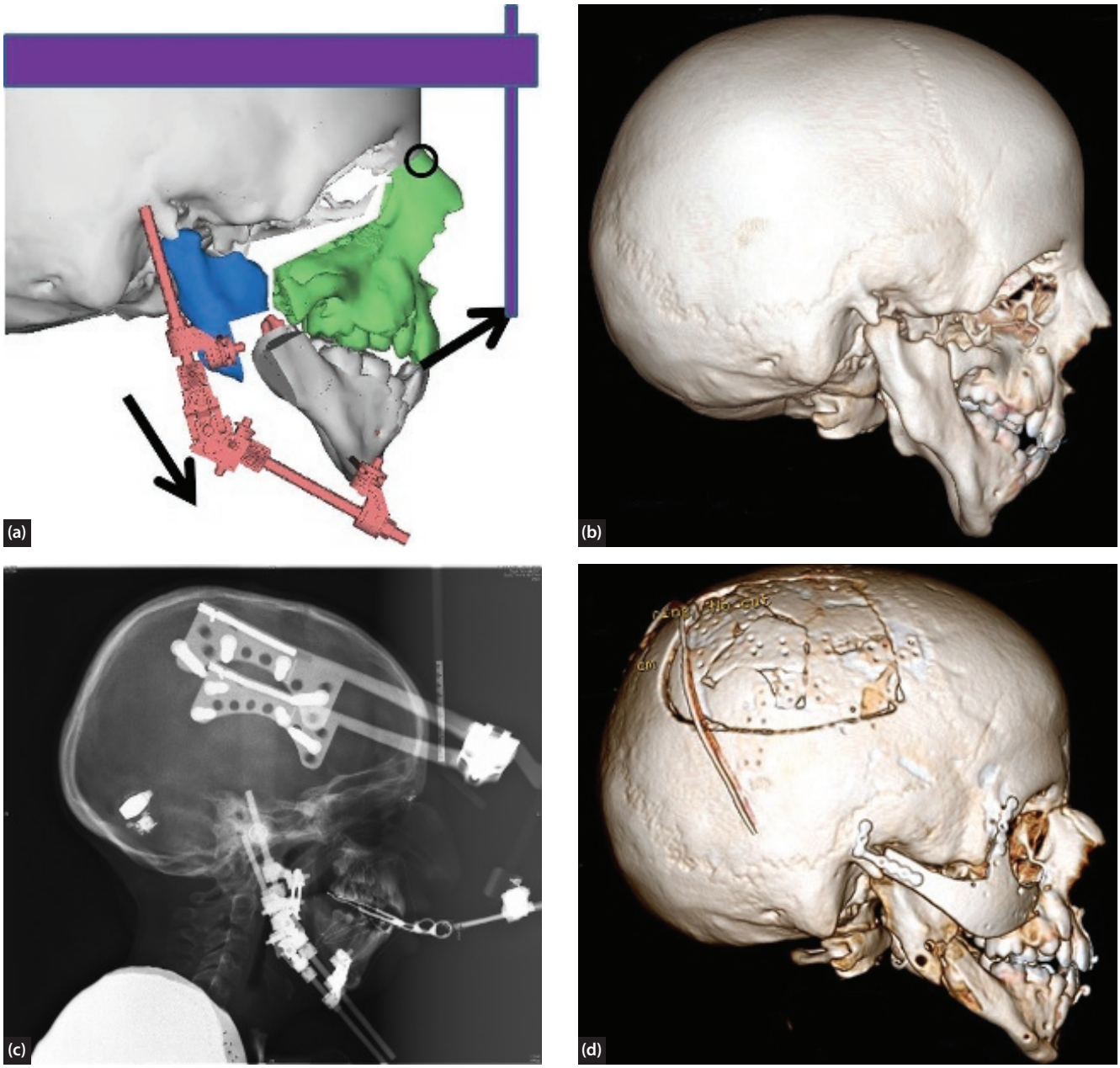


Figure 19.14 **(a)** Combination distraction osteogenesis allowing for lengthening of the mandible and rotation of the maxilla–madibular plane angle (by use of a nasion cerclage wire and traditional rigid external distraction to correct the occlusal plane). Image © Dr Richard Hopper MD. **(b)** Pre-operation. Steep mandibular occlusal plane angle with vertical mandibular growth pattern resulting in reduced retroglossal airway space. **(c)** Active distraction phase with combination RED (rigid external distractor) frame and mandibular distraction. **(d)** Post-operative 3D CT showing significant change in pogonion (chin point), normalization of occlusal plane angle and dentition. Calvarial onlay grafts used to reconstruct hypoplastic zygomatic arches. Photographs courtesy of Dr Richard Hopper MD, Seattle, Washington.

mandibular hypoplasia or choanal atresia. Early feeding difficulties may also need to be addressed. Further management may include repair of cleft palate, provision of bone-conducting hearing aid followed by a bone-anchored hearing aid, and close monitoring and intervention for speech and language development. Eyelid abnormalities may need surgical correction, hypoplastic or absent zygomas may be reconstructed, usually using calvarial bone grafts or alloplastic onlays, and mandibular deficiency can be corrected with conventional osteotomies or distraction osteogenesis (see **Figure 19.14**). Distraction techniques allow for both lengthening of the mandible in an AP direction (which addresses both the retrognathia and sometimes dental crowding) and, when combined with traditional osteotomies of the maxilla, rotation of the maxillomandibular complex in an anticlockwise direction. The latter addresses the occlusal plane and allows elevation of the chin point in a superior–anterior vector, in the hope to increase the retroglossal airway space as well as normalizing the bony skeleton and soft tissues.

ENCEPHALOMENINGOCOELE

Encephalomeningocoele represents a herniation of meninges with or without associated brain tissue, through a bony defect of the calvarium. They are a congenital anomaly representing one end of the spectrum of neural tube defects. Its diagnosis is based on the finding of either meninges and CSF (meningocoele) or nervous tissue (encephalocoele) beyond the confines of the calvarium.

The incidence of encephalocoele is reported to be as high as 1:3000 live births in South East Asia and as low as 1:10 000 live births in North America.[76]

Aetiology

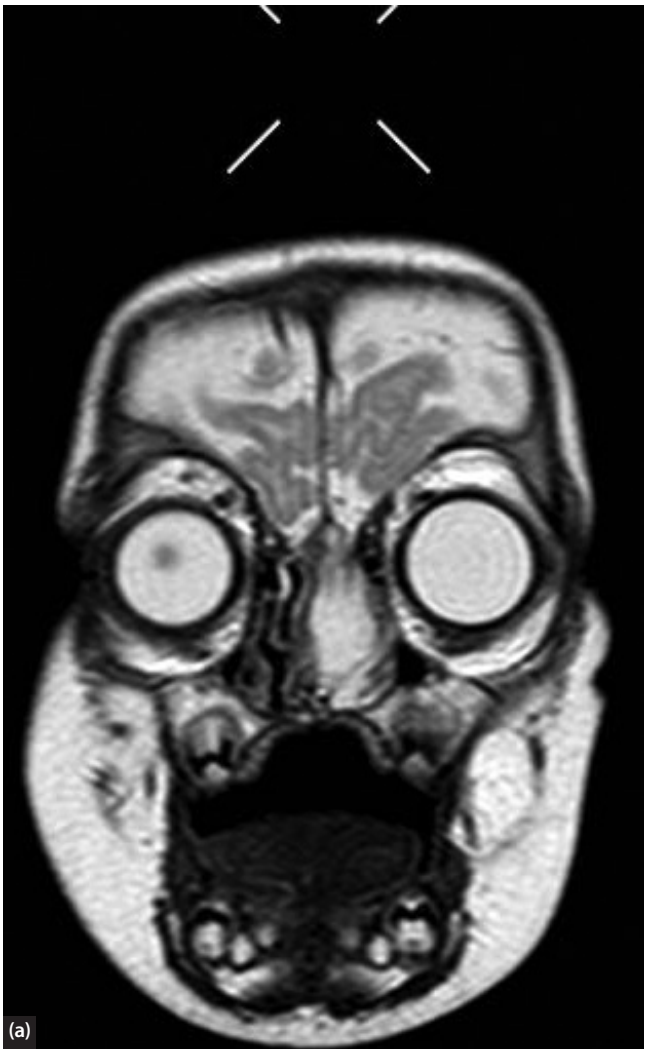
Encephalocoeles may be isolated or associated with other anomalies.When other problems coexist, causes include chromosomal abnormalities, single gene disorders, teratogens and disruptions such as amniotic bands. The primary abnormality in the development of an encephalocoele is a mesodermal defect that develops when the surface ectoderm fails to separate from the neuroectoderm. This results in a defect in the calvarium and dura. Within the calvarium itself there may be failure of bone formation or pressure erosion from expanding intracranial contents. The aetiology of isolated cases is thought to be multifactorial, with both genetic and environmental factors playing a part. The widespread use of folic acid prior to conception and during pregnancy aims to reduce the frequency of neural tube defects in the general population. After the birth of an affected child, the use of high-dose folic acid prior to and after conception is recommended for subsequent pregnancies.[77]

Diagnosis

Detailed imaging is required for any nasal mass in the neonate prior to biopsy since anterior encephalocoeles may be confused with dermoids, neurofibromas and teratomas. Investigations may include an MR scan demonstrating a mass with intracranial connection and a CT scan demonstrating a bony defect in the calvarium (see **Figure 19.15** and Chapter 23, Neonatal nasal obstruction).

Classification and treatment

There are various classification systems for encephalocoele, based on the contents of the sac, site of the swelling, location of the skull defect and whether the swelling is



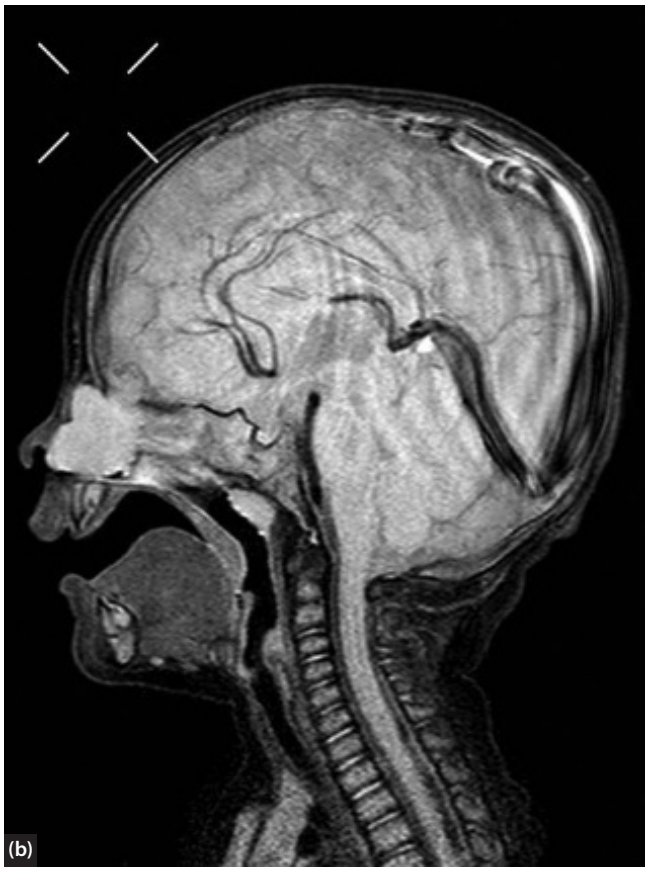


Figure 19.15 **(a)** MRI T2-weighted image of frontoethmoidal encephalocoele. Note the hypertelorism. **(b)** MRI-STIR TSE showing frontoethmoidal encephalocoele.

overt or occult. The most commonly applied system is that relating to the location of the cranial defect.

Encephalocoeles are classified as vault encephalocoeles and basal encephalocoeles based on their location in relation to vault and base of the skull. They are further subclassified as anterior (or sincipital) encephalocoeles and posterior (or occipital) encephalocoeles.

ANTERIOR ENCEPHALOCOELES

Anterior encephalocoeles have been studied extensively by Suwanwela.[78] Mahapatra further classified anterior encephaloceles[79] as follows:

A. Frontoethmoidal group
   i. Nasofrontal
   ii. Nasoethmoidal
   iii. Nasoorbital
B. Transethmoidal–nasopharyngeal
C. Transorbital
D. Transsellar–transphenoidal
E. Interfrontal (transmetiopic)
F. Anterior fontanelle

The commonest clinical presentation is swelling at the root of the nose, hypertelorism and nasal obstruction. Rare presentations are a leaking encephalocele and even with overt meningitis.

MRI of the brain and spine is the investigation of choice not only to define the lesion but also to identify associated anomalies of the entire central nervous system. Common associated anomalies are agenesis of the corpus callosum (15%), cortical dysplasia (5%) and hydrocephalus in as high as 20% of the cases.[79] CT with fine bone slices is used to define the bony defect and to better plan the bony/soft-tissue repair.

Basal encephaloceles (transethmoidal–nasopharyngeal, transphenoidal) have been at times mistaken for skull base lesions/tumours and biopsied, causing a surgical emergency in the process with CSF leak and meningitis.

Treatment

The frontoethmoidal group of encephalocoeles are managed through a bicoronal incision and craniotomy of the frontal bone and orbital bar in order to expose the neck of the encephalocoele. The neck is defined and incised to expose the contents (mainly gliotic brain). The neck is transected and repaired using dural graft. Though one-stage repair of encephalocele and correction of hypertelorism is practised by some centres around the world, our usual practice is to do a two-stage repair and defer the correction of the hypertelorism to a much later date once the upper facial growth is deemed to be complete.

The commonest post-operative complication is the development of CSF leak and hydrocephalus, which may necessitate insertion of a VP shunt in as many as 15–20% cases.

Both open and endoscopic modalities of treatment have been proposed. The recent development of endoscopic transnasal techniques has allowed the repair of these unique lesions in a minimally invasive manner as a joint neurosurgery–ENT procedure. The technique differs from the standard transcranial approach as the fundus of the encephalocoele is encountered first and the neck later. The sac of the encephalocoele sac is reduced in size with the help of cautery and the contents removed or replaced intracranial before the neck of the encepholocoele is encountered and transected. The authors' usual practice is the use of fascia lata and autologous fat to repair the skull defect and buttress the repair with a lumbar drain for a minimum of 5 days.

POSTERIOR ENCEPHALOCOELES

Vault encephalocoeles can vary greatly in size from being just a tiny skin blemish in the midline (cephalocoeles) to giant encephalocoeles. Large posterior encephalocoeles can present with difficult delivery because of their size, which can be at times giant (e.g. the size of the encephalocoele bigger than the size of the baby's head).[80]

Cephalocoele is often associated with venous anomalies such as vertical embryonic positioning of the straight sinus, splitting of the superior sagittal sinus, vein of Galen elongation, along with tenting of the tentorium.[81]

Treatment

Surgical management is primarily necessary where there is a risk of infection through communication of the lesion with the intracranial space or of rupture, or for cosmetic purposes. Surgical excision is curative in the majority of the vault encephalocoeles. Good pre-operative assessment of the venous sinus anatomy in relation to the lesion is useful in preventing serious vascular damage.

Giant encephalocoeles require semi-elective excision for fear of rupture and CSF leak and also to facilitate baby care and positioning in the cot. In the post-operative period more than 50% develop hydrocephalus and require VP shunt insertion. Associated secondary Chiari malformation and secondary sutural synostosis may require further treatment.

Prognosis

A significant percentage of the children who undergo repair of encephalocoeles will face growth, development and learning challenges and will require long-term follow-up in order to address these issues. Outcome for treated anterior encephalocoeles tends to be better than occipital encephalocoeles, with figures as low as 4 of 65 with long-term intellectual impairment.[76]

CRANIOFACIAL CLEFTS

A craniofacial cleft happens as a result of a failure of fusion of the various embryonic processes from which the craniofacial complex is formed. The exact incidence of craniofacial clefts is not known but can be estimated to be approximately 2 : 100 000 live births.[82]

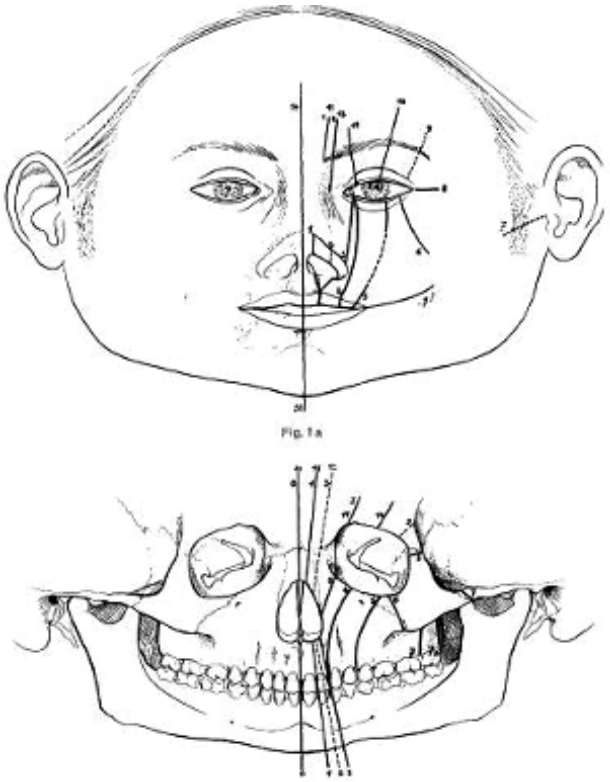


Figure 19.16 Tessier clefts. Reprinted from Tessier P. Anatomical classification of facial, craniofacial and latero-facial clefts. J Maxillofac Surg 1976; **4**: 69–92, with permission from Elsevier.[83]

Aetiology

The interplay of hereditary and environmental factors is complex and with few total cases is yet to be elucidated in detail. The majority of craniofacial clefts occur sporadically. Many factors have been implicated in the formation of craniofacial clefts, including drugs (e.g. anticonvulsants, corticosteroids and chemotherapeutic agents), radiation, infection, amniotic bands and metabolic disturbances during pregnancy. Craniofacial clefts may also be seen as part of wider syndromes such as Goldenhar syndrome.

Classification

Tessier[83] classified facial clefts according to their relationship with the orbit, nose and mouth. Numbering the clefts from 0 to 14 allowed the lower numbers to relate to the facial clefts and the higher numbers the cranial extensions (**Figure 19.16**) (see Chapter 18, Cleft lip and palate).

Clinical features

The clinical features are variable depending on the type of cleft. Clefts affecting the interorbital area result in hypertelorism and orbital dystopia (see **Figure 19.17**).

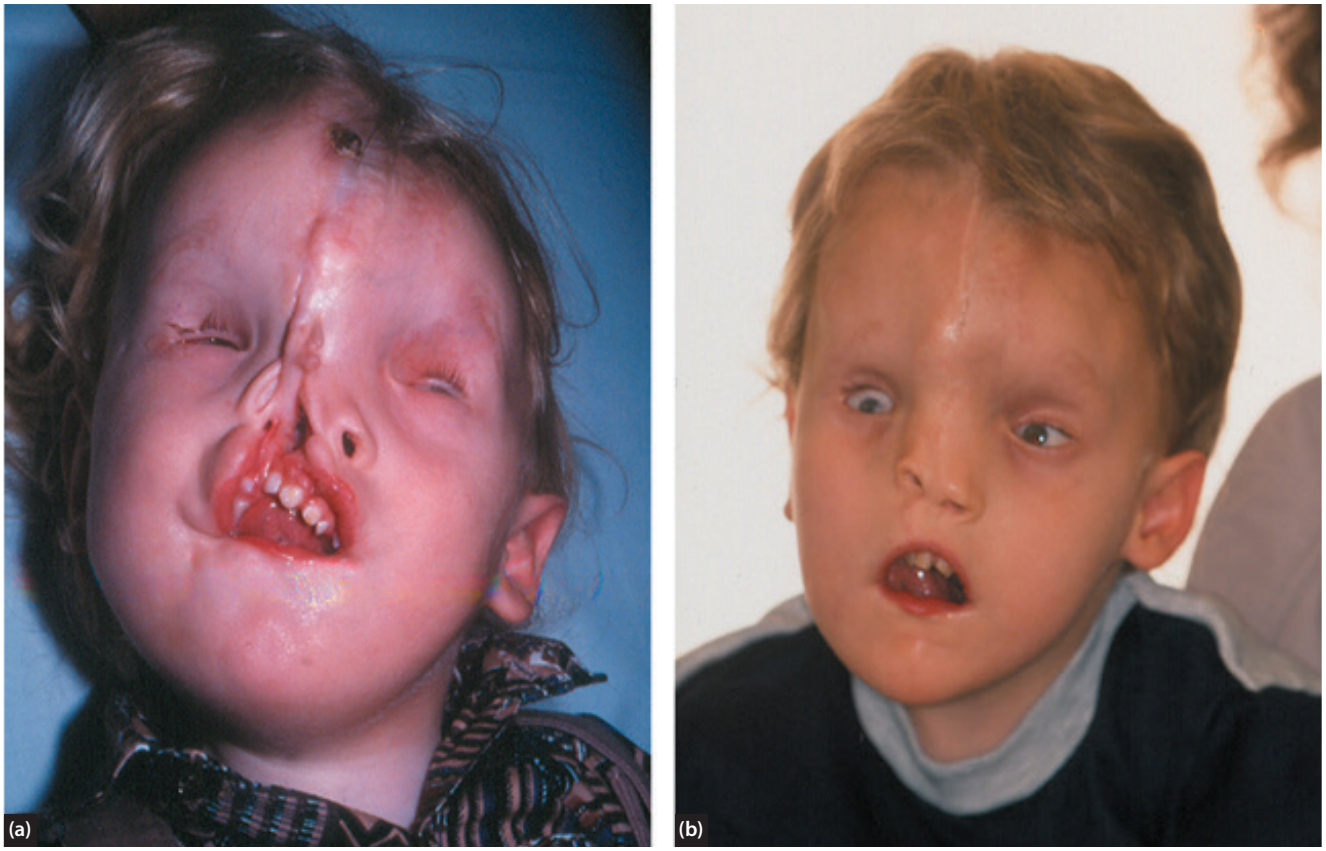


Figure 19.17 Facial cleft. Pre-operative **(a)** and post-operative **(b)** views.

Management

Surgical treatment will depend upon the site, size and severity of the cleft. The extent of the cleft can be variable, ranging from a notch in the soft tissues or soft-tissue deficiency to a severe cleft affecting skin, bone and brain.

Treatment will usually involve reconstitution of the layers, replacement of missing anatomical structures and normalization of secondary distortions.

FUTURE RESEARCH

- Technological advances have allowed the implementation of endoscopic instruments in the attempt to perform a relatively smaller craniofacial operation. The most common situation is currently to perform an endoscopic strip craniectomy for scaphocephaly combined with helmet therapy to achieve the desired morphological head shape change. Advocates of this technology and these techniques state that there is a smaller incision and also less blood loss intra-operatively. The converse argument, however, is that, if there is an intra-operative complication such as massive blood loss or dural tears/air emboli, surgical access is limited and significant blood is lost prior to being able to control it.
- Spring-assisted cranioplasty has been utilized in a number of conditions. Originally introduced by Lauritzen,[34] the procedure involves inserting an omega-shaped spring, made of stainless steel wire, usually after a osteotomy has been performed. The spring is then inserted and a constant force is applied across the osteotomy site. This technique shows great promise and has a proven track record from a safety point of view. Some criticism, though, has been received from not being able to modify the direction of expansion, sometimes a compromised aesthetic outcome and they require a second procedure to remove them.
- Mandibular distraction in children with mandibular hypoplasia to improve airway. Classically, this has been utilized in Pierre Robin sequence in an attempt to improve airway obstruction and prevent the need for tracheostomy, but there is growing evidence to suggest that most forms of significant mandibular retrognathia will benefit from distraction osteogenesis.[84] The procedure can be repeated in severe cases.
- High-resolution 3D imaging has allowed for the introduction of computer-assisted surgery. Detailed scans are imported into a proprietary program which allows manipulation of the 'bones'. Pre-surgery osteotomy cuts can be simulated by the computer, predicting the outcome of the operation. This then allows cutting guides to be fabricated intra-operatively and patient-specific plates to created. The significant benefits of this include an increase in speed of the operation and a predictable outcome that is visualized prior to surgery.

KEY POINTS

- Craniofacial surgery is undertaken in designated centres, with access to MDTs and critical care facilities.
- Children with syndromic craniosynostosis have a high incidence of airway problems, including OSA.
- Some children with severe craniofacial disorders will need long-term tracheostomy.
- Children likely to develop OSA should be monitored both clinically and with PSG to detect severity of OSA and to plan early investigation and intervention.
- Microtia is an important feature of many craniofacial disorders, particularly OAVS/hemifacial macrosomia and Treacher Collins syndrome
- Detailed imaging is essential for any nasal mass in the neonate prior to biopsy.
- Families of children with craniofacial disorders should be offered a consultation with a clinical geneticist.

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CHAPTER 20

BALANCE DISORDERS IN CHILDREN

Louisa Murdin and Gavin A.J. Morrison

SEARCH STRATEGY

A number of search strategies were employed for this chapter. Using dizziness, vertigo, paediatric/pediatric/child and the major conditions as keywords, the following databases were consulted: Embase, Ovid Medline (R) and Journals @ Ovid full text subset.

INTRODUCTION

Young children do not usually complain of vertigo; history and diagnosis can be elusive. Owing to this, the pattern of symptoms in the very young has a wide differential diagnosis. Once middle ear disease and congenital or hereditary sensorineural conditions have been excluded, a large percentage will have dizziness associated with migraine. Posterior fossa neurological disease should be considered; in older children, adult causes of vertigo may be seen. Reassurance that the prognosis is favourable, and antihistamines such as cinnarizine or, if appropriate, antimigraine treatments are usually effective.

Estimates of prevalence of vestibular disorders in children suggest that the experience of vertigo is not especially rare. In one community-based study of children aged 1 to 15 years, 8% had experienced vertigo and in 23% of these it was severe enough that it interfered with activity.[1]

MATURATION OF THE VESTIBULAR SYSTEM

The otic capsule develops early in gestation between the fourth and twelfth weeks of intrauterine life. As the vestibular system is phylogenetically older than its auditory counterpart, each stage in development is in advance of the auditory system and therefore less vulnerable to environmental insult. The semicircular canals have formed from the utricular portion of the otic vesicle by the 30 mm stage, while the cochlear duct has two and a half coils by the 50 mm stage.[2] The vestibular nerve myelinates by 16 weeks *in utero*. By 24 weeks there is even a primitive vestibulo-ocular reflex present.

After birth, at 4 months of age, the baby can tilt its head to keep it vertical. It is the first sensory system to develop. Vestibular function is present at birth. Full-term babies demonstrate a 'doll's eye response'. When the baby is rotated, eye and head deviation is seen in the direction opposite to the direction of rotation. This is akin to the nystagmus seen in adults on rotation, but without the saccadic fast phases that have not yet matured at this age. Maturation of the vestibulospinal and vestibulo-ocular reflexes continues so that responses are maximal at 6–12 months of age.

Beyond this, responses decline, as part of normal motor development, to reach adult values around 10–14 years of age. Bithermal caloric responses can be made in 9-month-old babies if necessary, to measure the vestibulo-ocular reflex. Vestibular nystagmus in children, however, tends to be of a lower frequency and greater amplitude. Maximum slow-phase velocity readings are often similar to those in adults, but the normal ranges for the canal paresis and directional preponderance calculations are wider than those seen in adults.

Infantile reflex responses and motor milestones

The Moro response comprises a sudden bilateral extension of the upper limbs evoked by sudden jarring of the cot or dropping the head backwards by a few centimetres. This response is present in normal children at birth, and disappears by the sixth month. The secondary inherent responses are righting responses and protective reactions. From 4 months, the infant will tilt the head to maintain it vertical if the trunk is tilted laterally through 30° (head-righting reflex). The ages of sitting unsupported, crawling and walking bear some relation to vestibular function but also depend upon neurodevelopment. Vision also plays an important part in postural control.

ASSESSMENT OF THE DIZZY CHILD

Symptoms of vertigo in children

Childhood vertigo results from a mismatch of information from the three different sensory systems: vestibular, visual and proprioceptive. Vertigo, however, is much more difficult to recognize in babies and children than in adults; younger children are not able to describe what they are experiencing and may present with other behavioural symptoms. Parents or carers may report seeing the child suddenly cry out and drop to the floor or cling to the legs of adults, pallor, sweating, vomiting, screaming, lying face down in the cot and showing reluctance to be moved.[3] Interestingly, children born with a congenital lack of normal vestibular function often have no balance disturbance at all although they may have mildly delayed motor milestones. Vision remains by far the most important sense for locomotor and balance acquisition.

It is helpful to direct the history taking with a number of principal and most likely diagnoses in mind. In the paediatric age group the principal conditions to consider are:

- benign paroxysmal vertigo of childhood
- migraine associated vertigo
- epilepsy
- central causes of ataxia and loss of balance
- vestibular neuronitis
- BPPV
- adult causes, e.g. Menière's disease.

A more complete list is given in **Box 20.1**.

The presentation of vertigo varies quite dramatically according to the age of the child. While it is possible for 2-year-olds to experience acute vertigo, young children cannot describe this and may even present with torticollis. If there is a delay in motor milestones, children may present with poor balance or falling; this can also be associated with simple conditions such as 'glue ear'. By 5 years of age, short-lived dizzy episodes can be described, the common cause being benign paroxysmal vertigo (BPV) of childhood. By the teenage years, migrainous vertigo, psychogenic vertigo and the adult vertiginous conditions are much more common.

BOX 20.1 Causes of childhood vestibular symptoms

Conditions with hearing loss	Conditions with normal hearing
OME	Motion sickness
Suppurative ear disease	BPV of childhood
Cholesteatoma with fistula	Basilar migraine
Temporal bone trauma	Seizure disorders
Barotraumatic perilymph fistula	BPPV
Menière's disease	Post-traumatic vertigo
Post-traumatic vertigo	Viral labyrinthitis or neuronitis
Enlarged vestibular aqueduct syndrome	Posterior fossa tumours
Other congenital temporal bone anomalies, e.g. CHARGE association	Cardiac causes: syncope and arrhythmias
Dehiscent superior semicircular canal syndrome	Acute poisoning
Drug-induced ototoxicity	Multiple sclerosis and Lyme disease
Congenital syphilis	CNS infections: Coxsackie A and B, echovirus encephalitis or HIV infection
Herpes zoster oticus	Meningitis: viral or bacterial
Congenital CMV infection	Chiari malformations
Metabolic conditions: Hurler syndrome, hypothyroidism	Hereditary cerebellar ataxias
Usher syndrome	Acute cerebellar ataxia

History taking

It is helpful to establish the nature of the dizziness, whether it is true vertigo, loss of balance or a light-headed faint feeling. The duration and periodicity can be useful guides, as may precipitating factors such as head or neck injury.

The presence of frequent headaches and whether they occur with vertigo or at other times is important. Associated vomiting may be an indication of an acute true vertigo, a migraine phenomenon or the presence of raised intracranial pressure. Associated hearing loss, otalgia or otorrhoea are important. It can be helpful to categorize childhood dizziness into conditions with normal hearing and those with associated deafness (see **Box 20.1**).

A neurological history is essential, specifically if there is anything to suggest temporal lobe seizures, visual or olfactory hallucinations. The developmental history, in terms of the motor milestones, or any regression should be ascertained. The presence of a recent pyrexial illness, the drug history both current, past and, indeed, *in utero* can be important, and various sorts of poisoning should be borne in mind in the child who becomes acutely ill with vertigo and may have ingested something while playing. In the ill, febrile child a range of serious infectious diseases should be considered. In a slightly older child, it may

be more apparent that the problem is one of fainting or hyperventilation, or that there are cyanotic attacks or palpitations in association with the dizziness.

The family history is relevant, especially one of maternal migraine, familial sensorineural deafness or neurofibromatosis type 2 (NF2).

Examination of the dizzy child

Much of the paediatric vestibular examination can be carried out through observation of the child from the waiting area, moving into the consulting room. The routine paediatric examination will include otoscopy. Facial nerve function, tongue movements and the gag reflex should be checked. It is important to look at eye movements. This should include a cover test to check for strabismus and latent nystagmus, and, in particular, to search for nystagmus both with and without visual fixation. Head-shaking nystagmus can also be used effectively in children to unmask a unilateral peripheral vestibular deficit. Smooth pursuit, saccades and optokinetic nystagmus can be elicited using visually attractive targets. The standard clinical balance assessments can be undertaken, such as Romberg's test, Untenberger's stepping test and the tandem heel–toe gait. It is helpful to make this fun for the child by introducing games, such as hopping and kicking a football, to assess balance function better. Head thrust testing can be helpful in diagnosing a unilateral peripheral deficit. Dix-Hallpike positional testing should also be undertaken (see Chapter 62, Evaluation of balance).

Neurological examination of the limbs should be undertaken to seek signs of spasticity, myopathy, sensory neuropathy or other causes of gait abnormality. Rotation testing is easily carried out on an office chair with the child on the parent's lap. Cerebellar ataxia is seen on heel-toe tandem gait with dysmetria, but with normal ranges of lower limb motion and unchanged gait velocity and stride length. Characteristically, gait is wide based with dys-synergia and dysrhythmia, and balance is poor.[4]

Investigations

Audiometry is mandatory. This should comprise a pure tone audiogram or alternative threshold assessment, such as visual reinforcement audiometry, if the child's age or development demands it. Objective testing with brainstem auditory-evoked responses may be indicated. Tympanometry should also be undertaken.

Routine blood tests to exclude anaemia or other blood dyscrasias are worthwhile. The white cell count and inflammatory markers (erythrocyte sedimentation rate – ESR- or C-reactive protein) may give a clue to an infective condition which could have led, for example, to cerebellar encephalitis. Serology should exclude congenital syphilis, and human immunodeficiency virus (HIV) disease might be considered.

Depending on the history and the level of concern, other investigations might include formal rotation testing, bithermal caloric testing with videonystagmography or electronystagmography recordings. Vestibular evoked myogenic potentials (VEMPs) have also been successfully recorded in children and babies.[5] Ocular VEMPs are also suitable to record in children over 2.[6]

Imaging the head and inner ears with magnetic resonance (MR) scanning and/or a high-resolution computed tomography (CT) scan for the bony labyrinth and temporal bones will be indicated in selected children. For example, reassurance that there is no space-occupying lesion in a child with headaches and vertebrobasilar migraine, or defining an enlarged vestibular aqueduct in association with sensorineural hearing loss could be important. If the diagnosis is clinically obvious, however, it is unnecessary to undertake brain scanning.

Where the history indicates it, referral for an electroencephalogram (EEG) and neurological opinion or for an electrocardiogram and cardiac review may have to be considered.

CAUSES OF CHILDHOOD VESTIBULAR SYMPTOMS

The diagnostic flow chart (**Figure 20.1**) summarizes the diagnostic process in managing the child with vestibular symptoms. The conditions are discussed in more detail below.

VESTIBULAR CONDITIONS WITH NORMAL HEARING

Box 20.1 lists most of the conditions that can present with childhood vertigo, dizziness or balance problems. Although the differential diagnosis is extensive, in over half the children who present to the paediatric otolaryngologist with dizziness or disequilibrium, the cause will be otitis media with effusion (OME or 'glue ear'), BPV of childhood or dizziness as a migraine phenomenon.[7] A further study indicates the most common causes for vertigo in children to be migraine in 31% and BPV of childhood in 25%.[8] Other less frequent causes include trauma with deafness, delayed endolymphatic hydrops, benign positional vertigo and, more rarely, cerebellopontine angle tumour, seizures, acute vestibular neuritis or juvenile rheumatoid arthritis. In this study, abnormalities were found in hearing in 24%, in positional testing in 5%, in 11% of bithermal caloric tests, and in 65% on rotational chair testing.[8]

Motion sickness

Motion sickness is caused by a conflict in the kinetic input, often with an excessive vestibular stimulation. Girls are more commonly affected than boys and it tends to settle at puberty. Interestingly, motion sickness can occur in people with blindness, but can also be caused by purely visual stimulation. There is an association with migraine and vestibular dysfunction.[9]

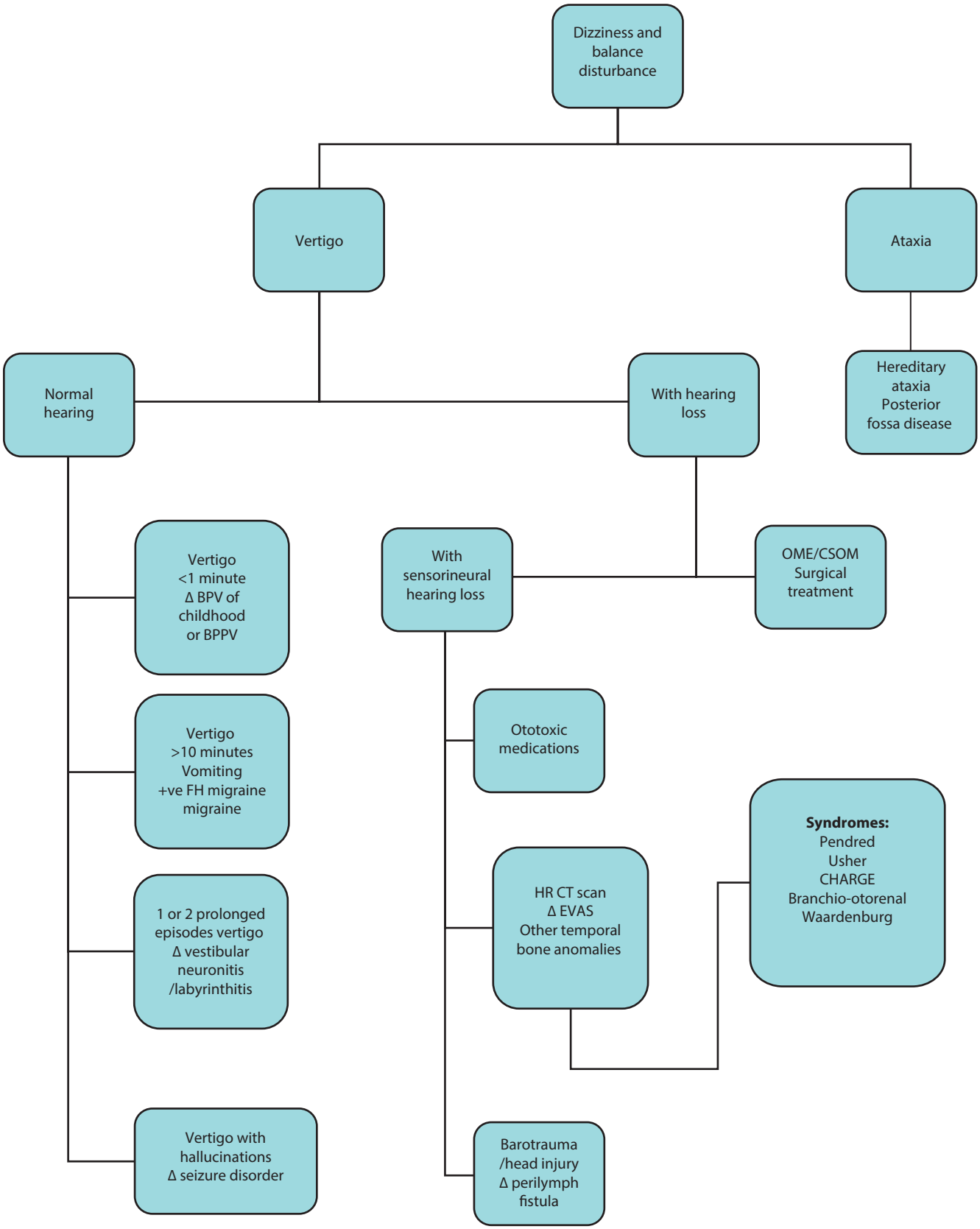

Figure 20.1 Diagnostic flow chart for balance disturbances in children.

Benign paroxysmal vertigo of childhood

Benign paroxysmal vertigo of childhood is not a positional vertigo and is quite different from benign paroxysmal positional vertigo (BPPV). It occurs in children who are aged 4 or over, with no obvious precipitating factors. It is a very frequent cause of paediatric dizziness, being found in 35% of children with dizziness in one series.[10] The child experiences short-lived acute vertigo for 30–60 seconds. He or she may fall or hold onto something suddenly and cry, becoming anxious, pale and sweaty and frequently vomiting. There is then a rapid return to complete normality a few minutes later. Nystagmus is present during attacks which are recurrent and variable in frequency, but interictal neurological examination is normal.[11] Attacks can continue in older children but usually subside. Half of these children go on to develop migraine in adolescence. Most have a family history of migraine. Caloric abnormalities are quite likely to be present if recordings are made.

A related condition that presents in a slightly younger age group is benign paroxysmal torticollis. Torticollis is not related to vertigo, however. There is a suggestion that creatinine kinase levels are likely to be elevated in BPV of childhood, and measurement may be helpful in diagnosis.[12]

BPV has a very favourable long-term prognosis. In one study the condition had resolved by about 8 years of age, and on long-term follow-up 21% had developed migraine but none had any vertigo or balance disorder.[13] The differential diagnosis of a child or baby presenting with marked torticollis is large and varied and should include congenital torticollis, paroxysmal torticollis with vertigo, mastoiditis or neck abscess, skull base tumour and neurological extrapyramidal spasmodic torticollis or psychogenic spasmodic torticollis.

Migraine and vertigo

Migraine is a common multifactorial neurovascular disorder. Several mutations have been discovered for rare forms of migraine; one within *CACNA1A* on chromosome 19p13, a gene encoding for part of a neuronal calcium channel codes mutations for familial hemiplegic migraine type 1 and also in episodic ataxia type 2. Genome-wide association studies have been carried out for more common forms of migraine; however, these are genetically complex with many different contributory genetic variations.

The prevalence of migraine in children and adolescents over periods between 6 months and lifetime is 7.7% (95% CI 7.6–7.8). Migraine presents differently in children when compared to adults, with shorter headaches that are more likely to be bilateral.[11] Vestibular migraine is a subtype of migraine present in the Appendix of the most recent International Classification of Headache Disorders (ICHD) classification. Basilar-type migraine is diagnosed when other symptoms attributable to the posterior circulation are present and ascribed to aura phenomena. Migraine is identified as a primary diagnosis in around 25% of those children presenting with dizziness. Headache need not be present with all attacks of dizziness. In one study into migraine-related vestibulopathy, common vestibular test abnormalities included a directional preponderance on rotational testing, unilateral reduced caloric responsiveness and vestibular system dysfunction patterns on posturography.

If dietary triggers are identifiable, they can be avoided, but there is no evidence that cutting out foods such as cheese or chocolate reduces frequency of migraine, and restricting children's diets is unlikely to be productive; in some cases it has been the cause of malnutrition.[14] Fasting, by contrast, is a proven trigger so encouraging regular meals and snacks is prudent. If attacks are occurring more than once a week, prophylaxis and prescribing prophylactic antimigraine medications may be considered as an option. Symptomatic relief has also been provided using anti-motion sickness medications, vestibular rehabilitation and pharmacotherapy directed at any associated anxiety.[15] Associated headache can be treated acutely in children over 12 years old with triptans.[16] Some more recent evidence supports selected use in 6–12-year-olds.[14] Electroencephalographic changes are seen during and shortly after a migraine attack but fully resolve in time. EEG, carried out within 4 hours of the onset of symptoms (initial stage), shows a diffuse polymorphic subdelta–delta activity. EEG, performed 16 hours after the onset of symptoms, shows delta–theta activity predominant over the occipital regions.[17]

Videonystagmography studies in children with migraine, undertaken during spontaneous nystagmus, gaze nystagmus, eye-tracking test, optokinetic and positional nystagmus and caloric testing, showed that all patients with migraine had abnormalities in vestibular testing. Analysis of the results suggested a mainly central localization of vestibular dysfunction.[18]

Vestibular neuronitis

Vestibular neuronitis presents as it does in adults, with acute severe vertigo, nausea and often vomiting but normal hearing. Characteristic nystagmus is seen during acute attacks. Children recover more quickly from this disorder than do adults. Half of patients can have repeated episodes, although within a few years attacks become progressively less severe and are likely to cease. Treatment is with vestibular rehabilitation, which in children takes the form of games (ball games, picking up of toys on the floor, and rapid head movements with gaze fixation on fixed targets).[19]

Benign paroxysmal positional vertigo

While in adults BPPV most commonly occurs spontaneously or follows vestibular neuronitis sometime previously, in children it is rare and BPPV is more likely to occur following a head injury or marked whiplash injury. The characteristic nystagmus seen in adults has been documented in children.[20] It has a good prognosis. In one study on children's temporal bones in Boston, 12.7% of paediatric temporal bones examined had basophilic deposits, many of them with otoconial crystals in the semicircular canals. That is much higher than the incidence in children

who had any vertigo symptoms, a temporal bone finding mirrored for this condition in adults.[21] The exact pathogenesis of BPPV is not yet fully explained.

Post-traumatic vertigo

The complaint of dizziness and headaches quite commonly follows head injury in children. The relatively high incidence of these persistent post-traumatic symptoms in children and adolescents presents a diagnostic challenge. It is often difficult to differentiate between functional complaints generated by psychological trauma or compensation seeking and an organic aetiology.[22]

Seizure disorders

Recurrent unprovoked seizures due to epilepsy are either generalized or localized (focal). Seizure disorders can give rise to vertigo in two ways: first, in the aura of a generalized (grand mal) fit; second, as vertiginous epilepsy or vestibulogenic epilepsy. In temporal lobe or occipital lobe focal epilepsy there may be transient loss of consciousness or amnesia; the child may describe the sensation of movement and may have visual or auditory hallucinations. There may be motor or emotional components. Convulsive epilepsies are generally unmistakable. Absence epilepsies may be recognized by the provocation of an episode during hyperventilation. Complex partial seizures in children can be difficult to distinguish from behavioural problems, shuddering attacks, paroxysmal vertigo, breath-holding spells, cardiogenic syncope, night terrors and movement disorders, such as paroxysmal kinesigenic choreoathetosis.[23]

A comparison of the elementary visual hallucinations of 50 patients with migraine and 20 patients with occipital epileptic seizures showed that in epileptic seizures they are predominantly multicoloured with circular or spherical patterns as opposed to the predominantly black and white linear patterns of migraine. This simple clinical symptom of elementary visual hallucinations may be helpful in distinguishing between classic or basilar migraine and visual partial epileptic seizures, particularly in children.[24] Referral to paediatric neurology is required if vertiginous epilepsy is suspected.

Psychogenic (conversion reaction) vertigo

Psychogenic dizziness should be diagnosed after excluding organic pathology. Sometimes seen in adolescents, more commonly girls, it is said to occur in children who are put under parental pressure to achieve. Recurrent fainting episodes can be seen in adolescence, when the possibility of a cardiac cause should be considered. In surdocardiac syndrome, for example, there is a prolonged QT interval, fainting and a risk of sudden death.

Psychogenic vertigo as a conversion reaction can be seen alone or in association with psychogenic hearing loss. The discrepancy between symptoms and findings in audiometric or vestibular tests is the essential clue for reaching a diagnosis of a conversion disorder. Referral to a psychiatrist may be necessary because many patients have problems in school or at home, and recovery may take a long time.[25]

Miscellaneous conditions with normal hearing

There are a number of other conditions which can mimic vertigo that are worth considering in the infant or child with unusual symptoms. These include toddler breath-holding attacks.

POISONING

In a child with dizziness, nausea and vertigo, among other symptoms, acute poisoning from plants, chemicals or drugs should be considered.

ATAXIA

Ataxia and other primarily neurological, hereditary or degenerative conditions are rare. They are discussed in a separate section (see 'Persistent imbalance and ataxia: central disorders' below).

VESTIBULAR CONDITIONS WITH ASSOCIATED HEARING LOSS

Otitis media with effusion and chronic suppurative ear disease

Glue ear may be detected in the clumsy child with poor balance who is more prone to falls than his siblings or peers. Chronic suppurative otitis media (CSOM) with perforation and infections can influence general balance and CSOM with cholesteatoma carries the possibility of a fistula to the lateral semicircular canal or oval window accounting for dizziness or leading to suppurative labyrinthitis.

Menière's disease

Childhood or adolescent onset of Menière's disease, although uncommon, is well documented. In one series, sporadic Menière's disease began in childhood in less than 3%, although, in the less common familial Menière's disease in more than 9%, no doubt due to the phenomenon of anticipation. The clinical features are indistinguishable from those in adults; however, early onset tends to be associated with more aggressive disease and a likelihood of relatively early bilateral involvement.[26, 27]

Associated temporal bone abnormalities and hearing loss

In numerous conditions and syndromes there is sensorineural hearing loss with temporal bone anomalies. In only a small number of these conditions are children likely

to present with vestibular symptoms. Vision remains the most important special sense in acquiring balance. Children with bilateral vestibular impairment may be delayed somewhat in motor development but rarely present with vertigo. Not surprisingly, in conditions where there is abnormal or absent vestibular development and visual loss, children are more likely to present with balance disturbances. Children with Usher syndrome have vestibular hypofunction and may therefore have balance difficulties when vision is also impaired.

In CHARGE association (see Chapter 23, Neonatal nasal obstruction) there are frequently abnormalities, for example a primitive otocyst, and such children may have absent semicircular canals and an aberrant facial nerve. A study from Ann Arbor researched patients with severe sensorineural hearing loss and agenesis of the semicircular canals. Most had CHARGE syndrome, some were non-syndromic, and one had Noonan syndrome. They did not present with vertigo.[27] X-linked hereditary deafness is another example in which vestibular symptoms are uncommon despite vestibular hypofunction. Vestibular hypofunction may be present in Down syndrome.

Enlarged vestibular aqueduct syndrome

Enlarged vestibular aqueduct syndrome is a rare congenital anomaly; vestibular disturbance is uncommon but is seen in 4% of children. Fluctuant and progressive sensorineural hearing loss is the norm and is bilateral in 87% of cases. A vestibular aqueduct radiologically wider than 1.5 mm at its midpoint or wider than 2 mm at the operculum is defined as enlarged.[28] Most patients maintain stable hearing in at least one ear over a 4-year period. It can occur in non-syndromic conditions but is also found in 50% of patients with Waardenburg syndrome (types 1 and 2), in which there may be significant widening of the vestibular aqueduct at its midpoint together with other temporal bone anomalies.[29] These children tend to have profound or severe hearing loss. Up to 30% of children with Waardenburg syndrome have vestibular impairment and some experience episodic vertigo. Enlarged vestibular aqueduct syndrome is also seen in Pendred and the branchio-otorenal syndromes, often with an associated Mondini deformity in the former. Patients with enlarged vestibular aqueduct syndrome may show an autosomal recessive inheritance (see Chapter 10, Management of the hearing impaired child).[30]

Avoidance of head injuries is recommended but this may not influence the progression of deafness. The pathogenesis is ill-understood. Surgery to occlude the vestibular aqueduct remains controversial. Conservative management is advised.

The patent cochlear aqueduct

The cochlear aqueduct at its narrowest portion is 0.14 mm wide. It widens as it opens into the posterior fossa with a very variable size at this point. The late Peter Phelps, who had extensive experience in the histopathology of temporal bones, stated that his study of 1400 normal temporal bones and 29 with dysmorphic labyrinths had failed to show a dilated cochlear aqueduct, and he believed that sensorineural deafness attributed to this, in fact, related to defects at the fundus of the internal auditory canal (Phelps P, personal communication).

Dehiscent superior semicircular canal syndrome

Dehiscent superior semicircular canal syndrome has been described. It can be demonstrated on high-resolution CT scanning. Typically, vertigo or oscillopsia is evoked by loud noises or by stimuli that result in changes in middle ear or intracranial pressure. The Tullio phenomenon (vertigo in response to sound) and Hennebert's sign (a positive fistula test with a normal middle ear) may therefore be found. Three-quarters of patients also experience chronic dysequilibrium – often the most debilitating symptom.[31] The condition may also present with an apparent conductive hearing loss. Evoked eye movements, by Valsalva manoeuvre against pinched nostrils, tragal compression or sounds over 100 dB at 500–2000 Hz, produce vertical and torsional components. Surgical repair via the middle fossa approach is successful. Radiologically, dehiscence in children is fairly common (27.3% of children under 2), but the degree to which this correlates with clinical symptoms is unclear.[32]

Perilymph fistulae

Perilymph fistulae in children are usually seen in association with temporal bone anomalies and pre-existing severe or total hearing loss in the affected ear. They may present with recurrent meningitis or with cerebrospinal fluid (CSF) behind the tympanic membrane. Perilymph fistulae can arise directly from blunt trauma to the middle ear or from temporal bone fractures and, iatrogenically, after ear surgery for CSOM or poststapedotomy. More rarely, marked barotrauma may lead to a fistula from the round or oval windows. In all these situations surgical exploration to seal the fistula is indicated. Spontaneous perilymph fistula in the normal temporal bone, however, is probably almost never seen.

In the late 1980s there was a vogue for clinically diagnosing a spontaneous perilymph fistula in children and adults who presented with symptoms of hearing loss, vertigo and sometimes tinnitus. These patients were subjected to surgical exploration of the middle ear with sealing of the apparent fistula. In general, the hearing outcomes from surgery did not seem to correlate with the finding of a fistula and, indeed, it can be very difficult at surgery to be sure if there is any real perilymph leak. To address some of the problems inherent in the diagnosis and treatment of perilymph fistulae, records of patients operated on at the House Ear Clinic over 12 years were reviewed retrospectively. Eighty-six patients were surgically explored for fistulae during this period. Thirty-five (40.7%) fistulae were found and 51 ears were patched whether fistulae were found or not. Of the 80 patients who were seen

for follow-up, 35 (43.8%) were subjectively better and 45 (56.2%) were the same. Although the number of fistulae found and the number of patients improved were similar, the composition of the two groups was different. On the basis of audiometric results, improvement in hearing happened in only 18.7% of patients. None of the demographic factors or diagnostic tests was predictive of either the presence of a fistula or the therapeutic outcome.[33]

Another retrospective study by Bluestone et al. on patients undergoing perilymph fistula repair compared pre- and post-operative hearing levels, vertiginous complaints and recurrences. In 92% of ears there was either stabilized or improved hearing and in 3% a decrease was noticed, but this was much later and believed not to be related. The results were similar, however, in the non-perilymph fistula ears, of which 95% had stabilized or improved hearing and, again, 3% had a much delayed decrease. Of the children with vertiginous complaints before surgery, 91% were improved or stable. Only one child felt somewhat worse, but, as with hearing loss, this was later than 6 months after the surgery.[34]

In yet another series of cases operated on for suspected perilymph fistula, ears with a surgically demonstrated fistula and sensorineural hearing loss had either flat or downward-sloping audiograms. At follow-up, vestibular symptoms were found to be eliminated or improved in 96% of cases with surgically demonstrated fistulae and in 68% of cases in which no fistula was detected at tympanotomy, but hearing improved significantly in only one ear (4%) of the former group and in five ears (20%) of the latter group.[35]

To conclude, perilymph fistulae can be a cause of hearing loss, vertigo or tinnitus and these symptoms may be fluctuant and possibly progressive. There is currently no good diagnostic test for a small fistula. In the paediatric population the most frequent cause is a congenital fistula. Severe or profound hearing loss is, in this instance, always associated with temporal bone anomalies when a perilymph/CSF leak may be present with fluid behind the tympanic membrane. A defect in the stapes and continuity with the fundus of the internal auditory meatus is one such example. This can be found with a true Mondini deformity, in which case some hearing from the basal turn of the cochlea is possible. These cases will require surgical exploration and closure of the leak, not to improve or restore hearing but in an attempt to prevent subsequent meningitis.

Traumatic perilymph fistulae with normal temporal bone anatomy are rare. They are described following head injury and penetrating injury to the middle ear with or without temporal bone fracture, but diagnosis is difficult.[36] A persistent perilymph fistula following ear surgery requires re-exploration. Severe barotrauma can also produce a fistula from the round window or oval window. Clinical suspicion will lead to the decision to explore the ear surgically. More obvious bony erosion with fistula is not infrequently encountered in the presence of cholesteatoma. Exploration and closure of the fistula is indicated. Spontaneous perilymph fistula, in the absence of head injury, direct injury or barotrauma can be virtually discounted.

Drug-induced vertigo or imbalance

Ototoxic medications, in particular aminoglycosides, can cause marked vestibular dysfunction with acute vertigo at the time of administration or poor balance, ataxia and motor delay. These drugs might have been administered systemically prenatally to the mother or in postnatal life, but occasionally topically in the presence of a chronic perforation or grommets. Fortunately, however, hearing loss from systemic aminoglycosides given to an infant is unusual. Some degree of vestibular loss may be more common and underdiagnosed. Streptomycin and gentamicin are more selectively vestibulotoxic. In one study, children who had previously been treated with streptomycin commonly showed delay in walking.[37]

Antimalarials such as mefloquine, which is cleared only slowly from the body, can cause dizziness or hearing loss. Platinum-based cytotoxic agents can cause ototoxicity, usually high-tone hearing loss and tinnitus rather than dizziness.

Miscellaneous conditions with hearing loss

Infectious aetiologies such as congenital cytomegalovirus (CMV) infection can include sensorineural hearing loss with vestibular symptoms and metabolic diseases such as Hurler syndrome can be seen with a retrocochlear type of hearing loss and vestibular impairment. Herpes zoster oticus can occur in children.

PERSISTENT IMBALANCE AND ATAXIA: CENTRAL DISORDERS

Toddlers may present with imbalance and a delay in motor development, or with a subsequent deterioration in vestibular function. They can have falls, fear of the dark, abnormal gait and vomiting. Primary developmental delay with motor delay and poor balance suggests a congenital or early acquired neurodevelopmental disorder, while regression of balance and locomotor function that was previously acquired indicates the need to exclude a space-occupying lesion such as meningioma or medulloblastoma. A family history of NF2 would raise suspicion. Any severe illness or even major surgery in a baby or smaller child will not infrequently lead to temporary loss of previously acquired skills such as the ability to walk.

ATAXIA

Ataxia is a common mode of presentation of cerebellar, posterior column and vestibular disease in children. The aetiology of ataxia covers a broad range, from infections to rare hereditary metabolic diseases. The importance of recognizing potentially reversible conditions such as vitamin E deficiency and Refsum's disease has been stressed.[38]

Hereditary cerebellar ataxia

Hereditary cerebellar ataxia presents with a slowly progressive ataxia although a posterior fossa tumour must be excluded by imaging. Cerebellar disorders display a variety of inherited and sporadic causes. Advances in genetics have led to the successful classification of over 20 forms of autosomal dominant and recessive cerebellar ataxia with variable phenotypes and have shed light on the underlying pathophysiology of many of these disorders. Successful disease-modifying or symptomatic treatments for these conditions, thus far, have remained limited.[39]

Refsum's disease

Refsum's disease is a disorder of lipid metabolism with pigmentary retinopathy, demyelinating neuropathy, ataxia and hearing loss. There is progressive difficulty in walking which develops between the ages of 4 and 7 years. In some cases the site of the hearing abnormality in Refsum's disease may be 'post-outer hair cells'.[40]

Charcot–Marie–Tooth disease

The most common hereditary degenerative condition is Charcot–Marie–Tooth disease. Inheritance is autosomal dominant. Perineal muscle atrophy is usual, congenital sensorineural deafness is present in some cases and there can be vestibular weakness. These children develop spinal scolioses and pes cavus.[41]

Acute cerebellar ataxia

Acute cerebellar ataxia occurs, usually in the first 3 years of life, in a child who was previously normal. It follows a viral febrile illness a few weeks beforehand. There is sudden ataxia, and the condition may take a number of months to resolve or leave some permanent sequelae. Neuroimaging should be considered in all children with new-onset ataxia.[42]

Chiari malformations

Type 1 Chiari malformation is characterized by cerebellar tonsil herniation through the foramen magnum. Children most commonly present with bilateral vocal cord paralysis and associated upper airway obstruction but they can also present with positional vertigo and a central type of nystagmus. The condition can be more severe and associated with syringomyelia, in which case there can be neurological improvement after foramen magnum surgical decompression. Type 1 may present to otolaryngologists.

Type 2 Chiari malformation is the same as type 1, except that in addition there is a non-communicating hydrocephalus and lumbosacral spina bifida. Type 3 can have any of these features but with cervical or occipital bifida. Children with types 2 and 3 have widespread neurological abnormalities and are unlikely to attend ENT clinics.

Miscellaneous conditions

Demyelination can present in post-pubertal children, in which case vertigo is quite commonly seen. NF2 with posterior fossa meningiomas or vestibular schwannoma are occasionally seen in children, and other intracranial posterior fossa lesions such as medulloblastoma may present with ataxia and vomiting.

Infectious causes

Infectious causes include Lyme disease. Viral infections include meningitis, Coxsackie A and B and echovirus; they can involve the central nervous system with vertigo, nystagmus and cerebellar signs. HIV infection is another possible cause. Bacterial infections include primary meningitis, labyrinthitis as a complication of meningitis or CSOM and tertiary or congenital syphilis.

TREATMENTS FOR VERTIGO

Medical treatments

The causative condition should be treated directly if possible. The mainstay of treatment, however, is usually an explanation to the parents and the child and reassurance.

Symptomatically, vestibular sedatives can be helpful. Antihistamines such as cyclizine or cinnarizine can be taken for more prolonged attacks. Hyoscine patches have been advocated and domperidone is helpful for associated sickness. Use should be limited to acute attacks rather than for chronic symptoms.

Dopamine antagonists including phenothiazines such as prochlorperazine are effective vestibular suppressants. However, there is a greater risk of extrapyramidal side effects when using phenothiazines, especially in children. They should be avoided in babies under 10 kg. Should these medications lead to extrapyramidal effects such as oculogyric crisis, it can be treated acutely with the antagonist, procyclidine, by injection.

HT3 antagonists such as ondansetron are powerful antiemetics, which block serotonin binding at vagal afferents in the gut and in the regions of the central nervous system (CNS) involved in emesis, including the chemoreceptor trigger zone and the nucleus tractus solitarii. Although principally used in post-operative nausea and vomiting or with cytotoxic drug therapy, they may have a role in the vertiginous child, especially if vomiting.

Attacks of vestibular migraine can be treated with domperidone, cinnarizine or cyclizine for nausea, vomiting or dizziness. Serotonin 5-HT1B/1D receptor agonists such as sumatriptan may be useful in management of headaches. Rizatriptan is reported to be more effective than other drugs of this class and other simple analgesics.[14] Preventative measures, if necessary, would be those currently recognized – pizotifen or propanolol – and if those fail, a neurologist might prescribe the full range of antimigraine medications available to use in adults.[16] Topiramate and flunairizine have randomized double-blind placebo-controlled trials in

children that support their use, and there are open label studies in favour of sodium valproate.[14]

Menière's disease may be treated with betahistine, a low-salt diet and possibly diuretics or intermittently by dehydration therapy such as glycerol taken orally. Surgery may occasionally be indicated in severe variants of the disease.

The seizure disorders are usually well controlled with anticonvulsants under the paediatric neurologist's guidance.

Physical treatments for vertigo

If there is benign positional vertigo, the Epley manoeuvre (see Chapter 64, Benign paroxysmal positional vertigo) can be employed successfully. Other vestibular rehabilitation exercises for children who have suffered unilateral labyrinthine damage might be helpful in achieving full central compensation and in speeding recovery.

Surgery for vertigo

Surgery relates to that indicated for specific underlying conditions. Unilateral glue ear with poor balance can be corrected by insertion of grommets (preferably bilaterally, the contralateral ear as a prophylactic measure).

If there is a perilymph fistula from barotrauma, middle ear or mastoid disease, or following surgery, that should be explored and closed. Likewise, suppurative ear disease and congenital or acquired cholesteatoma will require tympanomastoid surgery.

A perilymph/CSF fistula from congenital temporal bone anomalies should be closed surgically in an attempt to prevent future meningitis.

Childhood-onset Menière's disease tends to run an aggressive course with debilitating bilateral disease later in life. Destructive surgery is not advised at an early stage although endolymphatic sac decompression and drainage may have a role.

BEST CLINICAL PRACTICE

- ✓ A full history, neurotological examination and audiometry are required in assessing any child with vertigo.
- ✓ Middle ear disease and congenital sensorineural conditions with vestibular deficits should be excluded.
- ✓ Posterior fossa disease must be excluded where there is ataxia.
- ✓ In some cases, a full blood count, inflammatory markers, glucose, creatinine kinase, thyroid function and special serological tests are helpful.
- ✓ High-resolution CT scanning of the temporal bones and an MR brain scan are often indicated for dizziness with hearing loss.
- ✓ An MR brain scan is indicated for ataxic conditions.
- ✓ Special vestibular tests including bithermal caloric stimulation and rotational chair testing can be helpful in reaching a diagnosis and planning treatment.
- ✓ Referral to a paediatric neurologist is recommended if the diagnosis of a seizure disorder or basilar-type migraine is considered probable.
- ✓ Treatment should comprise explanation and reassurance about the condition and symptomatic medical treatment for the vertigo.
- ✓ Surgical treatment is recommended for significant balance disturbance with OME and for CSOM with cholesteatoma as well as for a persistent perilymph fistula from other causes.

FUTURE RESEARCH

- ➤ The value of bithermal caloric tests, videonystagmography and rotational chair tests has not been demonstrated in the varied paediatric population with vertigo.
- ➤ The benefit of vestibular rehabilitation exercises overencouraging straightforward everyday activities has not been studied in children's treatment regimens.
- ➤ Motion sickness has been subject to observational studies and effects of drug treatments but further research into aetiology and other treatments could be profitable.
- ➤ The role and efficacy (if any) of HT3 antagonists such as ondansetron in the management of childhood vertigo has not been studied.

KEY POINTS

- Vertigo results from a mismatch of three different sensory inputs for balance, i.e. vision, proprioception and the vestibular system.
- Presentation of balance disorders in children differs from that in adults; very young children cannot complain of vertigo.
- Fifty percent of cases of childhood dizziness and imbalance are caused by one of the three most common causes: BPV of childhood, migraine or OME.
- Neurological disease is a rare cause of vertigo in children but must be recognized.
- Adult causes of vertigo are seen in older children/adolescents.
- The mainstay of treatment is reassurance; symptomatic control with medication such as cinnarizine or antimigraine treatments is usually effective.

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CHAPTER 21

FACIAL PARALYSIS IN CHILDREN

S. Musheer Hussain

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the following keywords: facial paralysis, otitis media, congenital facial paralysis, ear trauma, facial nerve injury, granulomatosis with polyangitis, Bell's palsy and parotid surgery. The focus was restricted to neonates and children.

INTRODUCTION

Bell's palsy remains the most common aetiology for facial paralysis in children[1] although it is much less common than in adults. In their study of 170 patients aged from birth to 18 years May et al.[2] found the following aetiology for facial paralysis: Bell's 42%, trauma 21%, infections 13%, congenital 8% and neoplasm 2%.

Bell's palsy in children is considered to have a better prognosis than in adults, regardless of treatment.

EMBRYOLOGY AND APPLIED ANATOMY OF THE FACIAL NERVE

Knowledge of the embryology and developmental anatomy of the facial nerve allows for a clear understanding of the various anomalies and clinical presentations of disorders of the facial nerve.

By the third week of embryonic development the facioacoustic crest is visible on the dorsolateral aspect of the hindbrain just cranial to the otic placode. The otic placode forms the otocyst, giving rise to the membranous labyrinth in the fourth week and the facial nerve becomes distinct. The geniculate ganglion has formed by the fifth week (Figure 21.1). The facial nerve divides into its main trunk, descending into the second branchial arch and the chorda tympani, which being the pretrematic branch curves cranially into the first branchial arch (Figure 21.1).

A pretrematic branch of a cranial nerve is one that supplies the arch preceding the arch to which the cranial nerve belongs. The chorda tympani and the main trunk of the facial nerve are equal in size at this stage. Malformations of the branchial arches are associated with anomalies of the chorda tympani such as elongation of the posterior canaliculus, reduplication and low position of the nerve.[3–4]

The facial nucleus is formed by neuroblasts in the pons, with the sixth nerve nucleus in close proximity. As the brain develops and the pons expands, the sixth nucleus ascends so that the facial nerve fibres have to whirl round the sixth nucleus forming an internal genu. Clinically, therefore,

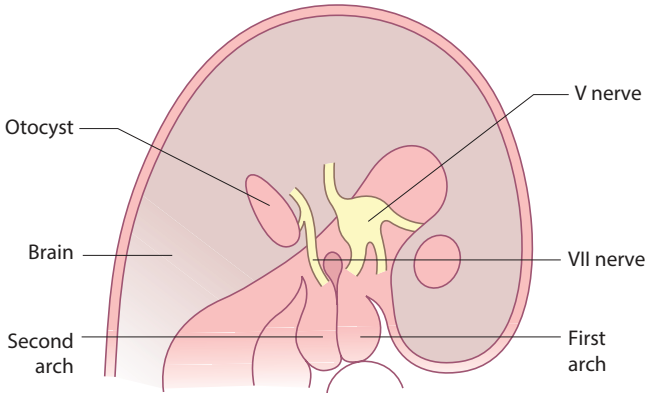

Figure 21.1 Line diagram of the fetal head at 5 weeks, showing the facial nerve.

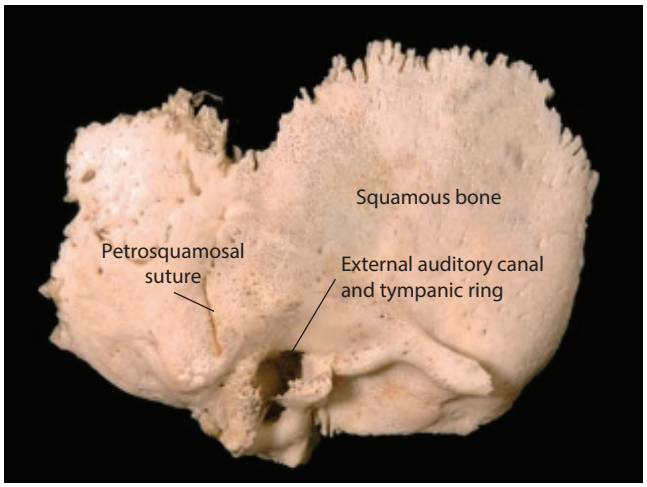

Figure 21.2 Neonatal temporal bone.

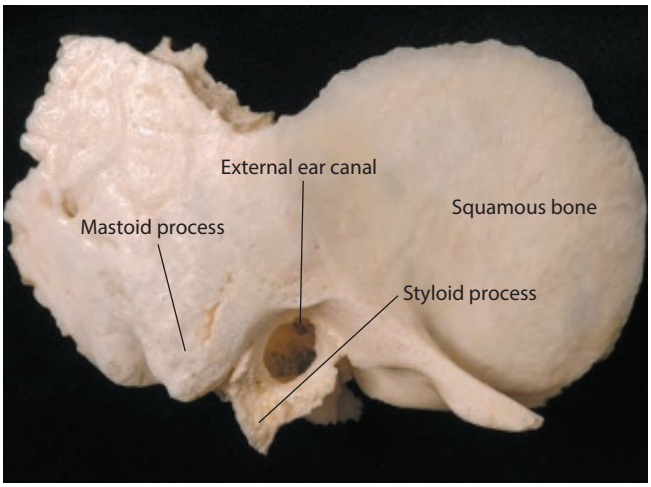

Figure 21.3 Temporal bone of a 1-year-old child.

an inflammatory or vascular event in this part of the brain will necessarily involve both these nerves. In developmental anomalies such as Moebius syndrome there is agenesis of the facial nucleus and among other defects there is also agenesis of the sixth nucleus.[5]

The geniculate ganglion has a separate origin from the facial nerve.[6] It is well defined by the seventh week and gives rise to the sensory roots that form the nervus intermedius. As the main facial trunk descends down the second branchial arch there is caudal movement of the first arch due to rapid expansion, producing the horizontal segment and the first and second genu of the vertical nerve with the greater superficial petrosal nerve acting as an anchor. Proctor and Nager's seminal papers[7, 8] describe the many variations encountered in the vertical segment of the facial nerve including a bipartite nerve, an anteriorly displaced nerve or one with a posterior hump. Failure to appreciate an anomaly of the facial nerve during surgery can have serious consequences.[9–12] Conditions related to malformations of the first or second arch such as Treacher Collins and Goldenhar syndromes will usually mean that the facial nerve is abnormal too.

At birth the normal temporal bone has no mastoid process and an incomplete tympanic ring. The 'U-shaped' tympanic ring has nodular prominences on each arm, which separate the annulus from the future external canal and the foramen of Huschke (**Figure 21.2**). By the end of the first postnatal year these processes fuse, lengthening the canal (**Figure 21.3**). The foramen usually closes some time later. The chorda tympani and the facial nerve may exit through the stylomastoid foramen in the newborn. The mastoid process and external auditory canal are undeveloped so the nerve is very superficial.

The mastoid process develops and reaches adult proportions by the age of 12 years. In neonates and small children the second genu of the facial nerve is more acute and courses more laterally. The most common variation in the course of the facial nerve canal involves the tympanic segment; the bony wall may be dehiscent in 35–55% of the population particularly above the oval window.[7, 8, 13, 14] Acute suppurative otitis media in neonates and children may therefore present with facial paralysis from neuropraxia or bacterial infiltration of the nerve sheath within an enclosed middle ear. Dehiscence of this segment of the facial nerve may be associated with a persistent stapedial artery in its course from the tympanic cavity to the middle cranial fossa where this becomes the middle meningeal artery.[15, 16] The foramen spinosum is absent on the side of the persistent stapedial artery on plain X-ray or CT.

On leaving the stylomastoid foramen the facial nerve enters the parotid gland in a more anterior location than in the adult, as the parotid gland is smaller and more anteriorly placed.[17] The nerve divides into two main divisions and these give rise to branches that supply the face and the upper neck muscles. The lower division of the facial nerve in young children runs very superficially over the angle of the mandible and can be damaged by a skin incision during surgery.

Surgery of the parotid region in children requires an understanding of the differences between adult and child facial nerve topography (**Table 21.1**).

DIAGNOSIS

This is discussed in general terms in this section. Individual conditions are covered under separate headings.

History taking and examination

A detailed clinical assessment is important in the diagnosis of facial paralysis. There may be good muscle tone so that it is difficult to identify the paralysis until the child cries. Associated symptoms that teenagers with facial paralysis may volunteer will not be available in a younger child. Careful attention to the mother's story will be rewarding.

Examination should include careful assessment of each branch of the facial nerve and whether the paralysis is complete or incomplete. The forehead wrinkles are absent and the eyebrow droops in lower motor neuron paralysis. The lower lid tends to fall away from the globe with tears

TABLE 21.1 Differences in the anatomical relationship of the facial nerve in adults and children

Feature	Child	Adult
Mastoid process and tympanic ring	Absent mastoid process and incomplete tympanic ring. The chorda tympani may exit through the stylomastoid foramen with the main trunk in the neonate	Mastoid process present and tympanic ring is complete by adolescence. The chorda tympani exits separately and proximal to the stylomastoid foramen
Second genu of facial nerve	Second genu of the facial nerve is more acute and more lateral	Second genu of the facial nerve is less acute and more medial
Position of nerve trunk	Nerve trunk on exit from the stylomastoid foramen is more anterior and lateral	Parotid is more posteriorly placed and the nerve trunk is less anterior and deeper
Position of nerve	Nerve very superficial over the angle of the mandible	Nerve less superficial over the angle of the mandible

collecting in the eye and spilling onto the face. The cheek may sag and the nasolabial fold may be lost. Speech may change as plosives are distorted with air blowing out on the paralysed side. The appearance of the non-paralysed side of the face is also characteristic as unbalanced muscle action accentuates the difference. The House Brackmann grading is limited but has the advantage of being widely known and may be used in children. Otoscopy is usually possible in even the smallest baby and signs of inflammation should be looked for in the head and neck. Other anomalies of the head and neck and the cranial nerves are noted.

Investigations

IMAGING

Imaging of the facial nerve in children may be useful in delineating the site of neural injury. Indications include persistent paralysis, trauma and suspected nerve involvement in systemic diseases.

MRI is the only modality that demonstrates the facial nerve comprehensively from the pons to the parotid gland; with gadolinium enhancement it is capable of showing inflammatory changes. CT makes it possible to see bony detail and is ideal when facial nerve involvement is in the middle ear cleft.

ELECTROPHYSIOLOGICAL TESTS

Electrophysiological tests allow objective assessment of function. Eavey et al.[18] found that 95% of children can be successfully tested with electroneurography (ENoG). Waveform amplitude and morphology were consistent with adult values except in infants. The most clinically helpful use of this test is to objectively assess facial nerve function, once spontaneous motion is lost in acquired paralysis or if it had never been seen in congenital paralysis. The authors maintain that the test is not an absolute predictor for return of function but that the added data when used with clinical information make assessment of prognosis more rational.

Glassock and Shambaugh[19] recommend a muscle biopsy in neonates with facial paralysis when the electromyography is silent. If muscle is found early, reanimation is advisable.

CONGENITAL FACIAL PARALYSIS

Syndromic and non-syndromic forms of developmental facial paralysis occur. These may be unilateral or bilateral, complete or incomplete. Prognosis is poor.[20, 21] Craniofacial anomalies associated with the first and second arch derivatives are common in this form of facial paralysis.

Nerve exploration is unrewarding in this situation.[22] Reanimation may be considered. There is a wide range of procedures for reanimation; the most desired neural tissue source for rejuvenation of the paralysed face is direct reanastomosis or interpositional grafting. Carr et al.[23] reviewed 186 children with congenital facial paralysis (60% male and 85% with bilateral paralysis) and found 29 in whom reanimation was performed (24 females and 5 males). All 5 males and 9 females had unilateral isolated facial nerve paralysis. Fourteen females had bilateral paralysis; only half of these were isolated. Other involved cranial nerves included abducens, hypoglossal, oculomotor and trochlear. The cranial nerve least likely to be involved was the accessory nerve, suggesting that this may be a reliable donor for reanimation procedures. As previously stated, early reanimation is advised by Glassock and Shambaugh[19] if muscle is found on biopsy in neonates with facial paralysis when electromyography is silent.

Moebius syndrome

Moebius syndrome is a rare cause of facial paralysis in neonates. It is characterized by the absence or underdevelopment of the sixth and seventh cranial nerves. It may be unilateral or bilateral. Agenesis of the facial nucleus is suspected, hence the sixth nerve involvement. Other cranial nerves may also be involved. Autism and mental retardation may be seen in a third of these patients.[5]

Goldenhar syndrome

Goldenhar syndrome (oculo-auriculo-vertebral dysplasia) is a wide spectrum of congenital anomalies that involves structures arising from the first and second branchial arches.[24] Involvement of the internal auditory meatus and the eighth nerve has been reported[25] as well as progressive hearing loss.[26]

Asymmetric crying facies

Congenital asymmetric crying facies is an uncommon condition caused by congenital hypoplasia or agenesis of the depressor anguli oris muscle on one side of the mouth. Although the functional deficit is small, the anomaly may be associated with cardiovascular, head and neck, musculoskeletal, respiratory, gastrointestinal, central nervous system or genitourinary anomalies in 45% of cases.[27]

CHARGE syndrome

The acronym CHARGE is used to describe specific congenital birth defects in children: **c**olobomata, **h**eart defect, **a**tresia of the choanae, **r**etarded development, **g**enital hypoplasia, and **e**ar anomalies and hearing loss. Facial nerve dysfunction has been noted in 38% of patients,[28] and an aberrant course may interfere with cochlear implantation.[29] Many children with the CHARGE association also have feeding and swallowing difficulties, and facial paralysis and pharyngeal in-coordination may be important diagnostic indicators of CHARGE association.[30]

Familial facial paralysis

Familial congenital facial paralysis has been reported in three male members from three generations in a family.[31] The paralysis becomes more pronounced with every successive generation.

Widening of the facial canal

Widening of the facial canal has been reported as a cause of multiple ipsilateral facial palsy in a child of 13 months.[32] The child had recurrent fever and facial palsy and the facial nerve appeared thickening in the widened canal, said to be the result of pressure from inflammation and oedema.

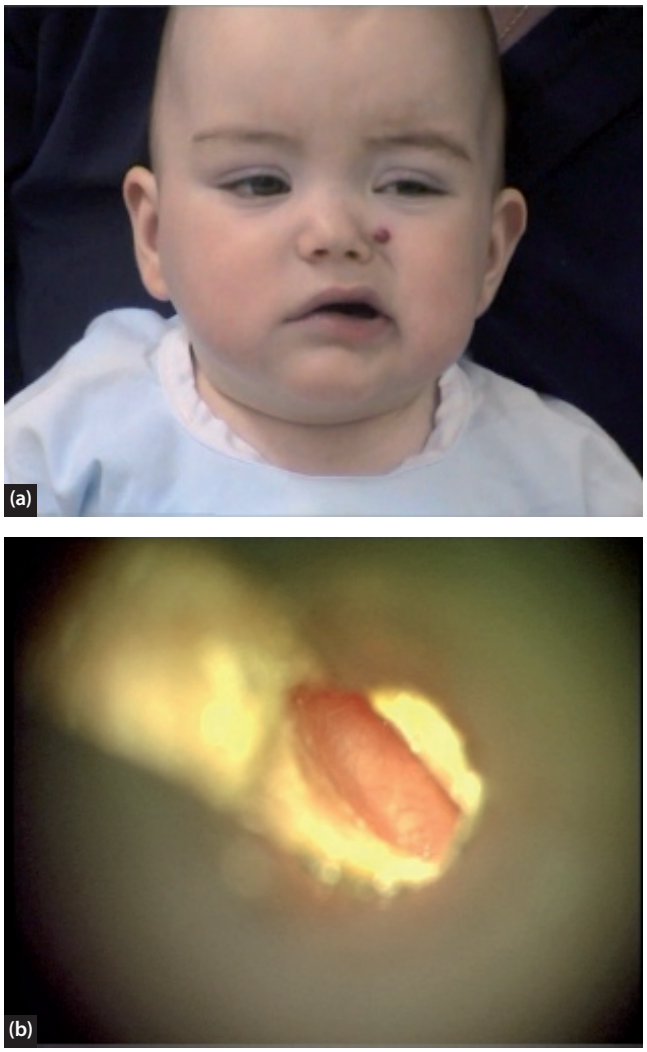

Figure 21.4 (a) Facial paralysis in a neonate caused by acute otitis media; **(b)** the state of the eardrum.

ACQUIRED FACIAL PARALYSIS

Infections

ACUTE OTITIS MEDIA

Acute otitis media in neonates and children gives rise to facial paralysis (**Figure 21.4a**). This is usually incomplete but the paralysis may progress in the first 2–3 days of onset. There is suppuration in the middle ear behind an intact tympanic membrane, which may appear red and bulging (**Figure 21.4b**). The child may be toxic but is typically not unwell. In some cases where antibiotics have been given, the signs of acute inflammation may not be pronounced.

The underlying pathology may be an erosion of the bony Fallopian canal or congenital dehiscence and nerve inflammation. Spread along structures such as the stapedial tendon, chorda tympani or posterior tympanic artery has been suggested. Moreano et al.[14] studied 1000 temporal bones and noted at least one facial canal dehiscence in 56% of temporal bones with the most common site of dehiscence being the oval window area. They introduced the concept of micro-dehiscence of the facial canal and found this in one third of the temporal bones. The most common pathogen in middle ear cleft infections in children is pneumococcus[33] (80%). A wide myringotomy and systemic antibiotics is the initial treatment. If mastoiditis is suspected, a CT scan and a cortical mastoidectomy may be needed. There is usually full recovery of facial nerve function.

CHRONIC OTITIS MEDIA

Facial paralysis in chronic otitis media is very uncommon. Sheehy et al.[34] report 11 cases of facial paralysis out of 1024 patients with chronic middle ear disease and cholesteatoma. Complications of chronic middle disease including facial paralysis are more common in the developing world.[35]

LYME DISEASE

This multisystem disease is caused by the tick-borne spirochaete *Borrelia burgdorferi*.[36] The incubation period is

1–4 weeks before a skin lesion appears. Ipsilateral or bilateral facial paralysis may appear weeks or months later in 11% of cases.[37] A report from Connecticut, an endemic area, describes Lyme disease as the cause of over 50% of facial paralysis in children.[38] Serological tests with ELISA (enzyme-linked immunosorbent assay) to detect IgG and IgM antibodies are used for diagnosis. Doxycycline is the oral antibacterial of choice, while amoxicillin and cefuroxime are alternatives that may be preferred in young children. Tick avoidance has long been the mainstay for preventing Lyme disease.[39]

VIRAL INFECTIONS

Recrudescence of *Herpes zoster* virus in the geniculate ganglion leads to the classical syndrome of Ramsay Hunt. The disease is uncommon in children. Hato et al.[40] in a retrospective study of 52 children with Ramsay Hunt syndrome found that facial paralysis was milder, complete recovery of the function more likely (79%) and associated cranial neuropathies less common in children than in adults. The timing of vesicle appearance tended to be delayed in children. The disease was rare in preschool children but relatively more common in older children. Treatment with oral or intravenous acyclovir and prednisolone has been recommended.[41–43]

Facial paralysis has been noted in Epstein–Barr virus infection and this may be bilateral in 40% of cases.[44] Facial palsy is an early ENT manifestation of HIV infection and is seen in 11% of cases.[45]

TUBERCULOSIS

The presence of facial paralysis with purulent otorrhoea that does not respond to conventional antibiotics should alert the physician to the possibility of tuberculosis. Antituberculous chemotherapy early in the disease may reduce the need for radical surgery[46, 47] and complications of otitis media.[48] CT scan is reported to be of value in the diagnosis of facial paralysis due to tuberculosis.[49]

Traumatic

BLUNT TRAUMA

Perinatal trauma

Birth-related trauma is a known cause of facial paralysis. The incidence of facial palsy in the newborn is 1.8 in 1000, the majority associated with forceps delivery.[50] In their report on neonatal facial paralysis, Smith et al.[51] found 74 out of 95 cases to be secondary to trauma associated with pregnancy and delivery. The diploic bone of the infant mastoid process, the paper-thin bone covering the facial nerve and the very superficial position of the marginal mandibular branch over the mandible all add to the problem. The pressure of the mother's sacrum on the infant facial nerve may also contribute.

In differentiating between congenital and perinatally acquired facial paralysis, the history and physical examination usually suffice. A history of forceps delivery, a baby weighing over 3.5 kg, a primipara mother, prolonged labour and the absence of associated craniofacial anomalies point to perinatal trauma as the cause. The presence of bruising of the side of the face and the mastoid region are suggestive of birth trauma, as are other complications associated with birth.

Electrophysiological tests may be used to aid diagnosis; voluntary action potentials on electromyography (EMG) indicate muscle innervation. EMG performed after 10 days of paralysis will show fibrillation or polyphasic potential in traumatic cases and absent electrical activity in congenital facial paralysis.[52] A CT scan may show a concealed fracture of the temporal bone.

Temporal bone fracture

An injury to the skull may cause temporal bone fracture. The fracture may be longitudinal or transverse or a combination of both. Classically, longitudinal fractures cause conductive hearing loss whereas transverse fractures usually cause irreversible sensorineural deafness. A third of fractures are transverse and these have associated facial paralysis in 50% of cases. Longitudinal fractures are more common and, although the incidence of facial paralysis is less (20%), longitudinal fractures cause more facial paralysis than transverse fractures. As discussed under embryology, the greater superficial petrosal nerve in the region of the geniculate ganglion tethers the facial nerve. In head injury the sudden deceleration creates a shearing force on the facial nerve leading to damage. Lee et al.[53] reviewed 72 children with temporal bone fractures ranging from 6 months to 14 years of age, with a bimodal distribution with peaks at 3 years and 12 years of age. The most common causes of fractures were motor vehicle accidents (47%), falls (40%), biking accidents (8%) and blows to the head (7%). Common presenting signs and symptoms[53] include hearing loss (82%), haemotympanum (81%), loss of consciousness (63%), intracranial injuries (58%), bloody otorrhea (58%), extremity fractures (8%) and facial nerve weakness (3%). The diagnosis of temporal bone fractures is best made clinically and radiographically.

The early care of temporal bone fractures is directed towards the treatment of CSF otorrhoea and immediate-onset facial paralysis. The delayed care is primarily concerned with hearing rehabilitation.[55]

Another classification[56] of temporal bone fractures is based on otic capsule sparing (OCS) and otic capsule violating (OCV) fractures. The otic capsule is spared in 90% of fracture and is a predictor of the absence of sensorineural hearing loss. However, conductive hearing loss or facial paralysis cannot be predicted by the OCS/OCV classification.

Surgical exploration as an option remains controversial, with no randomized controlled study. It does seem reasonable, however, to explore when nerve entrapment is suspected or where the integrity of the nerve is compromised.

PENETRATING TRAUMA

Injury to the face may damage the facial nerve or one or more of its branches. This may be the result of falling

onto a sharp object or a dog bite. The wound needs to be explored and the degree of damage established. This will allow repair with the functioning distal branches in a clean wound. Local control of infection should precede repair in a contaminated wound.

IATROGENIC TRAUMA

Ear surgery

Mastoid surgery in children caries a higher risk of injury to the facial nerve, even in experienced hands. This is due to the absence of the mastoid process in small children and the superficial position of the facial nerve, which is at risk from a low incision. The operating space within the mastoid cleft is small and, if in addition an anomaly is encountered, the problems multiply. The injury may not be identified at the time of surgery and may become obvious when the patient is awake.[57] The commonest site of injury is the tympanic segment and the second genu of the nerve.[58, 59]

Anomalies of the facial nerve encountered in patients with congenital malformation of the middle ear include displacement of the nerve and lack of bony cover.[10] A low-lying tegmen in a sclerotic mastoid is particularly serious and requires skill to protect the nerve at the second genu when drilling in this restricted area. The presence of granulating disease in revision surgery may obscure the usual landmarks and put the nerve at risk. Erosion of the bone by cholesteatoma and its spread to the supra tubal recess[59] puts the geniculate ganglion and the first genu of the facial nerve at risk of injury during disease clearance in the anterior attic. In patients with atresia or stenosis of the external canal the facial nerve may be damaged in its vertical segment due to the vertical segment being relatively lateral to the tympanic annulus. Intra-operative monitoring is advisable.

Injury to the facial nerve and the chorda tympani are recognized complications of cochlear implantation surgery.[60–62]

Parotid surgery

The superficial course of the facial nerve in infants and the underdevelopment of surrounding structures mean that the standard techniques for identification of the facial nerve trunk in adults could jeopardize the nerve in children. An alternative technique for identifying the facial nerve has been proposed by Farrior et al.[17] Anatomic dissections demonstrate that the facial nerve trunk can be consistently found in a triangle formed by the sternocleidomastoid muscle, posterior belly of the digastric muscle and the cartilaginous ear canal. As in the adult, the nerve canal can be identified in the mastoid cavity and followed into the neck. Unlike in the adult, it is inadvisable to use retrograde dissection of the marginal mandibular branch to find the trunk. If surgery is considered for non-tuberculous mycobacteria (NTM) of the intraparotid and adjacent lymph nodes, very careful dissection is required to preserve the facial skin and the nerve (**Figure 21.5**) (see Chapter 37, Cervicofacial infections).

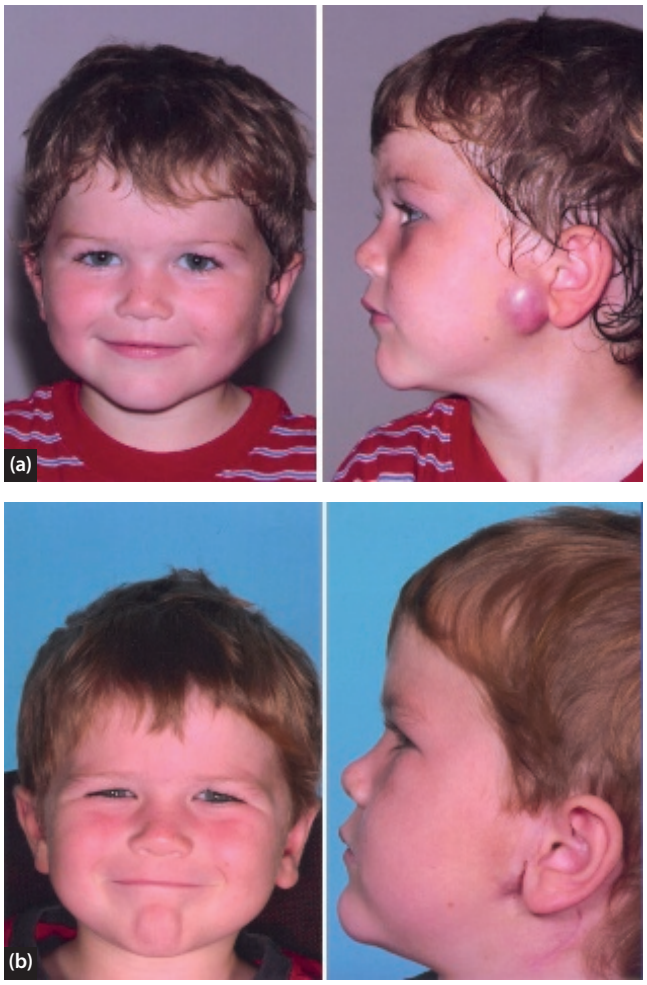

Figure 21.5 Non-tuberculous mycobacteria (NTM) of the parotid. (a) Presurgery; **(b)** 1 week after surgery with preservation of the facial nerve.

Branchial cleft sinus and fistula excision

The variable relationship of the branchial cleft sinus and fistula with the facial nerve makes the nerve vulnerable to injury during surgery. Very careful dissection with intra-operative monitoring is required. D'Souza et al.[63] reviewed the available English, French and German literature between 1923 and 2000 and found 158 cases with fistulae and sinuses. The fistulous tracts were more likely to lie deep to the facial nerve compared with sinus tracts. Lesions with openings in the external auditory meatus were associated with a tract superficial to the facial nerve. Younger children were more likely to have a deep tract with consequent increased risk of facial nerve damage. The fistula may be found anywhere along the anterior border of the sternocleidomastoid muscle.[64]

Solares et al.[65] in their report on ten patients with a mean age of 9 years found seven lesions medial to the

facial nerve, two lateral and one between branches of the facial nerve. (See also Chapter 41, Cysts and sinuses of the head and neck.)

Neoplasms

In children the two commonest causes of facial paralysis from malignancy are leukaemic infiltration of the temporal bone[66, 67] and rhabdomyosarcoma of the head and neck.[68–70] An intracranial tumour may present with facial palsy. Levy et al.[71] describe a case of acute mastoiditis and facial paralysis in a 5-year-old girl where the diagnosis of leukaemic infiltration of the middle ear cleft was made only after surgery and histological examination. Chemotherapy or combined chemo- and radiotherapy are the treatment of choice in known leukaemic patients without symptoms of superimposed infection of the ear or the mastoid process. Surgical management is restricted to cases in which tissue for histological diagnosis is required or drainage of acute infection is needed. A T-cell lymphoblastic lymphoma in the middle ear has been reported,[72] presenting with headaches, hearing loss and facial palsy in an 11-year-old that responded to intensive chemotherapy.

In the Durve et al.[68] series of 14 patients the median age at presentation of rhabdomyosarcoma was 4.5 years with a mean time of onset of symptoms to diagnosis of 21 weeks. Symptoms mimicked those of chronic otitis media, delaying diagnosis. The histological subtype was embryonal in 13 patients and alveolar in 1. All patients underwent multimodality treatment; the 5-year disease-free survival rate was 81%. Facial paralysis was the commonest regional post-treatment morbidity (8/14).

The presence of facial paralysis and lymphadenopathy or a mass with aural discharge, hearing loss and aural polyp should prompt urgent investigation and biopsy.

Benign neoplasm of the facial nerve is very rare in children. Facial paralysis from an intracranial neoplasm is uncommon.

IDIOPATHIC FACIAL PARALYSIS

Bell's palsy

Bell's palsy is the commonest cause of facial paralysis during childhood (42%).[2] It is an acute unilateral lower motor neuron facial paralysis diagnosed by exclusion. It is essential that otoscopy is normal, that there is no middle ear infection and that the hearing is not impaired. There is a body of opinion that attributes Bell's to infection by herpes virus due to a reactivation of latent *Herpes simplex* virus within the geniculate ganglion though the evidence for this is uncertain. There is a family history of Bell's palsy in a small number of patients and occasionally a viral prodrome.

Steroids are advocated in the acute stage for adults, with good evidence from a large randomized controlled trial to support this.[73] There is little evidence either way for children, however, and since the recovery rate is so high in children regardless of treatment (90%), it has been suggested that steroid administration is not required in children.[74]

Melkersson–Rosenthal syndrome

In Melkersson–Rosenthal syndrome, episodes of facial paralysis begin in early childhood or adolescence, predominately in the second decade of life. There is swelling of the lips, palatal mucosa and face, and the tongue is fissured.[75] The facial weakness usually takes a recurring course and is seen in 20% of cases. A conservative approach is usually recommended. A preliminary report suggesting facial nerve decompression for recurrent facial paralysis in Melkersson–Rosenthal syndrome has recently been further substantiated.[76–79]

Granulomatosis with polyangiitis

Granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis) is a systemic disease characterized by the classical triad of vasculitis, necrosis and granulomatous inflammation usually of the upper and lower respiratory tract and the kidneys. Primary otological presentation occurs in 20–25% of patients[80] and this includes facial paralysis.[81] A high index of suspicion, ESR, cANCA and histopathology help diagnose this condition. Combination therapy with corticosteroids and cyclophosphamide is given and cotrimoxazole may be used in the long term to reduce remissions.[82]

Hypertension

Hypertension is a rare cause of facial paralysis in children. Misdiagnosis may lead to serious consequences, as reported by Aynaci and Sen[83] in a case of a hypertensive child with facial paralysis. Bell's palsy was suspected and steroids were given, resulting in hypertensive pontine haemorrhage. Recurrent alternating facial paralyses have been reported in a child with hypertension. Antihypertensive treatment and control lead to cessation of further relapse.[84] A recent systematic review of facial palsy in patients with hypertension found 26 cases, of which 23 were children.[85] The palsy is usually unilateral and may recur in a quarter of cases.

CONCLUSION

The management of facial palsy in children includes treatment for eye exposure, smile asymmetry, drooling and lack of labial function and synkinesis. Free tissue transfer dynamic restoration is the preferred method for smile restoration[86] in this population. The outcomes are apparently better than in adults.

BEST CLINICAL PRACTICE

- ✓ MRI is the only imaging modality that demonstrates the facial nerve comprehensively from the pons to the parotid gland; with gadolinium enhancement it is capable of showing inflammatory changes.
- ✓ Electroneurography is a useful adjunct to clinical findings in predicting recovery from facial nerve palsy.
- ✓ In facial palsy secondary to acute otitis media optimum management is wide myringotomy and systemic antibiotics.
- ✓ Congenital and acquired facial paralysis in the neonate can be differentiated on the basis of examination supplemented as required by electrophysiologic investigations.
- ✓ It is standard practice to have facial nerve monitoring during parotid and tympanomastoid surgery in children with a high incidence of anatomical abnormalities of the facial nerve, e.g. Down syndrome, craniofacial anomalies.
- ✓ Retrograde dissection of the marginal mandibular branch of the facial nerve to find the trunk is particularly unreliable in children.

FUTURE RESEARCH

- ➤ The treatment for facial paralysis in children remains largely empirical; randomized controlled trials may help answer some of the questions. In view of the small number of cases and the generally good prognosis, multicentred trials with sufficiently large numbers of cases are required.
- ➤ The currently available monitoring systems for facial nerve function during surgery lack total reliability and are limited in scope.

KEY POINTS

- The commonest cause of facial paralysis in children is Bell's palsy.
- Knowledge of the embryology and developmental anatomy of the facial nerve allows for a clear understanding of the various anomalies and clinical presentations of disorders of the facial nerve.
- There are important anatomical differences between the topography of the facial nerve in adults and children.
- These differences and the confined surgical space can make tympanomastoid surgery and surgery of the parotid region in children particularly challenging. Surgeons operating in children must be extra vigilant to avoid iatrogenic facial palsy.
- The management of facial palsy in children includes treatment for eye exposure, smile asymmetry, drooling and lack of labial function and synkinesis.

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CHAPTER 22

EPISTAXIS

Mary-Louise Montague and Nicola E. Starritt

SEARCH STRATEGY AND EVIDENCE BASE

A literature search was conducted for systematic reviews and randomized controlled trials and guidelines with the focus on management of childhood epistaxis. The core search terms used for Medline, Embase, and the Cochrane Database of Systematic Reviews were epistaxis and nosebleeds and were limited to children 0–18 years. The guidelines databases on www.evidence.nhs.uk, NICE Clinical Knowledge Summaries and BestBETS (Best Evidence Topics) were also searched.

INTRODUCTION

Epistaxis, from the Greek *epistazō*, 'to bleed at the nose', is a common problem in children although it is rarely severe and seldom requires hospital admission. Most episodes resolve spontaneously and can be managed at home or in the community setting. Recurrent frequent nosebleeds can, however, cause distress and anxiety to children and their parents and can be disruptive to sleep, school and sporting activities. It is this group of children who are most frequently referred for assessment and treatment to an otolaryngologist along with children presenting with severe acute bleeding and those children in whom an unusual aetiology is suspected.

EPIDEMIOLOGY

There is a bimodal distribution in the incidence of epistaxis, with peaks occurring in children under 10 years and adults over the age of 50 years. In childhood, as in adulthood, it is more common in males than females. It peaks between the ages of 3 and 8 years, and becomes much less common after puberty. Up to 60% of children will have had at least one nosebleed by the age of 10 years.[1] A cross-sectional study of 1218 children aged 11–14 years reported that 9% had frequent episodes of epistaxis.[2] The incidence of recurrent childhood epistaxis is highest in the winter months in northern climates. This mirrors the seasonal increase in viral upper respiratory tract infections and low relative indoor humidity associated with central heating use.[3] The presentation of epistaxis under the age of 2 years is rare and should prompt consideration of either an underlying coagulation disorder or non-accidental injury.[4,5]

ANATOMY

In children anterior bleeds are by far the most common type, accounting for more than 90% of epistaxis.[6] They originate from Little's area on the anterior nasal septum either from Kiesselbach's plexus, a richly vascular arterial anastomosis just under the thin overlying nasal mucosa, or from retrocolumellar veins. Kiesselbach's plexus is formed by the anastomoses of the septal branches of five arteries: anterior and posterior ethmoidal arteries, sphenopalatine artery, greater palatine artery and the superior labial artery. Little's area therefore receives arterial supply from both the external and the internal carotid arteries.

PATHOGENESIS

The precursor to epistaxis in children is most commonly local dryness and crusting over Little's area (**Figure 22.1**).

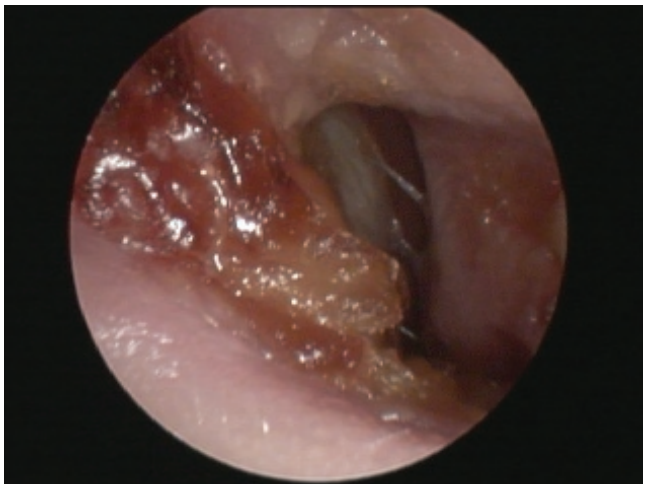


Figure 22.1 Endoscopic view of nasal septal crusting seen in children with recurrent epistaxis.

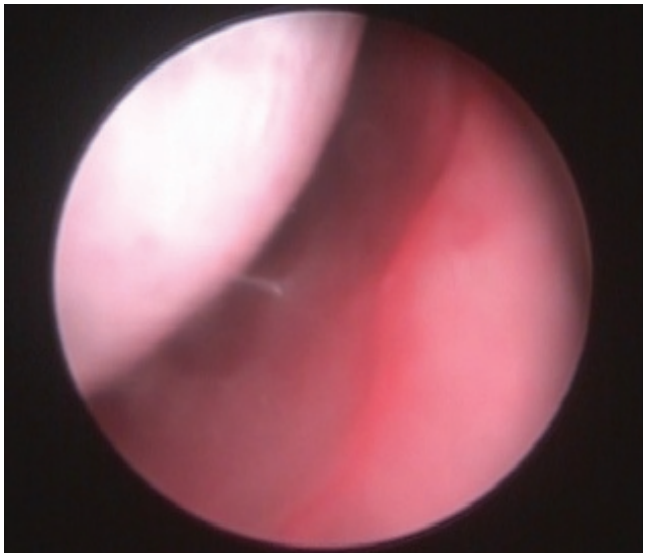


Figure 22.2 Endoscopic view of prominent septal vessels seen in children with recurrent epistaxis.

Most cases were historically labelled as idiopathic but recent evidence has led to the hypothesis that colonization of the nasal cavity by *Staphylococcus aureus* may contribute by causing low-grade inflammation.[7] Release of inflammatory mediators in response to more prolonged inflammation is thought to lead to neovascularization of the nasal septal mucosa. This may give rise to the frequently seen vessels on Little's area (Figure 22.2) which have been shown histologically to be thin-walled arterioles and capillaries with a surrounding inflammatory infiltrate.[8]

AETIOLOGY

Recurrent childhood epistaxis is usually attributed to digital trauma. Other common causes include allergic, viral and bacterial rhinitis and foreign bodies. Table 22.1 illustrates the range of local and systemic aetiologies one needs to consider in children.

TABLE 22.1 Local and systemic aetiologies of epistaxis in children

	Aetiology	Examples
LOCAL	Trauma	Nose picking or rubbing Blunt trauma or facial fractures Foreign body
	Inflammation	Upper respiratory infection Allergic rhinitis Vasculitis
	Anatomical	Septal deviation Septal perforation
	Neoplasms	*Benign* • Polyps • Pyogenic granuloma • Haemangioma • Juvenile nasopharyngeal angiofibroma • Inverted papilloma *Malignant* • Rhabdomyosarcoma • Nasopharyngeal carcinoma • Lymphoma
	Intranasal drugs	Steroids Decongestants Cocaine
SYSTEMIC	Bleeding disorders	*Coagulopathies* • von Willebrand Disease • Haemophilia *Platelet disorders* • Idiopathic thrombocytopenic purpura • Glanzmann thrombasthenia • Bernard–Soulier syndrome *Myeloproliferative disease* • Leukaemia • Thrombocytopenia
	Vascular abnormalities	Hereditary haemorrhagic telangiectasia (Rendu–Osler–Weber syndrome)
	Liver disease	
	Antiplatelet drugs	Aspirin Non-steroidal anti-inflammatory drugs
	Other drugs	Anticoagulants Valproic acid
	Parasitic infection	Dengue haemorrhagic fever

Tumours, such as juvenile nasopharyngeal angiofibroma (JNA) and rhabdomyosarcoma, are rare causes of epistaxis that can be both dramatic and difficult to control. JNA is a benign vascular hormonally sensitive tumour which arises in the lateral nasopharynx and occurs only in adolescent males. Although benign, it can cause severe problems through local invasion of adjacent structures.[9] Rhabdomyosarcoma is a rare malignant tumour occurring in young children presenting with severe intermittent epistaxis. It causes nasal obstruction with or without mucopurulent or bloody nasal discharge, often with signs of Eustachian tube dysfunction such as unilateral middle ear effusion. It can also present with pain and cranial

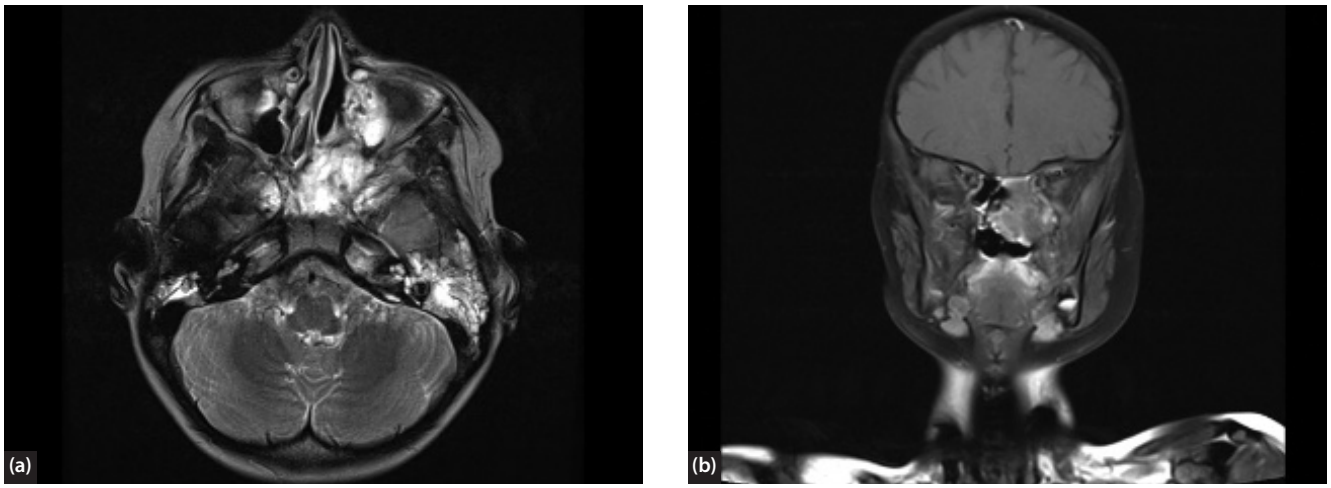


Figure 22.3 (a) Axial MRI and **(b)** coronal MRI showing nasopharyngeal rhabdomyosarcoma displacing the parapharyngeal fat space laterally. Opacification of right middle ear and mastoid air cells is also seen.

neuropathies (**Figure 22.3**). Nasopharyngeal carcinoma is fortunately rare in children. Approximately 50% present with epistaxis. It is often accompanied by a neck mass or neck pain.[10]

Primary and acquired coagulopathies are less common causes of nosebleeds in children but may present with recurrent or extremely refractory epistaxis. Von Willebrand disease (vWD) is the most commonly identified inherited coagulopathy with a prevalence of 5–10% in children with recurrent epistaxis when full coagulation studies including tests for vWD are performed.[2, 11] The haemophilias (factors VII, VIII, IX or XI deficiency) are much less common. Acquired coagulopathies are a rare cause of epistaxis in children in comparison to adults. They include various liver diseases with consequent depletion of clotting factors. An acquired form of vWD has also been described in children receiving valproic acid for epilepsy.[12]

Hereditary haemorrhagic telangiectasia (HHT) (Rendu–Osler–Weber syndrome), an autosomal dominant disorder of blood vessel walls characterized by extensive mucocutaneous telangiectasias, also causes recurrent epistaxis in more than 90% of those affected. Nosebleeds present at a mean age of 12 years and progressively worsen with age.[13] Gastrointestinal bleeding and pulmonary arteriovenous malformations can occasionally occur in childhood.

Nosebleeds often occur in children with thrombocytopenia either secondary to chemotherapy or a haematological disorder. It is rare, however, for haematological disorders to present with epistaxis as the primary symptom in children. Although rare, Glanzmann thrombasthenia, in which the platelet glycoprotein IIb/IIIa complex is either deficient or dysfunctional, is the commonest of the genetic platelet disorders.

ASSESSMENT

The assessment of children with recurrent epistaxis should begin with a careful history and physical examination.

History

The history should include the frequency, duration and laterality of the bleeding. Most epistaxis is bilateral, although one nostril may be more severely affected. One should also enquire about associated nasal and systemic symptoms and any precipitating factors including trauma. Past medical, family and drug histories and review of systems should also be covered.

UNILATERAL NASAL SYMPTOMS

When epistaxis is unilateral and accompanied by foul-smelling nasal discharge in a young child, a foreign body must be presumed present until proven otherwise. Having excluded a nasal foreign body, unilateral epistaxis should raise suspicion of a more serious local cause in the nose such as angiofibroma in a teenage boy or rhabdomyosarcoma in a younger child. Other 'red flag' symptoms include unilateral nasal obstruction, pain and facial swelling.

ALLERGIC RHINITIS

Nasal itch and blockage along with watery rhinorrhoea and sneezing are suggestive of allergic rhinitis.

SYSTEMIC SYMPTOMS

Bleeding from other anatomical sites or a history of easy bruising may indicate an underlying bleeding disorder. Symptoms of fever, arthralgia and weight loss may point to a diagnosis of vasculitis such as Granulomatosis with polyangiitis (Wegener's Granulomatosis), which may manifest in adolescence with epistaxis.

FAMILY HISTORY

A family history of bleeding disorders (e.g. HHT, haemophilia) should be enquired about. Often no definitive condition is identified but a positive family history of prolonged bleeding after surgery or dental extraction may warrant onward referral for haematological investigations.

DRUG HISTORY

Nosebleeds may be more frequent or more difficult to control in children taking certain medications, particularly anti-inflammatory agents (aspirin, ibuprofen) and anticoagulants (e.g. children with complex congenital heart disease or thromboembolic disease). Incorrect application of topical steroid sprays for rhinitis resulting in nasal septal trauma may be complicated by epistaxis.

ALLERGY HISTORY

A history of nut or soya allergy becomes pertinent if prescription of a topical antiseptic cream containing arachis (peanut) oil is being considered. There is a possible relationship between allergy to peanut and allergy to soya and it should not be used in children with soya allergy either.[14]

Clinical examination

Clinical examination focuses on the nose but complete ENT, head and neck and general examination of the child are also required. Younger children feel more secure sitting on a parent's knee. Initial assessment can be made with the child looking upwards by gently elevating the tip of the nose with a thumb allowing inspection of the nasal vestibule, anterior nasal septum, and anterior portion of the inferior turbinate illuminated by a headlight. Anterior rhinoscopy can also be performed with a well-illuminated otoscope with a large speculum.

The most common findings are crusting (two-thirds of children) and visible vessels (40–50% of children) on the anterior septum.[15, 16] Hallmarks of allergic rhinitis may be present including a transverse nasal skin crease ('the allergic salute'), and periorbital markers such as 'allergic shiners' and 'Dennie–Morgan lines'. Pale or bluish nasal mucosa and turbinates are also typical in allergic rhinitis. A nasal foreign body should be excluded. Distortion of nasal anatomy, an intranasal mass, polyps or cervical lymphadenopathy should raise the suspicion of tumour and also prompt a screen for cranial nerve palsies.

Rigid nasendoscopy is not tolerated well by children and, if a more posterior view of the nasal cavity and nasopharynx is required, a fine 2.2 mm flexible nasendoscope can be used after application of topical anaesthetic and vasoconstricting agent. Given the low yield of nasal endoscopy findings in younger children in particular, routine use is probably not warranted.[17] As the diagnosis of a nasal mass is most likely in adolescent males, nasal endoscopy should continue to be routine in their assessment.

Stigmata of systemic causes of bleeding, such as bruising, petechiae, cutaneous or mucocutaneous telangiectasia, should be looked for. Pallor may indicate significant blood loss or anaemia. The jaundiced child may have liver disease with a secondary coagulopathy.

In some circumstances, if an adequate view cannot be obtained or the child is not sufficiently cooperative, examination under general anaesthesia may be required.

INVESTIGATIONS

No consensus exists on the standard laboratory workup for paediatric epistaxis with clinician judgement largely guiding outpatient investigations. The routine use of blood testing is not advantageous from a healthcare cost perspective as there is such a low yield of significant findings.[17] Observational studies suggest that laboratory tests should be considered for children with prolonged (i.e. more than 30 minutes) or severe bleeding despite appropriate application of pressure, in children under the age of 2 years, and when the history and physical findings are suggestive of a bleeding disorder, malignancy, liver or other systemic disease.

Laboratory tests may include a full blood count (FBC) with differential white cell count and platelet count, and a coagulation screen comprising prothrombin time (PT) and activated partial thromboplastin time (APTT). The international normalized ratio (INR) should be checked if the child is receiving anticoagulants. Children found to have abnormalities should be referred for investigation to a paediatric haematologist. Further laboratory tests may include factor assays, von Willebrand factor and platelet function assays.

When tumour is suspected on the basis of history and examination including nasendoscopy, the diagnosis is usually confirmed by contrast-enhanced MRI. CT is often complementary. In the case of JNA a vascular-enhancing nasopharyngeal mass is seen (**Figure 22.4a**,**b**). Intranasal biopsy of JNA, which is a highly vascular tumour, should be avoided because of the risk of life-threatening bleeding. Selective digital subtraction angiography (DSA) elegantly demonstrates the vascular supply and allows pre-operative embolization of feeder vessels (**Figure 22.5a**,**b**). Post-embolization surgical resection is the treatment of choice.

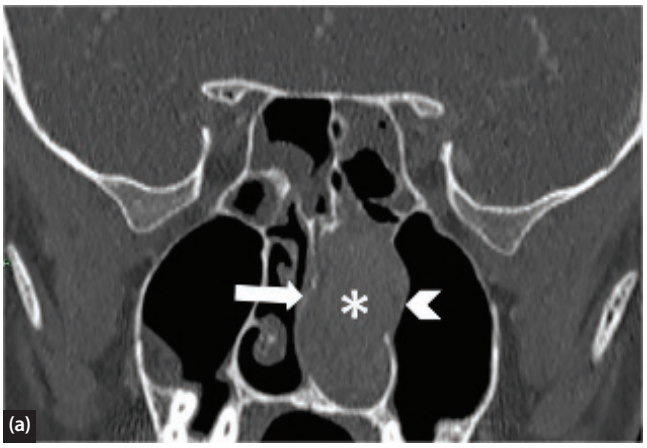
When tumour is suspected, multidisciplinary review and discussion are essential between paediatric otolaryngologist, oncologist and radiologist to ensure that appropriate laboratory tests, imaging and histopathological specimens are obtained.

MANAGEMENT

Epistaxis in children can present either as an acute spontaneous episode or as chronic recurrent intermittent episodes of bleeding. The management of both scenarios is outlined.

Management of acute episodes of bleeding

It is unusual for acute epistaxis in children to need urgent transfer to hospital for resuscitation, most responding to direct pressure over the soft cartilaginous part of the nose (alae nasi) for 10–15 minutes (the Hippocratic method) (**Figure 22.6a**,**b**). Urgent transfer to hospital should be arranged if the bleeding is not responsive to pressure.



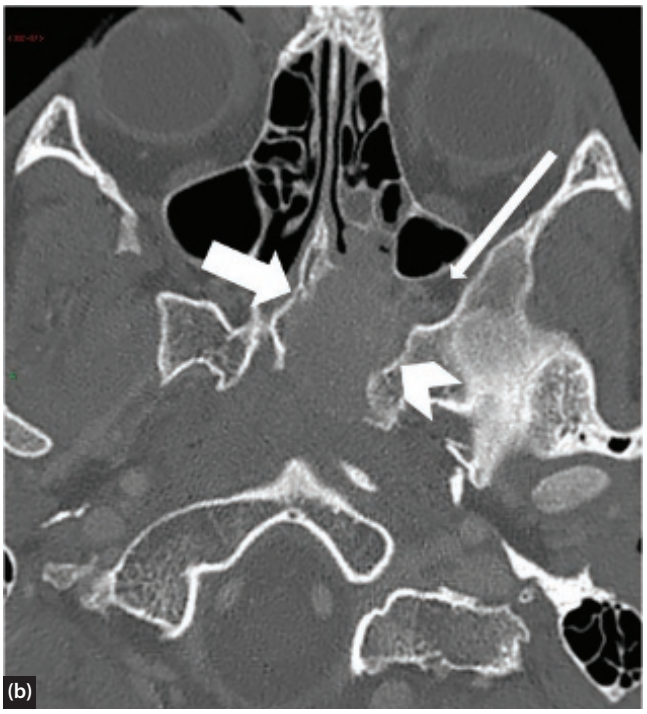
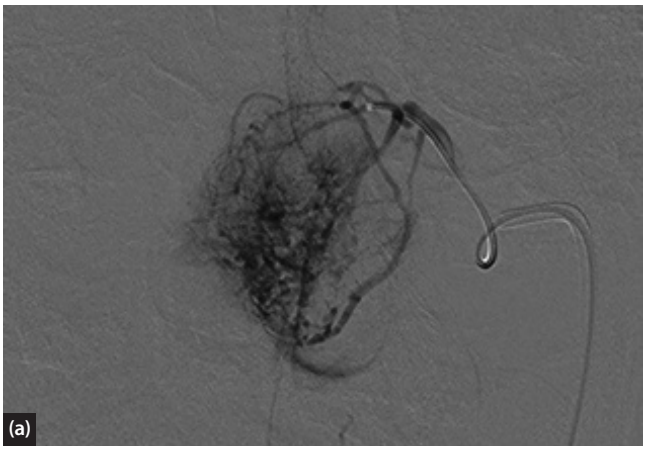


Figure 22.4 (a) Coronal CT. Juvenile nasopharyngeal angiofibroma (asterisk) extending into the choana with obstruction of the left nasopharynx, bowing of the vomer to the right (arrow) and bowing of the medial wall of the left maxillery antrum (arrowhead). **(b)** Axial CT. Bone windows showing erosion of the vomer (thick arrow), destruction of the pterygoid (arrowhead) and extension into the pterygopalatine fossa (thin arrow). Images courtesy of Dr S Goodwin, Consultant Paediatric Radiologist, Royal Hospital for Children, Glasgow.



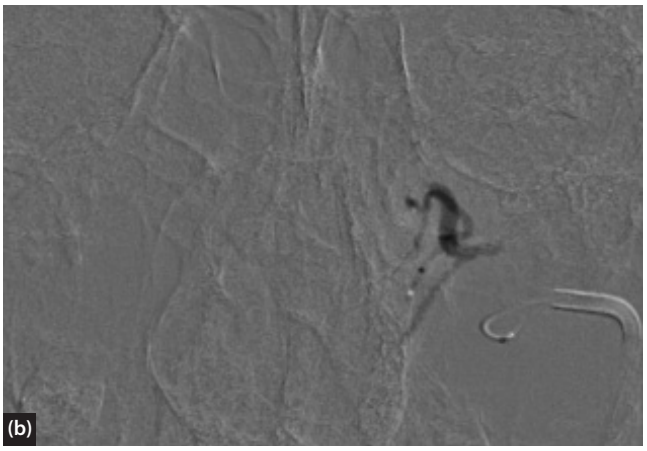


Figure 22.5 (a) Pre- and **(b)** post- embolization DSA demonstrating hypervascular tumour blush which has reduced significantly post-embolization of the distal left internal maxillary artery. Images courtesy of DR S Goodwin, Consultant Paediatric Radiologist, Royal Hospital for Children, Glasgow.

Initial assessment in the emergency department focuses on the child's airway, breathing and circulation. In a haemodynamically unstable child an effort should be made to assess blood loss, secure intravenous access and send venous blood for FBC, coagulation screen and blood group and save followed by fluid resuscitation. If the child is haemodynamically stable at presentation, laboratory blood tests do not need to be requested routinely. A careful history is taken from the parent or carer. The nasal cavity is examined, gently looking for a bleeding point anteriorly.

If the bleeding stops with first aid measures, a topical antiseptic cream (e.g. containing chlorhexidine hydrochloride 0.1% and neomycin sulfate 0.5%) can be applied and continued twice daily for up to 2 weeks to minimize crusting. If there is a history of peanut, neomycin or soya allergy, mupiricin ointment can be prescribed twice daily for 1 week as an alternative. Most acute nosebleeds in children respond to simple pressure and do not require referral to otolaryngology services.

Examination of the child who continues to bleed despite nasal pressure can be difficult. The oropharynx should be inspected for signs of posterior bleeding. Subsequent measures to control anterior epistaxis include nose blowing followed by gently placing cotton pledgets soaked in vasoconstrictor and local anaesthetic such as Co-phenylcaine

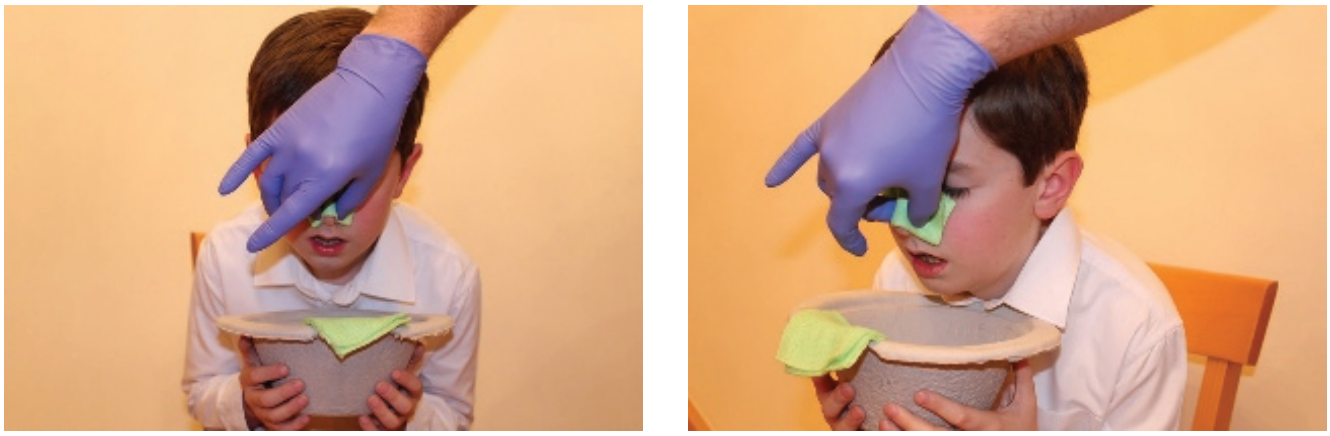


Figure 22.6 Demonstration of Hippocratic method to arrest bleeding with child seated, head tilted slightly forward and mouth open to prevent airway obstruction and swallowing of blood.

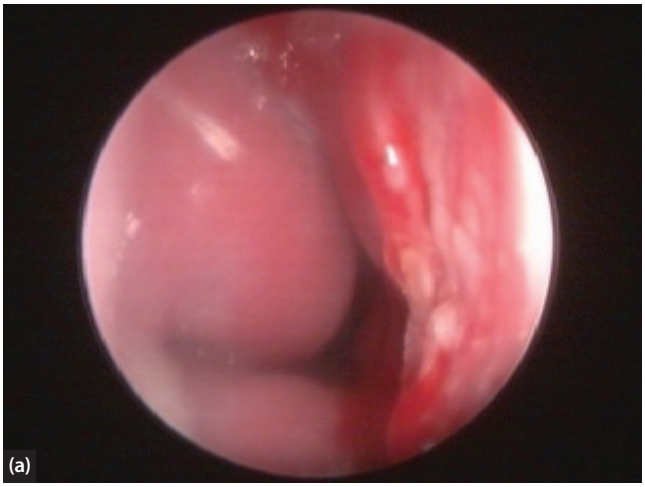
(lignocaine hydrochloride 5% with phenylephrine hydrochloride 0.5%) or Oxymetazoline in the anterior nasal cavity. This is followed by further digital pressure for 5 minutes. In small children the lowest concentration of phenylephrine should be used (e.g. phenylephrine 0.25% diluted with an equal volume of sterile saline to 0.125%).

If bleeding continues the next step is usually chemical cautery with silver nitrate if a bleeding point can be seen anteriorly and the child can tolerate the procedure. Using a stick, 75% silver nitrate is applied to the bleeding point for up to 5 seconds (Figure 22.7) until a grey-white eschar develops (Figure 22.8a,b). Excess chemical should be gently mopped away with a cotton bud, topical antiseptic applied to the site and a barrier lubricant such as soft white paraffin applied to the external skin to protect it. The topical antiseptic preparation is continued twice daily for up to 2 weeks. Local chemical cautery is sufficient to control most epistaxis in children.

The placement of an anterior nasal pack under direct vision may be required if the bleeding continues despite local cautery, in the presence of diffuse mucosal bleeding or in a child with a coagulopathy pending treatment directed at rectifying the bleeding problem. Absorbable packs such as gelatin sponge, alginate or oxidized cellulose are favoured in children over non-absorbable packs, having the obvious advantage of not requiring subsequent removal, which in itself may cause further trauma to the anterior nasal septum (Figure 22.9). If an anterior pack is placed, the child should be admitted to the ENT or children's ward for observation.

Examination under anaesthesia may be required if bleeding continues, or in a young child unable to tolerate

Figure 22.7 Stick with 75% silver nitrate used for chemical cautery.



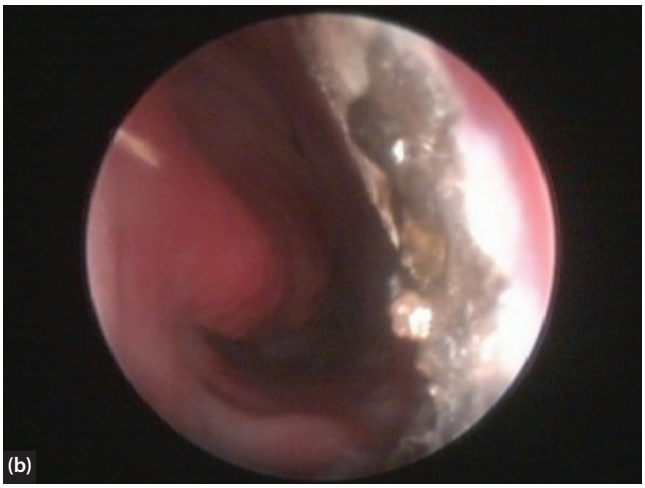


Figure 22.8 (a) Bleeding vessel on anterior septum before silver nitrate cautery and **(b)** the grey/white eschar that appears post-cautery.

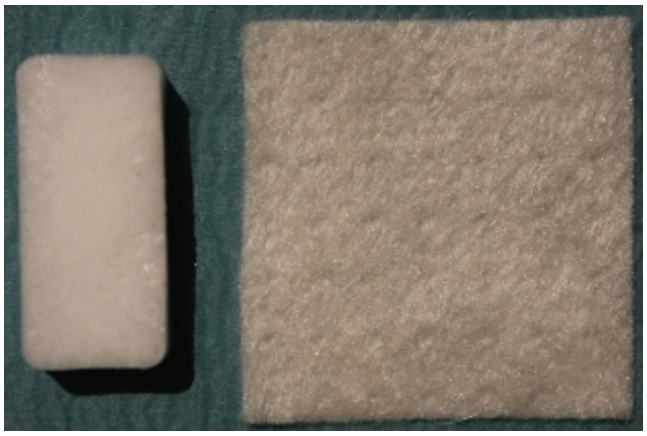


Figure 22.9 Gelatin sponge pack (left) and Alginate packing material (right).

chemical cautery or placement of an anterior pack under local anaesthesia. Chemical cautery or electrocautery can be undertaken with or without placement of an anterior pack.

Posterior bleeding in children is much less common but often more severe and should be suspected if the bleeding is profuse and bilateral, there has been no response to pressure and a bleeding site cannot be identified anteriorly. Rarely, placement of a posterior nasal pack or balloon inflated under general anaesthesia is warranted. Thorough examination of the nasal cavity and nasopharynx can be performed simultaneously. The child should be cared for post-operatively on the critical care floor until the post-nasal pack or balloon is removed, again usually under general anaesthesia.

The child with persistent anterior or posterior epistaxis refractory to these measures in the absence of a correctable bleeding disorder may require consideration of either arterial ligation or radiological selective arterial embolization. These are rarely necessary in children.

Management of recurrent episodes of bleeding

In children referred to the otolaryngologist for outpatient assessment and treatment of recurrent epistaxis a detailed history and examination should seek to determine if there is an underlying cause. It should also be established what treatment, if any, has already been provided in the primary care setting.

If the child is not at high risk of having a serious underlying cause for their recurrent epistaxis, treatment options should be discussed and include:

- mucosal hydration with saline drops or spray
- emollients, e.g. petroleum jelly
- topical antiseptic cream
- chemical cautery
- chemical cautery combined with antiseptic cream
- bipolar electrocautery.

The optimal management of recurrent epistaxis in children remains controversial as the available studies are limited by small numbers and short-term follow-up.[18] Petroleum jelly application to the nose is often recommended but it has no benefit over simple observation.[16] Topical antiseptic cream was found to significantly increase the resolution of recurrent epistaxis at 8 weeks when compared to no treatment.[15] Long-term benefit of topical antiseptic, however, has not been established.[19] It is not known if chemical cautery is better than no treatment but, if a child has been referred to a paediatric otolaryngology clinic and has already had treatment with an antiseptic cream, most would consider it reasonable to offer chemical cautery if a prominent vessel is visible as it is of low morbidity. Antiseptic cream would appear to be as effective as silver nitrate cautery in reducing the number of nosebleeds in children with recurrent epistaxis.[20, 21] It is therefore not unreasonable for antiseptic cream to be considered the first-line treatment for recurrent epistaxis in children in primary care. Treatment with chemical cautery and antiseptic cream may be more effective than antiseptic cream alone at 4 weeks after completing treatment in children with visible anterior septal vessels.[22]

It is recommended to use 75% rather than 95% silver nitrate for chemical cautery in children as it appears to be more effective, has fewer side effects and is less painful.[23] Simultaneous bilateral cautery is not recommended owing to the possible increased risk of septal perforation.[24]

Bipolar electrocautery may be superior to chemical cautery under general anaesthesia in children who will not tolerate outpatient chemical cautery. It has been shown to afford a longer epistaxis-free period and a lower incidence of recurrence within 2 years of treatment. After 2 years however, the outcomes of the two treatments are no different.[25]

Less commonly performed interventions in children include laser treatment, submucosal resection or limited septoplasty in the presence of septal deviation or a prominent septal spur and endoscopic diathermy but these are usually only applicable on an individual case basis and are not supported by a strong evidence base.

The management of HHT in children requires special mention as it may require unique approaches to treatment. Chemical cautery should be avoided and, when packing is necessary, absorbable packing is preferred. Treatment with topical fibrin glue or matrix sealant (e.g. Floseal), the anti-fibrinolytic agent, tranexamic acid, KTP laser, cold ablation and the anti-neoplastic agent Bevacizumab (Avastin) have been employed in some centres with some success though there is very little in the published literature with respect to their use, safety and efficacy in children. Septal dermoplasty remains a viable surgical option but has the disadvantage of a donor split skin graft site and associated discomfort for the child.

Prevention of further bleeds

After treatment for either acute or recurrent epistaxis, parents/caregivers should be educated in the correct first-aid management in the event of recurrence. Children's fingernails should be kept trimmed and clean. Management of suspected or proven allergic rhinitis is

essential to help prevent recurrence. Parents should be instructed how to apply their child's nasal steroid spray correctly, with advice to hold the bottle in the opposite hand (right hand for left nostril and vice versa) to ensure the spray is directed to the lateral nasal wall and away from the septum.

BEST CLINICAL PRACTICE

- ✓ In acute epistaxis the child's airway, breathing and circulation should be assessed and, if compromised, urgent transfer arranged to the emergency department.
- ✓ Adolescent boys with unexplained recurrent epistaxis require urgent referral to otolaryngology as JNA is possible, although rare.
- ✓ In children younger than 2 years of age consider referral to a paediatrician with child protection expertise as epistaxis is unusual in this age group.
- ✓ Laboratory investigations are not usually required unless an underlying cause for recurrent epistaxis is suspected.
- ✓ Chemical cautery with 75% silver nitrate in the hands of an appropriately trained clinician is a well-tolerated procedure with little morbidity and should be offered when there is a visible blood vessel.
- ✓ Antiseptic cream containing peanut oil must not be prescribed for children with known or suspected peanut allergy.

FUTURE RESEARCH

- ➤ It is unlikely that the role of silver nitrate cautery will ever be validated by randomized controlled trials as this treatment is operator-dependent.
- ➤ There is a lack of study data assessing the effect of recurrent epistaxis on the quality of life of the child and parent or the effect of intervention on quality of life indices.
- ➤ High-quality studies, with longer follow-up, are needed to ascertain which, if any, of the current treatments for recurrent epistaxis in children are optimal in its long-term prevention.
- ➤ As most epistaxis in children is managed in the primary care setting, large population studies on the natural history of epistaxis and the effect of intervention will need to be primary-care centred.

KEY POINTS

- Epistaxis in children is extremely common and usually innocuous.
- The most common cause of epistaxis in the paediatric population is digital trauma.
- Most episodes of acute epistaxis in children respond to simple compression and do not require hospital referral.
- Routine laboratory blood testing is not indicated for most children with self-limiting epistaxis.
- Spontaneous resolution of benign simple recurrent epistaxis in children is to be expected.

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CHAPTER 23

NEONATAL NASAL OBSTRUCTION

Michelle Wyatt

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keys nasal obstruction and neonatal and focusing on a variety of keywords appropriate to the individual topics. These include all the subheadings listed below (e.g. choanal atresia, piriform aperture stenosis). The Cochrane Database of Systematic Reviews and the National Electronic Library for Health for ENT were also consulted.

INTRODUCTION

The aetiology of neonatal nasal obstruction is diverse. Neonates are generally obligate nasal breathers for the first few months of life, and therefore they can present as acute respiratory emergencies, classically with cyclical cyanosis, relieved by crying. The extent of their problems will alter related to the neonate's ability to breathe orally which is dependent on their maturity and neurological development. Thus, an oral airway is often sufficient to relieve the respiratory distress until definitive treatment can be undertaken.

Neonates with nasal obstruction may also present with stertor and feeding problems. Failure to thrive particularly raises level of concern. Examination is essential.

BOX 23.1 Congenital causes of nasal obstruction in neonates

Anatomical/ skeletal anomalies	Congenital nasal cysts	Nasal masses
Choanal atresia	Dermoid cysts	Glial heterotopia
Pyriform aperture stenosis	Nasolacrimal duct cysts	Meningo- or encephalocoele
Midnasal stenosis	Thornwald's cyst	Haemangioma
Nasal agenesis	Nasoalveolar cysts	Teratoma
Craniosynostosis syndromes	Dentigerous cysts	Hamartoma
'Cleft palate' nose	Mucous cysts	Chordoma

BOX 23.2 Acquired causes of nasal obstruction in neonates

Structural	Inflammatory
Osseocartilaginous nasal deformity	Neonatal rhinitis

Flexible nasendoscopy is particularly useful and imaging via computed tomography (CT) and magnetic resonance imaging (MRI) is of great value in delineating both nasal and post-nasal lesions.[1, 2]

Boxes 23.1 and 23.2 list the variety of causes of neonatal nasal obstruction. This chapter aims to review those conditions not covered elsewhere in this book.

CONGENITAL DISORDERS

Skeletal anomalies

CHOANAL ATRESIA

This is a rare condition (incidence 1 in 7000 live births) in which there is complete obstruction of the posterior choanae on one or both sides (Figure 23.1). The blockage is thought to be either bony or membranous in origin, but in reality a mixed picture is usually seen (70% of cases), with the remainder being purely bony. It is believed to be secondary to persistence of the nasobuccal membrane.

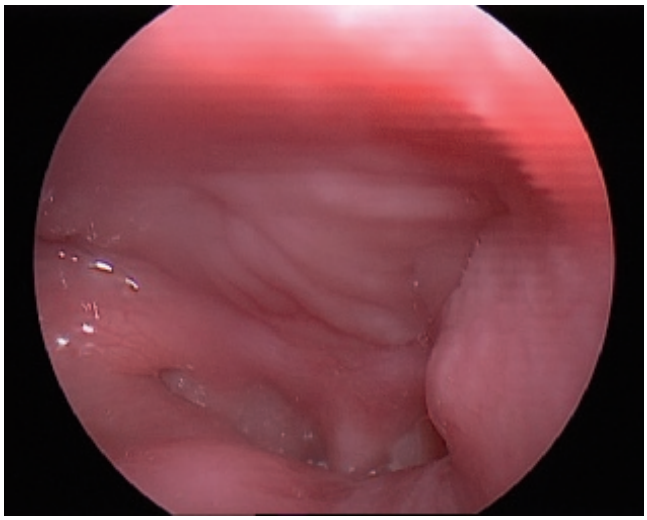

Figure 23.1 Bilateral choanal atresia as viewed from the nasopharynx with a 120-degree endoscope.

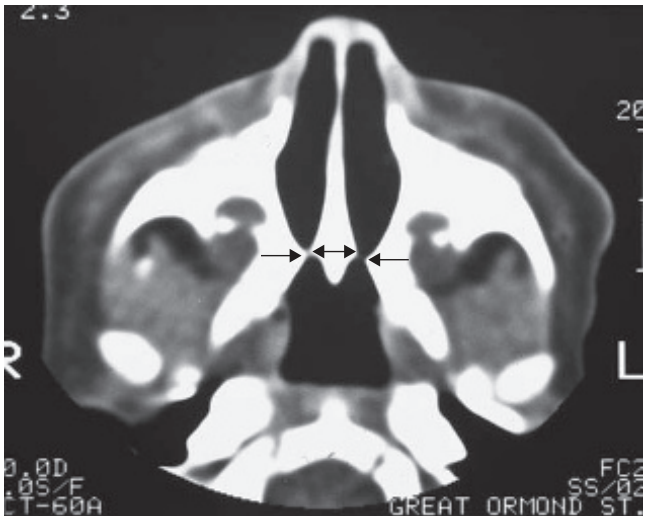

Figure 23.2 CT scan (axial view) to illustrate the expansion of the posterior vomer and medial maxillary walls of the nasopharynx in choanal atresia (arrows).

Bilateral choanal atresia in neonates presents as acute respiratory distress as neonates are obligate nasal breathers. Classically the neonate will have cyclical cyanosis relieved by crying, and placement of an appropriate-sized oral airway resolves the distress. Unilateral choanal atresia may present later in life, and can be picked up in neonates when there is an inability to pass a nasogastric tube through one nasal passageway.

Neonates with choanal atresia will have difficulty with feeding. The uvula and epiglottis usually form a respiratory channel from the nose to the larynx with two lateral pathways from the mouth to the oesophagus to allow for the safe passage of food. In neonates with bilateral choanal atresia this respiratory channel is lost and therefore cyanosis can develop during feeds.[1] McGovern nipples have been shown to be of benefit for children who develop feeding difficulties.

Misting upon placement of a metal spatula below the neonate's external nasal aperture excludes a diagnosis of choanal atresia, and this test can easily be performed in the clinic setting. If suspected, the diagnosis should be confirmed with flexible nasendoscopy, and CT scanning should then be performed to determine the extent and nature of the choanal atresia (with suction clearance of the nose and application of 0.5% ephedrine drops 30 minutes prior to scanning) (**Figure 23.2**). In neonates, often a simple oral airway is well tolerated, in which case endotracheal intubation can be avoided.

Choanal atresia can occur in isolation, but it can also be one feature of a number of associated congenital anomalies in the CHARGE (coloboma, **h**eart defects, **a**tresia choanae, **r**etardation of growth, **g**enital anomalies, **e**ar abnormalities) syndrome, due to mutations in the *CHD7* gene on chromosome 8. These abnormalities must be excluded in a child with choanal atresia and therefore the minimum investigations in addition to the nasal CT scan are cardiac echo, renal ultrasound scan, and an ophthalmology and audiology review.

The literature describes numerous techniques for the repair of choanal atresia, but there is little in the way of direct comparisons and outcomes are difficult to define objectively. Most studies report on the surgeons' assessment of the size of the nasal airway, and whether the family feel that the symptoms have resolved. The number of surgeries required and time taken to reach a satisfactory outcome are used to make comparisons. A recent Cochrane review concludes that there is no definitive evidence to demonstrate the potential advantages or disadvantages of any surgical technique for patients with choanal atresia.[3]

The two most common techniques for choanal atresia repair are the transnasal and transpalatal approaches, but the sublabial, transantral and transseptal approaches have also been described.[4] Transpalatal and transnasal surgery have been shown to have similar outcomes.[5] The transpalatal technique is not as common now, but it can be useful in those neonates with significant craniofacial anomalies where the dimensions of the nose and postnasal space are limited.

There are two methods described for the endoscopic transnasal approach. One involves using the zero degree endoscope transnasally, with serial dilatations using urethral sounds or using powered instruments such as microdrills. In cases where the nasal cavity is too small to accommodate both instruments a posterior septal window is created and expanded, thus allowing the endoscope through one nostril and the powered instrument through the other nostril, creating a 'neo-unichoana'.[6, 7]

The second transnasal approach involves a 120-degree endoscope being placed in the mouth and positioned in the nasopharynx behind the soft palate to give a view of the postnasal space. Instruments and the drill can then be introduced through the nose. This technique is described in three papers from Great Ormond Street Hospital in London and represents the largest reported experience at 161 patients using the endoscopic transnasal approach.[8–10]

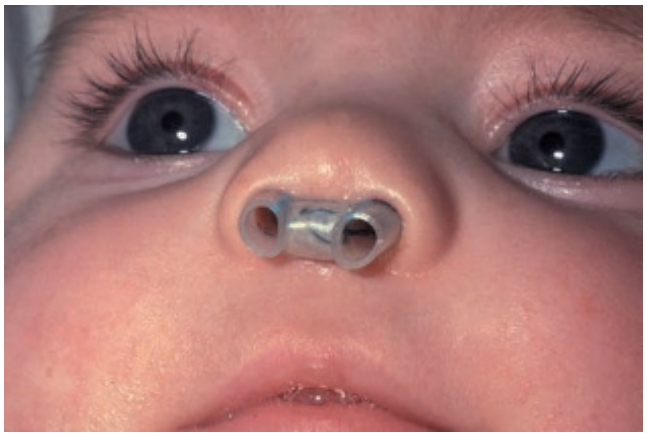

Figure 23.3 Bilateral nasal stents with an endotracheal tube bridging piece.

There are reports in the literature of high success rates using the endoscopic endonasal approach with balloon dilatation for choanal atresia, although the numbers involved in these series are still quite small.[11]

The role of nasal stenting post choanal atresia repair is also debated. If used, bilateral nasal stents can be fashioned from two ivory Portex™ endotracheal tubes cut to length with the bevelled end of each sitting in the nasopharynx orientated towards the septum. The philtrum is protected by either a small length of size 12 suction catheter cut to act as a bridging piece or a further small piece of endotracheal tube (**Figure 23.3**). The stents are secured by a circumseptal '0' prolene suture and left *in situ* for up to 6 weeks. An alternative is to use a single tube as a stent, with a window cut in the middle to allow access for the securing suture. This avoids the need for a bridging piece (**Figure 23.4**). There is debate as to the need for stenting, and a systematic review with meta-analysis has shown that the success rates for bilateral choanal atresia repair are similar with and without nasal stents, and that the use of stents may be associated with more complications.[12]

There is evidence that regular suctioning to clear secretions and daily washing with sodium chloride solution results in successful outcomes.[13] Authors who do not support using stents stress the need for resection of the posterior aspect of the vomer and early (1 week post repair) repeat examination for removal of granulations and dilatation as required.[13]

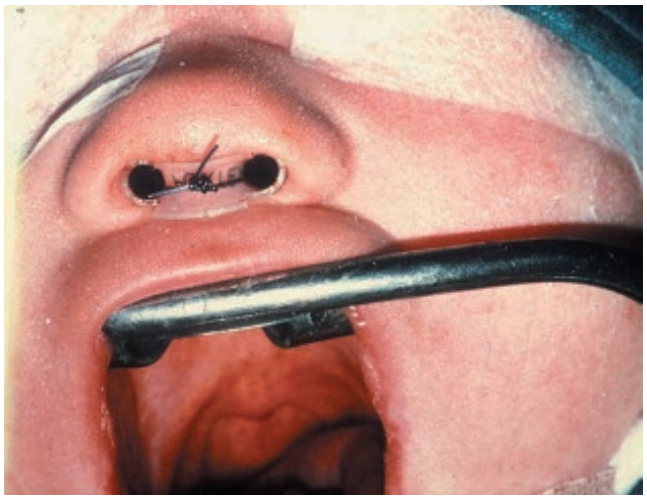

Figure 23.4 Bilateral nasal stents without a bridging piece.

Given the limitations in the definition of outcome as described previously, success rates have been shown to be similar over the past 20 years with the three Great Ormond Street papers showing rates of 68–80% for bilateral and 82–93% for unilateral choanal atresia. A group of 78 children from the Philadelphia Children's Hospital were followed up for 35 months on average with similar results.[14]

Mitomycin C is thought to act to reduce granulation tissue and fibrosis by inhibiting fibroblasts and angiogenesis leading to its use during stent removal. However, several papers have found no benefit in terms of outcomes whether mitomycin C is used or not.[12, 15] Carter et al. suggest, however, that mitomycin does have beneficial effects.[16] The KTP laser has also been shown to be helpful in the treatment of granulation tissue which develops post-operatively.[5]

PIRIFORM APERTURE STENOSIS

This abnormality, first described in 1988, is a very rare condition leading to nasal obstruction in the neonate which arises due to bony overgrowth of the nasal process of the maxilla (**Figure 23.5**).[17] The piriform aperture is the narrowest part of the nasal airway and so even minimal reduction in diameter here can cause significant problems. Symptoms similar to bilateral choanal atresia occur and epiphora is also often seen secondary to bony involvement of the nasolacrimal ducts. Diagnosis is suggested by the inability to pass a narrow gauge nasogastric tube or 2.2 mm endoscope through the anterior nasal vestibule due to the bony obstruction. CT scan confirms the diagnosis with an aperture width of less than 11 mm measured on an axial CT at the level of the inferior meatus (in a term neonate). CT can also demonstrate a single central incisor, which exists in some affected individuals. This single central incisor is associated with an absent upper frenulum and arch-shaped lower lip. In this subgroup with a 'megaincisor' there is a suggested association with holoprosencepaly, a rare condition in which the developing forebrain fails to divide appropriately to form the cerebral hemispheres, diencephalon, and optic and olfactory bulbs. These patients should undergo further evaluation for central nervous system defects with an MRI and particularly the hypothalamic–pituitary–thyroid axis. There are variable reports on the incidence rates of this condition with piriform aperture stenosis, but a figure of around 50% is generally accepted.[18]

Conservative treatment with nasal steroid drops or decongestants (for up to 2 weeks) and saline irrigation is generally recommended as first-line treatment.[19] If there is severe obstruction, respiratory distress or failure to thrive, surgical treatment is warranted. It has also been found that an aperture of less than 5 mm on CT is almost always associated with the need for surgical intervention.[20]

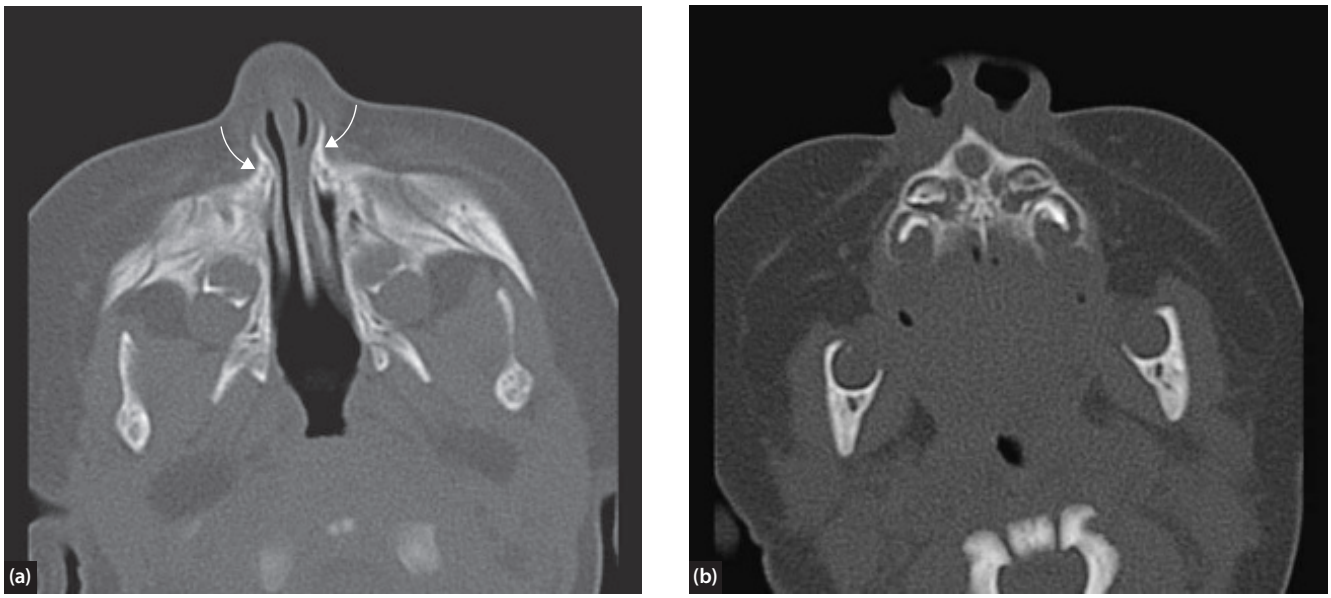

Figure 23.5 CT scan (axial view) of bilateral piriform aperture stenosis. Note the single central incisor.

Surgery involves either a transnasal approach with an alar-releasing incision or a sublabial approach with a gingival–buccal sulcus incision and elevation of the soft tissue and periosteum to expose the piriform aperture. The abnormal bone is drilled away using a diamond burr and the mucoperiosteal flap replaced. Post-operatively nasal stents can be used for up to 4 weeks, although more recent studies suggest that stenting is not necessary.[21] Complications include adhesions, septal perforations and septal ulceration, but the use of suctioning, nasal irrigation and treating gastro-oesophageal reflux minimizes this.[22]

MIDNASAL STENOSIS

Midnasal stenosis is a rare condition secondary to overgrowth of the nasal bones halfway along the nasal cavity. It usually occurs in association with syndromes characterized by midfacial hypoplasia, such as Apert syndrome, but cases in isolation are also reported.[23] Neonates will present in a similar fashion to those with piriform aperture stenosis or choanal atresia with apnoea, cyanosis and failure to thrive. Diagnosis can be confirmed with nasal endoscopy or CT scanning which will demonstrate isolated bony narrowing of the midpart of the nasal cavity or narrowing with stenosis of the rest of the nasal cavity (**Figure 23.6**). Treatment is usually conservative, allowing the child's midface to grow, such that by the age of 6 months the obstruction is relieved. For those children struggling with significant respiratory problems or failure to thrive, dilatations or stent placement can be considered.[1]

NASAL AGENESIS

Complete arhinia is very rare but can occur in isolation or as part of a syndrome. It originates at the fifth week *in utero* when the nasal placode fails to canalize to form the nasal passages. Presentation at birth with acute respiratory distress occurs. Management is initially with an oral airway and tube feeding. A tracheostomy may be required. Definitive surgical treatment usually involves a two-staged procedure aimed at reconstructing the nasal cavity as well as the external nose, and is usually delayed until facial development is almost complete.[24]

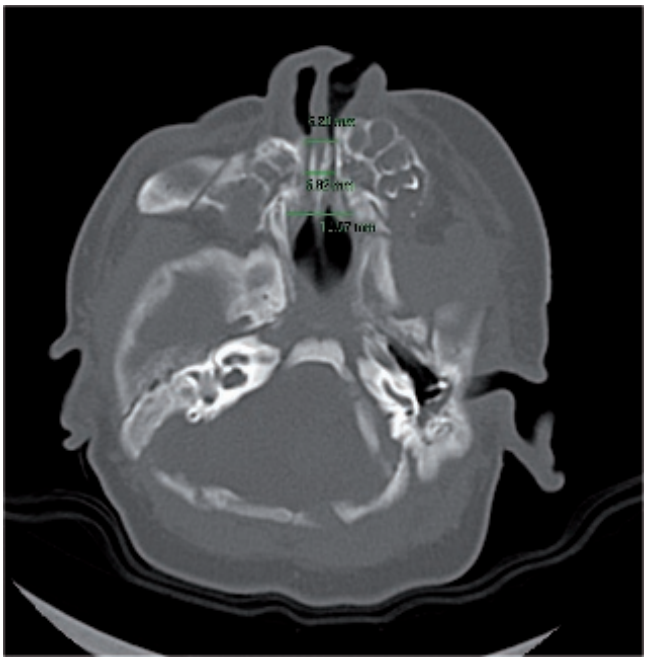

Figure 23.6 Midnasal stenosis associated with a patient with Apert syndrome.

Congenital nasal cysts

Congenital cysts, as listed in **Table 23.1**, can either obstruct the nose or cause discharge from an associated sinus tract.

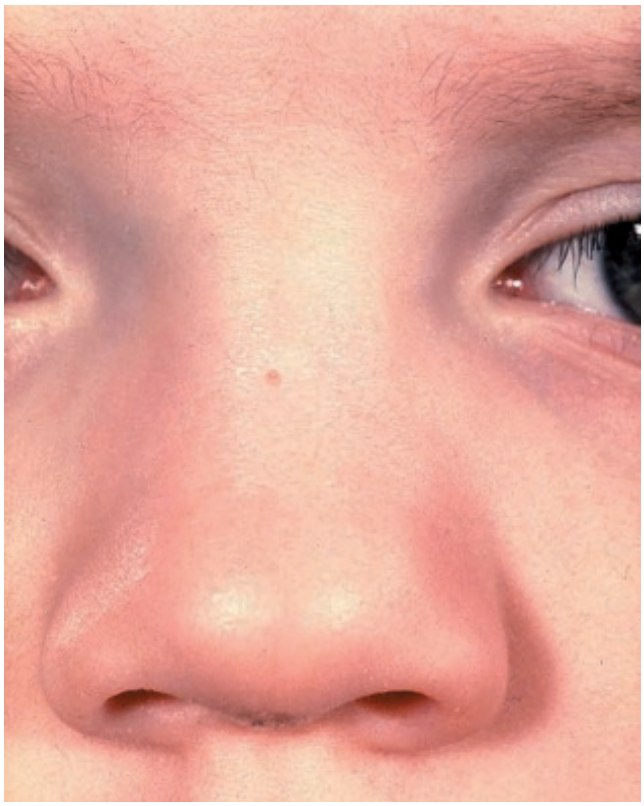

Figure 23.7 Midline nasal sinus associated with an underlying dermoid cyst.

DERMOID CYST

Dermoid cysts (**Figure 23.7**) arise from the ectoderm and mesoderm and usually contain all the structures of normal skin. They are the most common midline nasal mass, and account for between 1% and 3% of all dermoids.

These cysts usually present as a slowly growing cystic midline mass over the nasal dorsum. An associated pit is often seen in any position from the nasal tip to the glabella, and hair may be present at its opening. Occasionally these dermoids can become infected and thus present as an abscess requiring drainage.

Between 4% and 45% of dermoid cysts have an intracranial component, thus pre-operative imaging with CT (for bony anatomy) and MRI (to delineate any connection to the central nervous system) is essential.[25]

Nasal dermoids are discussed in more detail in Chapter 41, Cysts and sinuses of the head and neck.

NASOLACRIMAL DUCT CYST (DACRYOCYSTOCOELE)

The nasolacrimal duct system should canalize *in utero* from a superior to inferior direction and is usually complete by the sixth foetal month through a process of reabsorption; however, not infrequently, at birth the lower end can remain closed. This barrier can be combined with a proximal valve-like obstruction at the junction of the common canaliculus and lacrimal sac, thus the tear fluid builds up resulting in a cyst. This is a common problem for neonates and it is reported that 5–30% of babies are born with nasolacrimal duct blockage.[26] These lesions can cause epiphora and nasal obstruction, sometimes leading to respiratory distress and feeding difficulties, and may present with a bluish cystic mass at the medial canthus. They are more commonly unilateral but can be bilateral,[27] and their incidence is slightly higher in female infants. CT imaging confirms the diagnosis and shows a dilated nasolacrimal duct, an intranasal cyst and cystic dilatation of the lacrimal sac.

Initial management is with nasal decongestants but, if surgical removal is required, endonasal marsupialization under endoscopic guidance is recommended.[27] Endonasal ablation with the carbon dioxide laser has also been reported previously.[26] Opthalmology input is helpful as intra-operative nasolacrimal probing and stenting may be necessary (see Chapter 25, Lacrimal disorders in children).

THORNWALDT CYST

The pharyngeal recess or bursa sits in the midline of the posterior wall of the nasopharynx. It ends next to the adenoids and is lined by the pharyngeal mucous membrane. Cystic transformation of this recess was first described by Thornwaldt in 1885 and so it bears his name. Inflammation of the lesion causes nasal obstruction, occipital pain, fullness in the ears and discharge. It rarely causes significant obstruction in neonates.

Endoscopic examination confirms the diagnosis. Imaging by CT and MRI demonstrates any adhesion to the cervical vertebrae. Incision and excision of the cyst have been described while total clearance requires a palatal approach.[28]

NASOALVEOLAR CYSTS

These are rare, non-odontogenic, soft-tissue lesions arising from the incisive canal during the development of the maxilla. They present lateral to the midline at the alar base and can cause asymmetrical alar flare. Excision is usually via a sub-labial approach, but the transnasal approach has been recently reported.[29]

DENTIGEROUS CYSTS

Dentigerous cysts present in the floor of the nose or maxillary sinus and have a dental origin. Endoscopic marsupialization or removal via the nose is usually satisfactory.

MUCOUS CYSTS

Mucous cysts have been described anywhere in the nose but appear to be more common in the floor. They may be congenital but are more usually seen as a complication of rhinoplasty. Endoscopic and open approaches are used depending on the position of the lesion.[30]

Nasal masses

ENCEPHALOCOELE, MENINGOCOELE, GLIOMA

A nasal encephalomeningocoele represents a herniation of meninges with or without associated brain through bony defects of the calvarium. A meningocoele consists of either

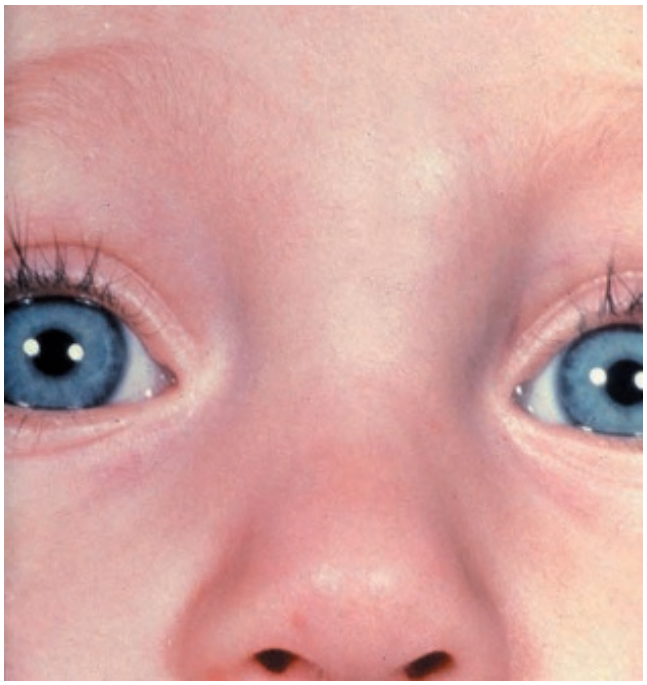

Figure 23.8 Broadened nasal dorsum in a child with a glioma.

meninges alone or with CSF and an encephalocoele contains nervous tissue. Their combined incidence is around 1 in 4000 live births and they have an equal male/female distribution. Encephalocoeles can be described as frontoethmoidal or basal.[31] Frontoethmoidal are usually associated with craniofacial deformity as they arise either at or anterior to the foramen caecum. The basal types present intranasally through defects in the skull base causing nasal obstruction and widening of the nasal bridge.

Nasal gliomas (**Figure 23.8**) are benign midline masses containing glial cells and fibrous and vascular tissue. They are similar to encephalocoeles but have become separated from the intracranial structures. Around 15% do, however, remain attached to the brain via a fibrous stalk. There is usually no associated abnormality of the brain. A better term for these lesions is 'glial heterotopia': glioma implies a neoplasm and these lesions are actually choristomas (aggregations of structurally normal tissue in an abnormal location). Presentation is usually early on as a firm, non-compressible, reddish swelling.

Differentiation between gliomas and encephalocoeles can be made in a number of ways. A probe will pass laterally but not medially to an intranasal encephalocoele while an intranasal glioma can arise from the lateral nasal wall. Furstenberg's test (compression of the internal jugular vein) usually causes an encephalocoele to enlarge but a glioma does not. Imaging is mandatory to confirm the nature of the lesion. MRI is the most effective modality due to its better resolution of soft tissue, and because the anterior skull base contains unossified cartilage which can be mistaken for bony dehiscence on CT, but CT has a role in image guidance. On MRI, an encephaocoele is seen as a mass in continuity with the brain with an associated skull base defect, while a glioma is discontinuous to the brain parenchyma and the tissue is dysplastic and gliotic, therefore more hyperintense on T2 compared to normal brain parenchyma.

Surgical excision is recommended for these masses, particularly if they are causing significant problems. As with dermoid cysts, masses in the lower part of the nose can be removed via the external rhinoplasty approach.[32] More recently, the endoscopic approach is advocated, and this has been shown to have successful outcomes with image guidance.[33, 34] The glial tissue can be removed with a zero-degree or 120-degree endoscope.

Encephalocoeles and meningocoeles that require surgery usually require a combined transnasal and neurosurgical approach. Ventriculoperitoneal shunting may be required pre-operatively. The intracranial portion can be excised via a bicoronal flap with a frontal craniotomy, but this can be associated with complications of epilepsy, anosmia, scarring and intracerebral haemorrhage. More recently, the endoscopic approach is advocated without the need for formal craniotomy.[35] The defect left by endoscopic excision can be closed with temporalis fascia graft, mucosa or a composite graft from the inferior turbinate, with Gelfoam® and packing (if small), or if a larger defect is present fascia lata and bone from the septum may be required. This prevents the risk of CSF leak potentially leading to meningitis. The role of prophylactic antibiotics is controversial.

NASAL HAEMANGIOMA

Vascular anomalies such as haemangiomas, arteriovenous malformations (AVMs) or vascular malformation (including lymphatic malformations) can present in the nose either externally or internally (**Figure 23.9**). Internal haemangiomas often arise from the inferior turbinate.

Classically, a haemangioma is either absent or flat at birth and then undergoes a period of rapid growth to present as a mass at around 6 weeks of age. Growth then continues for the first 6 months of life before gradual involution occurs, and the lesion generally disappears by around the age of 6 years. This natural history supports conservative management if possible. Ultrasound and MRI imaging are the recommended modes of imaging, particularly to exclude any intracranial connection, and treatment depends on the extent of involvement of the surrounding tissues.

Treatment for haemangiomas has been transformed with the use of oral propranolol and involvement of the appropriate paediatric medical team familiar with its use is recommended.[36, 37] In cases where there is encroachment on the orbit with a potential risk to vision, surgical excision has been used to good effect. The use of chemotherapy (such as methotrexate or vincristine) is reported but should be undertaken with caution due to the risks of side effects, and it has now largely been superseded by propranolol (see Chapter 42, Haemangiomas and vascular malformations).[38]

TERATOMA

A teratoma is a true neoplasm consisting of all three germ cell layers with cells varying in maturity. They occur in 1 in 4000 live births with less than 10% occurring in the

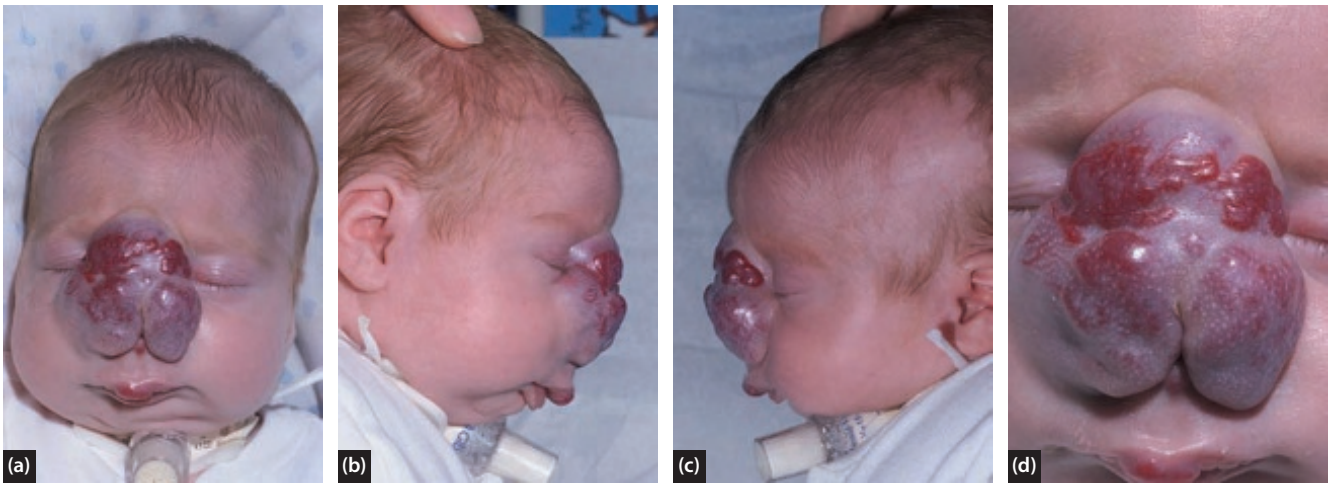

Figure 23.9 External nasal haemangioma in a 10-month-old girl.

head and neck. The cervical forms are the most common, followed by nasopharyngeal teratomas. They are associated with polyhydramnios, stillbirth and prematurity, and can result in significant airway compromise. They usually present as a firm mass.

Maternal serum alpha fetoprotein levels and beta HCG levels may be raised. Imaging is with CT and MRI. Teratomas will appear as heterogeneous masses on MRI, with fatty and bony components, and they may have a stalk, giving them mobility in different positions. Management is surgical, either endoscopic or open, depending on the size of the lesion.[39]

MISCELLANEOUS

Hamartomas, chordomas and craniopharyngiomas are extremely rare causes of nasal obstruction in the neonate.

ACQUIRED PATHOLOGIES

Osseocartilaginous septal deformity

The septum develops as an outgrowth from the merged medial nasal processes and nasofrontal process. At week 9, it fuses with the palate just posterior to the incisive foramen, and then fuses anteriorly and posteriorly.[40] A number of babies are born with a septal deviation either in isolation or in association with an abnormality of the bony pyramid. It is felt that the problem is due either to intrauterine positioning or to birth trauma. Closed reduction of the septal deformity with topical anaesthetic in each nostril in the first few days of life has been described and is thought to be successful if the deviation is severe.[41] However, most of the studies that advocate intervention have inadequate follow-up periods and there is little evidence for the adverse effects of conservative management.[42] Formal surgical repair is generally recommended later in childhood to avoid damage to the main growth centre of the nose; it is interesting, however, that the external rhinoplasty approach has been used for other pathology in very young children and no detrimental effects on nasal growth have been reported (see Vol 1, Chapter 103, Nasal septum and nasal valve).

Neonatal rhinitis

Swelling of the nasal mucosa in newborn infants can cause significant airway problems, particularly when feeding, as neonates are obligate nasal breathers. Idiopathic neonatal rhinitis is characterized by mucoid rhinorrhoea with nasal mucosal oedema in the afebrile newborn. This results in stertor, poor feeding and respiratory distress.[43] Structural abnormalities should be excluded. Treatment of neonatal rhinitis depends on the severity of symptoms. Nasal bulb suction with saline drops in the first instance is recommended. A short course of nasal steroid drops would be the next step. This should be closely monitored to avoid the potential side effects from systemic absorption.

It is important to consider chlamydia infection acquired in the birth canal. This usually results in conjunctivitis but involvement of the nose is seen in around 25% of affected individuals. Presentation is with obstruction, rhinorrhoea and a markedly erythematous nasal mucosa on examination. Swabs are diagnostic and the appropriate antibiotics should be given.

Rarely congenital syphilis (*Treponema pallidum*) can cause nasal symptoms in the neonate. Thin, clear secretions are seen between the second week and third month of life. This progresses to a mucopurulent discharge with significant obstruction and crusting of the nostrils. Antibiotic treatment is required both for symptomatic relief and to prevent chronic infection of the cartilage resulting in saddle deformity.

Fibrous dysplasia

This is an uncommon cause of nasal obstruction in older children and young adults. It is a benign fibro-osseous dysplasia and can present either as a solitary lesion (monostotic) or less commonly in multiple sites (polyostotic), typically in the craniofacial bones. Presentation is usually as pain with progressive facial deformity between the ages of 10 and 30.[44]

Nasal obstruction, with a mass on endoscopy or facial deformity due to growth of a lesion in the nose or sinus should raise suspicion. Imaging helps to confirm the diagnosis; normal healthy bone is replaced with a more radiolucent 'ground-glass' appearance. There can be endosteal scalloping of the inner cortex with a smooth non-reactive periosteal surface. Lesions have diffuse margins.

Management is expectant but surgical excision may be needed with the aim of preserving function and limiting disability. The mid-facial degloving approach has been shown to achieve good results with minimal cosmetic defect.

Medical treatment involves medication to increase bone density, for example biphosphonates.

A subgroup of polyostotic patients (around 3%) have associated endocrine abnormalities such as hyperthyroidism, adrenal disorders, diabetes, hyperpituitarism and hypercalcaemia with cafe-au-lait spots. This is termed McCune–Albright syndrome after the two physicians who first described it in 1937.

The condition usually becomes dormant by adulthood but there is a 1% risk of malignant transformation, mostly in the polyostotic form.

Neoplasms of the nasal bones

Juvenile ossifying fibroma (JOF) is a true neoplasm which is defined radiologically as a radiolucent, expansile, well-defined lesion with variable calcification. It can be unilocular or multilocular with cortical thinning and possible perforation. Pain is rare. There are two subtypes, trabecular and psammomatoid, which have different histopathological appearances.

Surgical excision is recommended and this may need to radical as recurrence rates are high (30–50%) probably due to the propensity of this disease to perforate cortical bone. Malignant change has not been reported.

Bony malignancies can rarely present as nasal obstruction or deformity; good-quality imaging will usually alert the clinician to the need for further investigations.

BEST CLINICAL PRACTICE

- ✓ Use of an oral airway in neonates with nasal obstruction can facilitate transfer for definitive treatment.
- ✓ Minimal additional investigations for a child with choanal atresia to look for CHARGE syndrome are echocardiography, renal ultrasound and ophthalmology/audiology review.
- ✓ Early surgical excision of dermoid cysts is recommended before infection or further expansion occurs.
- ✓ Nasal masses may not be as innocuous as they seem; always consider intracranial extension and imaging with CT (for bony anatomy) and MRI (to identify a CNS connection).
- ✓ Compression of the internal jugular vein (Furstenberg's test) usually causes an encephalocoele but not a glioma to enlarge.
- ✓ The treatment of nasal haemangiomas has been revolutionized by propranolol.
- ✓ Idiopathic neonatal rhinitis is underdiagnosed and improves with intranasal steroids.
- ✓ The endoscopic approach is rapidly becoming the procedure of choice for removal of neonatal nasal masses.

FUTURE RESEARCH

- ➤ Multicentre studies including long-term follow-up of patients who undergo surgery for choanal atresia.
- ➤ Studies looking at the success rates of the endoscopic approach for nasal encephalocoeles and gliomas are needed.
- ➤ Long-term follow-up of neonates who have had closed reduction of their septal deviation is unknown.
- ➤ Better evidence for the management of neonatal rhinitis is needed.

KEY POINTS

- Neonates are obligate nasal breathers; nasal obstruction can cause significant airway compromise.
- Affected neonates may develop stertor, mouth-breathing, feeding problems, sleep disturbance and rhinorrhoea.
- Immediate relief can be brought about by insertion of an oral airway.
- Choanal atresia may occur in isolation but is often one of a number of associated anomalies.
- A congenital nasal mass can consist of ectopic intracranial tissue.

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CHAPTER 24

PAEDIATRIC RHINOSINUSITIS AND ITS COMPLICATIONS

Daniel J. Tweedie

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: paediatric (pediatric) rhinosinusitis, sinusitis, complications, respiratory tract infections, immune deficiency, reflux, primary ciliary dyskinesia, cystic fibrosis, orbital cellulitis, endoscopic sinus surgery, adenoidectomy, and with particular reference to international consensus papers: the European Position Papers on Rhinosinusitis and Nasal Polyps (EPOS, 2007 and 2012).[1, 2] The American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) Consensus Statement on Pediatric Chronic Rhinosinusitis (2015)[3] and the International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR:RS, 2016).[4] These documents have made use of multinational consensus expert opinion and consider the latest available evidence.

OVERVIEW

Rhinosinusitis in children is extremely common, typically following viral upper respiratory tract infection, but other factors may be involved.

Paediatric rhinosinusitis (RS) and its complications describe a spectrum of disease, varying in aetiology, pathophysiology and duration, which influences clinical presentation and management. Apart from exposure to the common viral precipitants, known predisposing factors include allergy,[5–8] impaired cilial function,[9] immune deficiency, gastro-oesophageal reflux,[10] environmental pollution, malnutrition, and medical conditions such as diabetes mellitus and other metabolic conditions.[2] There are also specific congenital and acquired disorders in which rhinosinusitis is often a major component, for example cystic fibrosis and primary ciliary dyskinesia, and these warrant special consideration.

Rhinosinusitis is common in children[11–14] but frequently overlooked. It is significantly detrimental to quality of life[15] and costly in health economic terms. For example, the estimated annual cost of treatment of sinusitis in children under 12 years of age in the USA in 2012 was $1.8 billion.[16] While paediatric and adult rhinosinusitis are often considered together, these conditions are multifactorial, with predisposing factors and aetiology changing with age, and the childhood and adult forms differ in a number of ways. These have been summarized in the EPOS 2007 document[1] and are shown in **Table 24.1**.

ANATOMY

The paranasal sinuses are air-containing spaces which are positioned around the nasal cavities, communicating with these via natural ostia. They are lined by type II pseudostratified columnar ciliated epithelium (respiratory mucosal epithelium), with anatomical factors and cilial function optimized to facilitate mucus drainage and preserve a sterile environment.[17]

Sinus development is progressive throughout childhood. At birth, the maxillary sinuses measure 7 mm in depth, 3 mm in width and 7 mm in height.[1] The sphenoidal (sphenoid) sinuses and two or three ethmoidal (ethmoid) cells are found on each side at this stage, and the ethmoid labyrinth is complete by 4 years of age. The frontal sinuses,

TABLE 24.1 The differences between paediatric and adult chronic rhinosinusitis (reproduced with permission[2])

	Young children	Adults
Commensal microflora		
Coagulase-negative staphylococci	30%	35%
Staphylococcus aureus	20%	8%
Haemophilus influenzae	40%	0%
Moraxella catarrhalis	24%	0%
Streptococcus pneumoniae	50%	26%
Corynebacterium species	52%	23%
Streptococcus viridans	30%	4%
Immunity	Immature: defective response to polysaccharide antigens (IgG2, IgA)	Mature, except in a subset
History	Self-limited in time (improves after the age of 6–8 years)	No history of spontaneous improvement after certain age
Histology	Mainly neutrophilic disease, less basement membrane thickening and mucus gland hyperplasia, more mast cells	Mainly eosinophils
Endoscopy	Polyps are rare, except in CF	Polyps frequently present
CT-scan	Younger child more diffuse sinusitis, involving all sinus	Sphenoid and posterior sinus less often involved

not present at birth, develop from cranial extension of the ethmoid cells. Once the roof of these frontal cells reaches the level of the upper orbit, at around the age of 5 years, they are termed 'frontal sinuses'. These are demonstrable radiographically in 20–30% of children by 6 years[18] and more than 85% by 12 years of age. The maxillary sinuses expand in parallel, reaching the same level as the nasal floor by 7–8 years of age, and are 4–5 mm below this by adulthood. The sphenoid sinuses extend posteriorly over the first 7 years, and are radiologically distinct in 85% of cases by this stage, completing growth by 15 years, although some posterior extension can be seen into adulthood. Sinus expansion subsequently mirrors the dimensional changes of the midface during adolescence and towards adulthood. The maxillary and ethmoid sinuses reach full size by the age of 15 or 16, and the frontal sinuses by 19 years of age.[19]

DEFINITIONS

A number of consensus statements have sought to define rhinosinusitis in terms of symptoms and duration, but in practice the clinical diagnosis of rhinosinusitis in children can be challenging, and the diagnosis can be overlooked.

Rhinitis and sinusitis typically coexist in the same affected individual, given the close proximity of the nose and paranasal sinuses and their common mucosal lining. Guidelines and consensus documents including EPOS, ICAR:RS and statements from AAO-HNS now typically use the term **rhinosinusitis**, as opposed to sinusitis, reflecting the clinical and pathophysiological picture.[1–4, 20–22]

In a similar fashion as for adults, EPOS 2012 defines paediatric rhinosinusitis clinically as follows:[2]

'Inflammation of the nose and paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):

- +/– facial pain/pressure
- +/– cough (as opposed to reduction or loss of smell in the adult definition).

and either:

- endoscopic signs of:
  - nasal polyps, *and/or*
  - mucopurulent discharge primarily from the middle meatus, *and/or*
  - oedema/mucosal obstruction primarily in the middle meatus

and/or:

- CT changes:
  - mucosal changes within the osteomeatal complex and/or sinuses'.

These diagnostic criteria are very similar to those endorsed in the AAO-HNS Pediatric RS consensus statement.[3]

SEVERITY OF DISEASE

According to EPOS,[2] as for adults, the severity of paediatric rhinosinusitis can be classed as mild, moderate and

severe according to a patient-reported visual analogue scale (VAS). However, although also applied to children, this system has only been validated in adults to date. Using a 10 cm scale, between 0 (not troublesome) and 10 (worst thinkable), the patient (or parent) is asked to mark the severity, when asked 'How troublesome are your (or your child's) symptoms of rhinosinusitis?' A score of 0–3 is classed as mild, >3–7 moderate and >7–10 is severe. A score of greater than 5 indicates symptoms which affect patient quality of life.

DURATION OF SYMPTOMS: ACUTE VERSUS CHRONIC RHINOSINUSITIS

Paediatric chronic rhinosinusitis will be considered later in the chapter, although clinical assessment, investigation and treatment options are similar in certain aspects.

Acute rhinosinusitis (ARS) in children is defined by EPOS[2] as:

'Sudden onset of two or more of the symptoms:

- nasal blockage/ obstruction/ congestion
- *or* coloured nasal discharge
- *or* cough (daytime and night-time)

for <12 weeks (with symptom-free intervals if the problem is recurrent).'

The symptom profile defined by ICAR:RS[4] is similar, but with ARS defined by a duration of less than 4 weeks. Both consensus documents stress the inclusion of questions regarding allergic symptoms (sneezing, watery rhinorrhoea, itching of the nose and eyes), to help differentiate allergic from viral and bacterial RS.

The EPOS system[2] favoured the omission of previously used terms such as 'subacute' and 'acute or chronic' RS.

In practice, the diagnosis of ARS in children is challenging[2] due to the overlap with other conditions, including viral upper respiratory tract infections (URTIs) and the subjectivity of parental reporting of symptoms. Young children often do not tolerate nasal endoscopy, and radiographic investigations are often avoided on account of radiation exposure, particularly in children with a short-lived, uncomplicated history.

PAEDIATRIC ACUTE RHINOSINUSITIS

Epidemiology and pathophysiology

It is now known from CT[23] and MRI[24] studies that, in the majority of children with symptoms of mucous nasal discharge, the sinuses are also involved (in decreasing order of frequency: maxillary and ethmoid (60%), sphenoid (35%) and frontal (18%), with resolution of the changes seen on imaging in parallel with clinical improvement of symptoms.[24] Viral URTIs occur extremely frequently in young children (six episodes per year,[25] more in day care), and it is generally agreed (despite low rates of virus recovery from sinus aspirates[26]) that these are the precipitant for most cases of paediatric rhinosinusitis.[27,28] In prospective longitudinal studies in young children, some 8% of viral URTI cases in patients 6–35 months of age were complicated by acute RS, equivalent to 0.5 episodes per patient year.[25] Epidemiological studies also suggest that:

- RS is commonest in younger children, and the prevalence decreases sharply after 6–8 years of age, probably reflecting immune system immaturity at an early age.[29,30]
- Seasonal variations in the prevalence of RS reflect rates of viral URTI, with an increase in occurrence in autumn and winter.[29]
- Young children looked after in day care with other children have markedly higher rates of RS than those managed at home.

The annual medical visit rate in the USA for acute RS is stable, at 11–14 per 1000 children.[31] The durations of episodes of viral and bacterial RS are broadly similar between children and adults.

The commonest bacteria isolated from maxillary sinus aspirates in children with acute bacterial rhinosinusitis (ABRS) are *Streptococcus pneumoniae*, untyped *Haemophilus influenza* and *Moraxella catarrhalis*, and less often *Staphylococcus aureus, Streptococcus pyogenes* and *Streptococcus viridans* and anaerobes, including *Peptostreptococcus* and *Fusobacterium*, particularly in longer-lived cases.[26,32–41] Interestingly, adoption of the 7-valent pneumococcal vaccine (PCV) in the United States from 2000 onwards has resulted in a decline in positive samples of *Streptococcus pneumonia*, but relatively higher proportions of aspirates with untyped *Haemophilus influenzae*.[42,43] *Staphylococcus aureus* is relatively commonly isolated from cases of sphenoid sinusitis[39] and rates of methicillin-resistant *S. aureus* (MRSA) are increasing in cases of ABRS.[44,45] Importantly, such infections are often polymicrobial (about one-third of cases), and this should be borne in mind with respect to antimicrobial treatment. Similarly, less common pathogens must be considered in particular circumstances. Anaerobes comprise some 8% of bacterial isolates, often oral pathogens seen in cases of odontogenic origin, and particularly prevalent in cases persisting for more than 1 month.[36,46] *Pseudomonas aeruginosa* is associated with nosocomial infection, particularly in the immunocompromised[47] (including HIV cases), patients with nasal catheters and other devices, and those with cystic fibrosis.[48] In these sorts of cases, fungal rhinosinusitis may also develop (see below).

While remaining the gold standard for diagnosis of ABRS (≥10 000 colony-forming units per mL), antral puncture and aspiration is seldom undertaken. One should also bear in mind that improper decontamination of the paranasal mucosa before aspiration may lead to misinterpretation of results.[26,49–51] As an alternative, cultures

from the middle meatus can be obtained, for example with endoscopic guidance.[52] The maxillary sinus aspirates correlate well with specimens taken from the middle meatus of the nasal cavity (83%) but poorly with those from the nasopharynx (45%).[53]

Clinical presentation of paediatric ARS: symptoms and signs

In the paediatric group, ARS typically presents with a combination of prolonged URTI, chronic cough, nasal discharge, plus fever >39 °C and facial pain in many cases. Most cases are viral in aetiology, but bacterial infection should be considered in cases with persistent and severe symptoms and those with deterioration after initially mild symptoms.

In terms of relative preponderance between acute and chronic RS, nasal, local and systemic clinical features differ,[30, 54, 55] as summarized in the EPOS 2007 document[1] and shown in Table 24.2.

Apart from these symptom differences between acute and chronic forms, the distinction in definition is made according to symptom duration, as above, recognizing the common scenario of a child with symptoms of chronic RS who also has infection-related acute exacerbations.

Classification of paediatric ARS by aetiology

As with the definitions and criteria discussed above, there is some variation between consensus documents regarding the aetiological classifications and diagnostic features differentiating the subtypes of acute paediatric RS.

For children, as for adults, EPOS,[1, 2] ICAR:RS[4] and the American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS)[3] define **acute viral rhinosinusitis** (viral ARS, common cold), where nasal symptoms are present for less than 10 days. The most recent guidelines from the AAO-HNS included data on the duration of typical viral symptoms in support of the commonly accepted time frames used to differentiate acute viral RS from ABRS.

The EPOS 2012 statement[2] describes **acute post-viral rhinosinusitis** as an increase of symptoms after 5 days, or persistent symptoms after 10 days, but with symptom duration of less than 12 weeks. This is not recognized separately by the AAO-HNS guidelines.

Acute bacterial rhinosinusitis (ABRS) is diagnosed clinically, according to EPOS,[2] by the presence of at least three of:

- discoloured discharge (with unilateral predominance) and purulent secretion in the nasal cavity
- severe local pain (with unilateral predominance)
- 'double sickening' - deterioration after an initial milder phase of illness
- elevated erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP)
- fever (>38 °C).

The latter criterion is not considered diagnostically specific or sensitive for ABRS according to the AAO-HNS criteria.[3, 4]

For the clinician, the most common presentation of ABRS in children is a persistent and non-improving nasal discharge or cough (or both), which lasts for more than 10 days.[14] In children, the cough often worsens at night (in 80% of cases), with nasal symptoms (anterior/posterior discharge) in 76%, and associated fever for more than 3 days in 63%.[56] Halitosis is commonly seen in addition, but associated facial pain and swelling, headache and sore throats are unusual in children.

In terms of the variable clinical presentation, a number of consensus panels have identified the following three characteristic presenting features of ABRS which are diagnostically discriminating versus simple viral URTI.[57–60] Given the possible diagnostic difficulties already outlined, Wald identified three main clinical features which are suggestive of acute bacterial rhinosinusitis, over and above acute viral RS[61] which are supported by other studies:[9, 62, 63]

1. Persistent symptoms for more than 10 days, but less than 30 (although the EPOS documents define the duration of acute RS as up to 3 months).
2. Onset with severe symptoms (ill appearance, high fever >39 °C, purulent nasal discharge for at least consecutive 3–4 days at the onset of illness and other features including headache and facial pain).
3. Worsening after initial improvement (double sickening) is also strongly suggestive of ABRS.[58]

In non-allergic children, neutrophil proportions of ≥5% in nasal brushings have a 91% sensitivity and positive predictive value of 84% for maxillary sinusitis.[64]

TABLE 24.2 Presenting symptoms of rhinosinusitis in children (data reproduced with permission[2])

Symptom	Preponderance	Acute/chronic
Rhinorrhoea	71–80%	All forms
Cough	50–80%	All forms
Fever	50–60%	Acute
Pain	29–33%	Acute
Nasal obstruction	70–100%	Chronic
Mouth breathing	70–100%	Chronic
Ear complaints (recurrent purulent otitis media or OME)	40–68%	Chronic

Differential diagnoses

In children with nasal discharge, one should always exclude the possibility of a nasal foreign body or choanal stenosis or atresia. Dental disease may also give rise to sinonasal and facial symptoms. These cases most typically

present with unilateral findings, and often a suggestive history. These can usually be excluded with careful examination, including nasal endoscopy.

Hypertrophy and inflammation of the adenoids (adenoiditis) may also present with nasal obstruction and mucus. This tends to be more long-standing, with a suggestive parental history. Again, nasal endoscopy is useful to determine this.

Similarly, parental history may suggest allergic rhinitis as the basis for nasal symptoms.[65]

Clinical assessment of a child with acute rhinosinusitis

Considering the clinical features outlined above, the history and clinical examination should be focused towards confirming the diagnosis of ARS, distinguishing likely bacterial versus viral aetiology and excluding local and systemic complications.

HISTORY

The history should include enquiry about current symptoms, past history and risk factors (**Box 24.1**).

CLINICAL EXAMINATION

The clinical examination may be challenging in young children, but should ideally include:

- general observations, including temperature and neurological status
- complete ENT and head and neck examination (including the pharynx, oral cavity and teeth, orbits, ocular motility, vision, facial palpation and percussion over the paranasal sinuses, pupillary responses, cranial nerves)
- anterior rhinoscopy (oedema, inflammation, mucus/pus, foreign body) – this can by lifting up the tip of the nose and/or use of an otoscope[66, 67]
- nasal endoscopy (rigid or flexible), including middle meatal swabs for culture and sensitivity.

BOX 24.1 Clinical assessment – history

Current symptoms	Past history and risk factors
Onset	Similar episodes of sinusitis and RTI
Duration	Previous use of antibiotics
Precipitants (viral URTI, nasal foreign body)	Comorbidities
Improvement and deterioration in clinical picture ('double sickening')	Prior hospitalization and sinonasal surgery
Nasal/paranasal symptoms (congestion, mucopurulent discharge)	Allergy history
Facial/orbital pain or swelling	Day-care arrangements
Headaches and neurological sequelae	Exposure to cigarette smoke
Cough	Immunization history
Fever (severity and duration)	
Hyposmia	
Oral/dental/pharyngeal symptoms	

The nasal and pharyngeal mucosa is typically erythematous, with yellow/green nasal discharge of varying consistency. Studies have suggested the relative prevalence of associated features: post-nasal drip of mucus into the pharynx in 60%,[55] middle meatal pus in 50% and oedema of the inferior turbinates in 29%.[54] Adenotonsillar enlargement and modest, tender cervical lymphadenopathy is also sometimes seen.[66, 68]

Acute fungal rhinosinusitis in children

This is rare, and diagnosis and workup are already considered in Vol 1, Chapter 94. Allergic fungal rhinosinusitis is addressed later in this chapter.

Investigations in children with rhinosinusitis

The relevance and relative indications for investigations will depend upon the clinical presentation of rhinosinusitis, including the duration and severity of symptoms, complications and underlying comorbidities. For example, an acute, infective episode will direct a different investigative approach than a chronic, inflammatory case, where atypical organisms and/ or underlying inflammatory conditions or immunocompromise might be suspected.

Although microbiological and radiological investigations are certainly indicated in complicated cases, in most instances a clinical assessment of the child with acute RS is sufficient. In chronic RS, unusual organisms may be involved, and surgery may be warranted, prompting investigations to inform further management (see below).

MICROBIOLOGY

Cultures from nasal mucus are not needed in most cases of uncomplicated ARS. But there are some situations where this is needed. As mentioned above, antral aspiration, with measures to reduce contamination, remains the gold standard although it is impractical in everyday practice. This is reserved for particularly severe or resistant cases, or where surgical intervention is undertaken. An alternative method is to take a swab from the maxillary sinus[52] under endoscopic guidance. Nasal contamination is suggested by low bacterial quantities in the sample from a patient with significant symptoms, highly suggestive of acute bacterial RS, so isolates are considered positive when they contain more than 10 000 CFU/mL.[61]

Indications for culture are:[69]

- severe symptoms and toxic patient
- illness not improving after 48–72 hours of medical treatment
- immunocompromised patient
- suppurative complications (orbital, intracranial) or systemic sepsis.

IMAGING

The diagnosis of rhinosinusitis in children is typically clinical and usually does not require imaging. In any event, radiological investigations will not distinguish between viral and bacterial RS.[70]

Transillumination and ultrasound have been considered, but are limited in young children by thickness of soft tissues and the hard palate.[71] Plain sinus radiographs, once in common use, are now not indicated in the investigation of RS, as they correlate very poorly with CT findings. More than 50% of children with viral URTI will have abnormal maxillary sinus radiographs.[72] The radiation exposure is not justified in these circumstances.[23]

Imaging is occasionally indicated, for the same reasons as for microbiological culture above. Computerized tomography (CT) is the modality of choice, with intravenous contrast if intracranial complications are to be excluded. This is performed very quickly, usually without the need for sedation, and it is therefore favoured over MRI for these reasons.[73] But it is important to note that even asymptomatic children have a high incidence of abnormalities on CT,[72, 74] which by definition require no treatment. Additionally, in young adults, it has been found that 87% of those recovering from a viral URTI have maxillary sinus changes on CT.[27] Therefore any CT abnormalities in patients with RS must be correlated against clinical findings.

While CT has many advantages, MRI offers greater soft-tissue resolution[56] and does not involve any radiation exposure. The American College of Radiology has commented that CT and MRI are complementary modalities in the investigation of suspected orbital and intracranial complications of ABRS.[75] However, the bony resolution of CT is essential if surgery is considered, particularly given that the size of the developing sinuses in children often differs significantly on the two sides. This can be combined with image guidance systems at the time of surgical intervention. In addition, the practicalities and speed of CT and its widespread availability mean that it remains the most frequently used radiological modality in cases of RS, often as a sole imaging investigation.

Treatment of acute rhinosinusitis in children

The evidence based management of children with ARS has been presented very clearly in the EPOS 2012 document,[2] and is outlined in **Table 24.3**.

TABLE 24.3 Treatment evidence and recommendations for children with acute rhinosinusitis (reproduced with permission[2])

Therapy	Level	Grade of recommendation	Relevance
Antibiotic	Ia	A	Yes, in ABRS
Topical steroid	Ia	A	Yes, mainly in postviral ARS studies only done in children 12 years and older
Addition of topical steroid to antibiotic	Ia	A	Yes, in ABRS
Mucolytics (erdosteine)	1b (–)*	A(–)**	No
Saline irrigation	IV	D	Yes
Oral antihistamine	IV	D	No
Decongestants	IV	D	No

*1b (–): 1b study with negative outcome; **A(–): grade A recommendation **not** to use.

ANTIBIOTICS

Antibiotics are the mainstay of management of children with ARS. Meta-analysis of randomized controlled trials (RCTs), which included 17 studies (three of these in children), and 2915 adults and 376 children) showed an increase in resolution of symptoms. This effect was significant but modest,[76] and suggests that antibiotics may simply hasten slightly the resolution of uncomplicated cases of ARS, but that most cases will improve, irrespective of treatment.

The choice of antibiotics should ensure activity against the likely organisms, and include amoxicillin, amoxicillin-clavalunate and cephalosporins (the latter two covering beta-lactamase-producing organisms). Other options for patients with allergies to these agents include macrolides (azithromycin, clarithromycin) or trimethoprim/sulfamethoxazole. There is no formal recommendation for dose and duration of antibiotic use, which may be adjusted according to severity of symptoms and other factors.

INTRANASAL STEROIDS

There is evidence to support the use of intranasal steroids in conjunction with antibiotics in the management of children with ARS. In a specific paediatric trial, where 89 children received amoxicillin-clavalunate and either intranasal budesonide or placebo, significant improvements were seen by the end of the second week in those receiving intranasal steroids compared to placebo.[77] A number of other trials have considered adults and older children (12 years and above), demonstrating benefits in those receiving intranasal steroids during ARS, typically with antibiotics.[2, 77] However, while there is also evidence to

support the safety and efficacy of intranasal steroids for allergic rhinitis in younger children, data are so far lacking for ARS in this group, and the benefits are less certain. Therefore clinical judgement on an individual basis will determine whether intranasal steroids are offered in this context, most likely as an adjunct to antibiotics.

OTHER MEASURES

While saline douching may offer some benefit in children with ARS, there is no strong evidence to support the use of mucolytics and oral antihistamines in this context.[57]

Complications of paediatric acute rhinosinusitis

With the advent of antibiotics and improved standards and availability of medical care, the incidence and associated mortality from complications of paediatric ARS has declined. But these complications still occur and require prompt diagnosis and specialized management.

The overall rate of complications is 3–10 cases per million per year, equivalent to 1 per 12 000 ARS episodes.[2] Complications are more often seen in winter months,[78] and significantly more often in males than females. Importantly, studies from the Netherlands and the UK have shown that prescribing antibiotics in ARS does not prevent the occurrence of complications.[79, 80]

Complications occur as follows, although in some cases a combination may be seen:[81] orbital (60–75%), intracranial (15–20%), osseous (5–10%).

Rhinosinusitis is the presumed underlying cause in many cases of peri-orbital sepsis (10% of cases of preseptal cellulitis, 90% of cases of orbital cellulitis/subperiosteal abscess/orbital abscess)[82] and about 10% of intracranial suppuration.[83, 84]

Orbital complications are more often seen in small children, although intracranial complications can occur at all ages, particularly in the second and third decades of life.[79, 85]

ORBITAL COMPLICATIONS

Orbital complications can occur as a result of direct spread of infection across the lamina papyracea, or via a haematogenous route through small veins.[86] This is most likely from the ethmoid sinuses, and less often the maxillary, frontal and sphenoid sinuses in decreasing frequency.[79, 87] Such complications may occur with minimal pain or systemic upset.[88]

The Chandler classification is widely used to describe orbital complications of ARS[81] with respect to the orbital septum. This identifies five stages of orbital sepsis:

1. Inflammatory oedema (preseptal cellulitis)
2. Orbital cellulitis
3. Subperiosteal abscess
4. Orbital abscess
5. Cavernous sinus thrombosis.

It should be noted, however, that these are not necessarily seen clinically in a sequential manner. For example, intracranial complications including cavernous sinus thrombosis (see below) may occur without prior abscess formation. Additionally, the inclusion of preseptal cellulitis has also been questioned, which by definition is not an orbital infection, and is far less commonly seen as a result of ARS than true orbital complications. Other classification systems have therefore also been considered.[89, 90]

Preseptal cellulitis

Preseptal cellulitis describes inflammation of the eyelid and conjunctiva, anterior to the orbital septum). It may occur as a complication of upper respiratory tract infection, dacryocystitis or skin infection and less often sinusitis.[91–94] Presenting features include eyelid oedema and erythema, orbital pain, with or without fever and systemic upset. There is typically no proptosis or restriction of eye movements, but this can be challenging to assess in small children.

Preseptal cellulitis usually responds to an oral antibiotic but may spread beyond the orbital septum, with intraorbital complications. As such, it can usually be assessed clinically, but imaging is sometimes considered.

True orbital complications, while presented individually, can be considered together in terms of a more severe clinical presentation, and require far more aggressive investigation and management strategies.

Orbital cellulitis

Orbital cellulitis and subperiosteal abscess are seen more commonly than preseptal cellulitis as a result of ARS.[91, 93] Inflammation behind the orbital septum, within the tight confines of the orbit itself, will reduce the range of eye movements and produce pain on movement, diplopia, chemosis (conjunctival oedema) and proptosis. This requires a proactive management regime, including treatment with intravenous antibiotics and cross-sectional imaging to exclude orbital or intracranial abscess and other complications.

Subperiosteal and orbital abscess

A subperiosteal abscess forms between the periorbita (soft tissue orbital contents) and the sinuses, and is 'extraconal', lying outside the cone of ocular muscles. The clinical features of a subperiosteal abscess are similar to those of orbital cellulitis: oedema, erythema, chemosis and proptosis with painful, limited eye movements. Systemic upset and derangement of inflammatory markers may be more pronounced[95] but they cannot be relied upon to discriminate an abscess from cellulitis.

Orbital abscess is less commonly seen, with a frequency of between 8.3%[96] and 13% in studies of orbital complications in children.[97] This is 'intraconal', within the cone of the ocular muscles, and may result from diagnostic delay or immunosuppression.[98]

MANAGEMENT OF ORBITAL COMPLICATIONS

Orbital complications and their management are considered together, although in some cases these can coexist with intracranial and osseous complications, in many cases with similar investigation and treatment strategies. The child's vision is at risk, and there is also the possibility of life-threatening intracranial complications. The importance of a high index of suspicion, comprehensive history and clinical assessment cannot be overstated, as well as a considered, proactive approach to investigation, medical and surgical management. This mandates a multispeciality approach, with input from otolaryngology, paediatrics, ophthalmology, neurosurgery and microbiology personnel.

Clinical assessment

Considering the clinical features above, history and examination should include assessment of the eyes with respect to swelling, proptosis, movements, colour vision and acuity, plus assessment of the child's general condition, vital signs, level of consciousness and neurological status. This is undertaken with help from paediatric and ophthalmology colleagues. Twice-daily ophthalmology review of colour vision and acuity is recommended.[99] If there is failure to respond to medical management or otherwise any clinical suspicion, cross-sectional imaging is indicated.[99]

The first-line investigation is CT with contrast, including orbital detail, the paranasal sinuses and brain, with a view to assessing orbital and intracranial complications adequately. This is usually quick to perform and normally possible in an awake child. CT may allow distinction between cellulitis and orbital/subperiosteal abscess. In the case of subperiosteal abscess, findings include oedema of the medial rectus muscle, lateralization of the periorbita, and displacement of the globe downward and laterally. Orbital abscess is associated with obliteration of the detail of the extraocular muscle and the optic nerve by a confluent mass, sometimes with gas bubbles from anaerobic bacteria.

The predictive accuracy of a clinical diagnosis has been found to be 82% and the accuracy of CT 91%. MRI may be useful in cases of diagnostic uncertainty or when intracranial complications are suspected,[100, 101] but this usually requires sedation or general anaesthesia in young children, so this should not delay management.

Treatment

Initial medical treatment consists of high-dose intravenous antibiotics (according to local protocols), covering aerobic and anaerobic organisms, plus analgesia/antipyretics, intravenous fluids and adjuncts including intranasal steroids and saline douching. Antibiotics can be converted to an oral preparation when the patient has been afebrile for 48 hours.[102]

Where there is evidence of an abscess on CT and/or absence of clinical improvement after 24–48 hours of intravenous antibiotics, orbital exploration and drainage is indicated.[96] Current consensus from the EPOS 2012 document[2] suggests that preseptal and orbital cellulitis should be treated with antibiotics, while subperiosteal and intraorbital abscesses require surgical exploration.

In adults, drainage may be attempted endoscopically in expert hands, with adjuvant endoscopic sinus surgery (including ethmoidectomy)[95] and the consensus is to attempt to drain the abscess endoscopically by opening the lamina papyracea and draining the abscess after completing an endoscopic ethmoidectomy. However, in children with small noses and paranasal sinuses and marked nasal congestion, access and the quality of the endoscopic surgical field may be extremely unfavourable, such that external approaches (via a modified Lynch Howarth incision in the case of medial subperiosteal abscess or eyelid approaches for superior/lateral orbital abscess) are often used.

However, good outcomes can be seen with non-surgical management, with intravenous antibiotics in small children with subperiosteal abscess,[98, 100, 102] provided the following apply:

- There is clinical improvement within 24–48 hours.
- There is no decrease in colour vision or visual acuity.
- The abscess is subperiosteal and small (<0.5–1 mL volume) and medially located.
- There is no significant systemic involvement.
- The patient age is less than 2–4 years.

Sequelae of orbital complications

Where management has been prompt and appropriately directed, patients will usually recover very well with minimal long-term problems. However, in some cases vision may be permanently compromised or lost as a result of retinal artery occlusion and/or prolonged venous congestion, optic neuritis and corneal ulceration. There are also risks of diplopia and other long-term orbital complications resulting from the original infection and/or surgical drainage procedures. Sepsis may also spread intracranially.[103] Careful follow-up is therefore required to identify these issues.

INTRACRANIAL COMPLICATIONS

Intracranial complications include abscess formation (extradural, subdural or intracerebral), meningitis, cerebritis and dural venous thrombosis (including superior sagittal and cavernous sinus thrombosis).[83, 104, 105] These are most often associated with frontoethmoidal or sphenoidal ARS,[105] via direct extension or haematogenously via diploic veins.[106] Flora is often mixed aerobic/anaerobic, so the antibiotic cover should reflect this, if possible corroborated with culture of pus samples. Common pathogens in this context are *Streptococcus* and *Staphylococcus* species and anaerobes.[83]

A high index of suspicion is required, as the clinical presentation of intracranial sepsis is often non-specific, including high fever with severe, intractable headache, but

sometimes such symptoms are absent (masked), especially in immunocompromised patients and those who have had prolonged antibiotic therapy already.[101] However, in most cases, specific signs and symptoms are present, including nausea and vomiting, neck stiffness and altered mental state.[98, 103, 104, 106] Intracranial abscesses are often heralded by signs of increased intracranial pressure, meningeal irritation, and focal neurologic deficits, including cranial nerve palsies (III, VI and VII), or more generalized neurological deficit (altered consciousness, gait disturbance, confusion).[98, 107]

As with orbital complications, CT with contrast allows an accurate delineation of bone involvement. MRI is an excellent adjunct, especially where neurosurgical intervention is being considered. It is more sensitive than CT in discriminating intracranial complications,[108] with particular value in venous sinus thrombosis, or where there is soft-tissue involvement. The same considerations apply in terms of availability of MRI and likely requirement of general anaesthesia in young children.

Options for culture include swabs from the nose (with endoscopic guidance if practical), sampling of pus during formal sinus surgery or during neurosurgical drainage, plus blood cultures and lumbar puncture (after first excluding raised intracranial pressure).

As for intraorbital abscesses, drainage of intracranial abscesses is usually undertaken (neurosurgical burr hole drainage, craniotomy or image-guided aspiration), as needed. Combined drainage of the paranasal sinuses can be performed endoscopically or via an open approach.[108] In some cases, where abscesses are small and/or inaccessible, non-surgical management may be reasonable, only after expert neurosurgical consideration. High-dose long-term antibiotic therapy is often needed.[109, 110]

Cavernous sinus thrombosis

This potentially devastating complication is seen where veins around the paranasal sinuses are congested during ARS, and become phlebitic, with propagation centrally. This can lead to cavernous sinus thrombophlebitis causing sepsis and multiple cranial nerve involvement.[111] This accounts for around 9% of intracranial complications,[106] particularly after ethmoidal or sphenoidal sinusitis.[112] In adults, the mortality rate is 30%. No such data are available for the paediatric population, where the mortality rate for intracranial complications has been quoted at 10–20%.[113]

Clinical features include:[114]

- bilateral ptosis
- proptosis and chemosis
- ophthalmic nerve neuralgia
- retro-ocular headache, which can be severe
- complete ophthalmoplegia,
- papilloedema
- signs of meningeal irritation, associated with spiking fevers
- confusion and reduced level of consciousness.

Similar investigations will be required as for other forms of intracranial complications. MRI (in particular MR venography) is especially sensitive, with absence of flow in the thrombosed sinus. As an alternative, CT with contrast may show equivalent filling defects.

Treatment is undertaken in a specialist neurosurgical centre. Anticoagulants may be considered, as long as imaging has excluded intracerebral haemorrhage, in conjunction with intravenous antibiotics and/or steroids. Drainage procedures will include attention to the involved paranasal sinuses.

OSSEOUS COMPLICATIONS

ARS may lead to infection spreading to the surrounding bone, producing osteomyelitis and in some cases onward spread to the brain and central nervous system. The frontal sinuses are most often implicated, but ARS in any of the sinus groups may produce similar sequelae, particularly in infancy, where the maxillae can be affected.[114, 115]

Osteomyelitis produces avascular necrosis of bone and localized venous congestion. In the case of the frontal sinus, erosion of the anterior table in this way causes oedema of the overlying skin (Pott's puffy tumour). Spread via the posterior table can give rise to meningitis and other intracranial complications, with similar signs. The changes are well delineated by CT, with MRI as an adjunct if intracranial complications are suspected.

The incidence of these complications has been well documented in adults, but is less certain in children, although overall these are relatively rare events. Management, as with other complications, demands a circumspect, proactive approach, often requiring multimodality treatment under the care of a variety of specialities.

PAEDIATRIC CHRONIC RHINOSINUSITIS

Chronic rhinosinusitis (CRS) (with or without nasal polyps) in children is defined by EPOS[2] as:

'Inflammation of the nose and paranasal sinuses characterised by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):

- +/– facial pain/pressure
- +/– cough
- persisting for >12 weeks.'

This duration is endorsed by the ICAR:RS[4] and AAO-HNS[3] consensus statements.

Clinical overview

Paediatric CRS has not been as extensively studied as in adults. The relative contribution of anatomical and other factors will differ between children and adults. Only a minority of cases present for treatment, and this is

typically medical, with surgery reserved for more resistant and severe cases.[2]

While the above definition is clear, confirming a diagnosis of CRS in children is often challenging or even impossible.[2] The precise history may be difficult to establish, particularly separating persistent symptoms lasting more than 12 weeks from frequently recurrent symptoms, interspersed with short periods of remission. Examination is not always straightforward, nasal endoscopy may not be tolerated and imaging is withheld in most cases. Even when CT scanning is undertaken, it should be noted that 18–45% of normal controls may have sinus-related changes.[116, 117] In one study, children without CRS were found to have a mean Lund-MacKay score of 2.8.[118] With this in mind, it has been proposed that a Lund-MacKay score greater than 5 in children indicates CRS,[119] but in reality most children with CRS will be managed on a clinical basis and will not undergo imaging.

There is also significant overlap with other very common childhood upper respiratory conditions, including recurrent viral URTI, allergic rhinitis and adenoiditis and/or adenoidal hypertrophy. In fact, the EPOS 2012 consensus group deemed it impossible to distinguish CRS from adenoid-related pathology in young children.[2]

Given these clinical and diagnostic uncertainties, it is important to establish which clinical features have the highest positive predictive value for CRS. Studies have suggested that the four most common features are:[120, 121]

- cough, particularly chronic cough
- rhinorrhoea
- nasal congestion
- post-nasal drip.

One study examined the correlation between chronic cough (>4 weeks) and CT sinus changes. In these patients, abnormalities on sinus CT were found in 66% of cases, with mild changes in 14%, moderate changes in 19% and severe changes in 33% of all cases.[122]

Pathophysiology of paediatric CRS

Some of the contributing factors in children with ARS will also apply in CRS, but it is worth considering separately the particular factors involved in CRS. This also applies to the differences in aetiology, pathology and management of CRS between children and adults.

Normal function of the nose and paranasal sinuses depends upon the health and integrity of the ciliated, columnar mucosal epithelium, and the overall anatomical pathways for mucus clearance, aeration and sinus drainage. The osteomeatal complex (OMC) is central to these considerations, which functionally represents the final common drainage pathway for the majority of the paranasal sinuses (frontal anterior/middle ethmoid cells and maxillary sinuses). The OMC comprises five structures:

- **maxillary ostium:** the main drainage channel of the maxillary sinus into the middle meatus
- **infundibulum:** a common channel draining the ostia of the maxillary and ethmoid sinuses to the hiatus semilunaris
- **bulla ethmoidalis:** a single air cell which projects inferomedially over the hiatus semilunaris
- **uncinate process:** a crescent-shaped process arising from the posteromedial aspect of the nasolacrimal duct, forming the anterior border of the hiatus semilunaris
- **hiatus semilunaris:** the final drainage passage, between the bulla ethmoidalis superiorly and free edge of the uncinate process.

The sphenoid and posterior ethmoid cells drain separately into the sphenoethmoidal recess.

The region of the OMC is subject to significant anatomical variation, often with little effect on sinonasal function. But mechanical obstruction of this area, as a result of congenital malformation, trauma, surgery and, more commonly, mucosal inflammation, may greatly impair its functional efficacy. This is considered to be the key event in most cases of chronic rhinosinusitis, although a diverse group of precipitating factors are involved. Obstruction of sinus drainage leads to retained secretions, reduced sinus aeration, mucosal hypoxia and dysfunction. Mucosal oedema and cilial impairment, with stimulation of further mucus production, lead to mucus stasis, further secretion retention and secondary infection.[56]

Contributing factors in paediatric CRS

With these considerations in mind, contributing factors for CRS in children can be subdivided into local/anatomical, inflammatory and infective, and systemic (**Box 24.2**).[56]

BOX 24.2 Contributing factors in paediatric CRS

Local factors	Inflammatory and infective factors	Systemic conditions
Sinus obstruction (anatomical, e.g. concha bullosa)	Viral URTI	Immune deficiency
Septal deviation	Bacterial infection	Cystic fibrosis
Nasal polyps	Allergy	Primary ciliary dyskinesia
Adenoidal inflammation	Gastro-oesophageal reflux disease (GORD)	
Trauma/iatrogenic	Tobacco smoke	
Foreign body		

The variation in contributing factors, and indeed the heterogeneity of individual anatomical variations and comorbidities, necessitates a circumspect approach in the investigation and management of such cases. Some particular issues warrant special consideration and are discussed below.

MICROBIAL FLORA

Microbial involvement in the pathogenesis of CRS has been increasingly considered, in addition to the cases of acute and chronic infection with the typical bacterial pathogens associated with ARS (above). It has traditionally been thought that the paranasal sinuses are sterile, but some studies have now suggested that this is not the case. In fact, reduced diversity of sinus microbial flora has been demonstrated in some cases with CRS, compared to healthy controls.[123] *Lactobacillus sakei* was shown in murine models of CRS to have a protective effect. In cases of CRS, it could therefore be possible that use of antibiotics may reduce the naturally protective effects of these organisms.

BACTERIAL INFECTION: EXOTOXINS AND BIOFILMS

On the other hand, infection by pathogenic organisms (as opposed to colonization by non-pathogenic flora) is a precipitant in some cases. The organisms involved are those which are typically implicated in acute bacterial RS (above). The mechanisms whereby these infections lead on to CRS are under review. Bacterial exotoxins may have an important role, with provocation of an excessive immune response by these mediators. For example, in patients with inflammatory nasal polyps, staphylococcal exotoxins have been found to affect T-cell function.[124] Biofilms (aggregates of bacteria within an external matrix of proteins, nucleic acids and polysaccharides) are also thought to be important, greatly decreasing the efficacy of antimicrobials. In fact, biofilms have been found in up to 80% of sinus biopsies from patients undergoing functional endoscopic sinus surgery (FESS),[125] and adenoid tissue, abundant in young children, may also harbour large volumes of biofilms, contributing to these processes.[126]

ADENOIDS

The role of the adenoids in the pathogenesis of paediatric RS, especially in chronic cases, is increasingly appreciated. It is also known that adenoidectomy reduces or eliminates symptoms in a high proportion of children with CRS. This is covered extensively in the EPOS 2012 document.[2] Several findings from a number of studies have highlighted this presumed aetiopathologic relationship.

- **Bacterial 'reservoir'.** In children with CRS, the bacteria cultured from middle meatal swabs and adenoidal core cultures are very similar, including *Streptococcus pneumoniae*, group A streptococci, *Haemophilus influenzae*, *Staphylococcus aureus* and coagulase-negative staphylococci.[127] The positive predictive value of adenoid core culture in predicting middle meatal culture results in one study was 91.5%, with a negative predictive value of 84.3%.[127]

  Interestingly, adenoid size alone has not been shown to correlate with the severity of disease on CT,[128] suggesting that the role of the adenoids as a reservoir for bacteria and associated inflammation ('adenoiditis') is more relevant than the size of the tissues (pure adenoidal hypertrophy).
- **Biofilms** are thought to have an important role within inflamed adenoid tissues in cases of adenoiditis and are also implicated in CRS in children, in the same patients. One study compared the biofilm volume on the surface of the adenoids excised in cases of adenoiditis/CRS versus those removed purely for obstructive symptoms. Although carried out in small numbers of cases, there was a major difference in the surface area of the adenoid tissue covered in biofilms between children with CRS symptoms, (88–99% of the surface area) and those with simple obstruction (0–6.5% of the surface area).[129]
- **Immunological effects** of the adenoid tissue have also been considered. In cases of CRS, adenoid tissue has lower IgA expression than in comparable tissue of children with simple adenoidal hypertrophy but no CRS symptoms.[130] Conversely, inflammatory markers (such as tissue remodelling cytokines, transforming growth factor β (TGF-β1), matrix metalloproteases MMP-2 and MMP-9) were found at higher levels in the adenoids of CRS patients than in controls.[131]

These studies, while small, correlate well with the near-identical clinical pictures of CRS and adenoiditis in children, and the relative benefit of adenoidectomy, independent of adenoid size, in the management of these patients. This is further addressed in 'Surgical management' below.

GASTRO-OESOPHAGEAL REFLUX DISEASE

Gastro-oesophageal reflux disease (GORD) is now recognized as a feature in a proportion of children with CRS. A large retrospective study comparing children with a diagnosis of GORD with non-reflux controls showed significantly higher rates of diagnosis of concomitant RS than in the non-reflux group (4.19% vs 1.35% respectively).[132] Effective antireflux therapy has been shown to reduce the need for sinus surgery in many of these cases.[133] But the presence of these conditions together, while suggestive, does not confirm a causal relationship. Further controlled trials will be required before antireflux medical treatment of children with CRS can be recommended routinely.

ALLERGY AND ALLERGIC RHINITIS

Children with CRS will often have an atopic history, including allergic rhinitis. But both conditions are common within the paediatric population and, again, their coexistence within the same individual does not demonstrate causality *per se*.

A number of studies have examined this relationship, albeit comprising relatively small numbers of children. Their findings are mixed, suggesting that the link between the two domains is not clear-cut. One examined the correlation between radioallergosorbent test (RAST) test and CT findings in patients (children and adults) with CRS symptoms which were resistant to treatment. Of 42 patients, 40% were atopic and 60% had negative RAST tests; the RAST-positive group also had more pronounced CT findings than the RAST-negative group.[134] But other studies have not shown significant correlations between atopic and non-atopic groups, either in terms of CT changes,[135, 136] or in the prevalence of atopy between children with and without a history of CRS.[137] The lack of consistent data has led the EPOS consensus group to suggest that there is probably no link between allergic rhinitis and CRS in children.[2]

ALLERGIC FUNGAL RHINOSINUSITIS

Allergic fungal rhinosinusitis (AFRS) results from hypersensitivity to fungi. It has a relatively high prevalence in adults with CRS who undergo surgery, and is estimated to occur in 5% to 10% of adults with chronic sinusitis who require surgery.[138] Children with allergic fungal rhinosinusitis may present with proptosis and polyposis.[139] Treatment includes sinus surgery to remove inflammatory tissue, polyps and fungus. Evidence is lacking for other treatments in children, although topical and systemic steroids and immunotherapy may be beneficial. The clinical diagnosis is easily overlooked, so a high index of suspicion is needed. Typical CT findings are unilateral sinus opacification with non-erosive expansion of the sinuses on CT.

ASTHMA

Some small studies examining the clinical course of children with asthma and CRS have shown marked improvements in asthma-related measures after medical and/or surgical treatment of CRS[120] (need for asthma medications, spirometry, wheezing and inflammatory markers in nasal lavage).[140] The improvements were seen to reverse once the CRS relapsed. These findings suggest that successful treatment of CRS in patients with asthma will help better control their chest symptoms, as is the case for allergic rhinitis. But while the links between asthma and allergic rhinitis are well documented, the relationship between asthma and CRS in children has not been demonstrated definitively by controlled trials.

IMMUNODEFICIENCY

A number of studies have evaluated the relationship between CRS in children and underlying immune deficiencies. These comprise series where cases of persistent CRS, which have been resistant to medical treatment, were investigated for a number of different immune parameters. Relatively small numbers of children were investigated in each series, with very variable results, including low IgA, Ig1 and/or Ig3 levels, poor pneumococcal antigen 7 responses in some cases (but normal vaccine responses in others).[141–143] Additionally, one study examined the clinical response of six children with refractory CRS who were treated with intravenous immunoglobulin for 1 year.[144] This showed a significant reduction in sinusitis episodes, total number of days of antibiotic usage and improved CT findings. These results suggest that various forms of immunodeficiency may have a role in a proportion of children with CRS, particularly in resistant cases. The EPOS 2012 consensus group therefore suggest evaluation of immune function in such cases, with quantification of Ig levels, and responses to various immunizations, including pneumococcal conjugate vaccine, tetanus and diphtheria.[2]

CYSTIC FIBROSIS

Cystic fibrosis (CF) is an autosomal recessive condition affecting 1 in 2500 live births in the UK, and is associated with high incidence of CRS and nasal polyposis in children. The mutated *CFTR* gene (cystic fibrosis transmembrane conductance regulator gene, long arm of chromosome 7–7q31.2) leads to abnormal cyclic AMP-mediated transmembrane chloride transport in epithelia and exocrine glands. This gives rise to multiorgan pathologies, including chronic pulmonary infections and bronchiectasis, pancreatic dysfunction and infertility. CRS is extremely common in these patients, and nasal polyposis is a feature in 7–50%.[145, 146]

Genetic testing and screening for suspected CF

More than 1000 mutations of the *CFTR* are known. The most commonly encountered mutation leads to a single amino acid deletion at position 508 in the *CFTR* protein (ΔF508). However, such is the number of possible mutations, and possible allelic combinations between individuals, that CF is not always straightforward to diagnose. It may be missed with screening, and can present variably (a disease spectrum), sometimes even into late childhood or adulthood.

Neonatal screening for the condition (as part of the Guthrie heel prick blood tests) has been offered universally in the UK since October 2007, having commenced earlier in some areas. This is also undertaken in a number of other countries. Blood levels of immunoreactive trypsinogen (IRT) are known to be high in cases of CF,[147] and this forms the basis of the CF component of the Guthrie test, undertaken universally within 5 days of life.

Babies with high IRT levels at or above the 99.5th centile are forwarded for genetic testing across four common loci (a four-panel DNA test, including ΔF508), with subsequent protocols designed to maximize accurate CF diagnosis as early as possible, while limiting parental anxiety associated with delays and false positives.

Babies with mutations in both *CFTR* genes have a presumptive diagnosis of CF and are reported as 'CF suspected', before referral to a paediatric service for evaluation (clinical assessment, sweat test and confirmatory mutation analysis).

Babies with one mutation detected will most often have a normal second allele, and are therefore

asymptomatic carriers. But a minority have an abnormal second allele which is not detected by the four-panel test. To identify such cases, a second IRT test is undertaken between day 21 and day 28, using a repeat dried blood spot specimen. Those with a high IRT on this second sample are reported 'CF suspected' and are referred as above, while those with IRT levels below a defined cut-off are considered probable carriers with a low risk of CF.

Those babies who have no detected mutation and a first IRT above the 99.5th centile but below the 99.9th centile are reported as 'CF not suspected'. Babies with an initial IRT at or above the 99.9th centile require a second IRT, as above, at 21–28 days; a second IRT below a given cut-off is reported as 'CF not suspected', but those with a high second IRT above the cut-off are considered 'CF suspected' and are referred on, with a presumptive diagnosis.

Sweat test

Owing to the great genetic heterogeneity of the condition, however, any genetic screening is accompanied by a sweat test, assaying the chloride levels in sweat induced by pilocarpine iontophoresis.[148] At the test site (usually the forearm), an electrode is positioned over gauze containing pilocarpine (a parasympathomimetic alkaloid) and an electrolyte solution. A second electrode is placed on untreated skin nearby, and a small electric current is applied, which draws sweat out of the skin. This is collected using preweighed filter paper over 30 minutes under controlled conditions to prevent contamination and evaporation.

Weighing and subsequent analysis of the sweat sample will determine the chloride level, and this is compared against age-appropriate levels (for children under or over 6 months of age). The sodium level should be commensurate with the chloride level. If not, then technical errors may be responsible; the reliability of the sweat test may be compromised by an insufficient sample, evaporation, contamination and other metabolic conditions, for example. A reliable positive test with high chloride levels on two separate days is diagnostic of CF.

Endoscopic sinus surgery in patients with cystic fibrosis

Surgical management of this group has been considered in the EPOS 2012 paper,[2] but studies are relatively small. The limited evidence from these studies suggests a significantly increased incidence of nasal polyps in children with CF, when compared with non-CF patients with CRS, and a high correlation between positive culture of *Pseudomonas* from sinonasal samples and underlying CF.[149] A further study demonstrated that, although certain measures, such as hospital admissions, were unaffected by ESS in this paediatric CF group, quality of life, nasal obstruction, discharge and other symptoms were significantly improved by ESS/polypectomy.[150] It would therefore appear reasonable to consider surgical management of children with CF who have sinonasal manifestations, bearing in mind the existing disease burden and the likelihood of symptom recurrence requiring multiple procedures throughout life. As such, the extent of surgery should be carefully considered on an individual basis, with the aim of maximizing benefits but limiting the risks of morbidity and complications.

PRIMARY CILIARY DYSKINESIA

Primary ciliary dyskinesia (PCD) is an autosomal recessive condition, involving dysfunction of cilia, present in 1 of 15 000 of the population.[151] The normal movement of mucus by mucociliary transport toward the natural ostia of the sinuses and nasopharynx is disrupted. Half of children with PCD also have situs inversus, bronchiectasis and CRS, collectively termed Kartagener syndrome. The diagnosis of PCD, like CF, should be suspected in children with atypical asthma, bronchiectasis, chronic wet cough or rhinosinusitis. Additionally, in PCD, children are prone to chronic and resistant otitis media, with persistent middle ear effusion. This tends to respond poorly to ventilation tubes, with persistent mucoid discharge.[9] Screening tests for PCD include nasal nitric oxide (NO) (with lower NO levels than controls) and the saccharin test, demonstrating slower mucociliary transit time from the anterior nares to the nasopharynx. Specific diagnosis involves examination of cilia (from mucosal brushings) by light and electron microscopy. In cases of PCD, this most often demonstrates lack of outer dynein arms, or a combined lack of both inner and outer dynein arms.[152] In contrast to CF cases, nasal polyposis is not typically encountered, despite significant sinonasal symptoms in many cases.[153]

Management of chronic rhinosinusitis in children

ASSESSMENT AND DIAGNOSTIC WORKUP

The clinical assessment of children with CRS is similar to that already described in cases of ARS. History, examination and further investigations should be targeted according to individual presentation, bearing in mind the possibility of underlying aetiologies, including adenoidal hypertrophy, and rarer conditions including CF, PCD, allergic fungal rhinosinusitis and immunodeficiency, for example. This heterogeneity of conditions demands a high index of suspicion when managing children with CRS, altering the threshold for referral for other specialist consultations and diagnostic tests, including cross-sectional imaging (CT and MRI) and culture of nasal samples. The sensitivity and specificity of sampling from the middle meatus (directly or under endoscopic visualization) for microbial culture has already been addressed.[52, 53]

Similarly, the rationale for CT and MRI, and their advantages and limitations have also been discussed.[119, 120] Plain radiographs do not correlate well with CT findings in CRS.[154] CT offers an excellent road map for surgical treatment, identifying anatomical variants and areas of bony erosion or distortion from disease.[155] Particular diagnoses in the context of CRS may be revealed by CT, for instance in the case of allergic fungal rhinosinusitis and CF. Characteristic features of AFS are expansile disease with attenuation of the skull base and orbital wall,

often with a 'starry sky' speckled pattern of high attenuation on soft tissue and bone windows, as a result of thick allergic mucin and calcification. This is corroborated by MRI, with low signal on T1 weighting in areas of mucin, with signal void on T2 weighting, plus a high signal rim of surrounding mucosal inflammation.[156]

In patients with CF, CT demonstrates panopacification of the sinuses and medial displacement of the lateral nasal wall, which may obstruct the nasal passages.[157]

MEDICAL THERAPY

In contrast to CRS in adults, young children with CRS typically can be managed conservatively, as symptoms tend to resolve spontaneously.[158] A moderate-sized prospective study following 169 patients over 6 months demonstrated that no children with persistent runny nose developed severe clinical symptoms or complications of CRS.[30] Data regarding specific medical treatment for CRS in children are very limited. The levels of evidence for each treatment are summarized in the EPOS 2012 document[2] and shown in **Table 24.4**.

While antibiotics have a modest overall benefit in the management of short-term RS symptoms, no such benefits have been demonstrated in the long term for children with CRS in one study.[159] No studies have demonstrated conclusive benefits of topical steroids in children with CRS, although a number of studies have demonstrated significant benefits in rhinitis, such that the EPOS consensus supports their use in paediatric CRS, albeit with little supporting evidence.[2] Nasal steroids in asthmatic patients with CRS may also reduce bronchial hyper-reactivity.[140] Saline douching with normal[160] or hypertonic saline[161] has some demonstrable efficacy in CRS, and may also improve parallel asthma symptoms,[162] but antral washouts are not recommended, with little evidence to support them. Treatment of active gastro-oesophageal reflux is also believed to improve CRS symptoms in patients affected by both conditions.[133, 163]

SURGICAL MANAGEMENT

Adenoidectomy

The role of the adenoids in the pathogenesis of paediatric rhinosinusitis remains uncertain, but adenoidectomy is known to improve symptoms in at least half of young children with CRS.[2] Whether the most important factor is the presence of the adenoids *per se*, their size or related bacterial colonization and inflammation (adenoiditis) is unclear, but there is likely to be a degree of heterogeneity in this context among young children with CRS. Nasal obstruction, snoring and hyponasal speech occur more often in children with adenoid hypertrophy while symptoms of rhinorrhoea, cough, headache, signs of mouth breathing, and abnormalities on anterior rhinoscopy occur as frequently in children with chronic rhinosinusitis as in children with adenoid hypertrophy.[164] In one study, antibiotic-resistant bacteria were found on culture of adenoid tissue in 56% of children undergoing adenoidectomy for hypertrophy plus otitis media with effusion and CRS, compared to 22% undergoing adenoidectomy purely for hypertrophy without those complications.[165] In another study, no significant correlation was found between the size of the adenoid and the presence of purulent secretions in the middle meatus on fibreoptic examination in 420 children aged 1–7 years. There was, however, a very significant correlation between the size of the adenoid and the complaints of mouth breathing and snoring.[166]

Endoscopic sinus surgery

Functional endoscopic sinus surgery (FESS) is a common intervention in adults with CRS, but its role in the management of paediatric CRS remains controversial. Certainly, conservative measures, initial medical management and adenoidectomy should be considered first, and where appropriate other underlying conditions should be excluded, before FESS is undertaken. Surgical management decisions will also be influenced by the presence of underlying pathology such as CF, PCD and AFS.

Importantly, washout procedures which were previously commonly undertaken (antral washouts, inferior meatal antrostomy and Caldwell Luc procedures) are ineffective and not recommended in this context.[1, 66, 67, 167, 168]

Absolute indications for FESS in children are the following:[69]

- complete nasal obstruction in cystic fibrosis due to massive polyposis or due to medialization of the lateral nasal wall
- orbital abscess
- intracranial complications

TABLE 24.4 Treatment evidence and recommendations for children with chronic rhinosinusitis (reproduced with permission[2])

Therapy	Level	Grade of recommendation	Relevance
Nasal saline irrigation	Ia	A	Yes
Therapy for gastro-oesophageal reflux	III	C	No
Topical corticosteroid	IV	D	Yes
Oral antibiotic long term	no data	D	Unclear
Oral antibiotic short term <4 weeks	Ib(–)[#]	A(–)*	No
Intravenous antibiotics	III(–)[##]	C(–)**	No

[#] Ib (–): Ib study with a negative outcome; *A(–): grade A recommendation **not** to use; [##]III(–): level III study with a negative outcome; **C(–): grade C recommendation **not** to use.

- antrochoanal polyp
- mucocoeles or mucopyocoeles
- fungal rhinosinusitis.

For other cases, where CRS symptoms persist despite optimal medical management, FESS may also be considered[1, 2] and can be limited to uncinectomy, partial ethmoidectomy and opening of the bulla and/or maxillary antrostomy.

In terms of demonstrable benefits, a small number of studies have shown improvements after FESS in children with CRS. A metanalysis of eight published articles (832 patients) showed positive outcome rates of 88–92%. The average combined follow-up was 3.7 years.[169] This concluded that FESS is a safe and effective treatment for CRS which is refractory to medical treatment. Other studies have produced similar results.[170–172] FESS is unlikely to be successful in very young children[173] and its efficacy is reduced if the child is exposed to tobacco smoke.[174] Disease duration prior to surgery does not affect outcome.[175] No obvious long-term differences in facial growth have been demonstrated in children with CRS undergoing FESS rather than those managed conservatively.[172]

Overall, therefore, FESS is likely to be beneficial in selected cases of paediatric CRS, but should be considered only after a period of medical management (and/or adenoidectomy) and exclusion of underlying pathologies. When undertaken, FESS should be limited in most circumstances, and typically avoided in very young children.

KEY POINTS

- Paediatric rhinosinusitis is extremely common.
- Evidenced based management has been presented in the literature, for example in the EPOS and ICARS documents.
- The characteristic features are rhinorrhea and nasal obstruction, often in conjunction with a cough and systemic upset in acute forms.
- Most cases of acute rhinosinusitis result from viral upper respiratory tract infections and some have an additional bacterial component, with a variety of common organisms implicated (typically gram positive).
- The majority of cases are self-limiting, some require treatment with antibiotics and very few result in complications.
- The possibility of orbital, intracranial and systemic sepsis should always be considered in children with rhinosinusitis, particularly in cases with pronounced symptoms and systemic derangement. This should prompt immediate investigation and specialist management.
- Chronic rhinosinusitis is also common. Many cases are exacerbated by adenoidal hypertrophy, and other anatomical factors are less commonly involved. Underlying inherited conditions such as cystic fibrosis and primary ciliary dyskinesia should also be considered in resistant cases.

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CHAPTER 25

LACRIMAL DISORDERS IN CHILDREN

Caroline J. MacEwen and Paul S. White

SEARCH STRATEGY AND EVIDENCE BASE

PubMed MeSH searches were performed combining the terms lacrimal and disorders. Several thousand articles were identified, almost all too specific in context to guide this short overview chapter.

INTRODUCTION

The lacrimal system consists of a secretory portion and a drainage system. The secretory portion is made up of the lacrimal and accessory lacrimal glands which, together with the Meibomian glands and the goblet cells, secrete the components of the tear film. The accessory lacrimal glands produce basal tear secretion, and the lacrimal gland is largely responsible for reflex tearing in response to noxious or emotional stimuli. The drainage system consists of the lacrimal puncta, canaliculi, lacrimal sac and nasolacrimal duct (Figure 25.1). This active system pumps tears from the conjunctival sac into the inferior meatus of the nose. Clinical problems with the lacrimal system in children usually relate to the reduced drainage of tears. The underproduction of tears, causing dry eyes, is rare but more serious due to the potential for sight-threatening consequences.

ANATOMY

The lacrimal gland is an exocrine gland that sits in the anterior aspect of the supratemporal orbit. The ducts of the gland open onto the conjunctiva in the superior fornix. Embryologically the lacrimal gland develops from ectoderm that is supported by embryonic skull cap mesoderm. The lacrimal gland continues to grow up to the age of 4 years. Basal tearing is present in infants from birth, and reflex tearing begins at any time from birth to several months of age.[1] The lacrimal outflow system develops between the embryonic maxillary process and the lateral nasal process from a cord of surface ectoderm. By the end of the first trimester, this tissue begins to canalize and the nasolacrimal duct opens into the inferior meatus of the nose just before or after term birth. There may be a failure of this canalization process at any part of the system, but this is most frequent at the lower end.[2]

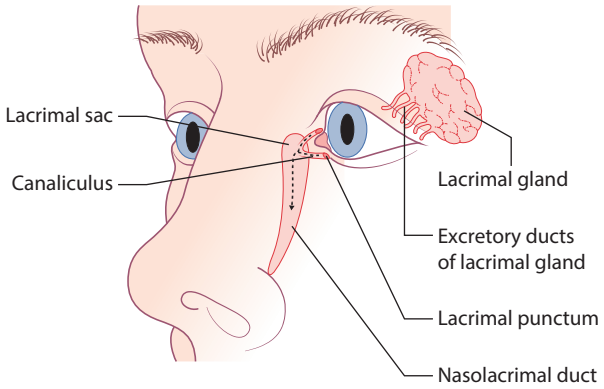

Figure 25.1 The lacrimal system, comprising the lacrimal gland, the lacrimal puncta, canaliculi, lacrimal sac and nasolacrimal duct.

Tears are actively pumped through the outflow system from the puncta and canaliculi and on into the lacrimal sac. This sits in the bony lacrimal fossa, separated from the middle meatus of the nose by the maxilla and lacrimal bone. The lacrimal sac extends superiorly under the medial canthal ligament as its fundus. The nasolacrimal duct exits from the lower end of the sac and passes in a downward, lateral and posterior direction. The duct is surrounded by bone in its upper part but becomes membranous inferiorly and opens into the medial wall of the inferior meatus of the nose through Hasner's valve. This can be located endoscopically in the inferior meatus approximately 1 cm posterior to the nasal spine.

DRY EYES IN CHILDREN

Children with dry eyes present with irritable, gritty eyes, which may be diffusely injected. On examination there is a reduced tear meniscus with punctate keratopathy, particularly affecting the interpalpebral zone. Staining occurs with fluorescein dye.

Congenital alacrima, or hyposecretion of tears, is rare. This may be due to absence of the lacrimal gland or to the lacrimal gland being ectopic. Alacrima may be associated with systemic conditions such as Allgrove syndrome (familial alacrima, achalasia of the cardia and glucocorticoid deficiency), anhydrotic ectodermal dysplasia and Riley–Day syndrome (familial dysautonomia),

Acquired tear insufficiency may be due to pathology of the lacrimal gland, causing failure of tear production, or to conjunctival damage, leading to ductule obliteration. The gland may be damaged by Epstein–Barr infection, as the result of HIV infection, or in patients following bone marrow transplantation (often associated with graft versus host disease). Sjögren's syndrome is rare in children; it can be a primary autoimmune event or secondary to rheumatoid arthritis or systemic lupus erythematosus (SLE). Children with Sjögren's syndrome often have lacrimal gland involvement, and they may have recurrent parotid gland swelling and salivary gland involvement. Sjögren's should be considered in any child with recurrent parotitis, keratoconjunctivitis sicca, and early tooth decay due to xerostomia.[3]

Isotretinoin treatment for acne can cause dry eyes in adolescence. This is usually reversible at cessation of the drug. Treatment of dry eyes involves copious use of artificial tears and temporary or permanent punctal occlusion in severe cases.

LACRIMAL TUMOURS AND GRANULOMAS

Lacrimal tumours are extremely rare in children. Orbital 'pseudotumour' (the preferred name is now idiopathic orbital inflammatory disease), causing painful swelling, is rare but may affect the lacrimal gland.[4] It is a non-infective inflammatory disease of unknown aetiology that occurs in the orbit and responds to steroids. Malignant epithelial tumours, including mixed-cell adenocystic and other carcinomas, have been recorded in childhood.[5] Lacrimal gland enlargement is also found in conditions such as sarcoidosis and leukaemia. Prolapse of the lacrimal gland, which is commonly bilateral, may present as a subconjunctival mass in the upper outer fornix. This may occur with craniofacial anomalies due to reduced orbital volume and increased orbital pressure.

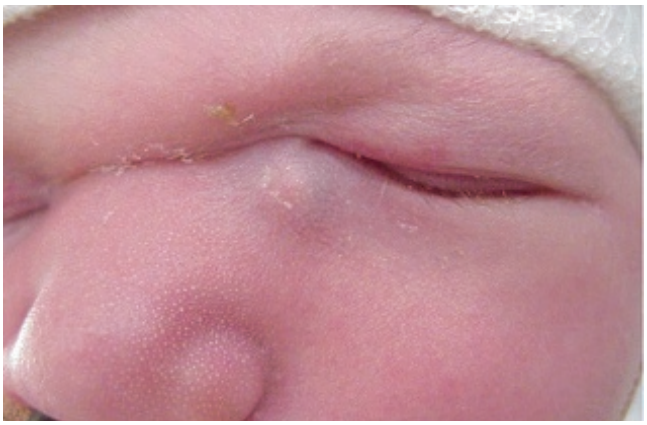

Figure 25.2 Congenital dacryocystocele. A bluish swelling is seen below the medial canthal tendon. It can present as nasal obstruction.

Dacrocystocoele is a congenital swelling located at the medial canthus due to trapped fluid inside the lacrimal sac and nasolacrimal duct.[6] This usually presents as a tense, blue, non-pulsatile swelling below the medial canthus that is evident at birth (**Figure 25.2**). Congenital dacryocystocoele must be differentiated from a meningoencephalocoele, a meningocoele, a midline nasal dermoid cyst or a capillary haemangioma. If there is any doubt, an MRI scan is helpful in identifying the dilated sac and nasolacrimal duct and in excluding other pathology. Routine imaging, however, is not necessary and the diagnosis is usually made clinically.

Treatment of a dacryocystocoele involves observation during the first 2 weeks of life, during which time most will improve spontaneously. If it has not settled by this stage or if acute dacryocystitis or respiratory difficulties develop, then surgical treatment is required. A skin scar can be avoided by drainage of the dacryocystocoele into the nose using an endoscopic approach.

CONGENITAL NASOLACRIMAL DUCT OBSTRUCTION

Congenital nasolacrimal duct obstruction (CNLDO) is clinically evident in up to 20% of infants, the vast majority of which become symptomatic with epiphora during the first month. The natural history is to spontaneously resolve with maturation (**Figure 25.3**).[7–9] Spontaneous resolution is rapid during the first year of life and continues, at a reduced rate, beyond this into childhood.[10, 11] CNLDO represents a delay in maturation of the lacrimal drainage system where it enters the nose, resulting in persistent membranous obstruction or stenosis (**Figure 25.4**)

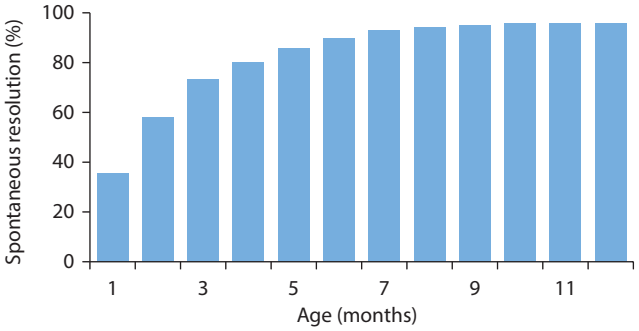

Figure 25.3 The rate of spontaneous resolution of nasolacrimal duct obstruction in 974 infants with congenital nasolacrimal duct obstruction as a function of age in months (adapted from MacEwen and Young[9]).

at the valve of Hasner. This should be differentiated from a dacryocystocoele.

Although usually an isolated abnormality, CNLDO may be more frequent in certain conditions, such as EEC syndrome (ectrodactyly, ectodermal dysplasia, clefting) branchio-oculo facial syndrome, craniometaphyseal or craniodiaphysial dysplasias, Down syndrome, lacrimo-auriculo-dento-digital (LADD) syndrome, and the CHARGE association.

On examination there is an increased tear meniscus and there may be stickiness or crusting on the lashes. A mucocoele may develop: the contents can be expressed into the conjunctival sac.

A fluorescein disappearance test (FDT) should be performed on children with epiphora as it provides objective evidence to support a diagnosis of lacrimal outflow obstruction.[12]

Treatment of congenital nasolacrimal duct obstruction

Congenital nasolacrimal duct obstruction has a very high rate of spontaneous resolution, so observation is recommended until the child is at least 1 year old. Under 1 year of age, probing is no better than observation and is generally not recommended. Between 12 and 24 months of age, the long-term results of probing and observation are the same but resolution is quicker with probing. Hence, most surgeons would recommend intervention some time after the first year of life.[10, 13–17]

Probing should be carried out in a stepwise fashion, identifying the patency or obstruction of each area between the puncta and the end of the nasolacrimal duct. The first stage of probing is a blind procedure and depends on awareness of resistance to the probe as it passes through the system. Thereafter the use of a 2.7 mm or 3.0 mm nasal endoscope will permit a direct view of the lower end of the nasolacrimal duct which assists in the diagnosis and management.[17, 18] The nose is first prepared with vasoconstrictor solution then a nasal endoscope is introduced into the inferior meatus after infracture of the inferior turbinate with a Freer elevator. This manoeuvre itself is often therapeutic as it opens up a narrow inferior meatus and may stretch a stenotic ostium.[19] Finally, fluorescein appearance is checked by syringing: stained fluid

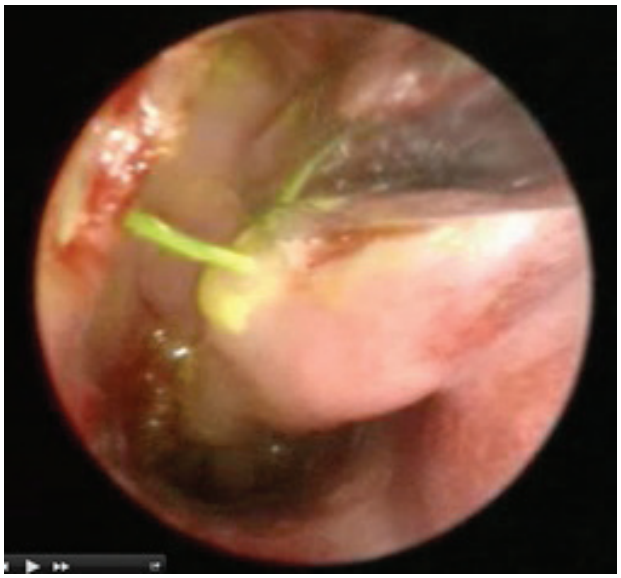

Figure 25.4 Stenotic flow of fluorescene flush through the valve of Hasner within the inferior meatus of the right nasal cavity.

should be gently syringed into the system from above and observed through the nasendoscope.

The system should then be probed via the upper canaliculus using the smallest probe available (usually a Bowman's size 0000), which can be observed via the nasendoscope entering the inferior meatus through the valve of Hasner (see **Figure 25.4**). In cases of atresia the membrane can be incised endoscopically in the inferior meatus using a phaco knife. Unsuccessful probings can occur when the probe creates a false passage by missing the valve of Hasner, and either carries on in a submucosal plane to the floor of the nose or enters the meatus through a false and usually ineffective passage. Distal bony atesia of the duct is rare but will usually be rectified by conversion of the procedure to an endoscopic dacryocystorhinostomy (DCR).

PHYSIOLOGICAL (FUNCTIONAL) EPIPHORA

Functional epiphora is persistent watering despite a clear, patent, free-flowing syringing, observed endoscopically in the inferior meatus, with no resistance felt on probing. All other causes of lacrimation or epiphora must be eliminated. The FDT demonstrates delay. The cause of functional epiphora is probably physiological pump failure but such children may have an upper respiratory cause, such as large adenoids, and a careful history should be taken regarding nasal symptoms.

COMPLEX ABNORMALITIES OF THE OUTFLOW SYSTEM

Complex abnormalities of the canaliculi or the proximal nasolacrimal duct become a commoner cause of persistent epiphora in older children, as the simpler abnormalities settle spontaneously. These abnormalities may be very complex, especially in children with abnormal facial skeletons.[20]

A major advantage of endoscopic probing over 'blind' probing is that the common causes of failure can be

identified and treated at the first probing, improving the success rate of the procedure.[18] If endoscopic probing was not performed on the first occasion, this approach is useful in reprobings as it will identify the most frequent causes of failure and permit appropriate treatment.[18] Another option is intubation of the system with silicone tubes;[21] but intubation carries the risk of damage to the canaliculi, may be unnecessary (e.g. in functional cases), and is no more effective than endoscopic probing in repeat cases.[22] Children with upper nasolacrimal obstruction can be treated by endoscopic dacryocystorhinostomy (DCR) which offers the advantage of direct visualization of the common canaliculus at entry into the lateral wall of the lacrimal sac where distal occlusion of the common canaliculus may be amenable to a stenotomy.

Possible complications of intubation include cheesewiring through the canaliculi, dislocation superiorly or inferiorly, infection, and scarring of any part of the drainage system.[23] The optimum time to leave tubes in place is not known, and anywhere between 1 and 6 months is recommended.[23] Tubes should be removed under general anaesthetic via the nose to prevent aspiration of the tube. This system is then syringed with fluorescein under endoscopic control to confirm patency. Balloon catheter dilatation of the lacrimal system is a possible alternative to intubation in patients with failed probing.[24]

DACRYOCYSTORHINOSTOMY

Children rarely require a dacryocystorhinostomy (DCR), but may do so for persistent epiphora despite probing, for complex congenital abnormalities of the lacrimal outflow apparatus such as bony atresia, those involving the upper nasolacrimal duct, or for acquired disease usually caused by infection or trauma.[25] External and endoscopic routes are possible, and excellent success rates, comparable to those of adult DCRs, have been reported for both.[26, 27]

The availability of microdrill techniques has led to increased popularity of the endoscopic techniques which enable wide sac exposure and flap creation without a facial skin scar.

CONGENITAL FISTULAE OF THE LACRIMAL OUTFLOW SYSTEM

Fistulae of the lacrimal system are rare anomalies in which tracts open onto the skin directly from the puncta, canaliculi, lacrimal sac or nasolacrimal duct. They may appear as double puncta, or appear in the region of the medial canthus. They usually pass unnoticed as they are non-functioning and should be left untreated unless they allow flow of tears onto the face or result in epiphora (which is rare).

PUNCTAL AND CANALICULAR ABNORMALITIES

Failure of the proximal end of the lacrimal drainage system to canalize may result in punctal stenosis or atresia. This is often asymptomatic, especially if only one punctum is abnormal. Narrow puncta should be dilated with a 'Nettleship' lacrimal dilator. Membranous obstruction should be pierced with a needle and dilated. These cases do very well but are often associated with distal abnormalities and a syringing should always be performed.

Overall, abnormalities proximal to the sac result in surprisingly few symptoms. Agenesis should be suspected if the papilla is not readily obvious.[28] If only one punctum is missing, syringing via the other one detects the extent of the damage. Surgery to construct these areas is specialized. Retrograde probing from an external DCR incision may be attempted through the sac; otherwise, a Lester Jones canalicular tube is required. This type of surgery may be left until the child is in their teens when referral to a specialist should be made.

ACQUIRED CONDITIONS OF THE LACRIMAL DRAINAGE APPARATUS

Acute dacryocystitis may occur as a complication in non-patent nasolacrimal systems or as a primary event in a patent system. This is particularly common in infants with a dacryocystocoele.[29] Treatment comprises prompt intervention with intravenous antibiotics as retrobulbar abscesses may occur. Cultures should be taken of any pus or discharge that can be expressed through the punctum. Probing should not be performed as damage to the congested epithelium may cause false passage formation and lead to orbital cellulitis and fistula formation.[30] Skin incisions should not be made during the acute phase as an external fistula may occur. If a mass remains after resolution or a pyocoele has developed, evacuation can be performed through the skin with a needle through the lower pole of the sac or by urgent endonasal DCR if the pus is found to be inspissated or loculated.

Acquired nasolacrimal duct obstruction may be caused by facial trauma, diseases of the nose or paranasal sinuses – especially chronic allergic rhinitis – or persistent upper respiratory tract infections. These are more common in older children and adolescents.[31] Rarely, acquired obstruction may herald a more sinister cause such as fibrous dysplasia, cranial metaphysial or cranial diaphysial dysplasia, or tumour formation. Treatment should be aimed at the underlying cause.

The commonest causes of watery eyes in children are listed in **Box 25.1**.

BOX 25.1 Causes of watery eyes in children

Excess tear production (lacrimation)	Drainage failure (epiphora)
Allergic rhinitis	Congenital nasolacrimal duct obstruction
Upper respiratory tract infection	Skeletal and sinus abnormalities
Epiblepharon	Lid malposition
Subtarsal foreign body	Punctal malposition
Iritis	Punctal occlusion
Corneal abrasion/ulceration	Anomalous drainage system
Conjunctivitis	
Glaucoma	

FUTURE RESEARCH

- Knowledge of the aetiology and best treatment choices for proximal CNLDO are less well developed.
- While surgery is almost invariably successful for treating distal block, the management of proximal obstruction remains challenging.
- The increased application of endoscope and microendoscope technology in the future may offer better diagnostic and therapeutic options for resistant cases of CNLDO.

KEY POINTS

- Congenital nasolacrimal duct obstruction (CNLDO) is common, being present in up to 20% of neonates.
- The majority of cases of CNLDO resolve spontaneously in infancy.
- Epiphora persisting in the second year of life may benefit from intervention.
- Endoscopic-guided probing is the investigation of choice.
- Underproduction of tears causing dry eyes is rare but more serious due to the potential threat to vision.

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CHAPTER 26

THE ADENOID AND ADENOIDECTOMY

Peter J. Robb

SEARCH STRATEGY

Data in this chapter may be updated by searches of The Cochrane Library, Medline, Google Scholar and PubMed using the keywords: adenoid, adenoidectomy and children. References from selected articles were reviewed after reading the abstract and included where relevant. The evidence in this chapter is mainly level 2/3/4, with some level 1 evidence.

INTRODUCTION

Santorini described the nasopharyngeal lymphoid aggregate or 'Luschka's tonsil' in 1724. Wilhelm Meyer coined the term 'adenoid' to apply to what he described as 'nasopharyngeal vegetations' in 1870. The adenoid forms part of Waldeyer's ring of lymphoid tissue at the portal of the upper respiratory tract. In early childhood this is the first site of immunological contact for inhaled antigens.

Historically, the adenoid has been associated with upper airway obstruction, as a focus of sepsis, and more recently with the persistence of otitis media with effusion.

DEVELOPMENT OF THE ADENOID

Lymphoid tissue can be identified at the 4- to 6-week gestational period, lying within the mucous membrane of the roof and posterior wall of the nasopharynx. The adenoid is clearly identifiable during the third month of gestation. Lymphoid tissue of the adenoid may extend to the fossa of Rosenmüller and to the Eustachian tube orifice as Gerlach's tonsil. The membrane is covered with stratified squamous epithelium. The adenoid receives a rich arterial supply from branches of the facial and maxillary arteries and the thyrocervical trunk. Venous drainage is to the internal jugular and facial veins. Lymphatic drainage is to the retropharyngeal lymph nodes and upper deep cervical nodes, particularly the posterior triangle of the neck. Nerve supply is from sensory branches of the glossopharyngeal and vagus nerves.[1]

The adenoid is visible using magnetic resonance imaging (MRI) from the age of 4 months in 18% of children.[2] At 5 months of age, the adenoid could be identified in all of 290 children studied. Growth continues rapidly during infancy and plateaus between 2 and 14 years of age. Regression of the adenoid occurs rapidly after 15 years of age in most children. The adenoid is at its relative largest in relation to the volume of the nasopharynx in the 7-year-old age group.[3] Clinical symptoms are more common in a younger age group, due to the relative small volume of the nasopharynx and the increased frequency of upper respiratory tract infections.

IMMUNE FUNCTION OF THE ADENOID

The function of the lymphoid tissue of Waldeyer's ring is to produce antibodies. The adenoid produces B-cells, giving rise to IgG and IgA plasma cells. Exposure to antigens via the mouth and nose is an important part of natural acquired immunity in early childhood. The adenoid appears to have an important role in the development of 'immunological memory' in younger children.[4] Removal of the adenoid in early childhood may be immunologically undesirable.[5] Evidence supports the concern that early adenoidectomy produces a detectable negative effect

on the development of serum IgG antibodies, resulting in impaired immunity to pneumococcus.[6]

In children aged 4–10 years, adenotonsillectomy does not appear to cause significant immune deficiency, although a slight decrease in IgG, IgA and IgM levels was found in the post-operative period 4–6 weeks after surgery.[7] The authors concluded that this represented a compensatory response of the developing immune system following a reduction of chronic antigen stimulation. Specific reduction in IgG may represent a reduction in antigenic stimulation. There appears to be no decrease in IgE after adenoidectomy.[8, 9]

The evidence that immune status is compromised by removal of the adenoid alone is inconclusive, as studies generally include children also having tonsillectomy.[10]

PATHOLOGICAL EFFECTS OF THE ADENOID

The adenoid may be implicated in upper respiratory tract disease due to partial or complete obstruction of the nasal choanae or as a result of sepsis. Pathological manifestations include rhinitis, rhinosinusitis, otitis media and otitis media with effusion. Adenoiditis, acute or chronic, is considered by some to be a related but distinct infective entity.[11]

Otitis media with effusion

The benefit of adenoidectomy in the management of otitis media with effusion (OME) has traditionally been ascribed to the relief of anatomical obstruction of the Eustachian tube.[12] While this may be a contributory factor, it is clear that adenoid size and physical obstruction alone cannot account for the benefit following adenoidectomy when the adenoid is small.[13] Adenoid size in children with and without OME is not significantly different. It is likely that recurrent acute or chronic inflammation of the adenoid and increased bacterial load, particularly of *Haemophilus influenzae*,[14, 15] results in squamous cell metaplasia, reticular epithelium extension, fibrosis of the interfollicular interconnective tissue and reduced mucociliary clearance in children with OME compared to those without OME.[16] These changes increase bacterial adherence, contributing to the development of a 'biofilm' infection resulting ultimately in middle ear effusion. (A biofilm infection may be defined as 'a structured community of bacterial cells enclosed in a self-produced polymeric matrix and adherent to an inert or living surface'.[17, 18]) Evidence from the MRC TARGET (Trial of Alternative Regimens in Glue Ear Treatment) study supports consideration of 'adjuvant' adenoidectomy in children over the age of 3 who are undergoing insertion of ventilation tubes (grommets)[19] (see Chapter 13, Otitis media with effusion).

RECURRENT ACUTE OTITIS MEDIA

A Cochrane intervention review concluded that adenoidectomy could not be recommended for the management of acute otitis media.[20] Randomized controlled trials of the management of recurrent acute otitis media have shown adenoidectomy was not effective in reducing episodes of infection in children younger than 2 years during the follow-up periods of 7–24 months after surgery.[21, 22] It is likely that a partial maturational selective IgA deficiency is a contributing factor in these 'otitis-prone' children.[23] Low-dose prophylactic antibiotic treatment is preferred to adenoidectomy in this group as a means of preventing recurrent acute otitis media and sequelae of infection until maturation of the immune system occurs naturally.[24]

Upper airway obstruction and sleep-disordered breathing

Sleep-disordered breathing in childhood is considered in detail in Chapter 27, Paediatric obstructive sleep apnoea. The prevalence of severe sleep disturbance in children due to upper airway obstruction is estimated to be approximately 1%, with a peak incidence between 3 and 6 years of age, and an equal sex incidence.[25, 26]

Airway obstruction due to adenoidal hypertrophy may produce depressed arterial PaO_2 and elevated $PaCO_2$ levels, which return to normal after adenoidectomy.[27] The respiratory improvement following adenotonsillectomy also results in a significant increase in serum insulin-like growth factor-1 (IGF-1),[28] accounting in part for the frequently observed growth spurt following surgery. Accumulating evidence suggest that habitual snoring, falling short of obstructive sleep apnoea may result in neurobehavioural morbidity, poor academic performance and hyperactive behaviour.[29, 30]

There is widespread recognition of sleep apnoea in childhood[31] and the acceptance of the benefits of adenotonsillar surgery in these children, with documented improvement in respiratory function following adenotonsillectomy.[32] In a prospective study of 40 children undergoing adenoidectomy, with or without tonsillectomy, for upper airway obstruction, the radiographic estimate of the adenoid size correlated highly with the improvement in polysomnographic scores following surgery. No significant correlation between tonsil size and grade of obstructive sleep apnoea was demonstrated.[33] Nevertheless, a Cochrane review of adenotonsillectomy for obstructive sleep apnoea found no randomized trials addressing the criteria required to nor the efficacy of surgery in managing obstructive sleep apnoea syndrome (OSAS) in children.[34]

Rhinosinusitis

In childhood, the adenoid is implicated in rhinosinusitis, acting as a reservoir for pathogenic bacteria.[35] In a retrospective study of 48 children with chronic sinusitis undergoing adenoidectomy or adenotonsillectomy, improvement was reported in the majority following surgery, and only three children subsequently required functional endoscopic sinus surgery.[36] A prospective study of children with recurrent rhinosinusitis showed that adenoidectomy was effective in abolishing infective episodes of infection, and that few children went on to require functional

endoscopic sinus surgery[37] (see Chapter 24, Rhinosinusitis and its complications).

Olfaction

Adenoidal hyperplasia may reduce olfactory sensitivity and, in particular, retronasal smell and taste, which improves following adenoidectomy.[38] It is, however, unlikely that physical obstruction of the airway alone impairs olfaction, and changes in the olfactory epithelium are a likely factor.[39] Where partial or total anosmia is reported, with no evidence of adenoidal hyperplasia, or failing to resolve after adenoidectomy, further detailed investigation is required to exclude congenital or hereditary causes for child's poor or absent sense of smell.[40]

Neoplasia

Unsuspected neoplasia of the adenoid (and tonsils) in childhood is rare. Non-Hodgkin lymphoma was reported in a series of six children.[41] Atypical lymphadenopathy, with persistent and asymmetric enlargement of the tonsils and adenoid, in the absence of infection are suspicious and should prompt early imaging and biopsy. Presentation is often assumed to be due to the more common infective and obstructive manifestations of adenotonsillar disease so diagnosis is frequently delayed. Consider lymphoma of the adenoid as part of a post-transplantation lymphoproliferative disorder when symptoms of nasal obstruction develop.[42]

ASSESSMENT AND MANAGEMENT

Clinical history

The history should form part of a full paediatric ENT history with special attention to symptoms of middle ear disease and nasal obstruction. Specific questions regarding sleep disturbance, eating and atopic symptoms are important. A family history of atopy may be relevant. A full history of medication, prescribed, over-the-counter and alternative or complementary, is important. In children in whom adenoidectomy is being considered, it is essential to positively exclude a history or family tendency of unusual bleeding or bruising, as a routine clotting screen may not confirm mild von Willebrand disease. In children with Down syndrome, consider potential atlantoaxial instability and cardiac abnormalities.

Clinical examination

Assessment of the external nose should be made prior to anterior rhinoscopy. In particular, look for a skin crease in the supratip region that may indicate frequent nose rubbing from symptoms of rhinitis. Simple anterior rhinoscopy in young children may be carried out using a halogen light otoscope with a large speculum. This is generally better tolerated than examination with a Thudichum speculum.

Assessment of the nasal airway may be made with a cold Lack tongue depressor or large laryngeal mirror. Posterior mirror rhinoscopy is not usually possible in children, but many will tolerate nasendoscopy,[43] using a flexible paediatric endoscope and topical intranasal local anaesthetic/vasoconstrictor spray, such as Co-phenylcaine. When examining children, topical cocaine must not be used.

In children, where adenoidectomy is the sole surgical procedure indicated, an assessment of the adenoid should be made prior to the decision to operate. Nasendoscopy is a highly accurate method to assess adenoidal status in an outpatient setting (**Figure 26.1**).

When endoscopy is not tolerated, assessment of adenoid size with lateral soft-tissue radiograph of the nasopharynx is helpful and correlates well with endoscopic assessment of adenoid size.[44, 45]

In children undergoing another surgical procedure, the adenoid size can be assessed per-operatively.[46] The adenoid can be classified, based on size and obstruction (**Table 26.1**).[47] Nasendoscopy of the nasopharynx to assess adenoid size at the time of surgery is probably the gold standard, while mirror examination underestimates choanal occlusion, and palpation is a poor measure of adenoid hypertrophy.[48]

Where the indication for adenoidectomy is OME rather than obstruction, the size of the adenoid is not relevant as

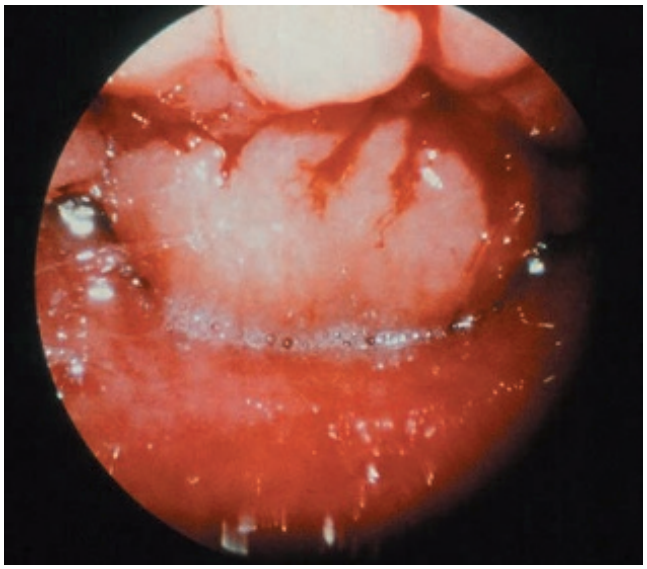

Figure 26.1 Endoscopic view of the adenoids.

TABLE 26.1 Clinical grading of adenoid size (reprinted from Clemens et al.,[47] with permission from Elsevier)

Grade	Description
Grade I	Adenoid tissue filling one-third of the vertical portion of the choanae
Grade II	Adenoid tissue filling from one-third to two-thirds of the choanae
Grade III	From two-thirds to nearly complete obstruction of the choanae
Grade IV	Complete choanal obstruction

an indication for removal (see Chapter 13, Otitis media with effusion).

While acoustic rhinomanometry is a useful research tool[49] and MRI provides extremely accurate volumetric estimation of the adenoid, these investigations are not applicable in clinical practice.

Pre-operative investigations

Routine pre-operative investigations are not indicated prior to adenoidectomy for children who are ASA grade 1 or 2.[50] Specific investigations for sickle-cell disease, thalassaemia, Down syndrome and congenital heart disease are indicated as appropriate. Management of type 2 diabetes mellitus should follow local paediatric guidelines for children with diabetes undergoing elective surgery.

MEDICAL TREATMENT FOR THE ADENOID

Traditionally, surgery and watchful waiting were the only options for symptomatic adenoid disease. There is now a reasonable amount of evidence that topical nasal steroid sprays can cause reduction in adenoid size with improvements in the presence of middle ear fluid, audiometric thresholds, nasal obstruction, rhinorrhoea, cough, snoring and sleep apnoea. This evidence comes from meta-analysis of a number of randomized controlled trials, although the trials themselves were judged to be of poor quality and further, better-quality studies are required.[51] Topical nasal steroids will probably find a role in clinical practice, although at present that role is unclear.

ADENOIDECTOMY

Adenoidectomy with or without tonsillectomy and/or insertion of ventilation tubes is one of the most frequently performed surgical procedures in children.

In the UK, blind curettage adenoidectomy continues to be the most used technique. Of these 79.2% use digital palpation and blind curettage, while only 8.1% use suction coagulation under direct vision.[52] It is surprising that curettage remains so popular, give the disadvantages of a blind procedure with unpredictable bleeding, poor access to choanal adenoid and risk of trauma to the Eustachian cushions. In contrast, suction diathermy affords direct vision with minimal blood loss[47] (mean 4 mL vs 50 mL), haemostasis and negligible risk of post-operative haemorrhage.[53] Suction diathermy is also effective in performing partial adenoidectomy, leaving a ridge of adenoidal tissue at the inferior part of the nasopharynx, reducing the risk of velopharyngeal insufficiency in those children where this is likely after removal of the adenoid.[54] Other direct vision techniques include Coblation® and microdebrider, which have the disadvantage of a high unit cost. KTP laser is associated with a high risk of nasopharyngeal stenosis.[55] This serious complication has not been reported in a small series using gold laser for adenoidectomy.[56] All single-use instrument techniques have the advantage of abolishing the potential risk of infection transmission.[57]

Of the direct-vision techniques, those with the largest clinical experience are the suction coagulator and the microdebrider. In a randomized controlled trial, the microdebrider was 20% faster than the curettage technique,[58, 59] but the suction coagulator is significantly cheaper than the microdebrider.[60] Coblation® is also suitable for adenoidectomy, with less blood loss and more complete adenoid removal,[61, 62] but cost limits it application to adenoidectomy as a sole procedure, while it is not a cost issue when tonsillectomy is performed using the same Coblation® wand.

A meta-analysis of suction coagulation adenoidectomy concluded that there was reduced intra-operative bleeding, reduced operative time, and a lower overall complication rate when compared to curette adenoidectomy.[63]

Where social and geographical factors allow,[64] and with appropriate surgical and anaesthetic techniques, pre-emptive fluid replacement, antiemetics and analgesia, the majority of children may be safely discharged home on the same day of surgery.[65, 66] Safe discharge home following adenoidectomy using the laryngeal mask airway within 20 minutes of surgery may be feasible but not preferable.[67]

COMPLICATIONS OF ADENOIDECTOMY

Bleeding

The reactionary haemorrhage rate, i.e. bleeding following adenoidectomy, within 6–20 hours of operation is reported as less than 0.7%.[68, 69] If bleeding is significant, early return to theatre and postnasal packing for haemostasis is the usual management. This study suggests that postnasal packing left *in situ* for 4 hours post-haemorrhage is as effective as packs left for 24 hours.[68] A small number of consultants in this questionnaire study (3/285) electively admitted children to an intensive care facility following postnasal packing and 4/285 routinely prescribed antibiotics. Increase in the use of direct-vision techniques and controlled haemostasis at the time of operation will make reactionary haemorrhage and the need for postnasal packing much less likely.

Secondary haemorrhage after adenoidectomy is rare. It may be due to bleeding from an aberrant ascending pharyngeal artery.[70] Unusual reactionary or secondary bleeding should raise the possibility of a clotting or coagulation defect. This requires specialist haematological investigation to confirm or exclude.

Dental trauma

Damage to the teeth during adenoidectomy may be accidental due to slippage of the gag or supports. Great care is needed, particularly if the secondary incisors have erupted: the teeth are large, but the mandible immature, and it is safer to use an adult gag, which will rest lateral to the incisors. It is customary to warn parents about damage

to teeth, but damage to the teeth will usually be considered indefensible. Where there are loose deciduous teeth, consent should be taken pre-operatively to remove these under anaesthetic to avoid the possibility of inhalation by the child during the operation or while recovering from anaesthesia.

Retained swab

If swabs are used, it is mandatory to confirm that the count is correct at the end of the operation before the gag is removed and the anaesthesia reversed. A swab may be retained either in the nasopharynx or in the laryngopharynx, hidden from the operator's view. While the early post-operative risk is of airway obstruction by a retained swab, late presentation months later with infection has also been reported.[71] Using direct-vision suction coagulation or Coblation® generally abolishes the need for swabs as haemostasis can be achieved during the procedure.

Nasopharyngeal blood clot

Blood may pool and clot in the nasopharynx during the procedure. The nasopharynx should be gently suctioned to clear any clot before removing the gag. Failure to do so may lead to the clot falling onto the larynx during recovery and causing potentially fatal acute airway obstruction ('coroner's clot'). Using a disposable rose-tipped sucker in the pharynx rather than a catheter via the nose reduces the risk of starting bleeding from the adenoid bed.

Infection

Infection in the nasopharynx following adenoidectomy is clinically uncommon, although many parents report foetor from their child in the week following surgery. Foetor is more common following suction adenoidectomy, and it is customary to prescribe a short course of antibiotics (e.g. azithromycin 10 mg/kg for 3 days post-operatively) to avoid this.[65] Rarely, retropharyngeal and mediastinal abscesses may occur as a result of trauma and secondary infection of the adenoid bed.[72] Post-operative chest infection in contemporary practice is uncommon.

Cervical spine

Non-traumatic atlantoaxial subluxation (Grisel syndrome) is rare, but it is recognized as a risk associated with adenoidectomy and tonsillectomy.[73] Early recognition is crucial in management, and post-operative torticollis should raise suspicion, leading to radiological investigation.[74] Overuse of diathermy must be avoided, either for removal of the adenoid or following curettage when used for haemostasis.[65] Minimum power settings for diathermy should always be used.[75]

Children with Down syndrome are at increased risk of atlantoaxial subluxation. Current evidence does not support routine pre-operative plain radiographs in asymptomatic children with Down syndrome. In any event, these are of limited value below the age of 3 years, at which age vertebral mineralization and epiphyseal development permit accurate radiographic visualization.[76] Special care of the child's neck during anaesthesia, surgery and recovery is essential.

Velopharyngeal dysfunction

Severe velopharyngeal incompetence is rare following adenoidectomy, estimated to occur in between 1:1500 and 1:10000 procedures. It may lead to significant problems with hypernasal speech and swallowing, severe enough to cause nasal regurgitation of fluids. It is mandatory to assess the palate and uvula for submucous cleft of the palate prior to surgery as adenoidectomy may unmask pre-existing palatal dysfunction.[77] Bifid uvula can be a marker of a submucous cleft, present in 59% of cases.[78] Using a direct-vision technique, it is possible to perform a partial adenoidectomy, clearing the choanal airway and superior nasopharynx, but leaving a rim of adenoid intact at the velopharyngeal junction, avoiding velopharyngeal insufficiency.[54]

Long-term velopharyngeal insufficiency is rare. Reconstructive surgery to correct hypernasal speech may be required if speech and swallowing are severely affected.[79]

Regrowth of the adenoid

A cross-sectional follow-up study of children after curettage adenoidectomy, 2–5 years after surgery concluded that 71% had no residual obstructing adenoid. However, the criterion for adenoid sufficient to cause nasal obstruction was tissue occupying more than 40% of the nasopharynx.[80] In a retrospective study of 3231 children, 1.6% required reoperation for recurrence of their symptoms following curettage adenoidectomy.[81] Direct-vision techniques are likely to minimize residual adenoid tissue and possible 'regrowth'.[63]

Death

Data separating the risk of death following adenoidectomy independent of tonsillectomy or general anaesthesia is limited. Expert reports from malpractice cases are the usual source of such data. Of 32 deaths related to bleeding following adenoidectomy and tonsillectomy, one followed direct vascular injury during adenoidectomy. In a review of malpractice cases from the United States, following tonsillectomy and adenoidectomy, during the period 1985–2006, 154 claims were identified.[82] Two deaths clearly followed infection secondary to aspiration of adenoid tissue. While not defined as adenoidectomy alone, four deaths were due to medication errors, route, dose or drug.[71] Following surgery in younger children with sleep-disordered breathing, special care should be exercised when prescribing opioid analgesics for both per-operative and discharge analgesia.[83] In those who are ultra-rapid metabolizers of codeine, toxic doses of morphine can develop, leading to fatal respiratory failure.

BEST CLINICAL PRACTICE

- ✓ It is no longer appropriate to combine adenoidectomy with tonsillectomy, unless there is a specific indication for adenoidectomy.
- ✓ Adjuvant adenoidectomy is effective as part of the surgical management of children over the age of 3 years with otitis media with effusion.
- ✓ Routine pre-operative investigations are not indicated prior to adenoidectomy for children who are ASA grade 1 or 2.
- ✓ Adenoidectomy under direct vision with single-use instrumentation – except the KTP laser – is more effective and safer than curettage.

FUTURE RESEARCH

For each of the following topics there is no evidence at level 1 currently available, and further studies are recommended.

- ➤ The role of topical nasal steroids in management of adenoid disease.
- ➤ Efficacy and morbidity of different techniques of adenoidectomy.
- ➤ Efficacy of adenoidectomy in the management of obstructive sleep apnoea in children.
- ➤ Efficacy of adenoidectomy in the management of chronic and recurrent acute sinusitis in children.
- ➤ The effects of adenoidectomy on the development of childhood immunity.
- ➤ The relationship between adenoidal hypertrophy and childhood rhinitis.
- ➤ The role of the adenoid in facilitating a biofilm infection in the upper respiratory tract.

KEY POINTS

- Adenoidal hyperplasia in childhood is common and self-limiting; mild symptoms of obstruction are not an indication for surgery.
- Significant obstructive symptoms, resulting in sleep-disordered breathing, short of obstructive sleep apnoea, may have signficant effects on daytime behaviour and cognitive function reversed by adenoidectomy.
- Adenoidectomy is effective as part of the surgical management of children with upper airway obstruction.
- Adenoidectomy may not be effective in the management of recurrent acute otitis media.

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CHAPTER 27

PAEDIATRIC OBSTRUCTIVE SLEEP APNOEA

Steven Powell

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the following keywords: sleep apnoea, tonsils, adenoids, sleep-disordered breathing, all child (0 to 18 years) in articles published in English. Abstracts were hand-searched and relevant articles were obtained and summarized.

HISTORY

Obstructive sleep apnoea in children existed for a long time without being widely recognized as a clinical syndrome. There were some exceptions to this. In 1889 Hill published an article in the *British Medical Journal* 'On some causes of backwardness and stupidity in children'.[1] There are a number of startling revelations in this work. Hill identified the neurobehavioural consequences of OSA:

> *'…children, the victims of nasal and pharyngeal obstructions, often suffer from headaches especially when engaged in study, and frequently evince marked inability to fix their attention on their lessons or work for any length of time…'.*[1]

Perhaps even more remarkably, he described the outcomes of treatment, recognizing that adenotonsillar surgery at the same time as treatment for glue ear resulted in neurobehavioural improvements over and above those expected for hearing improvement alone:

> *'I have been much struck by the fact that operations on children, undertaken for the relief of deafness associated with adenoidal growths, enlarged tonsils, and hypertrophic catarrhal conditions of the nose, have resulted in an immediate improvement in the mental acuteness of the patients as was altogether incommensurate with the often slight improvement in the sense of hearing.'*[1]

Many children who were being treated with adenotonsillectomies for various reasons from blocked noses to infections probably had unrecognized sleep apnoea. There had been some recognition of the cardiac complications of upper airway obstruction, but the first case series recognizing the syndrome of obstructive sleep apnoea was not published until 1976.[2] Guilleminault and colleagues described eight children with the night-time symptoms and the daytime consequences of obstructive sleep apnoea. It was the interest in this condition among the adult population that led to the recognition of the daytime symptoms in children. Six of the eight children underwent adenonsillectomy. Four of them had resolution of their symptoms, but two went on to have a tracheostomy.

Since then there has been growing interest in the condition and it has become the leading indication for adenotonsillectomy in young children.[3] The literature about the condition has expanded exponentially with over 2000 articles listed by Medline with relevance to paediatric sleep-disordered breathing in the last 3 years alone.

EPIDEMIOLOGY

Habitual snoring in children is quite common in the UK population, occurring in 12% of children.[4] Two large cross-sectional studies from the UK and Italy found the prevalence of obstructive sleep apnoea (OSA) to be 0.7–1.8%.[4, 5] In a German study looking at a community sample of children who went on to have polysomnography (PSG), the prevalence of primary snoring was found to be 6.1%.[6]

A large population-based cohort study with a wider remit had some questions geared towards mouth breathing, snoring and apnoeas. The Avon Longitudinal Study of Parents and Children (ALSPAC) studied 14 029 children. Nocturnal apnoeas always had a prevalence of 1–2% and were fairly steady throughout the first 6 years of the child's life. The prevalence of snoring always increased from 3–4% at the age of 1 year to a peak of 7–8% between the ages of 3 and 4. In terms of habitual snoring (which reflected snoring not being present all the time, but most), the prevalence rose from 10% at 1 year to 15% at 6 years. Habitual mouth breathing was present in up to 25% of children. Adenoidectomy reduced the risk of having sleep-disordered breathing by parental report in this study.[7]

NORMAL SLEEP

Paediatric sleep physiology is not completely understood, but what is clear is that a grasp of the basic elements is important to having a full understanding of the pathophysiology of sleep-disordered breathing.[8] Sleep is an essential human function and is part of the body's 'housekeeping' role, and good sleep is critical to normal daytime functioning. Sleep can be divided into phases of a cycle. There are phases of REM (rapid eye movement) sleep and nREM (non-rapid eye movement sleep). nREM sleep is divided into phases N1, N2 and N3. N3 is commonly described as 'slow wave' sleep. There is an orderly progression between the phases from N1 to N3 then REM sleep. The cycle in older children takes around 90 minutes. The proportion of time in slow wave sleep is higher at the beginning of the night and the proportion in REM sleep is higher at the end of the night. The proportion of time spent in REM sleep decreases from 50% as a newborn to 20% beyond the age of 4 years.[9] Premature babies and those up to 6 months of age can have central apnoeas, with cessation of breathing due to no respiratory effort, but it is rare for these to persist with any clinical significance beyond 6 months.[8]

Muscle relaxation occurs particularly during REM sleep, possibly as a protective mechanism to prevent sleep movements. The pharyngeal part of a child's upper airway is a tube with a soft collapsible wall held open only by active pharyngeal muscle tone. There can be relaxation of the pharyngeal constrictor muscles (hypotonia) and a narrowing of the airway at the pharyngeal level. A wide range of neural activity occurs during the sleep cycle which is critical to the consolidation and enhancement of memories within existing neural networks.[9]

DEFINITIONS

Obstructive sleep apnoea can be defined as 'a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction that disrupts ventilation during sleep and normal sleep patterns'.[10] **Primary snoring** is defined as noisy breathing (snoring) without obstructive apnoea, frequent arousals from sleep, or gas exchange abnormalities.[10] **Sleep-disordered breathing** is a term which can be used to describe both snoring and OSA.

PATHOPHYSIOLOGY

Pathophysiology of airway obstruction

It becomes clear from the key points in physiology that there are phases within sleep when children will be particularly at risk of airway compromise. REM sleep, with its hypotonia of the pharyngeal muscles, can lead to airway narrowing particularly at this point.

There are well-defined groups in which sleep-disordered breathing may occur. There may be overlap between the groups, but they can be considered individually.

Children with no underlying medical diagnosis who have adenotonsillar hypertrophy form the largest group overall.[11] Here the physical obstruction of the nasal airway by the adenoids and the oropharyngeal airway by the tonsils results in increased airway resistance. The peak incidence of OSA in this group is between the ages of 3 and 6 years when the adenoids and tonsils undergo hypertrophy.[11] The situation is more complex than simple obstruction by adenoid and tonsil hypertrophy as not all children with large lymphoid tissue have OSA reflecting variation between individuals in pharyngeal muscle tone.[11]

The second group reflects the increasing prevalence of obesity in the paediatric population.[12] This may be in a slightly older age group. It may occur in combination with adenotonsillar hypertrophy. The obstructive element is primarily caused by oropharyngeal crowding due to excess adipose tissue, but the full extent of the pathophysiology surrounding obesity is considerably more complex.[12]

In a third group of children the cause of OSA is multifactorial. Children with congenital abnormalities such as achondroplasia or craniofacial abnormalities have narrow pharyngeal airways which will predispose them to obstruction. In Down syndrome there is a combination of abnormally narrow upper airway and reduced pharyngeal muscle tone. **Up to two-thirds of children with Down syndrome have some form of sleep-disordered breathing and regular screening for OSA is advised.**[13]

Neurobehavioural consequences

Neurobehavioural clinical outcomes result from the disturbance to sleep from a number of mechanisms.[8] In the worst cases where there are desaturations, hypoxia may

play a role, but sleep fragmentation from repeated arousals can interfere with the neural pathways which would otherwise occur. Even in children who have no OSA and primary snoring alone, there has been a link to the slow wave activity changes of the EEG, which may reflect impaired restorative sleep function.[14] OSA has a profound impact on sleep and arousal patterns during the preschool years, when children are in a critical period for neurodevelopment.[15]

Inflammatory basis

There is an underlying inflammatory basis to OSA and there appear to be several biomarkers which measure this activity.

Children often have elevated levels of highly sensitive C-reactive protein (CRP). This is produced by interleukin activity in the liver. Some children seem to have a predisposition to this and in one study abnormal DNA methylation was found in patients with OSA and high CRP, and the abnormal methylation was strongly linked to the apnoea–hypopnoea index (discussed in 'Investigations' below).[16] This epigenetic discovery may lead to the basis of future prognostic or therapeutic advances.

High levels of CRP may enhance inflammation, oxidative stress and procoagulant activity which may promote atherogenesis.[17] Inflammatory markers do not change when measured the night before and the morning after in children with OSA.[18]

In a group of obese patients with OSA, there was no significant decrease in CRP from baseline to 6 months post adenotonsillectomy. This may have been because of a direct link from the obesity to the inflammatory markers, but also a high proportion of children had residual OSA.[19]

Endothelin 1 has been found to be elevated in some patients with OSA and to decrease post-operatively following adenotonsillectomy. This is a potent vasoconstrictor and may be associated with cardiovascular risk.[20] Tumour necrosis factor (TNF) levels are higher in children with OSA, compared with controls.[21] Myeloid-related protein 8/14, which has an important role in the formation of atherosclerosis, has been found to have higher levels in children with OSA and the levels are in proportion to the severity of the OSA.[22]

Cardiovascular pathophysiology

There is evidence that baroreceptor sensitivity may be impaired in adolescents with sleep-disordered breathing so they do not mount appropriate blood pressure changes to variation in heart rate. In adults this is a risk factor for cardiovascular disease.[23] Blood pressure can be consistently raised in children with sleep-disordered breathing when compared to controls when monitored continuously overnight.[24]

Children with OSA have been shown to have an increased level of urinary catecholamines.[25] The full implication of this is unclear, but it does suggest some cardiovascular effects from OSA. In a large cohort asthma study, children with snoring (based on survey) did not have any abnormal cardiovascular parameters at the age of 8.[26]

Endothelial dysfunction and impaired cognitive abilities appear both to be worsened by worsening OSA, when measured by tests of hyperaemia and neurocognitive tests.[27]

CLINICAL FEATURES/ PRACTICE POINTS

Day- and night-time clinical features

A full sleep history should be taken from children presenting with any adenotonsillar problem and enquired about in patients referred with ear pathology too. The history has two key areas: night-time symptoms and daytime symptoms (**Box 27.1**).

BOX 27.1 Symptoms of OSA

Night-time symptoms	Daytime symptoms
Do they snore? Do they get a good night's sleep or are they restless? Do they wake through the night? Do they struggle with their breathing or stop breathing? This should be explored fully with a clear explanation of respiratory effort with obstruction and respiratory effort with snoring to try to clarify the history. Do they sleep in an unusual position (e.g. extended head)? Do they sweat excessively? Do they wet the bed?	Do they have any behaviour or concentration problems? Do they mouth breathe? Do they struggle with eating? Are they growing normally?

A full ear, nose and throat examination should be undertaken:

- Make a general examination, looking for any craniofacial abnormalities.
- Listen carefully for stertor while awake, or asleep.
- Watch for mouth breathing.
- Carry out an oral examination, to determine the size of the tonsils (**Figure 27.1**). These can be graded by:
  - the Brodsky score[28]
    - 0 - tonsils in fossa
    - 1 - tonsils occupying up to 25% of the airway
    - 2 - 26% to 50%
    - 3 - 51% to 75%
    - 4 - more than 75%
  - the Friedman score[29]
    - 0 - no tonsils
    - 1 - tonsil within pillars
    - 2 - tonsil beyond pillars
    - 3 - tonsil extending ¾ to midline
    - 4 - tonsils touching in midline.

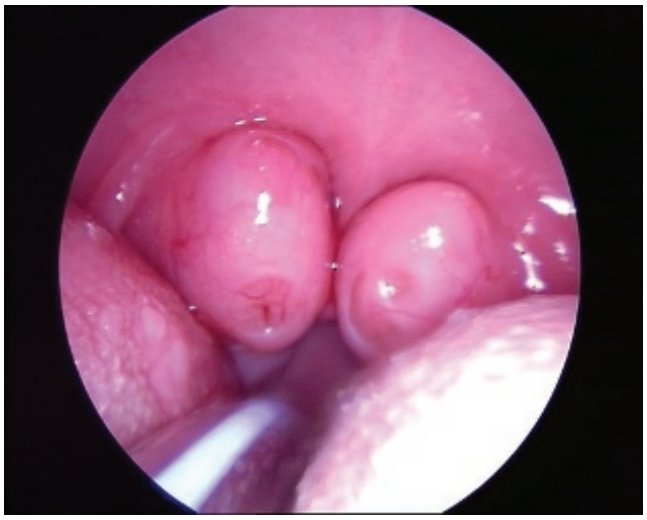

Figure 27.1 Enlarged tonsils in a child about to undergo an adenotonsillectomy for OSA.

- Examine the nose to establish whether there is coexisting rhinitis and whether there is likely to be adenoid hypertrophy.
- Examine the ears for coexisting otitis media with effusion.
- Look for neck lymphadenopathy.

Parents now regularly have access to mobile recording devices and examination of videos on phones or devices can be very helpful in establishing the presence of snoring and obstruction.

A systematic review of the literature has concluded that history is unreliable at predicting OSA.[30] This review was slightly limited as nearly one half of the studies were retrospective, but the others included some well-designed cohort studies. A meta-analysis of the raw data showed history and examination to have poor positive predictive value for obstructive sleep apnoea.

A recent review of the literature and meta-analysis of clinical findings in 10 studies with a total of 1525 patients has looked at the sensitivity and specificity of some of the key clinical aspects of sleep-disordered breathing history.[31] Tonsil size and a history of snoring were the most sensitive clinical findings, but were poorly specific. Conversely, parent reports of apnoeas and daytime somnolence were highly specific but poorly sensitive. It is possible to understand that this is the case. Almost all children with significant OSA will have large tonsils and snore as a sign of their airway obstruction, but not all children with large tonsils will have OSA, and of those who snore, a proportion will be primary snorers. In terms of the apnoeas, if the parents report these, they have a high chance of being significant but, as in reference to sleep physiology, these apnoeas are more likely to occur during REM sleep,[8] which is more prevalent in the latter part of the night when the parents may be sleeping too and may not see these events.

A recent systematic review of tonsil size and the link to obstructive sleep apnoea has found conflicting evidence as to whether tonsil size is predictive.[32] The authors conclude that limitations in the standard sizing system for tonsils, which does not account for overall tonsil volume, may be one of the reasons for this.

OSA is worse during the winter and spring.[33] This may have implications for the time of year that the child is being assessed.

The overall result is that, even in expert hands, a clinical assessment may be inaccurate. Most being assessed will be snorers, so the inaccuracy will lie in differentiating between primary snoring and OSA.

Neurobehavioural symptoms

The neurobehavioural consequences of paediatric obstructive sleep apnoea are now well established in the literature, but new studies continue to clarify the potential deficits.

In a study of 136 children with OSA, ranging from primary snoring to varying degrees of OSA, behaviour and attention were affected in children with both primary snoring and OSA compared to controls, suggesting that primary snoring is not completely benign.[34] Cognitive abilities were also impaired across all groups with sleep-disordered breathing.[35] Memory tasks were impaired in children with all degrees of sleep-disordered breathing too. Interestingly, parents of children with only primary snoring tended to overemphasize their child's memory problems compared to the other groups, possibly as a reflection of behavioural problems.[36]

In a clinical comparison study of 44 snoring children versus 51 non-snoring children derived from a large population survey, polysomnography, neurobehavioural testing and quality of life scores were undertaken. The primary snorers who did not have OSA had significant impairment in language and naming function as well as behaviour.[37] A large cohort of over 1000 German children were studied and those who had primary snoring were found to have hyperactive and inattentive behaviours as well as specifically lower scores in mathematics, science and spelling.[6] All of these changes occur in the absence of hypoxia, and there has been a link to the slow wave activity of the EEG in these children, which may reflect impaired restorative sleep function.[14]

A short-term study of infants showed that those who habitually snored in the first few months of life had significantly decreased cognitive abilities compared to non-snorers at 6 months.[38] This gives rise to the possibility that there is an earlier range of snorers and obstructive patients who are at risk of these deficits. An Australian study demonstrated that both primary snoring children and those with OSA have worse behavioural findings in preschool years, but the cognition was the same as a group of controls. They postulate that this gives a window of opportunity in which treatment can be offered.[39]

A case control study examined the effect of poor sleep hygiene on a group of habitually snoring children versus non-snorers. The poor sleep hygiene did not seem to result in any problem behaviours in the non-snoring group, but in the snoring group there were strong correlations between poor sleep hygiene and behavioural problems.

These included impulsivity, hyperactivity and oppositional behaviours.[40]

Children with OSA have been shown to perform worse in pictorial-based memory tasks when compared to controls.[41]

A cohort of 249 children found that 2-3 years following the birth persistent snoring was associated with higher rates of problem behaviours.[42] Aggressive behaviour at school has been found to have an association with sleep-disordered breathing in a cross-sectional study.[43]

Cardiovascular presenting features

The inflammatory basis of paediatric obstructive sleep apnoea may cast light on the basis of cardiovascular dysfunction in paediatric OSA, which may be subtle and clinically unrecognized in many cases.

An Italian study of 49 children with PSG-proven OSA, compared to 21 matched controls found a higher CRP in the OSA group, and also increased left ventricular mass and early diastolic dysfunction. The dysfunction was worse and the inflammatory markers higher with increasing severity of OSA.[44] This confirms that early aspects of cardiac dysfunction may be higher than appreciated.

Cor pulmonale secondary to pulmonary hypertension is rare, but in a cohort of Taiwanese children, 5 out of 30 had cor pulmonale secondary to OSA. The OSA was more severe in this cohort than the children without cor pulmonale. All children showed improvement in their cardiac status following adenotonsillectomy.[45] This is an unusually high amount of cor pulmonale.

Enuresis

In a population-based study, over 6000 children had questionnaires completed and then polysomnography was undertaken on 597. Nocturnal enuresis was found to be associated with increasing severity of OSA in girls but not in boys.[46]

COMORBIDITY

As discussed above, there are a number of conditions in which OSA has a higher prevalence.

Obesity

Some studies have associated high body mass index (BMI) with OSA.[47] A large population cohort, examining the interaction of obesity, sleep-disordered breathing and cognition, found complex and interdependent relationships between these factors, with each of the factors seeming to have an adverse effect on the others.[48]

A group of 163 overweight children aged 10–16 years underwent polysomnography and neuropsychological testing. Children with worsening OSA were found to have worse concentration, behaviour and academic grades.[49]

Syndromes and associated neuromuscular conditions

Patients with Down syndrome have a high prevalence of OSA.[13] In a radiological study of Down syndrome patients using cervical-spine X-rays which were taken primarily to check on stability of the spine prior to surgery, the lingual tonsils were assessed. A significant increase in the size of the lingual tonsils in the Down syndrome patients compared with control groups was found.[50] Pharyngeal collapse can be found commonly at sleep nasendoscopy of Down syndrome patients.[51]

OSA seems to be particularly prevalent in patients with CHARGE syndrome.[52]

A strong association between craniofacial abnormalities and OSA has been confirmed by a large epidemiological study of over 1000 children.[53]

OSA was found on polysomnography in 95% of a cohort of patients with Treacher Collins syndrome, although the clinical examination was not predictive.[54] As with all cases, a clinical assessment in a subgroup of 13 patients with Treacher Collins syndrome was found not to be reliable for predicting OSA, and the authors suggest use of a polysomnogram in these patients due to the higher prevalence of OSA.[55] The prevalence in this group of children was 54% and the obstruction was multilevel.[56]

Patients with cleft palate may have a higher incidence of OSA, particularly when the palate is closed.[57] In one American study, the prevalence of polysomnographically proven OSA in the cleft palate clinic was 8.5%.[58]

There is a very high rate of polysomnography positive for OSA in patients with syndromic craniosynostosis (see Chapter 19, Craniofacial anomalies). Multiple interventions failed to completely resolve the OSA.[59]

The incidence of OSA in a cohort of 30 French children with achondroplasia was found to be 87%.[60]

Children with Prader-Willi syndrome are at particular risk for OSA and this may worsen with the institution of growth hormone. Adentonsillectomy may decrease but not completely resolve the obstructive sleep apnoea.[61]

The British Thoracic Society guideline identifies that there is a high incidence of sleep-disordered breathing in children with neuromuscular disease.[62]

Interaction of OSA with other conditions

In a group of 131 children with polysomnographically proven OSA, 37 had symptoms of reflux. After 24-hour pH monitoring, 21 were found to have acid reflux. These were treated with a 1–2-month course of proton pump inhibitors and the sleep study was repeated. The reflux group had mean reduction in apnoea–hypopnoea index from 13 to 8. Three children in the mild group had complete resolution of their OSA, while six children with severe OSA had no change in their apnoea–hypopnoea index.[63]

A case control study has demonstrated that children with sickle-cell disease have significantly more upper

aerodigestive tract lymphoid hyperplasia than controls (using MRI) and that the prevalence of OSA in this group of 36 sickle-cell patients (by polysomnography) was 19%.[64] A high incidence (8.3%) of OSA has been noted in patients in Thailand with beta thalassaemia.[65]

An observational study of 108 children with asthma in a children's respiratory clinic found that asthma was worse at 1 year in children who had symptoms of sleep-disordered breathing.[66] In a cohort of 92 poorly controlled asthmatics, 58 were found to have OSA on sleep study, and there were substantial improvements in the asthma following adenotonsillectomy.[67]

An assessment of a clinic population of 84 children with epilepsy found that 44% of severe epileptics and 31% of mild epileptics had symptoms of obstructive sleep apnoea.[68]

BOX 27.2 Indications for paediatric respiratory investigations[69]

- Diagnosis of OSA unclear or inconsistent
- Age <2 years
- Weight <15 kg
- Down syndrome
- Cerebral palsy
- Hypotonia or neuromuscular disorders
- Craniofacial anomalies
- Mucopolysaccharidosis
- Obesity (BMI >2.5 SDS (standard deviation scores) or >99th centile for age and gender)
- Significant comorbidity such as congenital heart disease, chronic lung disease
- Residual symptoms after adenotonsillectomy

INVESTIGATIONS

A UK working party consensus statement on the role of adenotonsillectomy in children with sleep-related breathing disorders said that performing adenotonsillectomy in a child with a history suggestive of OSA and enlarged tonsils, without further investigations, is reasonable and this could be undertaken in a non-specialist unit.[69] If the diagnosis of OSA is unclear or if the child is very young or at the extremes of the weight centiles, then further investigations are indicated. In patients with a suspected underlying syndrome or serious illness, investigations are essential before undertaking further management (Box 27.2).

Diagnostic investigations

OXIMETRY

Overnight pulse oximetry (Figure 27.2) can be useful if more detailed tests of sleep-disordered breathing are not available. It does not require an overnight hospital admission. This investigation provides two pieces of information: heart rate and oxygen saturation. It will detect apnoeas where the oxygen saturations drop, usually with an accompanying rise in heart rate. An oximetry scoring system has been defined by a group from Canada, which was associated with increasing severity of OSA in a prospective cohort study.[70] Oximetry has a high positive predictive value (97%) but, because not

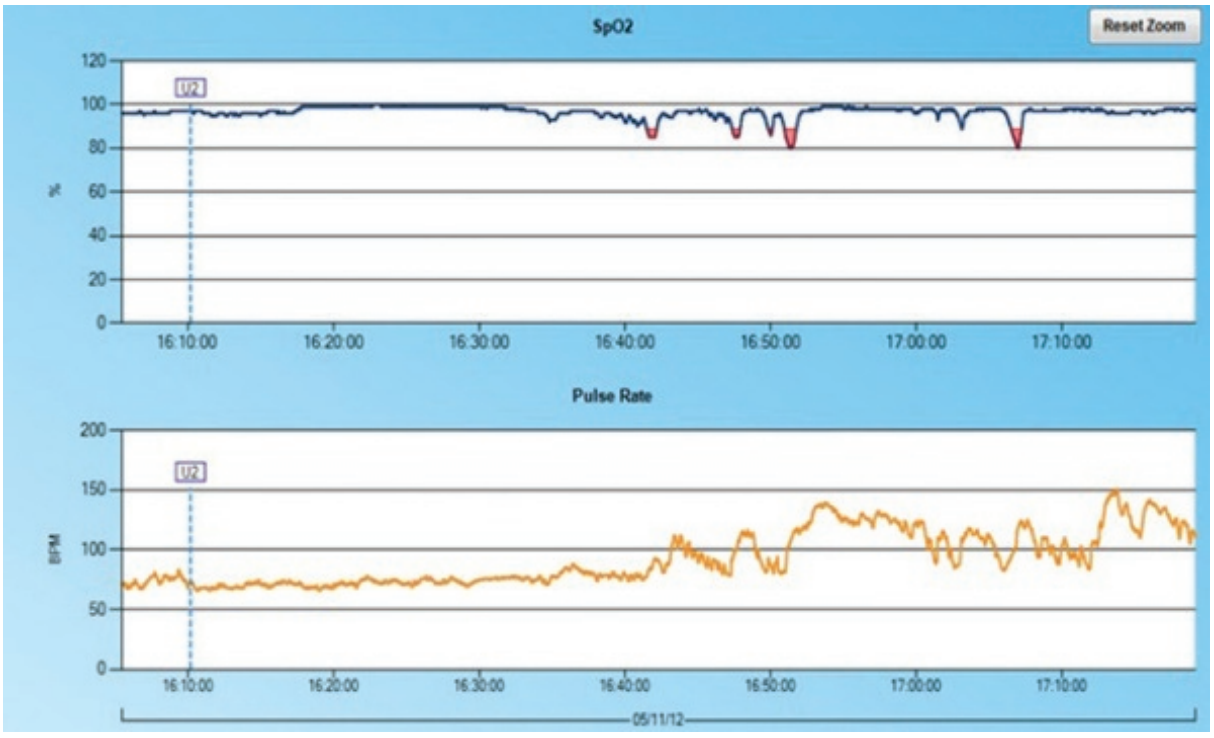

Figure 27.2 An oximetry trace showing periods of desaturation in red (SpO_2) with a rise in heart rate. With a positive history and examination, this has a high positive predictive value for OSA.

all apnoeas result in a drop in saturations, the negative predictive value is low (53%).[71]

POLYSOMNOGRAPHY

Polysomnography (PSG, a sleep study, **Figure 27.3**) is currently the gold standard of investigation. In this investigation, the child is monitored during sleep, usually in the hospital. This can be a variable quantity of measurements depending on local resources. The minimum features should be measurements of oxygen saturation, airflow, respiratory effort, electrocardiograph, video and sound.[13] This investigation can measure apnoeas (cessation in airflow) or hypopnoeas (reduction in airflow). These two are often combined as the apnoea–hypopnoea index (AHI) which is the total number of apnoeas and hypopnoeas per hour of sleep.

A study looking at visual scoring of arousals versus the interpretation of EEG found that the visual scoring of arousals was more appropriate than relying on the EEG alone.[72] A large case control study looked at the differences in sleep architecture on polysomnography for children of preschool versus school age and found some significant differences. Children of pre-school age were more likely to have central apnoeas, but less likely to awaken than older children with comparable levels of sleep-disordered breathing. This has implications for the interpretation of sleep studies for the different age groups.[73] Spruyt et al.[74] have demonstrated that children who have overnight polysomnography can be divided into six groups with clusters of severity based on polysomnographic criteria.

There is some questionnaire evidence that sleep patterns of children differ when in hospital having a sleep study, particularly in the under 3s group.[75] This indicates that caution needs to be applied to the interpretation of these tests and may be best assessed in the context of the parent's description of whether this was a typical night's sleep.

The way hypopnoeas are scored can make a large difference to the AHI. In a study looking at the American Academy of Sleep Medicine definition versus the Stanford definition (which requires no drop in oxygen saturation), the amount of OSA diagnosed varied from 19% to 99%.[76]

OTHER INVESTIGATIONS

- An ambulatory device (ApneaLink Plus, ResMed, Poway, Ca, USA) measuring nasal airflow, chest movement and oxygen saturation has compared favourably with polysomnography in the detection of obstructive sleep apnoea in a group of obese adolescent patients.[77]
- Actigraphy, using a wrist-worn sensor to detect sleep and wakefulness via motor activity, has been shown to be a good approximation to polysomnography in terms of sleep-wake pattern, but it gives no other information.[78,79]

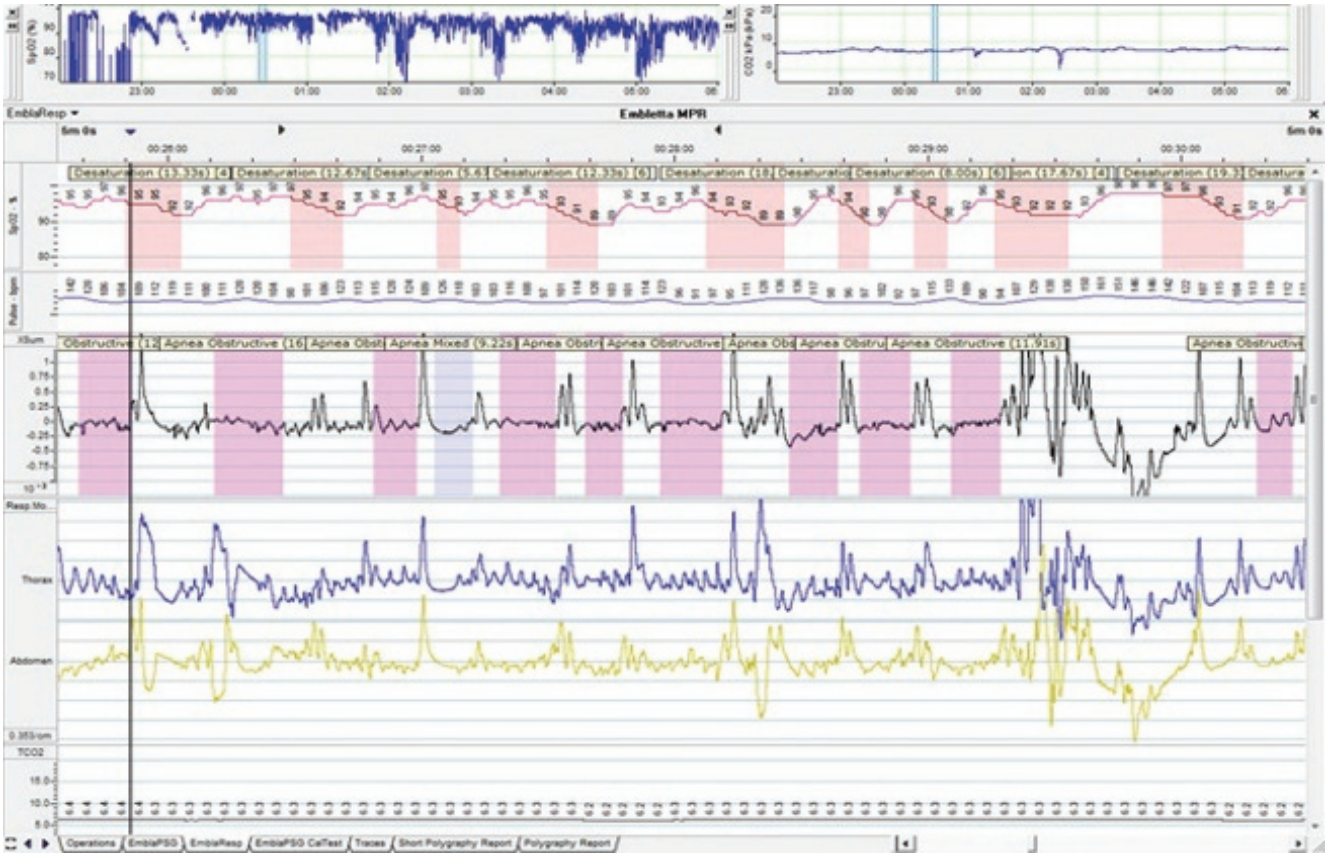

Figure 27.3 Part of a polysomnography study demonstrating desaturations (low SpO_2) and decreased airflow despite respiratory effort, confirming OSA.

- Cardiopulmonary coupling, using devices which measure the synchrony between pulse and respiration, has been proposed as a measure of sleep quality. In a study of OSA patients before and after adenotonsillectomy, the cardiopulmonary coupling appears to show improvement in sleep parameters for quality of sleep before the EEG.[80]
- Oesophageal pressure monitoring at the time of polysomnography to measure changes in intrathoracic pressure has been found to be more predictive for certain neurobehavioural variables.[81]
- Pulse transit time has shown some correlation with OSA at AHI above 3, but it is more limited at picking up milder OSA and differentiating between primary snoring.[82]
- Complementary investigations to measures of attention, such as the event-related potential, measured electrophysiologically, have shown some promise as measures.[83]
- Dynamic MRI is at an experimental stage, but has been used to demonstrate flow changes in paediatric patients with OSA.[84]
- Respiratory inductance plethysmography bands have shown promise in conjunction with oximetry as a pre-polysomnogram screening investigation.[85]
- Infrared monitoring of movements and chest/abdominal asynchrony during obstruction has also been proposed as a method of diagnosis.[86]

CARDIAC INVESTIGATIONS

If there are concerns about the severity of OSA, cardiac investigations in the form of ECG and echocardiography can be undertaken, but routine use of echocardiography has not been shown to be productive in the assessment of patients with OSA.[87]

TREATMENT

Diet and exercise

With the increasing proportion of obese patients, issues of body mass index and the underlying causes should be addressed.

A longitudinal study from Belgium looked at the impact of diet and exercise in a group of children with obesity and OSA. Of 114 obese patients, 41 had sleep apnoea. After weight reduction, 29 of the 41 patients had resolution of the OSA. Those who did not get resolution with weight loss were significantly more likely to have tonsil hypertrophy. Uric acid (a measure of oxidative stress) and CRP were significantly reduced by treatment.[88]

Medicines

A study in Brazil has looked at nasal douching and topical nasal steroids used in a sequential manner to treat adenoid hypertrophy. The study showed no change in the endoscopic appearance of the adenoids after douching alone, but a reduction after topical steroids for 40 days. The results of this are very restricted due to the lack of randomization and blinding.[89]

The Cochrane review has found in a short-term study that topical nasal steroid had a positive effect on the AHI of children with mild to moderate OSA.[90] There has been a well-produced double-blind randomized control trial of nasal steroids (6 weeks fluticasone) which has shown a reduction in the AHI.[91]

There is some evidence that treatment of reflux can help reduce the AHI in mild cases.[63]

Surgery

ADENOTONSILLECTOMY

Trials

The existing literature in this area demonstrates clearly the lack of level 1 evidence to inform treatment decisions. The 2015 Cochrane systematic review 'Tonsillectomy or adenotonsillectomy versus non-surgical management for obstructive sleep-disordered breathing in children' found only three trials meeting the criteria.[92]

The largest of these is the Childhood Adenotonsillectomy Trial (CHAT) from the USA, with 464 children randomized to early adenotonsillectomy or watchful waiting. The age inclusion criteria were 5–9 years and children who had polysomnographically proven OSA. The primary outcome measure was neuropsychological testing and there was no difference between the treatment and control arms, but secondary outcome measures of quality of life (paediatric sleep questionnaire, OSA-18, modified Epworth – all three of which are disease-specific – and pedsQL – measuring general quality of life) did show a significant difference. The control arm showed a spontaneous resolution rate of physiological sleep study measurements in 46% of the control arm versus 79% of the treatment arm. This was a negative trial for the primary outcome, and the high rate of resolution of symptoms in the control arm supports the clinical observations of spontaneous resolution beyond the age of 5 years due to reduction in the volume of adenotonsillar tissue.[93, 94]

In the second-largest study 80 patients with Down syndrome or muccopolysaccharidosis and polysomnographically proven OSA were randomized to adenotonsillectomy or CPAP. These comorbidities often result in more severe OSA and are therefore excluded from many larger studies.[95]

The final study was a small trial with just 29 patients with negative sleep studies and clinical symptoms randomized to adenotonsillectomy or watchful waiting and just 20 analyzed. This was judged to be a very poor quality study due to the dropout rate and the small initial sample size.[96]

There are several current trials comparing adenotonsillectomy versus watchful waiting in varying severities of sleep-disordered breathing from snoring to obstructive sleep apnoea. These include the Preschool Obstructive Sleep Apnoea Tonsillectomy Adenoidectomy (POSTA) trials from Australia, looking at younger age groups than the CHAT study.

A previous Cochrane review of treatment of obstructive apnoea by adenotonsillectomy only found one paper meeting the Cochrane criteria,[97] and this was primarily concerned with surgical technique.[98] Patients were randomized to either radiofrequency tonsil reduction and adenoidectomy or conventional adenotonsillectomy. There were no differences in the outcome measures.

An RCT looked at the addition of pharyngeal pillar closure to standard adenotonsillectomy. Patients with OSA were randomized to receive either a standard cold steel dissection adenotonsillectomy or the same procedure followed by apposition and closure of the pharyngeal pillars. Despite being adequately powered, there was a high dropout rate and a small length of follow-up. There was improvement in quality of life (QOL) scores and AHI for both techniques but no significant difference between them. In light of the limitations of the study these results should be treated with caution.[99]

Longitudinal studies

The main physiological outcome is the AHI from polysomnography as described above. There are a number of studies which demonstrate a reduction in the AHI and these have been summarized in a meta-analysis.[100] Included in this were paediatric patients with no underlying syndrome or diagnosis who underwent adenotonsillectomy with pre- and post-operative polysomnography. The meta-analysis pooled data on 355 children from 14 series. The data are limited by the fact that this is from case series and there are no control groups. An improvement of polysomnography to normal occurred in 83% and a reduction in the AHI of 14 events per hour was found.

More recently there has been a large multicentre retrospective analysis of outcomes of adenotonsillectomy at centres across North America. This analysis included 578 children and the AHI fell significantly from 18.2 pre-operatively to 4.1 post-operatively. However, only 27% of patients had a normal AHI of less than 1. Severe OSA pre-operatively and obesity were predictive of residual OSA post-operatively.[101]

A small study looked at outcomes of adenotonsillectomy in a group of patients with craniosynostosis and upper airway obstruction with moderate to severe OSA. Three out of five patients avoided a tracheostomy, and one of five patients had complete resolution of their symptoms.[102]

A study of 101 children with OSA, who underwent adenotonsillectomy, found that there was a significant reduction in central apnoeas, in those who experienced them, following the procedure.[103]

Adenotonsillectomy was an effective treatment for OSA in a cohort of cleft palate patients, with a reduction of mean AHI from 17.6 to 1.9.[57]

Use of a nasopharyngeal airway has been found to be a useful adjunct to surgery and seems to decrease reliance on PICU.[104]

Tonsillectomy technique

There is increasing evidence that intracapsular tonsil techniques may confer some advantages over conventional techniques. In a series of 500 patients who underwent Coblation® intracapsular tonsillectomy and adenoidectomy, the bleed rate was 0.4%. Requirements for analgesia were low and parental satisfaction and quality of life were high.[105] A study of quality of life by proxy at 3 months and 2 years found no difference between subtotal and full adenotonsillectomy.[106]

JAW DISTRACTION

Bilateral distraction osteoneogenesis has proven to be a reliable technique in producing an adequate pharyngeal airway in children with micrognathia and subsequent pharyngeal restriction secondary to tongue base collapse. In a report from Israel all 11 patients with tracheostomies were subsequently decannulated following jaw distraction with near normal oximetry.[107]

Rapid maxillary expansion has been proposed as an alternative technique in children with retrognathia. In a group of 15 children, 8 had a better respiratory distress index following treatment but 7 were either unchanged or worse.[108] For more detail, see Chapter 19, Craniofacial surgery.

TONGUE REDUCTION

In Beckwith–Wiedemann syndrome and other selected syndromes with macroglossia, tongue reduction may be indicated and results are usually good.[109]

Continuous positive airway pressure

Continuous positive airway pressure (CPAP) may be required in children where treatment is not possible, where treatment is awaited, or where treatment has failed. It is usually used in cases of moderate to severe OSA.

Adherence to CPAP can be poor, particularly in older children. In a sample of 51 patients the mean amount of time spent with CPAP on was just 3.3 hours per night. The authors developed a questionnaire to identify barriers to adherence.[110] A randomized controlled trial of different methods of administering CPAP showed no improvement in compliance with different delivery systems.[111] One American study linked socioeconomic factors rather than disease severity to poor compliance.[112]

CPAP is often reserved for treatment failures, complicated cases with comorbidities and in obesity. The first study to look at neurobehavioural outcomes in 52 patients on CPAP alone examined a heterogeneous group of patients. Assessments were performed at baseline and after 3 months of treatment. There were significant improvements in both disease-specific and general quality of life (QOL) scores. These improvements occurred with a mean use of just 3 hours per night.[113]

The only randomized controlled trial concerning positive airway pressure in paediatric OSA looked at the use of continuous or bilevel CPAP in children who were

unsuitable for adenotonsillectomy and found no difference between the methods.[114]

Nasopharyngeal airway

Nasopharyngeal airways can be used for the long-term management of patients with craniosynostosis and can result in significant improvements in quality of life (QOL) scores.[115]

Analgesia post-adenotonsillectomy for OSA

Paracetamol is considered part of the standard regimen for analgesia post-adenotonsillectomy. Non-steroidal anti-inflammatory medications are widely used in the UK, but there are concerns about a potential bleeding risk associated with their use. A recent Cochrane review with over 1000 children looking at post-operative bleeding in adenotonsillectomy with NSAIDs has shown no statistically significant increase in bleeding, but greater numbers would be needed to prove conclusively there was no increase.[116]

Opioid analgesics need to be managed very carefully. In 2012 the FDA in the US reported three deaths and one severe respiratory depression in children who had undergone tonsillectomy or adenotonsillectomy for obstructive sleep apnoea and had received codeine. It appeared that the children were 'ultra-rapid metabolizers' with a genetic variant which made the liver enzyme p4502D6 much more active. It is thought that this gene variant can exist in up to 7% of the standard population in the US, but up to 29% of those of Ethiopian origin. These children rapidly metabolize a standard dose of codeine, resulting in high serum levels of morphine.[117, 118]

The UK government has restricted the use of codeine in children, particularly those undergoing adenotonsillectomy. The relevant advice is shown in **Box 27.3**.[119]

A randomized double-blind study compared post-operative morphine with dexmedetomidine, a sedative medicine. The dexmedetomidine produced less respiratory compromise as measured by end tidal CO_2, but pain scores were higher.[120]

Location of post-operative care

While the majority of patients with OSA can be managed safely in a standard children's ward environment, careful consideration must be given to whether those at higher risk of respiratory compromise post-operatively need more specialized support (see below). In a prospective study looking at respiratory complications following adenotonsillectomy for OSAS the rate was found to be 10.4%. However, in children with no comorbidity, only 1.2% of these had a problem beyond 6 hours. This is suggested as a basis for day-case tonsillectomy in children without comorbidity. The rate of complications in those with comorbidity at 6 hours post-surgery was 21.6%.[121]

BOX 27.3 UK Government relevant advice on codeine use[119]

Codeine should only be used to relieve acute moderate pain in children older than 12 years and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen.

Codeine is contraindicated in all children (i.e. younger than 18 years) who undergo tonsillectomy or adenoidectomy (or both) for obstructive sleep apnoea.

Codeine is not recommended for use in children whose breathing might be compromised, including those with: neuromuscular disorders; severe cardiac or respiratory conditions; upper respiratory or lung infections; multiple trauma; or extensive surgical procedures. The symptoms of morphine toxicity may be increased in these settings.

In children aged 12–18 years, the maximum daily dose should not exceed 240 mg. This may be taken in divided doses, up to four times a day at intervals of no less than 6 hours. It should be used at the lowest effective dose for the shortest period. Duration of treatment should be limited to 3 days and, if no effective pain relief is achieved, treatment should be reviewed by a physician.

Information should be given to parents and caregivers on how to recognize the signs of morphine toxicity, and advice should be given to stop giving the child codeine and to seek medical attention immediately if their child is showing these signs or symptoms.

Symptoms of codeine toxicity include: reduced levels of consciousness; lack of appetite; somnolence; constipation; respiratory depression; 'pinpoint' pupils; nausea and vomiting.

Codeine is contraindicated in all patients of any age known to be CYP2D6 ultra-rapid metabolizers.

Post-operative complications

The main risk of adenotonsillectomy is post-operative haemorrhage, which has a rate of approximately 4%. A randomized allocation study of 50 children, allocated to either dissection adenotonsillectomy or Coblation® for obstructive sleep apnoea, found less time and less intra-operative blood loss with Coblation®. The failure to find a difference in secondary haemorrhage is not surprising given that this study is vastly underpowered to detect post-operative complications.[122]

A large case controlled trial undertaken in the US looked at over 9000 tonsillectomies, with an overall bleed rate of 2.4%. Using logistic regression, the bleed rate in tonsillectomies was found to be half the rate in those done for recurrent acute tonsillitis.[123]

Children who have OSA are at increased risk of peri-operative respiratory complications. They may be more sensitive to opiates and inhalational anaesthetic agents and are at risk of pulmonary oedema. In children who have been identified as high risk, surgery should be performed in a hospital with paediatric intensive care facilities.[124] In cases at high risk of airway compromise, a nasopharyngeal airway can help reduce the reliance on PICU.[125]

A retrospective review of 993 patients aged 3 years and under found a 9.9% complication rate, with airway obstruction, desaturations and bleeding being the three commonest complications.[126] Younger age (less than 2 years), nasal obstruction and cardiovascular

comorbidities were predictors of airway complications in this group.

Another retrospective review showed that young age, high apnoea–hypopnoea index and intra-operative laryngospasm were linked with complications.[127]

A systematic review has demonstrated that children with OSA put on a significant amount of weight post-operatively and this can predispose some to obesity.[128]

Treatment failure

Residual OSAS following adenotonsillectomy has been reported in 11.6% of children in one study following polysomnography.[129] It has been reported as high as 31% of children in some studies, with higher proportions in children with severe OSA, following surgery.[130] Hypertrophy of residual lymphoid tissue in Waldeyer's ring such as the lingual tonsillar tissue may be responsible for some failures.[131, 132]

Sleep nasendoscopy has been suggested as a method to assess the site of obstruction in airway failures. In a group of 13 children this was seen to be a combination of adenoid regrowth, inferior turbinate hypertrophy and tongue base collapse.[133] There may also be coexistent airway pathology. In a group of 43 patients with OSA secondary to laryngomalacia, 32 had already undergone adenotonsillectomy without resolution of symptoms. Sleep nasendoscopy was an effective way of diagnosing the condition and treatment with supraglottoplasty resulted in a statistically significant reduction in the AHI.[134]

Synchronous airway lesions were found in nearly two-thirds of patients in one series who were less than 3 years of age and undergoing adenotonsillectomy, but only a small number may require surgical intervention. Laryngomalacia and subglottic stenosis were the commonest pathologies.[135]

In a study looking at either supraglottoplasty or lingual tonsillectomy following adenotonsillectomy when there was residual OSA, there was improvement following these procedures, but less for lingual tonsillectomy in obese patients, and less improvement from supraglottoplasty in patients with other comorbidities.[136]

A retrospective analysis of 31 patients who had refractory obstructive sleep apnoea, who were subsequently treated with geniohyoid advancement, radiofrequency tongue base reduction and lingual tonsillectomy, resulted in a success rate of 61% judged by polysomnography.[137]

QUALITY-OF-LIFE OUTCOMES IN SLEEP-DISORDERED BREATHING

Measuring outcomes other than the physiological sleep outcomes is of increasing interest. Areas include neurocognitive outcomes and also quality of life by proxy. The first UK study to measure quality of life improvement was by Georgalas.[138] In a cohort of patients, adenotonsillectomy improved all domains of the Child Health Questionnaire. There has been further work on the use of disease-specific instruments in the UK.[139] In North America there is widespread use of disease-specific quality of life measures such as the OSA-18.[140] A review article found 11 publications measuring changes in behaviour, neurocognition and quality of life following adenotonsillectomy.[141] The authors probably overrate the quality of evidence as these studies are generally prospective single-sample observational studies, although 5 of the 11 do include a control group. Universal improvement in quality of life is reported in these studies. Behaviour and neurocognitive measures also show improvement. One year following adenotonsillar surgery in a group of preschool children, the OSA group showed fewer behavioural problems and a significant improvement in behaviour and quality of life.[142] Longer-term studies demonstrate that the quality of life improvement can be sustained over up to 4 years.[143, 144]

Quality of life studies generally fall into two categories: cross-sectional studies, which are looking at quality of life for a specific condition, and longitudinal studies, which look at the change in quality of life following an intervention.

Cross-sectional studies

Two of these studies were used to develop two of the main disease-specific quality of life tools: the OSA-18 and the Tonsil and Adenoid Health Status Instrument.[145, 146] The main differences between them are that the Tonsil and Adenoid Health Status Instrument was designed for any adenotonsillar disease, and children did not have polysomnographic investigation. The OSA-18 was designed specifically for sleep-disordered breathing and an abbreviated form of polysomnography was performed. The Tonsil and Adenoid Health Status Instrument has been used to derive the T14 instrument for UK practice. This instrument captures information in domains about the obstructive and infective symptoms which affect children, and the subsequent impact on quality of life through issues such as contact with medical services and time off school.

Three other studies looked at general quality of life measures in sleep-disordered breathing, and all found a negative impact of sleep-disordered breathing on quality of life.[147–149]

Two studies investigated obesity and sleep-disordered breathing using a general quality of life measure and found sleep-disordered breathing in obesity to impair quality of life.[150, 151]

Longitudinal studies

The OSA-18 had its development completed in one of these longitudinal trials.[140] It has been used to demonstrate large changes following adenotonsillectomy in the disease-specific quality of life for a general group of patients,[144, 152–159] and specific subgroups of severe OSA[160] and obesity.[161] The OSA-18 has also been used to demonstrate improvement in disease-specific quality of life in children with cerebral palsy[162] and attention deficit hyperactivity disorder (ADHD).[163]

One of the studies used a non-validated questionnaire so is difficult to compare to the others.[164]

The OSD-6 (obstructive sleep disorders 6) was developed in one of the studies[165] and subsequently used in longitudinal studies which show changes in all domains following adenotonsillectomy including improvements up to 3 years after intervention.[166, 167]

The Tonsil and Adenoid Health Status Instrument was used to evaluate the changes following adenotonsillectomy. This showed significant improvement across most scales in a longitudinal study.[168]

Most of the studies have the same limitations in that they feature usually consecutive or convenience samples of children and there is mostly one group. There is potential for bias in the inclusion criteria in a number of the studies. The intervention is made and there is a longitudinal design to the studies. While they all show improvement across the specified domains, there are no control groups in the studies who do not undergo the procedure, so it is not possible to state conclusively that the change is due to the intervention alone, or what magnitude of change there would be compared to a control group.

The only randomized controlled trial concerning quality of life was an evaluation of microdebrider tonsillotomy versus electrocautery to perform adenotonsillectomy. The microdebrider group were more likely to get back to normal activities and diet quicker than the electrocautery group.[169]

MANAGEMENT ALGORITHMS

For the purposes of discussion for this chapter, the term 'specialist children's hospital' refers in the UK to a hospital with specialist paediatric ENT surgeons, anaesthetists and intensive care facilities. The term 'non-specialist centre' refers in the UK to a unit without paediatric intensive care or specialist paediatric ENT or anaesthetic provision. Box 27.4 lists circumstances in which a child should be referred for treatment to a specialist children's hospital.

BOX 27.4 Children who should be referred for treatment in a specialist children's hospital[69, 124]

Age <2 years
Weight <15 kg
Failure to thrive (weight <5th centile for age)
Obesity (BMI >2.5 SDS or >99th centile for age and gender)
Severe cerebral palsy
Hypotonia or neuromuscular disorders (moderately severely or severely affected)
Significant craniofacial anomalies
Mucopolysaccharidosis and syndromes associated with difficult airway
Significant comorbidity (e.g. congenital heart disease, chronic lung disease. ASA 3 or above)
ECG or echocardiographic abnormalities
Severe OSA (described by polysomnographic indices including obstructive index >10, respiratory disturbance index (RDI) >40, and oxygen saturation nadir <80%)

Based on the evidence presented in this chapter the following management algorithm is suggested.

Non-specialist centre

A careful history and examination should be taken. Using the UK guidelines there are factors which can be derived from the history and factors which can be measured that would guide whether it is appropriate to treat in a non-specialist environment (without PICU support) (see Box 27.3).[69]

The factors derivable from the history are:

- age
- severe comorbidity which could influence the anaesthetic and post-operative course (heart/lung)
- comorbidity with impact on pathophysiology of OSA (cerebral palsy, hypotonia/neuromuscular conditions, craniofacial abnormalities, mucopolysaccharidoses or other airway syndromes).

Age 2 years or less would seem to be a sensible point at which a child should have an anaesthetic for adenotonsillectomy to treat obstructive sleep apnoea in a specialized children's hospital or a hospital with high-level children's facilities. The heart and lung factors make it more likely that a child could have intra- or post-operative difficulties therefore would be best managed in a centre with specialist paediatric anaesthetists and paediatric intensive care facilities. The comorbidity with an impact on pathophysiology are conditions which make it more likely that OSA will be more severe and more likely to have incomplete resolution following tonsillectomy and adenoidectomy alone. Removal of small amounts of tissue to try to make partial improvements in patients with OSA can also result in worsening of the condition if there is post-operative swelling.

Consideration should be given to referring these children to specialist children's hospitals prior to any investigations as it is likely that full polysomnography rather than pulse oximetry would be undertaken.

Factors which can be measured are:

- weight
- ECG – to look for cardiac complications
- oximetry – to exclude moderate to severe OSA.

In children over 2 years who have no comorbidity as listed earlier, it is sensible to undertake the above investigations. This is to ensure that children are not at the extremes of weight, do not have cardiac complications and do not have moderate to severe OSA. As discussed in 'Oximetry' above, the investigation has a high positive predictive value but a low negative predictive value.[71] Thus an oximetry trace showing clusters of desaturation is likely to represent moderate to severe OSA. A 'normal' oximetry trace may represent mild OSA/sleep-disordered breathing.

A child with minimal desaturations, none of the above comorbidity and not at the extremes of weight or age can

safely be managed in a non-specialist hospital environment. If the oximetry trace shows no desaturation in the presence of positive features of apnoea on history and large tonsils, the patient is likely to have obstructive sleep apnoea but may have primary snoring alone. Treatment with adenotonsillectomy in these circumstances will result in treatment for most patients with OSA, but may also result in treating primary snorers. There is increasing evidence that primary snoring is not a benign condition and may have neurobehavioural consequences, but there is no research or established role at this stage for adenotonsillectomy in the treatment of primary snoring.[34]

The other option in these circumstances is to refer the child to the local paediatric sleep team for a polysomnogram, which would give diagnostic clarity about the presence/absence of OSA.

Specialist children's hospital

A similar list of conditions exists in the UK guidelines for which children require investigations prior to treatment of OSA.[69]

In the specialist paediatric hospital setting the decision-making process will usually depend on establishing the need to investigate prior to intervention or proceed directly.

As with the non-specialist hospital assessment of the age, cardiorespiratory comorbidity and comorbidity causing or impacting on the severity of OSA can be derived from the clinical findings. Weight and ECG can be measured.

In many centres, in children with no significant comorbidity with clinical findings suggestive of OSA, the decision is taken to proceed directly to adenotonsillectomy. This should be an informed discussion with the parents explaining that, while there is a probability that a child with obstructive features in the history and large adenotonsillar tissue does have obstructive sleep apnoea, there is a chance that they may have primary snoring only.[31] Some parents and surgeons will prefer to investigate for improved diagnostic accuracy, and this can be in the form of oximetry or polysomnography.

If polysomnography is negative, the family can be reassured. If it shows evidence of OSA, treatment should be discussed. If it is mild, consideration could be given to intranasal steroids if the family are keen to avoid surgery.[91] If it is moderate or severe, consideration should be given to adenotonsillectomy.

If a child is at the extremes of weight, has serious cardiorespiratory comorbidity, craniofacial, muscle tone or syndromic problems, a polysomnogram should be performed prior to any intervention. This allows an improved diagnostic certainty in patients who are at higher risk for respiratory complications and also risk stratification. Surgery can be avoided in those who do not have OSA, while those who have moderate to severe OSA can have appropriate arrangements made for post-operative care. This will vary between centres from prolonged recovery, use of airway adjuncts to high dependency or intensive care beds. The intervention clearly needs to be tailored to the individual condition, and in those with syndromic or craniofacial problems it should be a multidisciplinary team decision.

CONCLUSION

Paediatric OSA is a common condition which will be seen by the majority of ENT surgeons. It is important to understand the pathophysiology, and to appreciate the limitations of history and examination in the diagnosis. Investigations need to be considered carefully in the context of their predictive values and a suggested algorithm for hospitals with and without paediatric anaesthesia and intensive care is suggested. Intervention in this condition can result in large and sustained quality of life, but a good awareness of the comorbidities which could result in complications or a poorer outcome is essential.

FUTURE RESEARCH

- Improved abbreviated diagnostic testing.
- Good randomized evidence to support decision-making.
- Increasing use of intracapsular tonsillectomy.
- Better understanding of the inflammatory basis of OSA.

KEY POINTS

- Paediatric obstructive sleep apnoea (OSA) is common, with an incidence of up to 2%.
- Clinical features in the history and examination can be unreliable in predicting OSA.
- Oximetry has a high positive predictive value but a low negative predictive value.
- There is good longitudinal evidence of physiological and quality of life improvement with adenotonsillectomy, but there has been only one completed large-scale randomized controlled trial.

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CHAPTER
28

STRIDOR

Kate Stephenson and David Albert

SEARCH STRATEGY

The senior author has a personal bibliography of key papers on paediatric airway obstruction. This was supplemented with a Medline search using the following keywords: stridor, child, neonatal, paediatric, laryngomalacia, tracheomalacia, vocal cord palsy, vocal fold palsy, vascular ring, stenosis, laryngotracheobronchitis, croup, tracheitis and airway obstruction.

The rationale for most interventions in childhood stridor is based on the practices of experienced clinicians. Few treatments have been subjected to controlled trials. Hence, apart from steroid and nebulized adrenaline therapy in croup, recommendations in this chapter are Grade C and D.

INTRODUCTION

This chapter discusses the evaluation and management principles of a child with stridor. It then reviews the usefulness of special investigations. The clinician is directed to the appropriate chapter for detailed information on specific conditions. Care of the acutely stridulous child is also described.

The challenge of managing a stridulous child

A child labelled with a 'diagnosis' of stridor may have significant underlying pathology. Stridor is a symptom and not a diagnosis. History and general examination alone are insufficient for a firm conclusion to be drawn. Deciding which patients to investigate is sometimes difficult. Even after non-invasive investigations such as imaging there may remain a number of differential diagnoses. Awake flexible endoscopy is very useful but gives little or no information beyond the level of the glottis.

The definitive diagnostic technique of laryngotracheobronchoscopy (LTB) requires an experienced team of surgeon, anaesthetist and nursing staff. Both the equipment and expertise required are highly specialized and are not available in all institutions. Transfer of the child with stridor may be necessary and should be carefully managed.

A child with stridor typically induces significant anxiety in the carer and should be a clinical priority for the medical professional. In the acute situation the paediatric airway can deteriorate rapidly. In a specialized unit this is rarely a problem, with experienced anaesthetists to intubate and surgeons to perform the rare emergency tracheostomy. In a paediatric ward, emergency room or non-hospital setting, rapid deterioration can prove a real challenge.

Anatomical and physiological considerations

Neonates and young children develop upper airway obstruction and respiratory failure more readily than older children and adults. A significant contributor to this increased risk is the structure of the airway in the younger child. Mucosal swelling is more likely to result in a comparatively greater degree of obstruction of the smaller upper airway.

AIRWAY DYNAMICS

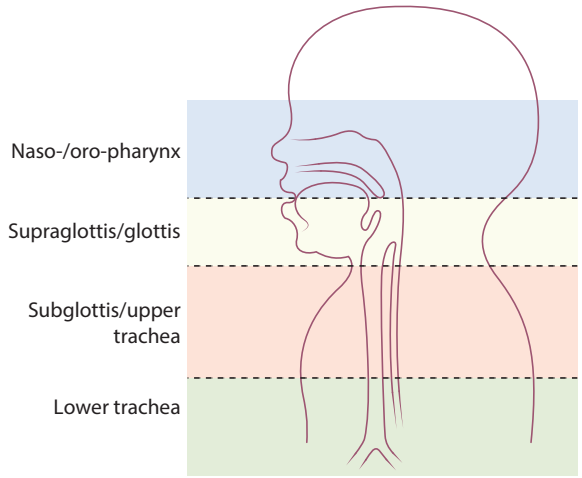
Poiseuille's law (the Hagen–Poiseuille equation) may be applied to the airway and dictates that the airway resistance is inversely proportional to the fourth power of its radius; a 50% reduction in the radius of the airway therefore results in a 16-fold increase in resistance to airflow. One millimetre of narrowing in a 4 mm diameter infantile airway thus results in a 75% change in airflow. As cross-sectional

area decreases, airflow velocity increases. The smaller the airway, the greater the impact of airway oedema and the more grave the concern.

The Bernoulli principle is also of fundamental importance in relation to the paediatric airway. Increased airflow velocity results in negative pressure on the walls of the airway leading to inward collapse. Previously smooth or 'laminar' airflow then becomes more turbulent. The 'Reynolds number' is a quantity described in fluid mechanics that defines the point at which the transition between laminar and turbulent flow occurs. Factors in the equation are the density, viscosity and velocity of the 'fluid', and the diameter of the 'pipe'. Increased turbulence is highly important, greatly increasing airway resistance. Increased airway collapse occurs with vibration of closely apposed tissues and the resultant noise of stridor.

Definitions and characteristics of stridor

Noise originating in the larynx or trachea is typically high-pitched and termed 'stridor'. It may have a musical quality. In contrast, the low-pitched snoring type of noise made by naso- and oropharyngeal obstruction (and rarely by the supraglottic larynx) has a rougher quality and is best described as 'stertor'. Obstruction of the small intrathoracic airways, such as in asthma, is termed 'wheezing'. A rigid differentiation between stridor and stertor cannot always be made and too rigid a distinction can lead to incorrect diagnosis (Figure 28.1).



	Airway noise	Voice/cry	Cough
Naso-/oro-pharynx	Stertor	Muffled	Typically absent
Supraglottis/glottis	Stridor-inspiratory	Hoarse (glottis)	Barking
Subglottis/upper trachea	Stridor-biphasic	Unchanged	Brassy
Lower trachea	Stridor-exspiratory	Unchanged	Wet sounding

Figure 28.1 Clinical presentation according to level of upper airway obstruction.

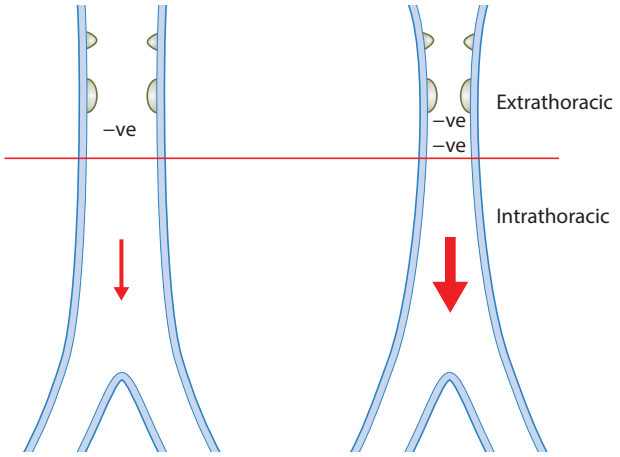


Figure 28.2 Increasing collapse on inspiration with extrathoracic obstruction.

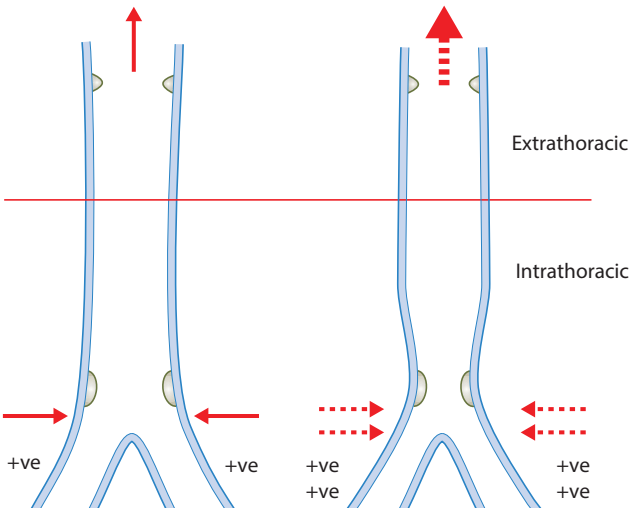


Figure 28.3 Increasing collapse on expiration with intrathoracic obstruction.

Typically, inspiratory stridor is due to an extrathoracic obstruction (Figure 28.2) from the larynx or high trachea. Bronchial or low tracheal obstruction produces an expiratory stridor. Biphasic stridor can occur with obstruction anywhere in the tracheobronchial tree. Even if expiratory stridor is absent, a prolonged expiratory phase may be present, indicating an intrathoracic obstruction (Figure 28.3).

EVALUATION OF THE CHILD WITH STRIDOR

The aim of the history, examination and special investigations is to determine not only the site and cause of the obstruction (the diagnosis) but also its effect on

the airway (the severity). It is important to consider the effect of airway obstruction on feeding, sleep, exercise and growth.

History

PERINATAL HISTORY

The obstetric and perinatal history is often relevant. This is particularly true if the child was born prematurely and required ventilation. Neonates admitted even for short periods to intensive care or a special care baby unit (SCBU) may have had endotracheal intubation but the parents may not volunteer this important information. Beware the term 'intubation', as this may be taken to mean the passage of a nasogastric tube or even suction of oronasal secretions. A history of a difficult delivery is also linked to vocal cord palsy.

Stridor that is present at birth, i.e. with the child's first breath, is unusual. This generally denotes a significant fixed congenital narrowing such as a laryngeal web, subglottic or tracheal stenosis or bilateral vocal cord palsy. Other dynamic conditions such as laryngomalacia typically become evident in the first few weeks of life. A gradual increase in severity of airway compromise implies progression of an obstruction which may be intrinsic (luminal), as in the case of a subglottic haemangioma, or extrinsic, as with a mediastinal mass.

TABLE 28.1 Symptoms associated with varying causes of airway obstruction

Symptoms	Typical diagnoses	
Prolonged expiratory phase	Tracheal and bronchial obstruction (e.g. tracheobronchomalacia, stenosis)	
Cough	TOF Vocal cord palsy Cleft larynx Foreign body Tracheomalacia Reflux	
Aspiration	TOF Vocal cord palsy Cleft larynx	
Hoarseness	Laryngeal lesion (e.g. vocal cord palsy, papilloma)	
Acute airway obstruction	Retropharyngeal abscess Tonsillitis Glandular fever Foreign body Epiglottitis Croup Bacterial tracheitis	
Dysphagia and feeding difficulties	Epiglottitis Tonsillitis Retropharyngeal abscess	NB Feeding affected with many causes of severe airway obstruction
Apnoeas	Tracheobronchomalacia	

PATTERN OF STRIDOR

Stridor is seldom constant. Any variation can help pinpoint the cause, though asking parents about the timing of stridor in the respiratory cycle is seldom profitable. Typically, laryngomalacia – as with other laryngotracheal causes of stridor – is better when the child is at rest or asleep but made worse by crying, feeding and excitement. Upper airway obstruction at the level of the pharynx is in contrast worse when the child is asleep and is associated with stertor. Airway obstruction greatest in a supine position can occur with a pedunculated laryngeal mass but more often is due to supralaryngeal obstruction such as micrognathia and resultant tongue base occlusion. Improvement in the airway with crying occurs in significant nasal obstruction such as bilateral choanal atresia.

ASSOCIATED FEATURES

Airway obstruction may be associated with a number of symptoms (Table 28.1) alongside stridor including apnoeas, cyanosis, 'dying spells', cough and hoarseness and increased work of breathing (dyspnoea, tachypnoea, recession, nasal flaring, head bobbing). Apnoeic episodes associated with cyanosis are typical of severe tracheobronchomalacia and are sometimes termed 'dying spells'. They may also be described as apparent life-threatening events (ALTEs) of which airway pathology is one of several causes. A newer potential label of 'brief resolved unexplained event' (BRUE) has also been proposed.[1] Parents will usually attempt resuscitation if these episodes are severe. It is often unclear how many of these attacks are otherwise self-limiting.

Tachypnoea and dyspnoea are not limited to upper airway obstruction but a clear description of exertional dyspnoea in an older child provides a useful functional assessment of severity. Cough is typical of tracheo-oesophageal fistula (TOF) and tracheomalacia and is rarely due to 'infantile asthma'. Hoarseness suggests a laryngeal lesion such as papillomatosis and also occurs in vocal cord palsy.

FEEDING HISTORY

Feeding is one of the most strenuous activities for a neonate and is closely connected with breathing. It is therefore vulnerable to compromise in upper airway pathology. A change in feeding or inability to feed is typically keenly noted by carers and is likely to be a key indicator of upper airway status.

An accurate picture of the feeding pattern must be obtained. Breastfed babies with airway obstruction will characteristically 'come up for air'; bottle-fed babies may require thickened feeds or a 'slow teat' (i.e. one with small holes). Aspiration suggests vocal cord palsy, tracheo-esophageal fistula, neuromuscular pathology or rarely a laryngeal cleft. Significant repeated aspiration may be associated with recurrent chest infections. Regurgitation ('posseting') is common in neonates and by itself may not represent significant gastro-oesophageal reflux. The end result of poor feeding may just be slow feeding which

troubles the carers more than the child or there may be failure to thrive with demonstrably poor weight gain. It is important not to assign failure to thrive to the common cause of laryngomalacia without first having considered and excluded other causes. Formal mapping of weight gain in a growth chart is useful in both the assessment of severity and planning of appropriate management. Figure 28.4 demonstrates an example of growth failure as might be seen in a case of significant prolonged upper airway obstruction.

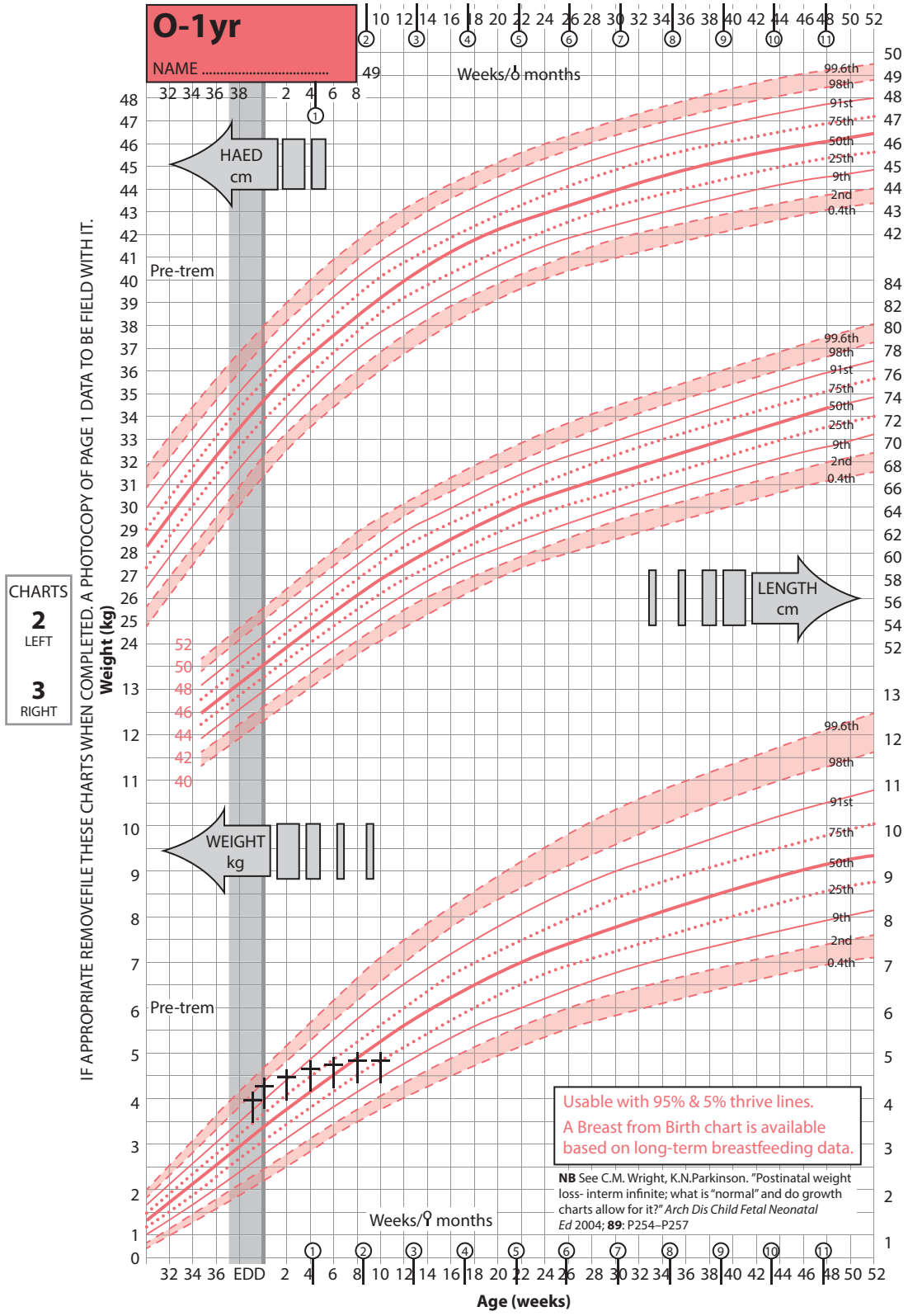


Figure 28.4 Growth chart demonstrating growth failure in the first 3 months of life. (Baseline data Child Growth Foundation.)

GENERAL MEDICAL CONDITIONS

Enquiry into the general past medical history may explain a vocal cord palsy occurring as a result of neurological disease or cardiothoracic surgery. It may also suggest vascular compression associated with congenital cardiac disease. The presence of any skin lesions is important; a cutaneous haemangioma may be associated with a subglottic haemangioma.

ACUTE OBSTRUCTION

In acute airway obstruction the history is taken in parallel with the examination and resuscitation. Take particular note of any possible foreign body aspiration or concurrent illness history. Rapid progression of airway obstruction typically occurs in acute infection and in foreign body inhalation.

Boxes 28.1, 28.2 and 28.3 give examples of congenital and acquired causes of upper airway obstruction and highlight the common pathologies.

Examination

OBSERVATION

Observing the child at rest before proceeding to formal examination provides not only an initial assessment of the degree of respiratory distress and the characteristics of any stridor but also gives time to gain the child's confidence. The characteristics of the stridor need to be observed as well as the effects of airway obstruction such as recession. An abnormal voice, wheeze or cough is a useful localizing sign. The site of the abnormal vibration can rarely be pinpointed with the aid of a stethoscope due to the variable transmission of sound through the thorax.

BOX 28.1 Examples of naso- and oropharyngeal causes of upper airway obstruction (bold = common causes)

Congenital	Acquired – neonates	Acquired – children
Choanal atresia	**Neonatal rhinitis**	**Allergic rhinitis**
Choanal stenosis		**Adenoiditis**
Mid-nasal stenosis		**Adenotonsillar hypertrophy**
Piriform aperture stenosis		**Foreign body**
Glioma		Non-allergic rhinitis
Encephalocoele		Retropharyngeal abscess
Meningocoele		Infectious mononucleosis
Dermoid/teratoma		Ludwig's angina
Craniofacial abnormalities		Thermal and caustic burns
Micrognathia – glossoptosis		
Lingual thyroid		
Lymphovascular malformation		

BOX 28.2 Examples of laryngeal causes of upper airway obstruction (bold = common causes)

Congenital	Acquired – neonates	Acquired – children
Laryngomalacia	**Intubation trauma**	**Intubation trauma**
Vocal cord palsy	Surgical trauma (e.g. laser)	**Croup**
Laryngeal stenosis	Laryngeal stenosis	**Recurrent respiratory papillomatosis**
Laryngeal cysts	Arytenoid fixation	Hereditary angioedema
Webs	Reflux laryngitis	Epidermolysis bullosa
Laryngeal atresia		**Foreign body**
Vallecular cyst		Dislocated arytenoid
Arytenoid fixation		**Epiglottitis**
Posterior laryngeal cleft		Trauma – fracture
		Caustic and thermal burns
		Haemangioma
		Lymphovascular malformation

BOX 28.3 Examples of tracheal causes of upper airway obstruction (bold = common causes)

Congenital	Acquired – neonates	Acquired – children
Tracheal stenosis	**Post- intubation/ instrumentation/ tracheal stenosis**	**Croup**
Tracheal atresia	Reflux tracheitis	Bacterial tracheitis
Trapped first tracheal ring		**Foreign body**
Complete rings		Localized malacia secondary to a tracheostomy or TOF repair
Micro (stovepipe) trachea		Thyroid masses
Haemangioma		Lymphovascular malformation
Primary tracheomalacia		Mediastinal tumours
Secondary tracheomalacia – vascular compression		

Auscultation is, however, useful to detect abnormal heart sounds and wheeze.

With rapidly advancing technology, it is increasingly commonplace for carers to have mobile devices with audiovisual recording capabilities. Useful information can sometimes be obtained from reviewing a parental recording of a symptomatic episode.

The pre-endoscopy assessment, though important, can be only a guide to the type and degree of pathology discovered at endoscopy. The combination of a thorough history, examination and limited investigation can in some

conditions (e.g. suspected mild laryngomalacia) provide sufficient diagnostic probability to give a working diagnosis and avoid progression to immediate endoscopy by default. The type of stridor may be characteristic of a particular pathology but is never diagnostic.[2] A second pathology alongside laryngomalacia may be present in up to 20% of cases though few will require treatment.[3] The diagnosis can only be confirmed by endoscopic evaluation. This does not mean that every child with stridor requires laryngotracheobronchoscopy. In most children seen in a secondary or tertiary referral centre, endoscopy will be required and in most conditions is the gold standard.

ASSOCIATED FEATURES

Subcostal, intercostal and suprasternal recession may occur separately or together and also be associated with 'see-saw' respiration. The severity of recession is a better indicator of the severity of airway compromise than the degree of stridor. Accessory muscles of respiration are not usually employed by the younger child, who depends predominantly on diaphragmatic movement. Nasal flaring and head bobbing are important and concerning signs, as is abnormal posturing; the child may adopt a position of neck extension and, in some instances, head rotation with airway obstruction as the position of greatest comfort.

The volume of stridor can paradoxically reduce as the obstruction increases due to the diminishing airflow. No comfort should be taken from the fact that a child still looks pink. Cyanosis is a very late event and suggests obstruction has been severe or prolonged.

If a supralaryngeal component is suspected, nasal patency should be assessed with a metal instrument or mirror, a wisp of cotton wool or using the bell end of a stethoscope. Make a conscious assessment of jaw and tongue size. Examine the ears, nose, throat and lastly neck with the usual caution that you must not use any instrumentation to examine the throat of child in whom pathology such as epiglottitis is suspected. Observing the child attempting to feed may be extremely valuable, particularly if there is a feeding or aspiration concern.

Investigations

Investigations need to be carefully selected on the basis of the history and examination. They may be categorized into pre- and postendoscopy investigations.

IMAGING

The value of radiological investigations was reviewed retrospectively by Tostevin et al.[4] Plain anteroposterior (AP) and lateral views of the neck, digitally enhanced to demonstrate the subglottis, oropharynx and nasopharynx, are rapid, inexpensive tests that do not require sedation or anaesthesia. The term 'Cincinatti view' describes a high-kilovolt filter AP film designed to highlight the soft tissues of the neck.

A chest radiograph may include the upper trachea and larynx in the smaller child, otherwise a separate AP neck film may be obtained. This can demonstrate the 'steeple sign' of croup and bulky lesions such as subglottic cysts, papillomata. Significant stenosis may also be delineated. A plain chest radiograph may show the ground-glass appearance of bronchopulmonary dysplasia or mediastinal shift resulting from a foreign body. If a foreign body is suspected in young children, diaphragmatic screening with videofluoroscopy is a more sensitive technique. In older children, inspiratory and expiratory films may demonstrate diaphragmatic immobility on the side of the obstruction. Foreign bodies that do not cause complete lower airway obstruction, those that are radiolucent and those located in the larynx represent particular diagnostic challenges.[5]

Airway fluoroscopy has been found to be highly specific in the diagnosis of both laryngotracheomalacia and fixed airway lesions, but its sensitivity is poor; it has not been proven to be a useful screening tool.[6] Airway fluoroscopy can be combined with a contrast swallow looking for vascular compression and aspiration. Contrast swallows are of limited diagnostic value in the investigation of paediatric stridor and may be best employed following endoscopy, particularly in cases in which a vascular ring or tracheo-oesophageal fistula is suspected.[7]

Bronchography may be performed using non-ionic contrast media. It requires expertise and is associated with risk, particularly in infants and those prone to apnoea. It is particularly useful for the lower airway, demonstrating tracheobronchial stenosis and malacia.[8] Opening pressures of the collapsed bronchi and lower trachea can be measured and used to determine the level of airway support needed.

Echocardiography can be used in cases of suspected vascular compression, demonstrating most but not all abnormal vasculature as well as coincidental or symptomatic congenital heart disease.[9] With experience, ultrasound of the vocal cords can be used to demonstrate vocal cord palsy with reasonable accuracy.[10] Laryngeal ultrasound may also demonstrate structural lesions such as cysts, polyps and papillomata; however, it is non-diagnostic.

Both computerized tomography (CT) and magnetic resonance imaging (MRI) can demonstrate the configuration of thoracic vasculature in cases of extrinsic tracheal compression and thus are particularly useful postendoscopy. CT and MRI may also aid in the evaluation of airway lesions although they are not usually sufficiently sensitive to fully characterize a lesion or stenotic segment. Helical or multidetector CT with multiplanar and 3D reconstruction offers increasingly better definition of fixed tracheal lesions, which are effectively 'virtual bronchoscopy'.[11, 12] Dynamic changes – primary and secondary tracheobronchomalacia – are not well evaluated by cross-sectional imaging. The degree, maturity and mucosal quality of a stenosis can be more accurately assessed at endoscopy.

Imaging may not be appropriate in situations of acute and severe upper airway obstruction. Should imaging be agreed to be of diagnostic and constructive use, it must be performed with close medical supervision so that the airway can be monitored and intervention provided in the event of deterioration.

RESPIRATORY FUNCTION TESTS

Lung function tests such as flow-volume-loops provide a graphical representation of inspiratory and expiratory flow. This can help to localize the site of obstruction; it may differentiate between intra- and extrathoracic obstruction and between fixed and variable pathologies. Other lung function tests such as peak flow testing may be best selected and reviewed with the advice of a pulmonologist. These tests require a degree of patient cooperation and are non-diagnostic. They may, however, assist in the assessment of severity, decision-making regarding management and monitoring of clinical progress.

Polysomnography or 'sleep studies' are also not often used in the assessment of the stridulous child. Airway obstruction that worsens during sleep is usually a feature of pharyngeal obstruction such as adenotonsillar obstruction or a craniofacial anomaly. Laryngomalacia and most laryngotracheal pathologies are rarely worse during sleep.

ASSESSMENT OF REFLUX

It is difficult to gauge whether reflux is secondary to airway obstruction with negative intrathoracic pressure drawing gastric contents into the oesophagus or if the reflux is a separate entity. Occasionally, reflux may be a primary causative factor with secondary reflux laryngitis.

Gastro-oesophageal reflux[13, 14] can be assessed with a radiopaque contrast study, milk scan (nuclear medicine), pH study or endoscopy. Contrast studies have low specificity and sensitivity and are dependent on positioning and radiological interpretation. The other investigations are more sensitive but are usually interpreted by gastroenterologists looking for reflux into the lower oesophagus. The laryngologist is interested in the pH in the upper oesophagus and pharynx, which can be measured using a second probe in the upper oesophagus. Episodes of reflux occur without an associated pH change. These events may be detected by impedance testing (multiple intraluminal impedance); this newer technique is, however, more expensive and less widely available.[15]

Reflux is considered in detail in Vol 3, Chapter 77, Reflux Disease.

Endoscopy

The two principal concerns in paediatric upper airway endoscopy are safety and diagnostic accuracy. To achieve these objectives requires not only a full range of specialized paediatric endoscopy equipment (**Box 28.4**) but, most significantly, a high level of experience in the endoscopist, anaesthetist and nursing staff. A systematic approach will provide a diagnosis in most cases.[16]

AWAKE FLEXIBLE ENDOSCOPY IN THE OFFICE/WARD

The introduction of ultra-thin endoscopes with good optics and a diameter of less than 2 mm has allowed even neonates to be evaluated without the need for a general anaesthetic.[17, 18] Peroral passage of an endoscope may be performed in the edentulous neonate using a finger between the gums to protect the instrument. This alternative approach is preferred by many to transnasal introduction in the young infant.[19]

Flexible laryngoscopy may be considered a diagnostic screening procedure. The view, particularly of the larynx, is often suboptimal. No invasive diagnostic or therapeutic procedure can be undertaken and, even if an abnormality is demonstrated (such as laryngomalacia), a second pathology can be missed. Awake flexible endoscopy is particularly useful to assess dynamic abnormalities such as vocal cord palsy. Flexible endoscopy under sedation in an endoscopy suite is widely practised by paediatricians and pulmonologists and is becoming more popular with otolaryngologists as an adjunct to rigid endoscopy.[20]

Awake flexible endoscopy is most feasible in the infant who may be swaddled (under 9–12 months) and in the older, cooperative child. Office-based flexible endoscopy of the lower airway to the level of the carina has also been described as feasible and safe in a paediatric population although this practice is not widespread.[21]

BOX 28.4 Suggested minimum equipment standards for paediatric airway endoscopy

- Adjustable laryngeal suspension system
- Operating microscope with 400f lens
- Selection of age-appropriate paediatric laryngoscopes of varying size and with a variety of viewing angles
- Dedicated laryngeal microsurgical instruments, e.g. microscissors, probes, cupped and straight forceps
- Selection of age-appropriate ventilating bronchoscopes with Hopkins rod telescopes to fit
- Suitable light source with fibre-optic cable
- Camera and monitor with image-capture facilities – video and still
- Colour printer
- Selection of forceps for the removal of foreign bodies
- Optical forceps with rigid telescope(s) of corresponding length
- Selection of fibre-optic bronchoscopes and a nasopharyngoscope
- Full range of paediatric tracheostomy tubes

LARYNGOTRACHEOBRONCHOSCOPY

Laryngotracheobronchoscopy (**Figure 28.5**) is the gold standard in the assessment of the stridulous child. It is a highly technical procedure. The whole team (surgeon, anaesthetist and nursing assistant) need to work closely together to perform the examination safely, and to optimize the assessment. The advent of video and high-quality image reproduction on a viewing monitor has been invaluable in training and teamworking. The anaesthetist and theatre team may also view the live image and may be able to anticipate interventions required.

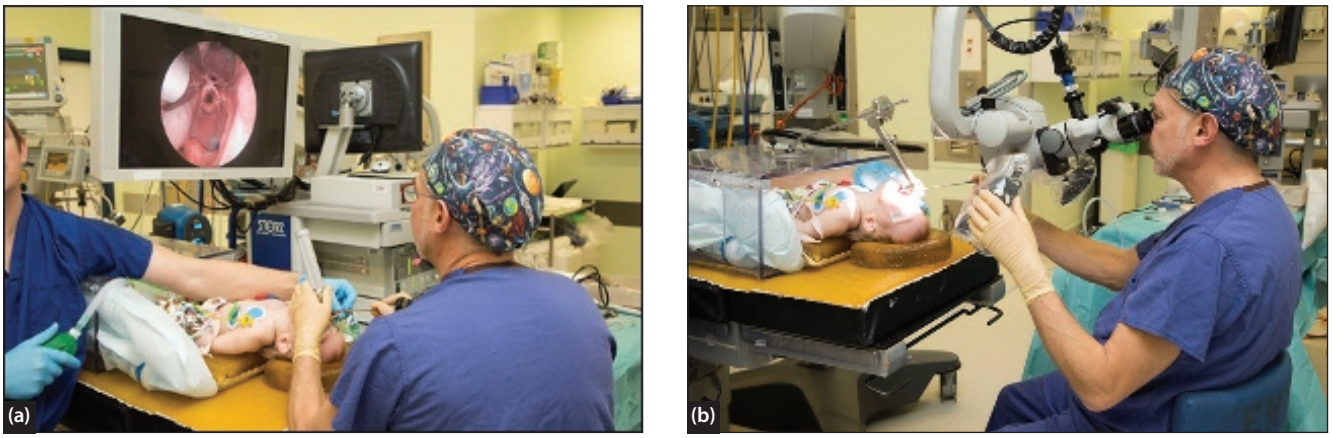


Figure 28.5 Laryngotracheobronchoscopy. (a) Handheld laryngoscope and Hopkins rod technique. **(b)** Supension laryngoscopy and microscope technique.

ANAESTHESIA FOR UPPER AIRWAY ENDOSCOPY

Major units around the world use a variety of techniques; it is probably more important that a theatre team work together effectively than that one particular technique is followed. High levels of cooperation and skill are required. Practice varies between centres as to whether intubation is used at the start of the procedure, however most units would now use spontaneous respiration rather than paralysis. Spontaneous respiration has much to recommend it as a technique: it maintains muscle tone, promotes gas exchange and is essential to detect dynamic conditions.

Induction

Some units will use a premedication such as atropine or glycopyrrhonium bromide to facilitate a dry surgical field and improve the efficacy of topical anaesthesia. Pre-operative steroids are a good safeguard if significant stenosis or likelihood of increased inflammation is suspected. Intravenous induction is preferable for older children; gas induction is best in infants, younger children, those with poor venous access and those with a precarious airway. Topical local anaesthetic spray (typically lignocaine) should be applied to the vocal cords when the anaesthetic level is sufficiently deep for this to be tolerated. This amount needs to be carefully measured as the preparations used in adults can easily result in overdosage.[22, 23]

Maintenance of anaesthesia

Two principal anaesthetic techniques are used for general anaesthesia with spontaneous respiration: maintenance with a volatile agent (e.g. sevofluorane) and total intravenous anaesthesia (TIVA) with an infusion such as propofol and remifentanil.[24]

A volatile agent and oxygen mix can maintain a level of anaesthesia that allows a thorough examination in a child who is breathing spontaneously. Sevoflurane is non-irritant to the airway and has the advantages of rapid onset and no pungency, allowing immediate delivery of high concentrations. This advantage of rapid induction may be offset by rapid termination of effect during periods of relative hypoventilation or airway obstruction. Now superseded by sevofluorane, halothane gas was also useful for this purpose. The anaesthetist needs to be able to control anaesthesia in response to surgical conditions and for this a video monitor visible to the anaesthetist is invaluable.

Airway tube technique

An endotracheal tube may be used as a nasopharyngeal airway or 'prong' to provide oxygen and volatile anaesthetic agent, if used. Should transnasal passage not be possible, an oropharyngeal tube may be used, placed at the angle of the mouth. A significant advantage of a non-intubation technique is that the endoscopist has a view of an airway that has not been altered by the passage of an endotracheal tube. Confusion relating to lesions caused by intubation for the procedure cannot occur and at any time airway control can be regained with intubation or the use of a bronchoscope.

An alternative technique is to intubate the child prior to withdrawal of the tube for endoscopy. This technique is not routinely used in our institutions. Intubation does facilitate rapid progress to the required level of anaesthesia. Nasotracheal intubation allows the endotracheal tube to be withdrawn into the nasopharynx once the child is breathing spontaneously. Careful positioning of the tube over the glottis by the endoscopist can also achieve good oxygen and volatile agent provision, when required.

Jet ventilation

This technique allows the child to be paralysed, preventing coughing and gagging. Gas exchange is maintained by short pulses of oxygen and anaesthetic gas. Subglottic jet ventilation may be provided in adults using a transglottic cannula but this is not only impractical but also risks barotrauma (pneumothorax and air trapping) in children. Supraglottic jet ventilation has been described although few centres use this technique.[25] Dynamic conditions such as malacia and cord palsy cannot be well identified.

Laryngeal mask airway

A laryngeal mask airway (LMA) is useful for fibre-optic tracheobronchoscopy, particularly if the patient is difficult to intubate because of mandibular hypoplasia.[26]

LARYNGOTRACHEOSCOPY TECHNIQUE

The following description assumes that the patient may have been intubated, suspension laryngoscopy is employed and that the larynx and/or trachea is to be examined with a rigid telescope or microscope.

A small sandbag or pad is usually required under the shoulders with sandbags laterally to support the head if required. A Mayo table supports the laryngostat (laryngeal support) clear of the chest.

It is important to prepare and check all equipment prior to the endoscopy so that the endoscopist is fully prepared for all eventualities. The range of Hopkins rod rigid endoscopes should include all lengths and diameters that could be needed. A 30° telescope may be able to better assess the supraglottic larynx without splinting. A microscope should be available, though is often not used unless surgical intervention is required when two hands are needed for manipulation. If a microscope is used, a 400 mm lens allows the use of standard laryngeal instruments but a 350 mm lens brings the patient closer, allowing easier laryngeal manipulation, which is particularly important in small neonates. For routine examination, the Hopkins rod and camera can be held in the left hand with a probe used in the right. The image quality available using a rigid endoscope is far superior to that of the microscope. Every unit should have a chart listing the appropriate sizes of bronchoscope for different ages. The age-appropriate bronchoscope should be checked and one at least a size smaller instantly available as well.

Laryngeal examination is usually begun by gently inserting the lubricated suspension laryngoscope, taking care to protect the teeth and lips and to keep the tongue central to provide a well-centred view. As in adults, it is important to check the overall appearance of the pharynx and supraglottis during introduction of the laryngoscope. The endotracheal tube, if present, is followed to the tip of the epiglottis. The epiglottis should be gently lifted forward making certain that it does not curl up in front of the laryngoscope preventing a complete view of the anterior commissure. An overall assessment of the larynx can be made with a tube *in situ*, providing a degree of stability that is particularly welcome in the child with a compromised airway.

Laryngeal examination with the endotracheal tube removed provides a superior view and, by using a probe to move the arytenoids independently, the mobility of the cricoarytenoid joints can be assessed. If an interarytenoid scar is present, the arytenoids will not move independently. A posterior laryngeal cleft is excluded by passing the probe between the arytenoids, comparing the lower limit of the interarytenoid groove with that of the posterior commissure. Finally, great care should be taken to pass through the vocal cords if a rigid endoscope is used to inspect the subglottis.

The time available for the examination will depend on the airway and respiratory reserve. In a child breathing spontaneously with a normal airway and normal lung function, anaesthesia can be maintained solely by the use of inhalational or intravenous agents and a nasopharyngeal airway. In some cases the time may be very limited and it is essential to be prepared to move ahead with bronchoscopy at any stage. If there is significant subglottic stenosis, an ultra-fine telescope passed through the laryngoscope will cause less trauma than a bronchoscope.

BRONCHOSCOPY TECHNIQUE

Traditionally, a ventilating bronchoscope (**Figure 28.6**) has been used which provides a means of actively ventilating the patient if required. With spontaneous ventilation, a smaller diameter rigid Hopkins rod telescope can be used with less trauma and reduced splinting of the airway.

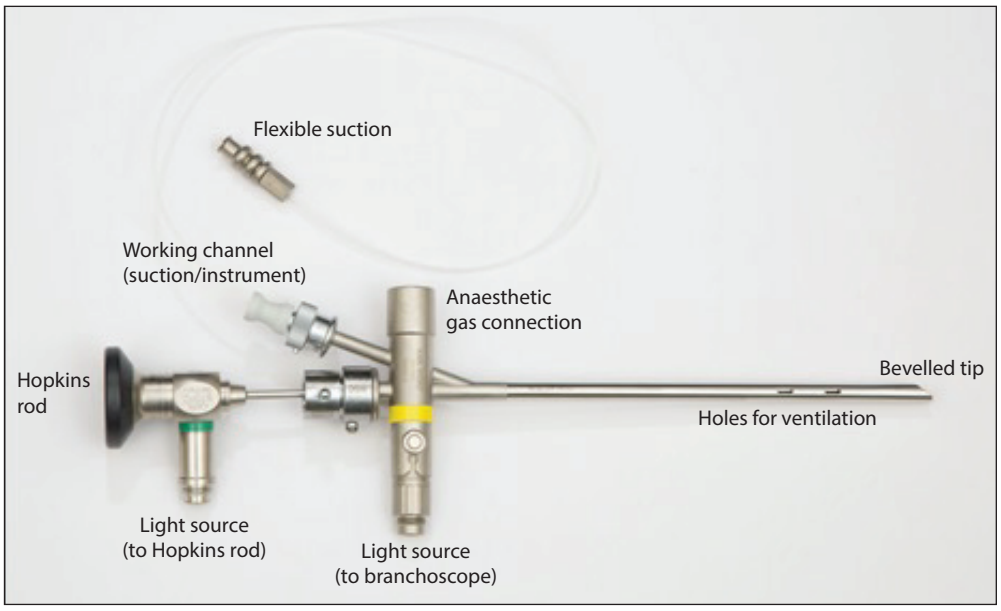


Figure 28.6 Ventilating bronchoscope and Hopkins rod.

An anaesthetic laryngoscope can be used in the vallecula to lift the larynx forward while passing either the tip of the Hopkins rod or the bevel of the bronchoscope through the vocal cords. If a bronchoscope is used, this can be performed under video control with a Hopkins rod coupled into the bronchoscope. Tracheomalacia should be observed with a small bronchoscope withdrawn from the area in question and without positive airways pressure to avoid splinting.

The subglottis, trachea, the carina and main bronchi are all systematically examined and videographs or digital images recorded. Photodocumentation of the endoscopic findings and printing of a compilation of images not only benefits the patient record but also is a useful visual tool for explaining findings to the family. A minimum of a 'four-shot view' of the supraglottis, glottis, subglottis and trachea, and lastly of the carina and main bronchi is suggested. Video recording of dynamic pathologies such as abnormal vocal cord movement, laryngomalacia and tracheobronchomalacia is also recommended.

It is vital that accurate records are kept. Use of a standardized data capture form facilitates this.[27] This provides an invaluable source of information for sequential clinical comparisons, medicolegal purposes and teaching. Use of a recognized staging system is important for research purposes, collaboration and publication of results.

DYNAMIC ASSESSMENT OF THE LARYNX ON RECOVERY FROM ANAESTHESIA

Typically, this can be achieved by withdrawal of the bronchoscope to just posterior to the tip of the epiglottis. This gives a good view of the vocal cords to exclude a cord palsy and of the arytenoids to exclude the common posterior form of laryngomalacia, though anterior collapse of the epiglottis may be masked. In this case, a 30° telescope can be used. The anaesthetist should describe the phase of respiration to enable the endoscopist to check for paradoxical vocal cord movements.

Techniques for dynamic assessment of the vocal cord movement are to insert a laryngeal mask with a fibreoptic bronchoscope passed through this to just above the laryngeal inlet or passage of the scope through a specially adapted face mask.[28] If a bilateral vocal cord palsy is suspected and structural abnormalities have been excluded with a full microlaryngoscopy and rigid bronchoscopy, it is sometimes necessary to reschedule the patient for a further examination in which a laryngeal mask and fibreoptic scope are used from the outset, reducing the influence of prolonged anaesthesia on the cord function.

MANAGEMENT OF ACUTE AIRWAY OBSTRUCTION

In the acute situation, assessment, history taking and resuscitation will often proceed in parallel. In the example of a child arriving in the emergency room with suspected croup, the physician will be assessing the child for the degree of airway obstruction by gauging the recession and dyspnoea at the same time as asking the parent/carer for the length of history and whether there is any possibility of foreign body inhalation. A nurse may be checking the oxygen saturation and setting up humidified oxygen. Another member of the team may have to call and alert the operating room that the child may need intubation as well as calling the anaesthetist and otolaryngologist. This situation clearly benefits from careful planning, with most units having a protocol for how to deal with the stridulous and airway-compromised child. The protocols vary considerably, with some units insisting on the presence of an otolaryngologist at intubation in case a tracheostomy is needed while others have managed for many years without.[29, 30]

In a child with a compromised but functional airway it is crucial that upsetting the child does not cause deterioration. Coughing, crying and distress may result and change obstruction from partial to complete. Significant consideration and skill are required in the management of such a patient. The child should be kept in a position of comfort with its carers in a calm environment and the applications of adjuncts such as pulse oximetry, oxygen and nebulized adrenaline carefully tailored. Interventions such as venepuncture, taking of radiographs and flexible nasendoscopy may jeopardize the critical airway.

Medical management

OXYGEN THERAPY

With an obstruction to airflow and normal alveolar function, raising the concentration of inspired oxygen will reduce the ventilatory requirement to maintain adequate oxygen saturation levels but will not aid carbon dioxide clearance. So long as the possibility of hypercarbia is appreciated, oxygen is a useful drug in the treatment of airway obstruction.

As previously emphasized, a face mask applied to the conscious child is likely to be upsetting and should be avoided. Use of nasal cannulae, wafting or 'head box' oxygen may be better options. Persistent hypoxia and cyanosis are very late signs in a child and are likely to precede rapid respiratory collapse.

HUMIDIFICATION

There is no objective evidence that raising the humidity of the inspired air is beneficial in upper airway obstruction and in croup.[31,32] Humidification has however been used for decades but few units still use humidity tents or 'croupettes' as these have the disadvantage of decreased visibility and may also frighten the child.

HELIUM-OXYGEN MIXTURES (HELIOX®)

Addition of helium to inspired gases is associated with a reduction in the turbulence of flow. Helium–oxygen mixtures are thus recognized to decrease airway resistance and have been used for several decades in the management of patients with upper airway obstruction.[33] Use of 70% helium/30% oxygen inhalation has been systematically

reviewed for use in treatment of croup in children; there is some evidence to suggest a short-term benefit in moderate to severe croup.[34]

PHARMACOTHERAPY

Intravenous and oral steroids such as dexamethasone have been shown to be beneficial in croup, with inhaled steroids having a similar effect.[35] Klassen summarizes: 'All children with croup symptoms who demonstrate increased work of breathing in the clinics or emergency departments should be treated with glucocorticoids.'[36] This treatment may be with nebulized budesonide (2 mg) or oral or intramuscular dexamethasone (the optimal dose needs to be defined; 0.15–0.6 mg/kg has been described). Oral glucocorticoids such as dexamethasone and prednisolone may be the best options due to ease of administration, widespread availability, and lower cost. Inhaled or nebulized budesonide can be used at home for children with recurrent croup.[35]

Nebulized adrenaline (400 µg/kg or 0.4 mL/kg of 1 : 1000 to a maximum of 5 mL) may result in a transient improvement within 10-30 minutes, lasting up to 2 hours. This should be considered in pathologies that have an inflammatory component, such as croup, with moderate or severe distress.[37] Again, a nebulizer should be applied only if it does not increase the distress of the patient.

Transfer of the child with stridor

Transfer of a seriously ill child with stridor to a centre of anaesthetic and surgical expertise may be necessary. The Advanced Paediatric Life Support (APLS) framework teaches that the right child should be taken at the right time, by the right people, to the right place, by the right form of transport, and receive the right care throughout.[38] This is often best achieved by a specialized children's retrieval team with advanced life-support capabilities.

It may be necessary and appropriate for the airway to be secured by intubation prior to transfer. Short-term placement of an LMA may be an alternative in cases where intubation is not possible.

The systematic approach requires preparation and planning for transfer. Frequent reassessment of the child by appropriately skilled staff is vital. Continuous monitoring should also be used where possible: oxygen saturations, pulse, arterial pH and gases, temperature, blood pressure, carbon dioxide monitoring (if intubated).

Surgical management

The increasing use of intubation as an alternative to tracheostomy in acute airway obstruction has been brought about by advances in anaesthesia and paediatric intensive management coupled with the appreciation that paediatric tracheostomy, even in the short term, can be associated with significant morbidity and potential mortality. Intubation may not be possible in all cases, despite anaesthetic skill, careful planning and monitoring. Severe subglottic stenosis, impacted foreign bodies and advanced epiglottitis are key examples; rarer conditions such as laryngeal atresia with ventilation being achieved via a tracheo-oesophageal fistula also necessitate a tracheostomy.

It is this uncertainty combined with the precipitate nature of paediatric airway obstruction that makes it mandatory in most hospitals for an ENT surgeon to be informed if a child with airway obstruction of unknown aetiology is to be intubated. Depending on the circumstances, it may be necessary to have an emergency tracheostomy set open with a tube of the correct size already selected.

Once the child has been slowly induced with a volatile anaesthetic agent it is possible to inspect the larynx and exclude epiglottitis. This may be all that is required; it may be possible to manage the child using a nasopharyngeal airway (prong) and/or continuous positive airway pressure (CPAP). If intubation is required, it is important to minimize any damage to mucosa that may already be inflamed; very gentle intubation with a small tube just large enough for adequate ventilation and suction of secretions is recommended. Even if an initial intubation is oral, which tends to be easier, the tube should be replaced with a nasal tube; this may be more secure and better tolerated. The sizing of the tube can be assessed by checking for a leak and the tracheobronchial secretions suctioned. If the secretions are very tenacious or there is still an element of airway obstruction, a ventilating bronchoscope should be passed to exclude bacterial tracheitis or a foreign body.[39,40] Significant tracheobronchomalacia is another reason for continuing airway difficulty after intubation and this will usually respond to CPAP.

EMERGENCY TRACHEOSTOMY

With experienced paediatric anaesthetists, this is now very unusual. Otolaryngologists are often asked to attend a potentially difficult intubation, but are rarely needed. A ventilating bronchoscope may be easier to pass than an endotracheal tube. An endotracheal tube mounted on a Hopkins rod telescope may also be particularly useful in a difficult intubation (**Figure 28.7**). If there is any potential for an emergency tracheostomy, the surgical set and appropriate tube need to be instantly available. It is important to stay strictly in the midline so the child needs to be carefully positioned without neck or head deviation. A finger either side of the larynx is helpful with a vertical incision through the skin and down to the trachea. If a paediatric tracheostomy tube is not available, a paediatric endotracheal tube can be used, ensuring it remains above the carina. Paediatric tracheostomy is described in detail in Chapter 35, Tracheostomy and home care.

'CHAOS' AND 'EXIT'

Advances in the availability and quality of antenatal imaging has led to significant advances in the recognition and treatment planning of children with congenital high airway obstruction syndrome (CHAOS). A significant risk of airway compromise at the time of delivery with associated morbidity and mortality at birth may be avoided by an

Figure 28.7 A Hopkins rod telescope with an endotracheal tube mounted and ready to introduce in a difficult intubation.

ex utero intrapartum treatment (EXIT).[41, 42] This highly specialized technique requires expert multidisciplinary input and is a broad topic with links and overlap with foetal surgery.

In brief, the underlying principle of the technique is to 'operate on placental support'; materno-placental and placento-foetal blood and gas exchange are maintained while the neonate's airway is secured. This is achieved by delivery of the foetal head and upper torso through a hysterotomy incision. Intubation, bronchoscopy, tracheostomy and excision of the obstructing lesion may be performed as permitted and indicated. Naturally, the EXIT technique requires an antenatal diagnosis of the pathology causing CHAOS and multidisciplinary care at a centre of expertise to coordinate this elective surgery.

Parental counselling and consideration of ethical aspects, particularly in the foetus with multiple congenital abnormalities, are of fundamental importance.

BEST CLINICAL PRACTICE

- ✓ In the acute situation, assessment, history taking and active resuscitation may proceed simultaneously.
- ✓ In suspected epiglottitis, instrumentation of the oral cavity and pharynx for clinical examination must be avoided.
- ✓ All children with croup who demonstrate increased work of breathing should be treated with glucocorticoids. Nebulized adrenaline may also be given. **[Grade A]**
- ✓ Wherever possible, endotracheal intubation is preferable to emergency tracheostomy.
- ✓ If a child with airway obstruction of unknown aetiology is to be intubated, an ENT surgeon should be informed. It may be necessary to have an emergency tracheostomy set open with a tube of the correct size already selected although this is very rarely needed.
- ✓ A difficult endotracheal intubation may be facilitated by the use of a small ventilating bronchoscope or by passing a Hopkins rod telescope on which a endotracheal tube has been mounted.

FUTURE RESEARCH

- ➤ The optimal glucocorticoid dose and agent for use in inflammatory upper airway obstruction conditions such as croup is yet to be determined.
- ➤ A growing trend towards specialization within otolaryngology will ensure that airway endoscopy in children is increasingly the remit of otolaryngologists with a special interest and training in this work.

KEY POINTS

- Stridor is the noise from a narrowed airway and is a symptom, not a diagnosis.
- The aim of the history, examination and special investigations is to determine not only the site and cause of the obstruction (the diagnosis) but also its effect on the airway (the severity).
- Hypoxaemia is a late feature of airway obstruction, particularly in children treated with oxygen.
- Improvement in stridor may paradoxically be due to worsening obstruction.
- Laryngomalacia is common but it is important not to assign failure to thrive to this without first having considered and excluded other causes.
- Rapid progression of airway obstruction typically occurs in acute infection and in foreign body inhalation.
- Laryngotracheobronchoscopy is the gold standard in the assessment of the stridulous child and is a highly skilled procedure involving a team approach between anaesthetist, endoscopist and operating room personnel. Adequate facilities are not available in all institutions.

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CHAPTER 29

ACUTE LARYNGEAL INFECTIONS

Lesley Cochrane

SEARCH STRATEGY AND EVIDENCE BASE

Data in this chapter may be updated by a search of Medline using the following keywords: croup, acute laryngotracheitis, acute laryngotracheobronchitis, acute epiglottitis, diphtheria, bacterial tracheitis and child. The Controlled Trials Register of the Cochrane Library and the Cochrane Database of Systematic Reviews were also searched. The search was initially restricted to randomized controlled trials and meta-analyses and then widened, focusing on diagnosis, management and immunization.

INTRODUCTION

Laryngeal infection in childhood causes airway obstruction, of which the cardinal symptom is stridor. In the developed world, 'croup' – a clinical scenario characterized by a combination of stridor hoarseness and a typical barking cough – is the commonest (90%) cause of acute airway obstruction in children. Epiglottitis has been the next most common infective cause but is now seen much less frequently due to the widespread introduction of *Haemophilus influenzae* b (Hib) vaccine; bacterial laryngotracheobronchitis and diphtheria are less common. The differential diagnosis of acute acquired stridor includes 'spasmodic croup', retropharyngeal abscess, angioneurotic oedema, neoplasia, acute laryngeal trauma and foreign body aspiration.

In this chapter the various clinical syndromes of acute laryngeal infection are discussed and their distinctive features emphasized. For a number of these conditions several terms have evolved over the years; these are included in the headings for ease of reference but the first term, that most commonly used in the UK, is used in the text. The effects of immunization programmes on the changing patterns of disease are examined. The efficacy of medical treatment and the role of endotracheal intubation and/or tracheostomy for safe airway management in the different conditions are considered.

Good management depends on teamwork involving the primary care physician, the paediatrician, the paediatric otolaryngologist, the paediatric anaesthetist and the paediatric intensive care physician. Multidisciplinary evidence-based protocols should be established and followed to optimize outcomes.

CROUP (ACUTE LARYNGOTRACHEOBRONCHITIS, VIRAL LARYNGOTRACHEOBRONCHITIS)

Croup typically presents as a clinical syndrome of hoarseness and a distinctive barking cough progressing to inspiratory or biphasic stridor. There is usually a preceding history of upper respiratory tract symptoms, malaise and pyrexia. Children with croup do not typically drool or appear toxic, in contrast to children presenting with epiglottitis. The symptoms are thought to be due to mucosal oedema of the larynx and trachea following a viral illness. Croup is classically caused, but not limited to, infection with **parainfluenza virus type I**. Other causative

viruses include: **parainfluenza virus type II, respiratory syncytial virus (RSV) virus types A and B** and **rhinovirus.**[1] Due to improving methods of detection, an increasing variety of viruses are being implicated in the cause of croup including *Metapneumovirus, Coronavirus* and most recently *Bocavirus* in Korea with less predominance of parainfluenza type I.[2, 3] Croup usually affects children between 6 months and 3 years of age with a peak incidence in 2-year-olds.[1] Boys are more commonly affected than girls.[1, 4] There is a seasonal variation: in the USA and in Canada a minor peak in hospital admissions for croup has been noted in February and a peak in the autumn in odd numbered years, coinciding with biennial epidemics of human parainfluenza type I infection.[4, 5] In Australia, seasonal variation has also been observed.[6] Although croup is a self-limiting illness, it is a large burden on healthcare systems due to frequent visits to doctors and accident and emergency rooms. The annual incidence of croup in children younger than 6 years ranges from 1.5% to 6%.[1]

The diagnosis of croup is a clinical one and laboratory tests and radiological tests are generally not needed. In severe cases, however, if there is a diagnostic dilemma, a radiograph of the thoracic inlet will show characteristic narrowing of the subglottis on an anteroposterior view ('steeple' or 'pencil-tip' sign) (**Figure 29.1**).

There are inflammatory changes throughout the airway in croup but the critical symptom of stridor is due to oedema in the subglottis, the narrowest part of the paediatric airway. Just 1 mm of oedema in an 18-month-old child with a subglottic diameter of 6.5 mm will reduce the cross-sectional area by approximately 50%. Laminar airflow (proportional to the fourth power of the radius – 'Poiseuille's law') is thus greatly reduced. Some children are more at risk of severe symptoms than others; factors predisposing to severe symptoms include pre-existing subglottic or tracheal narrowing, chronic lung disease and airway reactivity, characterized by a history of inhalant or food allergies.[7]

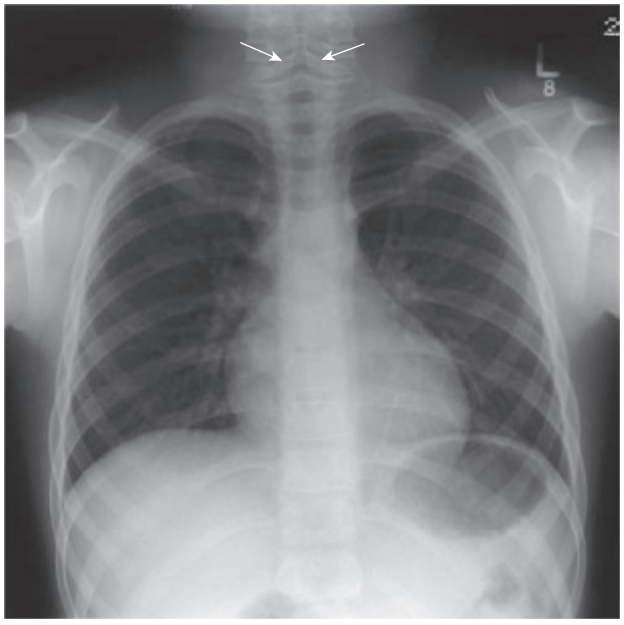

Figure 29.1 'Steeple' or 'pencil-tip' sign. Narrowing of the subglottic airway owing to mucosal oedema in croup (arrows). Image courtesy of Ben Hartley.

Croup is usually self-limiting; 50% of children improve within 24 hours of the onset of symptoms, and most recover within 4 days without treatment. Airway symptoms can become serious and life-threatening in rare cases. Mortality, however, is rare, with an estimated overall mortality of 1 in 30 000 cases in a large review.[8]

It is important to consider congenital or acquired mild subglottic stenosis in the differential diagnosis of infants presenting with 'recurrent croup'. In persistent cases endoscopy is mandatory.[9]

The management of croup consists of minimal disturbance while assessing the severity of the croup and guiding treatment accordingly. Croup severity can be classified using the Westley Croup Score (**Table 29.1**). The scoring system is based on five clinical features of croup (inspiratory stridor, retraction, air entry, cyanosis and level of consciousness). It has been clinically and radiologically validated, the total score correlating with the diameter of the tracheal lumen. A maximum score is 17, a score of 2–3 equates to mild croup, 4–7 to moderate croup and 8 or more to severe croup.[10] The scoring system is widely used in studies, although some authors report that it is less commonly used in daily clinical practice due to interobserver variance.

For mild croup, treatment can be supportive, with reassurance of both carers and child, and observation and monitoring of the child's symptoms, but without separating the child from its carer(s) as this will increase anxiety. Sedation is not advised because of the risk of respiratory depression, although chloral hydrate 30 mg/kg has been advocated if sedation seems necessary. Traditionally, it has been recommended that children with croup should be nursed in a humidified environment or mist tent; there is no evidence that this is of clinical benefit although it may be soothing.[11]

Corticosteroids

The mainstay of treatment for croup is corticosteroids. Corticosteroids have a systemic anti-inflammatory effect. There is a reduction in capillary endothelial permeability and therefore in mucosal oedema, and stabilization of lysosomal membranes, decreasing the inflammatory reaction. Topical corticosteroids theoretically have the added benefit of causing local alpha-mediated vasoconstriction. A number of studies have looked at clinical improvement after corticosteroid therapy. Clinical benefit can be measured by an improvement in croup score, reduced hospital admission rates, shorter length of stay, lower intubation rates or a reduced need for cointerventions such as the administration of epinephrine nebulizers.

In 2011, a Cochrane systematic review of the use of glucocorticoids in the treatment of croup analysed the results of 41 studies. The review concluded that, when compared to placebo, treatment with glucocorticoids resulted in a significant clinical improvement within

TABLE 29.1 Croup score based on Westley system (reprinted from Westley et al.,[10] with permission)

Score	0	1	2	3	4	5
Inspiratory stridor	None	Audible with a stethoscope	Audible without a stethoscope			
Retraction	None	Mild	Moderate	Severe		
Air entry	Normal	Decreased	Severely decreased			
Cyanosis	None				With agitation	At rest
Consciousness level	Normal					Altered

6 hours of treatment. The benefit of glucocorticoids is maintained at 12 hours post-treatment but no longer significant after 24 hours.[12] Children treated with glucocorticoids spent less time in the emergency department and were more quickly returned to care, concluding that glucocorticoid use should be not be confined to moderate or severe cases but should be extended to children with mild croup.[11, 12] The small numbers of patients in each study they analysed and the confounding variables made it difficult to make definitive recommendations regarding the superiority of any glucocorticoid, dose, or route of administration.[12] In the absence of further evidence, an oral dose of dexamethasone (0.6 mg/kg) is preferred because of its safety and efficacy. In a child who is vomiting, nebulized budesonide (2 mg) may be considered. Although also efficacious,[8] intramuscular dexamethasone (0.6 mg/kg) cannot be advocated as a first-line treatment given the potential for muscle necrosis with that route of administration. The use of glucocorticoids in primary care in the early management of croup symptoms has transformed the management of this disorder; affected children now rarely require active intervention to support the airway.

Nebulized epinephrine

Nebulized epinephrine (1 mL of 1 in 1000 epinephrine diluted in 3 mL of 0.9% saline) has an established role in the acute paediatric airway in reducing mucosal oedema by an alpha-agonist effect causing vasoconstriction and bronchodilation; a maximum effect is achieved within 30–60 minutes but there is no lasting benefit beyond 2 hours.

The administration of epinephrine does not alter the natural history of the disease but it may postpone or eliminate the need for an artificial airway, or give symptomatic relief until effective treatment can be given.[13] It can be administered at the same time as glucocorticoids.[10, 13] In a recent systematic review evidence did not favour racemic epinephrine versus L-epinephrine or epinephrine delivered by intermittent positive pressure breathing (IPPB) over simple nebulization.[13]

Heliox®

Heliox® is a mixture of helium and oxygen generally supplied with a helium:oxygen ratio of 70:30 or 79:21. Helium is less dense than air or oxygen and is more viscous. Owing to these properties, heliox® is more likely to produce laminar and more efficient flow in the presence of a partially obstructed airway than air or oxygen. Inhaled heliox® delivered through a high-flow system should reduce the work of breathing and result in larger tidal volumes and improved gas exchange. Helium has a high thermal conductivity and so care is needed with humidification in order to avoid hypothermia.[14]

Heliox® has long been used in the management of respiratory conditions and in airway obstruction including croup. There have, however, been few trials examining the benefit of heliox® in the management of children with croup. A recent Cochrane systematic review of the use of heliox® in croup concluded that there was some evidence to suggest a short-term benefit of heliox® in children with moderate to severe croup who have been administered dexamethasone.[15] However, adequately powered randomized controls trials comparing heliox® with standard treatments are required to further assess the role of heliox® in children with moderate to severe croup.

BACTERIAL LARYNGOTRACHEOBRONCHITIS (PSEUDOMEMBRANOUS CROUP, BACTERIAL TRACHEITIS, MEMBRANOUS LARYNGOTRACHEOBRONCHITIS, NEONATAL NECROTIZING TRACHEOBRONCHITIS)

Bacterial tracheitis is a rare but potentially life-threatening cause of upper airway obstruction in children. It is a severe form of laryngotracheobronchitis characterized by the presence of profuse mucopurulent secretions with sloughing of the respiratory epithelium. Secretions are often adherent, are not effectively cleared by coughing and may occlude the airway causing respiratory compromise.[16] Bacterial tracheitis must be differentiated from croup and other causes of infectious upper airway obstruction in order to initiate proper management.

Classically the child with bacterial tracheitis appears toxic with high fevers and worsening stridor that fails to respond to treatment with steroids and nebulized epinephrine. It typically affects children older (mean age 4–8 years) than the usual age group for croup.[17] Like croup, however, it is more common in boys than girls, and there is no single

factor, clinical, radiological or laboratory-based, which reliably distinguishes it from croup.[18] A high level of suspicion is therefore required for early diagnosis. Bacterial tracheitis is a much less common condition than croup.[17] However, there is increased susceptibility in children with Down syndrome or immunodeficiency.[18, 19]

Diagnosis can only be confirmed on airway endoscopy; there is a pseudomembrane in the subglottis and trachea and thick mucopus and debris extending into the bronchi (**Figure 29.2**). Direct laryngotracheobronchoscopy under general anaesthesia and removal of all tracheal secretions, with pulmonary toilet, is mandatory. It is then often necessary to secure the airway by endotracheal intubation for a period of days.[16, 17] The distal airway and the tube itself remain at continued risk of obstruction by secretions, and vigilant expert nursing care is essential. Repeated endoscopic procedures are almost invariably required.

Once the diagnosis is established, broad-spectrum parenteral antibiotics should be commenced immediately. They can later be adjusted in line with the results of microbiological studies. *Staphylococcus aureus* is the pathogen most commonly isolated from tracheal cultures although *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* have also been reported.[16–18] Viral cultures are also frequently positive, indicative that many cases of bacterial tracheitis represent a secondary bacterial infection that follows a viral respiratory tract infection. Most commonly influenza A is identified, although other viruses including the H1N1 strain of influenza A and metapneumovirus have also been isolated.[2, 16, 17, 20]

Complications of this dangerous condition include airway stenosis, acute respiratory distress syndrome, respiratory failure, toxic shock syndrome, anoxic encephalopathy and death.[17]

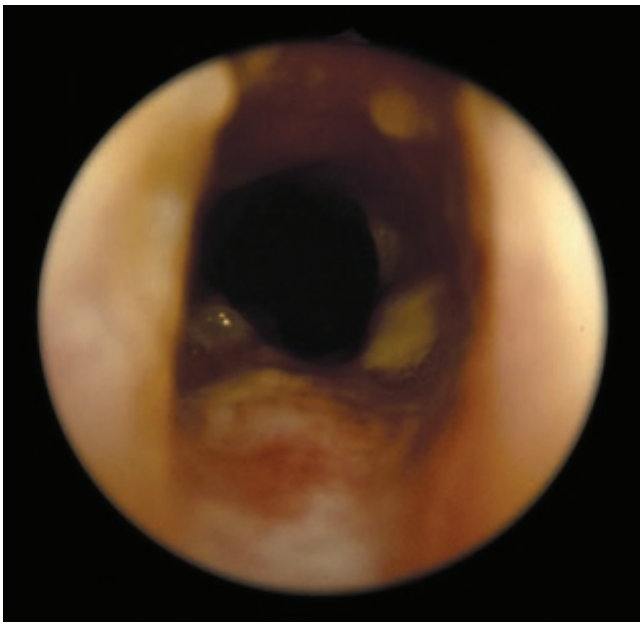

Figure 29.2 Tracheal pseudomembrane in bacterial laryngotracheobronchitis. Image courtesy of Ben Hartley.

Ventilated newborns with an unstable haemodynamic state are at risk of potentially fatal desloughing of the tracheobronchial mucosa. This may be characterized by repeated episodes of acute airway obstruction. Management involves repeated therapeutic tracheobronchoscopy to free the airways.[21]

Recent literature has raised awareness of a less severe clinical presentation which tends to elude diagnosis. There are several reported series of children presenting with a less severe form of bacterial tracheitis who have been effectively managed with antibiotics and endoscopic debridement without the need for endotracheal intubation. The term 'exudative tracheitis' has been proposed as an alternative nomenclature for those with a less severe form and are less systemically ill.[16]

DIPHTHERIA

Diphtheria is rare in countries which have a routine childhood immunization programme, but it continues to present a significant public health problem in the developing world. Diphtheria remains an important differential in the diagnosis of acute laryngeal infection in children, particularly in those who have travelled to endemic areas or have not been vaccinated. Every year there are several reported cases of diphtheria in the UK, primarily in patients who have recently travelled from endemic countries. In 2012, there was a case of fatal diphtheria in a non-immunized child in the UK.[22]

The causative organisms in pathogenic diphtheria are the toxogenic strains of *Corynebacterium diphtheria* and *Corynebacterium ulcerans*. The early clinical picture of upper respiratory tract symptoms is due to the effects of the organism itself. Delayed effects are due to the release of exotoxin.

Symptoms of diphtheria come on gradually and typically begin 2–5 days after exposure. Initial symptoms are of pharyngitis with sore throat and malaise. The child is feverish and on examination there is a typical appearance of the pharyngeal tonsils with necrosis and the development of a characteristic grey pseudomembrane over the surface. This consists of necrotic tissue, bacteria and a rich fibrinous exudate. Early removal causes bleeding but the pseudomembrane may separate more easily later in the course of the disease. There may be a bull-neck appearance due to cellulitis and regional lymphadenopathy.

Diphtheria infection may also involve the larynx. After initial symptoms of dysphagia and toxaemia, symptoms may progress to inspiratory stridor and a barking cough; the cough is frequently paroxysmal and exhausting. Death may follow owing to acute airway obstruction or as a result of the later effects of the exotoxin.[22]

The exotoxin can cause a toxic myocarditis in the second week of the disease and this may be fatal. Peripheral neuritis may also occur, palatal paralysis being the most common effect of peripheral neuropathy and presenting with nasal regurgitation of food and hypernasal speech.

Successful treatment depends on early diagnosis, and the timely administration of high-dose benzylpenicillin and antitoxin (10 000–100 000 units, depending on the severity of infection). Delaying the administration of the antitoxin is associated with increased mortality as the antitoxin does not neutralize toxin that is already bound to tissues. The decision, therefore, to administer antitoxin should be made based on clinical suspicion and should not await microbiological confirmation. Airway management consists of removal of the laryngeal membrane, administration of oxygen and humidification, and endotracheal intubation or tracheostomy if necessary. Systemic steroids may reduce the need for airway intervention.[23] Bed rest is recommended until the danger of myocarditis is past.

ACUTE EPIGLOTTITIS (SUPRAGLOTTITIS)

The classical presentation of acute epiglottitis is well described. It is of a toxic child with a short history of sore throat, inspiratory stridor, muffled voice and drooling due to odynophagia and dysphagia. Left untreated there is progressive respiratory distress. The child is febrile, tachypnoeic and classically will be sitting upright, with the neck extended to optimize the airway, and using the arms to provide support to the shoulder girdle to maximize the efficiency of the accessory muscles of respiration. It is commonest between the ages of 2 and 8 and there is an increased prevalence in winter.[24]

When acute epiglottitis is suspected, pharyngeal examination should not be attempted, as simple manipulation with a tongue depressor may precipitate acute airway obstruction, although the use of a fibreoptic or small rigid endoscope can assist the diagnosis in patients with an atypical presentation.[25] Direct examination of the airway should not be delayed, but should be undertaken in a controlled setting such as an operating room or paediatric intensive care unit by personnel skilled in airway intervention; endoscopic evaluation will confirm gross erythema and oedema of the supraglottic structures (**Figure 29.3**).

When the diagnosis is confirmed, the airway should be secured by endotracheal intubation. If this is unsuccessful, a rigid bronchoscope may be passed to allow tracheostomy. Endotracheal intubation is usually required for safe airway management.[26] Despite this, mortality remains as high as 3%.[27]

Investigations prior to securing the airway are contraindicated, but a soft-tissue lateral radiograph of the neck will typically show a thickened oedematous epiglottis – the 'thumb sign' (**Figure 29.4**). The causative organism can be identified from nasopharyngeal swabs, laryngeal swabs, sputum samples or blood cultures taken after intubation. Traditionally, acute epiglottitis has been a manifestation of invasive Hib infection. This can be confirmed as the cause in partially treated patients by Hib antigen detection in concentrated urine specimens. In the post-vaccination era, epiglottitis is more likely to be caused by 'vaccination breakthough' Hib infection or

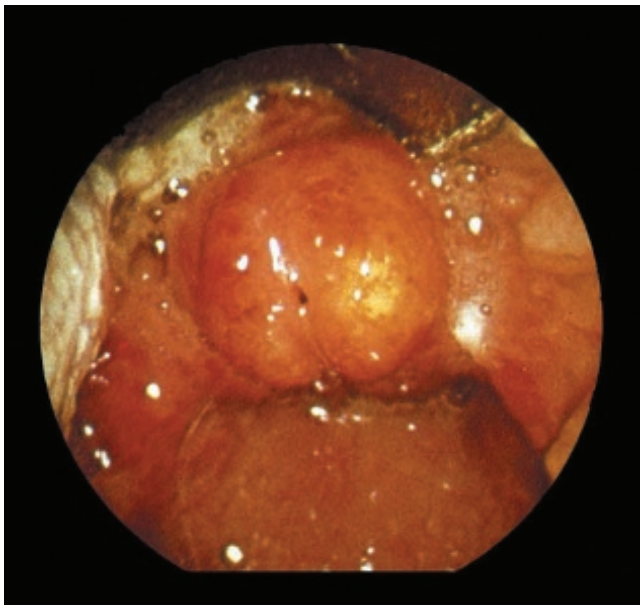

Figure 29.3 Acute epiglottitis. Endoscopic appearance. Reproduced by permission of Bruce Benjamin.

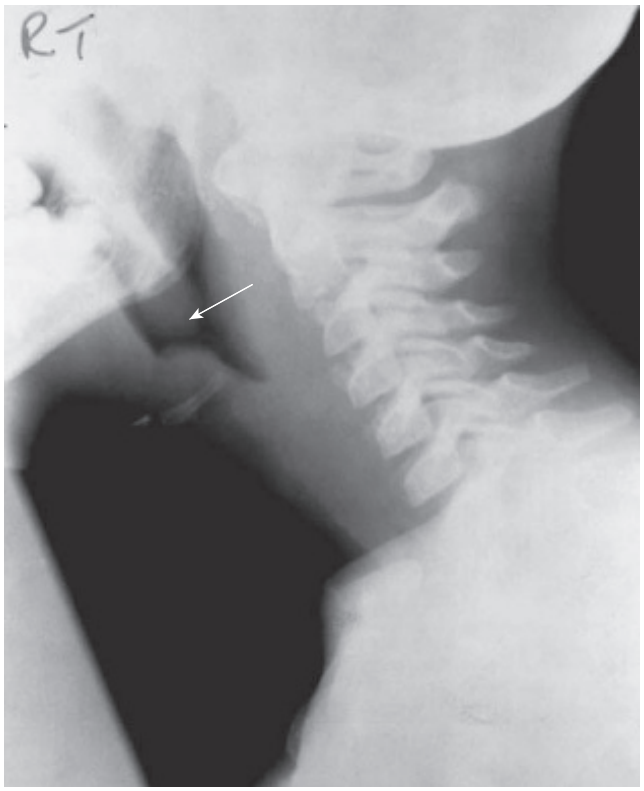

Figure 29.4 Acute epiglottitis. Radiological appearance of the oedematous epiglottis (arrowed).

by another pathogen, including meningococci, group A streptococci, pneumococci, *Haemophilus parainfluenzae* and *Staphylococcus aureus*.[14] Immunocompromised individuals are at increased risk of epiglottitis. It may then be due to atypical organisms such as *Herpes simplex* type 1, *Varicella zoster*, *Parainfluenza* or *Candida albicans*.[14] Children with acute epiglottitis should be screened after

recovery from the acute episode to ensure there is no underlying predisposing condition.

Treatment is with intravenous antibiotics; ampicillin resistance due to beta-lactamase production is now over 50% in *Haemophilus influenzae*, so empirical treatment with third-generation cephalosporins for 5–7 days is advised. Chloramphenicol and clindamycin are alternatives in the event of allergy to cephalosporins. Penicillin-sensitive streptococci are the usual cause of acute epiglottitis in children who have been immunized against Hib and they should be treated accordingly. Recovery is characterized by resolution of systemic symptoms and the supraglottic inflammation. The child can then be extubated and discharged from hospital. Since the introduction of Hib immunization, rifampicin prophylaxis has been recommended to eradicate the carrier state for the index case as well as household and school contacts.[28]

Despite the declining incidence of this disease and the changing bacteriology, there has been no change in its clinical presentation over time. It is critically important that reduced clinical experience is not accompanied by a sharp rise in mortality for affected children.

Haemophilus influenzae type b immunization

In addition to acute epiglottitis, other manifestations of invasive *Haemophilus influenzae* infection include meningitis, septic arthritis, septicaemia, pneumonia and osteomyelitis. Serious infections are usually caused by the capsulated forms, serotypes a to f. However, type b was responsible for more than 85% of invasive *Haemophilus influenzae* infection prior to immunization.[15] It has been estimated that, prior to the introduction of immunization, Hib meningitis accounted for 50% of Hib infections, epiglottitis being the next most common presentation.[28]

Routine infant immunization with conjugate Hib vaccine in the UK began in October 1992. Immunization is achieved by three primary doses followed by a late booster. The incidence of invasive Hib infections in children under 5 has fallen dramatically from an incidence of 35.5/100 000 for the year preceding vaccine implementation to 0.06/100 000 in 2012.[29] A reduction in the incidence of acute epiglottitis of approximately 90% has been documented in countries in which an immunization programme has been established. In the UK there was a resurgence of cases in 2003 with over 230 cases of Hib infection, causing a booster programme to be launched.[30] Vaccine failure does occur but in fewer than 10% of cases is there an identifiable clinical risk factor predisposing to infection. An increasing number of cases may be due to infection with an organism other than *Haemophilus* and continued vigilance among clinicians is required.[27] There is evidence that a longer duration of breastfeeding (more than 13 weeks) is associated with a significantly enhanced antibody response to Hib in children aged between 18 months and 6 years.[31]

In the Hib vaccine era, non-type b invasive *Haemophilus influenzae* disease has become more common than type b. It is likely to occur in younger children than is the norm for type b infection, but it is less likely to be meningitis or epiglottitis and more likely to be pneumonia or bacteraemia.[27, 32]

AIRWAY MANAGEMENT

For the child presenting with acute airway obstruction due to laryngeal infection, active intervention to secure the airway may be necessary if symptoms are severe. The options to provide an artificial airway include endotracheal intubation and tracheostomy. Prior to 1975 tracheostomy was the standard intervention, then endotracheal intubation was shown to be a safe alternative for acute epiglottitis and subsequently for croup. Endotracheal intubation is now considered preferable to tracheostomy if circumstances permit. However, the choice of intervention may be influenced by the availability of medical and nursing expertise and local hospital services. The intubated child will require specialized intensive care facilities for management whereas the child with a tracheostomy, while still requiring nursing expertise for optimal management, can be nursed on a normal paediatric ward.

A team approach to management is essential for optimal outcome. The paediatrician, paediatric anaesthetist, paediatric intensivist and paediatric otolaryngologist must collaborate to develop multidisciplinary evidence-based protocols which take into account the availability of local services. Immunization programmes and advances in medical management are changing patterns of disease and have resulted in a decline in the prevalence of acute airway obstruction due to acute epiglottitis, croup and diphtheria; clinicians with little experience of children with these conditions will depend on protocols for safe practice. If endotracheal intubation is to be undertaken, it should be performed in an operating room or paediatric intensive care unit with personnel and equipment available and ready to undertake tracheostomy if the airway cannot be secured.

Once an artificial airway is in place, humidified air should be administered to discourage the development of tenacious secretions. The tube should be aspirated regularly, using suction, to prevent tube obstruction. Nursing vigilance to prevent accidental displacement or self-extubation is essential. In ideal conditions, mortality rates can be as low as 1% for either intervention.[33]

Nasotracheal intubation

Endotracheal intubation for airway obstruction due to acute laryngeal infection is now widely practised with great expertise. When a prolonged period of intubation is anticipated, the nasotracheal rather than the orotracheal route is preferred; nasotracheal intubation is better tolerated so the child requires less sedation, the tube can be secured more reliably and nursing care is easier.

The tube is positioned with the patient anaesthetized and the child is then nursed under sedation, fed via a nasogastric tube. The cough and voice are absent during the period of intubation but after extubation there are normally no sequelae. Complications can occur, however, and include epistaxis at the time of intubation, the development of sinus sepsis during the period of intubation and hoarseness after extubation. The risk of acquired subglottic stenosis is small but is associated with younger age of the child, larger tube size, serial intubation and longer duration of intubation. It is more common in Down syndrome in which there may be an element of congenital subglottic stenosis as a predisposing factor. A tube one size smaller than that usually considered age-appropriate should be used.[34]

Extubation can be considered when the child is systemically well, with minimal tracheal secretions. The 'leak test' (air escape around the nasotracheal tube on application of positive pressure ventilation) is helpful but not an absolute prognostic indicator for successful extubation. In acute epiglottitis, visualization of the epiglottis with a flexible nasendoscope can be useful in monitoring resolution of inflammation. Likewise in laryngotracheobronchitis, whether viral or bacterial, the airway can be monitored using endoscopy until a reduction in tracheal inflammation shows that it is safe to extubate. Systemic steroids administered 6 hours prior to removal of the tube will minimize post-intubation oedema, and nebulized epinephrine can assist with airway patency after extubation.

For acute epiglottitis the period of intubation is usually less than 48 hours but for croup and bacterial laryngotracheobronchitis it may be up to a week.[17] If extubation fails after the acute laryngeal infection has resolved, and despite all the above measures being taken, this may be due to a pre-existing or developing subglottic stenosis. This, if acute and due to mucosal oedema and ulceration, may be successfully treated by a cricoid split (see Vol 3, Chapter 76, Laryngeal stenosis). If not, however, tracheostomy may become necessary and possibly later laryngotracheal reconstruction.

Tracheostomy

Tracheostomy is no longer considered the first choice to secure the airway in acute laryngeal infection. It may be chosen, however, if the availability of nursing expertise and intensive care facilities is limited such that nasotracheal intubation is contraindicated. It may also be necessary if there is severe acute subglottic narrowing precluding the passage of a nasotracheal tube of adequate size for ventilation, or if there has been significant intubation trauma. Equipment and personnel to perform an emergency tracheostomy should always be available in case attempted intubation fails.

Improvements in medical treatments in recent years have seen publications regarding tracheostomy in the management of acute laryngeal infections dwindle from case series to the occasional case report. The largest most recent published series of data on paediatric tracheostomy for croup is from the Red Cross War Memorial Children's Hospital in Cape Town. In that series, 75% of children were decannulated within 10 weeks of formation of the tracheostomy but 54% of children required one or more further procedures after tracheostomy to deal with granulation tissue, supraglottic collapse or subglottic stenosis prior to successful decannulation.[35] Clearly, nasotracheal intubation is preferable if it is possible and practical, depending on local circumstances.

BEST CLINICAL PRACTICE

- ✓ Pharyngeal examination is contraindicated if acute epiglottitis is suspected; it may precipitate acute airway obstruction.
- ✓ Children with croup, whether presenting with mild, moderate or severe symptoms, should be treated with oral dexamethasone at the time of diagnosis. [Grade A]
- ✓ Bacterial tracheitis should be considered in children presenting with croup who fail to respond to treatment with steroids and adrenaline.
- ✓ Nebulized epinephrine (1 mL of 1 in 1000 epinephrine diluted in 3 mL of 0.9% saline) has an established role in the acute paediatric airway. [Grade A]
- ✓ Subglottic stenosis should be remembered in the differential diagnosis of infants presenting with 'recurrent croup'. Consider endoscopy.
- ✓ Equipment and personnel to perform tracheostomy should be immediately available in case attempted intubation is unsuccessful.

FUTURE RESEARCH

- ➤ As Hib vaccination programmes are extended, the incidence of acute epiglottitis should fall even further.
- ➤ Further research is required to determine the optimum dose and route of corticosteroid administration in the treatment of croup.
- ➤ Further studies are required to assess the role of heliox® in the management of children with croup.

KEY POINTS

- The laryngeal airway in children is narrow, especially in the cricoid region. The mucosa is lax and a comparatively minor swelling may cause significant airway compromise.
- Immunization programmes and improvements in medical management have reduced the prevalence of acute laryngeal infection and its severity.
- Systemic steroids have transformed the primary care management of croup. Fewer cases now need hospital admission but vigilance is still required.
- Multidisciplinary evidence-based protocols influenced by the availability of local expertise and services should be formulated and followed to optimize outcomes.
- In acute laryngeal infections, nasotracheal intubation is preferable to tracheotomy if it is possible and practical, depending on local circumstances.

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CHAPTER 30

CONGENITAL DISORDERS OF THE LARYNX, TRACHEA AND BRONCHI

Chris Jephson

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the following keywords: congenital, anomalies, larynx, trachea and bronchi and focusing on diagnosis and treatment.

INTRODUCTION

The exact incidence of congenital abnormalities of the airway is uncertain, but a figure has been quoted for congenital laryngeal anomalies of between 1:10 000 and 1:50 000 births.[1] Some of these children will have more than one anomaly in the airway.[2]

LARYNX

The larynx is divided into three regions: supraglottis, glottis and subglottis. The supraglottic larynx comprises the epiglottis, aryepiglottic folds, false cords and ventricles. The glottis consists of the vocal cords (also referred to as vocal folds). In children, the subglottis extends from the under surface of the vocal cords to the inferior border of the cricoid cartilage.

Supraglottis

Laryngomalacia

Laryngomalacia is characterized by partial or complete collapse of the supraglottic structures on inspiration and is the most common congenital cause of stridor.[3] The pathophysiology is thought to be related to the characteristic anatomical abnormalities that are observed: the epiglottis is long and curled (omega-shaped); the aryepiglottic folds are short and tightly tethered to the epiglottis; there may also be redundant mucosa and submucosa of the aryepiglottic folds medially. The result is a tall, narrow supraglottis with a deep interarytenoid cleft where the epiglottis is soft and may curl and collapse and the mucosa may prolapse into the airway (Figure 30.1). It has been suggested that there may also be an element of neuromuscular immaturity and consequent incoordination of arytenoid movements.

The rather characteristic high-pitched, fluttering inspiratory stridor is usually present at, or shortly after, birth. It is very variable, typically being most noticeable when the infant is active or upset, and may disappear when the child is asleep. The severity of the stridor tends to increase as the child becomes more active during the first 9 months of life, and then gradually diminishes until by the age of 2 years it has generally disappeared. Very rarely, stridor may persist into late childhood.

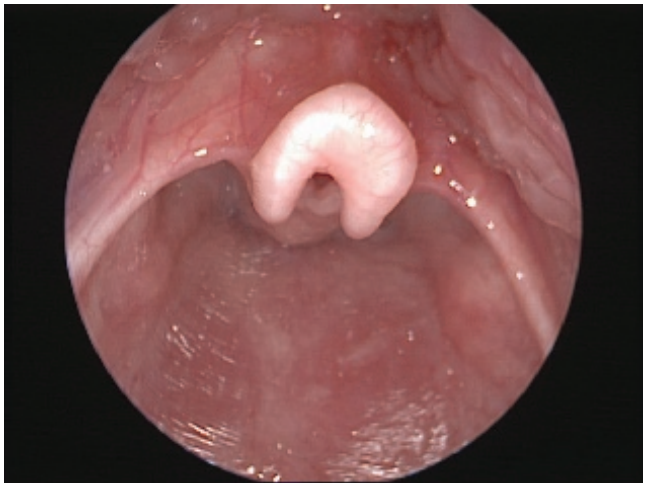

Figure 30.1 Laryngomalacia.

The diagnosis can be confirmed in the outpatient setting by flexible fibre-optic laryngoscopy. Nasendoscopy is usually possible in children up to the age of 1 year. The child should be wrapped in a blanket and held firmly by a nurse or parent. The supraglottic collapse on inspiration, which is typical of laryngomalacia, is easily seen. In approximately 90% of reported cases the condition is mild, no intervention is needed and the parents can be reassured accordingly.[4] In these cases a period of observation should be undertaken with documented regular weights to demonstrate no failure to thrive. A 4-week course of antireflux medication can be prescribed for those children with regurgitation and gastro-oesophageal reflux disease (GORD).

In severe laryngomalacia, however, there is serious respiratory obstruction with substantial sternal and intercostal recession together with feeding difficulties which may be compounded by reflux enhanced by the high negative intrathoracic pressures generated, and consequent failure to thrive. Matters are made worse if there are other factors increasing the level of cardiorespiratory embarrassment, such as congenital cyanotic heart disease. In the most severe cases, cor pulmonale may ensue and in cases of severe sternal recession a permanent pectus excavatum may develop. Therefore, in children where the stridor is severe, if there is failure to thrive or there are any atypical features (e.g. history of previous intubation, cutaneous haemangioma) that may raise the suspicion of a second, coexisting airway pathology, a microlaryngoscopy and bronchoscopy (MLB) under general anaesthesia is indicated. Optimum conditions for diagnosis require the child to be breathing spontaneously under a very light level of anaesthesia, with the beak of the laryngoscope in the vallecula; the supraglottic collapse is not seen under deep anaesthesia and will be prevented if the tip of the laryngoscope is introduced into the laryngeal vestibule.

Children who show signs of failure to thrive should undergo an endoscopic aryepiglottoplasty (sometimes termed a supraglottoplasty).[5] In this procedure, the larynx is visualized using a laryngoscope in suspension, with its beak positioned in the vallecula. Using cup forceps and microscissors, each aryepiglottic fold is first divided to release it from the edge of the epiglottis, and any redundant mucosa and submucosal tissue are then excised from over the arytenoids, together, if necessary, with part or all of the cuneiform cartilages. In less severe cases it may only be necessary to incise the tight aryepiglottic fold.[6] The 'bridge' of mucosa between the arytenoids is carefully preserved to prevent interarytenoid scarring. Bleeding is minimal and is easily stopped by the application of neurosurgical patties dipped in topical adrenaline (1:10 000). Neither antibiotics nor steroids are routinely given, complications are very rare, and the stridor is usually improved immediately following the surgery. In cases where the stridor and feeding difficulties persist, an underlying hypotonic neurological disorder is likely.[7]

Saccular cysts and laryngocoeles

Laryngeal cysts are rare, can be congenital or acquired and may present with respiratory obstruction in infants and young children (**Figure 30.2a**). They are divided into laryngocoeles and saccular cysts. The ventricle is the fossa bounded by the false vocal fold and the vocal cord. The anterior portion of the ventricle leads superiorly to the saccule. A laryngocoele is an air-filled dilatation of the laryngeal ventricle which communicates with the laryngeal lumen. It is an uncommon lesion which usually occurs in middle age but may rarely be seen in infancy, when it can produce respiratory distress which typically becomes worse on crying due to increased distension of the laryngocoele with air. However, a laryngocoele may obstruct and fill with mucus or become infected (laryngopyocoele), thus becoming indistinguishable from a saccular cyst.

A saccular cyst also represents an abnormal dilatation or herniation of the saccule of the ventricle of the larynx; however, it differs from a laryngocoele in that there is no opening into the larynx and it is filled with mucus instead of air. It is considered to form as the result of a developmental failure to maintain patency of the orifice between the saccule and the ventricle, and may be of anterior or lateral type. The anterior saccular cyst extends medially

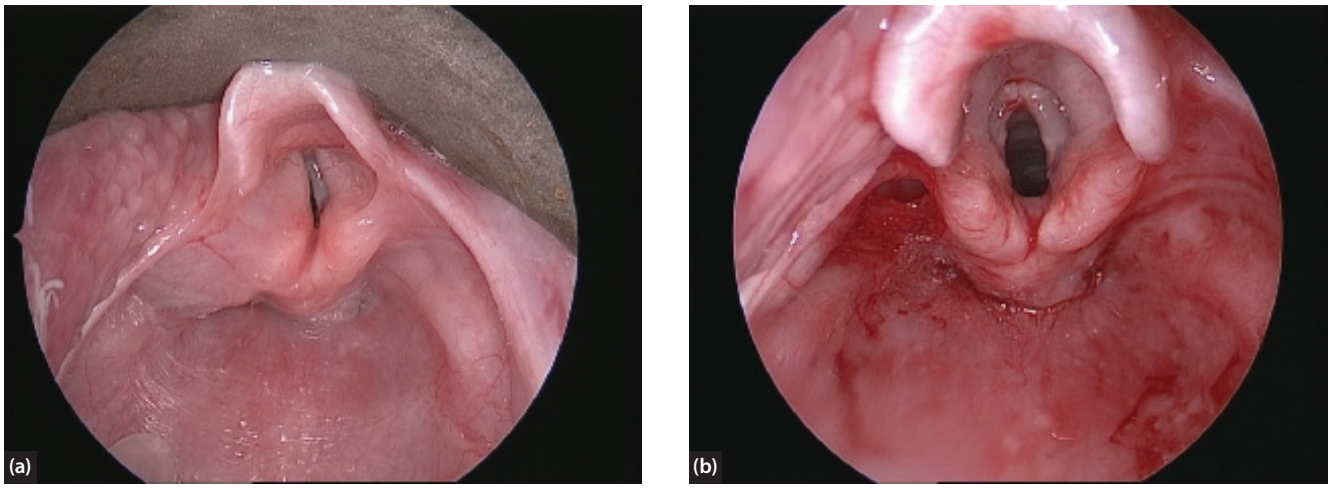

Figure 30.2 Left saccular cyst, showing **(a)** obstruction of the laryngeal inlet, and **(b)** post marsupialization.

and posteriorly from the saccule and so protrudes into the laryngeal airway between the true and false vocal cords. The lateral saccular cyst is most common in infants and expands posterosuperiorly into the false cord and aryepiglottic fold.[8]

Laryngeal cysts are classified as internal or type 1 if contained entirely within the laryngeal framework, and external or type 2 if it pierces the thyrohyoid membrane.[9] Diagnosis is confirmed by endoscopy, except in an external laryngocoele where no abnormality may be seen except on imaging. Saccular cysts are best treated at the initial endoscopy by wide endoscopic marsupialization (**Figure 30.2b**). If the cyst recurs, then the procedure of choice is a lateral cervical approach extending through the thyrohyoid membrane at the superior margin of the ala of the thyroid cartilage, with subperichondrial resection of a portion of the upper part of the ala. Through this 'window' the cyst can be completely excised, using short-term intubation to secure the airway post-operatively.

Vascular malformations

Vascular malformations include lymphatic malformations, venous malformations and arteriovenous malformations and are discussed in detail in other chapters. Vascular malformations are rare in the larynx, trachea and bronchi. Lymphatic malformations (also termed lymphagiomas or cystic hygromas) are cystic malformations that result from abnormal development of the lymphatic vessels. In the head and neck they may be macrocystic (usually infrahyoid), microcystic (usually suprahyoid) or a combination of the two. Occasionally, a microcystic lymphatic malformation may extend into the tongue base, valleculae and supraglottis, and airway obstruction may result. If the lymphatic malformation is very extensive, a tracheostomy may be required, but where supraglottic involvement is less severe it may be possible to debulk the lesion by endoscopic vaporization using a CO_2 laser or radiofrequency ablation.[10, 11]

Bifid epiglottis

Bifid epiglottis is a rare laryngeal anomaly in which the epiglottis fails to fuse in the midline and thus has a cleft extending down to its tubercle. It may be seen as a feature of Pallister–Hall syndrome, the cardinal elements of which are hypothalamic hamartoblastoma, hypopituitarism, imperforate anus and postaxial polydactyly. It usually presents with feeding difficulties due to aspiration and with stridor because of collapse and enfolding of the two halves of the epiglottis. Endoscopy establishes the diagnosis, and treatment options include amputation of the epiglottis and tracheostomy.

Glottis

Laryngeal webs

Failure of complete canalization of the larynx during embryogenesis may result in a glottic or, very rarely, a supraglottic web. The majority involve the anterior glottis, fusing

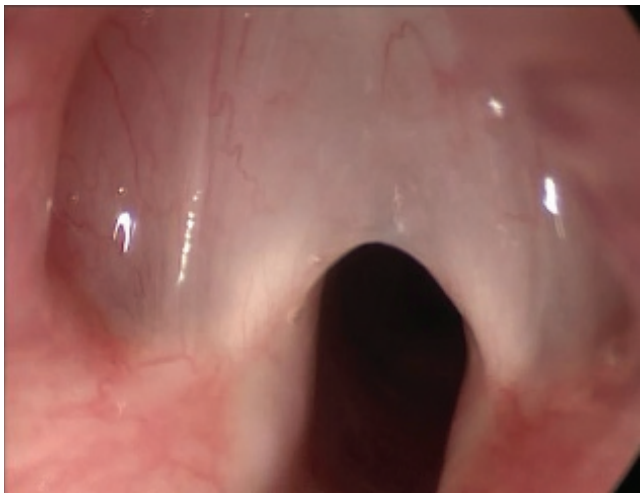

Figure 30.3 Anterior glottic web.

the vocal cords along a variable part of their length, and producing a correspondingly variable degree of respiratory obstruction and dysphonia (**Figure 30.3**). Characteristically there is inspiratory stridor and a rather weak, high-pitched, squeaky voice. The combination of a weak cry from birth and recurrent croup in infancy should always raise suspicion of a laryngeal web. Anterior laryngeal web can also be associated with 22q11 deletions, other chromosomal anomalies and cardiac abnormalities.[12] Occasionally, a congenital posterior, interarytenoid web occurs and may be associated with cricoarytenoid joint fixation.

Almost all anterior glottic webs are fairly thin posteriorly, close to their free border, but become progressively thicker anteriorly with increasing subglottic extension. Where the web is small and causing little in the way of symptoms it is usually best to treat conservatively. A longer isolated web with little or no subglottic involvement may be divided endoscopically along the margin of one vocal cord with a knife or CO_2 laser; if it is very thin, subsequent endoscopic dilatation may be sufficient to permit stable healing without the web reforming. However, most glottic webs are quite thick anteriorly and extend to varying degrees into the subglottis. A keel placed endoscopically following division can prevent recurrence. In the young child with a small larynx a covering tracheostomy is necessary for the 2 weeks that the keel is in place. In cases where the airway is very small and there is associated subglottic stenosis a laryngotracheal reconstruction (LTR) with anterior cartilage grafting is required. This can be carried out in the infant as a single-stage procedure with post-operative endotracheal intubation to stent the larynx for 5–7 days. However, in practice, most infants with a severe glottic web will have a tracheostomy performed in which case the LTR can be deferred to the age of about 1–2 years, when the larynx is larger and the vocal cord dissection can be undertaken more precisely.

Laryngeal atresia

Laryngeal atresia is incompatible with life unless there is an associated tracheo-oesophageal fistula (TOF) which

permits ventilation via a tube in the oesophagus, or unless an emergency tracheostomy is performed in the delivery room. However, there are now cases being recognized antenatally on ultrasound imaging and managed with an *ex utero* intrapartum treatment (EXIT) procedure, whereby a tracheostomy is undertaken following elective Caesarean section with the neonate still on placental circulation.[13]

Cri-du-chat syndrome

This syndrome is primarily characterized by a cat-like mewing cry in infancy, microcephaly, downward-slanting palpebral fissures, mental retardation and hypotonia. It is caused by chromosome 5p deletion. At endoscopy, observation during phonation reveals that the posterior part of the glottis remains open, giving it a diamond-shaped appearance.[14] There is no respiratory embarrassment and the cry becomes less abnormal as the child grows older.

Vocal cord paralysis

Vocal cord paralysis is the second most common congenital anomaly of the larynx after laryngomalacia. Up to 45% of patients may have other, coexisting airway pathology and so, although outpatient flexible fibre-optic laryngoscopy may indicate the diagnosis, a formal MLB under general anaesthesia is essential. Laryngeal ultrasound can be an accurate and reproducible method of assessing vocal cord movement, and it may be useful in monitoring a child with known vocal cord palsy and in the diagnosis of the very sick child who may be unfit for endoscopy under general anaesthesia.[15] Approximately half of cases are unilateral and half bilateral.

Unilateral vocal cord paralysis is usually not congenital, most cases being acquired as a result of surgical injury to the left recurrent laryngeal nerve, often following correction of a congenital cardiac anomaly. Patients present with mild stridor, dysphonia and sometimes aspiration. If the vocal cord lies in an intermediate position, surgical intervention is not usually necessary, and the voice can be expected to improve as time passes and either recovery occurs or the other vocal cord compensates. If the vocal cord lies in a more abducted position, the dysphonia may be more pronounced and aspiration more likely. Vocal cord medialization procedures such as thyroplasty and augmentation injection can improve the dysphonia and aspiration, but these may result in worsening of the stridor.

In contrast, bilateral vocal cord palsy is usually a congenital abductor paralysis. The vocal cords lie in the paramedian position with consequent inspiratory stridor, and a tracheostomy is necessary in approximately half of cases, most of which have other associated airway pathology. A classical cause of congenital bilateral vocal cord palsy is hydrocephalus with the Arnold-Chiari malformation. Once the diagnosis is made, prompt correction of the raised intracranial pressure with a shunt often improves vocal cord movement and a tracheostomy may thus be avoided. However, most cases of congenital bilateral vocal cord paralysis are idiopathic and the approach to management is greatly influenced by the fact that up to 58% will eventually recover, with 10% taking more than 5 years to do so and one reported case of recovery at the age of 11 years.[16] This strongly suggests that the problem is often one of delayed maturation in the vagal nuclei and argues convincingly in favour of a conservative management philosophy. Furthermore, where the airway is marginal, it may become adequate with laryngeal growth alone, and glottic enlargement surgery in order to avoid a tracheostomy or achieve decannulation may improve the airway at the expense of the voice.

The infant with an inadequate airway and failure to thrive will require a tracheostomy. If vocal cord movement does not develop and the airway does not become adequate as a result of laryngeal growth, then an endoscopic laser cordotomy or arytenoidectomy should be considered at the age of 11 or over, following a full discussion with the child and parents regarding the possible trade-off between airway and voice. If it is considered imperative to achieve decannulation earlier, perhaps because of poor social circumstances, an endoscopic laser cordotomy can be attempted as early as 2 years of age. If that fails, an external arytenoidectomy via a laryngofissure may be carried out at the age of 4–5 years with the prospect of an 84% decannulation rate;[17] however, there is a small risk of aspiration as well as loss of voice quality and the procedure is irreversible.

Subglottis

Congenital subglottic stenosis

Congenital subglottic stenosis is due to defective canalization of the cricoid cartilage and/or conus elasticus, resulting in either gross thickening of the anterior lamina of the abnormal cricoid (**Figure 30.4**)[18] or a small, elliptical, thickened cricoid with excessive submucosal soft tissue (**Figure 30.5**).[19] Alternatively, there may be anterior fusion of the vocal cords, forming a web with subglottic extension, as seen in 22q11 deletion syndromes. Subglottic stenosis is said to be the third most common congenital anomaly of the larynx, but its true incidence is hard to determine because many patients are intubated in the neonatal period and are then considered by definition to have an acquired stenosis. The reality in this situation may be a combined congenital plus acquired stenosis. Milder degrees of stenosis present as inspiratory or biphasic stridor as the child becomes older and more active, or as recurrent ‘croup’ owing to superimposed oedema from upper respiratory tract infections.

Diagnosis requires an MLB. The exact location of the stenosis with respect to the vocal cords, tracheostome and carina is measured and the number of normal tracheal rings above the tracheostome is counted. Passing endotracheal tubes and sizing the stricture measures the degree of stenosis. The Myer-Cotton grading system is widely used

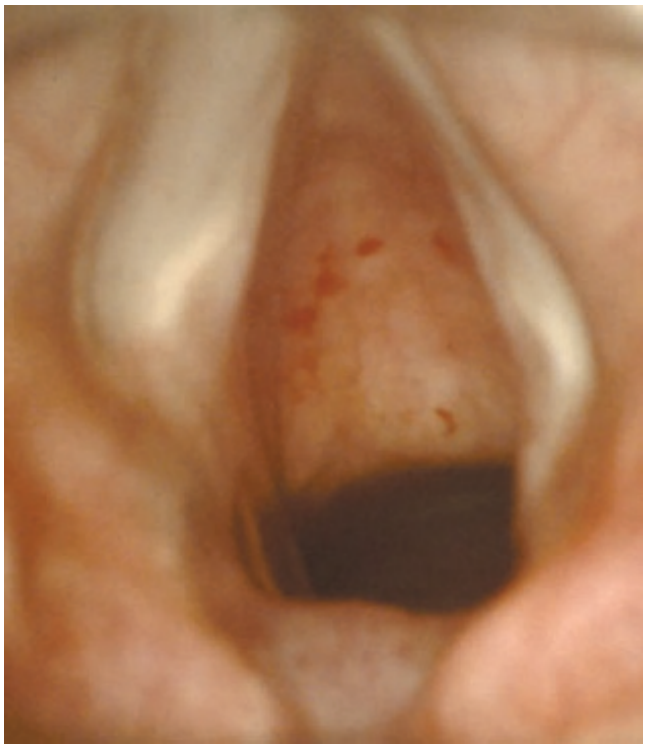

Figure 30.4 Congenital subglottic stenosis, showing anterior cricoid thickening. Reused with kind permission from C.M. Bailey and Springer Science and Business Media.[18]

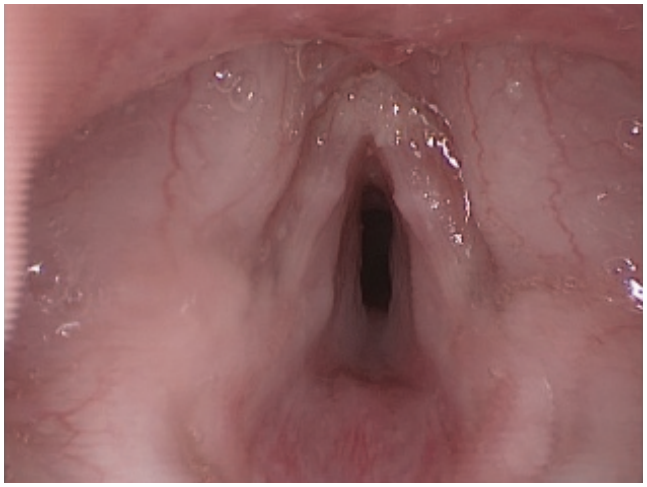

Figure 30.5 Congenital subglottic stenosis, showing elliptical, thickened cricoid with excessive submucosal soft tissue.

to classify paediatric laryngotracheal stenosis into four grades of severity:[20]

- **Grade I :** 0–50% obstruction
- **Grade II:** 51–70% obstruction
- **Grade III:** 71–99% obstruction
- **Grade IV:** 100% obstruction.

This helps to predict the outcome of surgical reconstruction.

If the airway is not severely compromised, surgery may not be required, especially as a congenital stenosis can be expected to enlarge with growth. Congenital cartilaginous stenosis represents a strict contraindication to dilatation or laser resection: any type of endoscopic treatment is liable to worsen the initial condition, and attempted dilatation is inevitably ineffective as the thickened ring of cricoid cartilage cannot be expanded.

If the airway is severely compromised, a tracheostomy is needed. This can sometimes be avoided in specialist centres where there are facilities for single-stage airway reconstruction in which an endotracheal tube is used as a stent, usually for a period of 5–7 days.

The surgical options have evolved from the classical castellated laryngotracheoplasty designed by Evans and Todd[21] in the early 1970s to achieve laryngeal framework expansion. This was superseded during the early 1980s by the LTR, devised primarily by Cotton.[22] The LTR involves augmentation of the laryngotracheal complex by anterior and/or posterior midline incision of the cricoid with insertion of costal cartilage grafts to expand the airway. This technique has now been supplemented by the partial cricotracheal resection (PCTR), which was introduced into the paediatric age group by Monnier et al.[23] in the early 1990s. This involves complete resection of the stenotic segment with end-to-end anastomosis of the tracheal stump to the thyroid cartilage.

Grade I subglottic stenosis usually requires no surgical intervention. Grade II stenosis can be reconstructed by means of an LTR with anterior cartilage grafting +/– posterior cricoid split. Mild grade III stenosis is likely to need an anterior graft with posterior cricoid split +/– posterior cartilage grafting. Severe grade III stenosis (a pinhole airway) requires both anterior and posterior grafts. Grade IV stenosis demands anterior and posterior grafts with prolonged stenting. For severe grade III and for grade IV stenosis, PCTR is an alternative technique with much to commend it. LTR remains the last surgical option after failed PCTR if it is impossible to resect a further segment of trachea.

In cases of congenital subglottic stenosis, the LTR may be combined with submucosal resection of cartilage to 'core out' the thickened anterior cricoid ring. A similar submucous resection technique can be used via a laryngofissure for thick anterior glottic webs with subglottic extension. In both situations stenting is essential.

The least severe grades (I and II) have a better outcome than the most severe grades (III and IV). For PCTR, however, the grading system is not a predictor of success or failure, because the stenotic segment is completely resected. Results from the most experienced centres[24, 25] show a success rate of over 90% for grades I and II subglottic stenosis following LTR and approximately 80–90% for grades III and IV subglottic stenosis. The latest results from the two centres with the largest experience in PCTR show a decannulation rate of 98% for primary surgery and 94% for salvage surgery after failed previous airway reconstruction.[26, 27]

For more detail on the management of laryngeal stenosis, see Chapter 31, Acquired laryngeal stenosis.

Subglottic haemangioma

Infantile subglottic haemangioma is a well-recognized cause of gradually worsening inspiratory or biphasic stridor presenting in the first few weeks of life, with 85% presenting within the first 6 months. Of patients with a cutaneous haemangioma 1–2% also have a subglottic lesion; 50% of patients with a subglottic haemangioma will have a coexisting cutaneous lesion. The natural history is typically a proliferative phase lasting 6–12 months followed by complete involution over 1–5 years.[28]

At endoscopy the typical appearance is of a compressible, pear-shaped red swelling in the subglottis on one side, left more commonly than right (**Figure 30.6**). Larger haemangiomas may be circumferential and, uncommonly, may extend down into the trachea or through its wall into the surrounding soft tissues of the neck or mediastinum. The appearance is so characteristic that biopsy is unnecessary; in rare cases where there is doubt, biopsy can be undertaken without fear of troublesome bleeding because the lesion is a benign endothelial cell tumour, not a vascular malformation. If extension outside the airway is suspected, magnetic resonance imaging (MRI) is indicated. Subglottic haemangioma is life-threatening because of its situation in the narrowest part of the airway and therefore requires rapid intervention.

Tracheostomy will maintain the airway until involution occurs. A review of the subject in 1984 by Sebastian and Kleinsasser[29] estimated that 50–70% of patients with airway haemangioma require a tracheostomy, and that children managed with tracheostomy alone could be decannulated at a mean age of 17 months. However, paediatric tracheostomy carries a mortality of 1–2% and a significant morbidity including delayed speech development.

Over the years, efforts have been made to develop alternative therapeutic strategies aimed at maintaining the airway without recourse to tracheostomy. Therapies used in the past include radiotherapy, CO_2 laser ablation, systemic steroids, intralesional steroid injection followed by intubation, and interferon alpha-2a. However, all of these are associated with unwanted side effects. Submucosal surgical excision of subglottic haemangioma was first described in 1949.[30] Surgery is carried out in a single stage and is stented with an endotracheal tube for 3–5 days. Surgical excision is unsuitable if the haemangioma is circumferential or extends onto the vocal cords.

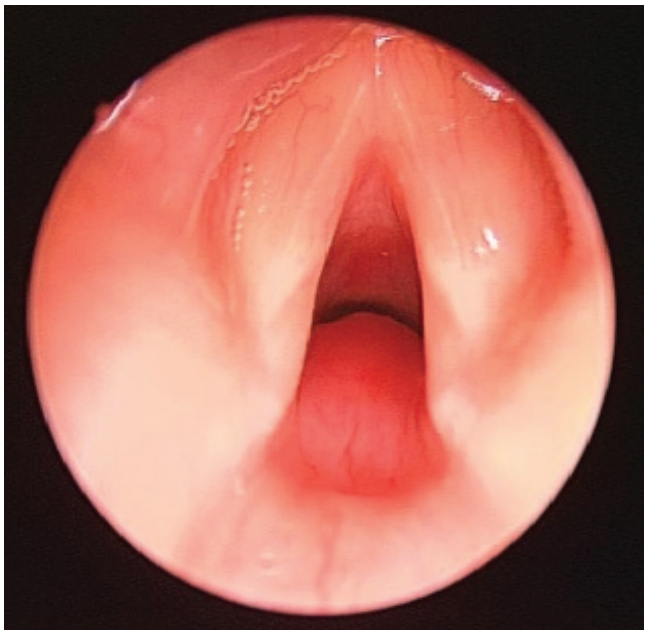

Figure 30.6 Subglottic haemangioma.

The treatment of subglottic haemangiomas was revolutionized with the incidental finding that propranolol is an effective treatment for cutaneous haemangioma and subglottic haemangioma.[31,32] Prior to treatment commencing, a baseline pulse, blood pressure and blood glucose should be assessed together with an ECG and echocardiogram. Treatment is initiated at 1 mg/kg/day for 1 week, then advancing to 2–3 mg/kg/day as tolerated.[33] Propranolol has proven to be effective at reducing/resolving stridor in as little as 24 hours. Side effects of propranolol are rare but may include hypoglycaemia, hypotension and bradycardia. Treatment should be for a minimum 12 months to cover the natural period of proliferation, then weaning of the propranolol dose over 4 weeks. These patients should be closely monitored for recurrence.

Propranolol is now considered to be first-line treatment for subglottic haemangiomas. Steroid therapy can be used in the acute setting and in conjunction with propranolol for unresponsive lesions. Submucous resection remains a valid alternative for non-circumferential haemangiomas and those not involving the vocal cords.

Laryngeal and laryngotracheo-oesophageal cleft

Posterior laryngeal clefts result from failure of the posterior cricoid lamina to fuse, and in the more extensive laryngotracheo-oesophageal clefts there is also incomplete development of the tracheo-oesophageal septum. The classification devised by Benjamin and Inglis[34] has been widely adopted because it relates well to symptoms and treatment. A type I cleft extends down to the level of the vocal cords; a type II cleft extends below the vocal cords into the cricoid (**Figure 30.7**); a type III cleft extends down into the cervical trachea; and the, fortunately rare, type IV cleft extends into the thoracic trachea and may even reach the carina. Approximately 25% of patients with a laryngeal cleft will also have a TOF, but conversely the incidence of laryngeal cleft in patients with a TOF is low. Abnormalities of the tracheal ring structure in cleft patients may result in associated tracheomalacia, which can add to the difficulties of management.

The majority of laryngeal cleft patients have associated congenital abnormalities, of which TOF is the most common. These may include tracheobronchomalacia, congenital heart disease, dextrocardia and situs inversus. Often there is severe gastro-oesophageal reflux. Laryngeal clefts are characteristic of two syndromes: the Opitz-Frias syndrome (G syndrome) comprising hypertelorism, cleft lip and palate, laryngeal cleft and

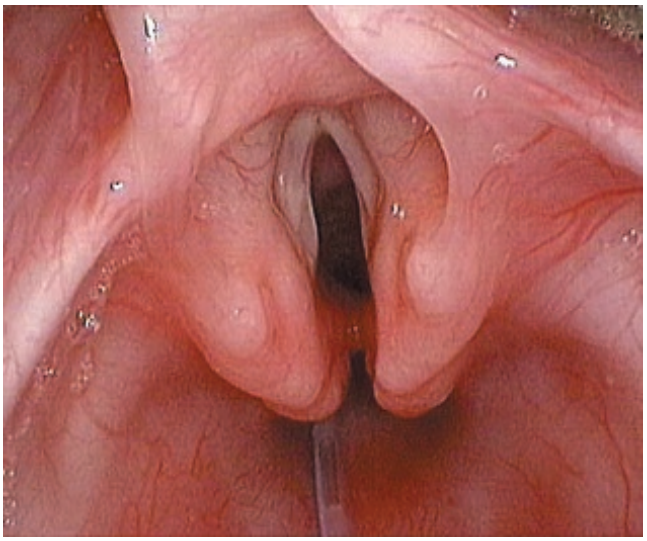

Figure 30.7 Larnygeal cleft (type II). Reused with kind permission from C.M. Bailey and Springer Science and Business Media.[18]

hypospadias; Pallister–Hall syndrome (described earlier in relation to bifid epiglottis), consisting of congenital hypothalamic hamartoblastoma, hypopituitarism, imperforate anus and postaxial polydactyly, and sometimes including a laryngeal cleft.

As might be expected, symptoms become more severe the longer the cleft. Type I clefts present with cyanotic attacks on feeding and recurrent chest infections. Stridor (similar to that of laryngomalacia) may be a feature, secondary to prolapse of the cleft edges into the airway. The differential diagnosis for infants presenting with these symptoms includes gastro-oesophageal reflux, neuromuscular incoordination of deglutition, vocal cord paralysis, raised intracranial pressure and TOF. Type II and III clefts produce dramatic aspiration with recurrent pneumonia, sometimes with stridor and an abnormal cry. Type IV clefts cause severe aspiration, cyanosis and incipient cardiorespiratory failure.

Investigation of the child with aspiration and stridor requires a careful MLB; no other diagnostic method can replace it.[35] Suspension microlaryngoscopy allows the use of two probes to part the arytenoids, and without this manoeuvre the diagnosis may be missed as redundant mucosa tends to prolapse into the defect and obscure it. A plain chest X-ray may show changes secondary to recurrent aspiration pneumonitis. A lateral neck X-ray may demonstrate vaguely increased laryngeal soft tissue and the nasogastric feeding tube may be seen protruding anteriorly into the airway. Videofluoroscopic contrast swallow studies may not differentiate laryngeal incompetence from neuromuscular incoordination, and a high index of suspicion is required.

The approach to treatment depends entirely upon the length of the cleft. A short type I cleft with no aspiration requires no treatment. Minimal aspiration may be managed by thickening the feeds. Significant aspiration requires endoscopic repair of the cleft in two layers, using a nasogastric feeding tube until the suture line has healed. A very short type II cleft may also be repaired endoscopically, albeit with difficulty, using a nasogastric tube. However, a long type II or a type III cleft needs to be approached anteriorly through an extended laryngofissure with a low tracheostomy to cover the procedure; a nasogastric tube will tend to erode through the suture line, and so a gastrostomy is required (usually combined with a Nissen fundoplication to control reflux reliably). These children take many months to learn to swallow after successful cleft repair and thus long-term gastrostomy feeding is necessary. Surgical repair of the cleft is undertaken in three layers in an effort to optimize healing: the two mucosal layers are reinforced by an interposition graft of tibial periosteum or temporalis facia.

The type IV cleft presents an altogether more difficult surgical challenge. Owing to the length of the cleft, a tracheostomy is unhelpful in stabilizing the airway, and the convexity of the tube would tend to erode through the party wall suture line; the repair must therefore be undertaken using a single-stage technique with endotracheal extubation taking place 7–10 days post-operatively. Short type IV clefts may be managed by an anterior approach through a cervical incision, if necessary pulling the trachea up into the neck to reach the lower end of the cleft. Longer clefts will require a lateral cervical approach in combination with a thoracotomy, or preferably an anterior cervicothoracic approach via a median sternotomy with repair on extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass. Post-operatively, tracheomalacia may prevent extubation and so a tracheostomy may be needed once the cleft has healed soundly.[36]

Mortality remains significant, being approximately 14% overall,[37] rising to 66% for type IV laryngotracheo-oesophageal clefts and up to 100% for full-length clefts ending at the carina.[38] A large proportion of the mortality is from causes unrelated to the cleft, and notable morbidity is produced by other associated congenital abnormalities and often by delay in reaching the correct diagnosis. Management should be in a major paediatric centre where a full multidisciplinary team is available with full neonatal and paediatric intensive care facilities.

TRACHEA AND BRONCHI

Advances in the field of airway regenerative medicine mean that tissue engineering is becoming a realistic potential therapy for congenital tracheal and bronchial malformations.[39] Initial research focused on engineering biocompatible and immunocompatible material to act as a scaffold to directly repair any defect, with the aim that the scaffold would become populated by the patient's own, normal-functioning cells – in particular, ciliated respiratory epithelium. Crucially in neonates and children, the scaffold needs to be able to grow with the child. Successful tracheal transplantation has occurred in paediatric patients using decellularized donated cadaveric trachea.[40, 41] The search for the perfect scaffold material, whether natural or synthetic, is ongoing.

Agenesis

Tracheal agenesis may be complete (full-length) or partial, but in either case there is no continuity between the larynx and the bronchi. Occasionally, short-term survival may be possible if there is a broncho-oesophageal fistula, which can permit some airflow into the lungs, but surgical efforts to use the oesophagus as a tracheal replacement have not been successful and long-term survival has not proved possible. The majority of cases are complicated by other severe congenital abnormalities.

Agenesis of one main bronchus and its associated lung is not as rare as tracheal agenesis and is compatible with survival, although such children often have coexisting congenital anomalies and are at risk from chest infections because of their much-reduced respiratory reserve. Bilateral bronchial and pulmonary agenesis is extremely rare and is, of course, fatal. Occasionally, localized atresia occurs in a peripheral bronchus, resulting in a distal mucocoele which may need to be resected if it is causing severe compression of the surrounding lung.

Stenosis

Occasionally, a membranous web may be encountered in the trachea with a normal underlying cartilaginous ring structure. Such cases usually fare well with endoscopic rupture and dilatation. Thicker congenital fibrous stenoses may be amenable to radial KTP laser incision and balloon dilatation, followed by application of mitomycin C to reduce the risk of restenosis[42] or tracheal resection with end-to-end anastomosis. A short stenosis may also be associated with one or two absent tracheal rings, although the most common finding in congenital tracheal stenosis (CTS) is a segment of complete tracheal cartilaginous rings with an airway lumen as narrow as 2 mm.[43]

CTS is usually described as being either short-segment or long-segment and according to whether it involves trachea alone, trachea and bronchus, or bronchus alone. A long-segment congenital tracheal stenosis (LSCTS) is one that is over 1 cm in neonates and 1.5 cm in infants or greater than 50% of the length in older children. Further classification depends on the associated anatomy of the respiratory tract: normal bifurcation, bronchial trifurcation, porcine bronchus or single lung.[44] Sixty per cent of patients with LSCTS will have associated malformations such as pulmonary artery sling, right-sided aortic arch, subglottic stenosis and tracheoesophageal fistula.

Children with congenital tracheal stenosis usually present with respiratory distress within the first year of life. Symptoms usually only appear when there is greater than 50% stenosis. Symptoms may become apparent in the neonatal period with biphasic stridor, respiratory distress, tracheal tug and episodes of cyanosis. However, presentation may be delayed until the infant is several months old when greater physical activity makes increasing demands upon the respiratory system. In addition, difficulty in breathing can develop rapidly as a result of a respiratory tract infection, with consequent oedema and increased secretions. In this situation the child may require endotracheal intubation, and it is then found that only a very small-sized tube can be passed. In the case of a long, tapering stenosis, which may narrow virtually to a pinhole, this is a dangerous situation. The tube tip tends to impact into the stenosis, granulations begin to develop and obstruct the already perilous airway, and endoscopic evaluation is then a procedure fraught with difficulty. In such cases the stenosis often seems surprisingly severe considering the child's mild symptoms prior to the precipitating illness.

Suspected LSCTS should be assessed and managed by a multidisciplinary team including cardiothoracics, ENT surgeons, upper GI surgeons, respiratory and cardiac paediatricians, interventional radiologists and allied healthcare professionals. Investigations should be targeted at identifying the extent of the abnormality.

Endoscopy remains the 'gold standard' investigation for a child with stridor. MLB demonstrates complete tracheal rings without the posterior bulge of trachealis (**Figure 30.8**). However, if LSCTS is found at MLB, great care must be taken not to traumatize the stenosis by attempting to pass an endoscope that is too large or the resultant oedema may convert an airway that is just adequate into one that is not. Frequently, the stenosis is too narrow to permit passage of the 4 mm rigid telescope or the smallest (size 2.5) bronchoscope, and it is necessary to use the unsheathed 1.9 mm telescope to survey the length of the narrow segment and assess the state of the distal trachea, carina and bronchi. Sometimes the airway is too narrow to admit even this extra-slim telescope, and then the surgeon must rely on contrast bronchography.

Bronchoscopy and bronchography (B&B) demonstrate the the size of the tracheal lumen and outline the trachea and bronchi distal to the stenosis, which may be too narrow to permit passage of a bronchoscope (**Figure 30.9**) and also provides a dynamic assessment of any malacic segments. Optical coherence tomography (OCT) can be combined with B&B to confirm the presence of complete rings if there is any doubt. Contrast CT and an echocardiogram are essential in view of the high incidence of associated anomalies of the heart and great vessels. CT is particularly helpful in assessing the vascular anatomy and its relationship to the trachea and 3D reconstructions allow better surgical planning.

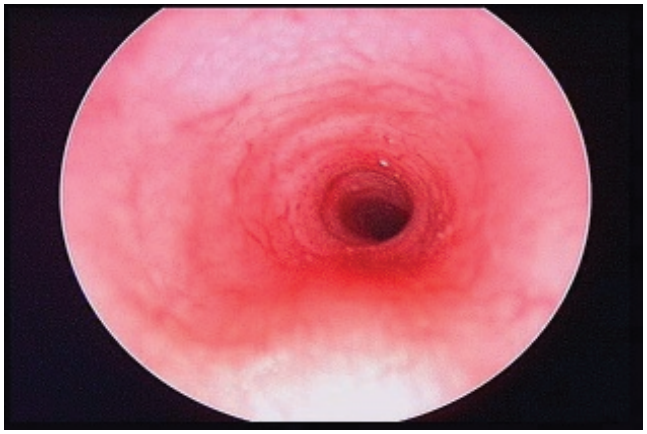

Figure 30.8 Complete tracheal rings.

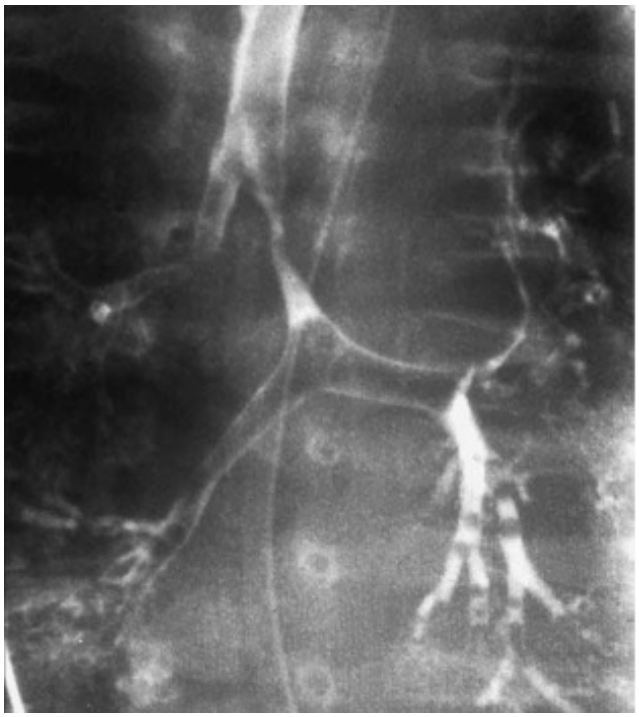

Figure 30.9 Tracheal stenosis: bronchogram of a long-segment lower tracheal stenosis with associated stenosis of the main bronchi and with a 'pig' bronchus at its upper end.

Mild cases with minimal symptoms may require no intervention after the diagnostic endoscopy, as the trachea can grow and there may be only slight limitation of exercise tolerance. Very narrow, short segments can be excised with end-to-end anastomosis. In the past, several techniques have been employed to treat LSCTS. Augmentation tracheoplasty with costal cartilage grafting or a pericardial flap or free patch have been described. However, if the stenosis is severe with only a pinhole lumen, cartilage grafting cannot be expected to achieve an adequate airway, and a large suspended pericardial patch carries high risk of subsequent tracheomalacia. The overall mortality associated with costal cartilage or pericardial patch tracheoplasty is substantial, ranging up to nearly 50%.[45]

Successful endoscopic balloon dilatation of LSCTS has been reported. However, it is difficult to see why the airway does not quickly close down again to its original size, as the 'spring' in the cartilage is not broken by splitting it in just one place and fibrosis is bound to occur at the site of the split. For this reason, balloon dilatation is used as an adjunctive treatment modality for granulations and fibrous stenoses such as may develop post-operatively at the site of an anastomosis.

For LSCTS, the gold standard treatment of choice is slide tracheoplasty with the patient on cardiopulmonary bypass with concurrent repair of coexisting cardiovascular anomalies. The slide minimizes shortening of the trachea and hence reduces anastomotic tension. The oblique anastomosis also seems less liable to post-operative stenosis than an end-to-end anastomosis. The tracheoplasty is performed by dividing the stenosis at its midpoint, incising the proximal and distal narrowed segments vertically on opposite anterior and posterior surfaces and sliding these together. The stenotic segment is thus shortened by half, the circumference is doubled, and the luminal cross section quadrupled. Long resections may require a laryngeal drop and/or hilar release to avoid undue tension upon the suture line.

Survival rates for LSCTS following slide tracheoplasty over the last decade have risen to nearly 90%.[44] Poor prognostic indicators include pre-operative bronchomalacia and bronchial stenosis, although these groups still have survival rates of over 70%. Balloon dilatation is used to treat granulations and stenosis. Absorbable PDS stents offer an advantage over metallic stents and are used to treat malacia, particularly bronchomalacia.

Slide tracheoplasty has proven to be very successful in treating LSCTS. However, for those children who have failed surgery or in cases not amenable to slide tracheoplasty, few strategies are available. The advent of tissue engineering may hold the key for this group of patients.

Tracheomalacia and bronchomalacia

Tracheomalacia is a condition in which there is reduced stiffness of the tracheal wall, resulting in abnormal collapse of the trachea during expiration which, if severe, can produce symptoms of airway obstruction. Bronchomalacia is the equivalent condition affecting the bronchi. There is, however, no association between tracheobronchomalacia and laryngomalacia, although because the latter is a common condition it may sometimes coexist.

Pathologically, the striking finding is an increased muscle-to-cartilage ratio seen on the transverse section of the trachea; in other words, a widening of the trachealis relative to the cartilage rings, which become C-shaped instead of horseshoe-shaped. Normally, the ratio is 1:4 or 1:5, but in tracheomalacia it may be closer to 1:2. However, in children the trachea and bronchi are more compliant than in the adult and some degree of collapse may be observed during endoscopy in normal children. This is particularly obvious if the level of general and topical anaesthesia is too light and the child tends to cough and strain in consequence, often with anterior bulging of the trachealis. To be clinically significant, more than 50% obstruction is probably required, as visualized at the end of expiration in the well-anaesthetized child.

Tracheomalacia is traditionally classified as primary (idiopathic), due to an intrinsic abnormality in the wall of the airway, or secondary, due to another associated anomaly or to external compression. The primary form is less common and tends to affect a longer segment of the airway. Secondary tracheomalacia is usually more localized and may be associated with TOF or laryngeal cleft or with extrinsic compression by an anomaly of the great vessels or a mediastinal mass. A common but special form of localized secondary tracheomalacia is the suprastomal collapse which arises above most long-standing paediatric tracheostomies, produced by pressure from the convexity of the tracheostomy tube.

The stridor of tracheomalacia becomes apparent during the first few weeks of life and consists of a very variable high-pitched expiratory noise. This may be accompanied by a harsh, barking cough, especially in the localized form of the condition. Characteristically, the stridor becomes much worse when the child is active, feeding, upset, coughing or crying, and it may be associated with cyanotic attacks which are sometimes sufficiently severe to be termed 'dying spells'. The pathophysiology of these seems to be that, with vigorous respiration, airflow through the trachea increases and in accordance with Bernoulli's principle the pressure within the airway correspondingly falls. This encourages further collapse of the malacic segment and a vicious circle is established that can result in complete collapse of the trachea with respiratory obstruction. These episodes are probably self-limiting but, faced with total obstructive apnoea and cyanosis, parents and caregivers will usually attempt resuscitation rather than wait and see.

The stridor of tracheobronchomalacia is typically episodic, thus on examination the child may seem perfectly well. There may be a prolonged expiratory phase to respiration, possibly with faint expiratory stridor. However, crying or feeding can dramatically change the picture to one of an infant who is clearly obstructed and in respiratory distress.

Plain X-rays are not usually helpful. A barium swallow may identify a TOF and can also demonstrate the airway collapse on lateral screening. Echocardiography may be useful in defining any suspected anomaly of the heart and great vessels. CT angiogram is extremely useful for identifying the cause of extrinsic compression of the trachea by normal or abnormal vessels, including vascular rings. Contrast bronchography may be the most useful radiological investigation: it is a dynamic study that not only demonstrates the areas of collapse but enables the opening pressures to be measured, which is extremely helpful in setting continuous positive airway pressure (CPAP) levels for children with very severe tracheobronchomalacia who are intubated or have undergone tracheostomy. Even if tracheobronchomalacia has been demonstrated radiologically, it is nonetheless important to undertake a full MLB to examine the collapse directly and exclude other abnormalities such as a TOF or laryngeal cleft. Typically, anterior tracheal wall collapse will be observed, with flattened tracheal rings and a wide trachealis (**Figure 30.10**). In addition, the common vascular anomalies have sufficiently characteristic features to aid diagnosis (see below).

Mild tracheobronchomalacia (less than 75% collapse) requires no intervention, and the stridor can be expected to resolve spontaneously by around the age of 2 years. However, parents will require careful explanation and reassurance, as well as being taught cardiopulmonary resuscitation if their child is prone to 'dying spells'. Severe tracheobronchomalacia (more than 75% collapse) may require treatment, especially if associated with failure to thrive. If it is secondary to a vascular anomaly, this should be corrected. The severe localized tracheomalacia often associated with a TOF usually responds well to an aortopexy, whereby the aorta is sutured to the back of the sternum. If this fails, an extended tracheostomy tube will effectively support a midtracheal malacic segment, but this is not a satisfactory solution for lower-end tracheal or for bronchial collapse. For the infant in intensive care with severe primary tracheobronchomalacia who cannot be weaned off CPAP, it may be necessary to resort to a tracheostomy in order to apply long-term CPAP. Alternative surgical solutions for this most severe end of the disease spectrum have been sought by cardiothoracic surgeons: these include internal or external stenting of the trachea, segmental resection and cartilage grafting, but all present formidable difficulties and complications with very variable outcome, and the risks may exceed those of the condition itself.

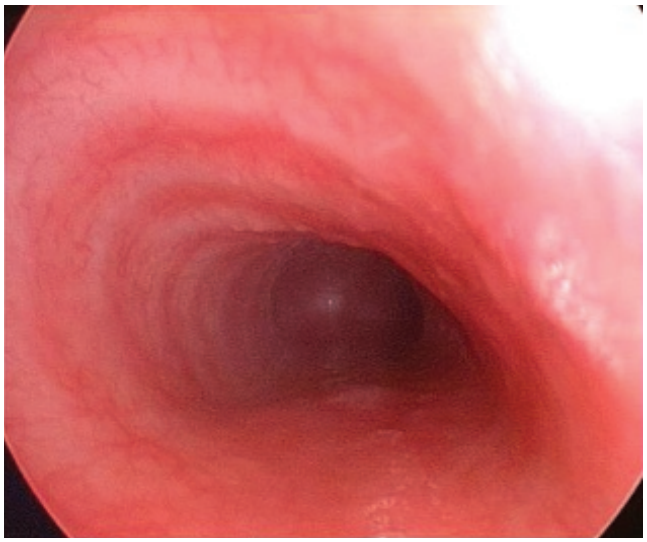

Figure 30.10 Tracheomalacia caused by external compression from an aberrant innominate artery.

Tracheo-oesophageal fistula

Tracheo-oesophageal fistula is a fairly common congenital malformation of the neonatal air and food passages, which usually occurs in association with oesophageal atresia. Eighty-seven per cent of cases have oesophageal atresia with a TOF communicating between the distal oesophagus and the mid- to lower trachea or a main bronchus. The remainder have oesophageal atresia without a TOF (6%); atresia with a proximal TOF (2%); atresia with a proximal and distal TOF (1%); or a TOF without atresia ('H-type fistula') (4%). Approximately 50% of infants with TOF have additional congenital malformations, and 10–20% have tracheomalacia (see Chapter 45, Oesophageal disorders in children).

Children who present to the paediatric otolaryngologist are invariably those with an H-type fistula. Since there is no oesophageal atresia, they are the least symptomatic of the group, with no swallowing difficulty, but small amounts of fluid pass through the fistula into the trachea and produce symptoms and signs of recurrent minor aspiration. The diagnosis is usually established by a barium

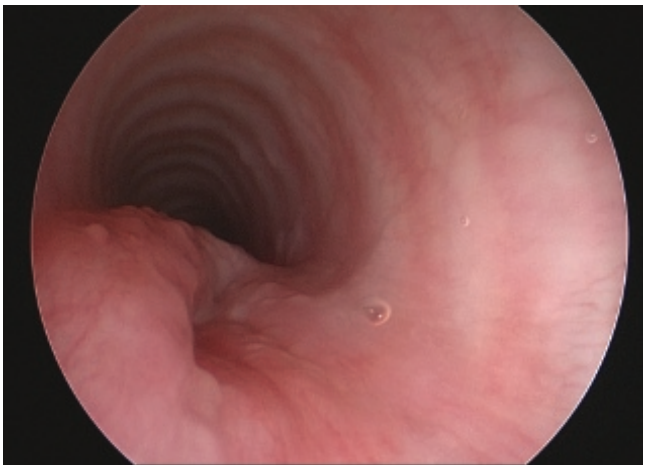

Figure 30.11 Tracheosophageal fistula seen at bronchoscopy.

swallow, but even thin contrast may not pass through a tiny fistula. In such cases MLB is required to identify the tracheal opening, which is typically characterized by a V-shaped mucosal fold around it in the posterior wall of the trachea (**Figure 30.11**). Treatment is by ligation and division of the fistula.

For further details on the management of TOF, see Chapter 101, Diseases of the oesophagus, swallowing disorders and caustic ingestion.

Vascular compression

It is estimated that 3% of the population have an anomaly of the great vessels, but only a few of these have symptomatic airway compression.[46] Such vascular anomalies are classified into vascular rings, which completely encircle the trachea and oesophagus, and vascular slings, which exert non-circumferential pressure.

VASCULAR RING

The commonest vascular ring is a double aortic arch. In this abnormality the ascending aorta divides into two arches, one of which passes to the right of the trachea and the other to the left, reuniting posterior to the oesophagus to form the descending aorta on the left. The left arch is usually smaller than the right, and the configuration of the main branches is variable, but the result is compression of both the trachea and the oesophagus, producing stridor, dyspnoea, dysphagia and a brassy cough.

A less common and less constricting ring is produced when there is a right-sided aortic arch and descending aorta associated with an aberrant left subclavian artery. In this situation the ring is completed by the ligamentum arteriosum which passes to the left of the trachea, connecting the descending aorta to the pulmonary trunk.

Patients with vascular rings tend to present earlier in life and with more severe airway symptoms than those with vascular slings. A barium swallow is diagnostic, showing a characteristic double impression upon the column of contrast, and an echocardiogram will confirm the anomaly. Surgical treatment, almost always necessary, is by dividing the lesser component of the ring, but there is invariably a localized area of tracheomalacia produced by the compression which may persist for months or even years.

VASCULAR SLING

The commonest vascular sling is an aberrant innominate artery. The artery arises further to the left and more posteriorly than usual, and crosses the anterior surface of the trachea obliquely just above the carina from the left inferiorly to the right superiorly.

Cases usually present during the first year of life with less severe airway obstruction than that caused by vascular rings. Typically, there is expiratory stridor, cough, recurrent chest infection and sometimes reflex apnoea. The bronchoscopic appearances are diagnostic, with a characteristic sloping, pulsatile compression of the trachea 1–2 cm above the carina which is most marked on its anterolateral aspect (see **Figure 30.10**). Upward pressure with the tip of the bronchoscope compresses the artery against the sternum and obliterates the right radial pulse. In severe cases, surgical relief of the obstruction is necessary: this can be achieved either by aortopexy, in which the vessel is suspended anteriorly from the sternum, or by reimplanting it further to the right on the aortic arch.

A 'pulmonary artery sling' is produced by an anomalous left pulmonary artery, which arises on the right and passes between the trachea and oesophagus, compressing both (**Figure 30.12**). This may be associated with lower-end tracheal stenosis which sometimes also involves the

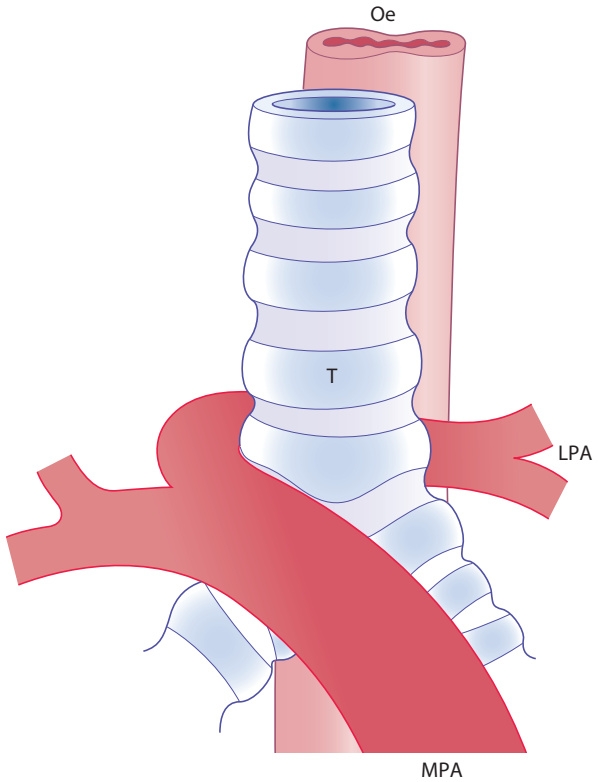

Figure 30.12 Diagram of a pulmonary artery sling. LPA, left pulmonary artery; MPA, main pulmonary artery; Oe, oesophagus; T, trachea. Redrawn with kind permission from C.M. Bailey and Springer Science and Business Media.[18]

carina and right main bronchus. Surgical reanastomosis may be needed to relieve the compression.

Enlargement of the pulmonary artery in association with a cardiac defect can also produce compression of the distal trachea and bifurcation. An aberrant right or, more rarely, left subclavian artery passing posterior to the oesophagus will compress the oesophagus alone, and so produces dysphagia but no stridor.

Anomalous bifurcations

The right upper lobe bronchus may take origin from the right lateral wall of the trachea above the carina, and is termed a tracheal bronchus or suis bronchus. This is the normal arrangement in a pig and so the anomaly in humans is often referred to as a porcine or 'pig' bronchus. It is usually an asymptomatic, incidental finding, but may sometimes be associated with tracheal stenosis. Minor alterations to the distal bronchial branching pattern are not unusual and, likewise, do not usually cause problems.

Congenital cysts and tumours

Tracheogenic and bronchogenic cysts are thought to originate from evaginations of the primitive tracheal bud and are sometimes termed reduplication anomalies. They may happen anywhere along the tracheobronchial tree: they are lined with respiratory epithelium, filled with mucus, and their walls may contain any elements of normal tracheobronchial wall. Bronchogenic cysts may communicate with the airway.

Some patients are symptom-free, but large cysts or those that become infected cause non-pulsatile compression of the airway and present with symptoms, signs and endoscopic appearances otherwise similar to those produced by vascular compression (see 'Vascular compression' above). CT or MRI will demonstrate the lesion clearly, and treatment is by thoracotomy and surgical excision.

Thymomas or teratomas may produce airway compression in the neck or mediastinum. CT or MRI is needed to define the size and situation of the mass prior to surgical excision.

BEST CLINICAL PRACTICE

- ✓ The diagnosis of mild laryngomalacia can be confirmed in the outpatient clinic by flexible fibre-optic laryngoscopy.
- ✓ Microlaryngoscopy and bronchoscopy under general anaesthesia are necessary if the stridor in laryngomalacia is severe, there is failure to thrive or any atypical features.
- ✓ Propranolol has become the first-choice treatment for subglottic haemangiomas, although surgical excision remains as a viable alternative for isolated, non-circumferential lesions.
- ✓ Slide tracheoplasty is the treatment of choice for long-segment congenital tracheal stenosis.
- ✓ Management of congenital disorders of the larynx, trachea and bronchi requires the multidisciplinary resources of a major children's centre.

FUTURE RESEARCH

- ➤ The rarity and often life-threatening nature of many congenital disorders of the larynx, trachea and bronchi means that evidence for their management tends to be confined to evidence levels 3 and 4. International collaboration between large centres is often the only way to generate sufficient patient numbers to generate evidence in this field.
- ➤ Advances in the field of airway regenerative medicine means that tissue engineering is becoming a realistic potential therapy for congenital tracheal and bronchial malformations.

KEY POINTS

- Laryngomalacia is the most common congenital disorder of the larynx, trachea and bronchi and is the most common cause of stridor, but be aware of the possibility of coexisting pathology.
- Congenital disorders of the airway may be asymptomatic but will tend to present in the first few weeks of life with stridor and/or feeding difficulties.
- Failure to thrive raises suspicion of a congenital airway disorder.
- Congenital disorders of the larynx, trachea and bronchi are often associated with underlying syndromes and other anomalies.

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CHAPTER 31

ACQUIRED LARYNGOTRACHEAL STENOSIS

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: paediatric, laryngeal, subglottic, glottic, posterior glottic, web, supraglottic, stenosis, laryngotracheoplasty, laryngotracheal reconstruction and cricotracheal resection. The focus is on evaluation, management and surgery.

INTRODUCTION

Over the past four decades, the presentation and management of paediatric laryngeal stenosis have changed significantly. Prior to 1965, this diagnosis indicated the presence of a congenital anterior glottic web or congenital subglottic stenosis (SGS). In many children, congenital SGS was expected to improve over time. Even in children requiring tracheotomy, decannulation could be achieved within a few years without requiring laryngeal reconstructive surgery. With advancements in neonatal critical care and the introduction of prolonged intubation, this clinical scenario became less common, and acquired SGS became and remains the most frequent cause of laryngeal stenosis. This condition is generally more severe than congenital SGS and typically does not improve over time. Modern paediatric laryngeal reconstruction was thus born of necessity to manage these otherwise healthy, but tracheotomy-dependent children.

Further improvements in neonatal care, particularly the use of nasopharyngeal continuous positive airway pressure (CPAP) and high-flow nasal cannulae, have led to a significant decline in the incidence of acquired SGS in children without other medical problems. These improvements have resulted in the salvage of premature and often medically fragile children whose laryngeal pathology is but one component of a myriad of health issues. The typical child who now presents with SGS is more likely to have problems associated with extreme prematurity or genetic or other birth defects. The management of these children is complex, ideally requiring an interdisciplinary team approach. In addition, their laryngeal pathology is more severe, with stenosis potentially involving not only the subglottis but also the supraglottis or glottis; while SGS is far more common, combined pathology is not uncommon.

Although the complexity and multifaceted needs of children with SGS have increased, so too have the management strategies used to treat these children. Endoscopic procedures, particularly balloon dilation, new open operative techniques (e.g. slide tracheoplasty), and new uses for medications (e.g. azithromycin and topical antibiotic and steroid combinations), have all made contributions to patient care.

Despite these advances, acquired laryngeal stenosis continues to cause significant morbidity and mortality, whether or not patients are tracheotomy-dependent. The primary aim of intervention is decannulation or preventing the need for tracheotomy. In selected patients, voice restoration or provision of a safer airway may be the primary consideration, with decannulation being a secondary goal.

Despite the large number of centres and surgeons that care for complex children with SGS, the needs of this patient population are often highly individualized. Similarly, the experience of managing surgeons and other healthcare providers may vary widely. As such, prospective randomized controlled trials of particular treatment strategies are lacking, and most recommendations are based on level 3 or 4 evidence.

PAEDIATRIC LARYNGEAL ANATOMY

Compared with the adult larynx, the infant larynx lies high in the neck, with the hyoid bone overriding its superior aspect. The narrowest point in the infant airway is the cricoid ring. Since this is the only fixed ring within the airway, it is the most vulnerable point for iatrogenic damage caused by intubation. In a term newborn, the diameter of the subglottis is between 4.5 and 5.5 mm. If the airway diameter in the term newborn is less than 4 mm, SGS is present. A useful guideline is that the outer diameter of a 3.0 mm endotracheal tube is 4.2 mm.

The superior margin of the supraglottis comprises the superior edge of the epiglottis, the aryepiglottic folds and the arytenoids, while the inferior margin is at the level of the true vocal folds. The glottis comprises the true vocal folds and the glottic chink. In the infant, the posterior 50% of the true vocal fold consists of the vocal process of the arytenoid. The subglottis lies between the undersurface of the vocal fold and the lower border of the cricoid cartilage. The subglottic mucosa is lined with respiratory epithelium. A transition to squamous epithelium occurs at the free edge of the true vocal fold.

EVALUATION

History

A child with laryngeal stenosis may present with stridor, extubation failure or tracheotomy dependency. In each of these clinical scenarios, a meticulous initial history forms the basis for further evaluation and investigation. It is important for clinicians to determine the overall health status of the child, exploring signs or symptoms and being aware of a past diagnosis of gastro-oesophageal reflux, aspiration, lung disease or cardiac disease.

In a child presenting with stridor, the duration of stridor must first be ascertained. If acute, stridor is a medical emergency. When it is more chronic, its mode of onset should be ascertained and the determination of whether it is stable or progressive should be made. In addition, the degree of compromise to the child's lifestyle should be assessed, particularly with regard to exercise intolerance and shortness of breath on exertion. Some children will also experience obstructive symptoms during sleep. These sleep problems are usually associated with supraglottic pathology although they may be indicative of a second non-laryngeal pathology such as adenotonsillar hypertrophy. The aetiology of the child's compromised airway should also be sought, in particular any prior history of intubation. If there has been such a history, relevant details such as the duration of intubation, the temporal relationship between intubation and the onset of airway symptoms, and whether an age-appropriate endotracheal tube was used should be determined.

In an intubated child, the reason for intubation should be assessed, as should any medical problems that could contribute to extubation failure. The relevant history should include the length of time the child was intubated, the size of the endotracheal tube, the number of attempts at extubation and whether extubation failure abruptly occurred following endotracheal tube removal or was due to gradual and progressive respiratory compromise necessitating reintubation.

In a child with tracheotomy dependency, the aetiology requiring initial placement of a tracheotomy should be ascertained and the duration of cannulation and size of the tracheotomy tube should be determined. Any history of airway reconstructive surgery is also extremely important. Another significant aspect of a thorough assessment is an evaluation of voice quality and the ability to tolerate a speaking valve.

Physical examination

Once a case history has been taken, the presence of stridor and retractions at rest should be assessed. The nature of the stridor — in particular whether it is purely inspiratory, expiratory or biphasic — should be noted. Nonetheless, retractions provide a better barometer of obstruction than stridor. Assessment of voice quality is particularly important in that it may provide an indication of the anatomic region of the pathology. Children with supraglottic stenosis usually present with a characteristic muffled or 'throaty' voice, while those with anterior glottic webbing tend to have a very hoarse voice. Those with posterior glottic stenosis and SGS usually have normal voice quality. In a child presenting with extubation failure, non-laryngeal causes such as nasal obstruction and glossoptosis are explored. In cases of tracheotomy dependency, the size of the tracheotomy tube, the child's ability to tolerate a speech valve and the possibility of tracheotomy tube plugging are pursued.

Imaging studies

Radiologic evaluation of the paediatric airway is most helpful in patients who are neither intubated nor tracheotomy-dependent. Imaging studies fall into two time-related categories: those that are performed prior to endoscopic evaluation and those that are best after endoscopic evaluation. Prior to endoscopy, soft-tissue airway films of the neck and chest should be performed in both lateral and anterior/posterior projections. These are useful in evaluating laryngeal stenosis and may also give timely warning of a possible tracheal stenosis. Anterior/posterior and lateral chest films indicate possible underlying lung pathology. A barium swallow study may not only provide information on the ability to swallow and the relative risk of aspiration but may also indicate the need to evaluate the airway for a posterior laryngeal cleft or a tracheo-oesophageal fistula. In addition, it may provide information on a child's propensity to gastro-oesophageal reflux, vascular compression of the airway and the presence of an oesophageal foreign body.

After endoscopic airway evaluation, more directed imaging studies are valuable. Spiral computed tomography (CT) scanning of the airway with contrast enhancement

provides a useful view of intrathoracic vasculature. If relevant, 3D reconstruction of CT axial images may be valuable in evaluating the intrathoracic airway. Although both magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) also provide excellent views of intrathoracic vascular anatomy, they require more time to perform and are more likely to require sedation or anaesthesia. In younger children, CT and MRI airway evaluation may complement endoscopic evaluation; however, they are not a substitute for it.

In children with upper airway compromise, sleep fluoroscopy or cine MRI may provide a valuable dynamic airway assessment.

Endoscopic airway evaluation

FLEXIBLE NASOPHARYNGOSCOPY

In a child who has not been evaluated previously, flexible nasopharyngoscopy with the child awake should be performed prior to rigid endoscopy. Although the nasal passages, nasopharynx, oropharynx, supraglottic and glottic airway should be assessed, and pathology such as choanal atresia, adenoid hypertrophy, tonsillar hypertrophy and laryngomalacia should be evaluated, the most important information to be sought relates to vocal cord movement. The ability of the vocal cords to normally abduct is critical information prior to any consideration of laryngeal reconstructive surgery, whether movement is compromised by unilateral or bilateral vocal cord paralysis, posterior glottis stenosis, or cricoarytenoid joint fixation. Although the risk of inducing laryngospasm is low, it is recommended that the nasopharyngoscope should not be advanced below the level of the glottis. Although the precise mechanism is unclear, even children with bilateral true vocal fold paralysis may have laryngospasm.

RIGID ENDOSCOPY

It must be emphasized that evaluation of the paediatric airway should not be considered a minor procedure, particularly when performed in a child with an unstable airway (see Chapter 28, Stridor). Extreme care must be taken not to exacerbate the child's condition. The surgical and anaesthetic team must work together closely and must have specific knowledge of the paediatric airway and of appropriate instrumentation. In a child with a compromised airway who does not have a tracheotomy tube, preoperative administration of dexamethasone, 0.5 mg/kg up to a maximum of 20 mg, is a prudent precaution.

Rigid endoscopy remains the 'gold standard' for paediatric airway evaluation, and this evaluation should begin with an assessment of the supralaryngeal airway. The possible presence of retrognathia and any associated glossoptosis or difficulty of laryngeal exposure should be initially assessed, as should tonsillar hypertrophy or evidence of pharyngeal scarring. The supraglottic larynx should be carefully assessed for scarring, laryngomalacia, short aryepiglottic folds and arytenoid prolapse. The glottis should be evaluated for scarring, anterior glottic webbing and posterior glottic stenosis, and care should be taken to exclude the presence of a posterior laryngeal cleft. If vocal motion is clearly seen, it can be assumed that neither true vocal cord is paralyzed. If, however, movement is not observed, nasopharyngoscopy with the patient awake should be performed. The subglottis should be evaluated, and any stenosis or scarring noted. If stenosis is present, its severity, length, position and physical characteristics should be noted. It may be characterized as soft or firm, as concentric or with lateral shelving, and with mucosa appearing either quiescent or actively inflamed.

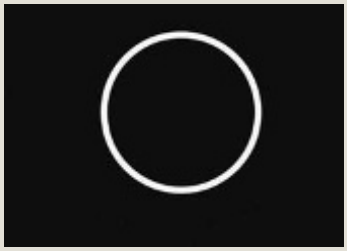
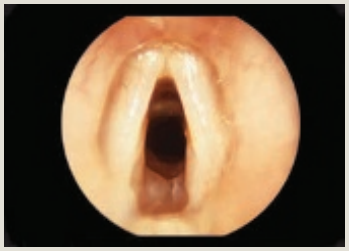
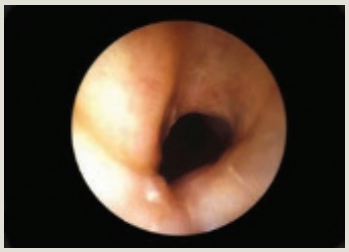
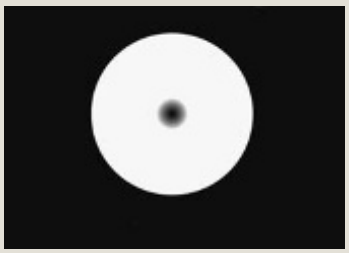
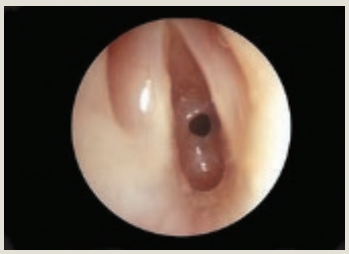
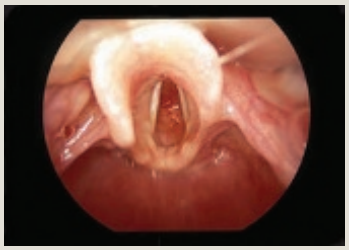
If there is a sufficient lumen to allow passage of the endoscope, the trachea is next assessed. Hopkins rod endoscopes with an outer diameter as small as 1.9 mm are available, and can negotiate most grade III SGS. An assessment is made of the upper trachea, including the tracheotomy stoma site, looking for suprastomal collapse or the presence of a suprastomal granuloma. Assessment is also made of possible tracheomalacia and vascular compression of the airway. Although complete tracheal rings are rare, their possible presence should be evaluated cautiously, so as not to induce oedema within an already compromised segment of airway. The carina and mainstem bronchi are also evaluated.

If SGS has been identified, the area of stenosis should be graded according to the Myer–Cotton classification[1] (see **Table 31.1**). This is best carried out utilizing endotracheal tubes, with a small tube being placed initially. If this tube leaks at less than 20 cm of water pressure through the subglottis, the next larger size is placed. It should be noted that the Myer–Cotton grading system is not designed to address supraglottic, glottic or tracheal stenosis (**Figure 31.1**).

ANAESTHETIC TECHNIQUE DURING BRONCHOSCOPY

A collaborative relationship with the anaesthetist is essential in deciding upon the specific anaesthetic technique to be used when performing rigid endoscopy. Possible options include spontaneous ventilation, assisted ventilation, jet ventilation, total intravenous anaesthesia (TIVA) and apnoea with intermittent bag and mask ventilation. Spontaneous ventilation offers the best dynamic assessment of the airway and is thus recommended. Endoscopy may be performed with the laryngoscope introduced into the airway and suspended in position. This frees both the surgeon's hands for introduction of a telescope and instruments as required. Some surgeons prefer to expose the larynx with an anaesthetic laryngoscope blade held in one hand and use the other hand to introduce a telescope. Endoscopy may also be performed with a ventilating bronchoscope or a Hopkins rod telescope, keeping in mind that the technique itself is not as important as the information gained. We prefer to use the Hopkins rod telescope, exposing the larynx with a straight anaesthetic laryngoscope blade. The child spontaneously ventilates a mixture of sevoflurane and oxygen through an endotracheal tube placed in the oropharynx, and with additional intravenous anaesthesia provided by propofol bolus.

TABLE 31.1 The Myer–Cotton classification (redrawn from Myer et al.,[1] with permission)

Grade	From	To	Examples
I	 No obstruction	 50% obstruction	
II	 51% obstruction	 70% obstruction	
III	 71% obstruction	 99% obstruction	
IV	No detectable lumen		

FLEXIBLE BRONCHOSCOPY

In selected children, flexible bronchoscopy may complement rigid bronchoscopy and both may occasionally be required to evaluate a child's airway adequately. Also, in many instances, these techniques can be used interchangeably. In some cases, however, each technique offers clear advantages. Rigid bronchoscopy provides a superior assessment of the larynx, especially the posterior glottic area. Flexible bronchoscopy is often extremely valuable in assessing a larynx that is difficult to access with rigid instrumentation and may provide valuable information about airway dynamics, such as the degree of pharyngeal collapse, glossoptosis and the presence of laryngomalacia, tracheomalacia or bronchomalacia. Flexible bronchoscopy also permits evaluation beyond the eighth generation of bronchi in older children and allows specific lavage of bronchial subsegments, which may provide information about silent aspiration if lipid-laden macrophages are found.

Gastrointestinal evaluation

OESOPHAGOGASTRODUODENOSCOPY, OESOPHAGEAL BIOPSY AND PH PROBE

In selected cases, particularly in patients with complex underlying medical conditions or in those who have failed previous airway reconstruction, oesophagogastroduodenoscopy may be beneficial in the assessment of a child prior to airway reconstruction. It can provide information about oesophagitis, gastritis, and the status of the lower oesophageal sphincter, especially in regard to whether a previous fundoplication is still functional.

Pre-operative evaluation of gastro-oesophageal reflux with dual probe pH or impedance monitoring and/or oesophageal biopsy is advisable and should be mandatory in a child with an active larynx or recalcitrant airway stenosis following previous reconstruction.[2] Oesophageal biopsy will also provide information about oesophagitis,

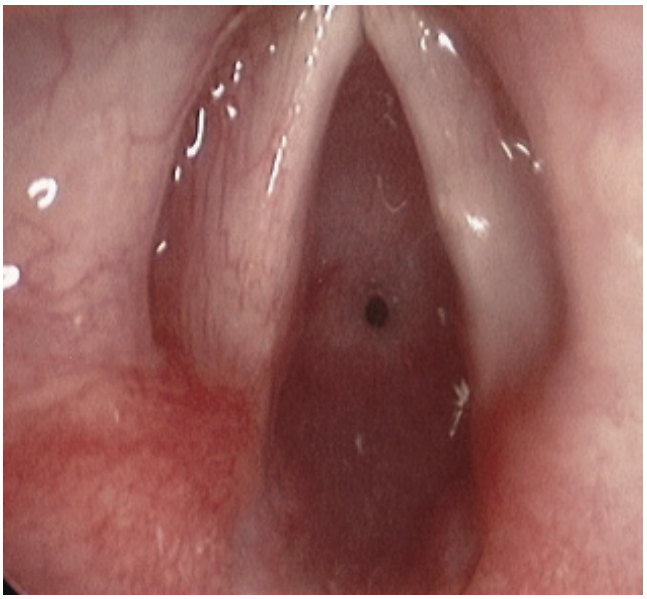


Figure 31.1 Grade III acquired subglottic stenosis.

including the possibility of eosinophilic oesophagitis, and is currently the best method of diagnosing and monitoring this condition.

Placement of a pH or impedance probe may be done at the time of oesophagogastroduodenoscopy, at the time of bronchoscopic evaluation, or may be performed as an elective procedure unrelated to endoscopic evaluation. Patients should be off antireflux medication for at least 1 week prior to pH probe placement. A dual pH probe with the upper port lying in the postcricoid region is desirable. While normal paediatric values for the upper port do not exist, positive readings should be viewed with suspicion. The impedance probe not only measures acid but can also provide an indication of the volume of a reflux bolus and the height in the oesophagus to which it progresses. Impedance technology also allows evaluation of non-acid reflux. This enables a child to remain on antireflux medication prior to evaluation.[3]

Evaluation of aspiration

Paediatric airway reconstruction runs the inherent risk of turning a child with laryngeal stenosis into a chronic aspirator. Although this risk cannot always be accurately evaluated pre-operatively, in most cases a thorough evaluation provides ample warning signs. Recurrent pneumonia and an insidious drop in a child's baseline oxygen saturation are highly suggestive of chronic aspiration. A history of previous aspiration or current aspiration is extremely important. In a child who is tracheotomy-dependent, copious tracheotomy secretions or secretions stained by food material indicate chronic aspiration. This is more difficult to evaluate in a child who is entirely gastrostomy (G-tube) fed. A simple solution is to intermittently place a drop of green food dye on the child's tongue and evaluate whether green-stained secretions are subsequently suctioned from the tracheotomy tube. Alternatively, a radionucleotide spit study may be performed: a drop of radioactive material is placed on the tongue and its passage is monitored to either the stomach or lung fields. In a child suspected of aspirating, a bronchoalveolar lavage, which can identify lipid-laden macrophages, may be useful. This does not, however, provide useful information in a child who is wholly G-tube fed. Children with grade IV SGS, in whom aspiration is not possible prior to laryngotracheal reconstruction, present a particular challenge. In these children, pre-operative evaluation to assess the relative risk of aspiration is strongly advocated.

A barium swallow or video swallow study may provide information not only on the presence of aspiration, but also on what substances are most likely to be aspirated. Thin fluids are more likely to be aspirated than purees or solids.

A functional endoscopic evaluation of swallowing, whereby the larynx is visualized with a nasopharyngoscope while a child swallows food or drink, can provide valuable information about the relevant risk of aspiration and the mechanism of aspiration as well as the presence or absence of normal laryngeal sensation.

Having knowledge of the possibility of post-operative aspiration allows for appropriate pre-operative counselling and management to minimize this risk. Innately, there are three things that may be aspirated, namely food and drink presented by mouth, saliva and gastric reflux. The respective risk of each can be minimized by conversion to G-tube feeding, reducing saliva production through a 'drool' procedure, and performing a fundoplication. Most children and families presented with the choice of a gastrostomy tube or a tracheotomy tube will choose the former.

Sleep evaluation

A formal sleep evaluation may be a useful method to evaluate a child's respiratory efforts and oxygen needs, whether or not a tracheotomy is in place. The primary aim of laryngotracheal reconstruction is decannulation, and this operative procedure is rarely warranted if decannulation cannot be achieved. In children with tracheotomy dependency, it is important to evaluate whether surgical correction of laryngeal stenosis will permit decannulation. In children with significant lung disease, particularly bronchopulmonary dysplasia or in those who are dependent on a ventilator or CPAP, decannulation may be imprudent. Similarly, children with progressive neuromuscular disorders, diaphragmatic weakness or central hypoventilation syndrome may not be candidates for decannulation. If results of a sleep evaluation indicate pulmonary compromise that precludes decannulation, laryngeal reconstruction may be futile.

Voice evaluation

Voice evaluation in children with laryngeal stenosis, tracheotomy dependency or following laryngotracheal reconstruction is in its infancy and is poorly understood. It is clear, however, that laryngeal reconstruction frequently has a negative impact on the voice, particularly

in children requiring supraglottic or glottic surgery and in those in whom a laryngofissure is required to reconstruct the airway. What is unclear is which underlying pathologies and reconstructive procedures place the voice at greatest risk, and also the extent to which a voice disorder relates to the initial aetiology of the laryngotracheal stenosis.

Children have a tremendous drive to communicate, which often compensates for severe anatomic dysfunction. Some children will retain a surprisingly good-quality voice, even with a grade III SGS. However, children with a grade IV SGS are aphonic unless they have learned oesophageal speech techniques. In these children, laryngotracheal reconstruction may be extremely beneficial in terms of regaining voice, even if decannulation is not achieved.

CONSIDERATIONS PRIOR TO LARYNGEAL RECONSTRUCTION

Surgical intervention for laryngeal stenosis is not always warranted, and the decision as to whether or not to perform such surgery is generally predicated by the overall health status of the child rather than by the stenosis itself. In a child with a high risk for aspiration or with certain craniofacial anomalies, surgical reconstruction may be inappropriate in that the laryngeal stenosis may actually protect the lungs from aspiration. In some children, ongoing aspiration may lead to a consideration of laryngotracheal separation rather than laryngeal reconstruction. Similarly, in children with other significant medical conditions, such as those requiring CPAP, bilevel positive airway pressure (BiPAP) or ventilator support, reconstruction is unwise. While not universally accepted or rigorously proven, most experts in paediatric laryngotracheal reconstruction believe that gastro-oesophageal reflux disease is both a cofactor for the development of SGS and a negative influence on the outcome of operative reconstruction. Oxacillin or methicillin-resistant *Staphlococcus aureus* (MRSA) screening prior to open airway surgery is also recommended, as post-operative infection may greatly compromise the surgical repair. Although a child with a progressive neuromuscular disorder may be considered for laryngotracheal reconstruction to improve vocal function, this seldom enables long-term decannulation.

In some children, a period of observation prior to considering surgical intervention is the best course of action. This strategy is most appropriate in a child with an active or inflamed larynx that is not amenable to medical intervention. An active larynx is generally related to gastro-oesophageal reflux disease or eosinophilic oesophagitis and is, therefore, potentially amenable to such intervention. In children in whom the aetiology of an active larynx is unknown, laryngeal reconstruction is unwise until the laryngeal inflammation has improved. In some of these children, azithromycin given as an anti-inflammatory drug on a Monday, Wednesday, Friday dosing regimen may be effective in reducing inflammation in up to 50% of children with an idiopathic active larynx. In children who do not respond to azithromycin, spontaneous resolution often occurs within a 1- to 2-year period. A waiting period is also advisable in a child who has recalcitrant stenosis after a recent airway reconstruction, or in a child whose larynx is healing from laryngeal trauma. While only a guideline, a 6-month 'cooling off' period is often advisable in such children.

Although weight is a less important factor than the overall health status of a child and the child"s laryngeal disease, it is a frequently used criterion for postponement of airway reconstruction. While laryngotracheal reconstruction can be effectively performed in children less than 3 kg if other criteria permit, a 10 kg guideline is often used. Nevertheless, airway reconstruction in a larger child is technically much easier to perform.

The child with complex medical problems

Historically, children presenting for airway reconstruction were otherwise healthy children with a stenosed larynx. Increasingly, however, children presenting for airway reconstruction have multifaceted complex medical problems, most commonly related to either extreme prematurity or syndromic conditions (see Chapter 5, The child with special needs). In such children, an interdisciplinary team approach is advisable for adequate assessment both before and after planned reconstruction. The most important decision to be made is whether it is advisable to even attempt reconstruction. If so, consideration must be given to other interventions indicated prior to proceeding with laryngeal reconstruction. In a child with reflux disease, a fundoplication may be required. In a child with aspiration, a 'drool' procedure may be required. It is prudent to have most of these children undergo additional evaluation by paediatric subspecialists in pulmonology, gastroenterology, medical genetics and neurology. Pre-operative evaluation and optimization improve outcomes.

THERAPY

Medical therapy

When the larynx is stable and quiescent, there is no role for medical therapy. In the inflamed or active larynx, however, medical therapy plays an important role in alleviating laryngeal inflammation; in turn, this enhances the potential for a successful operative outcome. In children with SGS, medical therapy alone occasionally obviates the need for laryngeal reconstruction by providing sufficient improvement to permit decannulation.

Medical therapy for an inflamed larynx revolves around treatment of gastro-oesophageal reflux disease or eosinophilic oesophagitis. If reflux is diagnosed or even suspected, then a low threshold for treatment with H_2 antagonists or proton pump inhibitors is recommended. In children with recalcitrant acidic reflux or significant non-acid reflux, consideration should be given to performing fundoplication.

A recent observation has been the correlation between eosinophilic oesophagitis, laryngeal inflammation and a poor outcome following laryngotracheal reconstruction.[4] Eosinophilic oesophagitis has a characteristic appearance on oesophagogastroduodenoscopy, with oesophageal furrows often having microscopic white plaques noted. However, the definitive diagnosis is made on biopsy, with greater than 20 eosinophils per high-power field being noted. In children with eosinophilic oesophagitis, evaluation for underlying food allergies is indicated. In children in whom a food allergy is not proven, treatment with oral fluticasone is suggested. An initial dosing regimen of 440 µg, sprayed on the tongue twice a day and swallowed, is usually efficacious. Follow-up oesophagoscopy with further biopsies to confirm resolution of disease is suggested prior to undertaking laryngeal reconstruction, which is usually delayed for 6 months.

Tracheotomy

In a child with an unsafe or unstable airway in whom laryngotracheal reconstruction is not immediately advisable, temporary placement of a tracheotomy tube is advisable to secure an adequate airway until laryngeal reconstruction can be performed. Placement of a tracheotomy should be performed with a view to the subsequent laryngeal reconstruction that may be required. A high tracheotomy close to the cricoid increases the risk of exacerbation of stenosis, but it may make subsequent cricotracheal resection (CTR) simpler, as a shorter segment of airway can then be resected. Tracheotomy through the second to fourth tracheal rings is still recommended.

Although a tracheotomy provides a safer airway in a child with laryngotracheal stenosis, the airway is by no means completely safe. Tracheotomy-related deaths continue to occur in children who could otherwise anticipate good long-term quality of life, and the greater the degree of obstruction, the greater the risk. A tracheotomy is a marked compromise on both a child's and a family's quality of life and emotional health.

Endoscopic management of subglottic stenosis

A range of endoscopic and open procedures are currently used for the management of SGS, and these approaches are not always mutually exclusive. Endoscopic approaches are used both as the primary treatment modality and as an adjuvant treatment before or after open airway reconstruction. Children with grade I or II stenosis and no history of endoscopic failure have a higher likelihood of successful endoscopic management, whereas those with more severe SGS or multilevel stenoses are more likely to require open reconstruction.[5, 6]

Although dilation has a considerable history, balloon dilation has been widely adopted only over the last decade, and bougienage dilation, with associated mucosal trauma caused by the shear forces inevitable with this technique, has fallen from favour.

Balloon dilation of the airway using high-pressure non-compliant balloons has evolved considerably in recent years and is now considered an invaluable addition to the tools used to manage SGS,[7–11] reportedly reducing the need for open airway surgery by as much as 80%.[10] Balloons offer a number of advantages, as they exert a purely radial force over the circumference of the stenosis, thus minimizing the risk of airway rupture or mucosal trauma. Pressures of over 20 atmospheres may be applied by some balloons. By using a device that incorporates a pressure gauge, they also allow the surgeon to fine-tune the force applied to the stenosis. A third advantage is that balloon dilation catheters are long, narrow and flexible — all of which allow the surgeon to steer through a severe stenosis. Selection of balloon size is based on the expected size of the normal airway. For example, a 4 year-old should be intubated with a 5.0 mm endotracheal tube with an outer diameter of nearly 7 mm. The balloon size selected would be 7–8 mm for the larynx. For tracheal lesions, balloon selection is typically 1 mm greater than the size predicted for the larynx. Repeated dilation at 1- to 3-week intervals on up to four occasions is recommended. Adjunctive interventions such as steroid injection and scar division may provide additional benefit, especially in patients with established thicker stenosis. Scar division may be performed utilizing a sickle knife, microlaryngeal scissors or a laser. In selected patients, subglottic or tracheal scarring may be divided prior to balloon dilatation (**Figure 31.2**).

Appropriate patient selection for balloon dilatation is critical to a successful outcome. Children who are likely to respond well to this technique are those with thin or web-like and soft stenoses consisting of immature scar tissue. In contrast, patients with firm or mature scar tissue, cartilaginous airway narrowing, and structural problems of the airway exoskeleton (e.g. subglottic lateral shelves, missing cartilage) are less likely to respond.[11] Dilation is also less likely to yield positive outcomes in longer stenoses and in patients with additional airway lesions.[11]

The recommended technique for balloon dilation is having the patient not be forcefully breathing during the procedure; therefore, after an initial evaluation of the airway, the patient is pre-oxygenated and then either briefly paralyzed or given a bolus of propofol to minimize spontaneous respiration. The balloon is introduced with direct visualization with a Hopkins rod endoscope, and then inflated to the rated burst pressure. Care should be taken that the balloon does not displace (watermelon seeding). The balloon is kept inflated for 2 minutes or until the patient desaturates to 90%, and it is then deflated and removed.

The potential complications of balloon dilation are rare. Negative pressure pulmonary oedema may occur with forced respiratory attempts against a closed glottis. Airway rupture may occur if an over-large balloon is selected. Distal displacement of the balloon due to watermelon seeding may occur and, if the balloon catheter is pulled and stretched trying to prevent displacement, the balloon may not be able to be deflated and may need to be ruptured with a needle or knife to remove it from the airway. Although newer balloon designs are less prone to

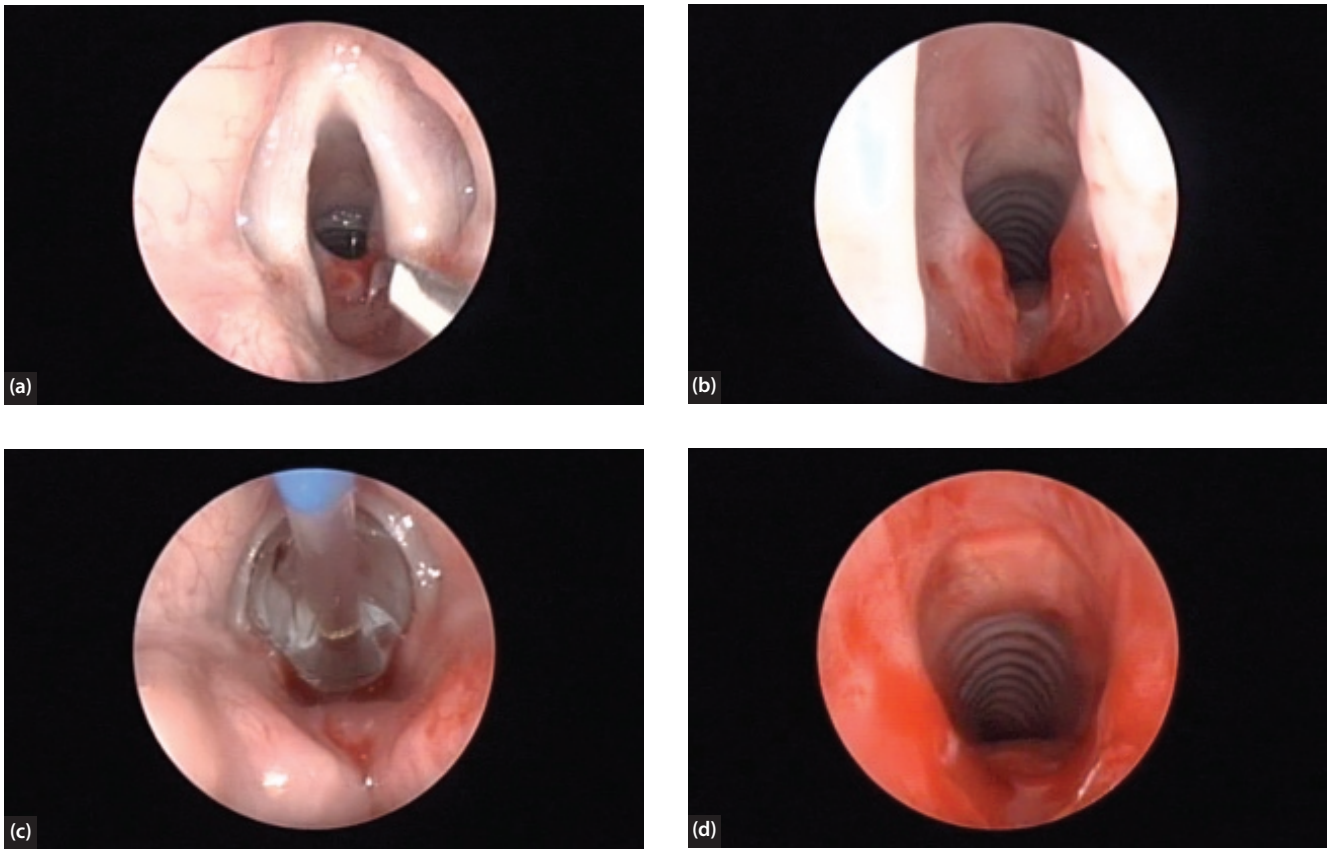


Figure 31.2 **(a)** Grade III acquired SGS immediately prior to endoscopic division with a sickle knife; **(b)** same stenosis after division in the midline posteriorly; **(c)** balloon dilatation in progress; **(d)** same child, immediately after balloon dilatation.

watermelon seeding, the main limitation of balloon dilation is that its success rate is lower than that seen with open airway reconstruction. If after four or five dilations the airway diameter has not significantly improved, then open surgery should be considered. Given that balloon dilation is relatively simple, fast and low-risk in children with mild to moderate degrees of SGS, it should be seriously considered prior to open airway reconstruction.

Laryngeal reconstruction

Laryngeal and upper tracheal reconstruction may be challenging and no single operation can adequately address all types of laryngeal stenosis. It is thus prudent to evaluate each child on an individual basis. In some patients, the most appropriate reconstruction technique may not become fully clear until the airway has been opened and the pathology directly inspected. The mainstay of laryngotracheal reconstruction is expansion cartilage grafting (**Figure 31.3**). In the subglottis, an alternative to this approach is resection and reanastomosis. Stenosis involving the supraglottis and anterior glottis is amenable to laryngoplasty without cartilage grafting. Whether congenital or acquired, tracheal stenosis may be best managed by a slide tracheoplasty (described later in this chapter).

In concept, laryngotracheal reconstruction may be managed either endoscopically or by expansion grafting, resection (tracheal or cricotracheal), or the slide tracheoplasty. Although the latter operation was conceived for the management of tracheal stenosis, it may extend into the larynx if appropriate.

GRAFTING MATERIALS

Costal cartilage is the most widely used grafting material, with excellent results noted on prolonged followup.[12, 13] It is readily available, robust, and easily shaped and carved. Moreover, it is possible to harvest more than one graft through the same incision. The usual donor site is the right fifth or sixth rib, with the incision being placed in the anticipated breast crease in girls for cosmetic reasons. The harvested graft should include the perichondrium on the lateral aspect of the graft, while leaving the inner perichondrial layer intact at the donor site to allow the potential for some cartilage regeneration. Once the graft is harvested, filling the wound with saline and performing a Valsalva manoeuvre will ensure that a breach of the pleura has not occurred. When the graft is carved to the desired shape, the perichondrium should face the lumen of the airway; lateral flanges will prevent prolapse of the graft into the airway.

When only a small graft is required, thyroid ala is a useful material. This is usually taken from the upper aspect of the thyroid cartilage on one side, at least 1 mm above the

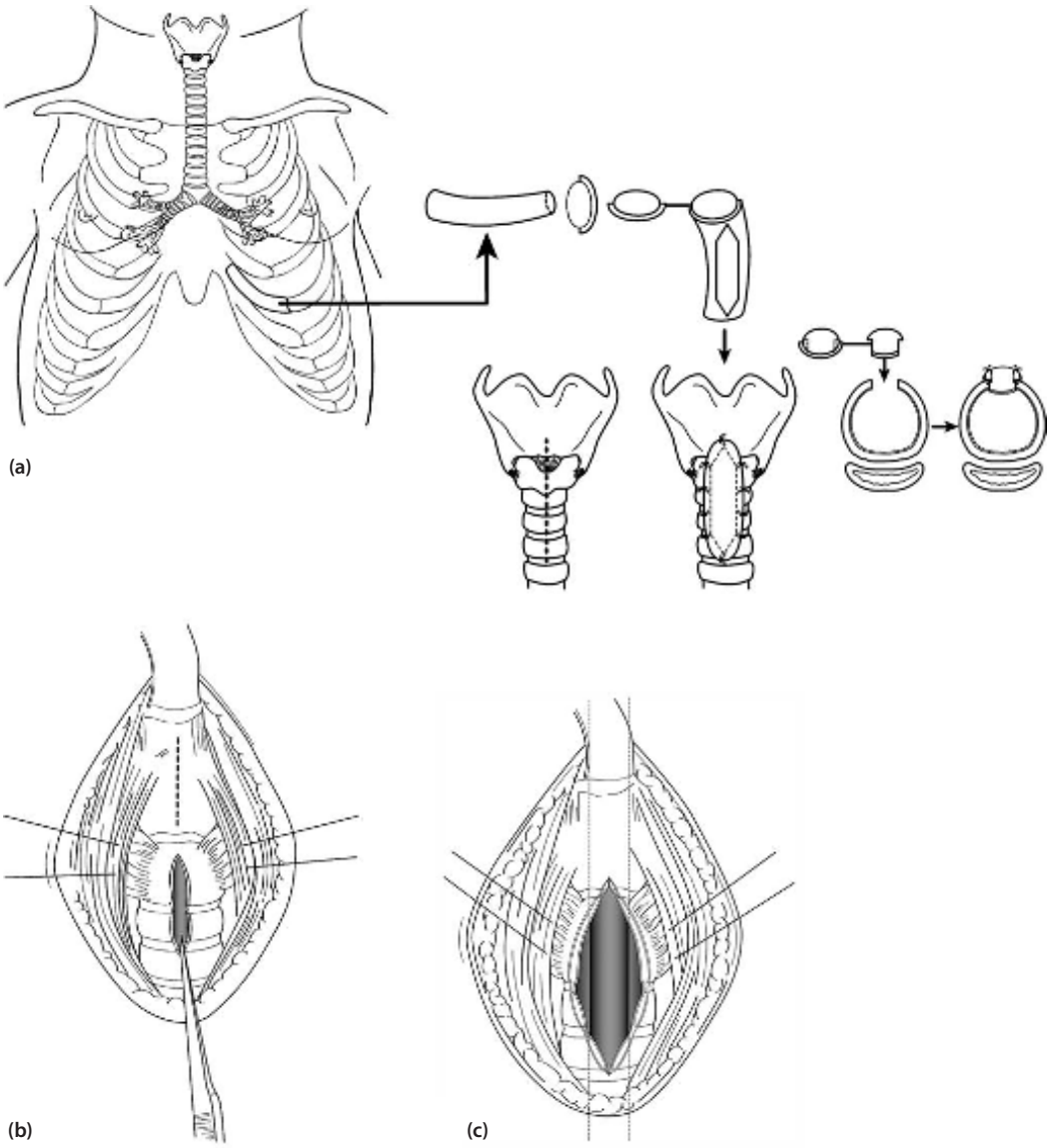


Figure 31.3 Expansion cartilage grafting.

level of the true vocal cord. Thyroid ala has the advantage of being quickly and easily harvested from within the surgical field. However, only a limited amount of grafting material is available and it is not amenable to being carved with flanges.

Auricular cartilage is also useful, in particular for the management of suprastomal collapse as part of a single-stage procedure. It is easily harvested and reasonably abundant. It makes an ideal cap or overlay graft, particularly over a stoma site, but it is comparatively weak and not appropriate for insertion between the cut edges of the cricoid. In both adults and older children, there is no cosmetic donor site deformity; however, in children younger than 1 year of age it is common to have some residual asymmetry of the ears.

Other grafting materials include buccal mucosa, septal cartilage, and a pedicled hyoid bone interposition graft. The results utilizing these grafting materials in children have been disappointing. Another described technique is the use of a clavicular periosteal graft, with its vascularity maintained by swinging the graft up on a pedicle of sternocleidomastoid muscle. This is a useful graft for older children in whom there is a significant deficit of tracheal cartilage, as after several months the graft will start to ossify, thereby providing support to the airway. In prepubescent children, the graft unfortunately seems less amenable to ossification, leaving the airway malacic.

STENTS

Not all laryngotracheal reconstruction techniques require stent placement. It may not be required in an anterior flanged graft for moderate SGS; however, it is advisable in virtually all other circumstances. Stenting maintains a lumen and prevents graft prolapse during post-operative healing, and it may remain in place for days to months. Longer-term stents are advisable when the laryngeal repair is unstable (e.g. when a posterior cricoid split has been performed in an older child without placement of a

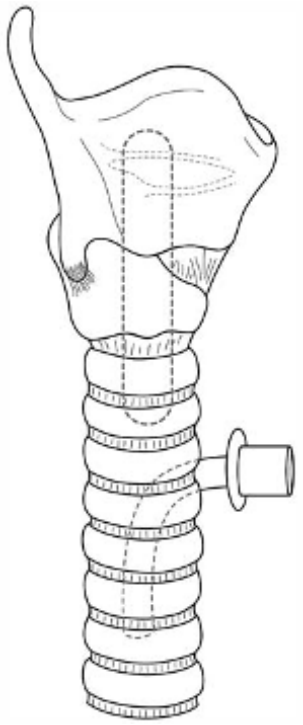


Figure 31.4 Rutter suprastomal stent.

cartilage graft) or in a recalcitrant larynx that has failed previous reconstruction. In patients in whom graft survival is threatened, such as diabetic patients and patients on continuous steroids, long-term stenting without cartilage grafts is advisable. The most commonly used stent is the silicone Rutter suprastomal stent (**Figure 31.4**), although Abouker, Monnier and Mehta stents are also available.

The Rutter stents are soft and deformable and do not interfere with placement of the tracheotomy tube. They tend to incite less granulation tissue at the distal end of the stent, and there is less dead space between the distal end of the stent and the tracheotomy tube in which scarring can occur. The proximal end of the stent is trimmed to the level of the false vocal cord and then plugged with a rounded cap that is less likely to induce epiglottic granulation tissue. Unlike the rigid Abouker Teflon stents, these soft silastic suprastomal stents may remain in place for longer than 6 weeks. There is a corresponding restriction of speech, as they permit only very limited air passage.

For longer-term stenting, tracheal T-tubes are recommended. Although T-tubes with an outer diameter of 5 mm are commercially available, because of the risk of crusting and obstruction, we do not routinely place T-tubes with an outer diameter of less than 8 mm. An 8 mm tube may be placed in a child as young as 4 years of age. Following laryngeal reconstruction, the upper end of a T-tube is generally passed through the vocal cords. Aspiration is therefore a significant risk and is expected for 2 weeks following stent placement. A supraglottic swallow technique is readily achieved by most children, minimizing the risk of aspiration. Unlike tracheotomy tubes, T-tubes cannot be easily changed. Meticulous T-tube care is thus essential.

SINGLE-STAGE RECONSTRUCTION

In children in whom a stenting period of less than 2 weeks is anticipated, an option to be considered is intubation, with the endotracheal tube acting as the stent.[14] Intubation for longer than 2 weeks, however, risks redevelopment of posterior glottic stenosis or SGS. For straightforward airway reconstruction, extubation may occur within a few days of the operation or, occasionally, even at the end of the reconstructive procedure. Although the optimal duration of intubation is not clearly defined, there has been a trend towards briefer periods of intubation following laryngotracheal reconstruction. Most children can be extubated within 2–7 days of a CTR or an anterior costal cartilage graft. Those with anterior/posterior cartilage grafts are usually intubated for 7–14 days. The older the child, the more forgiving the airway and the briefer the period of intubation required. For more complex airway surgery, a prolonged period of intubation is required.

A prerequisite for single-stage laryngotracheal reconstruction is an excellent intensive care unit (ICU) in which staff are familiar with the management of airway patients. It is undesirable for a child to have an unplanned self-extubation, and security of the nasotracheal tube is paramount. Therefore, in younger children, the use of arm restraints and sedation is usually required. Most children younger than age 3 require sedation, and children who have been previously intubated for long periods may require heavy sedation. Paralysis is undesirable, as in the event of accidental decannulation, the child is unable to maintain an airway and reintubation must be emergent. Since any child undergoing a single-stage procedure risks the need for reintubation, single-stage procedures should not be performed on children who are difficult to intubate. In the sedated child, commonly encountered problems include lung atelectasis, fluid overload from heavy sedation, pneumonia and narcotic withdrawal following extubation.

In children older than age 3 years with no major cognitive problems, sedation may not be required. Some of these intubated children may be able to ambulate, eat and visit the playroom. A fully awake child does not require ventilatory support and is less likely to have pulmonary complications from the intubation (**Figure 31.5**). The day prior to extubation, returning to the theatre to inspect the airway and downsize the tracheotomy tube is advisable (**Figure 31.6**). If the airway appears adequate to support extubation, a dose of dexamethasone, 0.5 mg/kg, is administered the night before extubation, and the patient is extubated while fully awake. Owing to the risk of laryngeal oedema, the patient should be closely observed on the ICU for the next 24 hours; oedema generally resolves within this period of time. In the event of airway distress following extubation, management options include the administration of racemic adrenaline, further steroids, helium/oxygen administration or even the use of CPAP or BiPAP. If the airway is still not adequate, the child may need to be reintubated. If so, a further trial of extubation should be performed a few days later. If this is again unsuccessful, a decision is

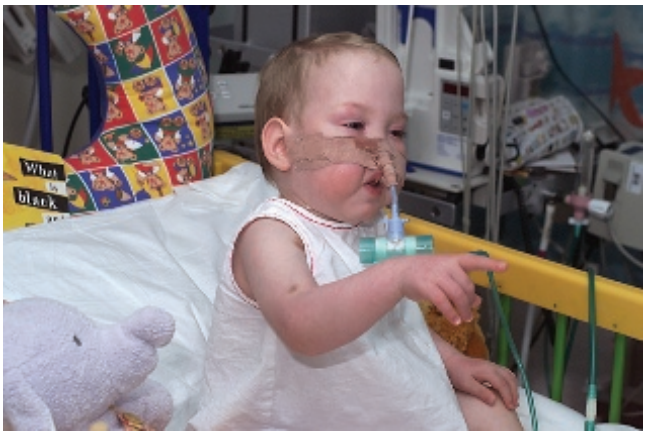


Figure 31.5 Single-stage laryngotracheal reconstruction. The child is intubated but awake in the intensive care unit.

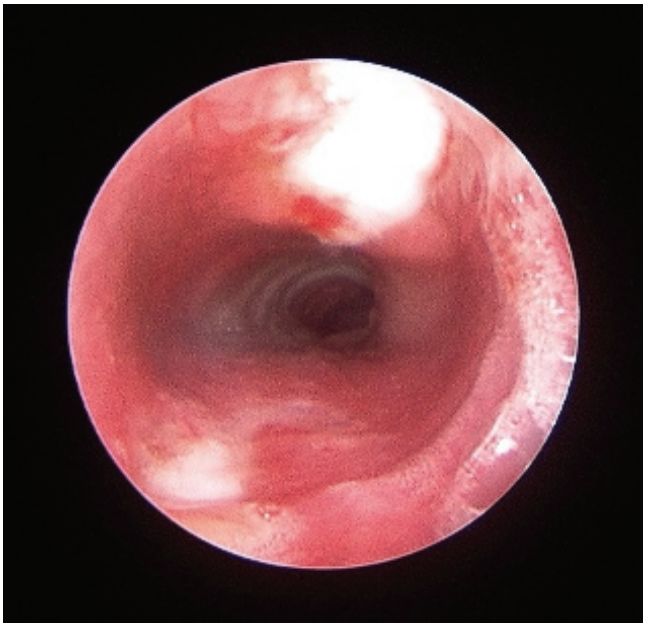


Figure 31.6 One week after single-stage laryngotracheal reconstruction the anterior and posterior costal cartilage grafts are visible but already partly covered in mucosa.

required as to whether to proceed to a third trial of extubation or to proceed with tracheotomy. If a tracheotomy is required, the stoma should ideally be placed low in the neck, below the graft site. Glottic oedema and granulation from endotracheal tube irritation are often the cause of failure during a single-stage procedure, rather than the reconstructed site itself. In such cases, the tracheotomy tube may be removed once the oedema has settled, usually within a few weeks.

The ideal patient for consideration of a single-stage procedure is one in whom a reasonably simple procedure with a stable larynx is anticipated. This single-stage approach is preferable in children in whom a tracheotomy tube has induced suprastomal collapse. Poor candidates for single-stage reconstruction include children with poor pulmonary function, those who are difficult to intubate, those with recalcitrant airway disease who have failed previous reconstruction, and those with complex disease involving multiple levels of obstruction.

Supraglottic stenosis

Supraglottic stenosis is rare, difficult to treat, and is frequently associated with supraglottic collapse. While severe supraglottic stenosis may present with stridor, the primary complaint is more commonly obstructed breathing during sleep. Therefore, a sleep study may be extremely useful in the non-tracheotomized patient or in the patient in whom the tracheotomy can be capped, even if for a brief period. The underlying aetiology is often traumatic, due to severe direct airway trauma or airway burns, or is of iatrogenic origin. Supraglottic stenosis with associated collapse is a feature of the airway that has undergone numerous laryngeal reconstructions. Visualization of the supraglottic larynx in cases of supraglottic stenosis and collapse may be misleading. Rigid endoscopic evaluation with the larynx suspended by a laryngoscope may distort the appearance of the larynx, providing false reassurance about the supraglottic airway. Flexible endoscopic evaluation with the patient spontaneously ventilating allows for superior evaluation of the airway dynamics. Nevertheless, what is observed may be deceiving. A larynx that looks extremely compromised in an anaesthetized patient may function quite adequately in the unanaesthetized state.

In children with mild to moderate supraglottic stenosis and collapse, nocturnal CPAP may be very beneficial. The most common patterns of supraglottic compromise are arytenoid prolapse and epiglottic petiole prolapse. Arytenoid prolapse is a dynamic instability of the arytenoid, either unilateral or bilateral. It is characterized by its anterior displacement during inspiration, which may cause significant airway obstruction. This problem most commonly follows previous CTR or previous laryngotracheal reconstruction involving division of the posterior cricoid plate. In CTR, the pathogenesis of arytenoid prolapse may be attributed to division of the lateral cricoarytenoid muscle. In laryngotracheal resection, the pathogenesis of arytenoid prolapse may be attributed to either direct damage to the posterior cricoarytenoid ligament or lateral distraction of the posterior plate of the cricoid.

Arytenoid prolapse is usually managed endoscopically, using a laser to perform a partial arytenoidectomy. The preferred technique is to raise a mucosal flap and debulk the prolapsing cartilage of the arytenoid without damaging the mucosal 'diamond' of the laryngeal inlet. Injudicious use of the laser in the laryngeal inlet predisposes patients to scar formation, fibrosis and narrowing of the supraglottic airway. This, in turn, may induce superimposed supraglottic collapse due to the Bernoulli effect.

Epiglottic petiole prolapse

This presents as a compromised laryngeal inlet owing to the base of the epiglottis (the 'petiole', from the term used to describe the footstalk of a leaf, i.e. the part which connects the blade to the stem) obscuring the anterior true

vocal folds and foreshortening the anterior/posterior diameter of the laryngeal inlet. This problem is most commonly seen in children who have had repeated previous laryngofissure and is a consequence of damage to the thyroepiglottic ligament, where it inserts into the thyroid cartilage just above the anterior commissure. Epiglottic petiole prolapse is rare, and challenging to treat. Injudicious use of a laser in the endolarynx tends to exacerbate the problem, with further scarring narrowing the laryngeal inlet. Suspension of the epiglottic base to the hyoid bone provides some benefit, but is technically challenging and causes the patient significant pain on swallowing for several weeks post-operatively.

Our current management of this challenging problem is to perform a complete laryngofissure and reposition the epiglottic petiole back up to the inner surface of the thyroid ala. The laryngofissure is then closed over a T-tube or suprastomal stent and left in position as a translaryngeal stent for at least 2 months. These patients may have problems with aspiration for some weeks post-operatively.

Acquired anterior glottic webs

Anterior glottic webs are most commonly congenital in origin, and are usually associated with a subglottic extension of the web resulting in coexistent SGS (see Chapter 30, Congenital disorders of the larynx, trachea and bronchi). Acquired anterior glottic webs are less common and are post-traumatic in origin. There are two common aetiologies: anterior neck trauma, often associated with a fractured larynx; and iatrogenic damage, often associated with injudicious use of a laser at the anterior commissure while managing laryngeal papillomatosis. It is rare for prolonged intubation to induce anterior glottic stenosis unless there is also associated SGS.

The management of acquired anterior glottic stenosis differs significantly from the management of the congenital anterior glottic web. The latter has normal mucosa within the remaining glottic inlet, and during reconstruction there may be sufficient mobility of the mucosal layer to reconstruct the anterior commissure without requiring the use of a laryngeal keel. In contrast, acquired anterior glottic stenosis is, by definition, associated with fibrosis and scarring. As such, during reconstruction, following laryngofissure, the mucosa is fibrotic and not amenable to reconstruction of the anterior commissure. Therefore, reconstruction with placement of a laryngeal keel is mandatory while the raw surfaces on either side of the laryngofissure remucosalize.

The usual technique for repair of an acquired anterior glottic web is an open approach with complete laryngofissure, and it is recommended that this is performed with endoscopic guidance. With the laryngofissure complete, the demucosalized raw scar of the anterior vocal folds is noted and, in some cases, there may be enough mucosal mobility to place a pexing suture from the cut edge of the mucosa on either side towards the thyroid ala. Unlike repair of congenital anterior glottic webs, it is unusual to be able to pex the mucosal edge up to the anterior commissure — hence the need for a laryngeal keel. An appropriate size laryngeal keel, such as the Montgomery Keel,™ is then selected and trimmed. The vertical limb of the keel should not impinge into the posterior commissure. The vertical height of the keel should separate the raw surfaces of the laryngofissure. The upper limit of the keel should not be so high as to disrupt the insertion of the epiglottic petiole.

The keel is then sewn into place and the laryngofissure closed. This procedure is normally performed as a two-stage procedure, although a single-stage procedure may be performed with the patient intubated and with the endotracheal tube lying on one side of the vertical limb of the keel. In some children, there is an associated component of SGS, and a decision should be made as to whether the cricoid can be closed adequately over an age-appropriate endotracheal tube. If this is possible, the lower end of the keel should not extend beyond the cricothyroid membrane. If it is not possible, an anterior cartilage graft is placed in the anterior cricoid, distal to the keel.

The keel is removed through an open approach between 10 days and 4 weeks post-operatively. The resultant midline deficit in the thyroid ala is then closed with laterally placed mattress sutures, as the cartilage edges of the laryngofissure are friable and easily damaged if sutures pull out. For this reason, antibiotic coverage and antireflux measures are advised during the period that the keel is in place, and for an additional few days after keel removal.

Endoscopic placement of the laryngeal keel is increasingly a consideration. Even in younger children, it is possible to suspend the larynx on a laryngoscope and endoscopically divide the web with a sickle knife or a laser. The keel may be fashioned from a thin piece of silastic sheeting, with a central suture orientated in the anterior midline across the divided web, and with the silastic sheet placed like the leaves of a book over the divided mucosa. The suture may be placed as an ‘inside-out’ technique using a Lichtenberger needle driver or as an ‘outside-in’ technique using a Keith needle and hollow angiocath.

Posterior glottic stenosis

Posterior glottic stenosis is frequently misdiagnosed and often confused with bilateral true vocal cord paralysis. It may exist as an isolated entity or in combination with SGS. The most frequent aetiology of this condition is prolonged intubation, with the older child being at greater risk than the neonate. The posterior glottis is also susceptible to damage from thermal injury caused by inhalational or airway fires or to iatrogenic damage from use of the laser in the posterior commissure. Occasionally, posterior glottic stenosis may be a result of direct laryngeal trauma.

If not already tracheotomy-dependent, patients present with stridor and exertional dyspnoea. Normal vocal function is usually preserved and, in this regard, presenting symptomatology is similar to that seen in bilateral vocal cord paralysis or cricoarytenoid joint fixation.

Definitive diagnosis requires assessment with rigid bronchoscopy, which confirms the presence of posterior glottic scarring, as a rigid telescope provides excellent visualization of the posterior glottis. Posterior glottic stenosis can, however, be misdiagnosed on bronchoscopy if the telescope is passed directly through the vocal folds to evaluate the subglottis without proactive inspection of the posterior glottis. Bronchoscopic evaluation should also include assessment of the subglottis, which is frequently involved with scarring. An assessment of arytenoid mobility is required as cricoarytenoid joint fixation is an occasional co-pathology. Formal sizing of the airway utilizing endotracheal tubes may be misleading. Posterior glottic stenosis may limit the size of the endotracheal tube that may be inserted. In some cases, however, the vocal folds easily bow laterally to accommodate an age-appropriate endotracheal tube despite still being tethered posteriorly, compromising the airway. It should again be emphasized that the Myer–Cotton grading system is only applicable to SGS.

While flexible bronchoscopy provides a poor view of the posterior glottis and is an inadequate method of diagnosing posterior glottic stenosis, awake flexible nasopharyngoscopy may be extremely useful in determining if vocal fold function is intact. The usual finding is that the vocal folds are mobile but tethered and unable to abduct.

The differential diagnosis for posterior glottic stenosis commonly includes SGS (which frequently may also be present), an interarytenoid scar band, and cricoarytenoid joint fixation. In children referred for the management of posterior glottic stenosis, it is rare to find vocal cord paralysis. By contrast, children referred for the management of bilateral vocal cord paralysis may, in fact, have posterior glottic stenosis tethering the vocal cords and masquerading as vocal cord paralysis. Bilateral vocal cord paralysis and posterior glottic stenosis rarely coexist.

Placement of a posterior costal chondral graft is the mainstay of management and is a highly effective way of achieving an adequate glottic airway.[15, 16] This procedure is best performed through an anterior approach, traditionally through a complete laryngofissure. This approach allows excellent exposure of the posterior glottis and direct visualization of the posterior glottic scar band. The posterior glottis is then infiltrated with 1% Xylocaine with adrenaline. The needle is guided through the posterior plate of the cricoid in the midline until it can be felt to pop through into the space between the posterior cricoid and the oesophagus. A further small amount of Xylocaine and adrenaline may then be injected in two or three positions down the cricoid. This has the advantage of providing not only haemostasis in the postcricoid region but also an additional buffer zone between the posterior cricoid plate and the oesophagus. The posterior cricoid can then be split vertically for its entire length, ensuring that the incision is kept completely in the midline. It is important that the interarytenoid scar band is completely divided. The incision may be continued superiorly through the interarytenoid muscles (which are frequently fibrosed) up to the level of the interarytenoid mucosa itself. Care must be taken not to inadvertently form a posterior laryngeal cleft. Following the posterior split, the cricoid should be easily distracted laterally. A costal cartilage graft is then harvested and carved so that its height is approximately the height of the cricoid split and its depth allows the graft perichondrium to lie reasonably flush with the cut mucosa of the posterior cricoid. The graft may be sewn in place with 4.0 Monocryl™ sutures on a P2 needle. An alternative approach is to form a flanged graft that can be snapped into place and stabilized with a small amount of fibrin tissue glue. With the posterior graft in place, the laryngofissure is then closed over an age-approximate endotracheal tube. If the cricoid does not easily close anteriorly, a further segment of costal cartilage is used as an anterior cricoid graft. A posterior graft rarely needs to be more than 6 mm wide as the primary aim of surgery is to incise the scar tissue and hold the raw edges apart while healing takes place. A graft surpassing this width carries an increased risk of aspiration and a poor vocal outcome.

It is possible to perform this procedure without performing a complete laryngofissure. If the anterior airway incision is carried up to the true vocal cords but not through them, there is usually sufficient access to perform a safe posterior cricoid split and allow insertion of a flanged graft. Such a graft is required, as there is not adequate access to comfortably place sutures with this technique. This technique can even be used in small children.

Posterior cricoid grafting may be performed as a single- or two-stage procedure. Other variations of open reconstruction include scar excision alone, buccal mucosal grafting and a posterior cricoid split without graft placement. However, a posterior split without a graft normally requires a considerable period of stenting before full stability is achieved. A posterior cricoid split without graft placement is most effective in children younger than 9 months of age, and even then, in a single stage procedure, usually requires a 10-day period of intubation.

A posterior costal cartilage graft may be placed endoscopically,[17] and this approach has become increasingly popular over the last 10 years. Patient selection requires no anterior component of SGS, and a larynx that can be adequately exposed. The posterior cricoid may be split with a laser of a sickle knife, and balloon dilation may be used to distract the posterior split. Pockets are created behind the posterior plate of the cricoid to accommodate the posterior flanges of the graft. Significant force is required to place the graft, and balloon dilation may assist with graft placement. This technique may be used to expand the posterior cricoid in posterior glottis stenosis, SGS, or bilateral vocal cord paralysis.

Other endoscopic techniques may also be efficacious; however, they are generally not as reliable as the open approach. Although a laser posterior cordotomy with or without partial arytenoidectomy is effective, there is a significant chance of restenosis. In order to prevent restenosis, the use of mitomycin C is a consideration, as well as placement of a temporary transglottic stent. Other described techniques for the endoscopic management of

posterior glottic stenosis include mucosal advancement flaps, microtrap-door flaps, vocal cord lateralization, and botulinus toxin (Botox) injections.

Whether reconstruction is open or endoscopic, there is a restenosis rate of 10–20%. This rate is higher in children who have had thermal injury to the posterior glottic stenosis. If a child has failed an endoscopic procedure, then open reconstruction is appropriate. Conversely, if a child has failed an open procedure, endoscopic management may be appropriate. In a recalcitrant airway, it is possible to place a second posterior costal cartilage graft if required.

Posterior glottic stenosis

Interarytenoid adhesion is a distinct variant of posterior glottic stenosis, with presentation similar to this condition or to bilateral true vocal cord paralysis. An interarytenoid adhesion results from prolonged intubation, when tongues of granulation tissue lying anterior to the endotracheal tube in the region of the vocal process unite in the midline to form a fibrous scar band. While this usually progresses to form posterior glottic stenosis, mucosal sparing of the posterior commissure sometimes occurs, resulting in the formation of an interarytenoid scar band (**Figure 31.7**). Endoscopic evaluation confirms a small posterior commissure air passage and a larger anterior glottic airway passage. However, there may be a marked limitation to the size of endotracheal tube that can be used for intubation if there is not a tracheotomy tube already present. Endoscopic resolution of this problem is simple and effective. In most cases, microlaryngeal scissors are used to excise the scar band, with immediate resolution of symptoms. In some children, this problem may coexist with either or posterior glottic stenosis.

Subglottic reconstruction

REPAIR TECHNIQUES

Anterior cricoid split

In the neonate who has failed extubation, the anterior cricoid split procedure is an alternative to tracheotomy (**Figure 31.8**). The criteria for anterior cricoid split are specified below:[18]

- failed extubation on at least two occasions
- weight >1500 g
- extubation failure secondary to laryngeal pathology
- no assisted ventilation for 10 days before evaluation
- supplemental O_2 requirement <35%
- no congestive heart failure for 1 month prior to evaluation
- no acute upper or lower respiratory tract infection at the time of evaluation
- no antihypertensive medication for 10 days before evaluation.

The procedure involves an anterior incision of the trachea from the second tracheal ring, up through the cricoid and into the lower third of the thyroid cartilage, just

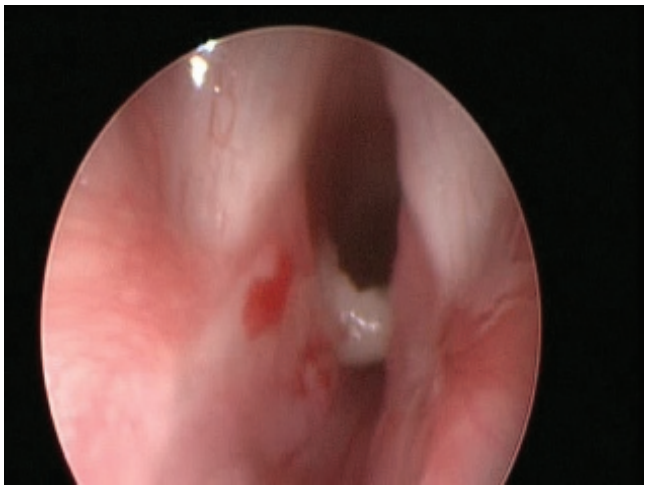


Figure 31.7 Interarytenoid scar band resulting from intubation trauma.

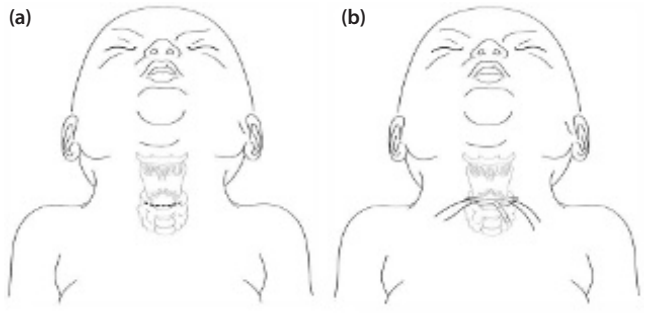


Figure 31.8 The anterior cricoid split procedure.

below the insertion of the anterior commissure. The child is then left intubated for 10 days, with the neck wound left at least partly open to minimize the risk of subcutaneous air build-up. A thyroid alar interposition graft is a modification that permits earlier extubation. It should be noted that while the success rates for this procedure were impressive in initial series, this rate has dropped over time, reflecting advances in neonatal care. Infants who failed extubation 30 years ago are no longer intubated due to the introduction of nasopharyngeal CPAP and high-flow nasal cannulae. Currently, infants requiring intubation and subsequently failing extubation are far more likely to be affected by extreme prematurity or to have other genetic or congenital comorbidities and, as a consequence, success rates for the anterior cricoid split are significantly lower.

Laryngotracheal reconstruction: anterior cartilage graft

Mild to moderate SGS is well managed with costal cartilage grafting to the anterior cricoid (see **Figure 31.3**).[19] The anterior airway is split from the tracheotomy site to the lower aspect of the thyroid cartilage. An age-appropriate sized endotracheal tube or suprastomal stent is then inserted, and a measurement is taken of the size of graft needed to comfortably close the deficit in the anterior airway. A costal cartilage graft is then harvested and carved

to allow a boat-shaped and perichondrium-lined insert to distract the anterior cricoid. An outer flange prevents graft prolapse into the airway. This technique is also useful for managing suprastomal collapse or narrowing of the upper trachea.

Laryngotracheal reconstruction: posterior cartilage graft

Costal cartilage grafting of the posterior cricoid for SGS may be performed in an identical fashion as for posterior glottic stenosis. If the anterior cricoid can then close comfortably over an appropriate sized endotracheal tube or stent, the additional anterior grafting is not required.

Laryngotracheal reconstruction: anterior and posterior cartilage grafts

If the anterior cricoid cannot comfortably close over an appropriately sized endotracheal tube or stent, then an additional anterior graft is required, as previously described. This is necessary for most grade III and all grade IV stenoses.

Cricotracheal resection

Cricotracheal resection (CTR) has an increasing role in the management of SGS. This procedure requires the removal of the subglottic scar tissue, with the anastomosis of healthy trachea to a healthy larynx. This is a technically more challenging operation than laryngotracheal reconstruction with cartilage grafts (**Figure 31.9**).

The success of CTR in infants and children has been documented in large series of patients in three separate centers.[20–22] The results reported are superior to those of the laryngotracheal reconstruction procedures for similar indications and stenosis grades. CTR with primary anastomosis is a safe and effective procedure for the treatment of severe SGS in infants and children. Diagnostic precision is essential, operative timing should be judged carefully, and operative technique must be precise. The reasons for the high success rate include the complete resection of the stenotic segment with restoration of a lumen using a normal tracheal ring, the preservation of normal laryngotracheal support structures without disruption of the cartilaginous framework, and full mucosal lining on both sides of the anastomosis, thus minimizing or preventing granulation tissue and restenosis.

The possible complications of the surgery, however, should not be underestimated. The first is injury to the recurrent laryngeal nerve. Typically, this nerve is not identified during the procedure as it lies posterior to the cricothyroid joint and the resection margin is anterior to the cricothyroid joint. The second complication is dehiscence of the anastomosis. This is most likely to happen if the operative site gets infected or if there is tension at the site of the anastomosis, or because of forceful reintubation if the endotracheal tube becomes dislodged. In the paediatric larynx, the technique of laryngeal release is not required in most cases of CTR. If mobilization of the trachea is difficult or tracheal resection is extensive (more than five tracheal rings), laryngeal release should be performed to minimize the risk of dehiscence. If granulation tissue is allowed to grow, there is also a risk of restenosis. For this reason, sutures through the cartilage should emerge submucosally at the edge of the anastomosis.

Experimental data in primates show that when CTR and primary tracheal anastomosis are performed with a good initial result, the thyroid cartilage and tracheal ring sutured together continue to grow normally. A further advantage of the CTR technique may be that voice quality should not deteriorate because the anterior commissure of the larynx is maintained in its initial position and there is no widening of the larynx posteriorly with an interposition graft. However, in older children, CTR may limit the ability to tilt the thyroid cartilage on the cricoid cartilage, in turn restricting cord tensioning and leading to a loss of vocal range.

Slide tracheoplasty

The slide tracheoplasty was originally conceived as an operation to expand a congenitally stenotic trachea due to complete tracheal rings[23] and is currently the operation of choice for the management of complete tracheal rings.[24] It is a versatile operation and may also be employed for patients with acquired laryngotracheal stenosis. Although originally described using an intrathoracic approach, a cervical approach allows access to the upper two-thirds of the trachea.[25] For patients with combined disease, if the associated SGS makes a graft to the anterior cricoid an option, then the lower trachea may be slid into the split anterior cricoid as an alternative to a costal cartilage graft.

The technique involves adequate exposure of the larynx and trachea, with the stenotic segment then being delineated by an assistant performing bronchoscopy (rigid or flexible) while the surgeon places a 30G needle into the airway. The proximal and distal aspects of the stenosis are marked on the anterior airway, and the length of the stenosis is measured. The trachea is then transected, typically with a bevelled transection commencing on the anterior trachea proximal to the midpoint of the stenosis, and extending over two rings distally, with the posterior transection point being at or just distal to the midpoint of the stenosis. The distal trachea is then split in the midline posteriorly to just beyond the stenosis, while the proximal trachea is split anteriorly to just beyond the stenosis – typically to thyroid cartilage. The most damaged and stenotic segment of trachea tends to lie at the midpoint of the stenosis, and this may be resected if desired. The trachea is then anastomosed with a double-armed PDS suture, typically a 4.0, with RB-1 needles in an older child or adult. A running suture technique is employed, with no attempt to keep the suture extraluminal but with care taken to tighten the running suture as the anastomosis is completed. A single proximal anterior knot completes the anastomosis. The airway is leak-tested and then sealed with fibrin glue, and the patient is typically extubated at the end of the procedure. While it is feasible to perform a slide tracheoplasty into the posterior cricoid, it is technically challenging, and the results are unpredictable. Because of this, it is not recommended.

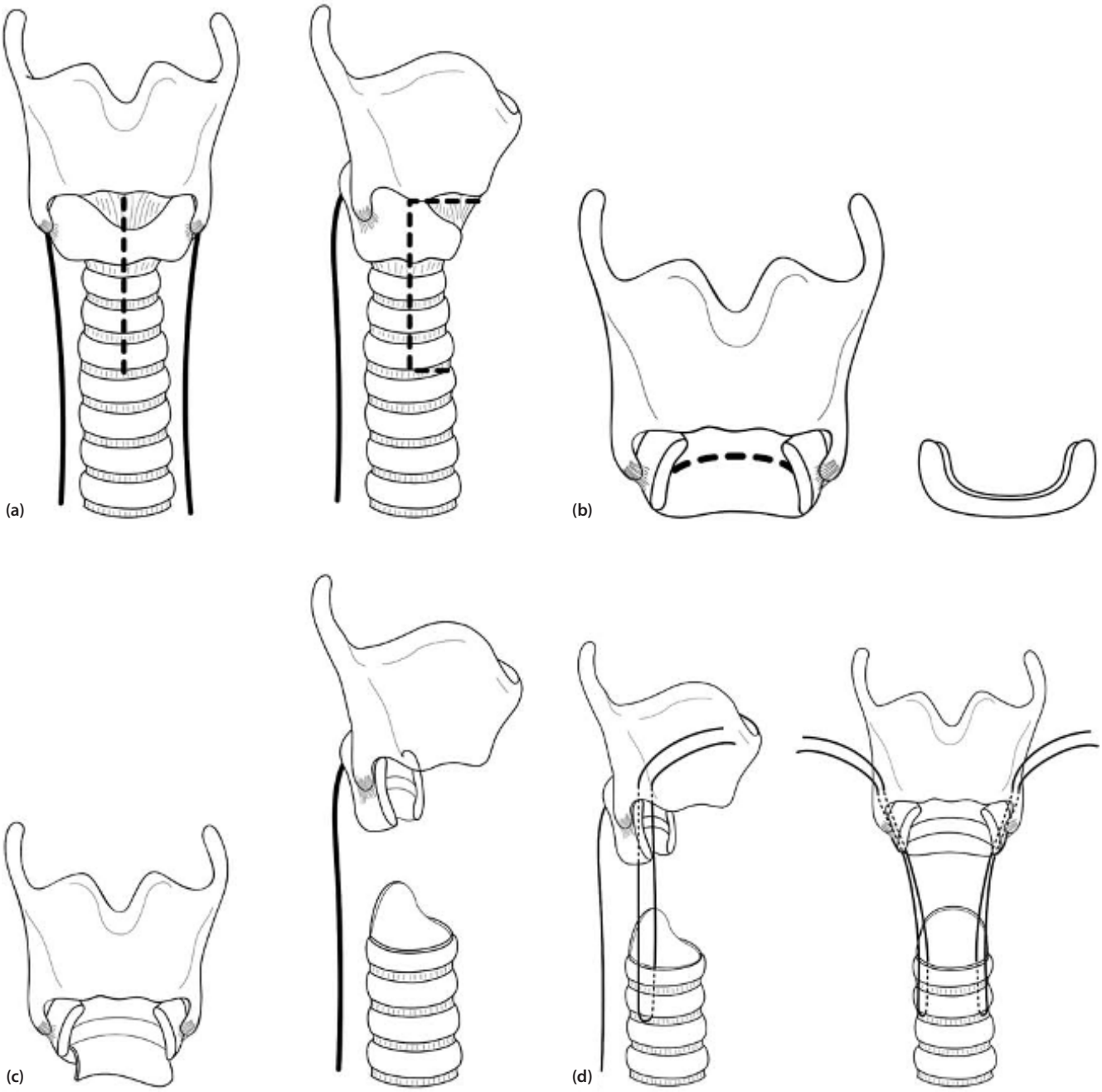


Figure 31.9 Cricotracheal resection.

(Continued)

CONTRAINDICATIONS

All contraindications to airway reconstruction are relative. Usually, airway reconstruction is not attempted unless decannulation is the goal. Gastro-oesophageal reflux disease and eosinophilic oesophagitis should be controlled pre-operatively, and pulmonary function optimized. Operating on a child requiring pulmonary pressure support to ventilate adequately is unwise. Single-stage reconstruction is inadvisable in a child who is difficult to intubate. In children with a history of sedation problems, past failure of airway reconstruction or multiple levels of airway pathology, single-stage reconstruction should be approached with caution. In children undergoing CTR, the risk of anastomotic dehiscence seems higher in the presence of Down syndrome, MRSA or a past history of distal tracheal surgery. The greatest disservice to a child is for airway reconstruction to cause or exacerbate ongoing aspiration.

COMPLICATIONS

Complications may be subdivided into intra-operative, early post-operative and late post-operative.[26] Intra-operative complications include bleeding, pneumothorax

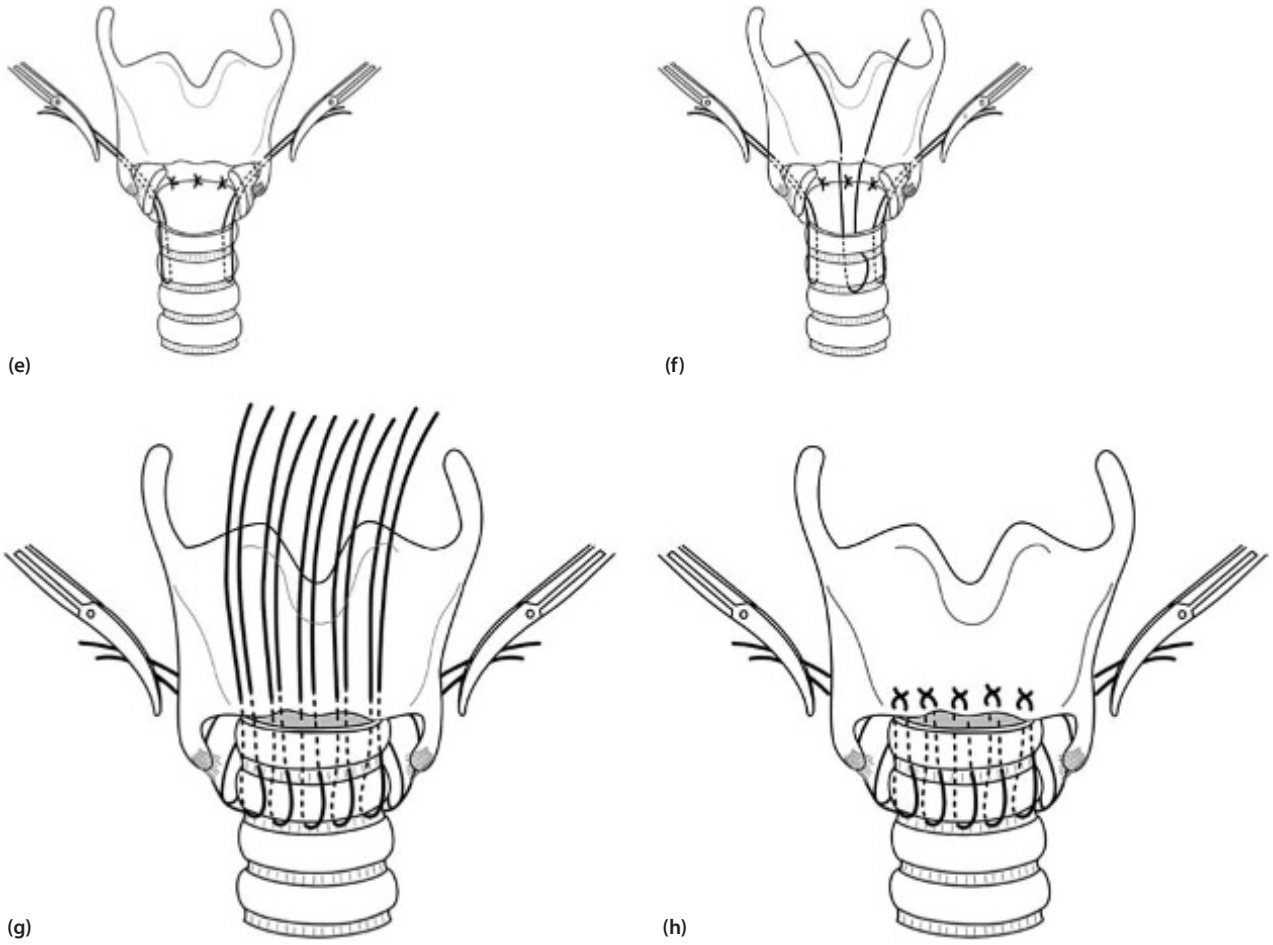


Figure 31.9 (Continued) Cricotracheal resection.

and loss of the airway with resultant hypoxia. Early post-operative complications include infection, air leakage from the operative site, dehiscence of an anastomosis and loss of a graft. The risk of air leakage and graft loss is highest when systemic steroid use is continued beyond two or three peri-extubation doses. With single-stage procedures there is a risk of accidental extubation and risks associated with paralysis or sedation. Extubation may be compromised because of glottic oedema and granulation caused by the endotracheal tube (Figure 31.10). The most significant long-term complication is failure of the reconstruction with restenosis of the subglottis, with an incidence between 10% and 20% in most series.

Revision airway surgery/ the recalcitrant airway

Failure of laryngotracheal reconstruction or CTR does not preclude further attempts at reconstruction but it may complicate further reconstructive efforts. In revision airway surgery, particular care should be taken to optimize the outcome by careful pre-operative evaluation of the patient and their airway. Failed expansion cartilage grafting may still be amenable to either further cartilage grafting or resection, while failed resection may still be amenable to further resection or cartilage grafting.

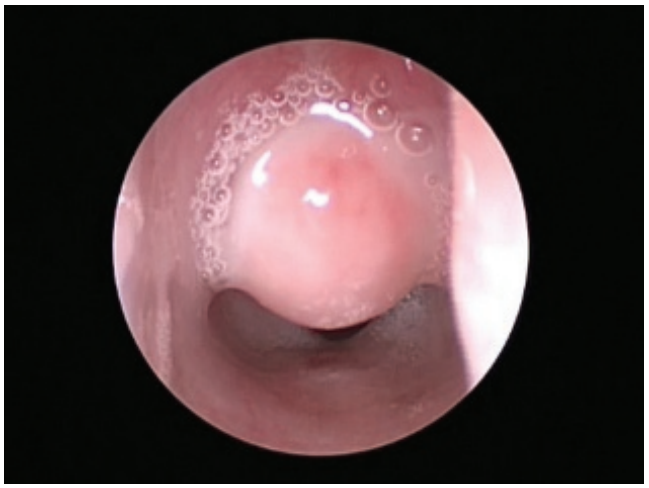


Figure 31.10 Large granulation arising on an anterior costal cartilage graft in the subglottis 3 days after extubation (10 days after surgery).

BEST CLINICAL PRACTICE

- ✓ In the neonate who has failed extubation, the anterior cricoid split procedure is an alternative to tracheotomy.
- ✓ Pre-operative evaluation of gastro-oesophageal reflux should be mandatory in a child with an active larynx or recalcitrant airway stenosis following previous reconstruction.
- ✓ Functional endoscopic evaluation of swallowing can provide valuable information about the risk and mechanism of aspiration as well as the presence or absence of normal laryngeal sensation.
- ✓ In a child who has not been evaluated previously, flexible nasopharyngoscopy with the child awake should be performed prior to rigid endoscopy.
- ✓ In children with significant lung disease, decannulation may be imprudent. Children with progressive neuromuscular disorders, diaphragmatic weakness or central hyperventilation syndrome may not be candidates for decannulation.
- ✓ In a child with a compromised airway who does not have a tracheotomy tube, pre-operative administration of dexamethasone, 0.5 mg/kg up to a maximum of 20 mg, is a prudent precaution.
- ✓ Spontaneous ventilation offers the best dynamic assessment of the airway and is thus recommended.
- ✓ In children in whom a stenting period of less than 2 weeks is anticipated, consider intubation, with the endotracheal tube acting as the stent (see 'Single-stage reconstruction').
- ✓ A prerequisite for single-stage laryngotracheal reconstruction is an excellent ICU in which staff are familiar with the management of airway patients.

FUTURE RESEARCH

- ➤ While laryngotracheal reconstruction and CTR have become accepted management techniques for SGS, supraglottic airway management remains poorly understood and managed.
- ➤ Pre-operative evaluation and optimization of patients prior to reconstructive airway surgery still requires refinement.
- ➤ Recent technological advances, such as impedance probe evaluation of gastro-oesophageal reflux, need critical evaluation.
- ➤ Balloon dilation of SGS is an area that would benefit from clinical and animal research to help formulate management guidelines.
- ➤ Paediatric voice research may be an area for future endeavour.
- ➤ An airway grading system that is not limited to just the subglottis needs to be developed.
- ➤ Tissue-engineering techniques may offer alternatives to current methods of airway reconstruction.

KEY POINTS

- The narrowest point in the infant airway is the cricoid ring. The only fixed ring within the airway, it is the most vulnerable point for iatrogenic damage caused by intubation.
- Acquired SGS secondary to prolonged endotracheal intubation remains the most frequent cause of laryngeal stenosis.
- Laryngeal stenosis continues to cause significant morbidity and mortality. The most common primary aim of intervention is decannulation or preventing the need for tracheotomy. In selected patients, voice restoration or provision of a safer airway is the primary consideration, with decannulation a secondary goal.
- Evaluation of the paediatric airway should not be considered a minor procedure, particularly when performed in a child with an unstable airway. Extreme care must be taken not to exacerbate the child's condition.
- Rigid endoscopy remains the gold standard for paediatric airway evaluation.
- SGS may be managed endoscopically in selected cases, with balloon dilation being the most effective tool.
- Laryngeal and upper tracheal reconstruction may be challenging; no single operation can address all types of laryngeal stenosis. It is prudent to evaluate each child on an individual basis.
- The most significant long-term complication of surgery for laryngeal stenosis is failure of the reconstruction with restenosis of the subglottis, with an incidence of 10–20% in most series.
- CTR has an increasing role in the management of subglottic stenosis. CTR is particularly effective as a salvage procedure following failed laryngotracheal reconstruction.
- The greatest disservice to a child is for airway reconstruction to cause or exacerbate ongoing aspiration.

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CHAPTER 32

JUVENILE-ONSET RECURRENT RESPIRATORY PAPILLOMATOSIS

Rania Mehanna and Michael Kuo

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed (NLM) search using the keywords: respiratory papillomatosis and laryngeal papillomatosis.

INTRODUCTION

Recurrent respiratory papillomatosis (RRP) is a potentially life-threatening disease characterized by the development of papillomata anywhere in the respiratory tract from the nasal vestibules to the terminal bronchi. Predominant sites are where there is a change of epithelium (e.g. from squamous to ciliated) and especially the tonsillar pillars, uvula, vocal folds and laryngeal commissure. There is a bimodal age distribution with a juvenile-onset peak occurring at 3–4 years of age and an adult-onset peak occurring at 20–30 years of age. A younger age at onset tends to reflect more aggressive disease. Boys and girls appear to be nearly equally affected in juvenile-onset RRP (JORRP). This contrasts with adult-onset RRP, which is a disease transmitted via sexual contact or via indirect contact with anogenital lesions, preferentially affecting men by a ratio of approximately 3:2. Although adult-onset respiratory papillomatosis and juvenile-onset respiratory papillomatosis share many features, this chapter addresses only JORRP.

AETIOLOGY

Juvenile respiratory papillomatosis was first described by Morrell Mackenzie in 1880. By 1923, Ullmann had demonstrated an infective aetiology by injecting homogenized papilloma from a child's larynx into his own forearm and inducing local growth of papillomas. Further direct evidence of the association between human papilloma virus (HPV) and RRP came from the identification of HPV DNA within laryngeal papillomas by Southern blot hybridization and the subsequent recognition in papillomas of HPV types 6 and 11.[1] Human papillomavirus is a naked, double-stranded, icosahedrally shaped virus with circular supercoiled double-stranded DNA genome surrounded by an outer capsid of protein that belongs to the papovavirus family. There are over 200 known subtypes of HPV – although many vary only slightly in their DNA sequence – but only types 6, 11 and rarely 16 are associated with RRP, with HPV 11 conferring a more aggressive course than HPV 6.[2] HPV types 6 and 11 are also associated with condyloma acuminata (genital warts). Types 16 and 18 have been implicated in carcinogenesis, particularly in the uterine cervix and in squamous cell carcinoma of the head and neck. HPV is thought to first enter traumatized epithelium and reside in the basal layer of the mucous membrane, where it replicates by a process known as episomal maintenance. This replication interferes with the normal process of cell maturation, causing epithelial proliferation and neovascularization. Conversely, the virus may lie dormant, causing subclinical infection, and can often be recovered from apparently normal tissue adjacent to papillomas. Viral protein, DNA synthesis and virion assembly only takes place in the granular and cornified layers of the terminally differentiated epithelium.

EPIDEMIOLOGY

Juvenile-onset RRP is an uncommon condition, with a prevalence of only 4 in 100 000 children. The oft-quoted triad of susceptibility factors for JORRP – young mother, vaginal delivery and low maternal socioeconomic status – is of limited predictive usefulness.[3] Latent or active HPV has been detected in cervical swabs from 10–25% of women of childbearing age. The associations between HPV, JORRP and a history of maternal genital warts are well established but what is uncertain is the influence, if any, these associations should have on obstetric management. HPV DNA has been found in one-third to one-half of aerodigestive tract swabs of children born to affected mothers. However, the majority of these children do not develop disease. Calculations suggest that only 1 in 400 infants delivered to women with genital warts subsequently develops JORRP. This relative risk is much lower than that for sexually transmitted diseases.

Although a history of maternal genital warts is not universal, a large retrospective study has shown that children born to mothers with genital warts carry a 231× relative risk of developing JORRP. A prolonged delivery time (exceeding 10 hours) conferred a twofold increased risk but delivery by Caesarean section did not appear to reduce that risk.[4] The clinical corollary of this is whether elective Caesarean section should be recommended for subsequent deliveries when one child has RRP. The overwhelming majority of children born to women with HPV do not develop RRP. In addition, many individuals with HPV in the tissues of the respiratory tract never develop papillomas. Additional host factors, such as immunological or genetic ones, determine the development of RRP in individuals with HPV. Other factors such as timing, length and volume of exposure to the HPV also play a role.[5] The evidence for protection from vertical transmission of HPV into the baby's upper respiratory tract by Caesarean section is conflicting and therefore the decision on method of delivery must be made on a case-by-case basis. Current evidence does not warrant Caesarean section as a prophylaxis against RRP.

Variation in the susceptibility of the host to viral infection may be associated with specific HLA polymorphisms, several of which have been reported. Two recent, large independent studies have shown an association between HLA-DRB1*0301 and severe disease.[6, 7] T-cell responses were shown to be the same by one group between HLA-DRB1*0301-positive patients and negative controls, leading to speculation that the clinical severity of disease is due not to a failure of T-cell proliferative response to HPV but a delay in that response due to a low frequency of HPV-specific T cells or modulation of the T-cell response by immunoregulatory networks.[7] Bonagura et al.[6] showed that HLA-DRB1*0301-positive patients exhibited reduced interferon-gamma expression. While the associations between JORRP and HLA-genotype are being increasingly well recognized, the underlying mechanism for evasion of the cellular immune response is far from clear.

CLINICAL PRESENTATION

Although respiratory papillomas can arise in any respiratory mucosa, their initial presentation is usually in the larynx. The diagnosis requires the surgeon to have an awareness of the condition as the presenting symptoms can be variable and mimic many common laryngeal and respiratory pathologies in children. In addition to hoarseness and stridor, children may present with a chronic cough, paroxysms of choking, recurrent respiratory infections or failure to thrive. These latter symptoms may lead to a misdiagnosis of asthma, laryngitis, bronchitis or croup and a delay of diagnosis of JORRP of up to 8 years.[1]

DIAGNOSIS

If at all possible, the clinical diagnosis should be established with awake fibre-optic nasolaryngoscopy (using an infant 2.2 mm or 2.7 mm endoscope) because the difficulties presented to the anaesthetist by unexpected laryngeal papillomas prolapsing into and obstructing the glottis cannot be overstated.[8–10] The preferred anaesthetic technique in our institutions is that of spontaneous respiration without endotracheal intubation. General anaesthesia is induced either by intravenous propofol or, more frequently, by inhalation of sevoflurane in oxygen. The larynx is topically anaesthetized with 2% lidocaine and anaesthesia maintained by sevoflurane in oxygen through a nasopharyngeal airway, of a size and length appropriate for the child's age. This allows excellent surgical access to the airway but carries the disadvantage that the lower airway is not directly protected from bleeding. Meticulous haemostasis is therefore required during the procedure using topical epinephrine (1:10 000 applied on neurosurgical patties). Regardless of the surgical technique, it is important for the child to recover from anaesthesia with humidified oxygen. Many units use pre-operative dexamethasone to reduce laryngeal oedema but some surgeons feel that anti-inflammatory agents are best avoided during active manipulation of papilloma tissue. Laryngopharyngeal exposure to gastric acid is increasingly being recognized as a cause of laryngeal pathology. This is particularly relevant during the immediate post-operative period where laryngeal mucosa has been breached.[11] Therefore it is our practice to give prophylaxis against gastro-oesophageal reflux with an H_2-antagonist or a proton pump inhibitor for 48 hours after all laryngeal surgery, including surgery for JORRP.

Macroscopically, papillomas can be pedunculated or sessile, spread over the mucosal surface of the larynx (**Figure 32.1**). They tend not to be friable and can be grasped using microlaryngeal instruments and excised for histological examination. Microscopically, the papillomas appear as exophytic projections of keratinized squamous epithelium overlying a fibrovascular core, with varying degrees of dyskeratosis, parakeratosis and dysplasia. Koilocytes (vacuolated cells with clear cytoplasmic inclusions) are often seen indicating viral infection.

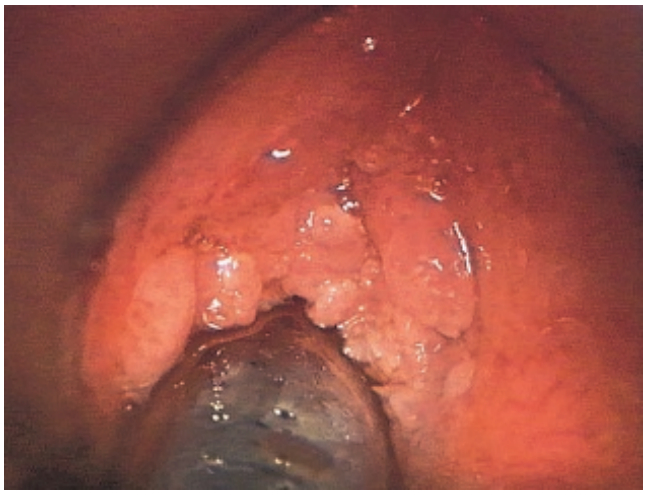

Figure 32.1 Recurrent respiratory papillomatosis in the larynx.

STAGING

Staging of disease is not universally undertaken even in units with a large caseload of RRP. The staging system proposed and modified by Derkay (Figure 32.2)[12, 13] is based on a combination of the anatomical distribution and extent of lesions and their clinical effects on voice and the child's airway. It is increasingly used by members of the American Society of Pediatric Otolaryngologists (ASPO). Widespread adoption of a universally agreed staging system would enable comparison of results between centres and facilitate multicentre trials, particularly of adjuvant treatments.

For each site, score as:
0 = none, 1 = surface lesion, 2 = raised lesion, 3 = bulky lesion

Larynx	
Epiglottis:	Lingual surface _____
	Laryngeal surface _____
Aryepiglottic folds:	Right _____ left _____
False vocal folds:	Right _____ left _____
True vocal folds:	Right _____ left _____
Arytenoids:	Right _____ left _____
Anterior commissure	_____
Posterior commissure	_____
Subglottis	_____
Trachea	
Upper one third	_____
Middle one third	_____
Lower one third	_____
Bronchi:	Right _____ left _____
Trachotomy stoma	_____
Other	
Nose	_____
Palate	_____
Pharynx	_____
Oesophagus	_____
Lungs	_____
Other	_____
Total score all sites	_____

Figure 32.2 Derkay staging for RRP.[12]

TREATMENT

The aim of surgical treatment is the removal of papillomas and restoration of a safe and patent airway while minimizing trauma to the mucosa and vocal cords. Risk of scarring and webbing can be reduced by the avoidance of two opposing raw surfaces, especially at the anterior commissure. In children requiring repeated extirpations of extensive papillomas, especially if they predominantly occur in the larynx, it may be ultimately impossible to achieve normal voice. Though the papillomas do not extend beyond the basement membrane, there is often inevitable inadvertent damage to surrounding tissues.[14] It is in these patients that the surgical technique, balance of the extent of lesion removal against interval timing, and application of adjuvant therapies must be combined and finely judged to ensure minimal dysphonia and airway stenosis, both of which can be extremely difficult to manage. No single treatment modality is better than another. The heterogeneity of the disease and its natural history is reflected in one series of 118 patients who underwent surgical management for their JORRP; the total number of operations per patient ranged from 2 to 402.[15]

Surgical treatment

POWERED MICRODEBRIDER

The use of the powered microdebrider is a relatively new development in the surgical removal of laryngeal papillomas, but one which has become the gold standard for papilloma removal in the larynx (Figure 32.3).[16] A non-serrated laryngeal blade is used with a setting of 300–700 rpm which allows the papillomas to be suctioned into the debrider with minimal cutting trauma to surrounding normal tissues. The laryngeal debrider blade allows gentle but comprehensive removal of papillomas with minimal contamination of the lower respiratory tract with blood or papillomas. There is no thermal trauma and, using direct endoscopic control, it is extremely precise with minimal mucosal damage. Small retrospective studies demonstrate that, compared with the CO_2 laser, patients undergoing laryngeal papilloma debridement have good disease clearance, require a shorter procedure and experience less post-operative pain. One retrospective study showed no incidence of delayed soft-tissue complications using the microdebrider.[17–20]

COLD STEEL SURGERY

Advocates of papilloma removal using microlaryngeal instruments claim that the use of a microflap technique minimizes trauma to the vocal fold while satisfying disease clearance. Thermal damage to neighbouring tissue is also avoided, as is the vapour plume. Cold steel surgery has

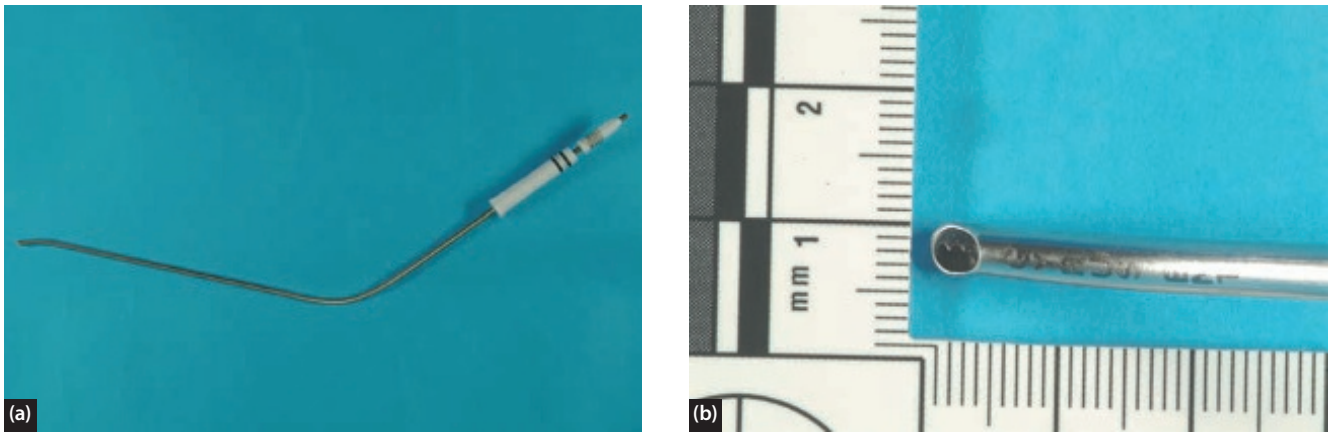

Figure 32.3 (a) Microdebrider; **(b)** close-up of blade.

the distinct disadvantage of having no direct haemostasis when dealing with a very vascular lesion. Nevertheless, such surgery is successful in the hands of the exponents of this technique.

CO_2, KTP, ND:YAG AND PULSED DYE-LASER

The carbon dioxide (CO_2) laser has been, for many years, the mainstay of surgical management of JORRP. It remains the treatment of choice for many surgeons because of its ability to ablate the papillomas with minimal bleeding and its ease of use with a microscope and micromanipulator. However, the frequency of late soft-tissue complications, such as vocal fold fibrosis, interarytenoid fibrosis and stenosis, glottic webbing and arytenoid fixation, has been reported to be 13–45%.[8, 21, 22] This increases with frequency of treatment and the number of laser ablations the child has received. Soft-tissue complications can be minimized by appropriate laser settings and careful assessment of depth of ablation. A Japanese group has suggested, based upon a single case, a two-stage procedure whereby the bulk of the papillomas are removed at the first operation, which is then followed by a repeat endoscopy and laser ablation 10 days later, by which time the coagulum and carbonized tissue have resolved, allowing a more precise laser clearance of residual papillomas.[23] It is also important to have an effective plume extractor. This serves to allow a clearer image of the larynx, but also removes the potentially infectious laser vapour plume which carries a significant viral load. The latter may be simple conjecture as there has only been one reported case of a surgeon developing laryngeal papillomas with a history of repeated laser treatment to a patient with anogenital condylomas, *in situ* hybridization showing HPV types 6 and 11 in both the patient's and his lesions.[24]

The KTP laser and the Nd:YAG laser are as effective as the CO_2 laser in papilloma ablation and haemostasis but, in addition, can be delivered through an optical fibre. Fibre-delivered laser systems play a role predominantly in the treatment of tracheal and bronchial papillomas. A new fibre-guidance system with a bendable distal tip developed for the Nd:YAG laser achieves a 50° range of directional manoeuvrability with minimal power loss.[25] In adult patients, the delivery of pulsed-dye laser through a flexible bronchoscope can render it an outpatient procedure.[26]

The advantages of the pulse-dyed laser are that it can be fibre-delivered and causes minimal vocal-fold fibrosis and consequently minimal voice damage. However, it also distinguishes itself from the other forms of laser treatment in its mode of action. Rather than direct vaporization of tissue, it has been proposed that the 585 nm pulsed-dye laser is a vascular laser which causes photoangiolysis of sublesional microcirculation, denaturation of epithelial basement membrane linking proteins, and cellular destruction.[26] Therefore, it is less effective against large exophytic lesions and can be used as an adjunct to surgery either before or after the laser application.[27] The application of the pulsed-dye laser in the paediatric population is still under evaluation, but the results in adults with recurrent respiratory papillomatosis are very encouraging.

Photodynamic therapy

Photodynamic therapy (PDT) relies upon the observation that rapidly proliferating tissue selectively takes up a number of photosensitizing agents when administered intravenously, and that these agents release tumouricidal oxygen derivatives when activated by laser light of the appropriate wavelength. A non-blinded randomized prospective trial using dihaematoporphyrinether (DHE) at two different doses in combination with 50 J of 630 nm argon laser light was compared with laser treatment alone. The patients remain photosensitive for 6–9 months and may experience skin erythema, blistering and ocular discomfort. Patients on the higher dose of DHE (4.25 mg/kg body weight) were reported to show a significantly larger decrease in papilloma growth rate but, despite that, only approximately half of the 48 patients receiving DHE showed a response, and no response was seen in patients previously treated with PDT.[28] A further randomized trial by the same group using meso-tetra (hydroxyphenyl) chlorin (mTHPC) as a photosensitizer showed reduction of severity of laryngeal papillomas in the mTHPC group, but this was not maintained and there was no effect on tracheal disease.[29] It should be noted that this trial recruited only 23 patients,

of whom only 15 completed the study. In both trials, there was a combination of juvenile-onset and adult-onset patients.

Coblation®

Coblation® is a minimally invasive low-heat technology that delivers a plasma layer to dissolute target tissue while maintaining the integrity of surrounding tissues. The wands (**Figure 32.4**) are designed to function at temperatures as low as 40–70 degrees Celsius (°C), thus minimizing rapid heating, charring or burning. In comparison, commonly used bipolar devices function at temperatures of approximately 400 °C. There are very limited data on the use of Coblation® for JORRP, with most of the literature being case reports or retrospective results on small number of patients.[30, 31] A recent cross-sectional study in the United Kingdom showed that Coblation® procedures accounted for 3% of interventional treatment conducted in the UK RRP population.[32]

Adjuvant therapy

Adjuvant medical therapies can be broadly divided into antiviral therapies and drugs with antiproliferative or immunomodulatory properties.[33–35] The decision to implement adjuvant therapy must depend on a careful consideration of the benefits against potential adverse effects of the therapy.[36] Adjuvant therapies which have been described in isolated case reports have been included for reference because, while their use in 'routine' cases may not be justified, one may wish to consider their use when other better-tested avenues are exhausted.

INTERFERON-α

Interferons are naturally produced by human leucocytes although, as a pharmaceutical, interferon is now produced via recombinant DNA technology. Interferon-α can claim to have antiviral, antiproliferative and immunomodulatory properties. Interferons exert an indirect antiviral action by interfering with normal host cell translation mechanisms and by inducing synthesis of intracellular enzymes that act to control viral growth. By depleting essential metabolites in papilloma cells, interferon-α increases the length of their multiplication cycle, thereby slowing target cell growth. Interferon-α also facilitates recognition of papilloma cells by circulating leucocytes by enhancing expression of cell surface antigens. It is administered systemically by subcutaneous injection at a dose of 2–5 MU/m^2 of body surface area.[37] It is the most well studied of the adjuvant therapies for JORRP. A large randomized trial of 123 patients showed significant reduction in papilloma growth rate within the interferon arm. However, this was only significant for the first 6 months and the difference was not statistically significant during the second 6 months.[37] In another randomized crossover trial of 66 children, there was significant reduction in disease bulk in the interferon arms of the trial.[38] This was extended to longer follow-up, at which data on 60 children were still available, showing complete remission in 22 children, partial remission in 25 patients and no response in 13.[39] The main problem preventing more widespread use of interferon-α is that there are many serious, idiosyncratic and unpredictable side effects including pancytopenia, hepatorenal failure and cardiac dysfunction. There is also a rebound phenomenon associated with withdrawal of the drug therapy. There is anecdotal evidence of the use of intralesional interferon in combination with laser debulking of JORRP, but this has not found widespread use.[40]

Figure 32.4 PROCISE laryngeal Coblation® wand (courtesy of Smith & Nephew).

BEVACIZUMAB

Bevacizumab (Avastin) is a recombinant monoclonal antibody that inhibits angiogenesis (VEGF-A). It is licensed for use in a wide range of metastatic cancers. Trials involving small numbers of patients with recurrent respiratory papillomatosis have shown promise both by systemic and intralesional administration. A series of five patients treated with systemic bevacizumab responded dramatically with 18 surgical interventions being required in the 12 months prior to treatment and only one in the 12 months following treatment.[41] Usually administered at a concentration of 2.5 mg/mL for three consecutive injections at 2–3 week intervals, it can be used in conjunction with cidofovir (see below) and/or the KTP laser. Early studies report an increased time interval between operations, and thus a reduced number of procedures per year. They also report improved voice quality of life when using the Paediatric Voice-related Quality of Life (PVRQOL) score.[42]

CIDOFOVIR

Cidofovir is an acyclic nucleoside phosphonate which is active against a broad spectrum of DNA viruses including cytomegalovirus, Epstein–Barr virus and HPV. Its mechanism of action is by inhibition of viral DNA polymerases essential for viral replication. The principal application of this drug has been in the treatment of cytomegalovirus (CMV) retinitis in human immunodeficiency virus (HIV)-infected patients by intravenous injection. This mode of administration and high doses is associated with neutropenia and nephrotoxicity. Intralesional injection

of cidofovir in JORRP is not associated with similar side effects. A canine model has shown that local irreversible soft-tissue damage could be avoided in twice weekly cidofovir injections if the dose is limited to below 40 mg/mL.[43, 44]

Based on their animal work, Chhetri and Shapiro[45] have proposed a schedule for treatment of JORRP based on intralesional injections of cidofovir at a concentration of 1 mg/mL. Injections were given at 2-weekly intervals for four treatments and then the interval between treatments extended by 1 week after each and every subsequent treatment. Concomitant laser surgery was reserved for bulky lesions. Five patients were treated with this schedule with a mean follow-up time of 66 weeks. The mean papilloma stage decreased from 9.2 at initial presentation to 3.4 within 2 weeks of the first injection, and continued to decrease for the remainder of the follow-up period. After 9 weeks of treatment, no patients required further laser surgery. The authors counsel caution that the potential long-term carcinogenic effects of cidofovir are unknown and a 'response' may be related to the natural history of the disease.[46]

In vitro studies have shown that the use of cidofovir raised the HPV E6 RNA levels by 8-fold in low-risk and 20-fold in high-risk E6 expressing HPV cervical cancer cells.[47] A cross-sectional study incorporating adult and paediatric laryngeal surgeons found that the incidence of upper aerodigestive tract cancers was not significantly increased in patients in whom cidofovir was deployed. Thus, the RRP Task Force recommended that intralesional cidofovir should be considered in patients with RRP that require surgery at less than 3-month intervals, with regular biopsies. Administration should remain below the established safe dose of 3 mg/kg. In all cases, informed consent must be obtained including off-label use and possible side effects.[48] A recent meta-analysis by Fusconi et al.[14] looked at all published data using cidofovir as an adjuvant treatment option for RRP since 1998. It looked not only at the concentration of cidofovir used and the response rate, but also at the incidence of dysplasia secondary to cidofovir injections. There still appears to be no consensus on the ideal dose, frequency of administration and duration of cidofovir treatment. Importantly, there was no evidence that cidofovir promotes evolution towards dysplasia even after cumulative doses.[14]

RIBAVIRIN

Ribavirin is a synthetic nucleoside which has activity against a broad spectrum of viruses, but which is principally used as an aerosol in the treatment of respiratory syncytial virus pneumonia and systemically in the treatment of hepatitis C. There have been reports of its use both as an aerosol and systemically.[49–51] However, these remain anecdotal reports and ribavirin is not widely used as an adjuvant treatment of JORRP.

ACYCLOVIR

The evidence on the efficacy of acyclovir is weak and conflicting.[52, 53] Although HPV is a DNA virus and acyclovir has a medium spectrum of antiviral activity, it does not directly inhibit HPV. Acyclovir is a nucleoside analogue, which inhibits thymidine kinase, which is present in herpes simplex viruses (HSV) but not HPV. Adult patients, but not paediatric patients, with RRP have been shown to have molecular evidence of coinfection with other viruses, particularly HSV, which may have a potentiating effect on HPV. It has been suggested that the mechanism of action of acyclovir is to eradicate HSV, thus removing this synergism. Side effects are rare and include nausea, vomiting, diarrhoea, fatigue and headache.

INDOLE-3-CARBINOL

Indole-3-carbinol is a substance derived from cruciferous vegetables (e.g. cabbage, broccoli, cauliflower, brussels sprouts), which has been shown to alter growth patterns of JORRP cell cultures *in vitro*. It affects oestrogen metabolism, shifting production to antiproliferative oestrogen. A prospective observational study with a mixed adult and paediatric population who received indole-3-carbinol as an adjunctive treatment to surgical removal showed partial or total responses in 21 of 33 patients. Within the paediatric subgroup, four out of nine showed partial or total response with no evident side effects.[54]

CIMETIDINE

Cimetidine – a histamine receptor type 2 (H2) antagonist – has been reported as a useful treatment for cutaneous warts. It has also been successfully used in treatment of an 11-year-old boy who had an 8-year history of diffuse conjunctival papillomas. The mechanism for this is attributed to immunomodulatory side effects of cimetidine at high doses. There is a single case report of very advanced JORRP with tracheobronchial-pulmonary involvement being treated successfully with adjuvant cimetidine at a dose of 40 mg/kg for 4 months with remarkable improvement.[55]

NATURAL HISTORY

The natural history of RRP is extremely variable. This makes it difficult for the surgeon to be able to reliably counsel the anxious parents on how their child's pathology will behave or at what age they might expect remission. Pathologically, severe disease is strongly associated with HPV-11 infection and thus patients should have viral typing as part of their initial pathology workup. Poor prognostic signs include onset of disease before the age of 3 years, and birth by Caesarean section. In the United States, Medicaid insurance – often seen as a proxy measure of low socioeconomic status – is also associated with severe disease.[56] However, there are no other studies showing correlation between socioeconomic status and disease severity. Most affected children require debulking of papillomas at 2–3-month intervals during periods of disease activity. Severe disease may necessitate weekly surgical intervention to prevent

airway obstruction from rapidly growing papillomas. The median number of debulking procedures required in a patient is reported to be 7–13.[57, 58] Not surprisingly, the repeated debulking of laryngeal papillomas results in chronic voice changes.

There is a tendency for remission in the early teenage years and this has been attributed to hormonal changes occurring with the onset of puberty. Interestingly, women with adult-onset RRP commonly experience severe exacerbations of their disease during the hormonal fluctuations of pregnancy. What is clear is that remission is not related to the clearance of HPV from the mucosa as viral DNA is detected in previously affected mucosa in patients in remission as well as in normal mucosa of patients with active disease.[59]

TRACHEOBRONCHIAL DISEASE

Extralaryngeal spread of JORRP beyond the larynx occurs in approximately one third of patients, with spread to the trachea in approximately one quarter of patients. Tracheal involvement may appear as cobble-stoning of the mucosa coupled with the presence of papillomas. Factors predisposing to tracheal spread include the presence of subglottic papillomas, presence of a tracheostomy and a long duration of disease.[60] More distal bronchopulmonary involvement is reported in 4–11% of children with long-standing disease and may result in obstructive pneumonias.[37] Patients may develop cavitary pulmonary lesions leading to fever, sepsis and pulmonary atelectasis. Radiographically, these lesions may appear as solid or cystic pulmonary masses (**Figure 32.5**).[61] A high index of suspicion must be maintained for malignant degeneration of bronchopulmonary lesions.

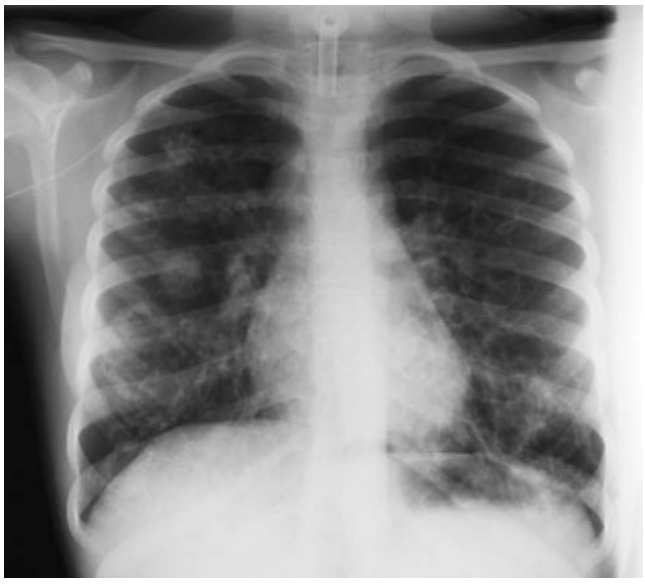

Figure 32.5 Chest radiograph showing extensive pulmonary involvement with papilloma.

TRACHEOSTOMY

The indications for tracheostomy in patients with JORRP continue to divide clinicians. The source of this debate is that tracheostomy essentially constitutes an iatrogenic squamociliary junction and may present an additional area of predilection for papillomas.[62] There is anecdotal evidence that tracheostomy may promote extensive tracheobronchial 'seeding' of disease. However, it is not universal that all patients with a tracheostomy develop either stomal papillomas or tracheobronchial disease. Tracheostomy is very much a last resort but in patients with severe disease it may be life-saving. It may also facilitate a longer interval between debulking procedures to restore some normality to the child's life.

MALIGNANT DISEASE

Malignant degeneration of papillomas is a rare but devastating sequel. It is universally fatal.[61] There is a higher incidence of invasive carcinoma ex-papilloma in children with a younger age of onset (2 vs 6 years old; $P = 0.009$) and those with tracheal involvement.[63] Irradiation of papillomas dramatically increases the risk of malignant transformation but as this is no longer used as a treatment modality, it is of only historical relevance. Most instances of malignant transformation have been reported in adult patients and have been associated with other risk factors including tobacco use and long-standing disease. Malignant transformation appears to be more likely with HPV 16, an unusual cause of JORRP, but HPV 6 and HPV 11 have been shown to oncogenically transform cell culture lines *in vitro*. In adults, malignant degeneration usually involves the larynx, unlike children where cancer usually develops in the bronchopulmonary tree.

Approximately 20 paediatric cases of malignant degeneration have been reported, all of which have been fatal. The currently proposed mechanism of malignant transformation involves oncoproteins E6 and E7. HPV types 6 and 11 produce transforming oncoproteins E6 and E7 that have been implicated in growth dysregulation through their ability to inactivate the tumour suppressor proteins p53 and the retinoblastoma tumour-suppressor gene product (pRb). The inactivation of the tumour suppressor genes results in a loss of control over proliferation and cell division and contributes to the development of the malignant phenotype. It is also becoming clear that the E6 and E7 proteins function to promote tumorigenesis through direct interactions with cell-cycle regulatory proteins.[64] Unfortunately, apart from closer clinical and radiological surveillance particularly in children with tracheal and/or pulmonary disease, there is little to aid the clinician in predicting the rare cases of malignant transformation.[65] There is no evidence of a papilloma–carcinoma sequence while *p53* overexpression is variable and not a marker of malignant transformation.[64] HPV expression may be lost in malignant transformation but this may not be a sufficiently robust clinicopathological predictor.

VOICE MORBIDITY

Although there are numerous papers on the various treatment on options for JORRP, there are limited data on the vocal outcomes of these patients. The majority of data are based on adult-onset RRP looking at voice both due to the papillomas themselves and the resultant morbidity of multiple surgical procedures. Well-recognized voice assessment scales include the GRBAS (grade, roughness, breathiness, asthenia and strain) scale, the Voice Handicap Index (VHI), Short-Form 36-Item Health Survey (SF-36).[66]

Objective assessment of voice by GRBAS scale and Visi Pitch II 3000 acoustic analysis has shown significant difference between JORRP patients in remission and normal controls, but a Voice-related Quality of Life Questionnaire (V-RQoL) showed that the dysphonia does not have any impact on quality of life.[67]

A high number of surgical procedures correlates with a poorer voice in acoustic analysis using the GRBAS. This was statistically significant for grade. Interestingly, Ilmarinen et al. showed no statistical significance in VHI score. When comparing post-op acoustic voice parameters, patients treated with the microdebrider appeared to have lower scores for jitter, shimmer and perceptual scores, thus indicating a better voice outcome with the microdebrider when compared to the CO_2 laser. Increased frequency of interventions using the CO_2 laser is associated with poorer voice quality.[66, 68]

VACCINATION/PREVENTION

There are currently two HPV vaccines, Cervarix® and Gardasil®. These vaccines contain no live virions and are thus incapable of causing an infection, but they are designed to induce an antibody response. Cervarix® is bivalent vaccine against HPV 16 and 18. Gardasil® is a quadrivalent vaccine against HPV 6, 11, 16 and 18 containing virus-like particles of the L1 protein of the four strains. The vaccination schedule comprises three intramuscular injections: the initial dose, 2 months later, and finally 6 months after the initial injection. More recently, Gardasil® has been enhanced to a nonavalent vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58). Ideally, the vaccine should be given to young boys and girls, from the age of 9 years old, prior to them becoming sexually active, thus reducing the spread of HPV and its sequelae in the general population.

Australia was the first nation to introduce a nationwide government-funded vaccination programme in 2007, directed towards the eradication of cervical cancer. Vaccination resulted in a statistically significant decrease in the prevalence of HPV 6, 11, 16 and 18 in cervical samples in the post-vaccination period (2010–2011) as compared to the pre-vaccination period (2005–2007).[69] Much interest has been directed at evaluating the use of HPV vaccination in influencing the clinical course of RRP. Only one study explored this in an entirely juvenile-onset population. There was no change in the clinical or anatomical scores, the number of relapses or the intervals between surgeries before or after vaccination with Gardasil®.[70] Other studies involving juvenile-onset and adult-onset patients have shown more promising results. Albeit involving small numbers of patients, these studies have demonstrated both a clinical and an immunological response to quadrivalent HPV vaccine, suggesting vaccination may have both a preventive and a therapeutic role.[71, 72]

BEST CLINICAL PRACTICE

- ✓ Current evidence does not warrant Caesarean section as a prophylaxis against RRP.
- ✓ Ideally, the clinical diagnosis should be established with awake fibre-optic nasolaryngoscopy prior to general anaesthesia.
- ✓ Patients should have viral typing as part of their initial pathology workup.
- ✓ The powered microdebrider is the 'gold standard' for papilloma removal in the larynx.
- ✓ Spread to the tracheobronchial tree is associated with a greatly worsened prognosis.

FUTURE RESEARCH

- ➤ JORRP has a great impact on the child's life during active disease and constitutes a big surgical load for the surgeon. While the majority of patients enjoy spontaneous remission, a small number continue to develop distal disease which may be fatal. Improvement in surgical technologies have reduced operative time and improved operative morbidity.
- ➤ There is consistent level 3 evidence that cidofovir extends the treatment interval and promotes remission of disease. Consolidation of this evidence will require multicentre collaboration in order to standardize protocols and increase patient recruitment. Such a multicentre initiative has already been proposed to seek critical genes in the pathogenesis of RRP.[73]
- ➤ The future of the management of RRP lies in a better understanding of its pathogenesis.
- ➤ Trials for the HPV vaccine have yet to demonstrate any therapeutic efficacy for children with established RRP while immunological and clinical benefit has been shown in pilot studies in adults. Longitudinal studies will also be needed to explore the impact of HPV vaccination on the pathogenesis of RRP in a preventative role, as with cervical cancer.
- ➤ Despite extensive and sophisticated molecular immunology research, the precise relationship between the human papilloma virus, host immunity and the development of papillomas eludes us. The elucidation of this relationship holds the key to conquering this disease.

KEY POINTS

- Juvenile respiratory papillomatosis can affect any part of the respiratory tract.
- While it is uncommon, its management can constitute a major surgical burden to the otolaryngologist.
- The mainstay of treatment is by surgical debulking.
- The role of adjuvant therapy is uncertain but supported by level 3 evidence.
- In the majority of cases, the disease goes into spontaneous remission.
- Some children develop uncontrolled disease, which in rare cases may be fatal.

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CHAPTER 33

PAEDIATRIC VOICE DISORDERS

Ben Hartley and David M. Wynne

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: paediatric, voice and dysphonia.

INTRODUCTION

There have been tremendous advances in the understanding of voice disorders and their management in recent years. The subspecialty of phoniatrics has evolved principally in adults and this knowledge may now be applied to voice disorders in children. Disorders of voice – where the predominant symptom is hoarseness or 'dysphonia' – must be distinguished from disorders of speech, articulation and language. Speech and articulatory disorders are characterized by difficulty in producing speech sounds, often in the presence of normal laryngeal function. In language disorders, the child uses words and sentences inappropriately, again usually despite normal laryngeal function.

Voice disorders are largely a manifestation of laryngeal pathology. Six to 23 percent of 5–18 year olds have some form of voice 'problem'.[1, 2] In school aged children 6–9% of children have been reported to have a voice disorder.[3] Actual prevalence rates are thought to be higher as many children present directly to speech and language therapy rather than direct to paediatric otolaryngology.[4] In the UK it is estimated that the prevalence is around 6% when perceptual evaluation was undertaken by speech and language therapy and around 11% based on parental reporting.[5, 6]

The identification and subsequent management of paediatric voice disorders is important. Paediatric dysphonia may negatively impact on a child's education, emotional and psychosocial development.[7, 8]

In adults the European Laryngological Societies (ELS) recommend evaluation of five parameters of voice, namely perceptual evaluation, videostroboscopic evaluation, aerodynamic performance, acoustic analysis, impact.[9] In children there is still much debate on the 'minimum' level of evaluation, especially if laryngoscopy requires general anaesthesia.[5, 6]

The spectrum of voice disorders seen in a specialist paediatric voice clinic is very wide. Patients range from child performers who have a normal conversational voice but whose parents have been concerned about a loss of the upper range of their singing voice, to children with severe congenital or acquired laryngeal disease with no voice at all.[6]

With careful assessment, voice therapy and occasionally surgical intervention, most paediatric dysphonias can be corrected or improved.

GROWTH AND DEVELOPMENT OF THE LARYNX

The paediatric larynx is quite different from that of the adult (**Figure 33.1** and **Table 33.1**). The embryonic development of the larynx is described in detail in Vol 3, Chapter 58, Anatomy of the larynx and tracheobronchial tree. This section focuses on those aspects relevant to voice disorders and on normal growth and development after birth. Current knowledge stems largely from the detailed studies of Hirano et al.[10, 11]

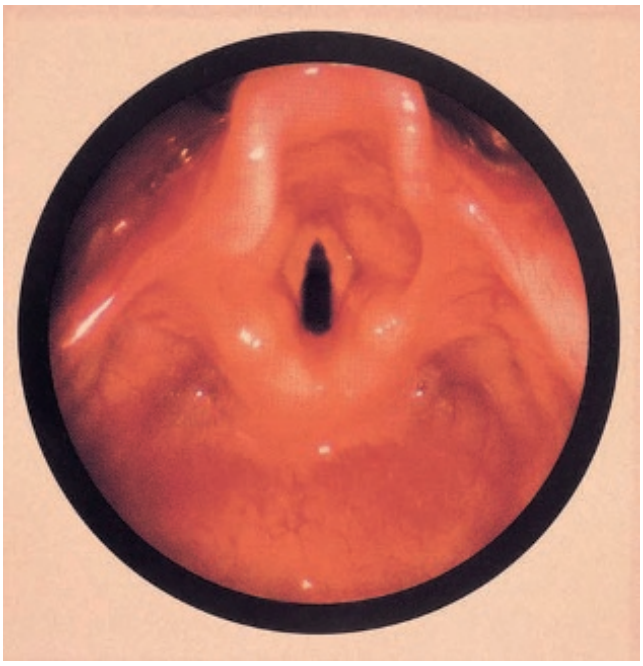

Figure 33.1 Normal larynx in a 6-month-old child.

TABLE 33.1 Differences between the larynx of an adult and child

Feature	Difference
Size	The paediatric larynx is relatively smaller
Position	The child's larynx is relatively higher
Shape	Curled epiglottis, shorter vocal folds
Mucosa	More reactive and prone to airway obstruction Croup is uncommon in adults
Laminar vocal fold structure	Immature in young children

Elongation of the vocal folds

Hirano found that up to the age of 10 years, the length of the vocal fold was very similar in both males and females (6–8 mm). At puberty there is a substantial increase in growth, much more marked in males with the membranous vocal fold increasing to 14.8–18 mm (more than double). In females the increase is to 8.5–12 mm – an increase in length of a third. The cartilaginous portion of the vocal fold also grows with age but less rapidly, with a relative increase in the ratio of the membranous to cartilaginous vocal fold from 1.5 in the newborn to 4.0 in the adult female and 5.5 in the adult male. Hirano devised the concept of the respiratory glottis posteriorly with a wider aperture and the phonatory glottis anteriorly. These concepts are useful in planning surgical procedures. For example, in bilateral vocal cord paralysis it is possible to increase the airway by performing an ablative procedure, such as a laser arytenoidectomy. If this procedure is kept to the posterior part of the larynx, the anterior membranous vocal fold can be preserved for phonation.

Changes in vocal fold laminar structure

Much has been written about the layered structure of the vocal folds and its importance both to the understanding of disease and the development of phonosurgical treatment.

The five layers of the vocal fold are the **epithelium, superficial layer** of lamina propria (Reinke's space), the **intermediate layer** and **deep layer** of the lamina propria and the **muscle layer**. The first two are referred to the as the 'cover' and move freely over the deeper layers which form the 'ligament' and 'body' of the vocal fold.

This laminar structure is not present at birth, but starts to differentiate over the first few months of life. It becomes more developed throughout childhood and the adult form is quite easily recognizable by puberty. One surgical implication of this is that microflaps are more difficult to raise in early childhood due to a less well-developed plane for dissection in the superficial lamina propria.

Changes in pitch

An important feature of the paediatric voice is its pitch. This drops throughout infancy and childhood in males and females, with a marked change at puberty, particularly in males. This change in pitch corresponds to the anterior growth of the thyroid cartilage in response to testosterone and coincides with the development externally of the thyroid prominence or Adam's apple. The fall in pitch is approximately proportional to the growth of the membranous vocal fold.

ASSESSMENT OF THE CHILD'S VOICE

Children with voice disorders may present to a general clinic or to a specialist voice clinic. An otolaryngologist and speech and language therapist should staff paediatric voice clinics. Videostroboscopic equipment and the expertise to use it should be available. The history and basic otolaryngological examination is the same in both settings. Whether laryngeal videostroboscopy and/or speech therapy assessment is required will depend on the clinical situation.

History and examination

Mild or moderate dysphonias that have been present for some time tend to be accepted as part of the child's personality and not a medical disorder. Often, an incidental remark years later leads to the parents seeking medical assessment to exclude an underlying disorder. Some children and families see no problem with their dysphonia. Alternatively, some children and families find a mild

dysphonia very troublesome, particularly if they are performers or have aspirations to perform.

Information should be sought from both the child and the parents. If the problem has been present from birth, a congenital lesion is likely. However, a history of endotracheal intubation around the time of birth or around the time of onset of symptoms may suggest laryngeal stenosis, cricoarytenoid joint fibrosis, intubation granuloma or cyst formation. Much more commonly, symptoms start with an upper respiratory tract infection that has been accompanied by laryngitis, a situation made worse by habitual patterns of voice misuse.

The severity of the disorder may range from a loss of singing voice to complete loss of conversational voice. The time course of the dysphonia is also important. For example, dysphonia is often persistent with discrete vocal fold lesions and rarely returns to normal, although it may fluctuate and fatigue during the day.

Enquire about symptoms suggestive of gastro-oesophageal reflux, as this may irritate the larynx and cause dysphonia. Post-nasal drip associated with allergic rhinitis will do the same, particularly if there is a habit of forceful or constant throat clearing. Cough is quite harsh on the vocal mechanism and constant coughing associated with respiratory disease may lead to hoarseness.

Restrictive respiratory disease may cause reduced infraglottic pressure and subsequent dysphonia. The use of corticosteroid inhalers can also cause dysphonia and this can be helped by modification of drug regime or possibly inhaler technique and the use of spacer devices.[12]

Hearing loss may make the child shout. This can be the underlying cause of a dysphonia secondary to vocal misuse. Voice misuse – shouting – is common in children and may lead to disorders of hyperfunction such as nodules. Other abusive behaviours, such as smoking and alcohol, may occasionally be relevant.

It is extremely important to enquire about exercise intolerance and stridor, symptoms and signs that may be caused by laryngeal stenosis. Swallowing problems or choking may be the first indication of laryngeal paralysis. A general otolaryngological examination, including assessment of the ears and hearing, should be performed. Important clues can be gained by carefully listening to the quality of the child's voice during history taking. Laryngoscopy should be undertaken in all cases.

Laryngoscopy

The objectives of laryngoscopy are twofold, first to identify any structural lesion, such as a vocal nodule or papilloma, and second to assess laryngeal mobility during phonation.

Older children may be cooperative enough for indirect laryngoscopy but examination of the paediatric larynx has traditionally been performed under general anaesthetic. Detailed structural information can be obtained but little information is gained with regard to mobility. It is usual to watch vocal mobility on awakening from general anaesthesia. This can provide information with regard to vocal paralysis, but it should be recognized that by today's standards this is a very crude method of assessment. Awake laryngeal and voice examination should be the standard of care in a compliant child.

Most focal lesions can be excluded by awake fibre-optic laryngoscopy. This can be performed on a child of almost any age. It is usually quite straightforward, performed transnasally with a 2.2 mm fibre-optic endoscope. The optics of the larger fibre-optic endoscopes are better and, if possible, a 4 mm endoscope should be used. These larger fibre-optic endscopes are commonly being replaced with newer 'chip in the tip' videoendoscopic systems. These give an excellent view of the larynx with high quality images.[5, 6] From age 1 to age 5 years, compliance is limited and general anaesthesia and microlaryngoscopy may need to be considered. Some images are of sufficient quality to permit stroboscopy with examination of the mucosal wave.

Rigid laryngoscopy requires significant cooperation, which can only be obtained in children over 6 years of age. High-quality images of the larynx combined with stroboscopy give unparalleled information on vocal fold movement and structure. They also provide an important educational tool for parents and older children. Paralysis of a vocal cord is generally obvious but this technique gives insight to more subtle mobility disorders such as limited posterior glottic closure (glottic chink) and supraglottic constriction. This degree of information is useful and relevant to planning voice therapy.

ACOUSTIC ANALYSIS

With greater availability and use of computerized speech systems, acoustic data are increasingly being recorded. Unfortunately, in the paediatric population (unlike adults) there are no agreed protocols or standards to compare studies from different centres.[9] The most useful acoustic comparison in keeping with ELS guidelines would be measurements of perturbation.[13, 14] There is ongoing research and much debate in how to advance this.

PERCEPTUAL EVALUATION

Perceptual evaluation is one of the most important and available measures of voice. The most common scales currently used are 'GRBAS' and 'CAPE-V'.[15, 16] Both of these were developed for adult voice disorders and completion of the full data set may be difficult in children.

IMPACT/QUALITY OF LIFE

Although there are numerous questionnaires designed to assess the impact of a voice disorder, these were developed for adults. There have been a few developed for children based on their adult counterparts, including paediatric VOS,[17] paediatric V-RQOL,[18] paediatric VHI.[19] One of the issues with paediatric questionnaires is that the parent/carer is acting as a proxy for the child and their view may not match.[20] There is increasing evidence that children should be self-assessed and questionnaires are being designed for this purpose.[21]

SPECIFIC DISORDERS

Vocal nodules and functional voice disorders

Vocal nodules – now regarded as an organic manifestation of laryngeal hyperfunction – are the commonest cause of dysphonia in children (**Figure 33.2**).[22] The mainstay of treatment is voice therapy to correct the hyperfunction. While in adolescents this therapy is similar to that employed in adults, different strategies are necessary in younger children.

The traditional view, based on clinical experience, was that most vocal nodules in children could be expected to improve at puberty.[23] Puberty is a time of great change in the larynx, with tremendous growth of the membranous vocal fold in the male and, to a lesser extent, in the female. One can see how the dynamics of vocalization might change with potential improvement in the nodules. Mori,[24] however, reported that 12% of nodules did not improve at puberty. In the same study it was found that those treated with vocal hygiene alone (i.e. general advice regarding voice care) did not improve. Those given voice therapy under the supervision of a speech and language therapist did tend to improve and the degree of improvement was related to the number of therapy sessions. The essentials of voice therapy include reduction of vocal strain. Various techniques can be employed to reduce shouting, whispering, coughing and throat clearing and to encourage the use of a smooth easy voice. Periods of quiet play are recommended after noisy activity (e.g. football) to allow vocal fold recovery.

Surgery for nodules is rarely recommended in children. Concerns about the potential effects of scarring are very real. On occasion it can be justified when prolonged voice therapy has failed. Bouchayer and Cornut[25] reported cysts, polyps and sulci in children previously diagnosed as having nodules when examined at microlaryngoscopy. Some children with nodules have vocal cord cysts with a nodule on the contralateral cord and this might explain why some fail to respond to voice therapy. The use of videostroboscopic techniques in the voice clinic should help diagnose these conditions earlier. Cysts are treated by microsurgical excision.

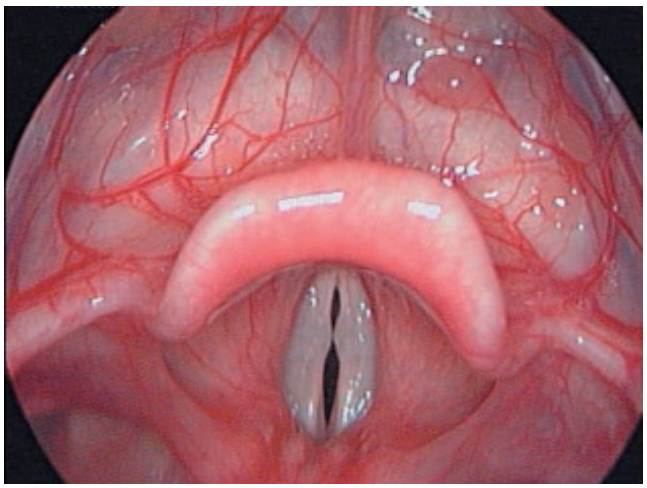

Figure 33.2 Vocal cord nodules.

A wide range of functional voice disorders can be demonstrated in children without demonstrable nodules. These children may present with dysphonia, or even aphonia, secondary to underlying psychological factors. For these children, voice therapy may need to be combined with a psychological assessment. Aphonia in the presence of a normal laryngoscopy evaluation is suggestive of psychological disturbance. A normal cough or laugh adds support to this contention. Puberphonia, when the prepubertal voice persists into adolescence or adulthood, is another condition associated with psychological disturbance. Highly specialized voice therapy, possibly in conjunction with a psychologist, is important to help these children develop an adult voice.

Laryngeal papillomatosis

A detailed account of laryngeal papillomatosis is given elsewhere (Chapter 32, Juvenile-onset recurrent respiratory papillomatosis). From the voice perspective, there are a number of important considerations.

The emphasis of modern surgical techniques is to minimize damage to the underlying lamina propria and to restrict surgery to the papillomas. In this way, voice quality will be optimized in the long term. Glottic scarring and webbing are well-known complications of surgical intervention with the laser.[26] The use of a microdebrider and cold steel instruments has much to commend it. After all, surgery cannot cure papillomatosis. Medical treatments have been advocated including intralesional acyclovir with some reported success.[27] In theory, any medical adjunct that reduces the number of surgical procedures would be beneficial in terms of voice preservation, although voice outcomes following these therapies have yet to be reported. Cidofovir is showing some promise and its use is considered in Chapter 32, Juvenile-onset recurrent respiratory papillomatosis.

Intubation injuries and voice

Much has been written about acquired subglottic stenosis consequent on prolonged endotracheal intubation in premature infants. Surgical techniques have evolved to correct this abnormality and allow eventual decannulation.[28–31] Voice problems following this surgery have been documented and are not uncommon.[32]

Subglottic stenosis is just one example of laryngeal injury caused by intubation. More minor scarring may affect the voice but not the airway (**Figures 33.3** and **33.4**). Damage to the vocal fold or underlying lamina propria causes dysphonia. Cricoarytenoid joint fixation and posterior glottic scarring may also be caused by endotracheal intubation and reduce vocal fold mobility. It is easy to confuse these conditions with vocal cord paralysis.

Voice therapy can be successful in some children. Surgical treatment of voice problems caused by intubation trauma remains a significant challenge. There is

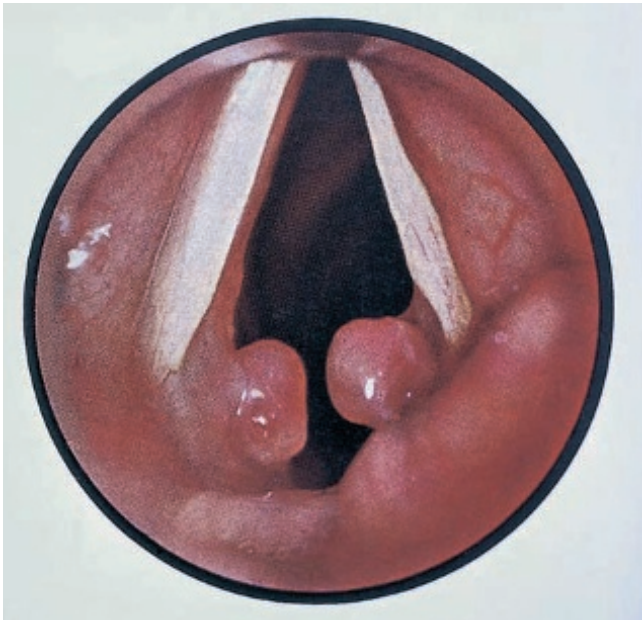

Figure 33.3 Intubation granulomas.

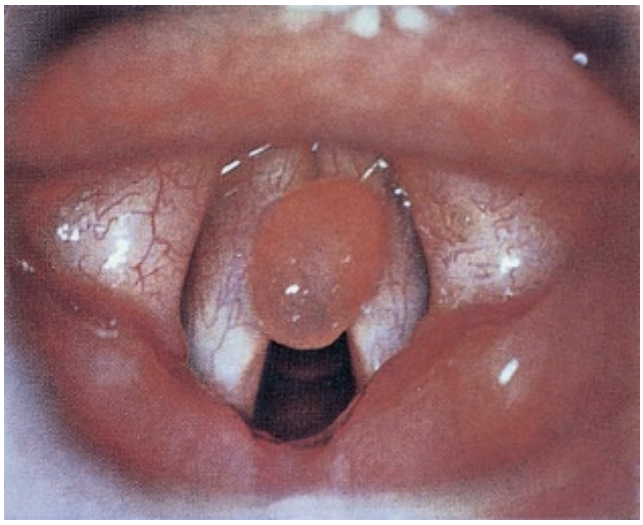

Figure 33.4 Vocal cord polyp following prolonged endotracheal intubation.

potential for the introduction of medialization techniques in this group of children, but there must be an adequate airway before this can be considered and this situation is uncommon.

Vocal cord paralysis

In general terms, children with bilateral vocal cord paralysis have a good voice or cry. It is the airway that gives concern. Spontaneous recovery of function takes place in some, but after 2–3 years of observation this is unlikely to happen.[33] A number of lateralization procedures can be performed to develop a wide posterior glottis for respiration while preserving the anterior glottis for phonation. Either laser arytenoidectomy[31, 34, 35] or endoscopic suture lateralization can achieve these goals.

In contrast to bilateral cord paresis, children with unilateral cord paralysis present with aspiration and a weak cry. The airway is relatively spared. Most improve with time due to compensation from the contralateral nonparalyzed vocal fold or to spontaneous recovery.

Medialization thyroplasty can be considered for those who do not improve and continue to have a significant voice problem. However, there is limited published information on this and it should be remembered that its efficacy to diminish aspiration has been limited.[36]

The concept of placing a silastic implant before puberty has raised concerns that this might interfere with the anticipated physiological growth spurt. It is the author's practice to consider medialization using a fat injection in dysphonic, prepubertal children and to restrict silastic thyroplasty techniques for dysphonic post-pubertal patients. There is also increasing use of newer laryngeal injectables such as calcium hydroxyapatite in children.

The concept of re-innervation is attractive. In a series of eight children with unilateral vocal cord paralysis, three underwent implantation with ansa cervicalis/strap muscle pedicles. This, together with post-operative voice therapy, gave 'good' results.[37] There has to be some scepticism about these procedures as re-innervation techniques are capable of restoring laryngeal tone but have had limited success in achieving voluntary movement. Nevertheless, children seem to be the ideal population on which to carry out these procedures as nerve grafting in general is more successful in this age group.

It is worth restating that it should never be assumed that an immobile vocal cord is paralyzed. Vocal cord immobility in previously intubated children may be due to joint fixation or posterior glottic scarring. The distinction between these diagnoses is extremely important, particularly when vocal cord immobility is bilateral. The management of paralysis is conservative with a tendency towards spontaneous recovery. Fixation and scarring do not improve and children may be subject to years of unnecessary waiting with a tracheotomy before a surgical lateralization procedure is contemplated.

Tracheotomy and voice

Children with tracheotomies will often have impaired voice; this may also result in a speech and communication delay. This is only partly due to the tracheotomy tube diverting air from the glottis. The main factor is usually the laryngeal lesion that required tracheotomy formation in the first place. Children with a healthy larynx can obtain good voice by occluding the tube on expiration (with a finger or speech valve) and projecting air around the tube and up through the glottis. To facilitate this, the tube needs to have sufficient space around it and may need to be 'downsized'. This is usually possible without restricting the airway. Speech valves are frequently used in the author's practice for children. As well as helping with speech they help with secretion management and swallowing.

BEST CLINICAL PRACTICE

- ✓ Laryngeal microflaps are more difficult to raise in early childhood due to a less well-developed plane for dissection in the superficial lamina propria. **[Grade A]**
- ✓ An immobile vocal cord is not always paralyzed. Consider joint fixation and posterior glottic scarring, especially if the child has been intubated.
- ✓ The term 'vocal abuse', often used to describe adult dysphonias, is best replaced by 'voice misuse' in the paediatric setting. Beware the sensitivity of recording the word 'abuse' in children's records.
- ✓ Advances in endoscopic equipment are such that awake laryngeal and voice examination should now be the standard of care in a compliant child.
- ✓ Due to the potential for permanent scarring, surgery for nodules is rarely recommended in children. It should be considered only as a last resort when prolonged and skilled voice therapy has failed.

FUTURE RESEARCH

- ➤ **Laryngeal transplantation for voice.** Perhaps the most challenging of paediatric voice conditions is the child with no voice due to complete laryngeal stenosis which is beyond surgical reconstruction. Such children are encountered after severe burns or caustic ingestion. They are tracheotomy-dependent and communicate with signing and non-oral devices. Laryngeal replacement using transplantation carries the best hope for these children and, although there has been one successful adult patient, this has yet to be repeated.
- ➤ **Re-innervation of the paralyzed larynx.** Phonosurgery can be helpful for the voice in laryngeal paralysis with medialization using injection or thyroplasty techniques. However, the biggest concern for children with laryngeal paralysis is not voice but aspiration. We do not have a universally accepted solution for aspiration due to laryngeal incompetence. Withdrawal of oral feeding and gastrostomy remains the mainstay. Fortunately, compensation frequently takes place for unilateral lesions but often not bilateral problems. Laryngeal re-innervation may hold the key but it is still in its infancy.
- ➤ **Repair of damaged vocal cords with synthetic 'SLP'.** Vocal cords damaged by intubation or surgery have lost the mucosal wave due to destruction of the important superficial layer of the lamina propria (SLP layer). Medialization of damaged vocal cords has had only limited success and attempts are being made to create a synthetic substitute for this important gel layer for potential replacement by injection into Reinke's space.

KEY POINTS

- Voice disorders in children are common; few require medical intervention.
- The impact of dysphonia in children should not be dismissed.
- A diagnosis can usually be made by careful history taking and examination to include laryngoscopy and ideally videostroboscopy.
- The child's perceptual reporting should be sought.
- Laryngeal muscle hyperfunction with or without nodules constitutes the commonest group of disorders.
- These disorders respond well to skilled voice therapy (speech and language therapy - 'SALT').

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CHAPTER 34

FOREIGN BODIES IN THE EAR, NOSE AND THROAT

Adam J. Donne and Katharine Davies

SEARCH STRATEGY

Data in this chapter may be updated by PubMed searches using the keywords: foreign body and ear, nose, throat, inhalation and oesophagus. The searches returned the following numbers of articles: ear, nose, pharynx, larynx and trachea/bronchus. The majority of the articles identified were level 3 in the form of retrospective reviews.

Hospital episode statistics data were accessed via the public access website. The Susy Safe project statistics were accessed via a public access website.

INTRODUCTION

For the purposes of this chapter a 'foreign body' is an object or substance that is inappropriately situated in a particular anatomical location. Children commonly present with a foreign body in the ear, nose or throat. Young children tend to explore using their mouths and this puts them at risk of the foreign body entering the aero-digestive tract.[1] Impaired behavioural development due to a neurological diagnosis or attention deficit/hyperactivity disorder[2, 3] may increase the risk of foreign body insertion, ingestion/inhalation. In adults, poor dentition, alcohol consumption and old age may be important factors for eating-related airway obstruction.[4] Adults may also have neurological or psychological factors.[5]

Child abuse by neglect or direct non-accidental injury (NAI) may be relevant. However, adults also present with foreign bodies which may be due to a chance event or accident (e.g. pin inhalation or an insect in the ear) or may herald an underlying pathology (e.g. oesophageal malignancy and food bolus obstruction). Foreign bodies can be categorized by location and type. The location of the foreign body may be life-threatening as in the larynx, or benign, such as a bead in the ear. They can be subdivided into organic and inorganic. The nature of the foreign body may pose a direct threat to tissue (e.g. battery ingestion).

INCIDENCE

The largest active registry of non-food foreign body incidents is the Susy Safe project.[6] The number of foreign body incidents in the European Union in children aged 0–14 years is 50 000 per annum, and 1% are fatal. Around 10 000 are inorganic and 2000 involve toys.[6] Unfortunately, it has been reported that up to 22% have a repeat of the foreign body incident,[7] therefore education must be essential for the long-term management of this risk.[8]

It is difficult to determine the relative frequency of foreign bodies within the trachea, bronchus and oesophagus compared to ear and nose as little has been published to demonstrate the complete range of ear, nose and throat foreign bodies in any particular series. A literature review would indicate foreign body frequency is higher in ear and nose compared to throat.[9] An eastern European retrospective study (over 10 years with 849 patients) identified the following relative proportions: tracheobronchial 11%, pharyngo-oesophageal 17%, and ear, nose and post-nasal space 72%.[10] Using data from the Susy Safe project, it is possible to determine the following relative percentages for foreign bodies: ear 25.9%, nose 27.4%, pharynx and larynx 4.3%, trachea, bronchus and lungs 12.8%, and mouth, oesophagus and stomach 29.7%.[11] This Susy Safe publication used ICD9-CM codes and reported on a total

of 8593 incidents. As the categories differ from the eastern European study, it is not possible to make close comparisons. However, it is clear that ear and nose form around half of the incidents recorded. Both studies agree that incidents affecting the tracheobronchial region constitute around 11–12%. The Susy Safe project identified that foreign bodies were food in 26% of cases. The data specifically for food-related foreign bodies indicates a difference in proportions of anatomical site affected: ear 7%, nose 19%, pharynx and larynx 16%, trachea, bronchus and lungs 50%, and mouth, oesophagus and stomach 8%.[12] Clearly, there is a different profile, which might be explained by the fact that the Susy Safe project originally attempted to identify non-food foreign bodies with only later collection of food foreign bodies. A further compounding factor is that different countries and cultures eat different food types, which may be significant and skew the data.

Self-inserted foreign bodies may occur more frequently in children with attention deficit or hyperactivity disorder.[2] Children with neurological disorders have been shown to present later with foreign body in the aerodigestive tracts. Furthermore, these children remain in hospital for longer and may have a more complicated management.[13] For children who are otherwise healthy before foreign body inhalation, reviews suggest that the majority (96%) did not require supplementary oxygen support beyond 2 hours.[14] This implies that, even though foreign body inhalation is potentially life-threatening, for most patients the removal is without complication. If there is a pre-operative respiratory impairment, the risk of post-operative complication is higher.[15] Immediate post-operative chest radiographic features are predictive of pulmonary complications.[16] However, the mortality for foreign body inhalation is still high.

Hospital Episode Statistics (HES) data for Accident and Emergency admissions in England are available online from the Health and Social Care Information Centre (hscic) at NHS Digital.[17] These data indicate that for the years 2011–2012 and 2012–2013 the attendances for 'foreign bodies' as a group represented about 1% of attendances – and during 2012–2013 there were a total of over 18 million Accident and Emergency attendances. These data are crude as there is no indication of the anatomical location of the foreign body. However, it is clear that foreign bodies are an important problem.

The Susy Safe project was supported by the European Commission and resulted in the development of toy safety directives which aim to make small parts on toys safe for children 0–3 years but also control the use of heavy metals in toys. In general, boys tend to present with foreign body incidents more commonly than girls[18] and they are more frequently involved with more severe injuries.[19] However, when the foreign body is jewellery, 76% of those presenting are female.[20]

EAR FOREIGN BODIES

Right-handed children tend to insert foreign bodies into their right ear and left-handed children into their left ear.[21] However, bilateral foreign bodies have also been reported in ear (and nose).[22]

Inert foreign bodies may be identified as an incidental feature.[18] However, as there are significant consequences of delayed removal of certain items (e.g. button batteries) examination is appropriate with a positive history. The isthmus of the external auditory meatus is the narrowest section and foreign body impaction may occur at this point. Many aural foreign bodies will migrate out of the ear. Grommet extrusion is testimony to this fact. The urgency of removal of foreign bodies should be based upon the foreign body in question. Potentially corrosive foreign bodies should be removed without delay. However, inert foreign bodies are often found incidentally in the ear and nose as they are asymptomatic in 47% and 43% of cases respectively.[18]

Management of ear foreign bodies

A variety of techniques to remove aural foreign bodies exist and the technique adopted is determined by the foreign body characteristics (i.e. size, shape, consistency), position and cooperation of the patient. A smooth, hard foreign body (e.g. bead) is difficult to grasp and evidence suggests that non-graspable foreign bodies are better removed by otolaryngologists with fewer complications compared to emergency department staff removal.[23] Methods include microsuction, wax hook and irrigation.[24] The cooperation of the child is essential and up to 30% require a general anaesthetic to allow safe removal.[25] It has been reported that up to 47% sustain trauma such as laceration and tympanic membrane perforation. Approximately half have had previous attempts before seeing an otolaryngologist,[26] which suggests that aural foreign bodies should be dealt with by otolaryngologists as a matter of course.

Irrigation should be a safe technique as long as the tympanic membrane is intact. Studies indicate that the pressure exerted may be sufficient to cause tympanic membrane rupture, ossicular disruption and round window fistulae.[27] If the irrigation fails to expel a foreign body which is organic (e.g. dried pea), swelling may occur, which can result in further removal difficulty and pain due to pressure exerted against the canal wall skin.[25, 28] Adults more frequently present with insects in their ears (**Figure 34.1**). These cause irritation and distress and a consequent urgency to remove.[26]

NASAL FOREIGN BODIES

A nasal foreign body must be considered in any child with unilateral nasal discharge (especially with unilateral excoriation of nasal rim).[29, 30] The most common age of presentation is 2–4 years. A nasal foreign body usually requires a minimum of 4 days before discharge occurs[22] unless it is a button battery when discharge is immediate. Inert nasal foreign bodies may be present for a considerable number of years.[31, 32] With prolonged indwelling a foreign body granulation develops (**Figure 34.2**) and may result in rhinolith formation. Rhinoliths consist of salts of

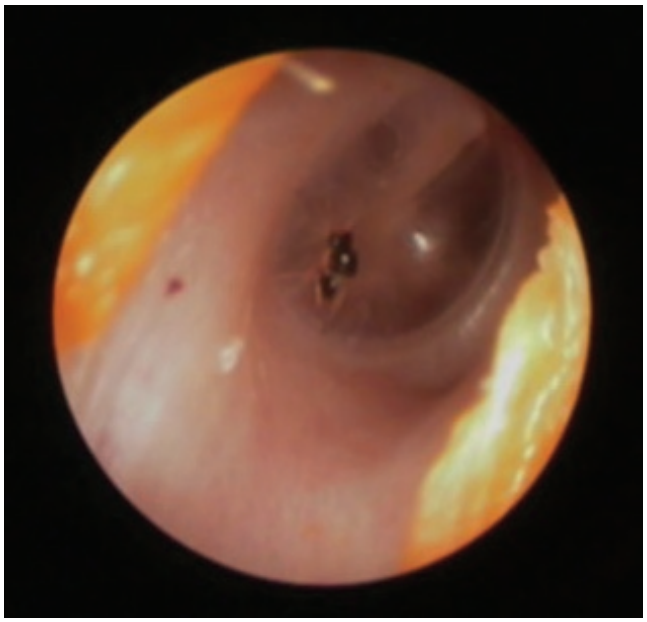

Figure 34.1 Otoscopic image of an insect in an ear.

calcium, magnesium phosphate and carbonate[33] and are radio-opaque.[34] A long-standing nasal foreign body may even result in hypoplasia of the inferior turbinate.[35]

Management of nasal foreign bodies

The usual technique for removal of a nasal foreign body is the placement of a hook or preferably a bent Jobson Horne probe over and behind a foreign body. The foreign body is then pulled forward.[36] If the foreign body moves posteriorly, there is a theoretical risk of inhalation.[37] Other techniques include the 'mother's kiss' whereby there is mouth-to-mouth gentle blowing into the mouth of the child with the unaffected nostril being held closed. This may allow the foreign body to be expelled in around 60% of cases.[38] Hollow foreign bodies may be resistant to this technique.[39] Balloon catheters (Fogarty) have also been used placed intranasally behind the foreign body then partially inflated and pulled out of the nose, bringing the foreign body ahead of it.[40] Occasionally, it may be difficult to remove a foreign body through the anterior nose and therefore pushing it into the pharynx of the anaesthetized patient is an option for removal.[41] An alternative may be to break the foreign body *in situ* and remove it in numerous pieces.[35]

There is a risk that nasal foreign bodies may be inhaled;[42] however, this is more probable if the gag reflex is impaired. A foreign body falling into the laryngopharynx would usually be swallowed or coughed up. In the past, many of us were taught that 'the sun should never rise or set on an inhaled or ingested foreign body' but it is almost certainly safe to leave nasal foreign bodies in neurologically normal children for operative removal during normal working hours if required.

INHALED FOREIGN BODIES

Most inhaled foreign bodies occur in the under 3 years age group.[11, 43, 44] They are more common in boys than girls.[45] In children younger than 3 years the foreign body is typically organic (food) whereas in children older than 5 years they are more often inorganic.[46] A large variety of foreign bodies have been published.[47, 48] The lack of molar teeth is thought to be significant due to the reduced ability to chew food adequately.[1, 49] Young children tend to put objects in their mouths which may additionally explain the high incidence of foreign body aspiration.[50] The mortality from foreign body inhalation is around 1% and the commonest cause of accidental death in children under 3 years of age. Foreign bodies in the tracheobronchial system seem to cause more complications that in other anatomical sites.[51]

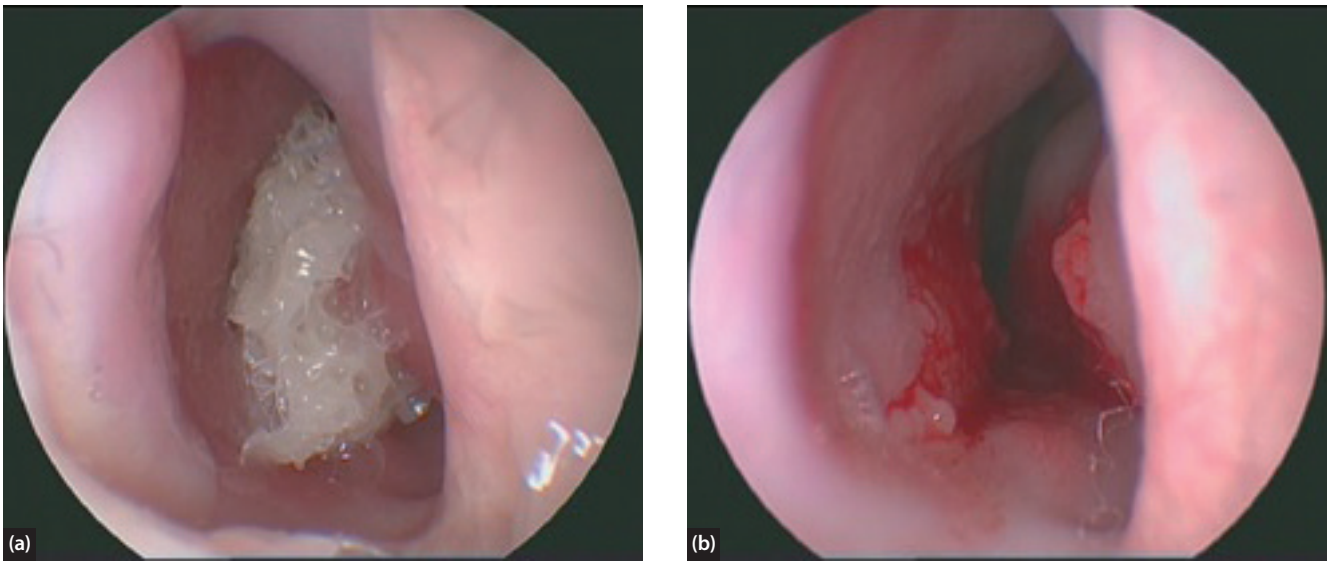

Figure 34.2 Endoscopic images of a fabric foreign body in a nose **(a)** and the immediate post-removal appearance of granulation at the point of contact with the foreign body **(b)**. This indicates chronic contact.

It has been shown that children are often able to clear their own airways, but this ability is less well developed in the younger the child. In one report 85% of inhaled objects were cleared before emergency medical services arrived at the scene. Food and coins have been identified as the main culprits.[52] In 1975 Heimlich published a report on a manoeuvre to expel laryngeal foreign bodies.[53] A report suggests that this manoeuvre may be responsible for reducing deaths in the under 15 years age group from foreign body inhalation.[54] There may be significant complications to the procedure but doing nothing commands a greater risk. Serious complications include oesophageal-gastric rupture,[55, 56] diaphragmatic hernia[57] and emphysema (in subcutaneous space[58] and mediastinum[59]).

Inhaled foreign body presentation may vary depending upon the exact site of obstruction with the airway. The history may present with a witnessed foreign body in the mouth or even no apparent foreign body presentation in a young child, and this can delay diagnosis. Symptoms and signs of foreign body inhalation include choking, coughing, hoarseness, shortness of breath, wheeze, increased work of breathing, cyanosis, asphyxiation and death. Foreign bodies arising anywhere within the large respiratory airway may result in stridor. Laryngeal foreign bodies may give rise to hoarseness which is unlikely with an object in the right main bronchus. The history is paramount as a parent/guardian is present in about half (49%) the incidents and the child was eating in 34% of cases.[1] Indeed, even if the child is symptom free, if no object is fully expelled by coughing after a choking episode, further evaluation is indicated. A low threshold is essential so that the asymptomatic foreign body[60] or occult foreign body is not missed.[61] Delayed presentation is not uncommon in children and may have been treated as asthma due to the low-grade cough and noisy breathing. In almost 40% of cases the diagnosis was delayed for more than 24 hours.[48] One report of flexible bronchoscopy for respiratory symptoms (where foreign bodies were coincidentally identified) indicated that symptoms (due to the foreign body) were present from 1–132 months. The longer the duration of foreign body placement, the increased probability of long-term complications. When present for less than 1 month, all patients recovered completely but, if present for more than 3 months, only 30% recovered. The remainder had chronic cough and wheeze or bronchiectasis.[62]

The location of the foreign body within the airway has been identified from meta-analysis to be in decreasing frequency for the following locations: bronchus (right more frequent than left side),[63] trachea, larynx and lung.[48]

Laryngeal foreign bodies are relatively infrequent (2–12%)[64, 65] compared to the rest of the tracheal and bronchial incidence. They present with either partial or complete airway lockage. The former may result in voice issues (hoarseness), stridor, dyspnoea, prolonged atypical croup or even odynophagia[66] and as such can result in misdiagnosis and delay in identifying the laryngeal foreign body.[67] The latter will result in hypoxia and/or laryngospasm and death by asphyxiation[64] and classically require the Heimlich manoeuvre. The shape of the foreign body within the larynx is either spheroid or flat.[68] However, sharp metallic items that may penetrate the vocal cord or wall of trachea such as safety pins present a surgical challenge.[69, 70, 71] Within the larynx foreign bodies can be very difficult to identify even with spiral CT scanning.[72] If there is a delay in diagnosis, there can be significant associated granulation tissue at the glottis level where the foreign body is in contact with the mucosal surface, similar to the bronchus.[73]

Radiographic findings on chest films will often be normal (11%–26%)[74, 75] unless there is a radio-opaque foreign body present.[48] Additional radiographic features include atelectasis, hyperinflation, mediastinal shift, pneumonia and pneumothorax. Classically there is hyperinflation of the lung on the side of the foreign body due to the 'ball-valve' effect. The intrathoracic pressure is decreased on inspiration such that air can enter the bronchus. On expiration the intrathoracic pressure reduces to compress the bronchus (somewhat) around the foreign body (**Figure 34.3**). The sensitivity and specificity of radiographs for airway foreign bodies have been calculated to be 73% and 45% respectively,[76] which implies that the radiological investigation is an aid but should not deter an airway endoscopy. Fluoroscopy improves foreign body detection but even this additional modality radiology does not identify a significant proportion.[75]

Computed tomography virtual bronchoscopy is highly sensitive at identifying a foreign body within the airway[77] but, if this requires a general anaesthetic, most would consider a rigid bronchoscopy as the patient's condition may change suddenly while anaesthetized. In asymptomatic patients CT bronchoscopy may therefore be a reasonable option but it cannot replace endoscopy.[78, 79]

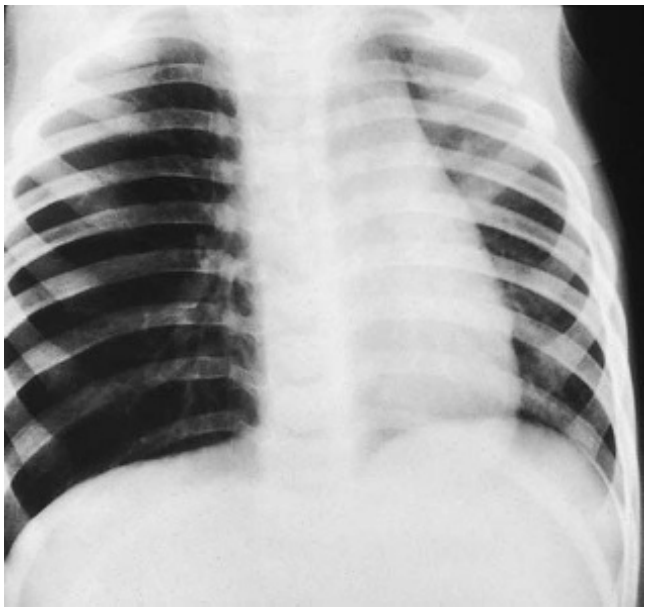

Figure 34.3 Chest X-ray showing hyperinflation of the right lung due to a foreign body in the right main stem bronchus.

Management of inhaled foreign bodies

Some surgeons advocate flexible bronchoscopy via a laryngeal mask or endotracheal tube to diagnose and remove foreign bodies.[80] Some have reported very high success rates,[63] and the benefit of flexible endoscopes is that they are flexible and able to approach the bronchus at a different angle. However, the flexible endoscope cannot ventilate the patient and presents a significant obstruction.[63] Flexible bronchoscopy may be possible in older children and adults without general anaesthesia but rigid bronchoscopy under the controlled conditions of a general anaesthetic is the mainstay for foreign body removal.[62] Use of the urological basket with flexible bronchoscopes has been reported in cases where rigid bronchoscopy has failed.[81, 63] There is genuine value in flexible endoscopy in the repertoire for foreign body removal.

A direct laryngotracheobronchoscopy or microlaryngotracheobronchoscopy (MLTB) should be performed to diagnose and remove the foreign body without undue delay. The level of urgency depends on the clinical condition of the patient and resources available. The endoscopy is best performed during daylight hours. If a child presents during an evening with a history of possible foreign body inhalation and is well, it is reasonable to delay endoscopy until the morning.[82] This remains somewhat controversial. The exceptions include unstable symptoms, type of foreign body (e.g. peanut, **Figure 34.4**), and broken seeds as these cause oil release and granulation formation,[83] beans (especially dried as these cause swelling and inflammation)[47] and batteries (see below).

MLTB for removal of foreign bodies is best performed for children using inhalation anaesthesia as this has been shown to be associated with fewer complications.[44]

MLTB to remove a foreign body is best performed in children without endotracheal intubation as there is a small risk that the foreign body may be lodged at the larynx or immediate subglottis and the endotracheal tube may push the object in such a way as to cause complete airway closure. It is therefore advisable that the rigid bronchoscope is ready for use. Furthermore, paralysis is not advised until the airway has been assessed and secured. Topical anaesthetic on the larynx prevents laryngospasm, which is undesirable during such cases.

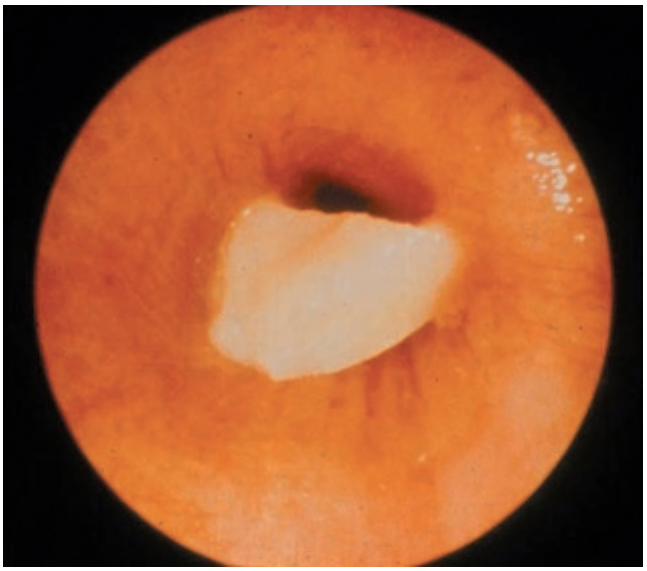

Figure 34.4 A peanut in the bronchus.

Topical adrenaline is very useful to decongest the area immediately around the foreign body, especially if there is any granulation present, with the inherent risk of bleeding.[63] On successful removal of the foreign body an immediate second look is necessary to ensure other fragments are not retained. Steroid is typically administered to reduce effects of oedema due to airway instrumentation as steroids have been well described to reduce oedema of airway surgical intervention and prolonged intubation.[84] Most patients require post-operative observation until the following day.

There is a reported risk of up to 4% for life-threatening complications following endoscopic removal of foreign bodies. The risks include pneumothorax (unilateral and bilateral),[47] tracheal laceration, pneumonia, haemorrhage into the airway, and cardiac arrest due to hypoxia.[85] Even if foreign body removal is successful, delayed pneumothorax can occur post-operatively. The risk of hypoxia during foreign body removal by MLTB is higher if the child is less than 1 year of age,[86] with certain types of foreign body[47] and the longer the duration of procedure.[44, 86] The latter may indicate the increased difficulty of removing the foreign body from the airway. Further risk factors for hypoxia for the patient during endoscopic removal include pre-existing pneumonia[87] and foreign body fruit seeds.[87, 88] Extracorporeal membrane oxygenation (ECMO) may be a useful technique to maintain oxygenation where the patient is too unstable and when the tracheal foreign body removal is otherwise impossible without complete airway obstruction and significant risk of cardiac arrest.[89] The risk of death during endoscopy for foreign body removal is significant and reported at 0.42%[90] yet a more recent study using USA nationwide data over 3 years indicated a death rate of nearer 1.8%.[91]

A negative MLTB is not a failure as the threshold to suspect foreign body inhalation must be low. The negative rate has been reported to be as much as 60%.[91] However, since delayed diagnosis occurs in a significant proportion and may result in bronchiectasis, the index of suspicion should be low.

In some circumstances it may be impossible to remove a foreign body using endoscopy. An alternative strategy may include tracheal fissure (as tracheostomy incision) for tracheal foreign bodies or thoracotomy for bronchial sites.[47]

INGESTED FOREIGN BODIES

A variety of foreign bodies are ingested by children. Peak incidence is in children less than 4 years of age (up to 75%). The most common item ingested is probably the coin (up to 70% of cases) (**Figure 34.5**). Symptoms include drooling, pain, dysphagia and odynophagia. Small, blunt foreign bodies may pass through unhindered. Foreign bodies such as chicken and fish bones may stick in the tonsil, tongue base, cricopharyngeus and pharyngeal wall

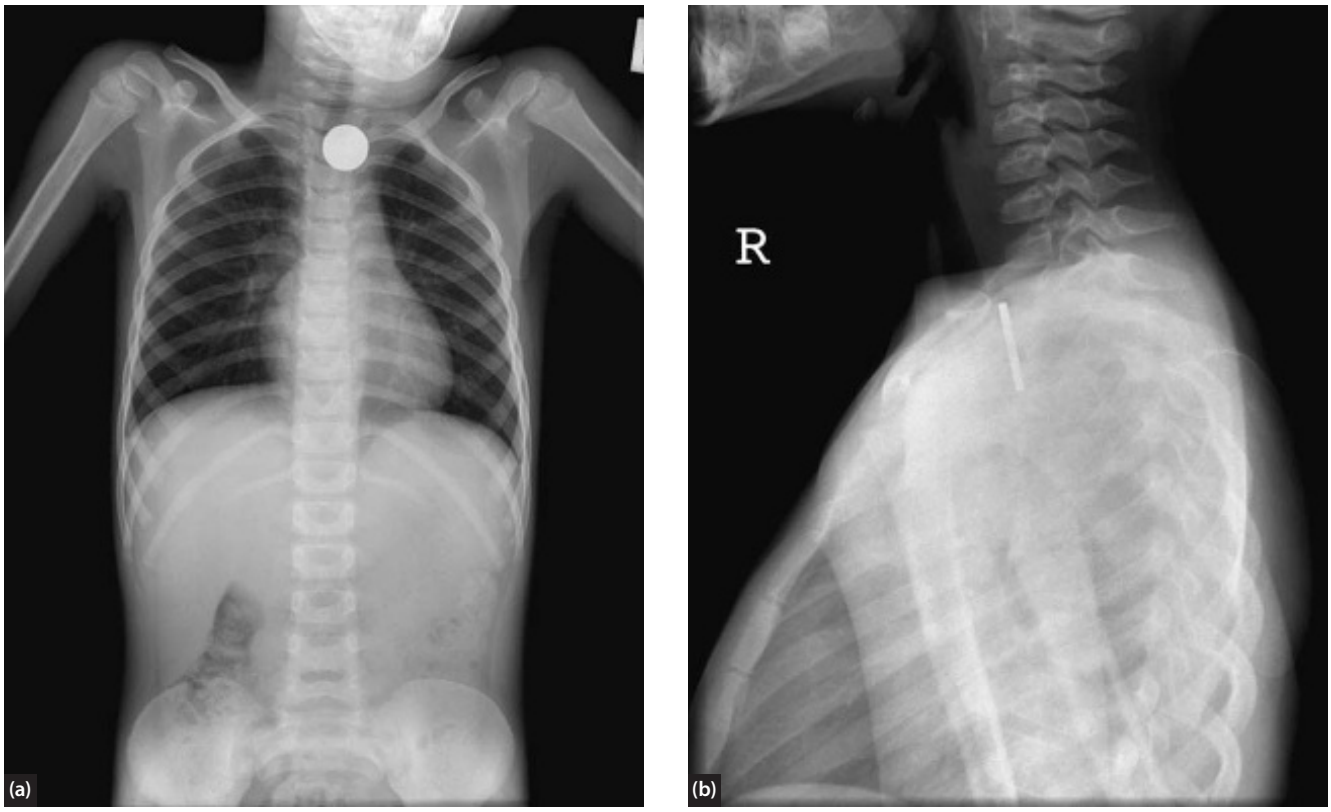

Figure 34.5 (a) Foreign body (coin) in the oesophagus. **(b)** The lateral view confirms the position.

in reducing order of occurrence.[92] Larger items typically stick at the cricopharyngeus or upper oesophagus above the aortic arch. Pathology within the oesophagus can present with foreign body impaction.[93]

Management of ingested foreign bodies

For food-related impaction, medical management is often trialled. Agents include hyoscine (buscopan) and diazepam. The evidence for the use of buscopan or diazepam in this situation is inconclusive. Small retrospective studies have indicated that effervescent fluids may confer some benefit.[94] Food bolus impaction is quite uncommon in children and should raise the possibility of eosinophilic oesophagitis. This condition is discussed in more detail in Chapter 44, Reflux and oesinophilic oesophagitis. When a food bolus is found in a child, the surgeon should take three biopsies from the lower oesophagus for histology and specifically request examination for eosinophils.

Flexible nasendscopy may either identify the foreign body in the pharynx or demonstrate saliva pooling in the pyriform fossae indicating a hold-up in the oesophagus. Metallic foreign bodies may be detected by metal detector or more usually radiography (see **Figure 34.5**). Contrast swallow is not an appropriate initial management as it obstructs endoscopy and may result in aspiration.[95]

Whereas foreign bodies such as small fish bones may absorb without removal, most will require surgical removal.[96] If not removed, some foreign bodies migrate into the soft tissue of the neck.[97] Controversy remains around the choice of flexible or rigid endoscopy (**Figure 34.6**). The latter has a significantly higher perforation rate compared to flexible type (0.2–1.2 versus 0.02–0.05),[98] yet both methods have similar success rates.[99] Early intervention confers benefit of reduced complications in particular for sharp foreign bodies such as bones and pins.[98, 100, 101] Complications include perforation, mediastinal infection/abscess, retropharyngeal abscess and oesophageal stenosis.[102] Delaying intervention beyond 24 hours may increase duration of therapeutic endoscopy.[103]

SPECIAL CONSIDERATIONS

Batteries and magnets

Special consideration needs to be given to batteries as foreign bodies. There has been a significant and increasing rise in battery foreign body incidents since one of the earliest reports of battery ingestion in the 1970s.[104] This was a camera mercury battery which was removed by gastrostomy. Between 1985 and 2009 there was a 6.7-fold increase.[105] The increase in incidence is thought to be due to the increased usage in small electronic devices, the size, shape and smoothness of the button battery and the extent of injury due to the battery power output.[106] There is a male preponderance (57%).[107]

Batteries cause harm in a variety of ways:

- soft tissue forming an electrical circuit between the terminals (sides) of the button battery, hydrolyzing tissue by forming hydroxide at the negative terminal[105, 108]

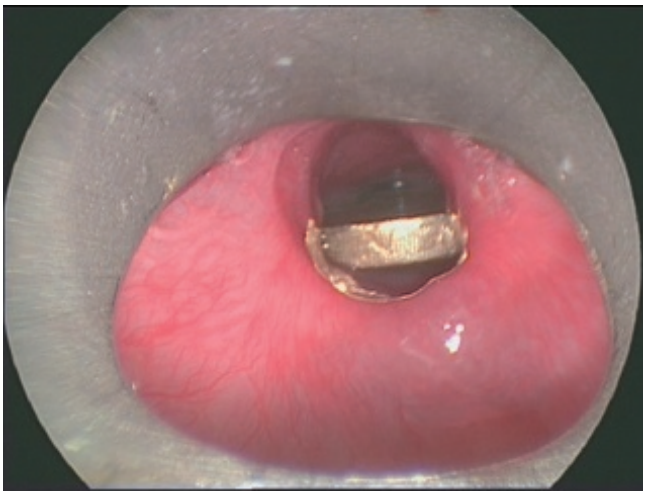

Figure 34.6 Image of a coin in the upper oesophagus on endoscopy.

- leakage of alkaline[109] from the battery when in a saline environment
- pressure necrosis[110] if compressed at a particular site
- release of toxic compounds[111] (e.g. mercury) to cause systemic toxicity.

The majority of batteries are the alkaline variety.[107]

The Susy Safe project has a button battery database component and a report on 348 cases has revealed the following anatomical sites affected. Most cases occurred in the mouth, oesophagus, stomach (188/348), nose (112/348) and ear (44/348).[106] There was only a single case of an inhaled battery. This report identified that 30% of children had dysphagia and perhaps surprisingly 26% had fever and cough.

The size of the battery seems to be important determinant for complications. The highest risk is a 20 mm battery in children under 4 years old.[105] A battery causes a rise in temperature and pH when ingested.[112] Burns occur within 2–2.5 hours. Fifty-four per cent of cases with a fatal outcome were misdiagnosed.[105] This indicates the importance of urgent X-ray investigation and removal. The X-ray feature of button batteries is a double contour.[107] The larger size of button battery is important as it may get stuck at sites of anatomical narrowing such as within the oesophagus at the arch of the aorta. If the battery is past the stomach, serial abdominal X-ray investigation may be appropriate. MLTB is also of value during pharyngo-oesophagoscopy and battery removal to rule out tracheo-oesophageal fistula or prodromal granulation within the airway.[113, 114, 115] Other complications of button batteries in the oesophagus include oesophageal perforation, haemorrhage,[116] vocal cord palsy,[117] ulceration/necrosis and death.[118] A report of a 2-year-old child with an 8-month history of a battery impacted in the oesophagus but still able to swallow has been reported. This case is of significance as the battery had become implanted into the oesophageal wall and surrounded by granulation so dense that the metallic nature of the foreign body was not identifiable intraoperatively. A decision was made to perform an external approach (right posteriolateral thoracotomy) the following day with success.[119]

Debate surrounds the post-operative management of the patient following pharyngo-oesophagoscopy and battery removal. An initial post-op chest X-ray may identify a pneumothorax (around 0.8%)[15] or pneumomediastinum.[112] Possible options include nasogastric tube, proton pump inhibitors, repeat endoscopy or contrast swallow a few days to a week later.[120] Steroids have not been shown to confer a clinical benefit following caustic ingestion, even though there is a theoretical expectation that fibrosis and stricture formation might be reduced.[121] The placement of a nasogastric (NG) tube serves to allow adequate nutrition and perhaps is a form of stenting. However, the blind placement in a corroded oesophagus may present increased risk.[122]

Nasal button battery foreign bodies have been shown to cause septal ulcerations, septal perforation, inferior turbinate ulceration and necrosis.[123] An external auditory canal button battery foreign body may cause skin ulceration, serosanginous discharge and tympanic membrane perforation.[123]

Magnets have been used to remove metallic nasal foreign bodies.[124] Magnets can be problematic as foreign bodies. The danger arises if either more than one magnet is inserted (e.g. nose or swallowed) or one magnet and another metallic object is inserted. The median number of magnet-associated foreign body incidents was two items. Again, there is a prevalence in boys (63%). Magnetic foreign bodies have a larger median volume compared to non-magnetic foreign bodies.[125] The fashion for magnetic earrings across the nasal alar region has inadvertently resulted in some cases of the magnets being misplaced and attracting across the nasal septum resulting in septal injury and even septal perforation due to pressure necrosis.[126, 127] When swallowed, the same mechanism is responsible for attraction across different regions of intestine, with resultant perforation and death.[125]

Caustic agent ingestion

Caustic ingestion is important in young children as these liquids typically have no flavour or odour. Strong alkalis cause injury by tissue liquefaction and necrosis. Furthermore, thrombosis of the supplying vessels results in reduced blood flow to hamper healing. A significant proportion in older teenagers and adults are due to a suicide attempt.[122] Detergents in the home are regulated by legislation. Since 2013 there has been a voluntary change by industry to prevent infant access to laundry tablets as these are alkaline. Liquitabs (liquid detergent parcels/tablets) are responsible for 1500 incidents each year in the UK.[128] The liquid within these tablets can also be inhaled and cause ocular injury and even death has been reported.[129] Caustic ingestion injury to the oesophagus can be graded 1–4 based on the

depth of injury. A review of caustic injury to children indicates that grade 1 is erythema and oedema, which can be managed conservatively. However, grade 4, which is perforation, has a poor prognosis.[122] Most strictures occur within 8 weeks of caustic ingestion and the subsequent dilatations may result in perforation. Furthermore, the risk of subsequent carcinoma is significantly higher (1000-fold). The carcinoma develops at the site of stricture.[130] For more detail on caustic ingestion, see Chapter 45, Oesophageal disorders.

KEY POINTS

- Foreign body-related incidents are common.
- Battery foreign bodies are increasing in frequency and can be fatal.
- Battery foreign bodies require removal without delay.
- A history of possible foreign body inhalation despite a comfortable patient should prompt bronchoscopy, even when chest examination and X-ray are normal. Neither examination nor plain chest films can exclude foreign body, and the risk of lung damage from an undiagnosed foreign body outweighs the small risk of complications of bronchoscopy in experienced hands.

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CHAPTER 35

PAEDIATRIC TRACHEOSTOMY

Michael Saunders

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords tracheostomy and child. The author has a personal bibliography of key papers on tracheostomy in children.

INTRODUCTION AND HISTORICAL PERSPECTIVE

Widely acknowledged as one of the oldest documented surgical procedures, detailed historical accounts of tracheostomy are many and vivid. Use of the procedure in children developed in the 19th century after Trousseau used the technique to relieve airway obstruction in diphtheria. Subsequently, the procedure was widely used in the treatment of poliomyelitis. With the introduction of extensive vaccination programmes these diseases have largely disappeared in the Western world.

Until the late 1970s many tracheostomies in children were performed to relieve airway obstruction in acute airway infections such as epiglottitis and acute laryngotracheobronchitis (ALTB, or croup).[1–3] As the standard of paediatric intensive care facilities improved and prolonged endotracheal intubation became a practical alternative to surgical tracheostomy, progressively fewer procedures were carried out for these indications. By the time haemophilus influenza b (Hib) vaccine was introduced in the 1990s, endotracheal intubation rather than tracheostomy had become the accepted mode of airway management for acute bacterial epiglottitis.[4]

In a series of 153 paediatric tracheostomies, Line et al.[2] report that prior to 1980 38% of tracheostomies were performed for acute airway infections whereas after 1980 this figure had dropped to 12%. Similar findings were reported by Friedberg and Morrison[5] when comparing a series of tracheostomies from 1981 to 1985 to a similar series from the same institution from 1976 to 1980. Crysdale et al.[6] also report an overall reduction by half in the incidence of tracheostomy in the same period, attributed to the change in management of epiglottitis. Corbett et al.[7] reviewed 116 cases over a 10-year period (1995–2004) and reported a further shift in indications, with no tracheostomies for acute airway infections alone and an increasing proportion required for congenital defects such as craniofacial anomalies and major upper gastrointestinal defects. Eighteen children (15.5%) required tracheostomy for acquired airway lesions including subglottic stenosis, vocal cord palsy and respiratory papillomatosis, while 14 tracheostomies (12.1%) were to facilitate management of airway malacia (laryngotracheal, bronchial or a combination). Tracheostomy was also required for long-term ventilation in patients with neuromuscular disorders (14; 12.1%) or ventilator dependency (31; 26.7%).

Tracheostomy in children is now an uncommon operation. Due to a shift in tertiary paediatric treatment to larger centres in the last decade and the lack of a reliable means of collecting data on a national basis, it is difficult to estimate the true incidence of paediatric tracheostomy. A survey of 2065 tracheostomies across the United States estimates a rate of 6.6 tracheostomies per 100 000 child years, with the highest incidence in the first year of life

but with a second peak in incidence in the late teens due to increased risk of serious injury and trauma.[8]

A more recent study of indications in 501 tracheostomies between 1984 and 2014 has found that the commonest indications for tracheostomy in children are now cardiopulmonary disease (34%), neurological impairment (32%) and airway obstruction (19%).[9]

As a consequence of the relative scarcity of the procedure, the medical literature relating to paediatric tracheostomy is generally related to level 3 and 4 evidence. There are no significant randomized controlled trials and the majority of publications tend to document the authors' own series of tracheostomies and their complications in larger children's hospitals. Reports of changing indications from such institutions may also be skewed by changes in medical practice in individual units.

INDICATIONS FOR PAEDIATRIC TRACHEOSTOMY

The general indications for tracheostomy are as follows:

- to relieve upper airway obstruction
- to prevent complications of prolonged intubation
- to reduce anatomical dead space
- to allow suction toilet of the trachea.

In practice, tracheostomies in children are nearly always performed to relieve upper airway obstruction or to allow or assist with mechanical ventilation.

Obstruction of the upper airway

The upper airway (from the lips and anterior nares to the carina) may become obstructed at one or more anatomical levels by a range of pathologies (Table 35.1). If the obstruction is significant and life-threatening and no other means of relieving the obstruction (e.g. nasopharyngeal airway or prong) is appropriate, then a tracheostomy must be considered.

Increasing availability and standard of paediatric intensive care facilities has allowed surgical procedures involving the airway to be undertaken without the need for a covering tracheostomy. Instead, the risk of post-operative airway obstruction is avoided by a period of intubation and ventilation (the 'single-stage' approach).

TABLE 35.1 Examples of obstruction of the upper airway potentially requiring tracheostomy

Anatomical site	Example
Oropharynx, tongue base	Macroglossia Treacher Collins/Goldenhar syndrome Cystic hygroma
Nose, nasopharynx	Choanal atresia
Supraglottis	Supraglottic cyst
Glottis	Vocal cord palsy Physical trauma
Subglottis	Subglottic stenosis, haemangioma
Trachea	Tracheomalacia High tracheal stenosis

The relative indications for tracheostomy continue to evolve: until the late 1990s, tracheostomy was considered the mainstay of management for obstructing subglottic haemangioma. Tracheostomy can be avoided using drug treatment[10] or surgical excision[11, 12] Similarly, the introduction of the cricoid split[13] and single-stage laryngotracheal reconstruction[14] has reduced the need for tracheostomy for extubation failure due to subglottic oedema or stenosis.

Prolonged intubation

The long-term complications of prolonged endotracheal intubation are well recognized: ulceration at the level of the glottis and, particularly in children, the subglottis, can lead to cicatrization and stenosis of the airway.[15] Being softer and more flexible than the adult and with correct selection of tube size and appropriate intensive care, the neonatal larynx is able to tolerate prolonged intubation for relatively longer than the adult.

There is no clear consensus as to the maximum safe duration of intubation. Premature babies may now be intubated for several weeks before permanent damage becomes a risk. Although practice varies in different units, tracheostomy should normally be considered in older children after 2–3 weeks of endotracheal intubation.

Long-term and home ventilation

An increasing number of children are now surviving previously lethal conditions, resulting in chronic respiratory failure because of the availability of long-term ventilation, either in a hospital setting or at home. In a 2011 survey of centres offering this service, out of 933 home-ventilated children in the UK, 206 had tracheostomies.[16] Indications for long-term ventilation include:

- congenital central hypoventilation syndrome
- spinal injury
- congenital myopathy
- airway malacia
- chronic lung disease.

Increasingly, these patients can be ventilated at home rather than in hospital although the cost in terms of manpower and equipment is high. The demands placed on the tracheostomy itself are higher and there is a higher risk of tracheostomy-related complications in home-ventilated children.

Tracheal toilet

In practice, very few children now require tracheostomy for toilet of the airway. Children with intractable aspiration may need regular suction but the presence of a tracheostomy can predispose to aspiration in itself and increase the risk of respiratory tract infection.

TECHNIQUES OF TRACHEOSTOMY SPECIFIC TO CHILDREN

Strictly speaking, a **tracheotomy** is the creation of a hole into the trachea. A **tracheostomy** is the fashioning of a permanent opening or stoma between the trachea and the skin. Although this difference has been largely semantic until recent years, it is now an important distinction as surgical technique in children's tracheostomies has evolved.

Positioning

Under general anaesthesia the infant is positioned supine on the operating table. Neck extension is achieved with a rolled towel or gel pillow under the shoulders. The neck can be fixed in extension and stabilized in the midline using adhesive tape such as Elastoplast® (Figure 35.1) or by using a horseshoe-shaped head rest. Theoretically, extension of the neck in infants increases the risk of injury to the great vessels in the root of the anterior neck; in practice, with careful dissection and identification of structures this is rarely a clinical problem. Overextension does, however, risk exposing a significant part of the intrathoracic trachea and can lead to an incision in the trachea which is too low.

Skin incision

In adult practice the conventional skin incision used is horizontal, situated halfway between the cricoid and sternal notch. Traditionally, a vertical incision has been avoided for fear of a poor cosmetic outcome after decannulation. However, after removal of a long-standing tracheostomy, the resulting scar is such that it is unlikely that the orientation of the original incision will make a significant difference. In the last two decades a vertical skin incision has become more popular with specialized paediatric otolaryngologists[17] and is now standard practice in most major children's units (Figure 35.2). A vertical incision has a number of advantages over the horizontal incision: it tends to keep dissection in the midline, reducing a tendency to stray away from the trachea in a difficult dissection, and allows easier placement of maturation sutures. The incision is placed halfway between the cricoid ring and the sternal notch. The skin incision does not need to be a great deal longer than will allow the insertion of the selected tube; surgical retraction of infant skin during surgery tends to lead to the skin defect appearing larger at the end of the procedure than the original incision.

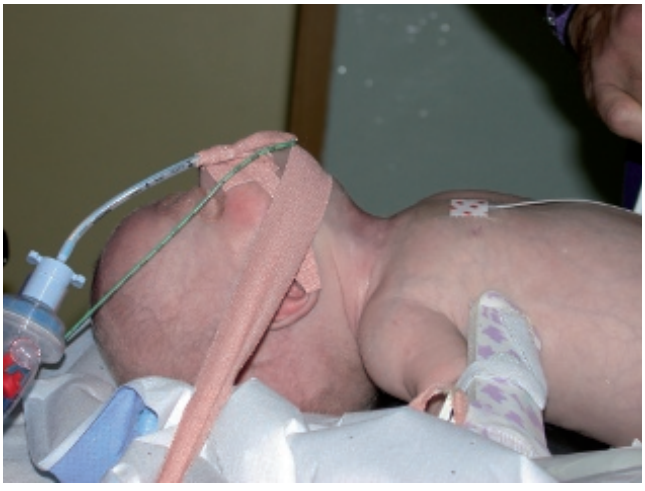

Figure 35.1 Child positioned on the operating table for tracheostomy.

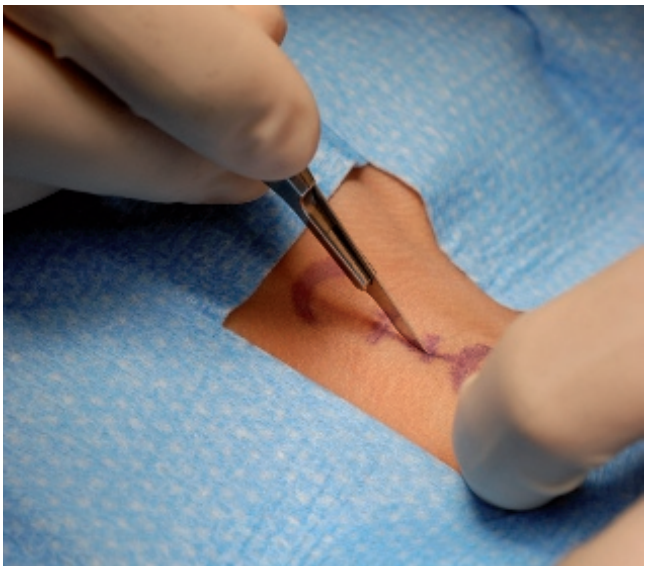

Figure 35.2 Skin incision in paediatric tracheostomy.

Removal of subcutaneous fat and maturation sutures

A disc of subcutaneous fat immediately surrounding the incision should be removed after completing the skin incision. This allows the skin edges to invert slightly so as to create a stoma lined with healthy squamous epithelium. This effect can be increased by suturing the edge of the skin incision to the edge of the tracheal incision (maturation sutures)[18] using absorbable sutures (the author's preference is 4/0 Vicryl Rapide). The resulting opening is more secure and tends to stay open even without the tube *in situ* and is therefore more akin to a surgically fashioned stoma (Figure 35.3) rather than the traditional approach which is essentially an incision in the neck and trachea only held open by the tracheostomy tube itself. Theoretically there is a lower risk of the tracheostomy tube being misdirected into the soft tissues at an emergency post-operative tube change (a false passage).

Stay sutures are placed in the wall of the trachea on either side of the vertical incision. These are generally a removable suture (e.g. 4/0 PROLENE) and are left *in situ* until the first tube change. In the event of accidental decannulation, upward and lateral traction on the sutures will open the tracheostomy to make tube reinsertion simpler. The sutures may be taped to the chest wall (Figure 35.4) to prevent accidental removal.

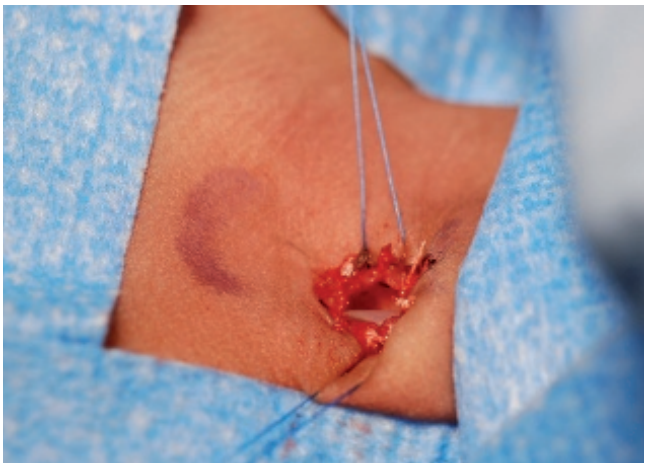

Figure 35.3 Maturation sutures and stay sutures in a paediatric tracheostomy prior to placement of the tracheostomy tube.

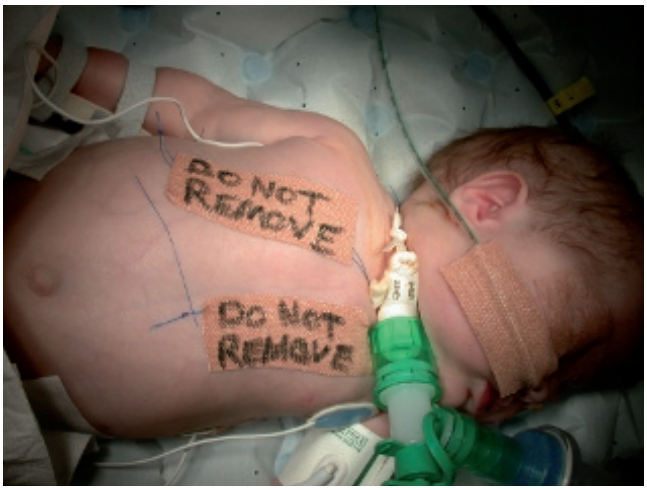

Figure 35.4 Stay sutures taped to the chest wall at the end of the procedure.

Dissection

Dissection using monopolar or bipolar diathermy is advisable in small children to minimize blood loss and should be restricted to the midline to avoid risk to other structures in the neck. Although in adults and larger children the thyroid isthmus is traditionally divided and transfixed to prevent haemorrhage, in infants it is usually adequate to divide the isthmus of the thyroid with bipolar diathermy.

Given the relatively small size of the infant neck and trachea, and secondly the relative proximity of the carotid sheath, it is advisable to palpate the trachea regularly throughout the dissection to ensure that the direction of dissection has not strayed from the midline.

Tracheal incision

A vertical incision is made in the midline, usually in tracheal rings 3–4. It is vital that the cricoid cartilage is identified before the incision is made so that the correct incision can be made. It has long been established that too high an incision in the trachea predisposes to subglottic stenosis.[19] A variety of other incisions has been advocated, including excision of an anterior tracheal window, a superiorly or inferiorly based tracheal flap which is raised and sutured to the skin or, recently, a cruciate incision in the trachea, the tracheal edges being closely apposed to the skin edges.[20] The theoretical advantage of most of these techniques is increased stability of the initial tracheostomy tract and therefore greater safety in the event of accidental decannulation. However, although there is no evidence available from randomized clinical trials, animal experiments[21] suggest that tracheal flaps may lead to an increased risk of long-term stenosis and the majority of authors currently favour a simple vertical incision.

Securing tracheostomy tubes

Until the tracheostome has epithelialized and matured, the risks associated with accidental decannulation are more significant. Initially, it is the author's practice to fix the tube into position in the neck using the inelastic linen tapes supplied with the tube. The tapes are tied in a secure knot, sufficiently tight to allow one finger to be inserted between the tapes and the neck skin (**Figure 35.5**). The tapes should be tightened with the neck flexed, rather than in the operative position with the neck extended. Suturing the flange of the tracheostomy tube to the skin should be avoided in children; infant skin is flexible and thin and does not provide a strong enough anchor point for fixing the tube.

After 7 days the first change is undertaken and the linen tapes may be changed for a Velcro® fastening (**Figure 35.6**) which allows for easier changing and is less traumatic to the skin of the neck. It is vital that, whatever fixing devices are used, they are applied correctly and at the right tension to prevent accidental decannulation.

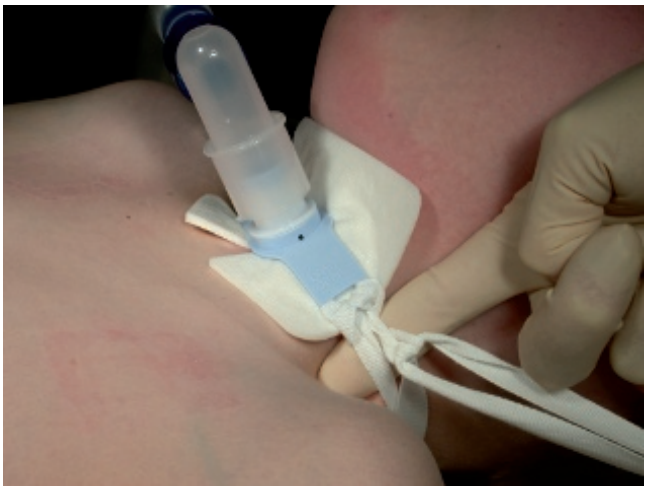

Figure 35.5 Adjusting the correct tension of securing tapes.

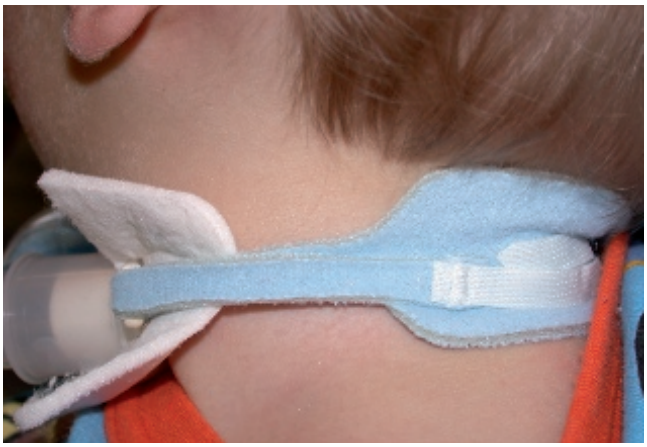

Figure 35.6 Velcro® tracheostomy fitting.

TRACHEOSTOMY CARE

Adequate tracheostomy care is critical in the first 2–3 post-operative days. It is during the formation of the tract of the stoma that the risk of tube displacement is at its highest as initially the tract can close very quickly, making reinsertion difficult. It is difficult to overstate the importance of tracheostomy nursing care in the post-operative period. With meticulous and skilled care, most of the complications of tracheostomy can be avoided. Inexperienced staff with no specific training are often reluctant to intervene. It is therefore essential that hospitals maintain a high standard of internal training in this regard, and many units have specific teams and regular training programmes for nursing staff.

Suction

Immediately after tracheostomy, the change from air that is warmed and humidified by the upper airway to dry, cold air leads to a rapid increase in airway secretions. This gradually reduces after a few weeks. Secretions dry on the inside of the tracheostomy tube and gradually reduce the effective lumen. Humidification of inspired air and regular suctioning will reduce this tendency. Suctioning is required as often as is necessary to keep the tube and airway clear. Overzealous suctioning may lead to mucosal trauma in the distal trachea if the catheter is inserted into the tracheal lumen itself[22] and eventually granulation may form at the tip of the tracheostomy tube, which in itself may lead to tube obstruction. It is suggested that the suction tube be inserted as far as the tip of the tracheostomy tube and withdrawn with a finger occluding the side port. The exact distance may be measured and marked on the suction tube.

The need for suctioning decreases in frequency over time, although with lower respiratory tract infections, secretions may become thicker and more profuse. On such occasions, irrigation of the tracheostomy tube with sterile saline to loosen secretions prior to suctioning is often advocated but there is little evidence to support this practice and it may increase contamination of the lower airway.[23]

Humidification

Initially, humidification should be given via nebulizers and a tracheostomy mask. After a week or so, secretions reduce and the level of humidification required is less. A few weeks after tracheostomy, more mobile devices can replace permanent humidification. Longer-term humidification may be achieved by using a Swedish nose or a tracheostomy bib (Figure 35.7). A heat and moisture exchanger (HME or 'Swedish nose') attachment (Figure 35.8) contains a filter which becomes saturated by the moisture in exhaled air; this in turn humidifies the inhaled air. The tracheal bib works in a similar way. Both devices have the advantage of acting as filters for inspired air.

Skin care

The tracheostomy wound itself becomes rapidly infected with skin commensals and is impossible to keep sterile. The wound heals by secondary intention and eventually the tract becomes lined with squamous epithelium and organized scar tissue. Securing the wound edge skin to the trachea with maturation sutures hastens the development of an epithelialized tract. At this stage the tracheostome is considered mature. Until this point there is usually a considerable discharge from the wound itself and, if the skincare in the first few days is not meticulous, skin and wound breakdown will occur. Usually a dry gauze or foam

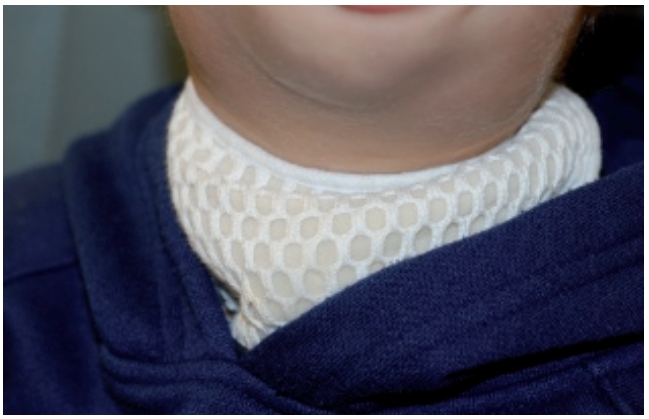

Figure 35.7 Tracheostomy bib.

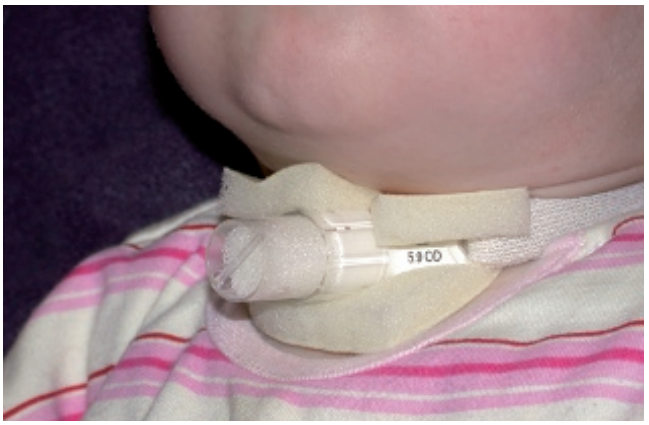

Figure 35.8 Heat and moisture exchanger (HME).

(e.g. Lyofoam®) dressing is inserted between the peritracheostomy skin and the flange of the tube. This is rapidly saturated and needs to be changed regularly. Of course the action of changing the dressing increases the risk of accidental decannulation and there is often reluctance on the part of nursing staff to do this. Adequate training in tracheostomy care is essential in a hospital where regular paediatric airway surgery takes place.

Large skin incisions are generally not required in elective paediatric tracheostomy. If not adequately closed, a large incision will lead to gaping and wound breakdown. It is futile to attempt closure in this instance because of the bacterial colonization of the wound and inevitable infection. Large tracheostomy wounds require careful dressing and packing similar to a healing ulcer, and a range of wound products are available. The wound will eventually close by secondary intention.

The tapes used to secure the tube in place can lead to ulceration of the neck skin if they are left too tight or for too long. Although the linen tapes supplied with tubes are secure, they are inelastic and have a tendency to cut into the skin. Again, meticulous nursing and skin care is vital. The problem can be reduced by tying the tapes inside a sleeve of Tubigrip™ or part of a large plastic (e.g. endotracheal) tube (Figure 35.9). When the tracheostomy matures, wider softer bands with Velcro® fittings may be used and are less traumatic to the neck skin.

Change of tracheostomy tube

The first change of tube is generally undertaken at around the seventh post-operative day. This allows some time for maturation of the stoma but is short enough to reduce the risk of tube obstruction from dried and thickened secretions. The first change should be undertaken by an otolaryngologist; in the relatively rare instance of difficulty reinserting the second tube, an emergency surgical procedure may be required.

If oral intubation is difficult or impossible (e.g. retrognathia, laryngeal stenosis), it is advisable to undertake the first change in the operating theatre in case further surgical intervention is needed. In children who can be easily intubated (including the majority of children tracheostomized for prolonged ventilation), it is more usual to undertake the first change on the intensive care unit, with an intubation trolley and senior ITU medical staff on hand should reinsertion be difficult and re-intubation be required.

If this procedure is uneventful, the nursing staff can carry out subsequent changes. If discharge home is anticipated, the parents must be taught the tube-changing technique in a secure environment.

There is no standard proscribed interval at which tubes should be changed; this varies between children and also in the same child given variation in season and in the health of the lower airway. The tube needs to be changed before dried secretions start to reduce the lumen of the tube. The old tube should be inspected after removal to determine the degree of contamination and this will influence the interval until the next change. If a tube visibly contains dried secretion on external inspection (Figure 35.10), has an audible whistle due to obstruction ('if you can hear a tube, you should change it') or if the suction catheter cannot be passed due to obstruction, then it should be changed. If the suction catheter does not pass freely after changing the tube, the advice of an otolaryngologist should be sought. (The manufacturers recommend that the commonly used Bivona® and Shiley® tubes are changed after a maximum of 28 days although most tubes are changed more frequently than this on clinical grounds.)

TRACHEOSTOMY TUBES

Diameter

Modern tracheostomy tubes are sized in relation to the diameter of the lumen in millimetres and the length of the tube from the skin flange to the tip of the tube. Some older silver tubes still use the French gauge system of sizing. The age-appropriate size for a tracheostomy tube can be derived from the guide shown in Figure 35.11. In general terms, smaller-sized tubes become obstructed more easily

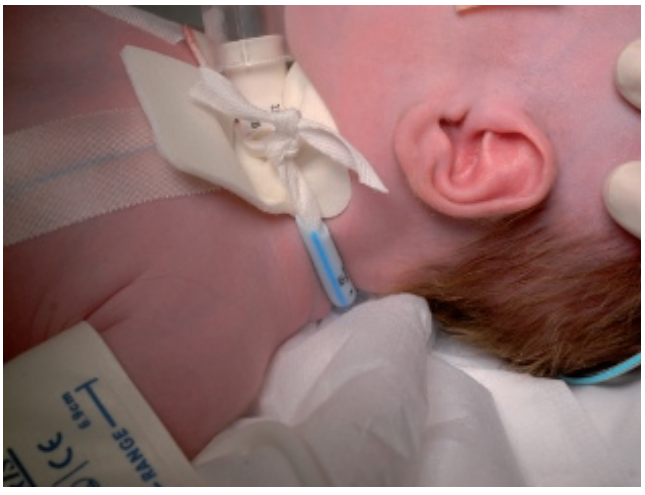

Figure 35.9 Modified endotracheal tube used to protect the neck skin from tracheostomy tapes.

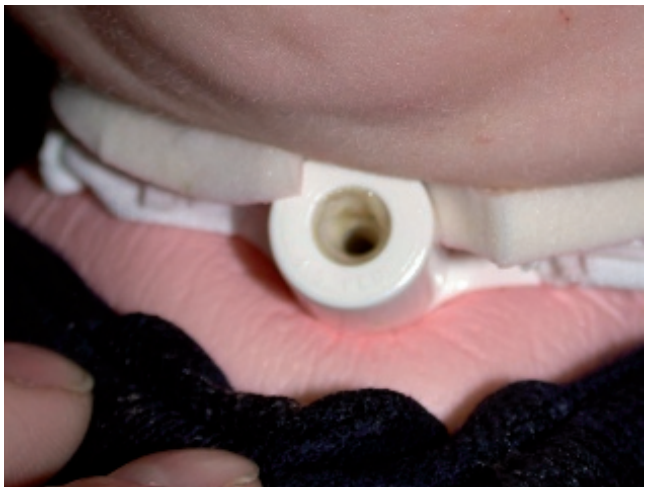

Figure 35.10 Tracheostomy tube partly obstructed with secretions.

			Preterm – 1 Month	1–6 Months	6–18 Months	18 Months – 3 Years	3–6 Years	6–9 Years	9–12 Years	12–14 Years
	Trachea (Transverse Diameter mm)		5	5.0–6.0	6.0–7.0	7.0–8.0	8.0–9.0	9.0–10	10–13	13
PLASTIC	Great Ormond Street	ID (mm)	3.0	3.5	4.0	4.5	5.0	5.5	6.0	7.0
		OD (mm)	4.5	5.0	6.0	6.7	7.5	8.0	8.7	10.7
	Shiley	Size	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5
		ID (mm)	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5
		OD (mm)	4.5	5.2	5.9	6.5	7.1	7.7	8.3	9.0
		Length (mm) Neonatal	30	32	34	36				
		Paediatric	39	40	41*	42*	44*	46*		
	* Cuffed Tube Available	Long Paediatric					50*	52*	54*	56*
	Portex (Blue Line)	ID (mm)	3.0	3.5	4.0	4.5	5.0	5.0	6.0	7.0
		OD (mm)	4.2	4.9	5.5	6.2	6.9	6.9	8.3	9.7
	Portex (555)	Size	2.5	3.0	3.5	4.0	4.5	5.0	5.5	
		ID (mm)	2.5	3.0	3.5	4.0	4.5	5.0	5.5	
		OD (mm)	4.5	5.2	5.8	6.5	7.1	7.7	8.3	
		Length Neonatal	30	32	34	36				
		Paediatric	30	36	40	44	48	50	52	
	Bivona	Size	2.5	3.0	3.5	4.0	4.5	5.0	5.5	
		ID (mm)	2.5	3.0	3.5	4.0	4.5	5.0	5.5	
		OD (mm)	4.0	4.7	5.3	6.0	6.7	7.3	8.0	
	All sizes available with Fome Cuff, Aire Cuff, & TTS Cuff	Length Neonatal	30	32	34	36				
		Paediatric	38	39	40	41	42	44	46	
	Bivona Hyperflex	ID (mm)	2.5	3.0	3.5	4.0	4.5	5.0	5.5	
		Usable Length (mm)	55	60	65	70	75	80	85	
	Bivona Flextend	ID (mm)	2.5	3.0	3.5	4.0	4.5	5.0	5.5	
		Shaft Length (mm)	38	39	40	41	42	44	46	
		Flextend Length (mm)	10	10	15	15	17.5	20	20	
SILVER	Alder Hey	FG		12–14	16	18	20	22	24	
	Negus	FG			16	18	20	22	24	26	28
	Chevalier Jackson	FG	14	16	18	20	22	24	26	28
	Sheffield	FG	12–14	16	18	20	22	24	26	
		ID (mm)	2.9–3.6	4.2	4.9	6.0	6.3	7.0	7.6	
	Cricoid (AP Diameter)	ID (mm)	3.6–4.8	4.8–5.8	5.8–6.5	6.5–7.4	7.4–8.2	8.2–9.0	9.0–10.7	10.7
	Bronchoscope (Storz)	Size	2.5	3.0	3.5	4.0	4.5	5.0	6.0	6.0
		ID (mm)	3.5	4.3	5.0	6.0	6.6	7.1	7.5	7.5
		OD (mm)	4.2	5.0	5.7	6.7	7.3	7.8	8.2	8.2
	Endotracheal Tube (Portex)	ID (mm)	2.5	3.0	3.5	4.0	4.5	5.0	6.0	7.0	8.0
		OD (mm)	3.4	4.2	4.8	5.4	6.2	6.8	8.2	9.6	10.8

Figure 35.11 Chart for sizing tracheostomy tubes. Reproduced from Tweedie et al.[25]

and may impair respiration if too small for the age of the child. A child with a long-standing tracheostomy should undergo regular age-appropriate 'upsizing'. However, tracheostomy tubes tend to almost completely fill the trachea in very young children, making normal speech difficult. In some cases – for example, if the airway above the tracheostome is not completely obstructed – a smaller-sized tube will allow air to flow up thought the glottis and aid in normal speech production. Too large a tube will predispose to suprastomal collapse and may increase the risk of granulations and stenosis.

Tube length

When inserted correctly, the end of the tracheostomy tube should sit comfortably proximal to the carina. Too long a tube will abut the carina and lead to ventilation problems, mucosal injury and potentially subsequent scarring. Too short a tube increases the risk of accidental decannulation. Ideally, the tube should be at least 2 cm, inside the stoma and 1–2 cm clear of the carina.[24] Tube tip position can be assessed on chest X-ray, at regular rigid bronchoscopy or by passing a flexible endoscope down the lumen of the tube to inspect the carina.

Material

The use of metal and very rigid plastic tracheostomy tubes in children has been largely superceded. Soft or siliconized PVC is now the most widely used material in paediatric tracheostomy tubes and materials may be hydrophobic to reduce the deposition of secretions. The relative flexibility of newer tubes reduces the risk of mucosal trauma during neck movements and the soft flange is less likely to lead to skin injury around the tracheostome. One advantage of metal tubes was that, as the stronger metal wall could be made thinner, it was possible to achieve a larger lumen for the same outside tube diameter and as a result an inner tube could be used. The thickness of the wall of standard tubes makes inner tubes impractical in all but the largest children's tracheostomy tubes.

Fenestration

Fenestrated tubes allow air to pass upwards through the glottis in expiration to improve phonation. These are less practical in smaller children as the fenestration tends to become a focus for granulation and mucosal trauma on suctioning. Adequate passage of air upwards into the larynx is usually achieved by selecting a smaller tube diameter and allowing air leakage around the tube on expiration.

Cuff

There are two specific indications for cuffed tubes in children: first, where there is a significant risk of aspiration (although a cuff will not completely protect against this) and, second, where there is a decrease in lung compliance with intercurrent infection in a ventilated child and ventilation pressures need to be raised temporarily. In this instance, the risk of tension pneumothorax is significantly increased. In the author's institution, children on the home-ventilation programme are admitted to hospital for observation if the ventilation pressures become high enough to require a cuffed tube.

The presence of a cuff increases the risk of mucosal ischaemia and subsequent tracheal stenosis, particularly if high cuff pressures are employed. Traditionally, cuffed tubes are rarely indicated in paediatric practice; until adolescence, a sufficient seal to allow positive pressure ventilation can normally be achieved with an uncuffed tube. In the last decade there has been an increase in the use of cuffed endotracheal and tracheostomy tubes in paediatric intensive care units. This may reflect the increasingly complex nature of children being treated in hospital but it is not currently clear if this will lead to an increase in the rate of subglottic and tracheal stenosis.

Types of tube

An increasingly wide variety of tracheotomy tubes is available for specific indications. An excellent review of available tubes is given by Tweedie et al.[25] The commonest standard tubes used in the UK at the time of writing are the Shiley® and Bivona® tubes. They are available in neonatal and paediatric lengths, and the Shiley® tube is also available in a paediatric long (PDL) size for older children.

The Bivona® Flextend™ tube is a silicone tracheostomy tube with a longer external component than a normal tracheostomy tube (**Figure 35.12**). This allows a greater degree of flexibility in children who are mechanically ventilated and is particularly useful in very small infants with a limited gap between the chin and chest (**Figure 35.13**). The main disadvantage of this tube is the increased length of tube, which increases the dead space and risk of obstruction by secretions.

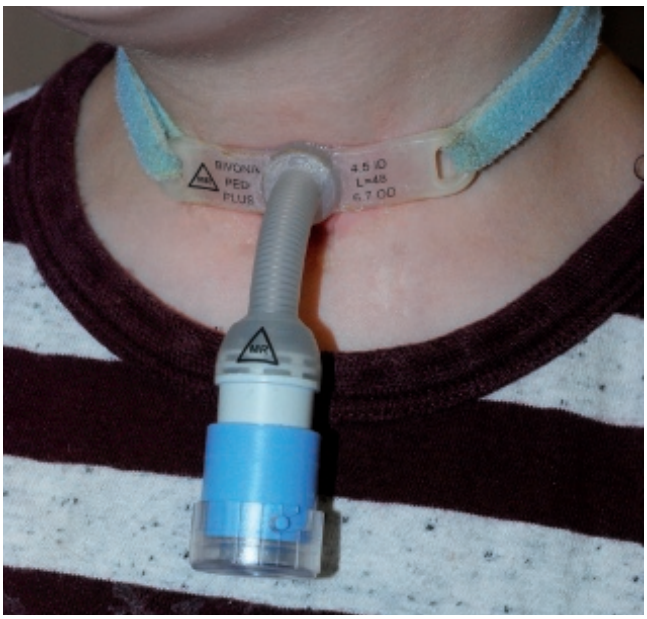

Figure 35.12 Bivona® Flextend™ tube (with Rusch speaking valve).

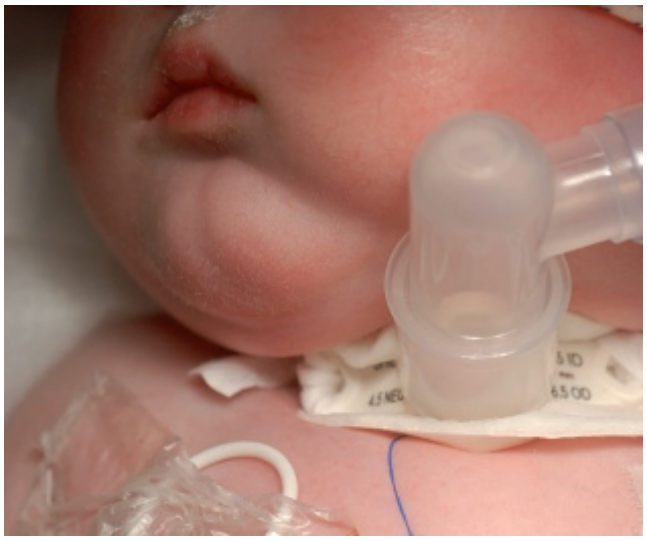

Figure 35.13 Anatomical difficulty with limited space between the chin and the chest wall.

The Bivona® Hyperflex™ tube has an adjustable flange which allows change of the effective length of the tracheostomy tube (Figure 35.14). This is useful in children with particular anatomical constraints, for example where a low tracheal obstruction needs to be bypassed by the tube and a standard length tube cannot be used. The disadvantages of this sort of tube are that it is expensive and that the wall of the tube is thick, resulting in a relatively small tube lumen. Other custom-made tubes are available for children with specific anatomical difficulties. Tube manufacturers should be approached directly for advice.

Speaking valves

Speaking valves are one-way valves which allow inhalation though the tube but force air upwards through the glottis on exhalation, creating sufficient subglottic pressure to allow phonation. As well as allowing speech, by increasing tracheal pressure on exhalation, these may improve lung function and reduce aspiration.[26] In addition to these possible benefits, it is beneficial to a child to get used to the sensation of expiration through the normal airway, particularly pre-decannulation. Speaking valves should be used under supervision and not while the child is asleep, and they are best used with advice from speech therapy. Small infants will not always tolerate the valve and quickly learn to blow the valve off the tracheotomy by coughing hard. Many children learn to occlude the end of the tube on exhalation by flexing the neck and occluding the end of the tube with the neck skin to achieve the same result to help phonation. Rusch speaking valves (see Figure 35.12) are open apart from in significant expiration whereas the Passy-Muir® valve (Figure 35.15) is designed to be closed apart from in inspiration and encourages use of the normal airway for expiration even in quiet respiration. The Passy-Muir® valve may be modified in children who find it hard to tolerate by drilling small holes to allow some expired air to escape.[27]

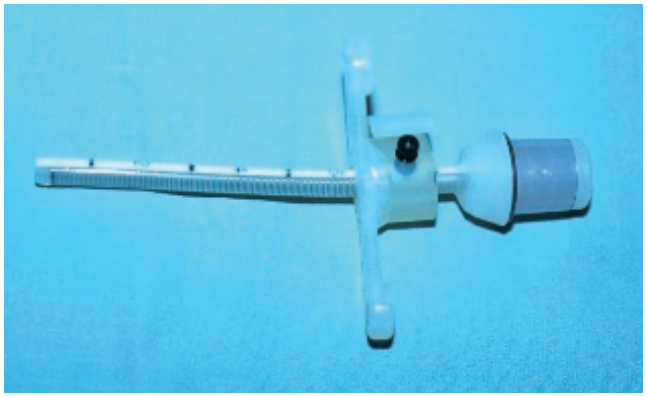

Figure 35.14 Bivona® Hyperflex adjustable tube.

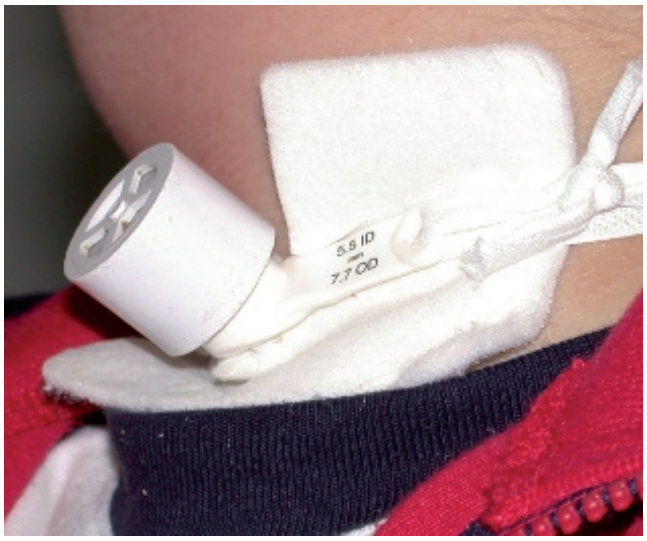

Figure 35.15 Passy-Muir speaking valve.

COMPLICATIONS OF TRACHEOSTOMY

General

Tracheostomy complications are more likely in children than in adults, and more common in children under 2 years of age,[1, 28] particularly preterm infants.[29] Overall complication rates are quoted between 25%[30] and 77%.[31] There is likely to be considerable variation in the documentation and reporting of minor complications – some authors do not consider granulation to be a reportable complication (Table 35.2).

The higher complication rate in smaller children is likely to reflect the relatively small diameter of the airway in small children and the ease with which the airway may be occluded (for example by secretions, granuloma or suprastomal collapse), but also the fact that younger children receiving tracheostomy may remain tracheostomized for a longer period.[31]

As with adult tracheostomies, emergency procedures are associated with a higher rate of complications[32] and longer duration of tracheotomy is associated with a higher risk of long-term complications.[33] Given the relative scarcity of

TABLE 35.2 Complications of tracheostomy

Time after tracheostomy	Complications
General	Tube obstruction Accidental decannulation General complications of surgery and anaesthesia Death
Early post-operative (up to 1 week)	Bleeding: post-operative, wound edge Pneumothorax Subcutaneous emphysema Infection Apnoea
Late post-operative (after 1 week)	Granulation Bleeding Suprastomal collapse Skin complications Aphonia, speech delay Psychological factors Adverse effects on family

paediatric tracheostomy and the limited number of large published series, it is difficult to accurately derive a risk for fatal complications of paediatric tracheostomy. Of larger studies reported since 1980, the mortality related to the tracheostomy tube itself ranges from 0% to 3.6% (Table 35.3).[30, 34] In nearly all cases, the cause of tracheostomy-related death is tube obstruction or accidental decannulation. Earlier reports quote higher mortality rates but paediatric otolaryngology practice has changed considerably in the last 30 years and older studies are unlikely to reflect current practice and safety. Mortality from non tracheostomy-related medical conditions, such as respiratory or cardiovascular disease, is consistently high (7–36%) in all series,[32, 35] reflecting the complex medical conditions of children requiring tracheostomy.

Accidental decannulation

If there is little or no natural airway above the tracheostomy or if a child is ventilator-dependent, accidental decannulation can be fatal. The risk is increased by insufficiently tight ties, too short a tracheostomy tube and excessive traction on the tube from ventilator tubing. In the first few days before the tract matures, it is likely to be harder to reintroduce the tube if decannulated. Wetmore et al.[1] report accidental decannulation in 29 of 420 (6.9%) children in the first week.

The risk of accidental decannulation may be reduced by meticulous tracheostomy nursing care, and surgical techniques (stay sutures, maturation sutures) may help reduce the morbidity by allowing easier and safer reinsertion of a displaced tube. In the event of accidental decannulation, the tube should be reintroduced in a controlled manner to prevent the creation of a false passage.

Tube obstruction

Immediately after tracheostomy the tube is most likely to become blocked with secretions. Regular suction is required. Humidification reduces the rate of secretion and helps to prevent the secretions drying in the lumen of the tube and narrowing the airway. In a mature tracheostomy, the tube is more likely to be obstructed by granulation as

TABLE 35.3 Large ($n > 100$) series of paediatric tracheostomies and complications

Study and publication year	Number of tracheostomies	Years of study	Overall complication rate (%)	Early complication (%)	Late complication (%)	Overall mortality (%)	Tracheostomy-related death (%)
Line et al. 1986[2]	153	1970–1985	38	12	26	22	3
Crysdale et al. 1988[6]	319	1976–1985	32	9	23	13.5	0.9
Carter and Benjamin 1983[30]	164	1972–1981	25	5 (est)	19 (est)	10.9	0
Carr et al. 2001[31]	142	1990–1999	77	14	63	15	0.7
Prescott and Vanlierde 1990[3]	293	1980–1985	32 (est)	–	–	10	2
Carron et al. 2000[34]	218	1988–1998	44	–	–	19	3.6
Midwinter et al. 2002[35]	143	1979–1999	46	–	–	7	2.8
Wetmore et al. 1982[1]	420	1971–1980	49	28.3	52.6	28	2
Ward et al. 1995[32]	103	1980–1990	45.6	30	15.6	36	2.9
Corbett et al. 2007[7]	116	1995–2004	45	11.2	44.8	19.6	1.8
Levi et al. 2016[36]	264	2001–2011	32.6	7.6	25.0	22.0	n/a
Mahadevan et al. 2007[37]	193	1987–2003	51	7.4	43.0	14.0	1.6
D'Souza et al. 2016[38]	302	2000–2014	19.9	13.9	3.4	n/a	0
Ozmen et al. 2009[39]	282	1968–2005	18.0	8.5	10.0	19.0	1
De Trey 2013[40]	119	1990–2009	23	–	–	23	0.84

(est) = figure estimated from text.

the tube tip, as a result of either use of suction catheters or direct trauma from the tube itself.

Pneumothorax, pneumomediastinum, surgical emphysema

In the infant the domes of the pleura extend well into the neck. Inadvertently straying from the midline during dissection increases the risk of post-operative pneumothorax. This should be detected immediately post-operatively on a routine chest X-ray. Small pneumothoraces can be treated conservatively while larger ones will require chest drainage.

If the tracheostomy wound is closed too tightly around the tube, or the dressings are too tightly applied to the neck skin, air may leak into the soft tissues of the neck (surgical emphysema) or track down into the mediastinum. In this instance the wound should be reopened to allow air to track back out through the tissues and a corrugated drain should be inserted. Pneumothorax is a rare complication in elective tracheostomy but commoner in emergency tracheostomy.[41, 42] Although it considered normal practice to perform a chest X-ray after all paediatric tracheostomies both to check tube position and to exclude pneumothorax, Genther and Thorne have suggested that the radiation risk from this may not be justified in an otherwise uncomplicated elective procedure.[43]

Bleeding

Bleeding in the first few days after tracheostomy usually arises as a result of failure to achieve complete haemostasis during surgery. Commonly, bleeding may persist from the wound edge, anterior jugular veins or their tributaries, or the edge of the thyroid isthmus. If direct pressure is not adequate to control haemorrhage, the wound may be carefully packed with haemostatic gauze (Surgicel or Kaltostat®). Re-exploration is rarely required.

Later, minor bleeding may arise from areas of granulation around the tube. This can normally be controlled with cautery and ongoing medical treatment such as application of steroid and antibiotic ointment.

Tracheo-innominate fistula

Tracheo-innominate artery fistula is a rare but lethal complication. There is no reliable estimate of the risk in children, which in adults has been estimated as 0.4%.[44]

In some children the innominate artery lies abnormally high in the neck (**Figure 35.16**). If this finding is made at the time of surgery, the decision to perform a tracheostomy should be reconsidered. If there is no safe alternative, it is acceptable to place the tracheal incision higher than one would normally advocate and accept the risk of subglottic stenosis. An abnormally low tracheostomy will also increase the risk. A fistula into the artery forms as a result of erosion of the arterial wall by direct pressure from the tube.

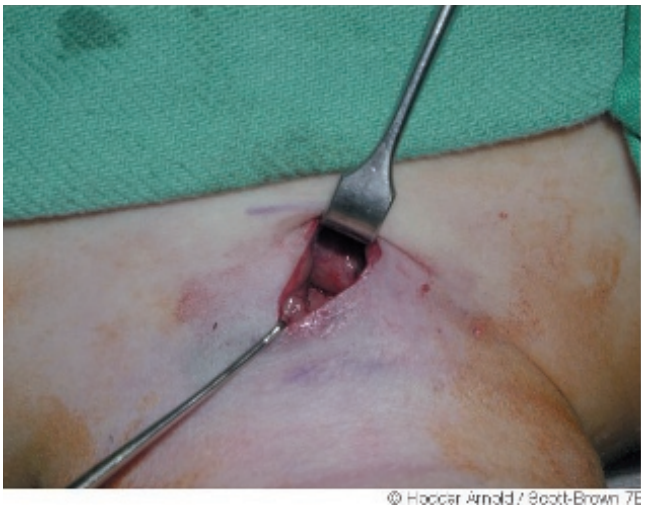

Figure 35.16 High innominate artery.

Although most bleeding coming from the tracheostomy tube itself is likely to represent granulation formation at the tube tip, in all cases the possibility of tracheal innominate artery fistula should be considered. The trachea should be examined by flexible bronchoscopy on the ward or by rigid endoscopy under anaesthesia. If the bleeding appears to arise from the anterior tracheal wall rather than tube-tip granulation, the wound must be re-explored immediately, ideally with the assistance of a cardiothoracic surgeon. It may be possible to tamponade the bleeding by using a cuffed tube temporarily and, if the laryngeal anatomy permits, endotracheal intubation should be established prior to exploration. The mortality from this complication remains very high.

Granulation

The presence of the tracheostomy tube as a foreign body and the persistent presence of bacterial flora in the tract act as an ongoing stimulus for the formation of granulation tissue. Granulation may form at the skin edge of the tract (peristomal granulation) and inside the trachea itself, both on the anterior wall of the trachea above the tube (suprastomal granulation) and also at the tube tip lower in the trachea. Excessive or overexuberant suctioning can lead to more granulation through mucosal trauma and the tube itself can cause mucosal injury. This was generally more common with more rigid tube designs, particularly the silver[45] and PVC designs.

Granulation tissue can pose a number of problems: on the surface, granulations tend to discharge and bleed and, when severe, they can lead to difficulty in changing the tube. More modern tubes made from less reactive silicone are more flexible and softer and are felt to reduce the problem both at the skin and inside the trachea.

Peristomal granulations can generally be controlled with topical steroid/antibiotic preparations. When more severe, they may be removed with bipolar diathermy. Caution needs to be exercised when using silver nitrate cautery as the silver nitrate solution can easily enter the

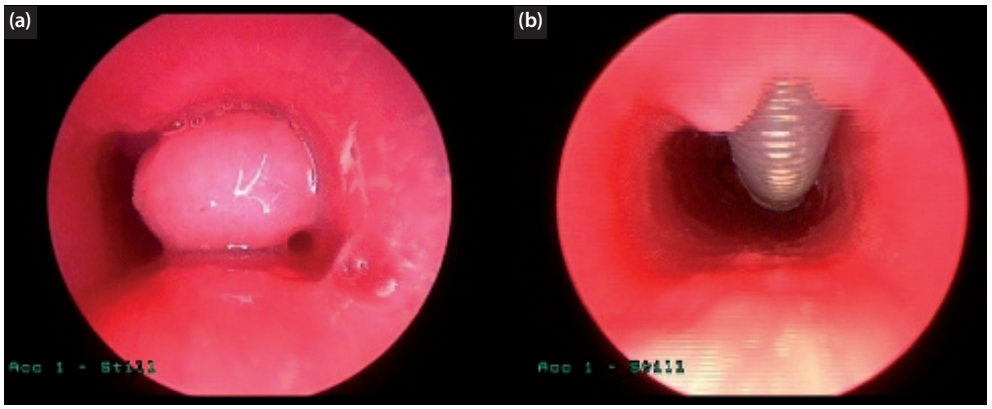

Figure 35.17 Obstructing suprastomal granuloma
(a) before removal, and
(b) 1 month after removal.

trachea itself, leading to irritation, coughing and mucosal injury. In the author's unit, this practice is avoided.

Suprastomal granulations are almost universal. In theory, if they are large, they will reduce the lumen of the supraglottic airway above the tube and increase the risks associated with accidental decannulation. Large suprastomal granulations can affect tube changing and make the use of a speaking valve impossible (**Figure 35.17**). Many authors advocate their removal at endoscopy on a regular basis,[46] however others feel that they are an inevitable consequence of tracheostomy; Rosenfeld and Stool[47] describe granulation in 80% of 265 tracheostomies at bronchoscopy and advise against interval endoscopy to remove granulation tissue. At microlaryngoscopy, immediately prior to planned decannulation, all granulation should be removed to maximize airway patency. After decannulation and stomal closure, granulation generally resolves spontaneously.

REMOVAL OF SUPRASTOMAL GRANULATION

If required, suprastomal granulations may be removed endoscopically using microlaryngeal instruments, a microdebrider using a Skimmer® or Tru-Cut® blade or by KTP or CO_2 laser. The KTP laser has the advantage of beam delivery using a flexible optic fibre in the relatively limited confines of the subglottis.

Large granulation may be removed using a small sphenoid punch or a sinus surgery backbiting forceps inserted into the tracheostome from externally, under endoscopic guidance at mircrolaryngoscopy. Alternatively, if the child can be intubated normally, the ET tube pushes the granulation externally out of the stoma where it can be excised by sharp dissection.[48]

Suprastomal collapse

Suprastomal collapse is distinct from suprastomal granulation although the two conditions often coexist. For reasons that are not completely understood, the anterior tracheal wall immediately superior to the stoma itself softens and prolapses into the lumen of the subglottic trachea (**Figure 35.18**). This can significantly reduce the available airway, which in turn increases the risks associated with accidental decannulation and also leads to decannulation failure.

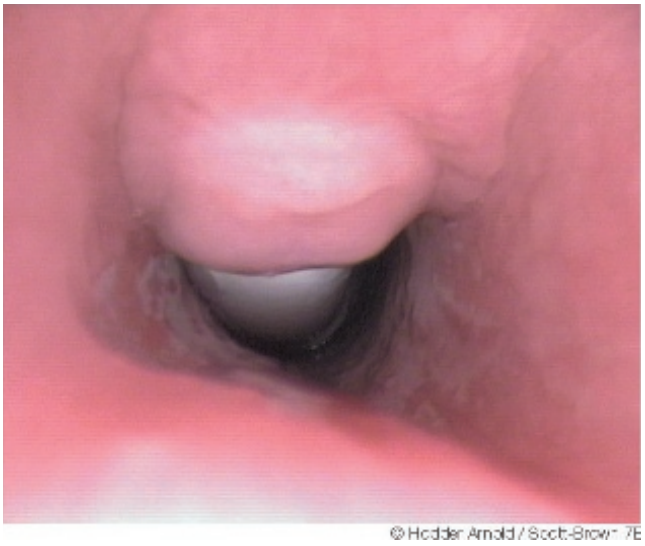

Figure 35.18 Suprastomal collapse.

Minor collapse may be left, as it will tend to improve after decannulation. More significant collapse will require surgical treatment. The simplest of these involves excision and transfixion of the tracheostomy tract followed by endotracheal intubation for 2–3 days to support the trachea as the stoma heals.[49]

The author's preference in mild to moderate suprastomal collapse is to explore the neck, identify the area of suprastomal collapse and pass a suture through the cartilage and around the strap muscles to elevate the collapsed section. This is carried out with excision and transfixion of the tracheostome skin. Sharp and Hartley[50] describe ablation of the collapsed segment with KTP laser, and a number of authors have described supporting the collapsed segment with a cartilage graft in more severe collapse.[51] The specific procedure will depend on the degree of collapse and the surgeon's personal preference.

Speech development

A tracheostomy may adversely affect the development of speech in children. Clearly, normal phonation will be impaired for the duration of a tracheostomy as insufficient subglottic pressure is generated, and small infants tend not

to tolerate speaking valves well. A significant proportion of tracheostomized children have coexisting developmental abnormalities which can make it difficult to assess the relative effect of the tracheostomy. If decannulation occurs in the first 12–18 months, before the time at which normal speech patterns begin to develop, the long-term outcome is favourable,[52] whereas longer-term tracheostomy may lead to longer-term impairment of speech function.

Effects on caregivers and family

Caring for a child with a tracheostomy puts a significant strain on carers and families. The demands on the caregiver's time may be exhausting and the extra effort required may prevent carers engaging in employment. As a result, mental health status[53] and social-economic status[54] are adversely affected in caregivers of children with tracheostomy. The degree of community nursing support that families currently receive in the UK is very variable and dependent on local healthcare policy and provision.

TRACHEOSTOMY SAFETY INITIATIVES

The majority of life-threatening tracheostomy-specific complications (tube displacement and blockage) should be avoidable with correct tracheostomy care. Furthermore, if these complications are recognized quickly, they should be rapidly treatable. Children with tracheostomies are unusual and the medical and nursing skills required are not always immediately available. The UK National Tracheostomy Safety Project[55] is a multidisciplinary collaboration devised to improve the management of child and adult patients with tracheostomies. The recommendations of the project include the following:

1. An emergency minimum set of equipment should accompany a tracheostomy patient at all times, including spare tubes, suction catheters and dressings (Figure 35.19).

Figure 35.19 Box containing emergency equipment for a tracheostomy patient.

2. Bedhead documentation should be displayed at all times providing immediately visible information including tube size and length, and existing upper airway abnormalities (Figure 35.20).
3. Emergency treatment algorithms should be provided for attending resuscitation teams (Figure 35.21).

It is hoped that making this information and equipment visible to first responders and resuscitation teams will improve the safety of patients with tracheostomies and

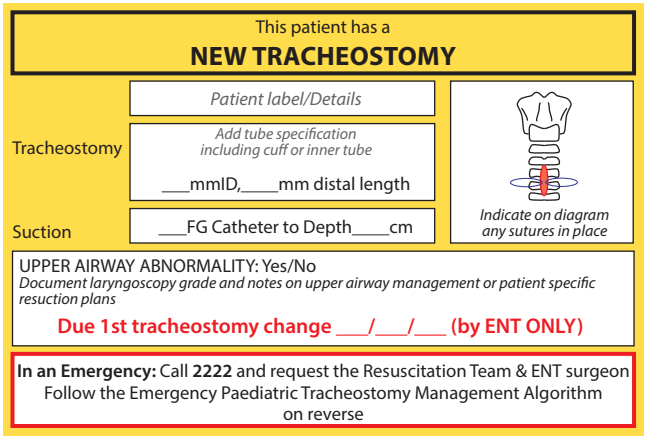

Figure 35.20 Bedhead documentation for a new tracheostomy.

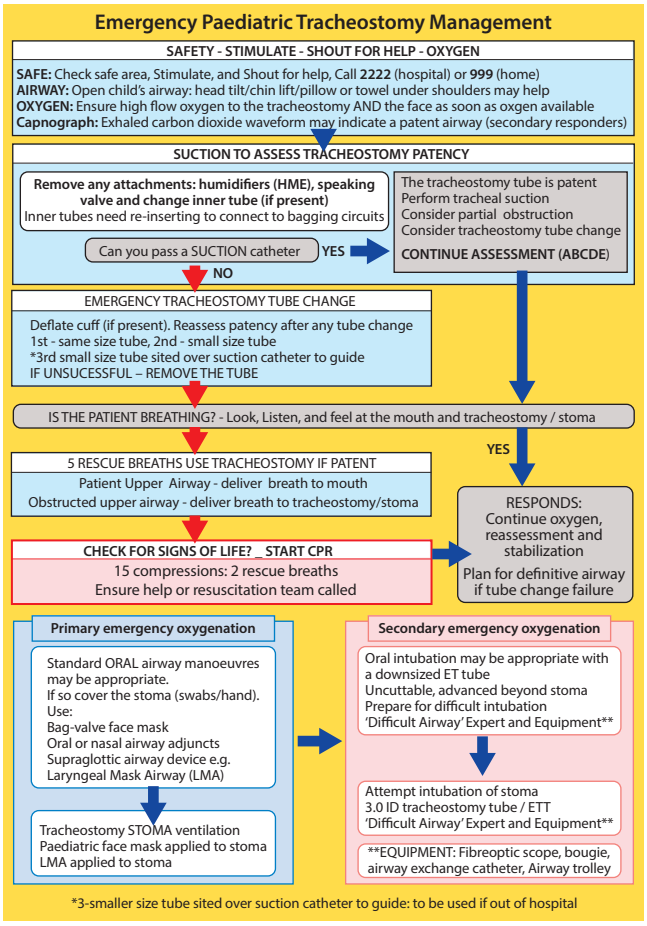

Figure 35.21 Emergency algorithm for resuscitation.

the outcome of complications. The Global Tracheostomy Collaborative formed in 2012 is a multidisciplinary and international organization which shares information and experience to disseminate best practices and improve outcomes.[56]

DISCHARGE AND HOME CARE

Discharge

Getting home with a tracheostomy is a complex and time-consuming process. Not all families will have sufficient support or resources at home to care for children with a tracheostomy. While in hospital, the caregivers must be educated to care for the day-to-day eventualities of tracheostomy, including tube changing, the recognition and initial treatment of complications and basic life-support training.[57] Generally, two responsible adults are required for tube change; home tracheostomy care is difficult but not impossible for single carers. Children who are included in home-ventilation programmes tend to be more carefully supervised and a national protocol for discharge requirements is well established.[58] Non-ventilated tracheostomized children tend to have less structured support. In some areas, specific local organizations exist for the community nursing care of children with complex illnesses; in other areas home care is shared between hospital and primary care district nurses who have little specific training.

With sufficient support and education of teachers and coworkers, tracheostomized children without other significant disabilities can now attend mainstream schooling in the UK, although certain activities must be avoided, particularly swimming, water-based sports and contact sports.

Physical requirements

Boxes 35.1 and 35.2[59] list the resources required for the child with a tracheostomy at home. In the author's experience, the ease with which equipment and accessories can be obtained by caregivers is extremely variable in the

BOX 35.1 Requirements for children at home with tracheostomy

Caregivers	Physical	Support
Generally two responsible adults	Home with adequate space, heating, electricity, telephone, access to transport	District nurse Community paediatrician Health visitor General practitioner Hospital-based support Specific community organizations where available

BOX 35.2 Equipment requirements for children at home with tracheostomy with and without home ventilation

Most of the items need to be duplicated in a portable set. A battery-powered suction machine is essential and, if the child is oxygen-dependent, portable cylinders. Reprinted with permission.[57]

Requirements for children without ventilation	Additional requirements for children on home ventilation
Appropriate-sized tracheostomy tubes and one a size smaller	Two ventilators/CPAP machines, one of which is portable plus batteries and chargers for use outside the home
Neck ties to hold tube in place	Disposable ventilator circuits
Scissors for emergency tube change to cut neck ties	Humidifier for ventilator circuit and water for inhalation to supply humidifier
Lubricant for inserting tube	Dry circuit for ventilation when outside the home
Sterile saline and syringes for saline suction if required	Heat and moisture exchanger for dry circuit
Tracheostomy dressing if required	Nebulizer
Gauze to clean stoma	CO_2 monitor
Appropriate-sized suction catheters	Rechargeable torch for use at night in the event of a power cut
Heat and moisture exchangers / Swedish noses	Uninterrupted power supply – battery which powers ventilator in the event of a power cut
Speaking valves	Suitable trolley in bedroom for equipment
Gloves – non-sterile for procedures and alcohol gel hand rub	Adequate power sockets in house, particularly child's bedroom
Plastic aprons and protective goggles	Trolley for children with a lot of equipment to transport equipment at nursery/school
Stethoscope	Larger than normal buggy when baby/toddler to transport child and equipment
Two suction machines, one of which must be portable. Most children keep a third machine at school as spare	
Saturation monitor and possibly portable saturation monitor for use outside the home	
Ambu bag	
Oxygen: concentrator if used on a daily basis, cylinders if used less frequently, portable cylinders	

community as financial constraints in the delivery of care lead to reluctance to supply regular consumables. Prior to discharge, it is essential to communicate with the child's general practitioner and other primary care workers and establish responsibility for provision of equipment.

DECANNULATION

Decision to decannulate

Decannulation may be considered when the original condition requiring tracheostomy has improved but, to make decannulation successful, the child must be able to maintain an adequate airway without the tracheostomy in place.

The majority of paediatric tracheostomies are short term, as the natural airway tends to improve with overall growth of the child or as a result of corrective surgery such as laryngotracheal reconstruction. The decision to decannulate is a complicated one which needs to be taken by a senior clinician after careful discussion with the parents and other relevant healthcare professionals.

In paediatric otolaryngology practice it is generally considered essential to undertake endoscopic assessment of the airway prior to definitive decannulation.[49] Suprastomal collapse and granulation lead to a considerable reduction in the lumen of the subglottic airway in children. Prescott[60] suggested that this was the most common cause of decannulation failure in children, finding significant granulation in 50 and significant suprastomal collapse in 52 of 300 tracheostomies. In addition, vocal cord mobility should be assessed at endoscopy. Granulation may be removed at the time of endoscopy using punch forceps or laser ablation. More significant suprastomal collapse requires KTP laser ablation or reconstructive surgery using cartilage grafting if the collapse is greater than 50%.[50] If the subglottic airway is deemed satisfactory at endoscopy, the child may then proceed to formal decannulation in the next few days.

One should also consider comorbidity, such as pulmonary, neurological disease, and the need for further surgery; if a child requires operations that may temporarily compromise the airway (e.g. mandibular advancement or cleft palate repair), decannulation should be deferred until these treatments are complete.

Decannulation technique

Removal of a tracheostomy leads to a significant change in the physiology of the upper airway. The dead space is doubled and airway resistance is trebled. With a long-standing tracheostomy, the child may have no memory of mouth and nose breathing and the new sensation may be distressing ('decannulation panic').

STAGED DECANNULATION

To effect these changes more gradually, decannulation protocols have been developed which involve tube 'downsizing' and reversible capping (**Table 35.4**).[61] To assess whether the child can breathe through the normal anatomical airway, the tube is capped off, either with a button, by taping or by inserting the obturator. However, the tracheostomy tube itself occupies a significant fraction of the tracheal lumen and, to try to reduce this effect, the tube size is reduced to a size 3.0 (or size 2.5 in children under 13 months[62]), either in stages or in one step. Leaving the small tube *in situ* allows a certain amount of respiration if required and also prevents the tract from closing down should decannulation fail.

TABLE 35.4 Great Ormond Street protocol for ward decannulation. Reprinted with permission[47]

Day	Procedure
1	Admission, downsize to 3.0 tube
2	Block for 12 hours from 8 a.m. If successful, continue overnight for a further 12 hours
3	Decannulate, occlude stoma with adhesive tape and dressing. Observe on the ward
4	Observe off the ward
5	Discharge

IMMEDIATE DECANNULATION

The tracheostomy tube may occupy as much as half of the lumen of the trachea in an infant. If a child can tolerate this degree of obstruction, the airway after decannulation is likely to be more than sufficient. However, some children will not be able to tolerate this degree of tracheal obstruction. In this instance, it may be considered appropriate to simply remove the whole tube and occlude the stoma with a dressing. However, it is vital that this be carried out in a controlled setting (i.e. intensive care) where facilities for intubation are available should decannulation fail and reinsertion of the tracheostomy not be possible. If the nature of the child's airway obstruction is such that oral intubation is not possible (e.g. some cases of Treacher Collins syndrome), then it is not safe to remove the tube in this manner, and decannulation should be delayed until the child is large enough to tolerate staged decannulation with capping off.

Persistent tracheocutaneous fistula

After decannulation, a fistula may persist between the trachea and skin. This may be small and only lead to problems with discharge of tracheal secretions. A larger fistula may continue to function as an alternative airway.

The incidence of tracheocutaneous fistula (TCF) is between 19% and 42% in various series. Certain factors lead to an increased risk: lower age at initial tracheostomy, duration of tracheostomy and, most importantly, persistent obstruction above the level of the stoma (e.g. inadequate reconstruction of subglottic stenosis). Although it is often felt likely that stomal maturation sutures lead to an increased risk of fistula formation, this has been disproven in larger recent series ($n > 100$).[36, 63]

There is no specific consensus as to how long a persistent TCF should be allowed to close before considering surgery. Most authors would allow 6–12 months before formal closure is attempted.

Closure of TCF

It is essential that the upper airway be reassessed prior to TCF closure to exclude persistent obstruction and tracheal granulation. Some children will still be using the fistula as an accessory airway if the original obstruction is not resolved. The persistence of squamous epithelium lining the tracheostome increases the likelihood of a persistent fistula. Surgically removing the skin lining the tract, or cauterizing the tract using diathermy, coblation or chemicals such as trichloroacetic acid may lead to scarring and satisfactory closure.[64] This has become known as **secondary closure** or closure by secondary intention.

More commonly, the tract of the stoma is dissected down to the level of the trachea and closed with transfixion sutures. This is referred to as **primary closure**. The strap muscles can then be reapposed to each other, which tends to fill in the cosmetic defect left after conventional decannulation. Lastly, the scarred skin surrounding the tracheostome can be excised in a fusiform incision with horizontal skin closure. This leads to a much improved cosmetic result. It is the author's practice to leave a drain in the wound for 24 hours in case of air leak from the closure, which might otherwise lead to surgical emphysema and pneumomediastinum.

Because of the increased risks associated with primary closure, some authors advocate secondary closure as the preferred technique[65] although a recent systematic review found no difference in outcome or complication between the two techniques.[66]

Revision of the tracheostomy scar

Revision of the tracheostomy scar (**Figure 35.22**) usually involves a fusiform horizontal incision to excise the scarred skin of the tracheostome with wide undermining of surrounding skin to assist in primary closure. The strap muscles should be identified and reapposed in the midline to eliminate the defect in the contour of the neck skin. Deep dermal/platysmal sutures are used to support the wound and then the skin edges are closed meticulously. Flexing the neck makes it easier to close a large skin defect.

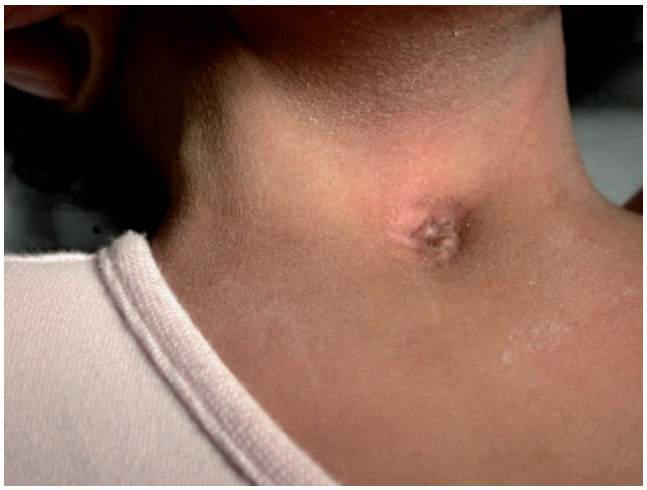

Figure 35.22 Scar following long-term tracheostomy.

BEST CLINICAL PRACTICE

- ✓ Endotracheal intubation rather than tracheostomy is the accepted mode of management for acute obstructing airway infection in children.
- ✓ Premature babies may be safely intubated for several weeks. Tracheostomy should normally be considered in older children after 2–3 weeks of endotracheal intubation.
- ✓ Large skin incisions are generally not required in paediatric tracheostomy. A vertical skin incision is preferred to a horizontal one.
- ✓ Careful dissection using diathermy is advisable in small children to minimize blood loss.
- ✓ Palpate the trachea regularly throughout the dissection to ensure that you have not strayed from the midline.
- ✓ A simple vertical incision to open the trachea is associated with the lowest risk of long-term complications. Avoid removing any cartilaginous tissue in children.
- ✓ Stay sutures in the wall of the trachea on either side of the vertical incision facilitate reintroduction of the tube in the event of accidental decannulation before a mature track has developed.
- ✓ Maturation sutures securing the edge of the skin incision to the tracheal wall lead to a safer and more secure tracheostomy in the initial post-operative period.
- ✓ In children who are difficult to intubate (e.g. retrognathia, laryngeal stenosis), it is safer to do the first tube change in the operating theatre in case surgical intervention is needed.
- ✓ The small diameter of the child's airway makes suction and humidification especially important as secretions can quickly occlude the airway.
- ✓ Tube obstruction or accidental decannulation may be fatal.
- ✓ An 'inner tube' reduces the diameter of the lumen and is therefore not practical in small children.
- ✓ Fenestrated tubes are impractical in smaller children: the fenestration tends to become a focus for granulation and mucosal trauma on suctioning.
- ✓ Cuffed tubes are rarely needed in children.
- ✓ Speaking valves should be used under supervision and not while the child is asleep.
- ✓ The airway should be thoroughly assessed prior to decannulation.

FUTURE RESEARCH

- Paediatric tracheostomy is now largely undertaken in specialist paediatric units. It is difficult for otolaryngologists in training to get experience in the management of children with tracheostomies outside these centres. This trend is likely to increase.
- Research in paediatric airway disorders is focused on conditions which give rise to the need for tracheostomy, such as laryngotracheal stenosis and major congenital anomalies.
- There is a need to improve training resources and support in primary care and community settings to enable families to look after tracheostomized children at home. The work of national and international organizations is helping to improve tracheostomy care.

KEY POINTS

- Tracheostomies in children are performed in the main to relieve upper airway obstruction or to assist with mechanical ventilation.
- A reduction in the incidence and change in the treatment of infections affecting the airway has led to a gradual change in the indications for tracheostomy. Many are now undertaken to allow prolonged ventilation in children with complex medical problems.
- Tracheostomy in children is now an uncommon operation.
- Tracheostomy technique in children has changed in the last decade. Vertical skin incisions and maturations sutures are now considered standard practice.
- Tracheostomy complications are more likely in children than in adults. Preterm infants are at particular risk.
- Specific medical and nursing skills are essential in postoperative care.
- Suprastomal granulations are almost universal in children.
- Getting home with a tracheostomy is a complex and time-consuming process. Not all families will have sufficient support or resources at home to care for a child with a tracheostomy.

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CHAPTER
36

PERINATAL AIRWAY MANAGEMENT

Pensée Wu, May M.C. Yaneza, Haytham Kubba, W. Andrew Clement, and Alan D. Cameron

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the term ex utero intrapartum. Reference lists were reviewed for further articles.

INTRODUCTION

Neonates with potentially fatal airway obstruction can have good outcomes if the abnormality is recognized prenatally and the pregnancy managed by a team with experience in interventional delivery. Prenatal and fetal imaging has improved, which allows for earlier and more detailed analysis of the abnormality and planning of the delivery. Advances in anaesthetic techniques and intervention at delivery improve outcomes and reduce morbidity and mortality in this group of patients.

This chapter summarizes developments in imaging, anaesthesia and delivery techniques for neonates with airway obstruction.

PRENATAL AND FETAL IMAGING

A potentially fatal airway obstruction in the fetus can be recognized at prenatal imaging, often initially identified at the routine 20-week ultrasound as part of the fetal anomaly screening programme.[1] Once a neck anomaly has been established, the remainder of the fetal survey is carefully conducted to detect the presence of any other abnormalities. Further information may be gathered via three-dimensional (3D) and four-dimensional (4D) ultrasound or magnetic resonance imaging (MRI), such as fetal swallowing, lung function and neck mass mapping, including the presence of calcifications.[2] Ultrasound modalities are more widely available than fetal MRI, which is currently offered in tertiary centres only. A detailed plan for delivery can then be made as well as preparation for postnatal management.[3]

A fetal neck mass may also present via a fetal growth scan requested due to suspected macrosomic (excessive birth weight) fetus and polyhydramnios (excess amniotic fluid in the amniotic sac) is discovered instead. A large neck lesion may compress the oesophagus and impede fetal swallowing, therefore leading to increased liquor volume, uterine irritability, and threatened preterm labour.

After diagnosis, the pregnancy is closely monitored with regular sonograms, in order to detect any development or worsening of fetal hydrops (accumulation of fetal fluid) – a sign of cardiac failure. Elective delivery with *ex utero* intrapartum treatment (EXIT) is planned if there are markers of hydrops or when the fetus is deemed mature.[4]

Ultrasound

Ultrasound is the mainstay of prenatal imaging as it is deemed safe for the fetus and the mother with prudent use. 3D scanning provides a reconstructed 3D volume

image of the fetus, whereas 4D ultrasound allows a 3D picture in real time showing fetal movements.

In addition to antenatal diagnosis of fetal neck anomalies, pre-operative ultrasound can be used to determine fetal position, mass location and placental site prior to an EXIT procedure.[2] In the case of a large cystic neck mass which may contribute to a difficult and traumatic delivery of the fetal head, ultrasound-guided percutaneous aspiration of the cystic mass can be performed prior to the EXIT procedure.

MRI

An adjunct tool to ultrasound is MRI (**Figure 36.1**). It has superior soft-tissue delineation and anatomical detail (i.e. assessment of tracheal distortion, compression and position). It has better differentiation between solid and cystic structures.[2] Furthermore, when using MRI, there is less adverse influence of raised body mass index, poor fetal positioning and oligohydramnios compared with ultrasound. As measurements can be made of fetal facial features and skeletal angles, syndromes and intracranial anomalies may be more easily identified on MRI.[5]

Static images of the whole fetus can be examined at MRI, therefore a more global view of the mass can be obtained and its spatial relationship to the airway more easily appreciated, in particular using the multiplanar function.[6] It has been suggested that ultrafast MRI without fetal sedation can provide a more comprehensive view regarding the size and position of the lesion.[7] In 50% of cases the MRI finding was different from the ultrasound diagnosis, however the MRI diagnosis was in agreement with final histology in 73% of cases.[8]

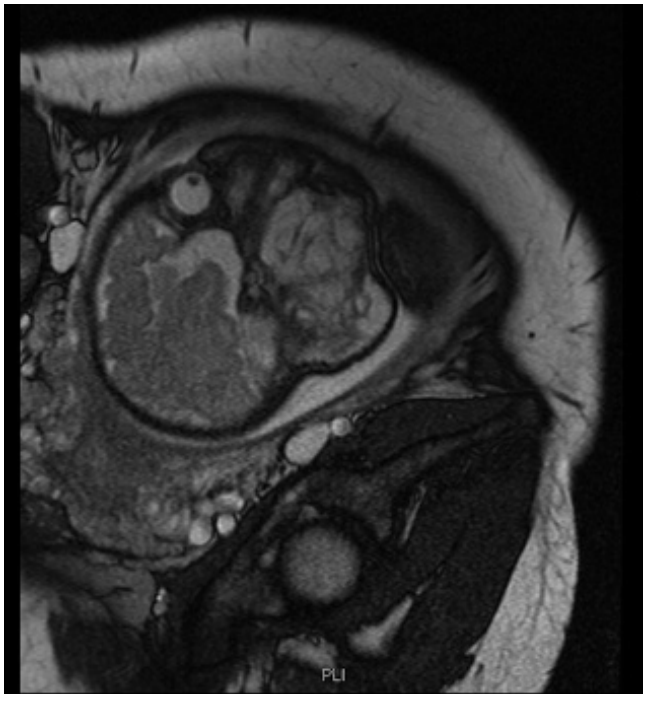

Figure 36.1 Fetal MRI. A large lymphatic malformation (*) is demonstrated.

EPIDEMIOLOGY

The most common fetal neck lesions causing airway obstruction are lymphatic malformations (formerly cystic hygroma) and teratoma. Other neck masses include haemangioma, branchial cleft cyst, cervical thymic cysts, fetal goitre, sarcoma, neuroblastoma, and kaposiform haemangioendotheliomas (**Box 36.1**).[9, 10]

BOX 36.1 Causes of congenital airway obstruction

External compression	Internal blockage	Developmental
Lymphatic malformation	Laryngeal web	Laryngeal atresia
Cervical teratoma	Laryngeal stenosis	Tracheal atresia
Brachial cleft cyst	Laryngeal cyst	Micrognathia
Cervical thymic cyst	Tracheal stenosis	
Thyroid goitre	Epignathus	
Ectopic thyroid	Choristoma	
Sarcoma	Glioma	
Neuroblastoma	Encephalocoele	
Dermoid cyst	Choristoma	
Granular cell tumour	Haemangiomata	
Vascular ring		

Cervical lymphatic malformations are typically located in the anterior and posterior triangles of the neck and appear sonographically as fluid-filled cysts with fine septae. Conversely, cervical teratomas are unilateral and asymmetrically located. They are characterized as complex masses with mainly solid components and well-defined edges, often with vascular spaces and calcifications.[11] Preterm labour from polyhydramnios due to local mass effect causing obstruction in the tracheo-oesophageal complex which leads to impaired fetal swallowing is more common in teratomas (up to 40%) than lymphatic malformations.[12] **[Level 1 evidence]**

Extrinsic compression of the fetal airway

LYMPHATIC MALFORMATION

The incidence of lymphatic malformation is 1 in 6000 to 1 in 16 000 live births. This congenital malformation of the lymphatic system is thought to be due to failure of the jugular lymph sacs to join the lymphatic system. As well as an association with chromosomal abnormalities in 60% of cases, in particular Turner syndrome and Down syndrome, they are also linked to underlying genetic conditions, such as Noonan syndrome and multiple pterygium syndrome.[2] Antenatal care therefore involves detection of other fetal structural anomalies, especially cardiac abnormalities, and the offer of prenatal karyotyping. There is a perinatal mortality rate of over 80% if fetal hydrops is detected. Postnatal intubation may be particularly difficult due to obstruction of the pharynx and larynx from very large lesions. Prognostic scores

such as de Serres staging or Cologne Disease Score have been used to predict long-term outcome.[13, 14]

CERVICAL TERATOMA

Teratomas contain tissue from all three germinal layers (ectoderm, mesoderm and endoderm). Cervical teratomas represent 3–5% of all teratomas and have an incidence of 1 in 35 000 to 1 in 20 000 live births.[15] Cervical teratomas cause airway obstruction via both compressive and distortive factors. A presumed prenatal diagnosis of teratoma is an indication for an interventional birth procedure. It is associated with lung hypoplasia and a higher mortality rate.[16]

Maternal serum alpha fetoprotein (AFP) levels may be very high as these tumours contain neural tissues as the predominant histological component. Only <5% undergo malignant transformation, which occurs in those who are diagnosed in later life. By undergoing EXIT procedure, the neonatal mortality rate is improved to 36% from 80% in those with untreated cervical teratomas.[16]

Intrinsic defects in the fetal airway

CONGENITAL HIGH AIRWAY OBSTRUCTION SYNDROME

There are several causes of congenital high airway obstruction syndrome (CHAOS); these include laryngeal web, laryngeal stenosis, laryngeal atresia, laryngeal cyst, tracheal stenosis and tracheal atresia. Antenatal imaging shows large echogenic lungs, dilated tracheobronchial trees and flattened or inverted hemidiaphragms. Fetal hydrops can develop from reduction in venous return due to compression of the lungs on mediastinal structures.[17] Extrinsic airway obstruction by vascular rings, such as right aortic arch with aberrant left subclavian artery or double aortic arch, can mimic CHAOS.

There is a low risk of future pregnancies being affected as most CHAOS occurs sporadically. However, laryngeal atresia is associated with other anomalies such as anophthalmia, hydrocephalus, syndactyly, absent radius, bronchotracheal fistula, oesophageal atresia, cardiac anomalies, Fraser syndrome, genitourinary anomalies, imperforate anus, uterine and vertebral anomalies.[4] Compared with laryngeal atresia, low thoracic tracheal obstruction or tracheal atresia has a much poorer prognosis for EXIT procedure.[18] It is difficult to diagnose laryngeal atresia on prenatal ultrasound in the presence of a tracheoesophageal fistula as the lung fluid can escape into the stomach or amniotic sac, rather than being trapped in the lungs.

Micrognathia

At the 20-week fetal anomaly ultrasound scan, fetal features of small chin, prominent upper lip or polyhydramnios may raise the suspicion of micrognathia. Fetal MRI can be used to further assess the severity of micrognathia by evaluating the relationship of the tongue to the airway (glossoptosis). Several congenital syndromes are associated with micrognathia, including Cornelia de Lange, Treacher Collins, Marshall syndrome, Stickler syndrome, the Robin sequence and 22q11 deletion.[3]

Oronasal masses

Fetal nasal masses amenable to prenatal ultrasound diagnosis include congenital midline nasal masses, such as dermoids, gliomas and encephalocoeles (extranasal or intranasal), and abnormal nasal anatomy seen in 22q11 deletion syndromes. In the case of fetal oral masses, congenital epulis (granular cell tumours), epignathi (teratoma of the oropharynx) and dermoid cysts of the floor of mouth or tongue base may be detected.[12, 19, 20]

INTERVENTIONAL DELIVERY

The concept of accessing the fetal airway in an elective, controlled and secure manner under placental support was first developed in 1990. The fetus underwent laryngoscopy and intubation prior to clamping the umbilical cord.[21] Previously, an ENT team would be on 'standby' to establish the airway in the neonate under time pressure.

There are currently a number of options for interventional delivery:

- operation on placental support (OOPS)
- *ex utero* intrapartum treatment (EXIT) procedure
- delivery then attempted airway intubation or tracheostomy.

Operation on placental support

Operation on placental support (OOPS) delivery is performed under maternal regional anaesthesia with the fetus completely delivered through a lower segment Caesarean section. The umbilical cord is unclamped and kept intact with the fetus on a Mayo table at the level of the placenta. In order to prolong the foetoplacental circulation, synthetic oxytocin administration to deliver the placenta is delayed. A window of 5–20 minutes for airway intervention has been documented before the umbilical cord goes into spasm.[22]

Ex utero intrapartum treatment (EXIT) procedure

The EXIT procedure has become the mainstay in the management of prenatally diagnosed fetal airway obstruction. Its initial indication was to manage fetuses with congenital diaphragmatic hernias who underwent *in utero* foetoscopic tracheal occlusion to increase lung growth.[23] An EXIT procedure to deliver a fetus with an airway-obstructing neck mass reduces the mortality rate from 10–57% to 8%.[24]

An EXIT procedure permits a longer interventional procedure as the neonate is only partially delivered. Via a lower segment Caesarean section the head and perhaps a shoulder are delivered to maintain uterine volume

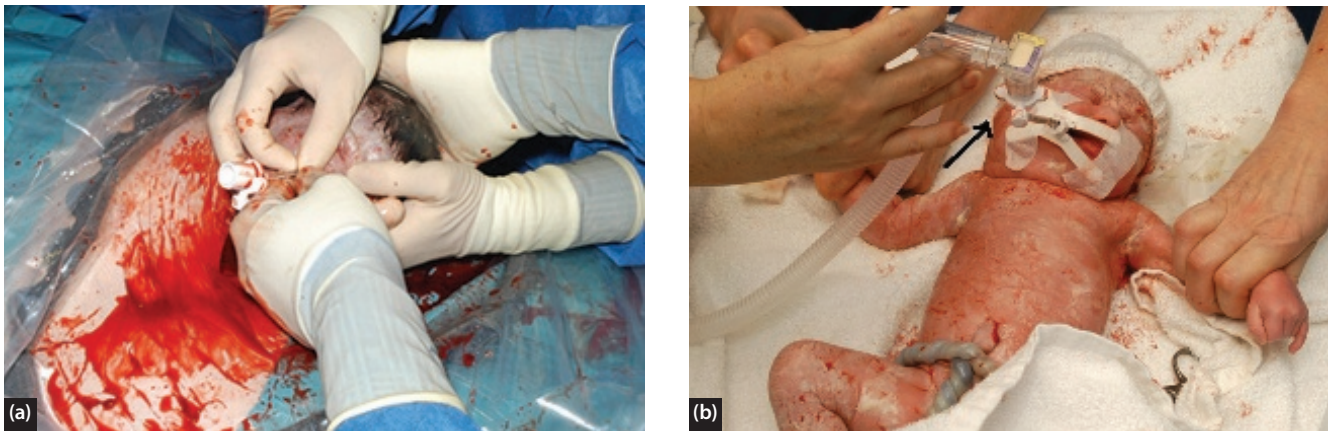

Figure 36.2 EXIT procedure. (a) Head of neonate delivered via lower segment Caesarean section and child intubated. The underlying abnormality was a large lymphatic malformation (fetal MRI of same child in Figure 36.1). **(b)** Intubated neonate with large lymphatic malformation (arrow) assessed by paediatricians.

which in turn avoids compression of the umbilical cord, and allows preservation of the uteroplacental circulation (**Figure 36.2**). A 2.5-hour timeframe is afforded on this circulation to perform airway interventions.[4] These include establishing an airway, direct laryngoscopy and bronchoscopy, performing a tracheostomy, surfactant administration, and resection of an obstructing mass. There is a greater chance of maternal haemorrhage due to uterine atony in an EXIT procedure compared with OOPS (**Table 36.1**).[25] Moreover, it may be difficult to perform fetal intubation and bronchoscopy with only the head delivered. Nevertheless, this procedure can be easily converted to an OOPS. Classically, an EXIT procedure is performed under maternal general anaesthesia[26] but it can also be performed under a spinal anaesthetic.[27]

Delivery then attempted airway intubation or tracheostomy

In certain circumstances, the risk of maternal haemorrhage is severe and a rapid, safe delivery of the baby and the placenta takes precedence. For example, in a mother with uterine fibroids and a fetus with other severe fetal anomalies,[10] a Caesarean section could be performed with the paediatric airway team in attendance to secure the neonatal airway by means of either rigid bronchoscopy and intubation or tracheostomy.

TABLE 36.1 Differences between EXIT and OOPS

	EXIT	OOPS
Anaesthetic	Traditionally uses inhalational general anaesthetic, hence greater risk of maternal haemorrhage Regional anaesthetic can be used	Regional anaesthetic or short general anaesthetic
After uterotomy	Partial delivery of fetal head and shoulders	Whole baby delivered onto Mayo table Umbilical cord left intact Placenta not delivered
Time for interventional procedures	20–50 minutes	5–20 minutes

PRE-OPERATIVE PLANNING

A multidisciplinary team (MDT) is involved in planning the procedure. The pre-EXIT rehearsal would consider the layout of the operating theatre and the location of the personnel and equipment. There should be a clear documentation of the prenatal counselling and consent, including a frank discussion of the options available and a realistic outlook for neonatal survival.[25]

Multidisciplinary team

Prenatal genetic counselling is invaluable in evaluating for underlying genetic syndromes based on the information available during pregnancy, such as fetal karyotype or other structural anomalies detected on antenatal imaging. The parents can then have an informed discussion on whether an interventional birth procedure is suitable for their baby in light of the probable prognosis. Neonates with an isolated airway obstruction (i.e. no other fetal abnormality) have a good prognosis and limited morbidity if delivered by a team with experience in interventional airway deliveries.[27] The prognosis is less good if multiple fetal abnormalities or lung hypoplasia is present.[27] Isolated cervical teratomas also have worse outcomes than compressible neck masses such as lymphatic malformations.

An MDT approach is essential for setting up an interventional airway delivery service (**Figure 36.3**). The team should include specialists from fetal medicine, otolaryngology, neonatology, paediatrics, paediatric anaesthesia and obstetric anaesthesia. Prior to meeting the parents the MDT meets to develop the birth plan. The following

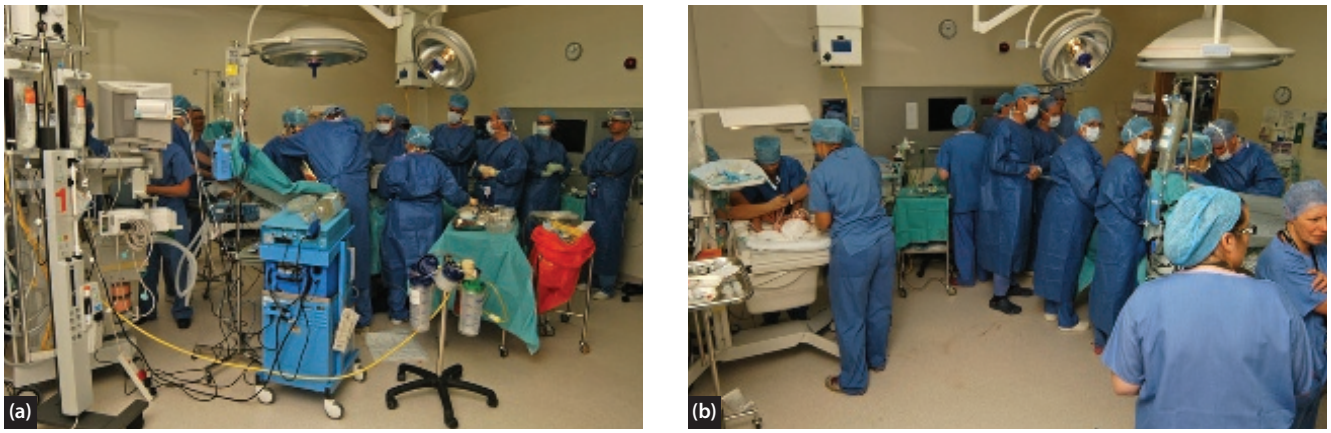

Figure 36.3 Multidisciplinary team involvement in EXIT procedure. **(a)** Surgical team; **(b)** neonatal team.

factors need to be considered when contemplating an interventional delivery:

- **Maternal factors:** comorbidities, risk of maternal haemorrhage (i.e. coexisting uterine pathology such as uterine fibroids)
- **Fetal factors:** suspected pathology (i.e. isolated neck mass causing airway obstruction, other fetal abnormalities, lung hypoplasia), gestational age
- **Anaesthetic factors:** this will be determined by risk to maternal health and anticipated length of time required to intervene to secure the neonatal airway
- **Access factors:** presentation of the fetus (breech, head first), size of mass, accessibility for OOPS, EXIT or other intervention
- **Timing of intervention:** an elective lower segment Caesarean section is planned at a gestation guided by the volume of amniotic fluid and the gestational age of the fetus
- **Primary intubator:** the person whose prime responsibility is to intubate the neonate
- **Time allowed for intubation:** this will be determined by the interventional procedure performed, i.e. OOPS or EXIT.

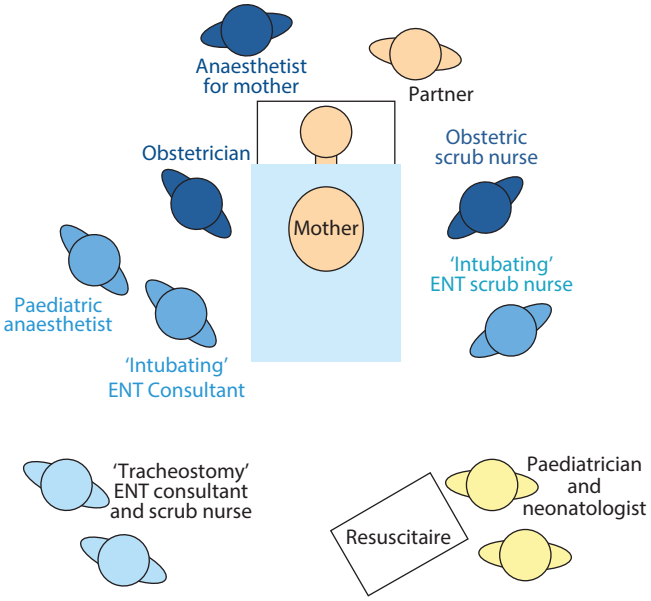

Figure 36.4 Example of theatre layout for an interventional delivery procedure (from Yaneza et al).[27]

A unit that undertakes interventional airway deliveries should be supported by an established framework, i.e. paediatric and neonatal intensive care, extracorporeal membrane oxygenation service, etc. A contingency plan is also developed at the MDT meeting should the mother present in spontaneous labour before her planned date of delivery with the availability and awareness of the on-call MDT able to conduct an emergency Caesarean section and EXIT or OOPS procedure. Extracorporeal life support to provide respiratory support may be considered in neonates with difficult access to airway but a good prognosis, such as a large vascular mass requiring resection followed by a tracheostomy.[25] Due to the number of team members involved, a large operating theatre is preferable (Figure 36.4).

Airway intervention

After the fetal head is delivered, the fetal medicine surgeon ensures maternal wellbeing and prevents placental separation, while the airway surgeon works simultaneously (Figure 36.5). The presence of two ENT consultants is recommended: an 'intubating' ENT consultant with rigid bronchoscopy skills (Figures 36.5b and c), and a 'tracheostomy' ENT consultant. In the event of a failed intubation, the other 'tracheostomy' ENT consultant and scrub nurse can perform a tracheostomy with fresh minds that are not adversely affected by the previous incident. Furthermore, having two ENT consultants allows for a consensus to be reached if a stressful or difficult situation is encountered. The primary intubator could also be a paediatric anaesthetist who specializes in ENT and thus is experienced at managing difficult airways.

Timing

In choosing the gestation for Caesarean section, the balance between early operation to avoid spontaneous labour and delayed delivery to improve fetal maturity

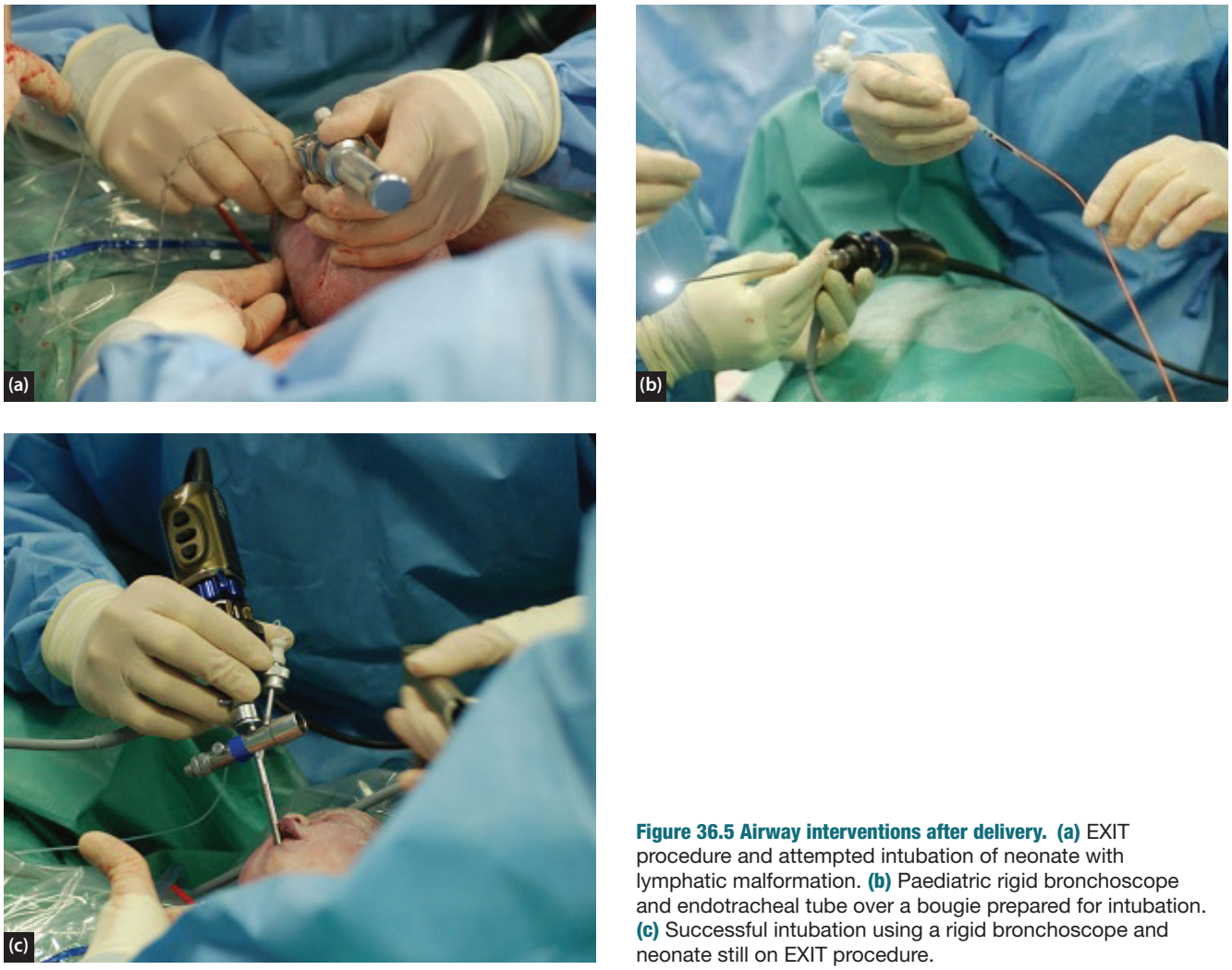

Figure 36.5 Airway interventions after delivery. **(a)** EXIT procedure and attempted intubation of neonate with lymphatic malformation. **(b)** Paediatric rigid bronchoscope and endotracheal tube over a bougie prepared for intubation. **(c)** Successful intubation using a rigid bronchoscope and neonate still on EXIT procedure.

is considered. In many cases, a Caesarean delivery is planned around 36–38 weeks' gestation, after corticosteroid administration to promote fetal lung maturation. However, the delivery may be expedited in the presence of polyhydramnios as the risk of preterm labour increases with the volume of amniotic fluid.[26]

Anaesthesia

A Caesarean section is usually performed using regional anaesthesia, i.e. spinal or epidural anaesthesia. An OOPS procedure can be performed on regional anaesthesia while an EXIT procedure is classically conducted under general anaesthesia to achieve uterine relaxation with a deep plane of anaesthesia. The mother is kept in a left lateral tilt position to avoid aortocaval compression from the gravid uterus, which reduces maternal cardiac output. EXIT procedures have been conducted under regional anaesthesia by the combined spinal epidural technique, with adequate uterine relaxation.[27–29] Agents such as glyceryltrinitrate can be used to induce further uterine relaxation if required.

Two anaesthetists should be present at an interventional airway delivery: an obstetric anaethetist for the mother, and a paediatric anaethetist for the neonate. Despite the intention to have two healthy patients by the end of the procedure, if any conflicts of interest arise intraoperatively, the mother's safety should override any fetal concerns.

During EXIT procedure, uterine relaxation is paramount as the uteroplacental circulation supplies oxygen and anaesthesia to the fetus. The preservation of maternal-fetal gaseous exchange at the placenta prevents fetal hypoxia and neonatal hypoxic-ischaemic encephalopathy. All volatile anaesthetics cross the placenta and fetal anaesthesia is related to uterine blood flow, drug solubility and distribution in the fetal blood circulation.[30] Narcotics or muscle relaxants can be administered to the fetus via intramuscular or intravenous routes to achieve additional anaesthesia.

Obstetric issues

At an elective Caesarean section, the average maternal blood loss is 500 mL,[31] whereas for an EXIT procedure it is 1500–1800 mL.[24] Haemorrhage can occur from the uterine incision, the placenta (premature placental separation) or from an atonic uterus once the baby is delivered.[7]

Bleeding from the uterotomy can be reduced with surgical haemostatic techniques including the placement of a uterine stapling device. Placental damage from the uterine incision should be prevented by mapping the placental edges on antenatal ultrasound and planning the uterine incision. However, a large neck mass may obscure the placenta at ultrasound. One should also exercise caution in the setting of polyhydramnios as the placenta can be compressed and give a false impression of its location on the antenatal scan. Furthermore, upon uterine incision, the sudden release of high volumes of amniotic fluid can lead to intrauterine pressure changes and early placental separation (i.e. placental abruption). Therefore, amnioreduction should be considered prior to EXIT procedure in such cases.

During EXIT procedure, delayed placenta separation is accomplished by uterine relaxation, maintenance of uterine volume and uterine and placental perfusion. Uterine relaxation can also cause uterine atony and further obstetric haemorrhage after full delivery of the neonate. In order to maintain maternal haemodynamic stability, the dose of inhalational anaesthetic agents is decreased and oxytocin administered just before umbilical cord ligation to deliver the baby. This is accomplished through good communication and close coordination between the fetal medicine surgeon and the obstetric anaesthetist.[32]

Immediate post-operative complications are more frequent in comparison to standard Caesarean sections. In a study of 34 EXIT procedures, there were longer operating times, higher estimated blood losses and more wound infections compared with 32 matched controlled Caesarean deliveries.[33] However, there was no statistical difference in the length of post-operative hospital stay and haematocrit levels.

In subsequent pregnancies, there is a higher chance of uterine scar dehiscence or uterine rupture because of possible unusual uterotomy sites. Instead of a lower uterine segment incision, other areas may have been used in order to avoid the placenta. Lazar et al. showed that mothers who delayed pregnancy for 2 years following an EXIT procedure were able to have an uncomplicated delivery of at least one more child.[24]

Fetal considerations

Fetal circulation is preserved via the maintenance of placental perfusion and prevention of respiration. In some centres, the fetus is given direct injections of narcotics and muscle relaxants to avoid respiration and establishment of neonatal circulation as well as to reduce fetal movements to aid airway management.[7, 21] Others have argued that the same effects are obtained by fetal airway obstruction and fetal anaesthesia via the transfer of maternal anaesthetic through uteroplacental circulation.

OUTCOMES

Experience in our centre has demonstrated that an interventional delivery decreases mortality from 50% (n = 2) to 14.2% (n = 1). All deaths were associated with other fetal abnormalities, i.e. where airway obstruction was not an isolated feature.[27] Of seven children delivered by an interventional team, two are tracheostomy-dependent. A case series of 12 children with giant neck masses after EXIT procedures demonstrated more cranial nerve palsies, feeding difficulties and speech delays in this group of children. However, the complications were thought to be linked to the underlying pathology rather than the mode of delivery. For example, the neck mass itself could have damaged and distorted local anatomy or the surgical resection of the mass could have led to iatrogenic injury.[24] In our case series none of the children have cranial nerve palsies or feeding difficulties.

A successful interventional airway delivery service is dependent on careful planning and infrastructures, local guidelines and protocols, as well as a continuous audit cycle of outcomes.

FETAL THERAPY

Intrauterine treatment may be considered in cases where there is a high risk of *in utero* demise or severe disability and a low risk to the mother.[34] Fetal hydrops may occur as a result of cardiac failure from a highly vascular neck mass, such as teratoma or kaposiform haemangioendothelioma, where intrauterine surgical resection has been offered.[35]

Complete obstruction of the larynx in laryngeal atresia causes lung fluid congestion, *in utero* pulmonary hyperplasia, pulmonary hypertension and fetal cardiac failure. Fetal therapy for laryngeal atresia and CHAOS has been reported using percutaneous fetoscopic tracheal decompression.[36, 37] Intrauterine sclerotherapy of large fetal macrocystic lymphatic malformations with a single injection of OK-432 (penicillin-killed *Streptococcus pyogenes*) has also been described.[38] Other sclerosant agents could be used as OK-432 is not available in the UK.

In certain circumstances, *in utero* treatment is contraindicated; these include lethal or severely disabling structural and/or genetic fetal anomalies or serious maternal comorbidities.

CONCLUSION

Congenital airway obstruction is potentially life-threatening and associated with high mortality rates.[17, 21, 39, 40] If there is a delay in establishing airway and ventilation in the neonate, the risks of hypoxia, acidosis and anoxic brain injury, which are associated with neonatal morbidity and mortality, increase. In contrast, for those with effective airway access at delivery, the long-term outcome is excellent in most cases.[27]

Ultimately, with advances in fetal interventions, such as *in utero* surgery, fetal transcutaneous transuterine bronchoscopy, intrauterine sclerotherapy, fetal airway assessment and fetoscopic tracheal decompression, we can expect improvements in prognosis for neonates with congenital airway obstruction.

BEST CLINICAL PRACTICE

- ✓ A unit that undertakes interventional airway deliveries should be supported by an established framework, i.e. PICU, NICU, ECMO.
- ✓ A multidisciplinary team including specialists from fetal medicine, otolaryngology, neonatology, paediatric anaesthesia and obstetric anaesthesia is essential.
- ✓ Decide on the timing of intervention, nominate a team member to undertake endotracheal intubation and consider the time allowed for intubation.

FUTURE RESEARCH

There are exciting future developments in novel therapeutic concepts in airway reconstruction. For example, in the field of fetal tissue engineering, an airway construct can be designed according to gestation using autologous fetal cells.[41–43] The proof of principle has been provided in a large animal model of perinatal airway repair.[44]

KEY POINTS

- Effective airway access at interventional delivery improves long-term prognosis.
- Better antenatal detection has greatly improved perinatal management of airway problems in the newborn.
- Careful planning of the delivery makes for better outcomes.

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CHAPTER 37

CERVICOFACIAL INFECTIONS

Nico Jonas and Ben Hartley

SEARCH STRATEGY

Data in this chapter may be updated by Medline and Scopus searches using the keywords: infection and child, neck, cervical node and cervical adenopathy, and focusing on the diagnosis and treatment of specific conditions. The Cochrane Library was also consulted.

TERMINOLOGY

Abscess formation refers to an accumulation of pus in a confined space as a result of an inflammatory response to a bacterial or parasitic infection or foreign material. The deep cervical fascia is arranged so as to create compartments or spaces between the various structures in the neck. A collection of pus in one of these spaces is often termed a **deep neck space infection** (**DNSI**).

Cellulitis refers to inflammation of subcutaneous or connective tissue and is usually characterized by fever and pain as well as redness, swelling and warmness of the affected area.

Fasciitis refers to inflammation of the connective tissue (fascia) that surrounds and binds muscles, blood vessels and nerves together.

Necrotizing fasciitis is an aggressive tissue infection that spreads rapidly across fascial planes causing necrosis of tissue along the way.

INTRODUCTION

This chapter will deal with cervicofacial infections in children. Because these infections usually present as a neck mass, we will also aim to discuss the general approach to a child with a neck lump.

Cervicofacial infections in children usually present as a neck swelling. The majority of infections are related to lymph nodes. These are rarely indicative of serious pathology. Lymphadenopathy secondary to the common acute upper respiratory infections that are a feature of normal childhood – notably pharyngitis and tonsillitis – is the most common cervicofacial infection in childhood. Lymphadenopathy is usually self-limiting but may progress to cellulitis, suppuration and abscess formation. Infections may also involve the parotid, the submandibular or the thyroid glands.

Congenital lesions do not always declare themselves at birth; they may present in older children. The onset of the swelling may be precipitated by an acute inflammatory episode.

Chronic infections are less common but need to be considered if the swelling persists.

In a very a small number of children, a neck swelling will be due to a malignancy. These are most often lymphoproliferative or connective tissue tumours. Squamous carcinoma is extremely rare in children. A child with a neck mass requires an entirely different approach to that required in an adult.[1] Open biopsy is rarely needed. Nevertheless, it is important to maintain an index of suspicion for malignancy in all persistent neck swellings in children.

BOX 37.1 Inflammatory adenopathy in children: Infective

Viral	Bacterial	Fungal	Parasitic
Upper respiratory: rhinovirus, adenovirus, enterovirus Common childhood illnesses: measles, mumps, rubella, varicella Infectious mononucleosis Cytomegalovirus (CMV) HIV	Acute lymphadenitis: *Streptococcus*, *Staphylococcus*, less commonly Gram-negative organisms Suppurative lymphadenitis with deep or superficial neck abscess; usually pyogenic organisms (*Streptococcus* and *Staphylococcus*) Mycobacteria: tuberculosis or non-tuberculous mycobacteria (NTM) – sometimes termed 'atypical mycobacteria' Other granulomatous bacterial infections: cat scratch disease, actinomycosis, brucellosis, tularaemia, bubonic plague, syphilis	Histoplasmosis Uncommon fungal infections (immunocompromised host) *Candida* and *Aspergillus*	Toxoplasmosis Filariasis

CLASSIFICATION OF CERVICOFACIAL INFECTIONS

- **Infections related to lymph nodes:**
  - Acute infective lymphadenopathy
  - 'Complicated/progressive' infective adenopathy causing cellulitis, suppuration and abscess formation
  - Chronic infective lymphadenopathy
- **Infections related to congenital lesions or malformations:**
  - Thyroglossal duct cysts
  - Dermoid cysts
  - Branchial anomalies
  - Lymphatic malformations / cystic hygromas
- **Infections related to acquired anatomical malformations:**
  - Plunging ranula
- **Infections of glands:**
  - Salivary gland infections
  - Thyroid gland infections
- **Infections of dental origin:**
  - Dental abscess
  - Ludwig's angina
- **Infected vascular structures:**
  - Infective thrombophlebitis
  - Lemierre's syndrome

AETIOLOGY OF INFLAMMATORY NECK NODES IN CHILDREN

Lymphadenopathy is one of the most common clinical problems encountered in paediatrics.[2] The precise incidence of lymphadenopathy is not known, but estimates of palpable adenopathy in childhood vary from 38% to 45%.[1] There are approximately 300 lymph nodes in the neck and they have considerable capacity to undergo growth and change.[3] With their high concentration of lymphocytes and antigen-presenting cells, lymph nodes are ideal for receiving antigens that gain access through the skin or gastrointestinal tract. They are barely perceptible in neonates, but a progressive increase in antigen exposure will lead to an increase in lymph node size until later childhood. Lymph node atrophy will start during adolescence and continues through later life.

BOX 37.2 Inflammatory adenopathy in children: Non-infective

Kawasaki syndrome
Sarcoidosis
Sinus histiocytosis with massive lymphadenopathy
Kikuchi-Fujimoto disease
PFAPA syndrome (periodic fever, apthous stomatitis, pharyngitis, cervical adenitis)
Langerhan's cell histiocytosis

Inflammatory lymphadenopathy can be classified into infective conditions (Box 37.1) and non-infective conditions (Box 37.2). Non-inflammatory disorders will need to be considered in the differential diagnosis of a neck mass, especially if there are unusual features.

CLINICAL ASSESSMENT OF A PATIENT WITH A NECK MASS

History

- **Age of child:** Most acute lymphadenitis presents in children older than 6 months. Swellings occurring at or shortly after birth are more likely to be pathological and may be neoplastic.
- **Duration of swelling:** A short history (a few days) suggests acute inflammation. After 6 weeks a swelling is regarded as chronic and further investigation should be considered – even earlier if there are suspicious clinical features.
- **Size:** Very large swellings or swellings that progressively enlarge despite antimicrobial treatment should be investigated.
- **Associated symptoms:** A preceding upper respiratory infection is often a feature of inflammatory lymphadenitis. Fever, rhinorrhoea, sore throat and malaise are common. With chronic swellings, enquire about weight loss, night sweats, chronic cough and swellings elsewhere in the body.
- **Contacts:** Enquire about tuberculosis, other infections and exposure to cats, farm animals and ticks. Recent travel should also be noted.

- **Medical history:** Identify any known illnesses. Note recent immunizations against polio, typhoid or DTP (diptheria, tetanus and pertussis). Document regular medication including carbamazepine, phenytoin or isoniazid.
- **Family and social history:** Identify any familial disease or congenital anomalies and any relevant social factors.

Site of the swelling

The anatomical site of the swelling within the neck provides important information about the possible aetiology.

LATERAL NECK SWELLINGS

Lymph nodes are distributed throughout the neck but the most common site is along the superficial and deep cervical chains. These lie deep to the sternomastoid muscle in the upper neck and along its anterior border in the lower neck. Enlarged lymph nodes are the most common cause of lateral neck swellings. The principal differential includes anomalies such as congenital cysts, which may also become acutely inflamed. Vasoformative lesions, haemangiomas and vascular malformations including lymphatic abnormalities may present as a lateral neck swelling. Benign and malignant neoplasms arising from the neural or connective tissue elements and rarely secondary lymph node metastases may present as a lateral neck mass.

CENTRAL NECK SWELLINGS

The principal causes of a neck swelling in the central area of the neck around the midline are thyroglossal duct cysts, lymph nodes and dermoid cysts. Thyroglossal duct or dermoid cysts may become acutely inflamed. Children can also develop inflammatory and neoplastic thyroid disease. Lymphatic vascular malformations can occasionally involve this region.

PAROTID SWELLINGS

Acute viral parotitis (mumps) is common and is a self-limiting infection. Although vaccination for measles, mumps and rubella (MMR) is now reducing the frequency of mumps and to some degree the clinical awareness of this condition, outbreaks still occur sporadically in the developed world. It remains a significant problem in the developing world.

Bacterial parotitis can occur in children and may be recurrent. It is usually characterized by acute painful swelling followed by resolution on antibiotics. Massaging the parotid will produce infected saliva or pus at the parotid duct opening opposite the second upper molar.

Occasionally, chronic inflammatory swelling persists and must be distinguished from neoplasia. Rhabdomyosarcoma or other connective tissue tumours can present in this way. Vascular malformations and haemangiomas can also present as swellings in the parotid region. Magnetic resonance scanning can be very helpful with this differential diagnosis.

The parotid gland in adults is mainly made up of parenchymal glandular tissue. In children, intraparotid lymphoid tissue is more prominent, hence parotid swelling is often due to lymphadenopathy (e.g. non-tuberculos mycobacteria, NTM), especially in the toddler age group.

SUBMANDIBULAR SWELLINGS

Enlarged lymph nodes, floor-of-mouth infections, acute sialadenitis, plunging ranula and occasionally lymphatic or vascular malformations can all cause swelling in the submandibular region. A more detailed discussion of salivary swellings can be found in Chapter 39, Salivary glands.

POSTERIOR TRIANGLE SWELLINGS

Most commonly posterior triangle swellings are lymph nodes but branchial anomalies, vascular malformations and neoplasia enter into the differential diagnosis.

Nature of the swelling

Classical signs of acute inflammation such as redness, tenderness and heat may be present. Chronic swellings usually do not show these signs. If abscess formation has occurred, the clinical sign of fluctuance may be present and the mass may feel cystic. A classical tuberculous abscess lacks the clinical features of acute inflammation and is described as a 'cold abscess'.

HEAD AND NECK EXAMINATION

A careful examination for a source of primary infection should be made. This should include examination of the pharynx, nose and ears as well as looking for any cutaneous lesion, including the scalp.

General examination

Fever, tachycardia or a rash should be noted. A general examination should include a search for any associated lymphadenopathy and hepatosplenomegaly. The otolaryngologist may wish to enlist the help of a paediatrician.

Investigation

In many cases no investigation is required. Symptomatic treatment of presumed viral infection or antibiotic treatment of bacterial infection with careful clinical follow-up will result in resolution.

Laboratory and skin tests

If the child is systemically unwell, a full blood count may demonstrate neutrophilia consistent with bacterial infection. A blood count may also be a screening investigation for suspected haematological malignancy. C-Reactive Protein (CRP) is raised in bacterial infections and can be useful in monitoring response to treatment.

Consider a 'Monospot 'test for infectious mononucleosis. Serological tests for toxoplasmosis, bartonella (cat scratch disease), or cytomegalovirus (CMV) should be considered for persistent lymphadenopathy. Mantoux or Heaf tests for tuberculosis may be helpful, particularly in the non-immunized.

Imaging

There is a limited place for plain radiographs, but calcification in a lymph node is highly suggestive of tuberculosis. A chest X-ray may be helpful in tuberculosis, and a lateral neck view may demonstrate a retropharyngeal mass. Ultrasound examination of a neck mass may be undertaken without sedation or anaesthesia. Ultrasound will help determine if a lesion is cystic or solid. An experienced radiologist can comment on the internal architecture of lymph nodes and may raise suspicion of malignancy. Benign characteristics include size less than 1 cm, oval shape with short : long axis ratio less than 0.5 to 1, normal hilar vascularity and a low resistive index with high blood flow on Doppler technology.[4] If an abscess is identified, sonography will help with determining the anatomical relationships of the abscess and with surgical planning.

Computed tomographic (CT) scanning may require general anaesthesia in small children. Good anatomical detail is provided and it is helpful in surgical planning. Neither ultrasound nor CT is absolutely accurate in the diagnosis of an abscess and in the presence of strong clinical features surgical exploration should be considered.[5]

Magnetic resonance (MR) scanning rarely adds useful information in the case of acute inflammatory lesions but is very useful for vascular malformations, salivary gland and soft-tissue masses.

SPECIFIC CERVICOFACIAL INFECTIONS

Viral infections

VIRAL UPPER RESPIRATORY INFECTIONS

Adenovirus, rhinovirus or enterovirus (Coxsackie A and B) may cause reactive lymphadenopathy. This is generally self-limiting.

INFECTIOUS MONONUCLEOSIS

This is an acute infection caused by Epstein–Barr virus (EBV). It occurs mainly in adolescence and is spread by close contact. Fever, fatigue, malaise and an exudative tonsillitis are characteristic (**Figure 37.1**). Cervical lymphadenopathy may be massive. Other lymphoid tissue including liver and spleen may be enlarged. There is a characteristic picture on the blood film with the presence of atypical lymphocytes. Serological tests such as Monospot or Paul–Bunnel will usually confirm the diagnosis. Although the aetiology is viral, intravenous antibiotics may be needed to treat any coexistent bacterial infection. Ampicillin and amoxicillin are contraindicated as they can cause a skin rash when used in Epstein–Barr virus infection.

In cases where the acute tonsillitis is associated with airway obstruction, steroids may be considered. On occasion, endotracheal intubation may be required to protect the airway until the swelling subsides, or acute –'hot' – tonsillectomy to remove the obstructive tonsils.[6, 7] Cases with hepatosplenomagaly should be managed in cooperation with a paediatrician. Patients should be warned that splenomegaly will last at least 4 weeks but can take as long as 8 weeks to settle and should refrain from contact sports during this time.[8]

HIV

Infection is associated with repeated opportunistic infections. Most cases of paediatric HIV infection are acquired from the mother by vertical transmission. Acute infection may mimic infectious mononucleosis. Persistent generalized lymphadenopathy including the cervical nodes becomes a feature as the disease progresses. Weight loss and recurrent fevers occur. Following HIV infection it may be years or decades before full acquired immune deficiency syndrome (AIDS) develops. There is significant evidence of increased life expectancy with early antiretroviral treatment.[9]

Investigation and management should be in cooperation with a specialist in paediatric infectious diseases.

Bacterial infections

MICROBIOLOGY

Group A *beta haemolytic streptococcus* and *Staphylococcus aureus* are the most common causative organisms for suppuration in the neck. Other bacteria that may be implicated include anaerobes (19%); *Haemophilus influenzae*, *Moraxella catarrhalis*[10] and beta lactamase-positive organisms.

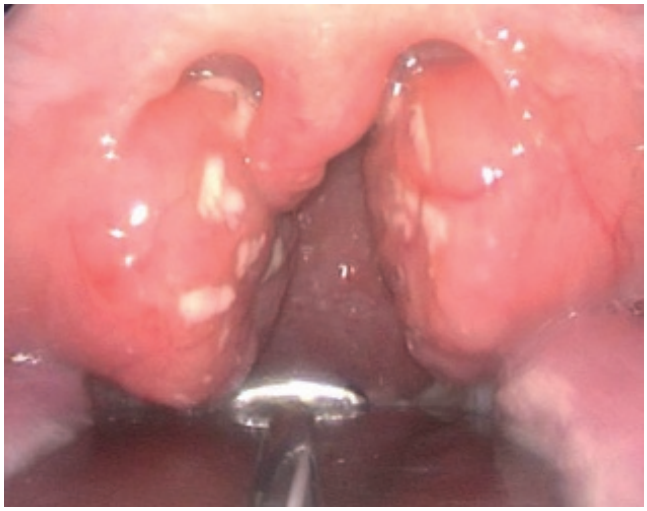

Figure 37.1 Exudative tonsillitis in infective mononucleosis.

ACUTE LYMPHADENOPATHY WITH SUPPURATION

Cervical abscesses

Bacterial infection within a cervical lymph node may progress to cause local cellulitis and abscess formation (Figure 37.2). Occasionally, a solid mass of inflammatory tissue forms due to coalescence of a group of lymph nodes and this is clinically referred to as a 'phlegmon'. The distinction between phlegmon and abscess is important, as abscesses usually require surgical drainage whereas phlegmons settle with intravenous antibiotics. The most important assessment is clinical. Abscesses are tender, usually reddened and exhibit the clinical sign of fluctuance, confirming their cystic nature. Imaging in the form of an ultrasound scan is helpful but not always required.

Many neck abscesses require surgical drainage. This may be performed by a neck incision, which is ideal for superficial lesions and the majority of deep cervical abscesses. A wide-bore needle aspiration may be adequate if the pus has coalesced and liquefied.

Dental abscess

An infected molar or premolar may cause extensive swelling extending into the face and neck and should be considered in the differential of a neck abscess (Figure 37.3).

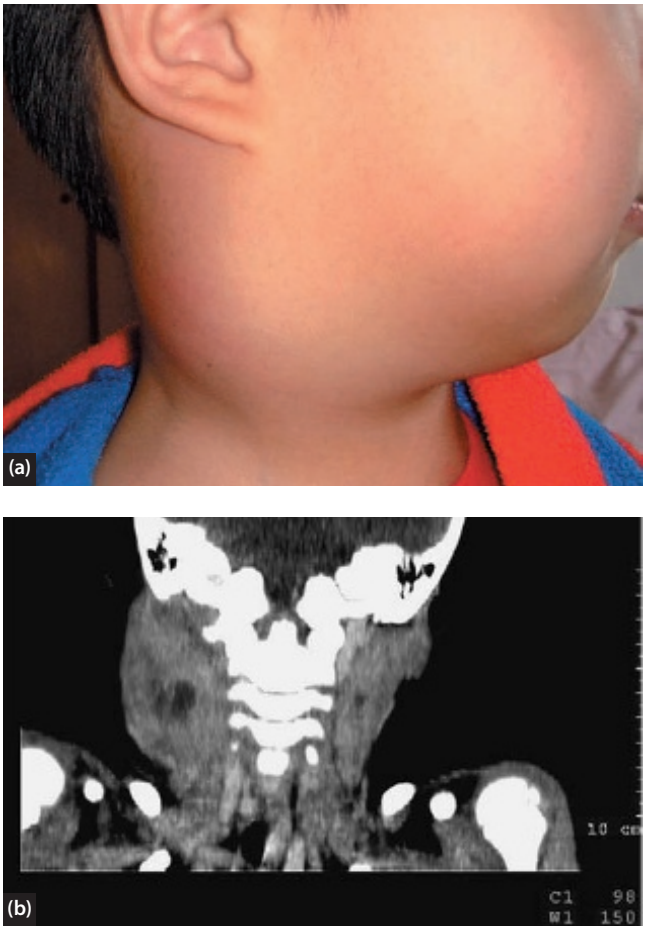

Figure 37.2 Cervical abscess. (a) Child with acute cervical abscess. **(b)** CT scan of the same child.

Deep neck space infections (DNSIs)

Deep neck spaces are described in relation to the hyoid bone. They can be suprahyoid, infrahyoid or comprise the entire length of the neck. A sound knowledge of the fascial layers and neck spaces is needed to correctly diagnose the affected space as well as plan the surgical approach. Deep neck space infection may lead to other severe and potentially life-threatening complications, such as mediastinitis, septic embolization, dural sinus thrombosis and intracranial abscess.

In paediatric patients, DNSIs are typically caused by the suppuration and perforation of parapharyngeal and retropharyngeal lymph nodes, which serve as a drainage pathway for adenoid and tonsillar infections in children aged 1–5 years. The retropharyngeal, parapharyngeal and peritonsillar spaces are therefore more frequently involved in children.[11]

Retropharyngeal abscess is now uncommon but should be recognized because of its potential to cause fatal airway obstruction.[12] The child is usually febrile, drooling and may adopt a characteristic posture with the neck flexed and the head extended. If suspected, the child must be admitted for intravenous antibiotics, rehydration and careful observation. Imaging is required to confirm the suspected clinical diagnosis, distinguish between drainable abscesses and cellulitis, define the precise extent of the disease, identify complications and also monitor infection progression. CT scanning with contrast is the modality of choice but may itself require anaesthesia (Figure 37.4).[13] In patients requiring a general anaesthetic the patient should be carefully intubated with the help of a skilled paediatric anaesthetist and arrangements should be made for surgical drainage if indicated as soon as the CT scan has been completed. Drainage can be via an intraoral or external approach.

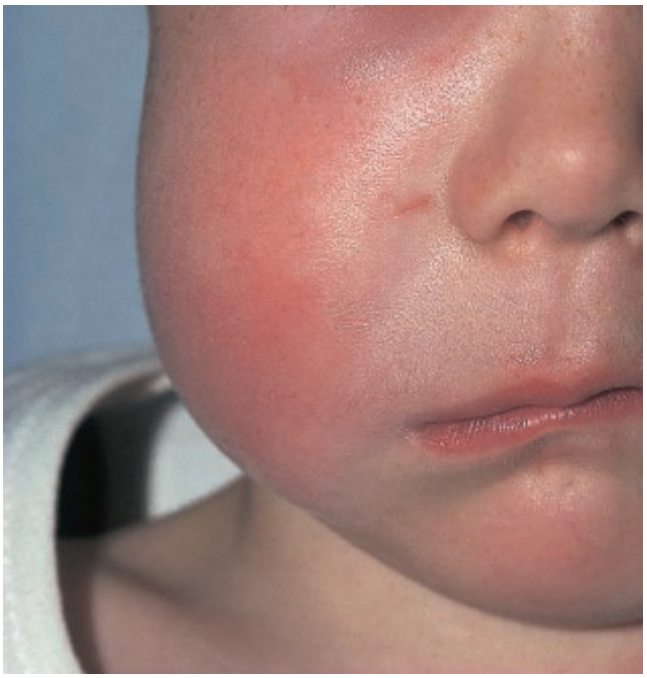

Figure 37.3 Dental abscess.

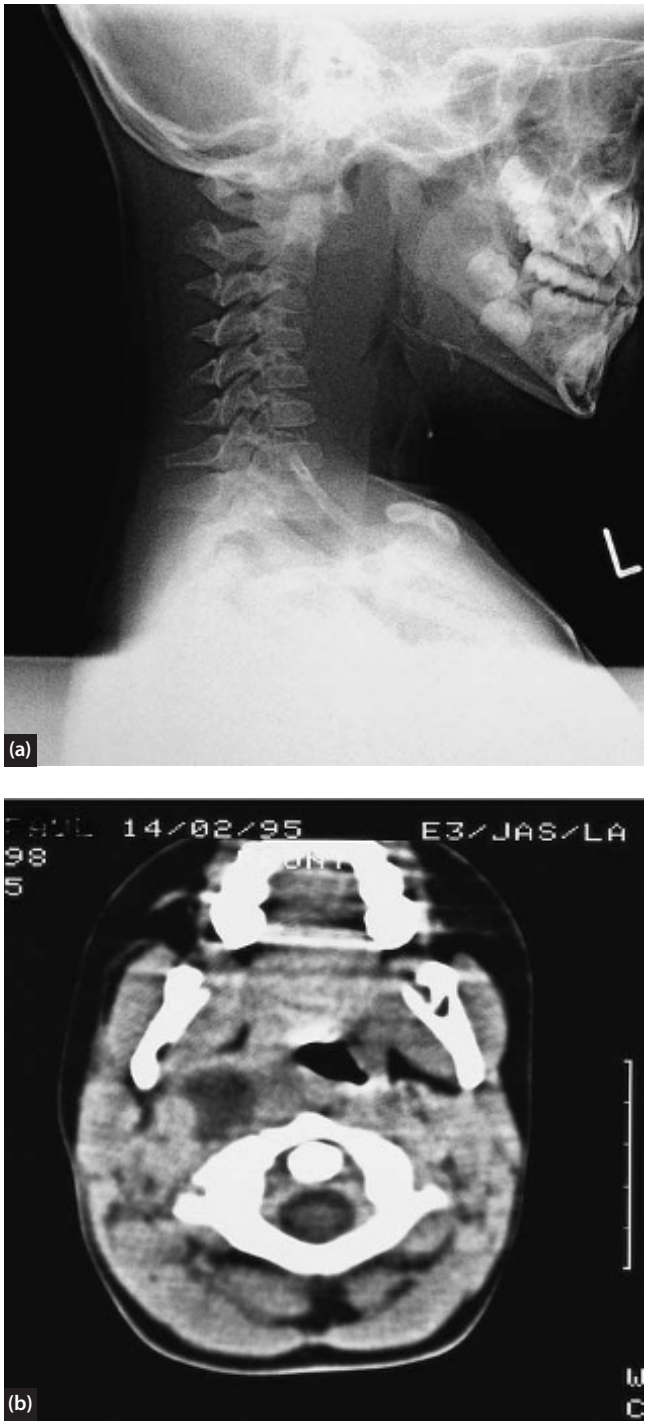

Figure 37.4 Retropharyngeal abscess. **(a)** Plain film showing large prevertebral shadow with compression of the airway; **(b)** CT scan of same child showing swelling filling the retropharyngeal space.

Ludwig's angina

This is a rapidly progressing cellulitis of the floor of mouth, involving the submandibular neck space. It is usually secondary to concomitant dental infections[14, 15] but has been described after frenuloplasty in an adolescent.[16] Causative organisms include *Streptococcus* species, Gram-negative rods and anaerobes. Patients usually present with swelling of the neck and submandibular space as well as firm induration of the floor of mouth, resulting in elevation and protrusion of the tongue, which can lead to airway obstruction.[17] Securing the airway is the mainstay of treatment, followed by intravenous antibiotics. Prompt initiation of antibiotics is usually sufficient and surgical intervention is reserved for persistent or progressive infections or when there is evidence of abscess formation.[18, 19] Surgical techniques for surgical decompression include intraoral and external approaches to ensure drainage of submaxillary and sublingual spaces.[20, 21]

Lemierre's syndrome

This is a septic thrombosis of the internal jugular vein. It is most often caused by the bacterium *Fusobacterium necrophorum*. It was common in the pre-antibiotic era, with a mortality rate exceeding 50%. Following an episode of upper respiratory sepsis the patient develops high spiking fevers with tenderness and fullness of one side of the neck. Pulmonary emboli may occur causing lung abscess formation (**Figure 37.5**). Incidence in the UK is rising, perhaps related to changing patterns of antibiotic use.[22]

Doppler ultrasound can detect flow rate and is useful in making the diagnosis. Unfortunately, it is suboptimal for detecting thrombosis deep to the mandible and clavicle.

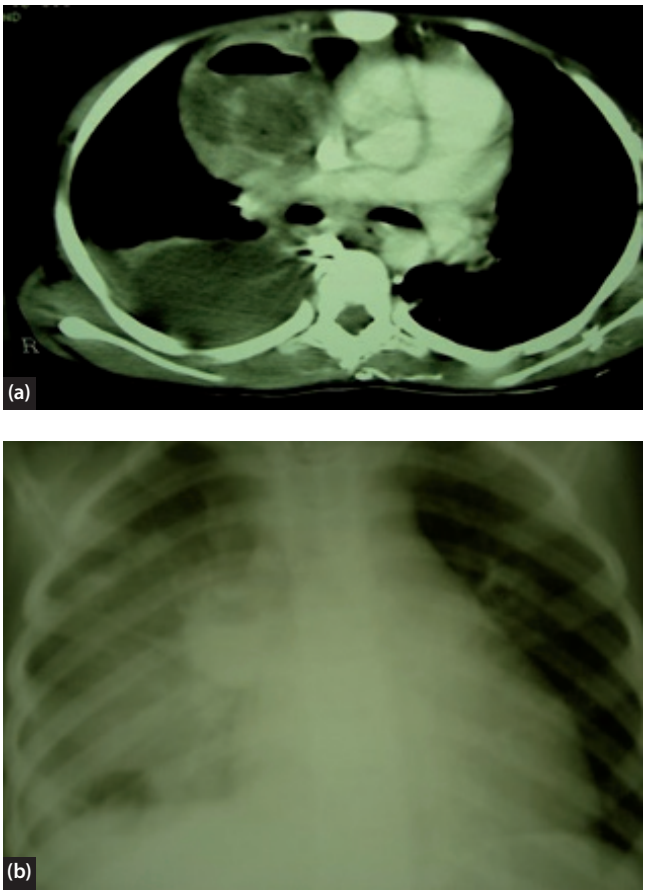

Figure 37.5 CT scan and chest X-ray demonstrating a lung abscess secondary to septic emboli from internal jugular vein thrombosis.

CT scan with intravenous contrast is considered by many to be the study of choice. Treatment with intravenous antibiotics and drainage of any abscess is usually curative. The role of anticoagulants is controversial and surgical treatment of the suppurating internal jugular vein is rarely required, although it has been used in cases of repeated septic emboli.

CAT SCRATCH DISEASE

This is a granulomatous condition characterized by lymphadenopathy with fever and malaise. The disease has been recognized for over 50 years but only recently has the causative organism been identified as the bacteria *Bartonella henselae*. It is spread by close contact with cats while kittens are more likely to carry the bacteria than adult cats. Fleas have been shown to serve as a vector for transmission among cats and viable *Bartonella henselae* has been isolated in the faeces of cat fleas. It has been postulated that transmission of *B. henselae* from cats to humans may be by inoculation with flea faeces containing *B. henselae* through a contaminated cat scratch wound or across a mucosal surface.[23–25]

Patients are mainly under 20 years of age and more than 90% have a history of feline contact.[26, 27] Serologic testing has a high sensitivity and specificity. Although there is no medical treatment, confirmation of the diagnosis by performing a blood test will reassure parents who often become concerned about possible malignancy. Lymphadenopathy may persist for months after other symptoms have disappeared.

TULARAEMIA

Tularaemia, named after Tulare County in California, is also known as rabbit fever or deer fly fever. It is caused by infection with the Gram-negative bacillus *Francisella tularensis*. It is transmitted to humans by rabbits, ticks or contaminated drinking water. Skin or mouth ulcers may be present with associated lymphadenopathy, fevers, malaise and headache. Diagnosis can be difficult but organisms can be isolated from blood cultures during periods of pyrexia. The diagnosis can also be confirmed by rising serological titres in the convalescent phase of the illness. The treatment of choice is streptomycin but tetracycline, aminoglycosides or chloramphenicol has also been used. Immunotherapy has shown promise in animals but is still not licensed in adult use.[28]

ACTINOMYCOSIS

Actinomycosis is caused by Gram-positive non-spore forming bacteria. The most common human pathogen is *Actinomyces israelii* but there are several other species which can rarely be pathogenic. Approximately 50% of cases are cervicofacial. Actinomyces are normal commensals in the oral cavity and infections arise from a breach of the mucosa (e.g. dental extraction). The most common presentation is a slow-growing painless mass near the mandible. Local lymph nodes may be involved and in a small number of cases metastasis of disease to liver or brain may occur. Untreated, the mass progresses to fibrosis and chronic suppuration with draining sinuses. A less common presentation is with an acute, warm, tender mass with fever. The presence of sulphur granules on pathological examination is suggestive but not diagnostic. If the diagnosis is suspected, special culture conditions increase the chance of culturing this organism. Most cases are treated by surgical excision followed by prolonged antibacterial therapy, usually penicillin for up to 6 months.

BRUCELLOSIS

Brucellosis is a zoonosis, i.e. an infection transmitted from animals to humans. It can be acquired through working with livestock or consumption of unpasteurized dairy products or infected meat products. It is caused by several species of the genus *Brucella,* which are small Gram-negative bacilli. There is lymphadenopathy involving the neck and other body regions associated with fever, malaise and migratory myalgia and arthralgia. Diagnosis is by serology and management is with tetracycline in adults and trimethoprim-sulphamethoxazole in children. Up to 10% of patients will present with relapse and treatment will have to be repeated.

SYPHILIS

This is a spirochaete infection caused by *Treponema pallidum*. Primary syphilis is associated with an ulcer (chancre) and local lymphadenopathy. Early presentation with a neck mass may occur in patients with HIV. It presents in the paediatric population as congenital syphilis and the majority of patients are asymptomatic at birth. If untreated, patients can present with late congenital syphilis. Head and neck manifestations include neurosyphillis, saddle nose deformity and Higoumenakis' sign, which is unilateral sternoclavicular joint enlargement caused by periosteitis in congenital syphilis.[29]

Serological diagnosis starts with venereal disease research laboratory (VDRL) and rapid plasma reagin (RPR) tests. Occasionally these tests can yield false-positive results and confirmation is required with treponemal-specific tests, *Treponema pallidum* haemagglutination assay (TPHA) or fluorescent treponemal antibody absorption (FTA-ABS) tests.[30, 31]

First-line treatment for uncomplicated infection consists of a single dose of intramuscular penicillin or oral azithromycin. Because of the poor penetration of penicillin into the central nervous system, treatment of neurosyphilis requires high-dose penicillin for a prolonged period (at least 10 days).[31, 32]

Mycobacterial infections

Two groups of mycobacterial infections involve the neck in children. The distinction is important and can be challenging. First there are infections caused by *Mycobacterium tuberculosis* (TB). Second are a group of infections caused by other mycobacteria. Commonly referred to as atypical

mycobacteria or environmental mycobacteria, these are most accurately termed non-tuberculous mycobacteria (NTM) or mycobacteria other than tuberculosis (MOTT). They include *Mycobacterium avium intracellulare*, *Mycobacterium scrofulaceum*, *Mycobacterium fortuitum* and *Mycobacterium haemophilum*.[33] They particularly affect children between the ages of 18 months and 3 years, presumably because younger children are less commonly exposed to the pathogens and because older children have developed immunity.

NTM is found throughout the environment and can be isolated from water, soil, dust animals and birds.[34–37] These organisms are low-grade pathogens in humans and cross infection is rare.

The typical presentation is of a painless, firm, enlarging mass in the neck. In NTM infection the overlying skin is frequently discoloured (**Figure 37.6**). In children with tuberculosis, weight loss, fever and anorexia may be present.

The differential diagnosis includes lymphoma. To exclude this, a tissue diagnosis is usually required. Biopsy specimens are sent for both histopathological examination and microbiology, including staining and culture specific to mycobacterium. The typical histopathological appearances of tuberculosis are of caseating granuloma formation. Acid- and alcohol-fast staining bacilli may be seen. However, it may not be possible histopathologically to distinguish tuberculous from NTM infection. Culture remains the cornerstone of diagnosis of opportunistic mycobacterium but may take several weeks. In this situation all patients should have a chest X-ray to identify features of tuberculosis. A tuberculous skin test is often helpful. A positive test in a non-immunized population (such as the US or children under 13 in most regions of the UK) is highly suggestive of tuberculous infection. Unfortunately, there is an incidence of positive testing with non-tuberculous infection and this test is not absolutely diagnostic for tuberculosis. In cases of doubt, antituberculous medication may be commenced pending the outcome of cultures. Genetic probing of the cultured organisms can also be used to try and make the distinction between tuberculous and NTM infection. Great promise is shown with the use of multiplex real-time PCR testing with targeting different housekeeping genes.[38]

The management of confirmed mycobacterium tuberculosis lymphadenopathy is medical treatment with a combination of antituberculous drugs. The management of NTM lymphadenopathy is controversial. Complete surgical excision of the involved nodes results in higher short-term cure rates compared to medical treatment.[39] Prolonged medical therapy is an alternative[40] but there is no evidence that it is any better than doing nothing and waiting for spontaneous resolution.[41] There is obviously a trade-off: with surgery there is a scar and possible injury to the facial nerve or its branches and, depending on the circumstance, this may or may not lead to a better cosmetic result than the scarring left after the disease has run its natural course; untreated NTM usually resolves in 3–6 months but a few cases can take a year or more.[42]

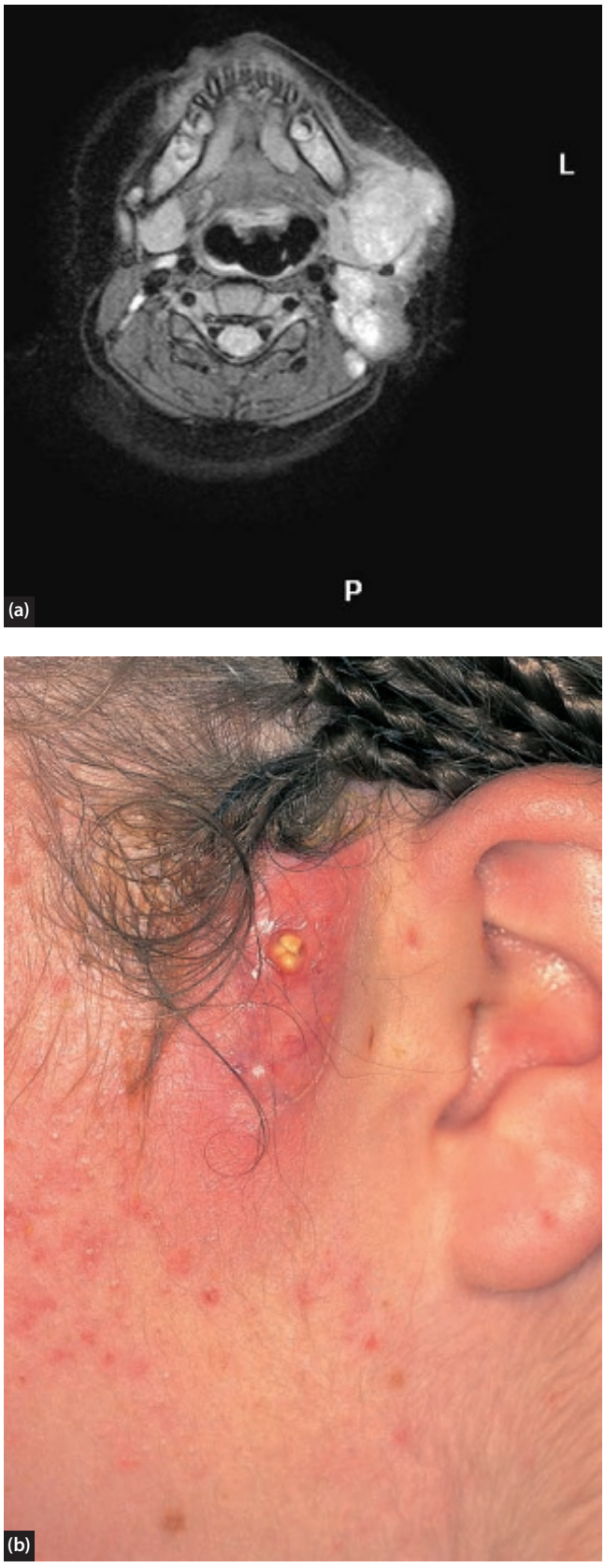

Figure 37.6 NTM. **(a)** MR scan showing large left neck mass; histology confirmed NTM. **(b)** Skin changes in NTM.

SINUS FORMATION AND DISCHARGE

If the nodes have been breached by the infection and there has been spread into the surrounding tissue, there is a risk of skin breakdown and formation of a sinus. These sinuses often persist for months with troublesome discharge. Once a sinus has formed, there is a stronger indication to perform surgery as the constant discharge is extremely disruptive to the life of an otherwise well child. Curettage has been advocated as a treatment for infection that has spread beyond the lymph nodes and is not amenable to complete excision. This may reduce the duration of the disease.

Primary medical treatment of non-tuberculous neck masses has been advocated using either macrolide antibiotics based on some *in vitro* experiments[43] or antituberculous therapy. This usually involves prolonged treatment as the organisms are notoriously resistant to antituberculous therapy. Whether such prolonged antibiotic therapy produces better results than doing nothing is currently unclear.[31]

Fungal infections

HISTOPLASMOSIS

Histoplasmosis is caused by the fungus *Histoplasma capsulatum*. It is associated with bird droppings and acquired via airborne spores. Infection in the central US is very common and typically asymptomatic. Pulmonary and systemic disease may occur in immunocompromised patients and is common in HIV/AIDS patients. Mucosal head and neck lesions may mimic squamous carcinoma and severe infections can cause lymphadenopathy.

The diagnosis is best established by urine antigen testing. Serum antigen tests can produce false-negative results in the first 4 weeks of the infection and blood cultures take 6 weeks to produce diagnostic growth.[44] Immunocompetent patients do not often require treatment as the infection usually resolves. Antifungals such as amphoterizine B and itraconazole are used to treat severe acute and chronic disseminated infections.

CANDIDA AND ASPERGILLUS

Mucosal candidiasis is a common problem in children but neck masses caused by these infections are extremely rare and limited to immunocompromised patients.

Parasitosis

TOXOPLASMOSIS

Infection with the parasite *Toxoplasma gondii* is usually through the ingestion of poorly cooked meat or of oocytes excreted in cat faeces. Cervical adenitis occurs in more than 90% of clinical cases.[45] Subclinical infection and positive serology may be found in asymptomatic individuals. It is estimated that up to a third of the world population carry *Toxoplasma* infection.[46]

Organisms can be detected by polymerase chain reaction in human blood samples.[47] The lymphadenopathy may persist for months and children may require a biopsy to rule out malignancy. Treatment is rarely required for cervical lymphadenopathy, which is self-limiting, but the infection responds to sulphonamides and pyrimethamine.

Non-infective inflammatory disorders

SARCOID

Sarcoidosis is a chronic multisystem disorder of unknown aetiology. It mainly occurs in the second decade of life and is rare in children. It causes generalized and pulmonary symptoms but may involve other parts of the body. Neck masses, parotid masses and facial nerve paresis, often bilateral, may result. Cervical nodes are typically bilateral and non-tender. The diagnosis is often suspected from the chest radiograph and can be confirmed by biopsy, which shows typical non-caseating granulomas. Angiotensin-converting enzyme blood levels are used in diagnosis and monitoring of sarcoidosis. Treatment is usually conservative although steroids, and in some cases more potent antineoplastic agents, can be used.

Conditions which simulate lymphoma

This heterogeneous group of benign lymphoproliferative disorders is characterized by prolonged unexplained cervical adenopathy which can give rise to concerns regarding lymphoma. Some authors refer to these conditions as 'pseudolymphomata'. They include Rosai–Dorfman disease, Castleman disease, Kawasaki syndrome and Kikuchi-Fujimoto disease.[48]

KAWASAKI SYNDROME

This is an acute multisystem vasculitis of unknown aetiology. It tends to affect children under 5 years of age and the clinical presentation is similar to many childhood infectious diseases. The diagnosis is clinical and children should have four of the five following criteria:

1. acute nonpurulent lymphadenopathy – usually unilateral
2. erythema, oedema and desquamation of the hands and feet
3. polymorphous exanthema
4. painless bilateral conjunctival infection
5. erythema and injection of the lips and oral cavity.

There may be a thrombocytosis and pericardial effusion. In the subacute stage, coronary artery aneurysms develop in 15–20% of cases. The goal of management is to reduce inflammatory responses with anti-inflammatory or gamma globulin therapy.[49] The vasculitis is self-limiting but unfortunately causes permanent cardiac damage in around 20% of untreated patients. All patients should have an initial echocardiogram and cardiac follow-up. A mortality of 1–2% is associated with this disease due to the cardiac sequelae.

SINUS HISTIOCYTOSIS (ROSAI–DORFMAN DISEASE)

Children present with massive cervical lymphadenopathy which is similar to infectious mononucleosis or lymphoma. This disease is thought to represent an abnormal histiocytic response to some precipitating cause, possibly a herpes virus or EBV.[50] Fever and skin nodules may be present. Treatment is expectant but biopsy is usually required to rule out malignancy. Histopathologic examination reveals dilated sinuses, many plasma cells and marked proliferation of histiocytes.

KIKUCHI-FUJIMOTO DISEASE

This is an idiopathic disorder, first described in Japan. It is characterized by lymph gland enlargement which may occur anywhere in the body but is typically cervical.

Fever chills and weight loss are common. Women and young adults are more commonly affected. The disease is self-limiting but biopsy is often performed to rule out malignancy. Histology shows a characteristic necrotizing lymphadenitis.

BEST CLINICAL PRACTICE

- ✓ A blood count is a useful screening investigation for haematological malignancy.
- ✓ Ultrasound will help determine if a lesion is cystic or solid. An experienced ultrasonographer can comment on the internal architecture of lymph nodes and may raise suspicion of malignancy.
- ✓ In NTM, once a sinus has formed there is a relative indication to perform surgery as discharge is extremely disruptive to the life of an otherwise well child.
- ✓ Needle core biopsies of suspicious lymph nodes under radiological guidance will usually be sufficient for histological diagnosis.
- ✓ Open biopsy may be the only way to exclude a lymphoma in the non-infective inflammatory lymphoproliferative disorders.

FUTURE RESEARCH

- ➤ The increasing survival of children with malignant disease, often with highly immunosuppressive chemotherapy, will produce therapeutic challenges in the management of infectious disease in the head and neck.
- ➤ Pooling of data on relatively uncommon conditions such as NTM may produce better treatment protocols.
- ➤ Imaging continues to be refined and, as spiral CT scanners permit higher-resolution images at lower radiation doses, imaging the architecture of cervical structures will improve.
- ➤ Aspiration biopsy cytology has proved disappointing in children and increasing specialization in pathology may expand the role of this technique.

KEY POINTS

- Lymphadenopathy is common in children and rarely requires investigation.
- Viral adenitis is the most common cause of neck swelling.
- Much anxiety can be caused by lesions that simulate lymphoma but careful clinical assessment supplemented by non-invasive investigations, and very rarely biopsy, will provide a diagnosis.
- Immunocompromised patients pose a particular challenge and liaison with a paediatrician is essential in this group of children.

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CHAPTER
38

DISEASES OF TONSILS, TONSILLECTOMY AND TONSILLOTOMY

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SEARCH STRATEGY

Data in this chapter may be updated by searches of the Cochrane Library, Medline, PubMed and Ovid databases using the keywords: tonsils, tonsillitis, pharyngitis, sore throat, children, paediatric and carrying out further subsearches for anatomy, microbiology, immunology, complications and therapy. These were complemented by hand searches of current English language texts and the following journals: *Journal of Laryngology and Otology*, *Clinical Otolaryngology*, *Laryngoscope*, *Archives of Otolaryngology*, *Annals of Otolaryngology*, *International Journal of Pediatric Otolaryngology*. The information available from the published results of the National Prospective Tonsillectomy Audit available on the Royal College of Surgeons of England website (www.rcseng.ac.uk) has also been taken into account. In addition, the UK Department of Health (www.dh.gov.uk) and the National Institute for Health and Care Excellence (NICE) (www.nice.org.uk) websites were consulted.

DISEASES OF TONSILS

STRUCTURE AND FUNCTION OF TONSILS

The palatine tonsils are paired structures consisting of lymphoid tissue. They are located in the tonsillar fossa between the anterior and posterior tonsillar pillars formed by palatoglossus and palatopharyngeus muscles respectively. Along with the adenoids, the lingual tonsils, the tubal tonsils and the diffuse aggregates of pharyngeal submucosal lymphoid tissue, they make up Waldeyer's ring.

Histologically the tonsils consist of aggregates of lymphocytes arranged in a follicular manner and embedded in a stroma of connective tissue. The epithelial lining is stratified squamous, which invaginates into the parenchyma forming crypts.

The organisms cultured from the tonsils are very variable, with recognized differences in surface and core samples.[1, 2] The most commonly identified organism from the surface of a diseased tonsil is the group A beta-haemolytic streptococcus (GABHS). This organism is also found on culture in nearly 40% of asymptomatic individuals.[3, 4] Other organisms found on the surface include *Haemophilus influenzae*, *Staphylococcus aureus*, alpha-haemolytic streptococci, *Branhamella* spp, *Mycoplasma*, *Chlamydia*, anaerobes and respiratory viruses.[5, 6] In recurrent tonsillitis the samples grew a range of pathogens but the predominant organisms were *Haemophilus influenzae* and *S. aureus* including methicillin-resistant *Staphylococcus aureus* (MRSA),[7] mixed flora being quite common. Beta-haemolytic streptococci were less common.

Function: Role of tonsils within the immune system

The tonsils are composed of lymphoid tissue with germinal centres located immediately submucosally. Both T- and B-lymphocytes are present though B-lymphocytes predominate. Tonsil serves both the cell-mediated and humoral immune function. The tonsils have no afferent lymphatics. The B-cells have the capability to synthesize specific antibodies. On exposure to antigen, immunoglobulin IgG and IgA plasma cells are produced. Contact with allergens in the upper respiratory tract therefore enhances

local immunity and also contributes to the development of systemic immunity.

There is no evidence to suggest that tonsillectomy results in impaired immunity, presumably as a result of the extensive 'back-up' in the immune system.[8] The role of bacteria and viruses in this process is also controversial. The evidence suggests that they may act synergistically, with the presence of certain latent viruses (particularly Epstein–Barr virus, adenoviruses and herpes simplex) sensitizing the pathogenic bacteria present incidentally on the tonsils of asymptomatic individuals.[9]

INFLAMMATORY DISORDERS OF THE TONSIL

Acute tonsillitis

Acute tonsil inflammation may be a localized episode, in association with an upper respiratory illness or as a part of generalized systemic infection such as infectious mononucleosis. The causative organism usually is GABHS, although a range of other organisms including viruses and anaerobes may be implicated.[3, 4]

Acute tonsillitis is diagnosed mainly on the basis of clinical assessment. There is a short history of sore throat with fever and pain on swallowing. Examination generally reveals erythema of the tonsils and posterior pharyngeal wall, with obvious exudates on the tonsils occasionally. This is usually associated with tender jugulodigastric lymph node enlargement. Both bacteria and viruses play a part in acute inflammation of the tonsils, either separately or together. Also, there is no evidence to suggest that viral tonsillitis is more or less severe than bacterial tonsillitis. In most of the cases both viral and bacterial tonsillitis tend to resolve quickly without treatment.[4] Corticosteroids (oral or intramuscular), in addition to antibiotics, expedite the resolution of pain.[10, 11]

The management of acute tonsillitis is mainly symptomatic, i.e. using analgesia and hydration until the symptoms subside. Antibiotics will shorten the illness and may reduce the risk of sequelae.[12] In those patients in whom the illness shows no sign of improvement within 48–72 hours, antibiotics should be started, benzyl-penicillin being the drug of choice. If there is clinical concern about the severity of disease at the beginning, antibiotics should be started soon.

Evidence suggests that corticosteroids provide symptomatic relief of pain in sore throat, in addition to antibiotic therapy, especially in severe cases.[13]

Complications of acute tonsillitis

Acute tonsillitis can lead to septicaemia and local abscess formations. The non-infective complications of streptococcal tonsillitis include rheumatic fever and glomerulonephritis.

PERITONSILLAR ABSCESS (QUINSY)

A peritonsillar abscess is a collection of pus lateral to the tonsil. The clinical symptoms include severe usually unilateral sore throat, odynophagia, trismus and lymphadenopathy. The treatment includes antibiotics, needle aspiration of pus or incision and drainage.[14] The antibiotics usually given are intravenous high-dose penicillin or a cephalosporin.[15] Indication for interval tonsillectomy should take into account any background history of tonsillitis or more than one episode of quinsy on the same side. Tonsillectomy during the acute attack is not a very popular treatment option,[16] as the release of pus into the oral cavity either spontaneously or therapeutically carries with it the risk of aspiration in severely ill patients. Using local anaesthetic before incision also increases this risk. The initial management of choice is aspiration of the abscess using a wide-bore needle along with intravenous antibiotics, usually high-dose penicillin or cephalosporin.

RETROPHARYNGEAL ABSCESS

This is a rare but serious complication of acute tonsillitis, seen mainly in infants and children less than 5 years of age. It presents as the infection tracks into the lymphoid tissue between the posterior pharyngeal wall and the prevertebral fascia. The child is usually systemically unwell and there may be evidence of airway compromise or an associated neck abscess. The diagnosis can be confirmed by CT scanning. Treatment is initially high-dose intravenous antibiotics.[17] If pus collection is suspected, urgent incision and drainage is done under a general anaesthetic by an experienced anaesthetist.[18] The drainage is usually done perorally but occasionally external drainage via neck may be appropriate. Very rarely, tracheostomy is necessary. Retropharyngeal abscess due to tuberculosis requires specific antibiotic treatment.

PARAPHARYNGEAL ABSCESS

Occassionaly, peritonsillar and retropharyngeal abscess may be complicated by spread of infection to the parapharyngeal space. Pus collection in this space presents with severe trismus and possibly airway compromise in a systemically unwell patient. The diagnosis is confirmed by ultrasound or CT scanning, which also helps in treatment planning. Treatment includes high-dose broad-spectrum intravenous antibiotics and drainage of the abscess. Deep neck space sepsis may be complicated by progression to life-threatening infections including mediastinitis or retroperitoneal sepsis. It is essential to be proactive in managing these conditions.[19]

LEMIERRE'S SYNDROME

Lemierre's syndrome is a rare but potentially fatal complication of oropharyngeal infection. It is characterized by septic thrombophlebitis of the internal jugular vein, at times associated with metastatic abscesses. The causative organism is usually fusiform bacillus. This condition should be suspected when there is severe neck pain and septicaemia in a patient with infection in the upper aerodigestive tract.[20] Treatment is with antibiotics for 6 weeks, usually penicillin with metronidazole or Co-amoxiclav.[21] If there is evidence of spreading thrombophlebitis,

anticoagulation may be considered. There is significant mortality associated with this condition.

IMMUNE COMPLEX DISORDERS

Acute tonsillitis caused by GABHS can occasionally lead to diseases related to immune complex formation, generated as a response to the infection. The two important diseases resulting from this phenomenon are acute rheumatic fever and acute gomerulonephritis.

TONSILLITIS AND PSORIASIS

There is possibly some association between GABHS tonsillitis and exacerbations of psoriasis, as a result of an immune phenomenon. Some dermatologists and otolaryngologists advocate tonsillectomy, but there is no good evidence to suggest that this relieves the condition.[22]

RECURRENT TONSILLITIS

Significant numbers of patients suffer from recurring episodes of acute tonsillitis. These episodes may gradually settle or may continue for several years. The infections need to be treated depending on the severity of the individual episode. There is no evidence of benefit of long-term antibiotics for this condition.

CHRONIC TONSILLITIS

Some patients get chronic throat discomfort associated with production of smelly white debris from tonsillar crypts. Occasionally, these debris may become inspissated, calcify and form a tonsillolith. There is no evidence to show a relationship to identifiable tonsillar pathology in these patients.

Infectious mononucleosis

Infectious mononucleosis commonly presents as acute tonsillitis. It is caused by Epstein–Barr virus (EBV) and is commonly seen in young adults. In addition to the throat symptoms, patients have significant systemic upset, splenomegaly and derangement of haematological and liver functions.[23] The diagnosis is helped with the Monospot test, which has sensitivity of less than 50% in children and 70–90% in adults. The diagnosis is confirmed by specific antibody titres. Although this is caused by a virus, in 30% patients secondary bacterial tonsil infection occurs. For those admitted to hospital, high-dose intravenous penicillin or cephalosporins is given. Ampicillin must be avoided if infectious mononucleosis is suspected as 90% patients can develop a significant rash as a result of transient immunostimulation. The incidence of rash with amoxycillin in these cases is 30%.[24]

In those patients with significant swelling of the tonsils leading to compromise of the airway and swallowing difficulty, a short course of corticosteroids is beneficial.[11] Steroids should be preferably given in combination with antibiotics. The use of antiviral medications (acyclovir) is debatable and should be considered only in severe cases.[25]

Other infective conditions

Syphilis and tuberculosis infections in the tonsils are potentially difficult to diagnose. The lesion in syphilis classically takes the form of a punched-out ulcer but the appearances are variable, as for tuberculosis. The differential diagnosis of a neoplasm should be borne in mind and the final diagnosis made by biopsy of the lesion.

NON-INFLAMMATORY DISEASES

Tonsillar asymmetry

Asymmetry of the tonsils is not an absolute indication for tonsillectomy, but in children, as adults, the clinicians need to be aware of the possibility of neoplasia (lymphoma). One study to measure actual size in cases of apparent asymmetry in children did not show any significant difference in size.[26] In general, the apparent size of the tonsils is not well correlated with disease within them. There is a wide variation in the degree to which the tonsils are buried within the tonsillar pillars, which can give a false impression of the actual size of the tonsil. In general, the tonsils tend to involute during late childhood, but this rate of involution is variable between individuals and can vary between the two tonsils, which can at times give an asymmetrical appearance.

Spontaneous tonsillar bleeding

Spontaneous bleeding can happen from inflamed tonsils occasionally. Bleeding can also be secondary to minor trauma. This usually will respond to topical cautery under local anaesthetic. If it persists, tonsillectomy is an option.

Neoplasia

Asymmetrical tonsils arouse suspicion of neoplasia especially if the surface of one of the tonsils is irregular or ulcerated. Difference in size is not always an indication for biopsy in children, but any unusual appearances need to be investigated. Lymphoma can occur within the tonsils in adults as well as children. In adults, squamous cell carcinoma is the most common malignancy encountered.

TONSILLECTOMY AND TONSILLOTOMY

TONSILLECTOMY

Paediatric tonsillectomy is one of the most commonly performed operations. In the 1950s in the UK 200 000 tonsillectomies were performed annually, which dropped down to 49 187 in 2008–2009 (www.hesonline.nhs.uk). Of the tonsillectomies carried out in 2008, 27 400 were in children. Among those 25% were for obstructive symptoms and the rest for infections. The proportion performed for obstruction rather than infection seems to be rising year-on-year. This may be due in part to more stringent criteria being applied to surgery for infections as a result of better

evidence from trials in addition to increasing awareness of obstructive sleep apnoea and its consequences in children.

Evidence base for tonsillectomy

Adenotonsillectomy is the treatment of choice for otherwise healthy children with obstructive sleep apnoea, with improvement in 90% cases, including improvement in their behaviour, growth and development.[27, 28] However, for recurrent infections there is a widespread perception that high-quality evidence of the efficacy of tonsillectomy is lacking. Certainly, the evidence for benefit of adenotonsillectomy for recurrent infections was sparse until quite recently.[29] A Cochrane review in 1998 concluded that there was no evidence from randomized controlled trials (RCT) to guide clinicians for setting up guidelines for tonsillectomy in children or adults.[30] However, trials have been carried out since then and the evidence base is a little clearer.

For a long time, the only trial of value was that done by Paradise[32] published in 1984. The Paradise group randomized children with sore throats into surgical and non-surgical groups and their inclusion criteria are widely known and still used: seven sore throat episodes in a year, five a year for the last 2 years or three a year for the last 3 years. Recruitment took many years as few families were willing to undergo randomization and a large parallel cohort of non-randomized children undergoing surgery was also studied. Efficacy was measured on the basis of reduction in the number and severity of throat infections. This trial showed that in severely affected children tonsillectomy was efficacious for 2 years and sometimes for a third.

The North of England and Scotland Study of Tonsillectomy and Adenotosillectomy in Children (NESSTAC) was a large multicentre randomized controlled trial which used broadly the same inclusion criteria as Paradise, and which also had a large parallel cohort of non-randomized children undergoing surgery.[32] This trial demonstrated significant improvements in episodes of sore throat, need for consultations, quality of life and health costs compared to medical management.

Two further trials (one by Paradise[33] and the other from the Netherlands[29]) looked at children with milder symptoms, who did not meet the original Paradise criteria. They both failed to show a significant advantage of surgery over watchful waiting, so it seems that the original Paradise criteria for tonsillectomy are a reasonable threshold for considering surgical intervention.

Studies looking at quality of life (QOL) before and after operation suggest that tonsil disease has a marked adverse effect on QOL and there is significant benefit from surgery.[34] The Scottish tonsillectomy audit was a large-scale audit to look at patient satisfaction after tonsillectomy in more than 5000 patients. This audit reported 97% satisfaction rate 1 year after tonsillectomy.[35]

Guidelines

Various guidelines are produced by the British Association of Otolaryngologists – Head and Neck Surgeons (see ENTUK, www.entuk.org). For tonsillectomy, the recommendations are in line with those of Scottish Intercollegiate Guidelines Network (SIGN, www.sign.ac.uk). The SIGN guidelines for tonsillectomy are based on the Paradise criteria outlined above and reflect the results of randomized controlled trials. According to these guidelines, patients for tonsillectomy for both adults and children should meet all the following criteria:

- sore throats are due to tonsillitis
- the episodes of sore throat are disabling and prevent normal functioning
- seven or more well-documented, clinically significant, adequately treated sore throats in the preceding year, *or*
- five or more such episodes in each of the preceding 2 years, *or*
- three or more such episodes in each of the preceding 3 years.

TONSILLECTOMY TECHNIQUE

The traditional methods of tonsillectomy are 'cold steel' techniques using metal instruments. Several other methods have been introduced with perceived advantages in terms of reduced bleeding, reduced pain, more rapid healing and ease of surgical technique. The National Prospective Tonsillectomy Audit (NPTA) was established in 2003 on behalf of the Royal College of Surgeons of England and ENTUK to look at the effect of surgical technique on complications of tonsillectomy. Data were collected on more than 50 000 patients and the results represent the nationwide practice and recommendations for the clinicians.[36] There are also good data available from the Swedish national tonsil registry which has prospective data on 37 530 patients undergoing tonsillectomy alone (17 319 patients) or adenotonsillectomy (20 211 patients).[37]

Cold steel tonsillectomy

The dissection technique is the most common method of cold steel tonsillectomy. In this technique, the tonsil is pulled medially and the mucosa overlying the tonsil capsule is incised. The dissection continues in the plane of loose areolar tissue between the tonsil tissue and the pharyngeal muscles using a dissector or gauze, and the tonsil is excised completely. The bleeding vessels are dealt with using diathermy or ligatures as required. Another technique is the guillotine technique, which involves using a specially designed guillotine to excise the tonsil.

In the NPTA, haemorrhage was defined as a bleed that prolonged the patient's stay in hospital, required blood transfusion or return to the operating theatre or for secondary haemorrhage readmission to hospital. The haemorrhage rates for various techniques are shown in Table 38.1. The Swedish registry gives similar results, with cold steel dissection and ties having a significantly lower bleed rate and less post-operative pain than any of the other techniques.

TABLE 38.1 Surgical techniques and primary and secondary post-operative haemorrhage

Surgical technique (n = 33 921)	Primary tonsillar haemorrhage rate (%)	Secondary tonsillar haemorrhage rate (%)
Cold steel and ties/packs	0.8	1.0
Cold steel and monopolar diathermy	0.5	2.4
Cold steel and bipolar diathermy	0.5	2.3
Monopolar diathermy forceps	1.1	5.5
Bipolar diathermy forceps	0.4	4.3
Bipolar diathermy scissors	0.6	4.6
Coblation®	1.0	3.6
Other	0.7	3.6

Source: Reprinted, with permission, from the National Prospective Tonsillectomy Audit, available from the Royal College of Surgeons of England website (www.rcseng.ac.uk), Table 4.6.

Diathermy tonsillectomy

Bipolar dissection tonsillectomy is an alternative method to traditional cold steel tonsillectomy. In a Cochrane review of dissection versus diathermy, it was demonstrated that diathermy reduced intra-operative bleeding but increased pain in the diathermy group with no difference in secondary haemorrhage rate.[38] In the NPTA, post-operative bleeding was more frequent with diathermy than with cold steel alone, and particularly worse with monopolar diathermy. Monopolar dissection is known to be associated with more post-operative pain than other techniques and has little to recommend it.

Recommendations from the NPTA are shown in Box 38.1.

BOX 38.1 Recommendations of the National Prospective Tonsillectomy Audit (2005)

- When a patient is counselled for surgery, the risk of tonsillectomy complications, and in particular post-operative haemorrhage, should be carefully explained to the patients/parents.
- This risk should be quantified, preferably using the surgeon's own (or department's) figures.
- National figures can be used, but this should be made clear to patients.
- Surgeons using monopolar diathermy should consider using an alternative technique. There are no advantages to using this instrument over other methods.
- All trainee surgeons should become competent in cold steel dissection and haemostasis using ties, before learning other techniques in tonsillectomy.
- Emphasis must be placed on teaching the correct use of, and the potential hazards of, diathermy and other 'hot' techniques. Checks should be made of the power settings before starting the operation.
- Inexperienced trainees must be supervised by a more senior surgeon until competency has been achieved. This recommendation is in agreement with the College's Standards on Good Surgical Practice issued in 2002.
- Irrespective of seniority and experience, surgeons who wish to start using new techniques, such as Coblation®, should undergo appropriate training.
- All ENT departments should have regular morbidity and mortality meetings to monitor adverse incidents affecting patient outcome. For tonsillectomy, data should be presented by the surgeon, indicating the technique used for dissection and haemostasis and power settings if applicable, type of instrument used, and any difficulties encountered.
- It is the responsibility of the surgeon, and if appropriate his or her trainer, to follow up any identified problems appropriately.

Source: Modified and reprinted, with permission, from the National Prospective Tonsillectomy Audit, available in full on the Royal College of Surgeons of England website (www.rcseng.ac.uk).

Coblation® tonsillectomy

This technique uses a specially designed probe which both coagulates and cuts the tissues. In the NPTA, post-operative bleeding rates were unacceptably high. It has been suggested that post-operative pain is less than conventional dissection but some studies have cast doubt on this and shown that morbidity was less with cold steel dissection.[39] The National Institute for Health and Care Excellence (NICE) advises that electrosurgery (diathermy and Coblation®) can be used for tonsillectomy but that surgeons must be appropriately trained.

Ultrasonic dissection

Ultrasonic dissection uses an oscillating blade, which acts as both a cutting and a coagulating device. Some studies claim reduced pain with this technique but evidence of benefits is lacking.[40]

Laser tonsillectomy

Using a laser as a tool to dissect out the tonsils has been claimed to have advantages in terms of reduced bleeding and post-operative pain, but studies have failed to confirm this. There is evidence that the rate of secondary bleeding[39] and pain is greater with laser.[42]

TONSILLOTOMY

Tonsillotomy involves removing a part of the tonsil lymphoid tissue, leaving the capsule intact. The technique is reminiscent of what was historically called guillotine tonsillectomy. Techniques include microdebrider, laser, or most recently radiofrequency ablation (Coblation®),[43] using the instrument from medial to lateral. The amount of tissue removed can be from just the lymphoid tissue up to the anterior tonsillar pillar, to leaving a cuff of tonsil tissue lining the tonsillar fossa, to taking the tissue all the way back to the capsule (sometimes called intracapsular tonsillectomy).

These techniques, particularly Coblation® tonsillotomy, have only recently started being trialled. Earlier studies have used the technique – when tonsils for example need

to be debulked in young children with obstructive sleep apnoea – but it was thought it might be desirable to leave some functioning lymphoid tissue.[44] Some studies have already shown that recovery-related outcomes (days until pain-free, secondary haemorrhage rate) for intracapsular tonsillotomy were better than for total tonsillectomy in children with obstructive symptoms.[45] In some parts of the world, such as Scandinavia, tonsillotomy has now become the most common operation performed for obstructive symptoms, more common than tonsillectomy.[43]

The fact that the muscle is disturbed less than in tonsillectomy may explain why post-operative pain can be reduced. If the technique is found to be of similar efficacy to tonsillectomy, with a similar or lower bleed rate, the technique could represent an important step forward in tonsil surgery, potentially being applicable to all tonsil surgery for children, except where the tonsils are needed for histology. With time it will become evident how much tonsil tissue to take to achieve the balance in terms of minimal complications and maximum benefit. This is an exciting area of research.

TONSILLECTOMY MORBIDITY

Pain

Significant morbidity is associated with tonsillectomy.[46] Post-tonsillectomy sore throat is normal for at least 1 week and on an average return to school or work can take 1–2 weeks.[35] Various articles have been written on the management of post-tonsillectomy pain (see 'Anaesthesia and analgesia' below).

Peri-operative complications

If the mouth is opened too widely during the tonsillectomy operation, the patient may experience temporomandibular joint dysfunction. Dissection beyond pharyngeal musculature can lead to injury to the glossopharyngeal nerve and rarely the carotid sheath. Non-traumatic atlantoaxial subluxation (Grisel syndrome) can occur secondary to any inflammatory process in the neck.

Bleeding

Bleeding after tonsillectomy can be primary (within 24 hours after the operation) or secondary (after 24 hours until 2 weeks). The NPTA reported that the readmission rate for bleeding was 4.57%, with 1.44% requiring return to theatre. The most likely explanation for secondary bleeding is infection with *Streptococcus* in the granulating tonsil bed. Treatment depends on the severity and potential cause of the bleed. Antibiotics are advised for secondary bleeding. Severe primary or secondary bleeds need to be controlled in theatre.

Infection

The first symptoms of post-tonsillectomy infection are fever and halitosis. Treatment should be administered according to the severity.

PERI-OPERATIVE MANAGEMENT

Post-tonsillectomy morbidity can be minimized by skilled anaesthesia, analgesia, and antiemetic and steroid treatments.

Anaesthesia and analgesia

In the UK, the technique used by anaesthetists is very variable. Total intravenous anaesthesia with propofol and remifentanil leads to fast wake-up, and propofol is a helpful antiemetic agent. Using inhalational agents for intubation obviates the need for muscle relaxants and speeds up the reversal process.

Adequate analgesia is important in the immediate post-operative period. Narcotics have a potent emetic effect and should be used with caution. Paracetamol is the drug of choice as it is safe and efficacious. Non-steroidal anti-inflammatory drugs (NSAIDs) have been shown to cause significantly less post-operative nausea and vomiting than narcotics. Also concerns that effect of these drugs on platelet adhesion might increase bleeding from the tonsil bed have been unfounded. Recent guidelines have suggested that codeine should not be used in children after tonsillectomy. Also aspirin should not be used in children because of the risk of Reye syndrome.[47] Studies have reported on injecting long- and short-acting local anaesthetic pre- or post-operatively into the tonsil beds. There is no current evidence to suggest any significant benefit from the use of these techniques.[48]

Steroid treatment

Use of pre-operative glucocorticoids has gained wide acceptance. A Cochrane review has shown that a single intravenous dose of dexamethasone was an effective and relatively safe treatment for reducing morbidity from paediatric tonsillectomy.[49] Some more recent studies have confirmed that a single dose of dexamethasone at induction reduces early incidence of nausea, vomiting and level of pain post-operatively.[50]

Post-op antibiotics

Using antibiotics prophylactically after tonsillectomy has been looked at in various studies.[51] A Cochrane review of these studies published in 2012 advocated against routine use of antibiotics after tonsillectomy.[52]

Day-case surgery

Tonsillectomy as a day-case procedure is gaining popularity. The main reasons for patients to stay in overnight are the risk of bleeding and associated morbidity from pain and vomiting. Day-case tonsillectomy in children has been demonstrated by numerous studies to be a safe alternative to surgery as an inpatient.[53, 54] Recently a study has demonstrated safety of adenotonsillectomy as a day-case procedure for children with mild obstructive sleep apnoea in a tertiary unit.[55]

BEST CLINICAL PRACTICE

- ✓ In acute tonsillitis clinical diagnosis alone should not be relied upon in distinguishing between a bacterial and a viral aetiology.
- ✓ Both throat swab culture and RAT are of questionable value in guiding prescription of antibiotics for sore throat.
- ✓ Widespread indiscriminate antibiotic prescription promotes the genesis of resistant organisms, allergy and anaphylaxis. There is no justification for routine use of antibiotics in children with sore throat. [Grade A]
- ✓ In those patients in whom the illness shows no sign of improvement within 48–72 hours or in whom there is clinical concern because of the severity of symptoms, antibiotic therapy is appropriate and the drug of choice remains benzylpenicillin. A 7-day course is usually adequate.
- ✓ A single dose of dexamethasone as adjuvant therapy reduces pain in acute pharyngotonsillitis.
- ✓ Aspiration using a wide-bore needle and syringe, together with antibiotic therapy, is now the management of choice for quinsy. As a significant proportion of peritonsillar abscesses grow anaerobes, metronidazole should be considered.
- ✓ Treatment of both parapharyngeal and retropharyngeal abscess is initially high-dose antibiotic therapy. When pus formation is suspected, incision and drainage under general anaesthesia, with the airway protected by intubation by a skilled and experienced anaesthetist is recommended.
- ✓ Ampicillin must be avoided in infectious mononucleosis as patients may suffer a severe rash in consequence.
- ✓ Systemic glucocorticoids are of value in infectious mononucleosis where there is extreme swelling of the tonsils with impending airway compromise.
- ✓ 'Cold steel' dissection tonsillectomy is widely available and associated with the lowest post-operative haemorrhage rates in the hands of most surgeons.
- ✓ Adequate analgesia is essential in the post-operative care of children following tonsillectomy.
- ✓ There is now a sufficient body of evidence supporting the use of peri-operative glucocorticoids to justify considering their use as routine. [Grade A]
- ✓ In secondary haemorrhage, surgery is rarely needed. Bleeding usually settles with antibiotic therapy alone.
- ✓ Continuing audit is essential; surgeons should familiarize themselves with the findings and recommendations of the NPTA.

FUTURE RESEARCH

- ➤ The role of the tonsil in the development of immunity needs to be more fully understood.
- ➤ Data to shed light on the natural history of recurrent tonsillitis and define any subgroups in which natural resolution of recurrent symptoms is likely to happen would be helpful.
- ➤ The precise place and value of antibiotic therapy is still not fully defined. Robust randomized controlled trials of antibiotic therapy versus placebo in sore throat/tonsillitis, both in the acute single episode situation and in recurrent tonsillitis, are required. The results should be applicable to everyday practice.
- ➤ High-quality randomized controlled trials of tonsillectomy versus standardized conservative management are essential to define the optimal management of recurrent tonsillitis. The trials need to consider outcomes other than reduction in number of episodes of tonsillitis.
- ➤ The morbidity of tonsillectomy remains significant. The optimal strategy for control of pain and emesis post-tonsillectomy still requires to be defined. The use of newer antiemetic agents and peri-operative glucocorticoids seems set to increase.
- ➤ The possibility that tonsillotomy, for instance by Coblation®, could be associated with better post-operative recovery than tonsillectomy is currently being investigated. With less tissue trauma, specifically to the muscle, recovery may be quicker. Given the great potential benefits, the key question that needs to be answered is how much of the tonsil to remove to keep the same effectiveness as tonsillectomy, and also if the bleed rate is truly less. If bleed rates are reduced, this could well represent a significant step forward in the continuing evolution of tonsil surgery.

KEY POINTS

- Acute tonsillitis is common and self-limiting.
- Complications are rare.
- Treatment is largely symptomatic with an emphasis on analgesia and rehydration.
- Antimicrobial therapy has a small but measurable effect on outcome.
- The tonsil rarely may be the site of presentation of lymphoma or malignant disease.
- Tonsillectomy is one of the most commonly performed surgical procedures in the developed world.
- The evidence base for current practice is poor.
- Tonsillectomy rates vary considerably in different populations. These variations are not accounted for by variations in disease prevalence.
- Improvements following surgery are particularly small in less severely affected children. The morbidity of surgery usually outweighs any potential benefit in this group.
- There is no evidence that the benefits of tonsillectomy for recurrent sore throat are prolonged beyond 2 years.

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CHAPTER 39

SALIVARY GLANDS

Neil Bateman and Rachael Lawrence

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the following keywords: saliva, salivary, parotid, submandibular, sialendoscopy, parotitis and sialadenitis, supplemented by articles from the author's own library.

INTRODUCTION

Diseases of the salivary glands are uncommon in children. Many are similar to those pathologies occurring in adults but some present mainly in children and form the focus of this chapter. The surgical management of these conditions requires knowledge of the anatomy and experience of surgical techniques in children.

CONGENITAL ABNORMALITIES

Salivary gland aplasia

Aplasia or agenesis of the salivary glands is very rare but well recognized.[1] Some or all of the glands may be affected; children present with the effects of xerostomia such as dental caries, fissuring of the lips and oral ulceration. The diagnosis can usually be made with imaging in the form of ultrasound or MRI, augmented with radioisotope scanning if necessary. Lacrimo-auriculo-dento-digital (LADD) syndrome is a rare genetic disorder characterized by abnormalities in the lacrimal apparatus, dentition and digits. Patients may have no salivary glands.

The management of xerostomia in these cases is supportive and symptomatic, with artificial saliva and meticulous dental care.

Congenital salivary cysts

These present more commonly in the parotid gland and most often as a mass within the gland which is confirmed as cystic with ultrasound imaging. Distinguishing between a congenital salivary cyst and a branchial anomaly (see Chapter 41, Cysts and sinuses of the head and neck) may be difficult but the treatment is similar in both conditions. Treatment options include aspiration, sclerotherapy and surgical excision.

Congenital ductal abnormalities

Duplicate or imperforate ducts are rare. They are diagnosed by sialography or MR sialography. They may cause problems associated but ductal obstruction and stasis of saliva. If they are symptomatic, duct 'marsupialization' is the preferred treatment.

Ectopic salivary tissue

Ectopic salivary tissue may be found in the neck, the mandible and cervical lymph nodes and can cause discharging sinuses in these areas. The distinction between these lesions and branchial cleft sinuses can be difficult and in many cases the primary pathology is a first branchial cleft anomaly. The treatment is the same for

both conditions: surgical excision with complete preservation of the facial nerve.

Cystic fibrosis

Like other exocrine mucus-secreting glands, salivary glands are affected by the autosomal recessive disease cystic fibrosis. Abnormal mucus produced by the glands obstructs their ducts and causes progressive damage to the related parenchyma. The parotid gland, which produces mainly serous secretion, is less affected than the submandibular gland.[2]

ACQUIRED DISEASES

Mucous extravasation cysts

These mucocoeles are relatively common and usually caused by trauma that tears the duct of a minor salivary gland allowing mucus to escape into the surrounding tissues. The commonest site is the lower lip but these cysts are sometimes found in buccal mucosa or in the floor of the mouth. They present as soft, dome-shaped, swellings with a bluish hue. They are rarely more than a centimetre in diameter. Mucous extravasation cysts inevitably require excision as they do not resolve spontaneously.[2]

Ranula

A ranula is a fluid-filled lesion arising from the floor of the mouth. It is an extravasation pseudocyst and can be classified into two types: the much commoner simple or intraoral ranula, and the 'plunging' cervical type. A simple ranula is localized to the floor of the mouth. In the plunging type, extravasation of mucus occurs beyond the confines of the floor of the mouth and the mucus collection is therefore in the infra-mylohyoid compartment of the neck, with or without a clinically apparent intraoral collection.

AETIOLOGY

They may be congenital but are more frequently acquired as a result of obstruction to one of the sublingual salivary glands or ducts. This obstruction may be spontaneous but is sometimes due to trauma to the sublingual gland duct, following procedures on the floor of the mouth.

PRESENTATION

A ranula presents clinically as a smooth swelling in the floor of the mouth with a bluish translucent appearance. If of sufficient size, elevation of the tongue may occur with subsequent interference with swallowing, speech, mastication or respiration.[3] A plunging ranula may appear as a swelling in the neck. It can be difficult clinically to differentiate a plunging ranula from a lymphatic malformation. However, histologically a ranula is contained by loose connective tissue whereas a lymphatic malformation has a simple epithelial lining.

INVESTIGATIONS

Imaging is unnecessary for confirming the clinical diagnosis of a simple intraoral ranula.[4] However, if there is a history of previous surgery, if the ranula has a cervical component or of if the diagnosis is uncertain clinically, then MRI is preferred.[5–7]

TREATMENT

Simple aspiration or drainage of a ranula results in a high recurrence rate. Marsupialization of a plunging ranula is inadequate with a recurrence rate of 80%.[8] Both intraoral and plunging ranulas should be excised together with the sublingual gland as excision of the gland results in a low rate of recurrence.[9, 10] A retrospective analysis of 65 patients with a diagnosis of ranula showed that treatments which included complete sublingual gland excision were associated with the lowest recurrence rate (3.6%) and that a statistically significant difference was observed in the recurrence rate between complete sublingual gland excision and ranula excision alone.[10] Laser excision is reported as an alternative treatment for intraoral ranula, with reported low rates of recurrence and surgical complications.[11]

A transoral surgical approach is common for masses that are located intraorally and an external transcervical approach for those presenting predominantly submentally or in the neck. Care must be taken to identify and preserve the lingual nerve, which lies in close proximity.

Injection of the sclerotherapeutic agent OK-432 has been reported as a primary, non-surgical method for treating ranulas, but experience with paediatric patients is currently limited.[12, 13]

Viral parotitis ('mumps')

Mumps is the commonest disease of the salivary glands in childhood. It is a viral infection of the parotid glands, caused by a paramyxovirus, spread via droplets or contact. The incubation period is 2–3 weeks. The characteristic clinical course is a prodromal illness of malaise and pyrexia followed by painful swelling of the parotid glands, typically bilaterally. Less commonly, other salivary glands may be involved. Asymptomatic infection can occur in 20% of infected individuals. The diagnosis is made clinically, although it can be confirmed serologically. There is no specific treatment for this usually self-limiting condition and symptomatic management is usually all that is required.

The disease has become less common in the UK following vaccination which is given as part of the MMR (mumps, measles, rubella) vaccine at 12 months with a preschool booster.

Post-pubertal males may develop a painful orchitis with an associated risk of subfertility. Other potentially serious complications are sensorineural hearing loss, encephalitis and pancreatitis.

Human immunodeficiency virus (HIV)

The salivary glands, most commonly the parotid, may be involved in HIV infection. Parotid enlargement,

which may be painful or painless, should raise suspicions. The British HIV Association recommends considering HIV testing in all children with chronic parotitis.[14] There may be associated xerostomia. Multicystic change in the parotid glands results from lymphepithelial lesions termed benign lymphoepithelial lesions (BLEL) or benign lymphoepithelial cysts (BLEC). These are thought to result from localized ductal ectasia and/or ductal obstruction from lymphoid tissue hyperplasia.

The clinical picture is similar to Sjögren's syndrome although patients with HIV salivary gland disease do not have anti-Ro or anti-La antibodies. Imaging may show cystic disease or lymphadenopathy.

The management of HIV salivary disease is largely symptomatic and supportive. There is some evidence that it is controlled with anti-retroviral treatment.[15] Otherwise, cyst aspiration and sclerotherapy, surgical excision and the supportive treatment of any patient with xerostomia are the mainstays of treatment. Localized radiotherapy has some role to play in adults but is likely to have limited application in children.

For more information about HIV, see Vol 1, Chapter 23.

Acute parotitis of infancy

Acute pyogenic infection of the parotid gland in infancy presents with a painful enlargement of the gland with erythema of the overlying skin. The child is typically unwell, pyrexial and reluctant to feed. The commonest organisms are *Staphylococcus aureus, Streptococcus pyogenes* and anaerobes.

Ultrasound is useful to distinguish inflammatory change from a collection of pus. Treatment consists of intravenous antibiotics, adequate hydration and drainage of any collection. Incision and drainage should be performed with caution because of the superficial position of the facial nerve in infants. Needle aspiration in many cases is a safer option (**Figure 39.1**).

Acute suppurative sialadenitis

Acute bacterial sialadenitis may also occur in older children and is associated with salivary stasis. Obstructive causes include salivary stones, which are considered below. Where there is no obstruction to salivary flow, children with comorbidities (cystic fibrosis, malignancy, HIV and cerebral palsy) are more commonly affected.[16] The typical causative organisms are *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus pneumoniae* and anaerobes. Children usually present with fever, pain, gland swelling and tenderness. Pus may be visible at the duct orifice of the affected gland. Treatment consists of broad-spectrum intravenous antibiotics, hydration and sialogogues.

Bacterial infection may lead to abscess formation which is diagnosed on imaging. Ultrasound is usually adequate to make the diagnosis. Drainage of any abscess is necessary but needs to take into account the superficial nature of the facial nerve in children.

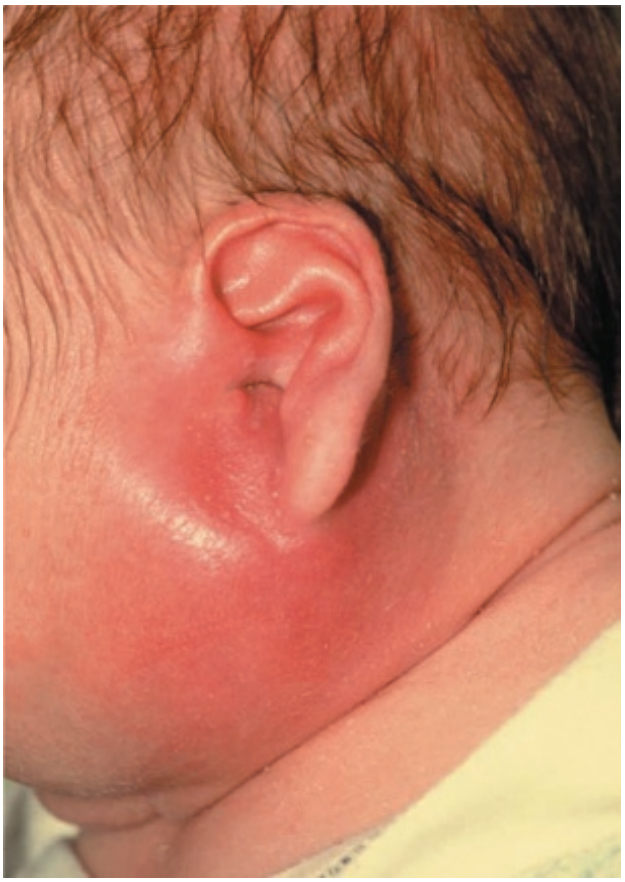

Figure 39.1 Acute suppurative parotitis in a baby aged 3 weeks.

Juvenile recurrent parotitis

Juvenile recurrent parotitis (JRP) is characterized by acute intermittent painful swelling of one or both parotid glands often accompanied by overlying cutaneous erythema, malaise and pyrexia. The usual age of onset is between 3 and 6 years. The condition is most commonly unilateral although may occur bilaterally. The swelling often settles within 2–3 days but may last up to 2 weeks.

Acute attacks are treated symptomatically with analgesia and anti-inflammatory drugs. Antibiotics are often used empirically although their use is controversial in the absence of obvious clinical infection (such as purulent discharge from the duct).

The diagnosis is made clinically, often after more than one episode has occurred. Sialography may show appearances of sialectasis but is often difficult to perform in children and unnecessary to establish a diagnosis. Ultrasound, in the correct hands, should confirm the absence of any mass lesion in the glands. In the absence of a mass apparent clinically or on ultrasound, no further imaging is warranted.

Many authors report resolution of the condition spontaneously, usually around puberty, and this appears to be the case in the majority of patients.[18] For this reason, and to control the effects on life quality of recurrent attacks, recent efforts have focused on reducing the frequency of attacks. There has been considerable interest in the use

of therapeutic sialendoscopy in this area with a number of authors reporting long-term resolution with its use.[19, 20]

Sjögren's syndrome

Sjögren's syndrome is a multisystem autoimmune disorder. The salivary and lacrimal glands are characteristically affected. When Sjögren's syndrome occurs in children and adolescents, swelling of the glands predominates over xerostomia and ocular symptoms, and systemic manifestations are less common.[21, 22] When the diagnosis is suspected, rheumatoid factor, antinuclear antibodies, and anti-Ro and anti-La antibodies should be measured. The diagnostic criteria for adults have a lower sensitivity for diagnosing the condition in children and a multidisciplinary approach to both diagnosis and treatment is recommended.

GRANULOMATOUS CONDITIONS

These are disorders of the intraparotid nodes rather than of the gland parenchyma. The salivary glands are composed of parenchymal tissue (i.e. salivary gland acini and ducts) and a surrounding stroma. Some of the stroma is lymphoid tissue, and the proportion of lymphoid tissue is much higher in children than in adults. Some cases of 'sialomegaly' in children – particularly in the parotid – are caused by lymphoid rather than parenchymal pathology. Non-tuberculous mycobacterial infection (NTM) and less frequently cat-scratch disease (*Bartonella henselae* or *B. quintana*) may present in this way. Non-tuberculous mycobacterium results from infection with a variety of species of mycobacterium including *Mycobacterium avium-intercellulare, M. scrofulaceum, M. kansasii, M. haemophilum* and *M. fortuitum*. The presentation, investigation and management of these conditions are considered in Chapter 37, Cervicofacial infections.

Sarcoidosis

Sarcoidosis is rare in children. When the parotid gland is involved, this can take the form of gland swelling, often as part of Heerfordt syndrome (or uveoparotid fever). Facial palsy can also occur. Non-caseating granulomas may be identified in minor salivary glands on sublabial biopsy and this was used as a diagnostic test, but it is now rarely needed. Cervical tuberculosis (caseating granuloma) can present in the parotid lymph nodes. Treatment is medical (see Chapter 37, Cervicofacial infections).

Salivary gland stones

The presentation, investigation and management of salivary stones in children is similar to that in adults, but salivary stones are uncommon in children. They are more common in the submandibular than the parotid glands. Children are less likely to tolerate local anaesthesia and may require a general anaesthetic if surgery (e.g. sialendoscopy) is considered.[23, 24]

SALIVARY GLAND TUMOURS

Salivary gland tumours are extremely rare in children. They can be classified as:

1. vasoformative tumours (most commonly haemangioma)
2. neoplasms of salivary gland tissue origin
3. proliferative disorders of the perisalivary lymphoid tissue (lymphoma).

Vasoformative tumours

A retrospective review of 324 consecutive cases of paediatric salivary gland masses showed 192 to be haemangiomas (59.2%), 89 to be lymphangiomas (27.5%) and the remaining 43 (13.3%) to be other solid masses.[25]

In 1982 Mulliken and Glowacki[26] created a classification system of vascular anomalies, dividing them into tumours and malformations. This classification system was recently expanded at the 2014 International Society for the Study of Vascular Anomalies (ISSVA) workshop.[27] The distinction between neoplasm and vascular anomaly is highly important when considering the management of these lesions.

Haemangiomas are reported to account for almost 60% of salivary tumours in children. Eighty per cent occur in the parotid gland, with involvement of the submandibular region in 18% of cases, while 2% are associated with the minor salivary glands.[28] Although not truly salivary in origin, the management of vascular anomalies requires an extensive knowledge of salivary gland anatomy.

PRESENTATION

The diagnosis of a haemangioma is primarily based on history and clinical examination. Haemangiomas are typically not present at but grow rapidly after birth. They exhibit rapid growth initially. This period of growth slows and stops after 9–12 months and a subsequent process of involution then follows over the next 3–5 years. Lesions have varying degrees of compressibility according to the extent of their underlying fibro-fatty architecture.[29] Skin involvement makes the diagnosis obvious although the absence of skin lesions does not exclude the diagnosis as the tumour may be deeply placed and lie within the parotid gland. Where the growth pattern exhibited by the lesion is not consistent with the pattern typical of a haemangioma, consideration should be given to further investigation including histological examination.

INVESTIGATIONS

The diagnosis of a haemangioma is a usually clinical. However, if lesions are more complex, where there is diagnostic uncertainty or if surgical intervention is being considered, additional investigations may be

helpful in determining the extent of involvement. The use of ultrasound (colour-flow Doppler) is useful for diagnosing vascular malformations in addition to identifying cystic and semisolid masses in the major salivary glands. The use of CT and MRI may also help to delineate the extent and depth of surrounding tissue involvement.[29]

TREATMENT

Almost all haemangiomas will involute and surgery should be confined to management of bleeding or ulceration, or to cases where the diagnosis is in doubt.[30] Kasabach–Merritt syndrome, a consumptive coagulopathy, is another indication for active intervention.

If the haemangioma is of such a size or position as to be life-threatening, treatment may be required. Several treatment modalities have been described in the literature and include systemic and intralesional steroids and more recently propranolol. However, systemic steroid therapy is associated with side effects and rebound growth is often seen after cessation of therapy. Intralesional steroids have fewer side effects but are effective only in actively proliferating lesions.[31]

The incidental observation of a clear response of haemangiomata to beta-blockers was published in 2008.[32] This revolutionized the therapeutic approach for infantile haemangiomas. Propranolol has been shown to significantly reduce the size of parotid haemangiomas with minor side effects[33] and has become the first-line treatment of choice where active therapy is required. Sclerotherapy for expanding parotid lesions has been shown to be successful, and a recent study that combined sclerotherapy and propranolol for the treatment of 26 infantile parotid haemangiomas demonstrated this to be a safe and effective treatment method.[34] Where active treatment is necessary and no response to propranolol is observed, embolization and/or surgical excision may be necessary.

Pulsed-dye laser treatment may be used for residual superficial skin discolouration, however it does not penetrate deeply enough to treat a haemangioma within the parotid gland. Previously, systemic interferon was utilized for its anti-angiogenic properties, but significant side effects were reported so it is no longer recommended as a treatment in children with haemangiomas.[31]

Salivary gland neoplasms

Salivary gland neoplasms are uncommon in children comprising approximately 1% of all paediatric tumours and less than 10% of all paediatric head and neck tumours. Approximately 5% of salivary tumours occur in children. Over 95% are epithelial with a minor group being mesenchymal in origin. The most common benign neoplasm is a pleomorphic adenoma; the most frequent malignant epithelial salivary gland neoplasm is a mucoepidermoid carcinoma. Rhabdomyosarcoma is the most common malignant neoplasm of mesenchymal origin.[29]

PRESENTATION

The most common presentation for a tumour affecting the major salivary glands is a painless, slowly growing mass. Pain is rarely a dominant symptom, whether benign or malignant.[25] The parotid gland is the most commonly affected salivary gland and is involved in over 85% of all reported paediatric salivary gland tumours.[29, 35–37] Facial nerve palsy is rare but usually indicates malignancy. Evidence of cervical lymphatic metastasis is uncommon, reported in 3.5% of patients at presentation.[38] Although uncommon, tumours affecting the minor salivary glands do occur, with the majority located in the oral cavity.[29] They most commonly present as a lump or submucosal nodule that is frequently non-ulcerated and firm to palpation, with pink or flesh-coloured surfaces. Others are described as being fluctuant, with colour alterations ranging from a light blue hue to purple.[29, 39]

INVESTIGATIONS

All cases of salivary gland neoplasms in children should be treated as potentially malignant. As previously mentioned, the use of ultrasound is very useful for identifying cystic and semi-solid masses in the major salivary glands and is easy to perform, non-invasive and generally well tolerated by children.[29] However, limitations include an inability to establish the extent of a lesion (i.e. extension into the deep lobe of the parotid gland) and to accurately differentiate between benign and malignant tumours.

CT imaging is unhelpful in distinguishing benign and malignant disease. However, certain MRI features, such as T2 hypointensity, restricted diffusion, ill-defined borders, and focal necrosis, although not specific, should raise concerns about malignancy.[40]

Fine-needle aspiration cytology (FNAC), while well established and routine in adult practice, is controversial in children. Younger children often require general anaesthesia for this procedure and assessment of salivary gland histology is reported to be notoriously difficult. Occasionally, however, the use of a diagnostic fine-needle core biopsy may be considered under certain circumstances, such as in cases of suspected lymphoma where major and unnecessary surgery could be avoided.[29]

Benign salivary gland tumours

PATHOLOGY

Pleomorphic salivary adenomas (PSA) are the most commonly encountered benign tumours and account for approximately 30% of all paediatric salivary neoplasms. Presentation is commonly between the ages of 8 and 18 years and the majority occur within the parotid gland. However, they may also occur in the submandibular gland and minor salivary glands.[41]

TREATMENT

Although a benign tumour, there is a risk of recurrence up to 30 years following initial presentation, and a lifetime

risk of malignant degeneration of between 2% and 25%. Treatment of these benign tumours consists of complete surgical resection[41, 42] by either superficial or complete parotidectomy, dependent on the location of the tumour. Surgery must aim for a complete resection of the tumour with a surrounding cuff of normal salivary tissue and complete facial nerve preservation. Submandibular gland resection is indicated for tumours in the submandibular gland, with complete local resection for the minor salivary glands. Incomplete resection is the cause of recurrences. This is particularly problematic in children, since adjuvant radiotherapy cannot be used safely in children to salvage an unsatisfactory surgical procedure.

Malignant salivary gland tumours

PATHOLOGY

Malignancies of the salivary glands in children and adolescents are rare, with an estimated annual incidence of 0.08 per 100 000.[43] Most malignant salivary gland tumours present in the older child, at an average age of 13.5 years.[38] In comparison with adults, children with salivary neoplasms are more likely to have malignant disease.[29, 35–37]

The parotid gland is the most frequent site for malignant salivary tumours (82%), followed by the submandibular gland (7%), minor salivary glands (11%) and sublingual gland (less than 1%).[29, 38] Mucoepidermoid carcinomas are the malignant tumours most frequently described in childhood followed by acinic cell carcinomas and adenoid cystic carcinomas. These three cancers account for 80–90% of all malignant salivary gland tumours in children and adolescents. Adenocarcinomas, basal cell carcinomas and squamous cell carcinomas of the salivary glands are less common.[28]

TREATMENT

The rarity of salivary tumours in children is such that treatment should only be in specialist centres. Management will involve a multidisciplinary approach with input from a paediatric oncologist. These children and their families are best treated in a designated centre where the whole range of support services for children with cancer is available.

Clinical stage and histologic grade are the main prognostic factors. As with benign tumours, complete excision (superficial or total parotidectomy) with preservation of facial nerve is the treatment of choice. It is, however, vital to counsel the child and parents carefully prior to operation regarding the possible need for facial nerve sacrifice. The facial nerve is smaller and courses more superficially within the parotid in children than in adults. Neck dissection should be considered when there is clinical evidence of regional metastasis, high TNM stage, high histologic grade, and involvement of regional nodes.[44] Radiotherapy should only be used in selected cases because of the possibility of long-term adverse effects in paediatric patients. Long-term follow-up is essential to monitor for late recurrence. The overall survival is 70–90% at 5 years, and 26% develop a recurrence.[29]

BEST CLINICAL PRACTICE

- ✓ Excision of a ranula together with the cyst wall and the sublingual gland results in a low rate of recurrence.
- ✓ HIV testing should be considered in children with otherwise unexplained salivary gland swelling.
- ✓ Bacterial infections should be treated with intravenous antibiotics and hydration. Ultrasound imaging should be used to exclude an abscess.
- ✓ Care should be taken in draining parotid abscesses in children to avoid damage to the facial nerve.
- ✓ Almost all haemangiomas will involute and surgery is rarely needed.
- ✓ Malignancies of the salivary glands in children and adolescents are rare. A solitary salivary gland neoplasm in a child, however, is more likely to be malignant when compared with an adult.
- ✓ Salivary tumours should be managed by an appropriate multidisciplinary team and surgery should be undertaken by surgeons with appropriate training and experience in paediatric head and neck surgery.

FUTURE RESEARCH

- ➤ Clinical trials are needed in the management of Juvenile Recurrent Parotitis in order to determine whether there is any benefit from medical therapies or sialendoscopy.
- ➤ It would also be helpful to have better clinical studies on the utility of investigations such as imaging and fine needle aspiration cytology for diagnosis of salivary gland tumours in children.

KEY POINTS

- Salivary gland agenesis may present late in childhood with dental caries.
- A ranula is an extravasation pseudocyst and may present intra-orally or in the neck.
- Mumps is generally a self-limiting disease but with the potential for serious complications.
- HIV salivary gland disease may mimic Sjögren's syndrome clinically and is characterized by gland swelling and xerostomia.
- Bacterial sialenitis occurs as a result of salivary stasis.
- Juvenile recurrent parotitis is a self-limiting disease which generally resolves around puberty although there is current interest in the use of sialendoscopy.
- Parotid haemangiomas present with a rapid enlargement of one parotid gland shortly after birth. The diagnosis can usually be made with a combination of clinical history and imaging.
- Salivary tumours are rare in children. The proportion of malignant tumours is greater in children than adults.
- Pleomorphic salivary adenoma is the commonest salivary gland tumour in children.

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CHAPTER 40

TUMOURS OF THE HEAD AND NECK IN CHILDHOOD

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SEARCH STRATEGY

Systematic reviews were identified using the key words: childhood cancer, head and neck, thyroid cancer, rhabdomyosarcoma, nasopharyngeal carcinoma, neuroblastoma, lymphadenopathy, Hodgkin's lymphoma, non-Hodgkin's lymphoma, sarcoma, and palliative care; these subject headings were used to search the Cochrane database of systematic reviews. Individual articles were then identified using the same search terms in Ovid Medline. A hand-search of the ensuing bibliographies completed the search.

INTRODUCTION

This chapter will focus on the epidemiology of childhood cancers of the head and neck region and the general principles of assessing and managing malignancy in children. It will then discuss the more common histological types individually. The long-term sequelae of treatment in survivors, palliative care and future developments will be addressed.

EPIDEMIOLOGY

After trauma, cancer is the most common cause of death in childhood. Approximately one-third of childhood malignancies are leukaemias, 25% are brain and spinal tumours, 15% are embryonal (neuroblastoma, retinoblastoma, Wilms' tumour and hepatoblastoma) and 11% are lymphomas. The remainder are bone and soft-tissue sarcomas and miscellaneous tumours (see 'Miscellaneous tumours' below). Up to 12% of primary childhood malignancies originate in the head and neck area and so may present to the otolaryngologist. Lymphoma is the most common diagnosis in all series, followed by thyroid and neural tumours. Sarcomas and salivary gland tumours are less common; squamous cell carcinomas are rare.[1] The distribution of histological types varies greatly depending on the age and sex of the child, with neuroblastoma the most common in infants and thyroid carcinoma the most common malignancy in adolescent females. There is a bimodal age distribution of malignancy in children. The most common age group affected is 15–18-year olds, closely followed by those under 4 years of age.[1–3] Incidence of head and neck malignancies in children increased throughout the decades leading up to the 1990s in line with a general increase in cancer diagnoses in children, but has now stabilized. In parallel, the consistent use of effective multimodality treatments, including combination chemotherapy, surgery and radiotherapy, has resulted in a significant improvement in prognosis. A study from the UK observed 5-year survival rates of 42% for diagnoses made between 1968 and 1977[4] but modern treatment strategies have transformed the outlook for children with cancer. Survival rates well in excess of 80% are now commonplace in the developed world and services are improving wordwide.[5, 6] Early recognition is therefore increasingly important.[7, 8]

Some malignancies in childhood are inherited. The underlying aetiology of the non-inherited types remains unclear but certain chemotherapeutic agents, viruses (e.g. Epstein–Barr) and irradiation are known to play

a role. Other potential carcinogens are suspected but not proven (pollution, parental exposure to toxins, electromagnetic fields).[1, 9] There is some evidence that exposure to dietary carcinogens *in utero* may lead to malignancies in early childhood.[10]

PRESENTATION AND ASSESSMENT

The most common presentation of a malignancy in the head and neck region in childhood is the asymptomatic mass. Otalgia, rhinorrhoea, otorrhoea and nasal obstruction may be present in both benign and malignant disease. More worrying symptoms would include stridor, dysphagia and haemoptysis.[11] Reactive lymphadenopathy in children is extremely common and gives rise to frequent therapeutic dilemmas. See Chapter 37, Cervicofacial infections in children.) Studies have suggested that the best predictors of malignancy in cervical lymphadenopathy are the size of the node, the number of sites involved and the age of the patient. Other concerning features would be lymphadenopathy in the supraclavicular region, an associated abnormal chest X-ray or fixed lymph nodes.[12, 13]

Examination would involve a complete assessment of the head and neck region and systemic evaluation with particular regard to the presence of lymphadenopathy elsewhere and the presence or absence of abdominal masses. Flexible nasendoscopy is possible in many children (**Figure 40.1**). Imaging with the help of a paediatric radiologist can often obviate the need for biopsy. However, full assessment of a mass may require examination under anaesthetic with biopsy.

Figure 40.1 Flexible nasendoscopy under local anaesthetic in the clinic setting.

BIOPSY

Fine-needle aspirate (FNA), sometimes referred to as aspiration biopsy cytology (ABC), has a more limited role to play in the child than the adult. Young patients may simply not tolerate this method of biopsy. With particular regard to cervical lymphadenopathy, the most likely neoplastic diagnosis is lymphoma and at the present time it is recognized that excision biopsy is the best method of confirming and typing this histologically.[14, 15] FNA, often under ultrasound control, can be useful in the assessment of thyroid and salivary gland lesions and these tumours often present in older children who may tolerate such intervention.[16]

The biopsy specimen should be sent to the lab fresh to enable molecular in addition to histopathological studies to be undertaken.

IMAGING

Ultrasonography, CT and MR scanning can all have their part to play in further assessment. Imaging of the neck is more accurate than clinical examination in detecting lymphadenopathy. CT and MR scanning may require a general anaesthetic in a younger child and it is helpful to discuss the available imaging options with a paediatric radiologist prior to proceeding, to avoid unnecessary and additional anaesthetics. Positron emission tomography (PET) scanning is also becoming increasingly used in the assessment of neoplastic lesions in the head and neck in children, but is not always readily available.[11]

THE CHILD WITH CANCER

The history and subsequent investigations of a child presenting with a suspicious lesion of the head and neck region must be tailored to the age and maturity of the child. In most situations, when the child is old enough, he or she should be included in any discussion about investigations and treatment and should also be involved in consent for any procedures required.

The diagnosis of cancer in a child has a tremendous impact not only on the patient, but also on parents, siblings, other family members and friends. Immediate involvement of a specialist paediatric multidisciplinary oncology team is mandatory. An open and realistic approach should include an explanation of what to expect from the investigations and treatment, the side effects and some idea of prognosis. This is vital in maintaining trusting relationships with the child and his or her family, in reducing uncertainty, preventing inappropriate hope and allowing proportionate adjustment.

Parents may feel guilty that they waited too long before seeking medical advice. They may be concerned that they

have, in some way, caused their child's cancer. They can also feel guilty about making their child go through a series of invasive investigations and radical treatments. This can put an immense strain on the parents' relationship with each other and with other family members and friends, not least the child involved. Also, siblings of the affected child may resent the additional time and attention that their sick brother or sister receives. Support services are therefore vital in reassuring and supporting all the individuals concerned.

The amount of information that any child will require regarding their illness depends to some extent on the age and maturity of that individual. Most children aged 6 years or more (and some more mature younger children) need to know their illness has a name and what that name is. All children require an explanation of the procedures to be performed and reassurance that any intervention is not a 'punishment'. In children between the ages of 6 and 11, these procedures and side effects of treatment may provoke much more anxiety than the illness itself. For example, loss of hair or a limb seems much more real and distressing than the prospect of death. Alterations in physical appearance can cause great insecurity in a child or adolescent, resulting in isolation and poor self-esteem. Children aged around 11 and over will have fears surrounding the diagnosis and its prognostic implications in addition to the above. Children should be encouraged to talk about their feelings or, if they are too young, they can express themselves in drawings or play.[15]

ONCOLOGY SERVICES

The importance of centralization of paediatric cancer services is widely recognized.[7] This enables care to be provided by highly trained and specialist paediatric oncologists and allied staff, and facilitates the progress of research. There are now 20 centres within the United Kingdom Children's Cancer and Leukaemia Group – CCLG.[17] Working in conjunction with the medical staff are social workers, nurses, dieticians, psychologists and other healthcare professionals in order to provide comprehensive support for children and their families. The emphasis on centralization of paediatric oncology services, the sharing of data and the establishment of international working groups has resulted in the publication of a number of treatment protocols that are widely used in the management of children with cancer.[17]

The practicalities of investigating and treating children with cancer provide some particular challenges. Venous access for blood sampling and to administer chemotherapeutic agents can be difficult, and indwelling venous catheters are usually inserted at an early stage. Radiotherapy may require general anaesthesia in younger patients to ensure that the child remains still during irradiation. Other interventions (e.g. lumbar puncture and intrathecal injection) may also require general anaesthesia. Children tolerate the immediate side effects of chemotherapy and radiotherapy much better than adults but the long-term sequelae of such interventions can have a very significant effect on the health of childhood cancer survivors (see 'Long-term sequelae of treatment' below).

THE MORE COMMON CHILDHOOD CANCERS

Lymphoma

Lymphomas are malignant neoplasms of the lymphoreticular system. Most lymphomas of the head and neck region in the paediatric age group present with enlarged cervical lymph nodes.

Cervical lymphadenopathy in childhood is common and although the huge majority of cases will be due to reactive hyperplasia, it may be necessary to exclude malignancy. Lymph nodes in the neck larger than 2 cm are unusual in childhood and systemic symptoms such as weight loss, fever and organomegaly are usually indicators of serious pathology.[12] FNA has a limited role and excision biopsy will provide the diagnosis.[16, 18]

Hodgkin lymphoma

This is distinguished morphologically by the presence of Reed Sternberg cells which are large and multinucleated with abundant cytoplasm. It has the propensity to involve the lower cervical, supraclavicular and mediastinal lymph node groups. There were several classifications for lymphomas but the most widely recognized now is the 'World Health Organisation / Revised European American lymphoma' system (WHO/REAL).[19, 20]

Nodular Lymphocyte-predominant Hodgkin Lymphoma (nLPHD) is now recognized as a separate entity. Classic Hodgkin lymphoma (HL) is further subdivided into 4 types: (1) Nodular sclerosis classic HL, (2) Lymphocyte-rich classic HL, (3) Mixed cellularity classic HL, and (4) Lymphocyte-depleted classic HL. The commonest type in children and young adults (0–24 yrs) is nodular sclerosing classic HL. There is an association with previous infection with Epstein–Barr virus.[21]

Staging of disease is based on the Cotswolds modified Ann Arbor system (see **Table 40.1**)

Hodgkin lymphoma most commonly presents with lymphadenopathy in the neck and two-thirds of all children will have mediastinal lymphadenopathy at presentation. It rarely occurs under the age of 5 years and there is a male predominance. 'Constitutional' symptoms such as fever, night sweats and weight loss are present in 25–30% and this is associated with a more aggressive disease and a poorer prognosis.[11]

Following careful examination and biopsy confirmation, the diagnostic workup of a child with Hodgkin disease (following thorough examination and biopsy confirmation) would include a chest X-ray, routine blood tests (although abnormal results are usually nonspecific) and staging scans (CT chest and MRI abdomen). Recently, PET scanning has become a routine part of staging and of assessing effectiveness of treatment. There is no longer a place for staging laparotomies. Bone marrow biopsy and bone scan are

TABLE 40.1 Stages of Hodgkin lymphoma according to the Cotswolds revision of the Ann Arbor staging system

Stage I	Involvement of a single independent lymph node region or lymph node structure
Stage II	Involvement of 2 or more lymph node regions on the same side of the diaphragm
Stage III	Involvement of lymph node regions or lymph node structures on both sides of the diaphragm
Stage IV	Involvement of extranodal sites beyond 'E'-sites
Annotations	
A	No B symptoms
B	At least one of the following systemic symptoms • Inexplicable weight loss of more than 10% within the last 6 months • Unexplained persisting or recurrent temperature above 38 °C • Drenching night sweats
E	Involvement of a single extranodal site contiguous or proximal to known nodal site.

only indicated in children with more advanced disease.[22] (see Volume 1, Chapter 25, Hamato-oncology.)

Treatment depends on the age and physical maturity of the patient, the disease stage and bulk and the potential treatment sequelae. In the paediatric population, the trend is to treat in multimodality fashion so as to reduce the morbidity and mortality associated with high doses of chemotherapy or radiation therapy needed for single-modality treatment. Disease-free survival is over 90% in many series.[23] Those children with intermediate risk of disease (constitutional symptoms, bulky disease or spleen involvement) may require an increased number of cycles of chemotherapy and, in some cases, an increased dose or volume of radiation therapy. Modern chemotherapy treatment protocols with newer agents such as dacarbazine have reduced the risks of sequelae such as subfertility. Radiotherapy is far less frequently needed, also helping to reduce the risk of later complications. Haematopoetic stem cell transplantation can be indicated in some children who relapse following more conventional treatment but the risk of transplant-associated morbidity and mortality is not insignificant.[21]

Non-Hodgkin lymphoma

Approximately 60% of paediatric lymphomas are non-Hodgkin lymphomas (NHL). There is a male predominance. The low-grade, relatively indolent NHLs seen in adults are exceedingly rare in children. Paediatric NHLs tend to be aggressive with a propensity for widespread dissemination and half of these are small cell lymphomas (Burkitt and Burkitt-like). The classification of NHL is confusing and controversial but paediatric NHLs are usually divided into three main histological categories. These are lymphoblastic lymphoma (predominantly of T-cell origin), small non-cleaved cell lymphoma (Burkitt and non-Burkitt subtype of B-cell origin) and large cell lymphoma (B- or T-cell origin).[24] The Revised European American Lymphoma (REAL) classification is used in paediatric NHL and is a useful guide to management and prognosis of NHL.[19]

The relative frequency and incidence of NHL varies quite markedly from country to country. In equatorial Africa, Burkitt lymphoma accounts for approximately 50% of childhood cancers. In Europe and the US, approximately one-third are lymphoblastic lymphomas, one-third are Burkitt and Burkitt-like lymphoma and the rest are predominantly large cell lymphoma. In some parts of the world, an extremely high number of these tumours are positive for Epstein–Barr virus (EBV), e.g. parts of Africa. In contrast, the percentage of tumours positive for EBV in the US is much smaller. There is an increased incidence of NHL in association with immunosuppression and congenital and acquired immunodeficiency.[24]

Many childhood NHLs are rapidly growing neoplasms and a significant number of children will have widespread disease at the time of diagnosis, which may involve the bone marrow, central nervous system or both. Involvement of extranodal sites, especially Waldeyer's ring, can be a particular challenge in children. Apparent activity in Waldeyer's ring on imaging may not always represent disease, hence the need for caution during disease staging. Lymphadenopathy occurs in 50–80% of all patients and 45% have cervical lymphadenopathy at the time of presentation. Bone marrow involvement is not infrequent and the replacement of more than 25% of the bone marrow by 'blast' cells is usually assigned a diagnosis of leukaemia. Children with endemic Burkitt lymphoma frequently present with involvement of the jaw and this is particularly common in the younger age group.[24]

DIAGNOSIS AND STAGING

Because NHLs in children progress more rapidly, a speedy diagnosis is extremely important. A biopsy will provide tissue for histological confirmation and surgery then has little further role to play. Staging investigations will follow and will include relevant blood tests (full blood count, urea and electrolytes and liver function tests) lactic dehydrogenase (LDH) is a useful marker of disease – bone marrow biopsy and cerebrospinal fluid (CSF) examination. Staging laparotomy is not advocated in patients with NHL and ultrasonography, CT (chest) and MR (abdomen) scanning are used in assessing spread.[24] FDG-PET scanning is increasingly used. The Ann Arbor staging classification can be applied to NHL (see Volume 1, Chapter 25, Haemato-oncology) although a new staging system for

TABLE 40.2 The International Pediatric Non-Hodgkin Lymphoma Staging System

Stage I	Single tumour with exclusion of mediastinum and abdomen.
Stage II	Single extranodal tumour with regional node involvement, two or more nodal areas on the same side of the diaphragm, or primary gastrointestinal tract tumour with or without the involvement of associated mesenteric nodes, that is completely resectable.
Stage III	Two or more extranodal tumours above and/or below the diaphragm, two or more nodal areas above and below the diaphragm, intra-abdominal and retroperitoneal disease, including liver, spleen, kidney, and/or ovary localizations, regardless of degree of resection, with or without involvement of associated mesenteric nodes that is completely resectable, any paraspinal or epidural tumour, and a single bone lesion with concomitant involvement of extranodal and/or non-regional nodal sites.
Stage IV	Any of the stage I—III findings with initial involvement of the central nervous system, bone marrow, or both.

paediatric NHL has recently been proposed by an international expert panel (Table 40.2).[25]

TREATMENT

The treatment of choice in childhood NHL is multiagent chemotherapy. The rapid doubling time of high-grade NHL makes it particularly chemosensitive. Chemotherapeutic regimens vary depending on the histological classification of the disease. Newer agents such as rituximab (an antibody to the B-cell marker CD20) have a role in B-cell NHL, allowing lower doses of standard chemotherapy agents to be used and thereby reducing morbidity from treatment.[26] Radiation therapy has a limited role in NHL and is generally reserved for selected anatomical sites such as the cranium where a child has overt central nervous system disease. Some children with high-grade NHL may need intrathecally administered chemotherapy.[22, 24]

PROGNOSIS

Long-term event-free survival (EFS) is excellent in lymphoblastic lymphomas. It ranges from 80% to 90% in patients with limited disease and from 65% to 80% in patients with advanced disease. In Burkitt lymphoma, where chemotherapeutic regimes are more intense and shorter, the long-term EFS ranges from 90–100% in patients with limited disease to 75–85% in patients with extensive disease. Even in patients with extensive bone marrow disease, the EFS is improving. Large cell lymphomas are more of a challenge to treat because of their biological heterogeneity and long-term EFS ranges from 50% to 70%.[22, 24]

Patients who relapse after receiving dose-intensive multiagent chemotherapy have an extremely poor prognosis. These patients are treated with high-dose chemotherapy regimes with or without bone marrow transplantation or would be candidates for newer drugs in trials.

Rhabdomyosarcoma

Rhabdomyosarcomas account for up to 60% of all sarcomas in the paediatric population and 40% occur in the head and neck region. Nearly half of these tumours occur in children under the age of 5 years.[7] The prognosis for this tumour used to be extremely poor but over the last 30 years survival rates have increased dramatically, particularly with the introduction of multimodality therapy in which surgery, multiagent chemotherapy and radiotherapy have been combined.[27]

Histologically, rhabdomyosarcomas resemble normal fetal skeletal muscle before innervation. Two types are identified and these are embryonal (80%) and alveolar (20%). The alveolar type is found in older children and is often associated with nodal spread and typically a poor prognosis[28, 29] where such tumours also harbour a chromosomal translocation that fuses two transcription factor-encoding genes together including the *FOXO1* gene.[30]

PRESENTATION

Rhabdomyosarcomas of the head and neck occur most frequently in the orbit or parameningeal sites and these include the paranasal sinuses, nose, nasopharynx and middle ear. The most common presenting symptoms are pain and swelling. Paranasal rhabdomyosarcoma may present with a gradual onset of nasal obstruction and bloody nasal discharge. Tumours within the ear may present with symptoms of bloody discharge and persistent otalgia, despite treatment. A polypoid mass may be visible in the ear canal or nasal cavity.[29] The reported incidence of lymph node involvement varies between 3% and 36%.[28] Metastases occur by both haematogenous and lymphatic spread.

ASSESSMENT

Assessment should include a thorough examination of the upper respiratory tract and head and neck region including the cranial nerves. Flexible nasoendoscopy may be employed in the clinic. An MRI scan should be performed to evaluate the primary lesion and to rule out metastatic disease (Figure 40.2). A CT scan may be a useful complementary tool, particularly in the paranasal sinuses and skull base, to determine bony erosion and it is the best method to assess the chest. Bone marrow examination should also be performed. The Inter Group Rhabdomyosarcoma Study (IRS) recommends the clinical staging shown in Table 40.3. The majority of children are stage II at the time of assessment[31] as it is rarely possible to completely excise these tumours.

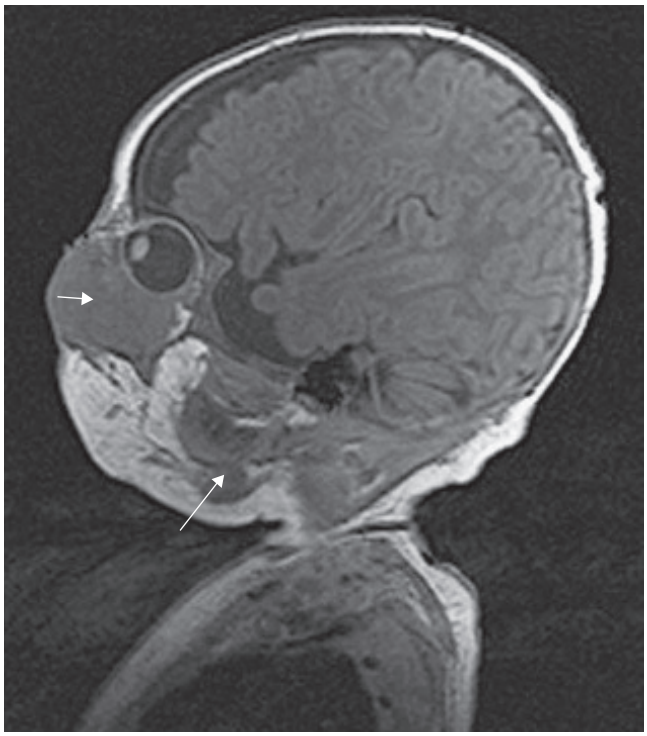

Figure 40.2 Paramedian T1-weighted MRI scan through the left orbit of a 3-month-old boy. There is a huge mass of rhabdomyosarcoma in the anterior orbit (short arrow) displacing the globe and submandibular lymphadenopathy (long arrow).

TABLE 40.3 Staging of rhabdomyosarcoma according to the IRS

Group I
Localized disease completely resected. No regional nodes
Confined to muscle or organ of origin
Contiguous infiltration outside muscle or organ of origin
Group II
Localized disease with microscopic residual disease, or regional disease (lymph nodes)
Group III
Incomplete resection or biopsy with gross residual disease
Group IV
Metastatic disease present at onset

TREATMENT AND PROGNOSIS

Since the establishment of the IRS Study Committee in 1972, protocols have been developed and are now widely adhered to. A multimodality approach has been adopted. In general, the role of surgery today is simply to evaluate the extent of the lesion and biopsy the tumour. Very occasionally, when the rhabdomyosarcoma is an easily accessible polypoid lesion, then wide surgical removal may be appropriate. A debulking procedure is rarely useful. Sophisticated skull base surgery can now be implemented in areas that were previously thought to be inaccessible, but is nearly always an adjunct to chemotherapy or radiotherapy.[29] Multiagent chemotherapy and radiotherapy are then implemented as appropriate.

Prior to 1960, approximately 10% of patients survived 5 years. Now the prognosis is excellent in patients with early tumours (over 80% survival). With more advanced tumours the prognosis is still relatively poor and in those with meningeal involvement the 5-year survival is less than 10%.[30] Although nodal mestastases at initial presentation are not synonymous with an unfavourable prognosis, development of nodes during follow-up does imply a poor outlook.[29, 31, 32]

Thyroid carcinoma

Thyroid carcinoma in the paediatric population is uncommon. In the US there are five new cases per million per year. It is much more common in adolescents than in younger children and is also much more common in females with a ratio of 4:1. Approximately 45% of these lesions in children will be differentiated papillary carcinomas with a further 45% of mixed papillary/follicular types with only 10% being follicular lesions.[33] Medullary thyroid carcinoma (MTC) is rare (only 10% of thyroid malignancies in children) and must be suspected in children with multiple endocrine neoplasia (MEN) types IIa and IIb (see 'Medullary thyroid carcinoma' below). Anaplastic and undifferentiated tumours are extremely rare in children and adolescents.

AETIOLOGY

A clear relationship has been established between the development of thyroid carcinoma and previous irradiation. In one study, as many as 17% of patients had previously received irradiation to the neck.[34]

PRESENTATION

Patients usually present with an asymptomatic solitary mass in the anterior or lateral neck. At presentation, there is often regional lymph node involvement (74%) and distant parenchymal metastases (25%).[32]

INVESTIGATIONS

Investigations will include an ultrasound scan, usually in conjunction with an ultrasound-guided FNA. Regional and distant metastases can be assessed with a chest X-ray and CT scan. Thyroid function tests and plasma thyroglobulin levels should be obtained and also plasma calcitonin where a diagnosis of medullary carcinoma is suspected.

TREATMENT

Controversy remains over the optimum treatment in differentiated thyroid carcinoma in children because the long-term mortality in these patients is low and serious operative and post-operative complications can occur following radical surgery. These include recurrent laryngeal nerve damage, hypocalcaemia and airway obstruction requiring tracheostomy.[32] It has become clear that these tumours in children are slow-growing and associated with prolonged survival rates, even in the presence of extensive disease. Some authors maintain that an aggressive approach is mandatory[35, 36] while others have adopted a more conservative approach with the use of lobectomy and subtotal thyroidectomy for small and isolated lesions.[33, 34, 37]

Ideally, treatment should include complete surgical excision if possible. Total or subtotal thyroidectomy should be performed if adjuvant radioiodine treatment is planned. Following surgery, a whole-body radioiodine scan is performed and ablative radioiodine treatment given if necessary. Plasma thyroglobulin can then be used as a tumour marker and suppressive levothyroxine should be given. Radiotherapy is rarely indicated in differentiated thyroid carcinoma in childhood.[11]

PROGNOSIS

A long-term study of 329 patients under the age of 21 confirmed only eight deaths over a long period of time and of these only two were disease related. The risk of progression of disease was more common in younger patients and those with residual cervical disease after definitive thyroidectomy. The majority of recurrences are in cervical lymph nodes or thyroid bed (54%), or lungs (16%).[37] The majority of relapses occur within the first 7 years but have been seen as long as 25 years after treatment.[33]

Medullary thyroid carcinoma

The detection of MTC in younger children is usually made following screening in 'high-risk' individuals who have a family history of MEN 2.[11] This is confirmed by elevated baseline levels of calcitonin or screening for the *RET* (rearranged during transfection) protooncogene on chromosome 10. If positive, the child should be considered for prophylactic total thyroidectomy.[11] See Volume 2, Chapter 63, Management of medullary cancer.

Nasopharyngeal carcinoma

In the US and Europe, nasopharyngeal carcinoma (NPC) is an uncommon tumour comprising only 1–2% of paediatric malignancies, but in other geographical locations, such as parts of Africa, 10–20% of childhood malignancies are due to NPC. There is a bimodal age distribution of this disease with an early peak of 10 to 20 years and a second peak between 40 and 60 years. NPC is one of few malignant tumours in childhood that emerges from the epithelium and there is an association with EBV. Males are twice as likely as females to develop NPC. Children with NPC almost invariably have the undifferentiated variant that is associated with higher rates of advanced locoregional disease and distant metastases.[38] Despite this, the 5-year disease-free survival is not significantly different to that of adults at 30–60%.[39]

PRESENTATION

Children may present with a cervical mass secondary to lymph node metastases. Other presenting symptoms and signs may include nasal congestion, epistaxis, otitis media with effusion, otalgia and cranial nerve palsy. As many as two-thirds of children with NPC have metastatic disease in the neck at presentation. Delay in the diagnosis occurs frequently because many of its symptoms mimic those of an upper respiratory tract infection.

ASSESSMENT

Nasopharyngeal examination and biopsy is required for tissue diagnosis. CT or MR scanning allows precise evaluation of the primary tumour and confirmation of the presence or absence of metastases, most particularly in the neck. The American Joint Committee in Cancer staging of NPC (see Volume 3, Chapter 8, Nasopharyngeal carcinoma) is used by most.

TREATMENT

Undifferentiated NPC is a radiosensitive tumour and as such is usually treated with external beam radiotherapy. Such therapy is limited to the primary tumour and its regional metastatic spread. Chemotherapy is required in patients with disseminated systemic disease. There is now evidence that combined chemotherapy and radiotherapy provides better disease-free survival as compared with radiotherapy alone and combined chemoradiotherapy – including consideration of Proton Beam Therapy is therefore becoming routine practice in the UK.[39, 40, 41] (see Volume 3, Chapter 8, Nasopharyngeal carcinoma).

Because of the tumour's close proximity to major structures, radiotherapy in this region is difficult to give and is associated with significant post-treatment morbidity. This includes mucositis, xerostomia, neck fibrosis and panhypopituitarism (see 'Long-term sequelae of treatment' below). Newer radiotherapy techniques, such as intensity-modulated radiation therapy (IMRT) and proton beam radiotherapy[39] may offer reduced morbidity following treatment as it becomes more readily available (**Figure 40.3**). As craniofacial surgical techniques improve, surgical resection is now becoming appropriate in certain situations, particularly in primary recurrence following treatment.

Neuroblastoma

Neuroblastoma is a common malignancy of early childhood and is the most common malignancy in infants younger than 1 year. These tumours arise from undifferentiated sympathetic nervous system precursor cells of neural crest origin. The adrenal gland is the most common site of origin and additional sites include the

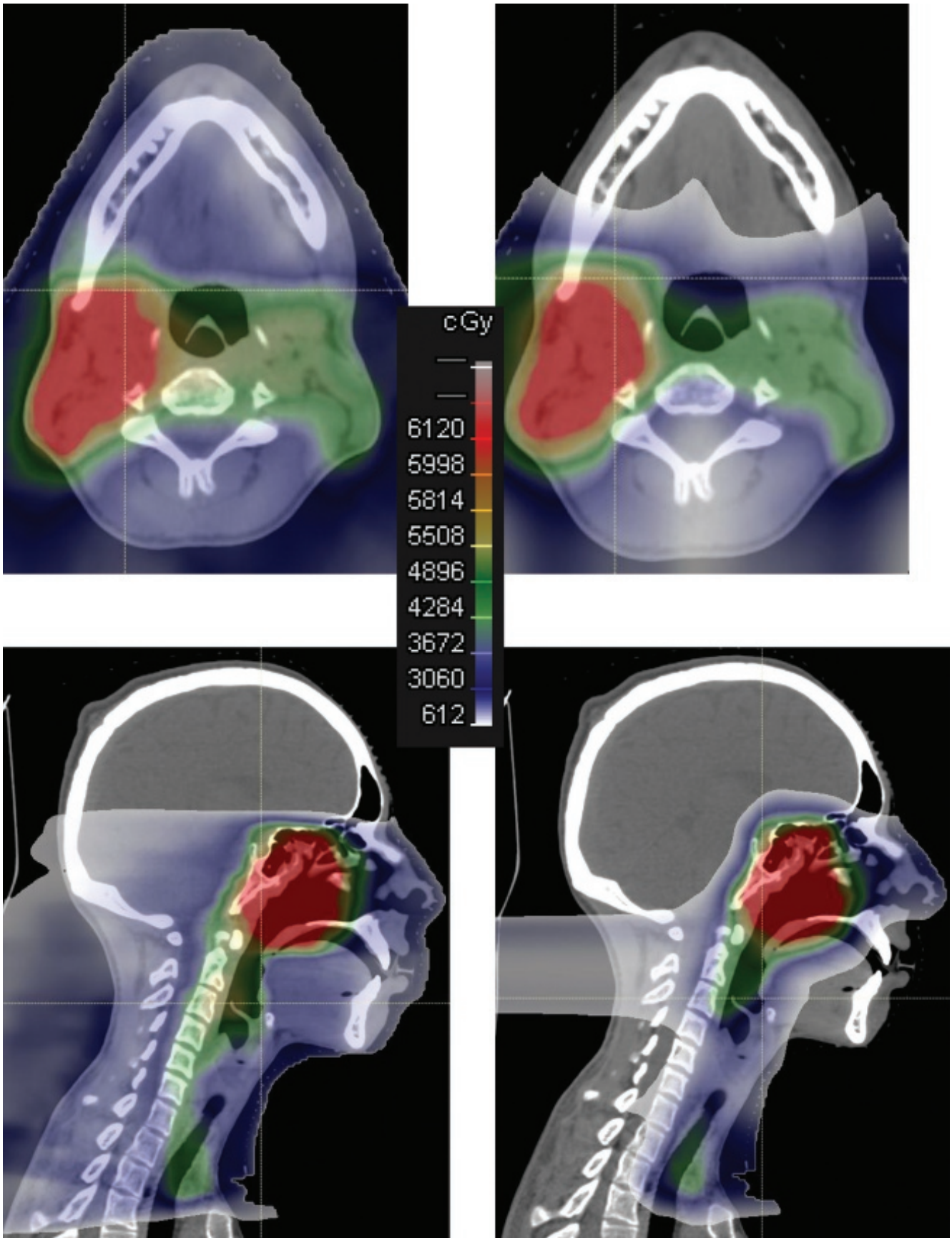

Figure 40.3 Sixteen year-old boy treated for nasopharyngeal carcinoma incuding a positive cervical lymph node. Panels on the left show planning scans using IMRT and on the right using Proton Beam Therapy. Note the reduced dose to the oral cavity and the brain using PBT. Image courtesy of Dr Danny Indelicato, Associate Professor, Department of Radiation Oncology, University of Florida.

sympathetic chain, posterior mediastinum and cervical regions. Neuroblastoma has a high propensity for lymphatic spread and regional lymph nodes are involved in up to 35% of cases. Metastases to the head and neck region are common, but primary neuroblastoma in the head and neck region is uncommon.[43]

PRESENTATION

Symptoms and signs will be dictated by the size and position of both the primary lesion and any metastases. Children with primary cervical neuroblastoma may present with a firm mass in the lateral neck, occasionally associated with a Horner syndrome (due to cervical sympathetic chain involvement). Classical ophthalmological manifestations include proptosis and periorbital ecchymosis (usually secondary to intraorbital metastatic deposits). Bilateral eye haematomas are a classical sign ('racoon' eyes). Chronic destruction of the ophthalmic sympathetic fibres in some children can lead to heterochromia of the irides. Involvement of the paranasal sinuses is also described.[43]

ASSESSMENT

A full assessment of the disease will include obtaining a histological diagnosis. Examination should include a visual assessment, intraoral inspection and a thorough neurological examination. MRI and CT scanning are usually employed to assess the primary and the extent of any metastatic spread (**Figure 40.4**). An iodine-123-metaiodobenzylguanidine (MIBG) scan is a useful method of assessing metastases. A bone marrow aspirate and trephine should be performed, with a bone scan reserved for those with a negative MIBG scan. Urinary catecholamine levels should be measured as they are raised in over 90% of cases.

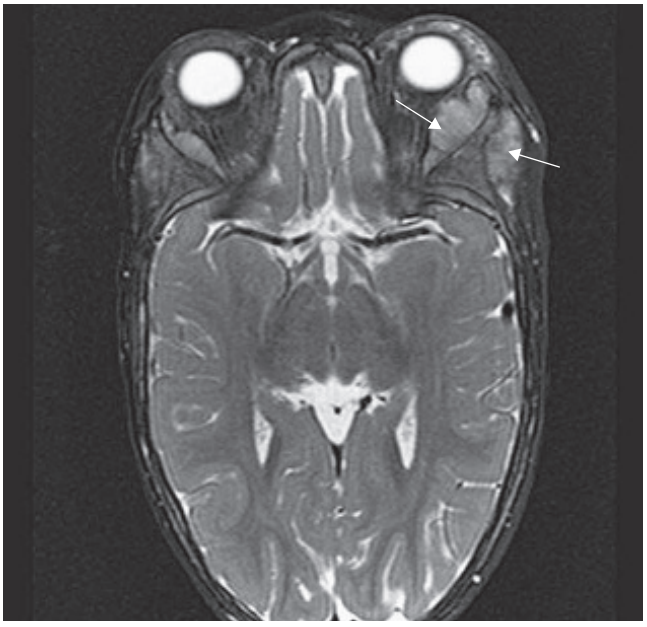

Figure 40.4 Metastatic neuroblastoma from an adrenal primary is extending out of both sides of the lateral orbital walls (more marked on left – arrows). Patient has incidental scaphocephaly.

TREATMENT

The choice of single modality or multimodality therapy depends on the individual patient. Localized cervical neuroblastoma may be treated by curative surgery. Multi-agent chemotherapy is usually indicated in patients if resection is incomplete, where there is amplification of the *MYCN* proto-oncogene or where there is evidence of metastases. The role of radiation therapy is becoming more clearly well-defined and many tumours are highly radiosensitive.[44, 45]

PROGNOSIS

In young patients with resectable disease, complete excision offers the best chance of cure and at least a 90% survival rate. Primary neuroblastoma of the head and neck has a better prognosis than that of other sites. Prognosis is poorer in children over the age of 1 year at presentation.[43]

MISCELLANEOUS TUMOURS

A large variety of tumours can rarely affect the head and neck region. The small numbers involved can make meaningful analysis of data difficult and it is not really feasible to address therapeutic questions in the context of randomized controlled trials. However, the UK CCLG have published guidelines for some of the rarer childhood cancers.[17]

Soft-tissue sarcomas

Sarcomas other than rhabdomyosarcoma can occur in the head and neck region of children. some features of these tumours are listed in **Table 40.4**. There is a bimodal age distribution with incidence peaking in the under-5s and in adolescents. Those in the younger age group tend to have lesions situated in the head and neck region while older children present with lesions in the extremities. In general, these tumours have a tendency to recur locally and to metastasize. The treatment is tailored to the individual case but in general involves chemotherapy often followed by surgery and radiotherapy (**Figure 40.5**). The prognosis remains relatively poor despite multimodality treatment.[29]

Squamous cell carcinoma

Squamous cell carcinoma (SCC) outside the nasopharynx is extremely rare in childhood. There is some evidence of an association between SCC and previous exposure to immunosuppressive medication, and also previous irradiation for laryngeal papillomatosis. Pre-existing xeroderma pigmentosum makes any patient extremely susceptible to the development of cutaneous SCC. The principles of management of SCC in the head and neck in children are the same as in adults.

Malignant teratoma (Germ cell tumour)

Malignant teratomas in the head and neck region are rare (most are benign) and usually present at birth, often as an airway emergency. Large tumours are usually diagnosed *in utero*, resulting in a multidisciplinary team being

TABLE 40.4 Some features of head and neck soft tissue sarcomas

Fibrosarcoma
Peripheral nerves
Slowly enlarging painless mass
Metastatic infrequent
Complete resection is treatment of choice
Good prognosis
Neurofibrosarcoma or Malignant Schwannoma
Neck, larynx, oropharynx (see Figure 40.5)
Foci of calcification typical
Peripheral nerves
Develops in 3–16% of children with Von Recklinghausen neurofibromatosis (NF1)
Arise from capillary pericytes
Skin lesions, lymphadenopathy
Can compress cervical spine
Multimodality treatment
50% five-year survival
Wide surgical excision
Cranial nerve deficits, local recurrence, lung metastases complicate treatment
Haemangiopericytoma
Nasal cavity and sinuses
Nasal mass, and epistaxis
Associated with HIV
Kaposi's Sarcoma
Ewing's Sarcoma

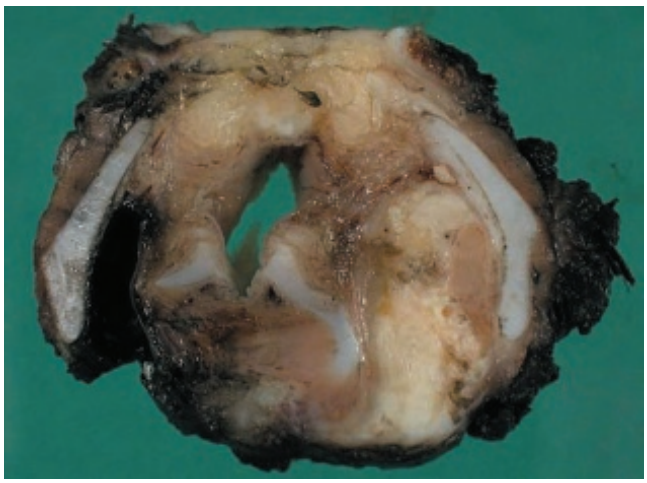

Figure 40.5 Cross-section of a laryngectomy specimen from a 12-year-old boy with residual synovial cell sarcoma despite chemoradiotherapy.

needed at delivery to secure a safe airway. Tracheostomy may be necessary. Assessment should include nasoendoscopy, alphafetoprotein (AFP) and beta human chorionic gonadotrophin (hCG) levels, and imaging. Metastases are rare. Treatment is surgical excision although salvage chemotherapy and radiotherapy may be required. The prognosis is good in the absence of metastases.

Chordoma

This is a rare slow-growing bony tumour which is locally aggressive and which arises from embryonic remnants of the notochord. The presentation depends on the site of origin which, in the head and neck region, is most commonly found in the nasopharynx and adjacent skull base. Patients present with headache and diplopia and compression of the lower cranial nerves can result in a number of neurological signs (see Volume 3, Chapter 8, Nasopharyngeal carcinoma). Biopsy is necessary for diagnosis and MR and CT scanning will delineate the tumour extent. Complete surgical excision is rarely possible because of the anatomical location and adjacent structures and so post-operative radiotherapy is usually employed. Proton beam therapy is increasingly employed in centres where it is available.

LONG-TERM SEQUELAE OF TREATMENT

The aim of cancer treatment in children is to maximize the chance of long-term survival and at the same time minimize the side effects, particularly in the longer term. With overall 5-year survival rates in children now over 80%, it is particularly important to examine the effects of the more recently employed multimodality treatments. The Childhood Cancer Survivor Study (CCSS) report that some 50.4% of survivors of childhood cancer have, by the age of 50 years, developed disabling or even fatal health conditions, as against 20% in a sibling control group.[46] Children tolerate the acute side effects of radiotherapy and chemotherapy reasonably well but other sequelae may not become apparent for several years.[47]

Second tumours may occur many years after treatment, particularly in a radiotherapy field.

Growth

Cranial radiotherapy can result in growth hormone deficiency and growth retardation and chemotherapy can also have significant effects on growth. Localized tumour treatments can also affect growth and function of specific organs or tumour sites. For example, radiotherapy to the maxilla in a child can result in asymmetrical growth of the midface.

Reproductive function

An important issue for survivors of childhood cancer is the impact of the disease and its treatment on reproduction and the implications for the health of any offspring. In males there is evidence for impaired spermatogenesis after treatment but it appears that any sperm produced carries as much healthy DNA as produced by the population in general. However, it is not always possible to predict fertility outcome in boys who receive treatment prior to puberty. Cryopreservation of sperm in young males (14–17 years) is effective but depends on the ability of the young patient to produce a specimen and, in the UK,

consent for storage requires him to be 'Gillick' competent (see Chapter 62, The paediatric consultation). Another technique is to harvest a 'wedge biopsy' of testicular tissue' for extraction of sperm. Radiotherapy to the hypothalamus or pituitary can result in precocious puberty in females and patients should therefore have their pubertal status checked regularly. There are now detailed CCLG guidelines on this topic.[17] Chemotherapy in general is less harmful to gonadal function in females but pelvic irradiation can affect ovarian function. Spontaneously conceived offspring of patients treated for cancer in childhood have no excess of congenital abnormalities or other diseases.[48]

Cardiac problems

Anthracyclines have a significant cardiotoxic effect and can cause cardiac failure in later life. Long-term echocardiogram surveillance is recommended for some follow-up regimes. Mediastinal radiotherapy can also result in impaired cardiac function (and an increased risk of breast carcinoma) and this should be monitored as appropriate.[49]

Thyroid disorders

Thyroid dysfunction can result from radiotherapy to the neck or to the hypothalmic/pituitary axis. Chemotherapy is a risk factor. Survivors require regular thyroid function evaluation. Radiotherapy to the neck is a recognized aetiological factor in the development of thyroid carcinoma in later years.

OTHER OTOLARYNGOLOGICAL MANIFESTATIONS OF TREATMENT

Radiotherapy to the head and neck region results in a large variety of long-term sequelae that can affect function and cosmesis. Damage to the major and minor salivary glands can cause xerostomia and subsequent tooth and gum disease. Post-radiotherapy scarring within the nasopharynx can result in middle ear effusions and subsequent deafness, and in the region of the midface can result in recurrent sinusitis, temporomandibular joint dysfunction and trismus. Certain chemotherapeutic agents – notably cisplatin – are known to cause deafness and tinnitus. Vincristine can cause bilateral vocal cord paralysis. Immunodeficiency with a propensity to develop opportunistic infections of the head and neck may complicate some chemotherapy regimens.[47]

Cognitive and psychological problems

Surgery and/or radiotherapy to the brain or adjacent structures can result in neurocognitive defects such as low IQ, learning difficulties and an increased risk of seizures. Survivors of childhood cancer are at an increased risk for a wide range of disabling psychological problems such as low mood, low self-esteem and anxiety.

Follow-up

It is important to follow up these children in the long term and to educate them and their parents about the possible late consequences of their treatment. It is also important to promote a healthy lifestyle and discourage cancer promoting behaviours such as smoking and excessive sun exposure.[48]

The dying child

The death of a child is one of the greatest tragedies that can befall a family. It is important to recognize that palliative care of the dying child should address not only the control of pain but the social, psychological and spiritual needs of children and their families. Planned terminal care for children has become increasingly community-based and therefore requires involvement of the primary healthcare team, including the patient's general practitioner at an early stage. An experienced and multi-skilled team is required with a named key worker and access to advice and support 24 hours a day. The child should participate in the planning and provision of this care as much as is realistically possible.[50]

Once the focus of treatment shifts from curative to palliative care, quality of life becomes of prime importance. Most children and their families will wish to maintain some semblance of normality while optimizing symptom control and minimizing medical intervention. For instance, many children will opt to remain at school for as long as they are able, mixing with friends and getting a break from the home environment. Others may benefit from a daily visit at home from a play specialist.[50, 51]

Regular respite should be offered to parents and it is important to explore the financial assistance, benefits and grants that families may be entitled to. Practical help with funeral arrangements should be given and it is important to continue to support the grieving family after their child's death and to withdraw support slowly and appropriately.[15, 50, 51]

NON-MALIGNANT CONDITIONS THAT RESEMBLE TUMOURS

Rosai–Dorfman disease

Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy) is an inflammatory condition of unknown aetiology. It typically causes massive bilateral cervical lymphadenopathy with fever and malaise in older children and young adults.[52] Histologically, it is characterized by histiocytes (an old-fashioned term for macrophages and dendritic cells) accumulating in large numbers in lymph nodes and occasionally other sites such as orbit, nose, oropharynx and salivary glands. In most cases it runs a benign course with spontaneous regression, but the disease can be quite prolonged. Excision biopsy of a lymph node is required to exclude lymphoma, and more extensive surgical debulking may be necessary for compressive symptoms.

Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH) can also present with lymphadenopathy, usually in the children under the age of 5 years. It is characterized by clonal proliferation of Langerhans cells and their accumulation in tissue. It is unclear whether this process is neoplastic or inflammatory

in nature. LCH is a spectrum of disease, ranging from unifocal (previously known as eosinophilic granuloma), which presents as a solitary bone lesion, to multifocal multisystem disease (previously known as Letterer–Siwe disease). The multifocal form can involve bone lesions (often in the mandible, causing jaw pain or loose teeth), skin eruptions (commonly on the scalp), pituitary gland lesions, chronic otitis media and bone marrow involvement. Fever, lethargy and weight loss may occur. LCH with cervical lymphadenopathy will usually be of the multifocal type. Diagnosis requires excision biopsy of an affected node for histological examination, together with radiology of the chest and any affected bones and MRI of the pituitary. Prognosis can be poor, especially under the age of 2 years, and aggressive treatment may be required with steroids and in severe cases cytotoxic chemotherapy. Mortality is approximately 10% overall, but 50% in multifocal disease in children under the age of 2 years.

Castleman disease

The main importance of Castleman disease is in the differential diagnosis of lymphoma. It presents as a mass of enlarged lymph nodes. The diagnosis is made on histology which shows a B-cell lymphoproliferative disorder, and some cases are thought to have a viral cause. Children most often have the unicentric form, with nodes confined to one area of the neck. Surgical excision is all that is needed. The multicentric condition is more common in adults and much more serious. It is sometimes associated with HIV infection and can run an aggressive course, requiring prolonged treatment with antivirals and monoclonal antibodies. For this reason, children with apparently unicentric disease should probably have imaging of the chest, abdomen and pelvis, and HIV testing.

Fibromatosis colli (sternomastoid tumour of infancy)

This condition is surprisingly common and important to recognize. It is often blamed on birth trauma but its aetiology is obscure and it is most likely an idiopathic fibrosing condition of the muscle. Fibromatosis colli is the preferred term as 'tumour' suggests neoplasia which is as frightening as it is inappropriate. It presents in newborns as torticollis and a palpable lump within the sternomastoid muscle. It is associated with developmental dysplasia of the hip so it is probably reasonable to get an ultrasound of the neck to confirm the diagnosis and the hips can be scanned at the same time. Treatment is simply physiotherapy to stretch of the muscle and encourage the baby to turn the head to the affected side. The tragedy of this condition is that, despite being common and simple to treat, it often goes untreated leaving the child to develop fibrosis and permanent contracture of the muscle. The torticollis becomes permanent and this can affect the development of the facial skeleton. The eyes and mouth develop on a cant so that even when the muscle is surgically released, the face remains abnormally aligned (Figure 40.6).

Figure 40.6 **(a)** Untreated fibromatosis colli on the right side presenting in childhood with contracure of the sternomastoid muscle. **(b)** After surgical release of both ends of the right sternomastoid muscle the resting position and range of movement of the neck are improved but note that the planes of the eyes and mouth are not parallel and the whole face has grown in an asymmetric fashion.

BEST CLINICAL PRACTICE

- ✓ The vast majority of enlarged cervical lymph nodes in children are harmless. Imaging should usually be considered before biopsy.
- ✓ FNA has a more limited role to play in the child than the adult.
- ✓ All children diagnosed with malignancy should be referred to a specialist centre.
- ✓ Children receiving chemotherapy should have central venous catheters placed for venous access and chemotherapy treatment.

FUTURE RESEARCH

- ➤ The long-term survival of children with cancer is improving, and a better appreciation of the long-term sequelae of treatment should result in an improved quality of life for children surviving cancer. We are likely to encounter more physical and psychological problems in adults related to cancer treatment in childhood.
- ➤ Basic science research should bring better understanding of the underlying aetiology of childhood cancer. This may help in introducing preventative measures such as vaccines and environmental interventions. Agreed protocols on the management of paediatric thyroid malignancy would be helpful. Centralization of services, the establishment of better databases and the implementation of multicentre trials will provide us with a better evidence base for the future management of childhood cancer.
- ➤ Better imaging techniques with wider access to sophisticated equipment will aid in more accurately assessing the initial disease and in detecting recurrence at an earlier stage. Greater knowledge of molecular genetics has resulted in new approaches to diagnosis and treatment. The advent of polymerase chain reaction (PCR) techniques has, for example, permitted the detection of cells bearing chromosomal translocations in the peripheral blood and bone marrow, thereby detecting minimal residual disease in lymphoma and even defining patients at high risk of relapse. Other novel strategies include the use of immunotherapy (immunotoxins or vaccines) to target specific cells or cell proteins. Radiotherapy techniques such as IMRT are allowing much greater flexibility in targeting tumours in awkward anatomical sites whilst avoiding some of the post-treatment complications. IMRT is an advanced mode of high precision radiotherapy where combinations of several intensity-modulated fields coming from different beam directions deliver a maximal dose to the tumour while minimizing the dose to surrounding tissues. Surgical advances, such as navigation systems with the use of endoscopes, mean that areas once inaccessible can now be approached surgically whilst maintaining good function and cosmesis. Proton beam therapy looks set to have a significant role in childhood malignancies.
- ➤ In conclusion, we have made major advances in the investigation and management of childhood malignancy in the last 30 years and a number of promising diagnostic and treatment developments promise much in the next 30.

KEY POINTS

- Head and neck tumours are uncommon in children. Early diagnosis is essential.
- Survival rates are improving.
- Multimodality treatment has improved the prognosis while reducing both early and long-term complications.
- Treatment should be provided by a specialized, centralized multidisciplinary paediatric oncology team.

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CHAPTER 41

CYSTS AND SINUSES OF THE HEAD AND NECK

Keith G. Trimble and Luke McCadden

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the following keywords: branchial arch, branchial cleft, branchial pouch, preauricular sinus, thyroglossal cyst, lingual thyroid, nasal dermoid and congenital midline cervical cord.

INTRODUCTION

A child with a congenital cyst or sinus in the head or neck is the quintessential paediatric ENT patient and can present a welcome diagnostic challenge in the humdrum of afternoon clinic. Although a preauricular sinus is common and easily diagnosed by the undergraduate student, it takes an experienced otolaryngologist to consider the infrequent first branchial cleft sinus diagnosis in a child with facial abscess repeatedly incised and drained elsewhere. For obvious reasons, an understanding of embryology of the branchial clefts is a prerequisite for the paediatric or adult otolaryngologist managing infected cysts or draining sinuses around the head and neck. Excluding reactive cervical lymphadenopathy as the most frequent cause of referral with neck lump and the common pilomatrixoma, which is slowly enlarging and fixed to the skin, thyroglossal duct cysts, branchial arch anomalies and dermoid cysts are seen in decreasing order of frequency.

This chapter discusses the best management of congenital cysts and sinuses of the neck, none of which is based on randomized controlled trials or meta-analyses, but rather single-surgeon, single-centre large case series or systematic review. Special mention should be made regarding modifications of Sistunk's procedure, which should be effecting lower recurrence rates following excision of thyroglossal duct cyst anomalies and endoscopic cautery of third pharyngeal pouch sinuses in older children to reduce complications of open surgery. Unusual entities such as the congenital midline cervical cleft and congenital sinus at the sternoclavicular joint (sinus sternoclavicularis) will also be discussed. Plunging ranulas, teratomas and vascular anomalies also present at birth but are discussed elsewhere in this book. Sternomastoid pseudotumours of infancy present as a painless unilateral mass low in the neck with decreased neck rotation and are easily managed with ultrasonography and physiotherapy; these are not discussed further in this chapter.

BRANCHIAL ANOMALIES

Branchial anomalies usually present as lateral neck masses with infection, cyst enlargement or an intermittently draining sinus. Treatment usually involves surgical excision with identification and preservation of nearby neurovascular structures. The embryology of the branchial apparatus is discussed in Volume 1, Chapter 53, Developmental anatomy of the thyroid and parathyroid glands. But it is worth noting the following brief points. The branchial arches are mesodermal structures that go on to form muscle, cartilage and bone. First and second branchial arch anomalies, therefore, will result in structural deformities of the face, as in Treacher Collins syndrome or hemifacial microsomia (see Chapter 19, Craniofacial anomalies). There are spaces between the arches on the

outside of the embryo, lined with ectoderm, called the branchial clefts. Branchial cleft anomalies, therefore, will result in a congenital sinus with an opening on a skin surface. This may be around the angle of the mandible or in the EAC (first branchial cleft sinus) or in the neck along the anterior border of sternomastoid (second branchial cleft sinus). There are also spaces between the arches on the inside of the embryo, as the arches bulge into the foregut. These are called the pharyngeal pouches and they are lined with endoderm. Pharyngeal pouch anomalies (third or fourth) will result in a sinus with an opening on a mucosal surface, typically in the left piriform fossa.

First branchial cleft sinuses

First branchial cleft sinuses are rare and account for less than 10% of branchial cleft anomalies.[1] The external opening in the neck varies in position but lies on a line between the tragus and the hyoid bone. The opening is often inconspicuous and appears as a skin-lined pit. The superior attachment of the sinus is variable: there may be an opening anterior to the tragus or the tract may form a true fistula running inferior to the floor of the EAC and opening at the osseocartilaginous junction in the external auditory meatus or rarely forming a frenulum-like band between the floor of the meatus and the umbo of the tympanic membrane (**Figures 41.1** and **41.2**).

Histology

The sinus (sometimes known as a collaural fistula) is usually a sizeable tract, often formed of cartilage, and lined with squamous epithelium. The original classification by Work and Work[2] divides them into two types according to the presence or absence of mesothelial elements within the wall.

- **Type I lesions** are of ectodermal origin and are present medial to the concha. They are usually superficial and simple in nature.
- **Type II lesions** are both ectodermal and mesodermal in origin and contain cartilage and hair follicles. The more inferior opening of the type II fistula is usually below the angle of the mandible and the tract is intimately related to the facial nerve trunk.

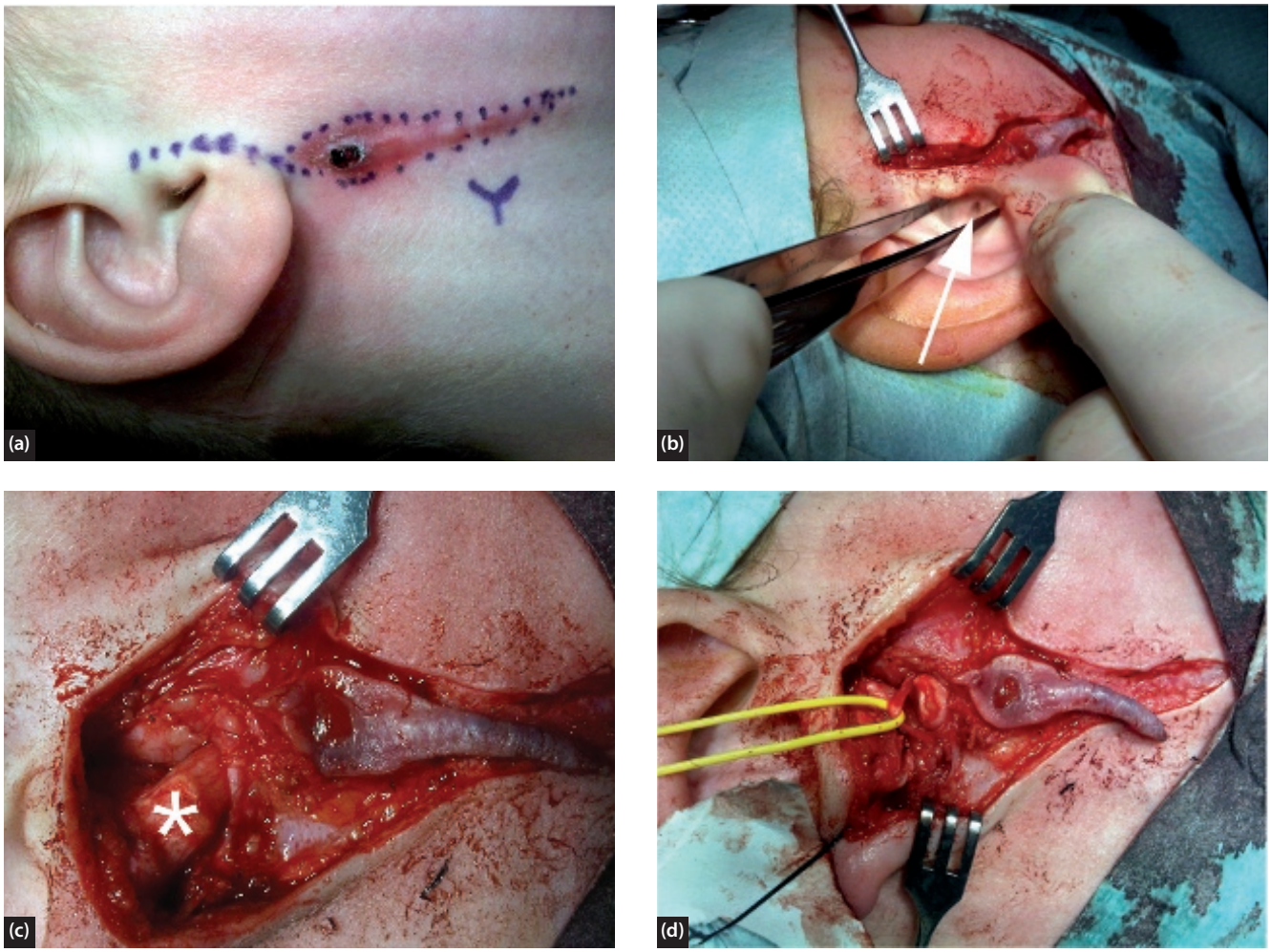

Figure 41.1 **(a)** Type 2 first branchial cleft anomaly with two previous incision procedures in another hospital. **(b)** Proximal fistula opening in floor of ear canal. **(c)** The fistula tract (*) passes over the angle of the mandible deep to the facial nerve trunk, intraparotid and terminates at the bony-cartilaginous junction of the external auditory meatus. **(d)** Yellow sloop over the main trunk facial nerve.

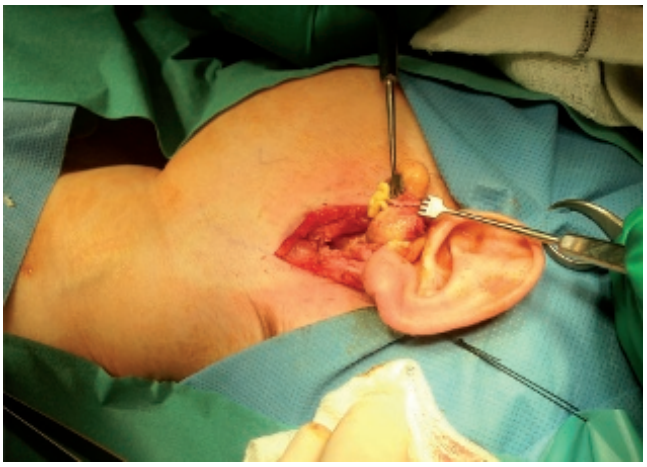

Figure 41.2 Type 1 first branchial cleft anomaly with ear canal duplication anomaly lateral to the facial nerve extending to the umbo of the tympanic membrane.

Presentation

The opening is present at birth and may become more obvious by the discharge of epithelial or sebaceous debris. The sinus may become acutely infected and may progress to abscess formation. Being lined with skin, these lesions do not discharge mucus.

Investigation

Cross-sectional imaging will usually show the tract, which is often substantial in calibre but will not clearly demonstrate its relationship to the facial nerve. MRI is preferable over CT in children to minimize exposure to ionizing radiation and provide excellent visualization of soft-tissue planes. However multislice helical CT may be preferred in some institutions because of cost, availability and speed of image acquisition which could obviate the need for sedation or anaesthesia. A radiopaque sinogram is not routinely indicated.

Treatment

Surgical excision of these lesions is usually advocated if at all symptomatic or if one or more episodes of infection have already occurred. Surgery is ill-advised during acute infection and a period of quiescence should be awaited followed by elective excision, which necessitates dissection of the tract in its entirety, assisted by intra-operative facial nerve monitoring.

A parotidectomy-type incision is modified to include the lower opening of the sinus. The sinus tract at this point can be followed for a small distance upwards; when its nature and direction are confirmed, the facial nerve trunk must be identified as it leaves the skull base and enters the parotid gland. The mandibular branch in particular should be followed so that it can be preserved while freeing the tract. Sharp dissection will often be required to free the nerve from the tract, particularly if multiple infections have ensued or previous attempts at incision and drainage have been made. In most instances the lesion will run deep to the branches of the facial nerve, which may be adherent if there has been recurrent infection, though the relationship is unpredictable. The superior part of the sinus tract also has an unpredictable relationship to the cartilages of the external auditory canal (EAC). It may terminate at the canal or may form a duplicated canal parallel and inferior to the EAC proper. The lesion does not extend medial to the cartilaginous canal but a strand may cross the lumen of the canal from the osseocartilaginous junction to be attached to the umbo.

Facial nerve exposure and protection is required in nearly every case of first branchial cleft sinus. If this is done, then risk to the facial nerve is minimized. The superficial position of the facial nerve in small children must be considered. The upper end of the lesion must be followed and excised to ensure that no squamous epithelium remains, and this may require opening of the EAC and use of the otological microscope and ear instruments.

Closure of the wound with suction drainage and, if necessary, light packing of the ear canal completes the operation.

Second branchial cleft sinuses

Second branchial cleft sinuses are the commonest of the branchial anomalies (up to 90%[1]) (**Figure 41.3**). The second branchial arch forms the epidermis of the upper neck and dorsal pinna. The mesoderm forms the facial muscles and the body of the hyoid, and the endodermal elements form the root of the tongue, the foramen caecum, the thyroid stalk and the tonsil. The second branchial cleft sits immediately caudal to these structures and it is persistence of this cleft that leads to the formation of the second branchial arch sinus.

Second branchial arch sinuses may be associated with branchio-oto-renal syndrome, especially if bilateral.

The second branchial cleft sinus presents as a congenital opening on the lower neck, anterior to the sternocleidomastoid muscle. The tract of the second branchial cleft sinus is directed proximally and medially to pass between the internal and external carotid arteries. The proximal end may communicate with the pharynx through the palatine tonsil to form a true fistula in some cases, although most lesions are not patent through their whole length. The sinus nearly always leaks clear or mucoid fluid from the distal external opening due to secretions from ectopic salivary tissue in the wall of the sinus itself rather than any leakage from the pharynx. In some cases the sinus may become infected and, on occasion, the infected tract may form an abscess in early infancy, requiring intravenous antibiotics or surgical drainage.

Second branchial cleft cysts are thought to be congenital in origin even though they rarely present in childhood and are much more common in young adults. They typically present as a spherical swelling inferior to the angle of the mandible, anterior to the sternocleidomastoid, although other unusual locations occur. It is helpful to

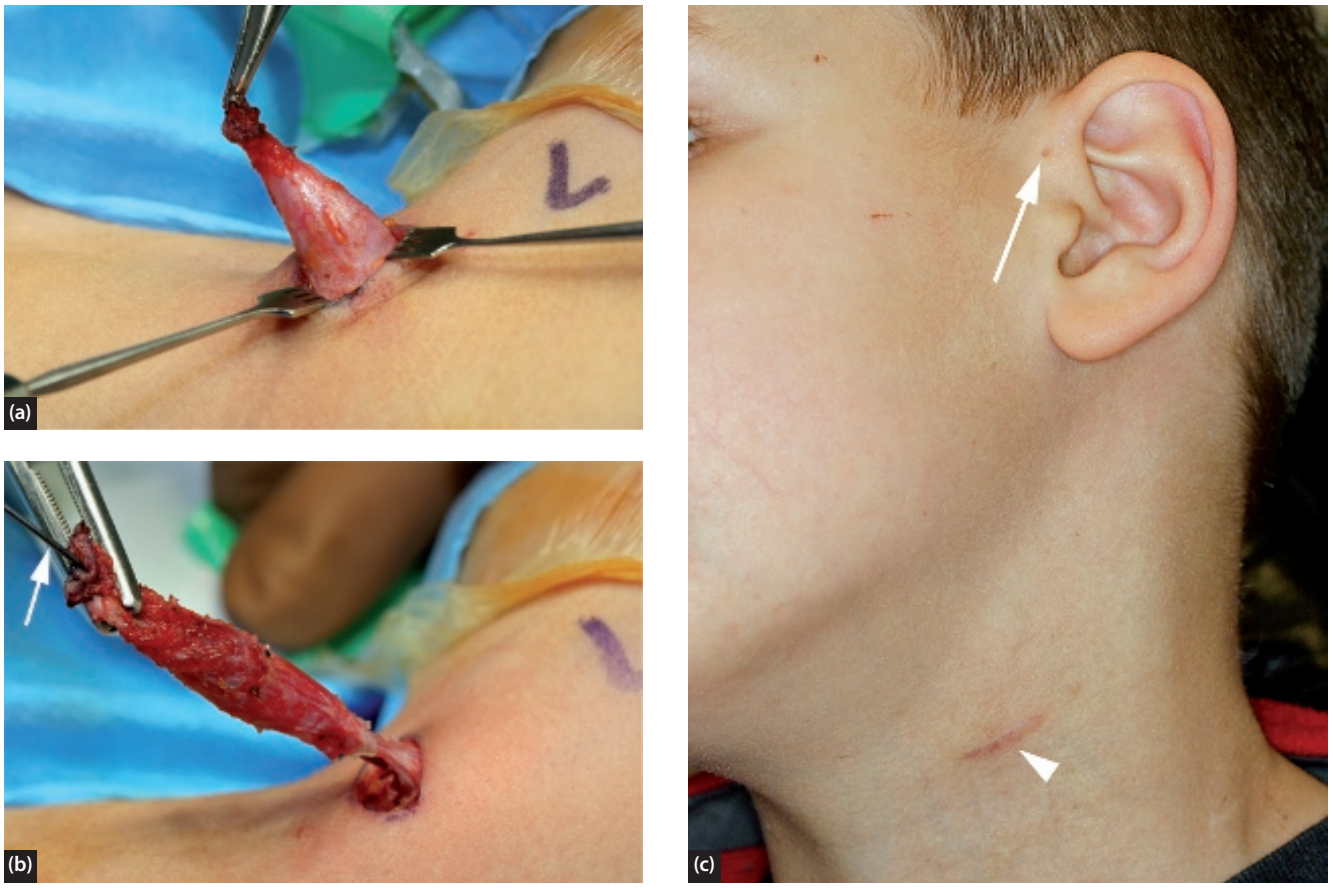

Figure 41.3 Second branchial cleft sinus tract dissection **(a)** peters out adjacent to the pharynx **(b)**. The white arrow indicates the lacrimal probe. **(c)** Post-operative image: note the asymptomatic preauricular sinus (white arrow) and the 1-week old post-operative scar (white arrowhead).

recall Bailey's classification of second branchial cleft cysts which provides a framework at the clinic for diagnosis and surgical planning of unusually placed cysts:

- **type I:** deep to platysma, anterior to sternocleidomastoid
- **type II:** abutting internal carotid artery and adherent to internal jugular vein (most common) (Figure 41.4)
- **type III:** extending between internal and external carotid arteries
- **type IV:** abutting pharyngeal wall and potentially extending superiorly to skull base.

Investigation

As a rule with second branchial cleft sinuses, the diagnosis is evident and no further investigation is required. Neck ultrasonography can characterize the size of tract or associated sharply demarcated cyst, and renal tracts can be imaged to exclude horseshoe or duplex kidney. However, a radiopaque sinogram is not routinely indicated. Cross-sectional imaging will usually show the close relations of a second branchial cyst and is particularly helpful for type III or IV presentations (Figure 41.5). MRI is preferable to CT in children to minimize exposure to ionizing radiation and provide excellent detail of soft-tissue planes.

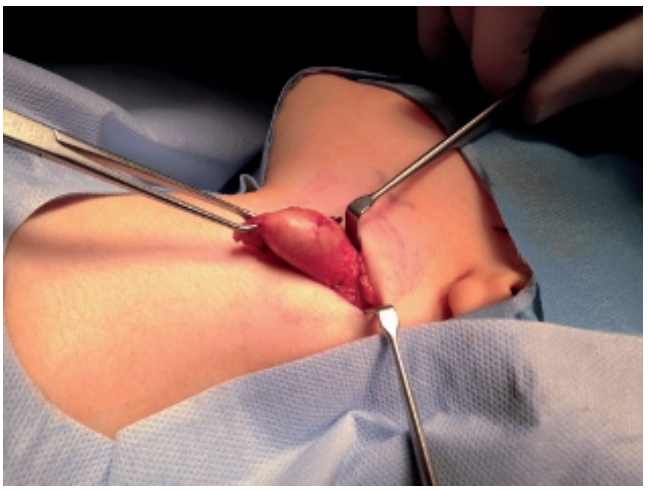

Figure 41.4 Excision of a common type II second branchial cleft cyst deep to the sternocleidomastoid muscle and abutting great vessels.

Treatment

Because of the risk of infection, excision of second branchial cleft sinuses is advisable. Surgery can be performed at any age and aims to excise the tract completely when no infection is present. A fusiform skin incision is made

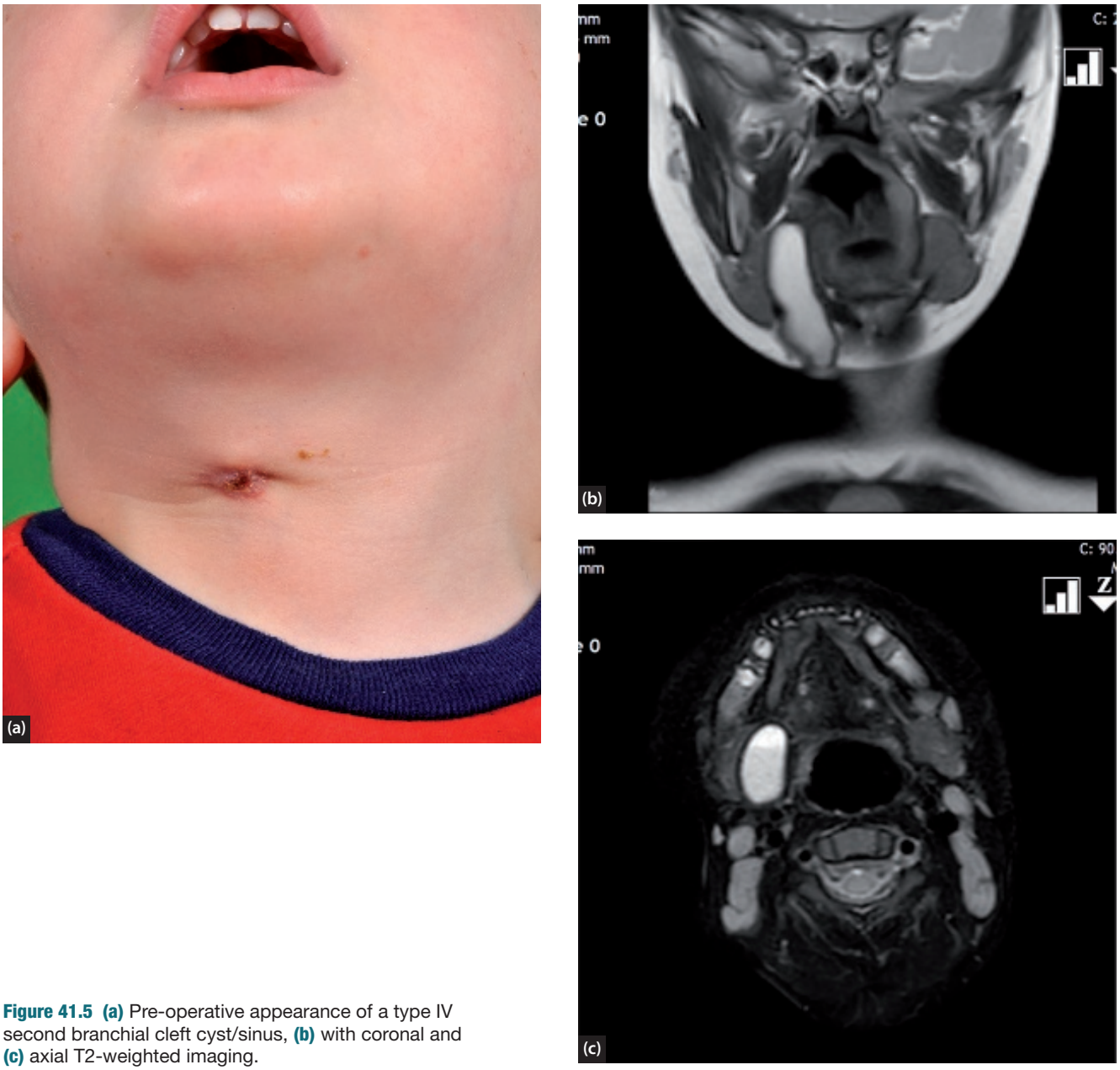

Figure 41.5 **(a)** Pre-operative appearance of a type IV second branchial cleft cyst/sinus, **(b)** with coronal and **(c)** axial T2-weighted imaging.

around the external opening and the tract can be followed upwards with microbipolar dissection and counter traction with lacrimal retractors. If the distance between the external opening and pharynx is too great to allow good access, a second stepladder incision is made superiorly in the neck to enable the cranial portion of the tract to be visualized and excised; however, this is rarely necessary in the young child. The tract will be seen to enter the pharyngeal muscle at the level of the palatine tonsil and can be ligated and excised at this level. Although ipsilateral tonsillectomy is unnecessary in the vast majority of cases, tonsillectomy should be considered in the larger type IV second branchial cleft cyst that abuts the pharynx (Figure 41.5). Care must be taken to avoid the hypoglossal nerve in the superior part of the dissection. Complete excision of the sinus should prevent recurrence. Surgery for second branchial cleft cysts should be planned when infection has resolved, taking care to avoid injuring the internal jugular vein and hypoglossal nerve superiorly.

Third and fourth pharyngeal pouch sinuses

Third and fourth pharyngeal pouch sinuses are rare abnormalities, accounting for 1–2% of branchial lesions, which can present as a sinus, cyst, thyroid gland abscess or even a fistula from pharynx to skin.[3] They almost always occur on the left side. They tend to present in early childhood with associated infections or in neonates with airway obstruction. The third and fourth branchial arches are related to the thyroid, parathyroid and thymus and

therefore tracts may course close to or through these structures: both originate at the pyriform sinus. The third arch is associated with the glossopharyngeal nerve whereas the fourth is related to the superior laryngeal branch of the vagus nerve. This can explain the theoretical course of third and fourth pharyngeal pouch anomalies, however case reports to demonstrate these are lacking. A proposed theory by James[4] is to consider these as branchial anomalies of the pyriform fossa. Development may arise from the incomplete closure of the thymopharyngeal duct of the third pouch, a similar concept of how cysts may form in the thyroglossal duct tract.

Presentation

These anomalies present most commonly with some form of infection, often recurrent thyroid abscess, which is treated with incision and drainage without recognition of the diagnosis and rendering recurrence inevitable.

Investigation

Various investigations have been proposed: barium swallow, radioiodine scan, ultrasonography and CT. However, MR imaging alone is suitable followed by rigid endoscopy under anaesthesia to identify an opening in the pyriform sinus.

Treatment

Although wide-field extirpation of the cyst, tract and ipsilateral thyroid lobe using a hybrid open and endoscopic approach to the pyriform sinus was the standard treatment, modern management utilizes endoscopic cautery of the pyriform fossa sinus alone as first-line treatment. Bailey described successful endoscopic diathermy of the pyriform fossa opening in two cases in 2004 which has become first-line treatment to obliterate the tract and avoid recurrent infection.[5] Garabedian recognized a higher recurrence rate in neonates in a series of 20 children and recommended resection via open approach rather than endoscopic approach in this younger age group.[6]

PREAURICULAR CYSTS AND SINUSES

Embryology

The external ear begins to develop at week 6 of gestation. Auricular hillocks, three from the first and three from the second branchial arch, surround the first branchial cleft below the level of the mandible. The hillocks will form the pinna and the first cleft will form the external canal. As they ascend, some mandibular hillocks contribute to the tragus, while the remainder form the bulk of the auricle. A blind-ended sinus results from incomplete fusion of the hillocks. The sinus is skin-lined and may result in recurrent discharge and infections. While a sinus found above the line of the tragus is usually an isolated preauricular sinus/cyst, a sinus found below the level of the tragus is more likely related to a first branchial cleft anomaly and checking the EAC for fistula is imperative.

One inherited (autosomal dominant with variable penetrance) disorder to be recognized is branchio-oto-renal syndrome which involves structural defects of the outer, middle and inner ear, branchial cleft anomalies and renal abnormalities. Bilateral preauricular sinuses and bilateral second branchial cleft sinuses may be present with hearing loss. Mutations in the *EYA1* gene on chromosome 8q13 are found in 40% of patients.[7] Hearing assessment and ultrasound of renal tracts are recommended management.

Presentation

Preauricular cysts and sinuses are common, with an incidence ranging from 0.9% in the Western European population to 10% in East Africa.[8] The majority of preauricular sinuses will remain asymptomatic and can be managed conservatively. However, frequent discharge or abscess formation following preauricular lymphadenitis should prompt early intervention.

Treatment

If the sinus or cyst is symptomatic, local excision is the treatment of choice (**Figure 41.6**). The sinus is explored under general anaesthetic with a lacrimal probe which usually shows deep extension towards the roof of the ear canal for 10 mm or more. The punctum is excised with a fusiform skin paddle and excised in continuity with the entire tract, which is usually adjacent to the underlying cartilage; excising a portion of this reduces the risk of recurrence. Some will use methylene blue to guide dissection but others avoid this in case of spillage into the field, which makes dissection more awkward. If there is skin breakdown secondary to lymphadenitis in the surrounding area, this can be left alone, as it will settle following successful removal of all epithelial tract related to the preauricular cyst and sinus.

THYROGLOSSAL DUCT CYST

Embryology

Thyroglossal duct cysts are the most common congenital abnormality in the head and neck region. The thyroid develops from the foramen caecum, which lies in the midline of the tongue at the junction of the anterior two-thirds and posterior one-third. In normal development, the thyroid descends through the tongue, passing caudally with an intimate relationship to the hyoid bone and finishing in the anterior neck overlying the trachea and laryngeal cartilage. In around one-third of cases the duct has been found posterior to the hyoid bone, which has important implications in surgical treatment. The duct may fail to

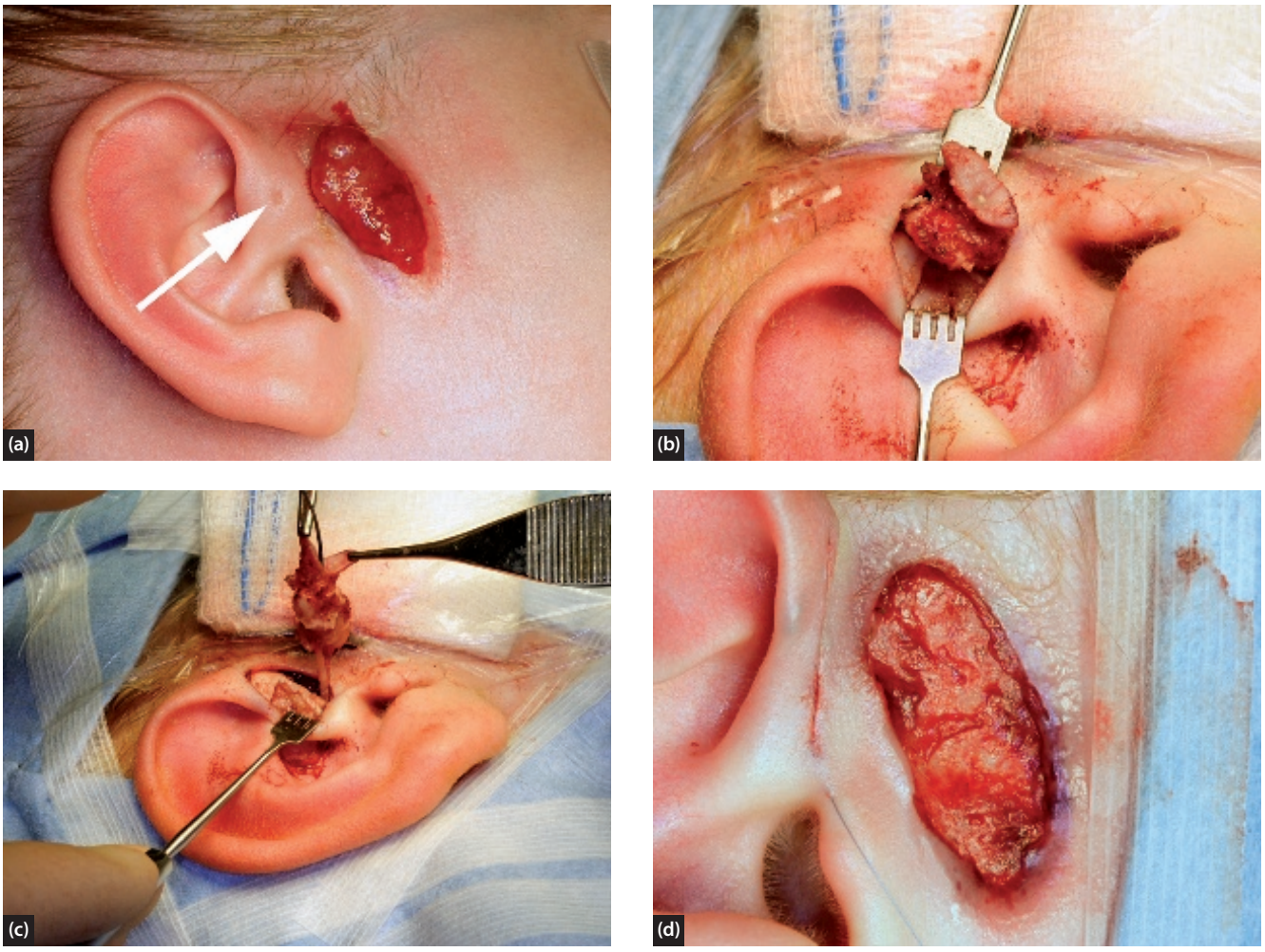

Figure 41.6 **(a)** Preauricular sinus right ear (white arrow) with lymphadenitis, skin breakdown and pre-parotid granulation tissue. **(b,c)** Excision of the sinus, cyst, sliver of cartilage and tract. **(d)** The area of skin breakdown heals by secondary intention following complete excision of the congenital epithelial tract.

involute during the weeks 8–10 of gestation and as a result an abnormal cyst may arise anywhere along the tract and may contain thyroid tissue.

Presentation

Despite being a congenital lesion, thyroglossal duct cysts often present later in childhood or early adulthood. The complaint is usually of a midline swelling in the neck although it can occur laterally, usually left-sided in around 10% of cases. The mass elevates on swallowing and tongue protrusion. It may present with a complication of infection or fistula formation to the skin if surgically drained.

Investigation

It is possible for the thyroglossal cyst to contain the only functioning thyroid tissue and therefore removal would result in hypothyroidism. Ultrasound is useful in confirming the diagnosis and the presence of a normal thyroid gland in the usual position. Cross-sectional imaging before revision surgery is advised to ascertain an intact hyoid bone or localize recurrent cyst.

Treatment

Treatment is nearly always surgical excision unless the cyst is very small and asymptomatic. If a fistula to the skin is present, this is excised with the underling cyst and tract. The definitive operation is that described by Sistrunk from the Mayo Clinic in 1920,[9] removing with the thyroglossal duct a portion of the hyoid bone, a portion of the raphe joining the mylohyoid muscles, a portion of each genioglossus muscle and the foramen caecum. If the surgery is performed as he described, recurrence rates can be kept below 5%; this was confirmed in a 2013 systematic review including 750 patients having primary surgery. Problems arise where there has been a deviation from Sistrunk's procedure resulting in an incomplete resection. Recurrence rates following incomplete excision rise to 27%.[10]

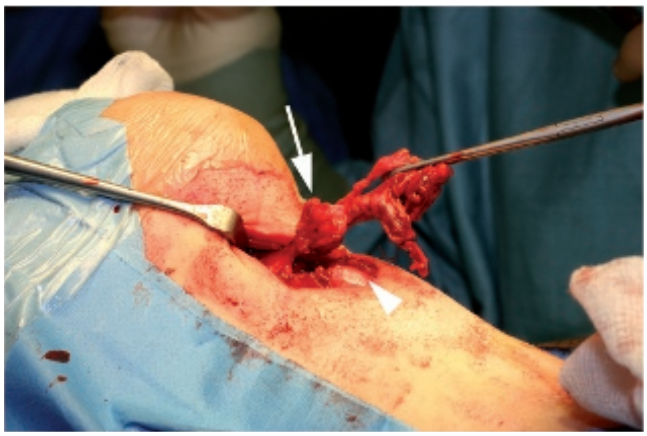

Figure 41.7 Extended Sistrunk procedure for thyroglossal duct fistula with skin paddle including fistula, soft tissue medial to straps, central hyoid (white arrow) and core of tissue towards foramen caecum. The white arrowhead indicates the laryngeal prominence/thyroid notch.

The operation has been developed further with an extended or modified Sistrunk procedure (Figure 41.7), which involves a wider block dissection incorporating the infrahyoid region to the thyroid isthmus initially used for recurrent disease but now applied to all patients to minimize complications.[11] Complications include haematoma, seroma, cyst recurrence, salivary fistula and hypoglossal nerve injury.

LINGUAL THYROID

Lingual thyroid is the result of failure of descent of the thyroid anlage from the foramen caecum of the tongue (Figure 41.8). It is a rare entity with prevalence of 1:100 000. Girls are more commonly affected.[12] In 70–80% of these cases, the lingual thyroid is the only thyroid tissue present. Up to one-third have hypothyroidism. Malignancy has been reported and seems to carry the same risk as thyroid in a normal cervical location.

Presentation

Depending on size, lingual thyroid can present with dysphagia, airway obstruction, haemorrhage or endocrine dysfunction. More often the patient is completely asymptomatic with suspicion only after other investigations, following routine ENT examination or detected on parental curiosity.

Investigations

Imaging will confirm lingual thyroid with either CT or MRI; sagittal views are particularly helpful. Unenhanced CT outlines the lingual thyroid well, given its hyperdensity compared with the surrounding tongue muscle, although MRI is preferred to avoid ionizing radiation. In addition to the lingual thyroid, imaging is used to identify if there is thyroid tissue in the normal cervical location. Ectopic thyroid has been reported in the oropharynx, larynx, infrahyoid neck, mediastinum, oesophagus and heart. Technetium (^{99m}Tc) thyroid scan will identify metabolically active thyroid tissue in the tongue base and no uptake in the neck. Thyroid function tests are usually normal but up to a third of patients demonstrate hypothyroidism; hyperthyroidism is rare.

Treatment

For small, asymptomatic lingual thyroids, suppression with TSH may be effective in checking growth. Reduction is often slow and dramatic results should not be expected. Paediatric endocrinology input is essential. Use of radioactive iodine for thyroid ablation is generally avoided in children. Surgical excision is occasionally required when significant obstructive symptoms are present or repeated or severe haemorrhage is an issue. Transoral resection is usually possible using nasotracheal intubation. For larger and deeper lesions, an external approach may be required. This may even necessitate planned tracheostomy for large masses where swelling and obstruction are inevitable. Lifelong monitoring of thyroid function is essential.

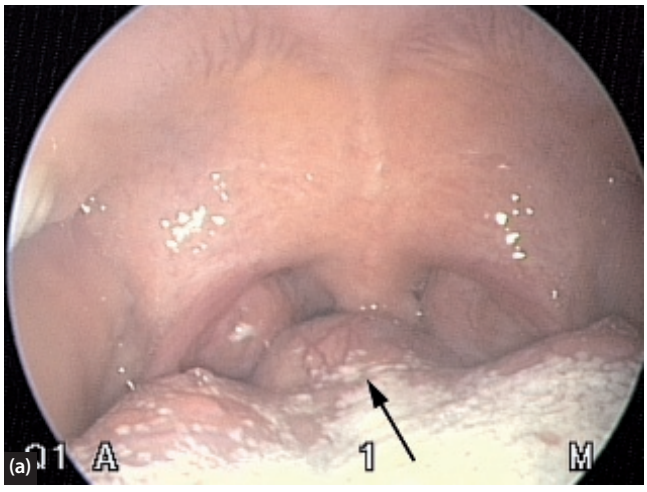

Figure 41.8 **(a)** Lingual thyroid arising from the foramen caecum on the tongue protrusion (black arrow). **(b)** Unenhanced axial CT imaging showing the lingual thyroid (white arrow).

NASAL DERMOID

Dermoid cysts contain ectodermal and mesodermal elements. They occur along the lines of embryonic closure. Nasal dermoids are a rare entity representing 3% of all dermoids and 12% of head and neck dermoids.[13] Incidence is estimated at 1:30000 births.[14]

There is debate over the origin of these cysts. One theory is that they originate from an embryological aberration resulting in inadequate closure of the fonticulus frontalis, allowing dermal tissue to extend between the nasal bones and cartilage. Dura can also extend through this area. The other theory involves the prenasal space, which is an area that runs in the midline between the developing nasal bone and underlying cartilage from the brain to the nasal tip. There is a suggestion that there is persistence of residual dura in this space which forms a contact with the skin and then it retracts to result in a sinus, in which a cyst develops.

A punctum may lie anywhere on the nasal dorsum and may discharge or even have hairs extruding, which is considered pathognomonic. The cyst will lie somewhere between the columella and the glabella (**Figure 41.9**). A tract may also extend superiorly and intracranially. Occasionally the tract connects with a median upper lip sinus.

Presentation

Clinical presentation may be simply a small punctum or isolated mass, often presenting at birth or soon after. Recurrent infection may be a problem and erosion through nasal bones, and periorbital and intracranial spread are unusual complications (**Figure 41.10**). Familial links have been reported.[15]

There are some reported associations with other congenital anomalies such as hydrocephalus, aural atresia and cardiac abnormalities.[16]

Differential diagnoses include glioma, encephalocoele and nasal polyposis.

Treatment

Complete excision is the treatment of choice. Early surgical excision is advocated to reduce bony distortion or atrophy and minimize infective complications. Bradley published results for surgery on nasal dermoids in children.[17] Lesions were classified into simple or complex, depending on involvement outside of skin and histologically described as true dermoid or epidermoid. Hartley et al. published a series of 103 cases and suggest a pragmatic staging system depending on deep extension of the lesion (**Figure 41.11**):[15]

- **superficial:** remain within the soft tissue and readily excised, also the most common
- **intraosseous:** extend to frontal and nasal bones, requiring drill out for excision
- **intracranial extradural:** breech the anterior cranial vault; can be accessed and excised through a frontonasal osteotomy and peeled from the dura
- **intracranial intradural:** most complex and may require bicoronal flap and frontal craniotomy; endoscopic transnasal approach may be possible.

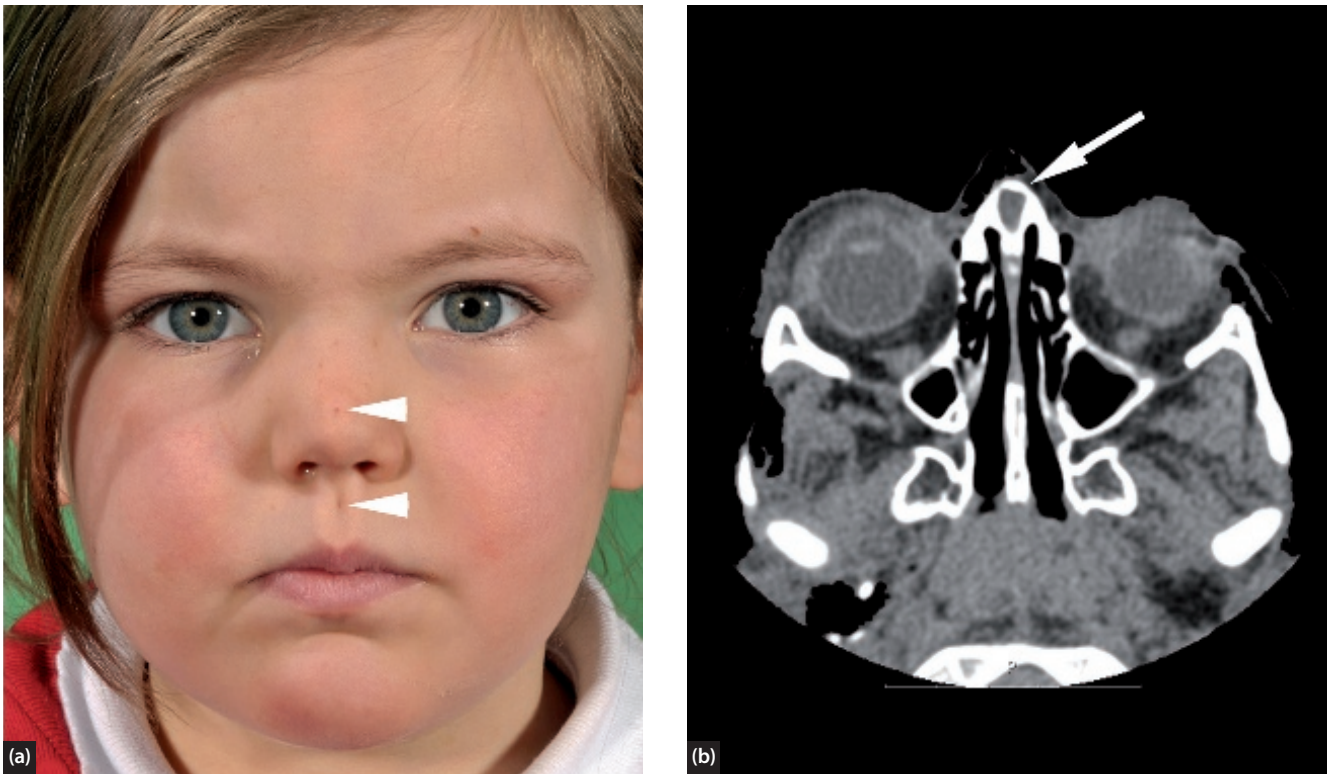

Figure 41.9 **(a)** Nasal dermoid sinus with associated philtrum sinus (white arrowheads). **(b)** Intraosseous extension nasal dermoid cyst deep to the nasal bones (white arrow).

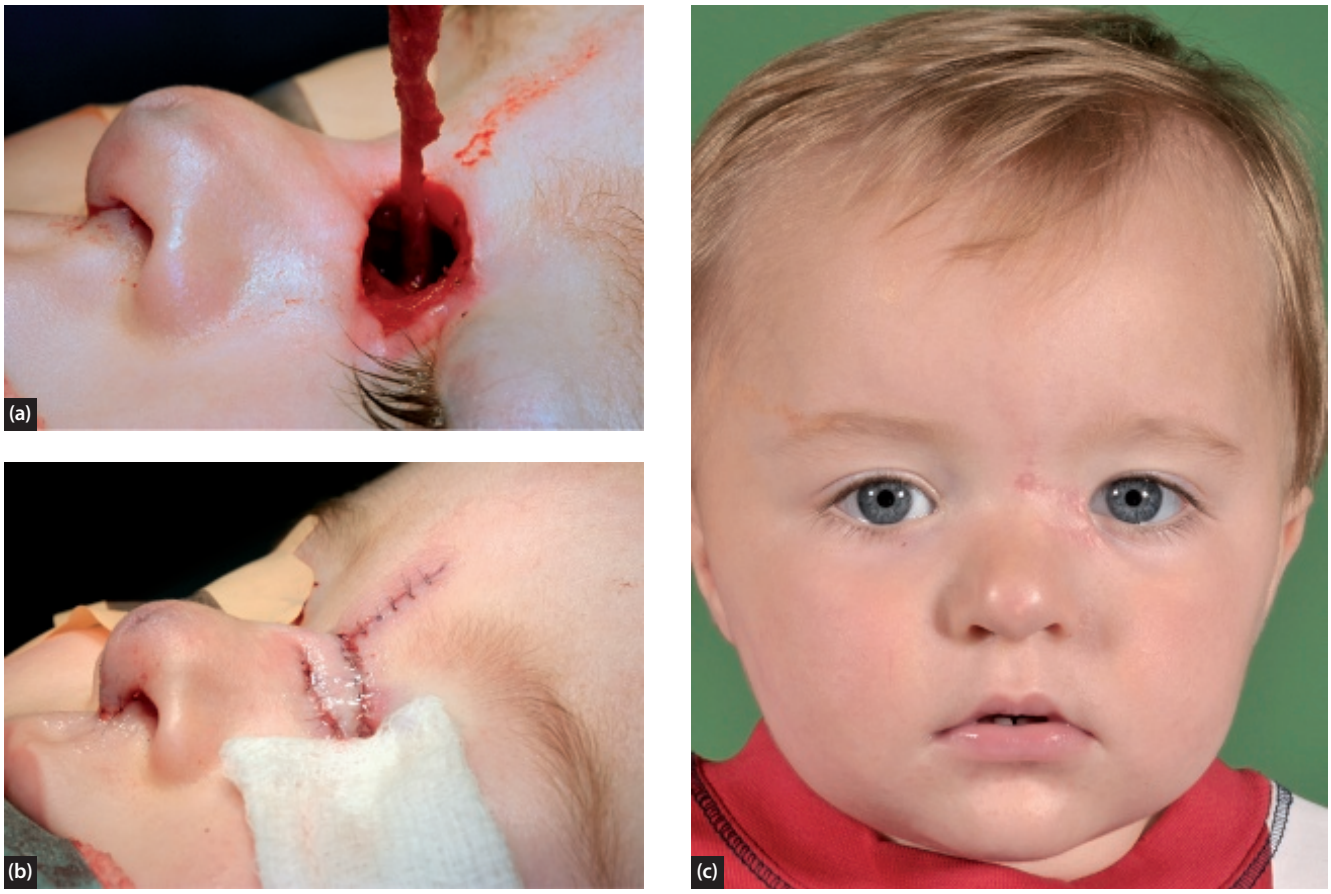

Figure 41.10 **(a)** Complication of intraosseous nasal dermoid cyst/sinus/tract with acute abscess and erosion with loss of skin and left nasal bone. **(b)** Combined surgical approach via external rhinoplasty and direct bishop-mitre rotation flap to replace skin loss. **(c)** Post-operative nasal contour satisfactory with new bone growth.

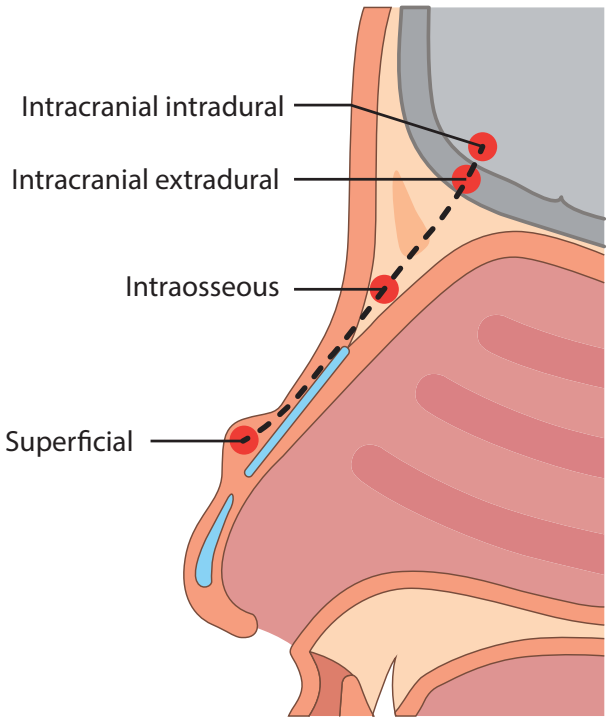

Figure 41.11 Hartley classification of nasal dermoids[15] (permission for reproduction granted from Elsevier publisher).

The position of the cyst or sinus does not predict the likelihood of intracranial extension. Extension has been reported in 4–45% of cases. Imaging is essential to exclude or confirm intracranial extension and planning surgical approach. Dual modality imaging with MR and CT is recommended for maximum understanding of bony and soft-tissue anatomy prior to surgical planning. Imaging is evaluated for size and location of the tract and signs of intracranial extension whether direct (intracranial high-signal cyst) or indirect (bifid crista galli, widened foramen caecum or cribriform plate defect).

Early surgical excision is recommended to prevent infections or further expansion, and consequent damage to surrounding tissue. In 1992 Koltai reported the external rhinoplasty approach for removal of complex nasal dermoids in children[18] and this has become the standard technique for superficial and intraosseous disease. The cosmetic results are good.[19] Identifying the superior limit and site of the dermoid will influence the surgical approach. Most will be adequately accessed via the external rhinoplasty approach or a direct midline incision as either allows access to the radix of the nose in a young child. Brow incisions and lateral rhinotomy are alternatives, and endoscopic techniques have been described more recently.[20, 21] If there is intraosseous extension, a median osteotomy of the nasal bones is required or in a young

child the otologic drill can be used to follow the disease superiorly. The post-operative appearance is very satisfactory and no bone reconstruction is required. A neurosurgical opinion is required for discussion around timing of surgery and to plan the single-stage craniofacial approach. In future, it may become possible to avoid an open craniotomy for some selected intracranial intradural lesions. Re et al. have described two paediatric cases of endoscopic endonasal removal of intracranial extradural dermoid cysts via hemitransfixion incision; however, resection of 1.5 cm superior septal cartilage is required for access to the nasal dorsum.[22] Long-term follow-up is required akin to management of cholesteatoma in the temporal bone; delayed interval MR imaging with diffusion restriction is advised to exclude recurrence.

CONGENITAL MIDLINE CERVICAL CORD AND CLEFT

Embryology

Congenital midline cervical cord/cleft (CMCC) is a rare congenital abnormality forming on the anterior neck which may extend to the mediastinum. It was first described by Bailey in 1924. Aetiology is unclear but it is felt to arise due to failed midline fusion of the second and third branchial arches.

Presentation

CMCC may present at birth with a cleft extending from the mentum to the sternum. There may be no external defect seen but a characteristic 'cord' seen or palpated below the skin when the neck is extended. If a cleft is present, serous discharge may be evident and the upper end will have a pseudonipple appearance.[23]

Imaging

CT or MRI allows characterization of the location and depth of the tract and differentiation from other midline congenital lesions.

Treatment

If there is no skin breakdown and the patient is asymptomatic, a conservative approach may be adopted. Surgery is indicated for cosmetic reasons and prevention of cervical contractures. Elective surgical excision is advocated using stepladder horizontal incisions or Z-plasty closure to avoid contracture (Figure 41.12).

SINUS STERNOCLAVICULARIS

Presentation

Sinus sternoclavicularis is usually present at birth with an asymptomatic sinus at or near the sternoclavicular joint, more often on the left side.

Imaging

Ultrasound allows characterization of the location and depth of the tract and confirmation of normal thyroid gland. Often no further imaging is required.

Treatment

If there is no skin breakdown and the patient is asymptomatic, a conservative approach may be adopted. Elective surgery is indicated for cosmetic reasons, usually involving excision of a blind-ending sinus which peters out adjacent to the sternoclavicular joint (Figure 41.13).

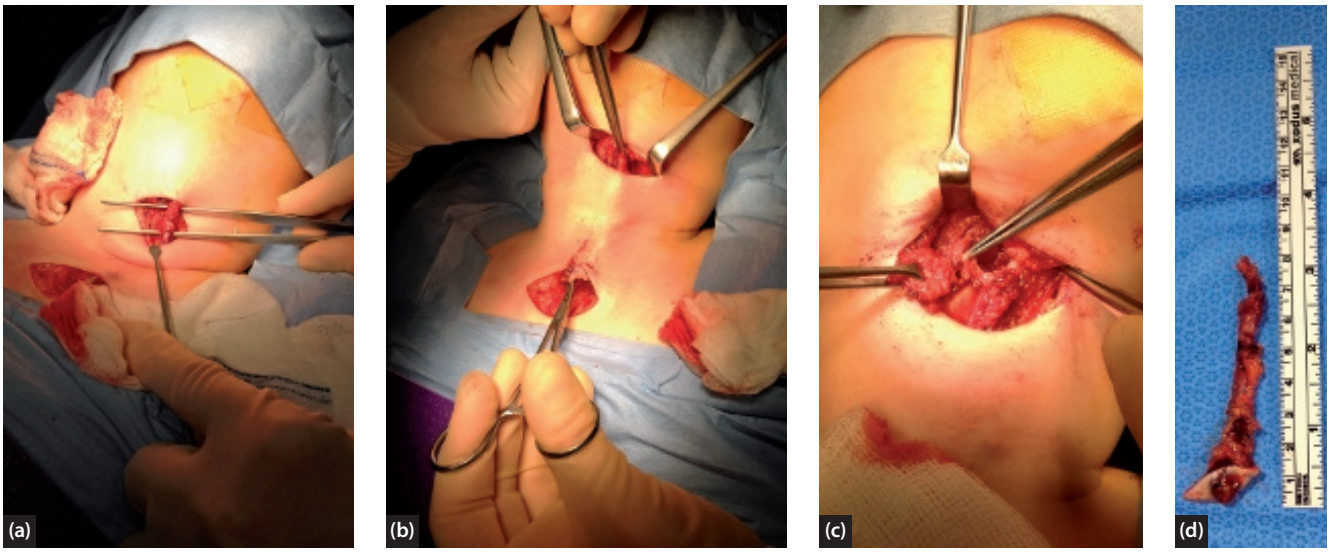

Figure 41.12 Unusual congenital midline cervical cord **(a)** with suprasternal sinus **(d)** removed using stepladder incision **(b)** attached to the thyroglossal tract **(c)**.

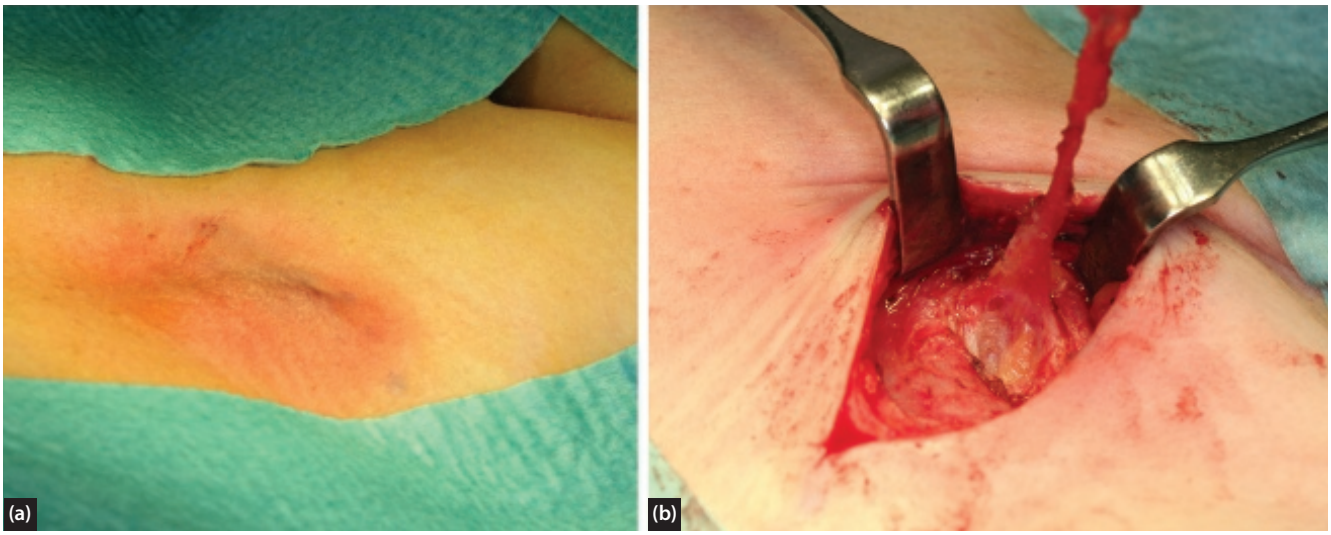

Figure 41.13 Excision of sinus sternoclavicularis.

KEY POINTS

- Congenital cervical anomalies can present as palpable cystic masses, infected masses, draining sinuses or fistulae.
- Thyroglossal duct cysts are most common, followed by branchial cleft anomalies and dermoid cysts.
- Branchio-oto-renal syndrome should be considered if bilateral preauricular pits and branchial sinuses present.
- Appropriate diagnosis and management of these lesions requires a complete understanding of their embryology and anatomy.
- Correct diagnosis, appropriate imaging, management of infection before planned surgery and complete surgical excision are essential to minimize recurrence.
- The extended Sistrunk's operation is the minimum procedure advised to reduce complication rate for thyroglossal cyst/ tract excision.

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CHAPTER 42

HAEMANGIOMAS AND VASCULAR MALFORMATIONS

Daniel J. Tweedie and Benjamin E.J. Hartley

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: vascular anomaly, vascular malformation, lymphatic malformation, venous malformation and haemangioma.

INTRODUCTION

Vascular anomalies include a number of conditions of distinct pathology, which may be classified as either vascular tumours or vascular malformations. Historically, these diverse lesions have been poorly understood. This is reflected in varied and often incorrectly applied terminology, difficulties in diagnosis and inconsistent approaches to management. This chapter considers the advances in our understanding of vascular anomalies, the subsequent evolution of nomenclature, classification and current management strategies. Such considerations are central to the optimum treatment of children and adults with these conditions and their sequelae.

HISTORICAL PERSPECTIVES

Vascular anomalies were first described histopathologically by Virchow. He separated them into angiomas and lymphangiomas, with later classifications of both groups into simplex, cavernosum and racemosum, according to histological appearance.[1] This system took no account of the varied biological behaviour of these lesions, nor their clinical characteristics. Subsequent attempts at classification were based on pathological and embryological properties, which again failed to correlate well with clinical behaviour. Poor understanding was further compounded by the use of a multiplicity of descriptive terms (such as port wine stain and strawberry naevus), often erroneously or ambiguously for several pathologically distinct entities.

Edgerton in 1976 proposed a three-category system according to whether the lesions remained unchanged without treatment, resolved spontaneously or alternatively progressed and/or caused growth in surrounding structures.[2] While recognizing a range of outcomes, this scheme failed to consider the underlying histological basis for the observed clinical manifestations.

Mulliken and Glowacki in 1982 were the first to produce a practical clinical classification for vascular anomalies according to histological appearance, histochemistry and clinical behaviour, separating them into haemangiomas and vascular malformations.[3] This classification has been supported by subsequent clinical, radiological and biochemical studies.

Widespread confusion surrounding terminology and appropriate management of vascular anomalies persists nonetheless. This chapter addresses the biological basis, clinical manifestations and natural history of these distinct diseases, the understanding of which is central to their proper management.

CORRECT NOMENCLATURE

The dichotomous biological system of Mulliken and Glowacki[3] originally considered vascular lesions in infants and children as haemangiomas (with proliferating and involutional phases) or malformations (capillary, venous, arterial, lymphatic and fistulae). This simple classification has since been modified somewhat by the International Society for the Study of Vascular Anomalies (ISSVA) in 1996, taking into account advances in histopathology, histochemistry and radiological imaging (**Box 42.1**).[4] **Vascular tumours** now represent a group of lesions which includes haemangioma subtypes in addition to other rarer tumours, and **vascular malformations** are now described according to whether they are **slow-flow**, **fast-flow** or **complex**. In parallel with these adjustments, the ISSVA has recommended that older terms such as 'angioma' and 'birthmark' should be discarded. The suffix -oma should be used only in the context of a proliferating tumour and should therefore not be applied to vascular malformations.

BOX 42.1 Updated ISSVA classification of vascular anomalies (1996)[4]

Vascular tumours	Vascular malformations

• Infantile haemangiomas
• Congenital haemangiomas (RICH, NICH)
• Tufted angioma (with or without Kasabach–Merritt syndrome)
• Kaposiform haemangioendothelioma (with or without Kasabach–Merritt syndrome)
• Spindle-cell haemangioendothelioma
• Other rare haemangioendotheliomas
• Dermatological acquired vascular tumours (pyogenic granuloma, targetoid, glomeruloid and microvenular haemangiomas)
	Slow-flow malformations
	• Capillary malformation (CM)
	  • Port wine stain
	  • Telangiectasia
	  • Angiokeratoma
	• Venous malformation (VM)
	  • Common sporadic VM
	  • Bean syndrome
	  • Familial cutaneous and mucosal VM
	  • Glomerulovenous malformation
	  • Mafucci syndrome
	• Lymphatic malformation
	Fast-flow malformations
	• Arterial malformation (AM)
	• Arteriovenous fistula (AVF)
	• Arteriovenous malformation (AVM)
	Complex combined vascular malformations
	• CVM, CLM, LVM, CLVM, AVM-LM, CM-AVM

C, capillary; V, venous; L, lymphatic; AV, arteriovenous; M, malformation; RICH, rapidly involuting congenital haemangioma; NICH, non-involuting congenital haemangioma.

VASCULAR TUMOURS

Vascular tumours may or may not be present at birth, and grow by cellular (predominantly endothelial) hyperplasia. Haemangiomas are certainly the commonest type although a number of other vascular tumours are occasionally seen, most often acquired, sometimes in the presence of syndromes. Advances in histopathology have allowed further subdivision within these groups adding to the original haemangiomas grouping of Mulliken and Glowacki.

HAEMANGIOMAS

Presentation and natural history

Haemangiomas are the commonest tumours in white infants, present in up to 10–12%.[5] Two-thirds are found in the head and neck, with a female : male ratio of 3–5 : 1. This is in contrast to vascular malformations, which have no gender preponderance. Extremely premature infants (birth weight <1000 g) are at particular risk, with around 30% affected. They are less common in non-Caucasians. Most lesions are solitary, with multiple cutaneous lesions being associated with a higher risk of visceral involvement. Facial haemangiomas tend to be found in a segmental distribution, and particularly along lines of embryological fusion.

Haemangiomas have recently been subdivided according to presentation and behaviour as **congenital**, by definition present and obvious at birth, and **infantile**, the commoner variants, which usually proliferate from original pink macules during the first 2 months of life.[6] Congenital haemangiomas (CH) have been further categorized by rate of involution as **rapidly involuting** (RICH), **non-involuting** (NICH) or **non-progressive**.

Their precise appearance may vary significantly according to their depth (superficial, deep or visceral) and subsite, but location does not influence biological behaviour (**Figures 42.1** and **42.2a**). Cutaneous lesions may appear as a patch of erythema, a blanched area or telangiectasia with a peripheral pale halo, and they may be confused with other vascular anomalies such as venous malformations. The child may alternatively present primarily with visceral

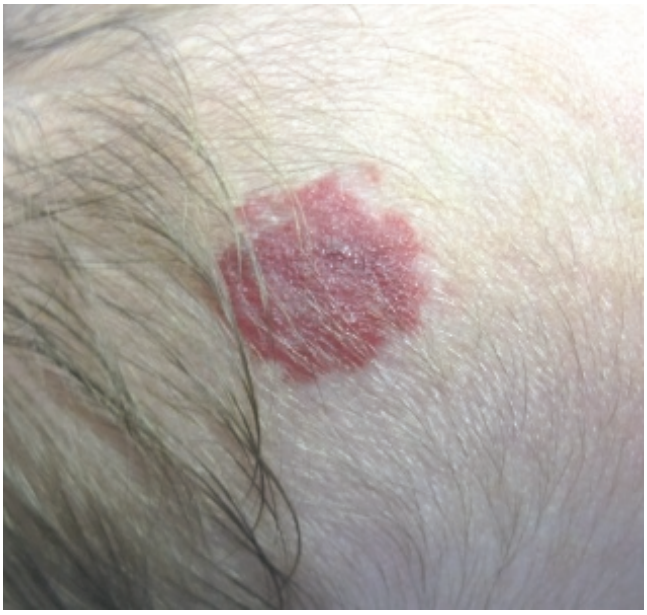


Figure 42.1 Cutaneous frontal haemangioma, infantile type. This child presented at the age of 2 months with worsening stridor secondary to a subglottic haemangioma.

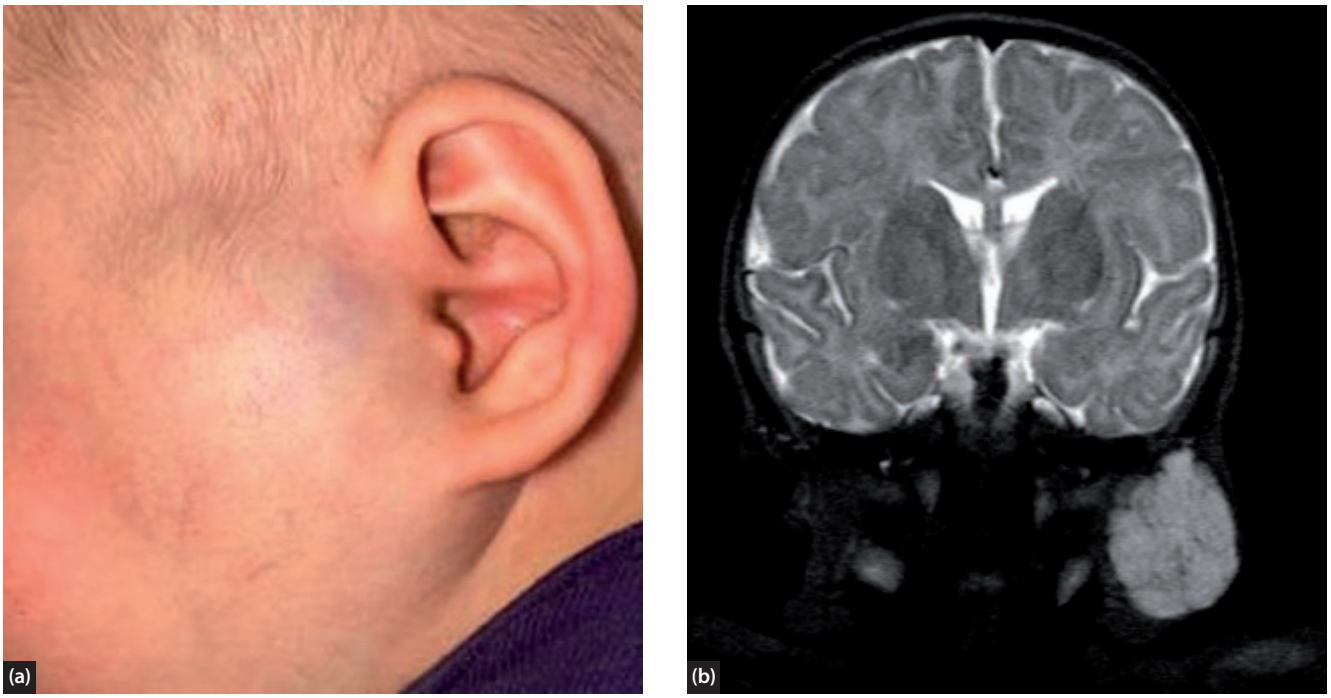


Figure 42.2 Parotid haemangioma. (a) Clinical appearance. Note the blue hue, hence the differential diagnosis of vascular malformation. **(b)** Coronal T2-weighted MRI of the same patient. The haemangioma is of moderately high-signal intensity, with small, scattered linear flow voids of associated vessels.

manifestations (such as stridor secondary to a subglottic haemagioma): only a small proportion of patients with cutaneous disease will also have visceral lesions, but around 50% of those with visceral haemangiomas will have no cutaneous manifestation. The overall picture, certainly for the infantile type, is one of proliferation and rapid tumour growth, resulting in a tense and minimally compressible mass which will tend to plateau in size by 4–8 months of life. This is reflected by progressive cutaneous and/or visceral effects which develop during early infancy. Alternatively, the progress of CH is more variable. Together with their presence at birth, this variability may also promote confusion with vascular malformations.

Involution of haemangiomas tends to begin at around 1 year of age, and continues for the next 5–7 years.[6, 7] An overlapping period of proliferation and involution may be seen.[5, 7] Some 50% of haemangiomas will have completely involuted by the age of 5 years and 70% by 7 years with some further involution seen in the remainder by age 12. The only factor associated with improved outcome is an early age of first involution. Importantly, patients and parents should be aware that permanent skin changes (loose skin, altered colouration, telangiectasia and scarring) may occur in over 50%, even after complete tumour involution.[7]

Most cases have no obvious genetic basis, although some may be inherited in an autosomal dominant fashion, with a possible locus on chromosome 5q.[8] Associations have also been noted. Large cervicofacial haemangiomas are seen in conjunction with other malformations in about 10% of cases (PHACES syndrome: **P**osterior cranial fossa malformation, including Dandy–Walker; **H**aemangiomas; **A**rterial anomalies, including absent carotid or vertebral vessels; **C**ardiac anomalies; **E**ye anomalies; **S**ternal anomalies, bifid or cleft).[9]

The majority of those affected are girls (90%), with a particular risk of thromboembolic stroke in childhood. Otherwise, there is thought to be an increased likelihood of laryngeal involvement in those with a facial haemangioma in a beard distribution,[10] and spinal, anorectal or urogenital abnormalities in patients with lumbosacral lesions.

Cellular basis

Histologically, haemangiomas comprise proliferating immature endothelial cells and disorganized vessels. Various theories for the development of haemangiomas have been proposed.[11] They are thought to arise as a result of abnormal angiogenesis, which leads to uncontrolled endothelial proliferation. This may be due to **intrinsic** endothelial cell anomalies (favoured by the chromosome 5q inheritance patterns), resulting in hyperplasia from a single abnormal cell, and/or as a result of an abnormal, **extrinsic** cellular environment. Implicated in either process is an interplay between a variety of angiogenetic markers, including fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), and angioinhibitory substances, such as tissue metalloproteases. Glucose transporter-1 (GLUT-1) is a specific marker for infantile haemangiomas, with 97% of these lesions testing positive for this.[12, 13] GLUT-1 is otherwise only found in the placenta and endothelium of the blood–brain barrier. This may have implications for the diagnosis and management of infantile haemangiomas versus other lesions, which will not have the same cellular markers, and respond differently to treatments including propranolol. Apart from endothelial cells, other lineages are also involved, including mast cells, fibroblasts and macrophages. The up- and

down-regulation of these cells at various times is believed to account for the variability in proliferation and involution manifested clinically.

Diagnosis

The mode of diagnosis will depend typically upon the site and clinical presentation. Cutaneous lesions are most often diagnosed clinically, although they may be difficult to distinguish from the main differential diagnoses, namely macular stains, vascular malformations and other rarer vascular tumours.

Macular stains are common vascular cutaneous lesions, also known by a number of terms such as 'stork bite' or 'salmon patch'. These are flat, usually pink to red, and are typically seen on the face or neck. They are physiological and will tend to resolve, without the dramatic proliferation exhibited by haemangiomas. Vascular malformations are usually distinguished by being present at birth and growing proportionally with the child, although these differences may be subtle, particularly in congenital cases during infancy.

Investigations may be required in those difficult cutaneous cases or where visceral involvement and/or other associations are suspected. Diagnostic imaging, in the form of ultrasound, magnetic resonance imaging (MRI), computerized tomography (CT) with contrast or arteriography will usually distinguish haemangiomas very well. For deeper lesions, MRI is preferred, demonstrating a lobulated soft-tissue mass with flow voids (feeding and draining vessels). The mass is iso- or hypo-intense on T1 and hyper-intense on T2 weighting, respectively (**Figure 42.2b**). Alternatively, other modes of tailored investigation, such as diagnostic microlaryngobronchoscopy, may be appropriate for visceral lesions.

Complications

The sequelae and complications of haemangiomas will depend upon their anatomical subsite, size and depth. There may also be complications associated with related pathologies.

Permanent skin changes and cosmetic abnormalities are anticipated in a significant proportion of cases, particularly those with large superficial facial lesions and where involution has been slow or incomplete.[7] Excisional surgery and scar management (by means of Z-plasty and other releasing techniques) may be indicated. Ulceration affects fewer than 5% of cases. This is most commonly seen with perioral and perineal lesions, perhaps related to increased day-to-day skin trauma in these areas. The risks of associated infection are significant. Scrupulous wound care and antibiotic ointments may allow these areas to resolve, but excision or medical treatment may be required.

Obstruction of the visual axis by periorbital haemangiomas is occasionally seen, and demands a circumspect, multidisciplinary management approach. In the case of large periorbital lesions, vision may be obstructed as a result of the haemangioma protruding across the globe, or alternatively pressing on and distorting the cornea. In rarer instances, intraorbital lesions may compress the conal muscles, producing diplopia. The mammalian visual cortex is extremely sensitive to stimulus deprivation during the first year of life, such that permanent amblyopia may develop within as little as 1 week of such insults. Urgent referral to a paediatric ophthalmologist is therefore mandatory, stressing the importance of treatment without delay.

The ear canal may also become obstructed by parotid haemangiomas, occasionally resulting in conductive hearing loss, with the secondary risk of speech delay.[5] Active treatment should be considered in these circumstances, particularly for rare bilateral lesions, albeit on a non-emergency basis.

Airway obstruction by haemangiomas may occur at several possible levels, and it should be noted that in up to 50% of cases there may be no cutaneous manifestation to raise diagnostic suspicion. Nasal obstruction from cutaneous haemangiomas is often obvious, although endonasal disease may lead to insidious, progressive obstruction in infants, who are obligate nasal breathers. Subglottic haemangiomas (**Figure 42.3**) typically present with progressively worsening stridor from 2–3 months,

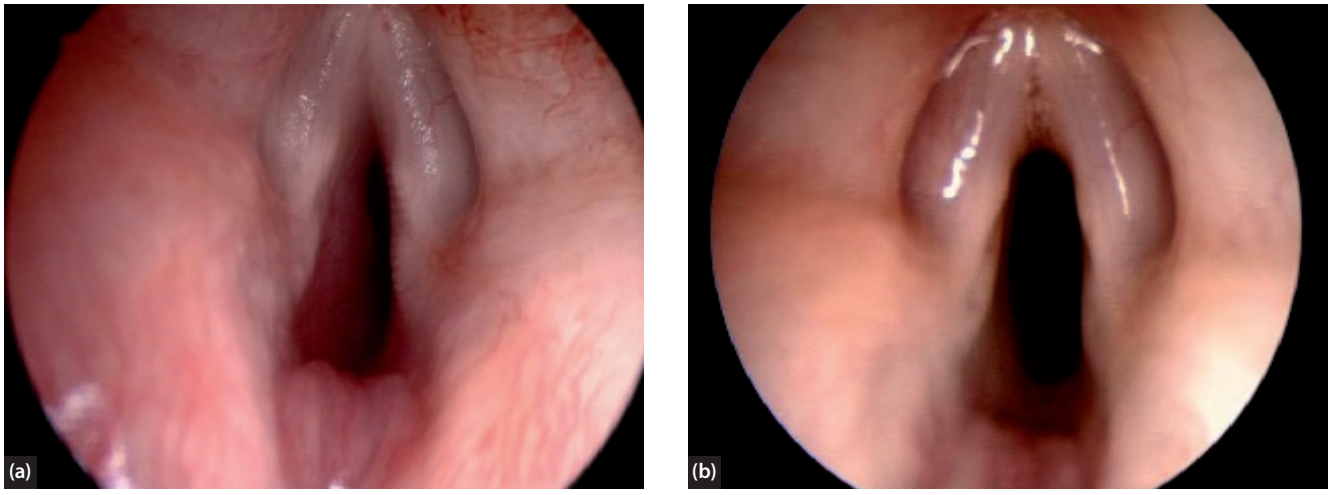


Figure 42.3 Subglottic haemangioma. (a) First presentation in a 3-month-old infant. **(b)** Same patient aged 6 months, after 3 months' treatment with propranolol.

with eventual airway obstruction, in the absence of other obvious precipitants or symptoms. Medical treatment with propranolol is now the mainstay of management of these cases, although tracheostomy and/or open excision via laryngofissure are occasionally still required.

Congestive cardiac failure is an unusual complication, seen most often in the context of either diffuse disease in the neonatal period or alternatively as a result of arteriovenous fistulation within large visceral haemangiomas, causing cardiac insufficiency.[10]

Management

Assuming a correct diagnosis is reached as early as possible, treatment of haemangiomas should be tailored according to the individual patient, taking into account the local and systemic effects of lesions and associated complications. For the majority of haemangiomas, particularly smaller ones, active monitoring and reassurance for the parents will usually suffice. But it is worth emphasizing that the onset and rate of involution are variable, and residual tumour, scarring and other skin changes may compromise the final cosmetic outcome. Lesions which are larger and affect function, or those resulting in significant complications, will usually require non-surgical treatment (typically propranolol) and/or surgical intervention. This is most appropriately delivered in a multidisciplinary setting, combining dermatologists, paediatricians and plastic, general paediatric and ENT surgeons as necessary. The merits of any intervention, medical and/or surgical, must be evaluated in each case, bearing in mind the long-term risks of waiting for natural resolution. Additionally, most medications are not licensed for these applications in young children, which should also be explicit from the outset.

Non-surgical treatment: Propranolol

Propranolol has revolutionized the management of children requiring active treatment for haemangiomas, largely replacing other medical treatments and, in many cases, surgery. Its efficacy was first described by Leauté-Labrèze and her team from Bordeaux, France, who noted a dramatic reduction in size of a nasal haemangioma in a child receiving propranolol for cardiomyopathy.[14] The mechanisms of action are not entirely clear. Vasoconstriction, a direct beta-blocker effect, will allow the haemangioma to become softer and paler, often within 24 hours of treatment, with decreased expression of FGF and VEGF and promotion of apoptosis perhaps accounting for accelerated resolution. Cyclic AMP (cAMP) and tyrosine kinase pathways are also now thought to mediate the actions of propranolol in promoting apoptosis.[15, 16]

Following successful use locally[17] at other paediatric centres, propranolol is the preferred option for children with subglottic haemangiomas and, with time and a better appreciation of the sequelae of propranolol use in children, this treatment can be considered for haemangiomas in other locations, particularly those impacting the vision, other functions, and large lesions in cosmetically sensitive areas. Patients are often managed jointly by ENT and dermatology departments, with additional input from other specialities as required. A full clinical assessment is made prior to treatment, and a number of blood tests are organized (to exclude anaemia, coagulopathy, diabetes, and renal, hepatic and thyroid abnormalities). Baseline pulse and blood pressure assessments, electrocardiography and echocardiography are also mandatory. Further radiological imaging and other investigations may be arranged in addition to the original diagnostic methods (including microlaryngobronchoscopy).

Although the precise regime varies between centres, a consensus statement in 2012 suggested a target dose of 1–3 mg/kg per day in three divided doses, after appropriate screening.[18] In our practice, propranolol is commenced at 1 mg/kg/day, in three divided oral doses. At this point, and at any time the dose is increased, pulse rate and blood pressure are checked every 30 minutes for the first 2 hours before allowing the child home. The dose is increased to 2 mg/kg/day after the first week of treatment, with further adjustments over the coming months to match the child's weight gain. Blood pressure is checked twice weekly for the first 2 weeks, and then weekly thereafter. Side effects are sought, typically minor (weakness, fatigue, altered sleep) or occasionally major (bronchospasm, hypotension, bradycardia and hypoglycaemia), although these are more often seen in neonates than in older children. Propranolol should not be used in asthmatics, or together with salbutamol and other selective beta-2 agonists.

Serial assessment (clinical and endoscopic, in the case of subglottic lesions) allows monitoring of initial response to propranolol. This is typically done at 6 weeks and then 3-monthly for the first year, covering the proliferative phase of disease. Weaning from propranolol in stages may then be possible, usually over about 4 weeks.

The response of infantile haemangiomas to propranolol occurs within a few days, during the proliferative period in 97% of cases.[19] Where minimal response is seen, one should consider differential diagnoses, and biopsy of the lesion, with staining for GLUT-1.

For smaller, superficial lesions, topical timolol has shown some benefits in the treatment of infantile haemangiomas.[20, 21]

Non-surgical treatment: Other

In some cases, the response to propanolol is less dramatic. In these circumstances, other medical treatments may be considered. These include corticosteroids, once the mainstay of medical management. Previous studies have confirmed resolution rates reaching 90% for haemangiomas treated with prednisolone 2–3 mg/kg/day, tapered down over several months.[22] But side effects are unfortunately frequently seen, including rebound lesion growth, Cushingoid facies, altered mood, gastritis and growth retardation. Oral steroids are therefore now seldom used for haemangiomas in our practice, given in conjunction with propranolol if the initial response to this has been limited, or if the lesions are large and complicated.

Injection therapy with corticosteroids and alpha-interferon has been used historically, with variable success reported, mainly for those patients with poor response to oral steroids. Similarly, systemic chemotherapy (with cyclophosphamide and vincristine) and radiotherapy have both been shown to arrest the proliferative phase of haemangiomas. However, these modalities may all produce serious local and systemic side effects and are not used routinely in our current practice. Other non-surgical treatments have included cryotherapy. While effective in some superficial lesions, it often results in unacceptable scarring, and has therefore fallen out of favour.

Compression therapy has been attempted, although formal data regarding its efficacy are lacking, and it is not usually a practical option for head and neck lesions, particularly in infants. Embolization is occasionally attempted for larger, highly vascular haemangiomas, particularly those associated with life-threatening complications. This is most often done to facilitate surgical excision, although there are reports of embolization alone leading to rapid regression.[23]

Surgical treatments

Excision, via a variety of methods, remains a reasonable option in some cases, particularly those with poor response to propranolol and other medical treatments. Alternatively, as a primary treatment, direct excision of cutaneous and subglottic disease, for example, will have the potential for complete cure from the outset, in contrast to medical therapy which requires a long period of treatment, regular follow-up and carries significant risks of its own. The relative benefits of surgery in this context should not be overlooked, and must form part of the initial multidisciplinary discussion of treatment options. It is also very reasonable in some cases to employ a dual modality approach, using propranolol to reduce proliferation, followed by excision as necessary.

Laser therapy, using a variety of types (carbon dioxide, pulsed dye, Nd-YAG, argon and KTP) has been used predominantly for cutaneous lesions. Partial laser-assisted excision of lesions around the eye, for instance, allows rapid clearance of the visual axis, in contrast to medical treatment, which may take longer to achieve the same effect. The laser energy may be delivered superficially or intralesionally, particularly for deeper haemangiomas. The authors caution against laser treatment for subglottic haemangiomas because of the risks of circumferential scarring and stenosis, and favour open excision via laryngofissure as a second-line treatment after propranolol.

OTHER VASCULAR TUMOURS OF CHILDREN

Kaposiform haemangioepitheliomas

Kaposiform haemangioepitheliomas are vascular tumours which behave far more aggressively than simple haemangiomas, from which they have only recently been definitively distinguished. They are often associated with thrombocytopaenia, known as Kasabach–Merritt syndrome (KMS). Consumptive thrombocytopaenia is believed to occur as a result of platelet trapping within extensive lesions. This may itself result in secondary coagulopathy, as clotting factors and fibrinogen are used up. Disseminated intravascular coagulation may then develop, with an overall mortality risk in KMS of 30–50%.[24] Importantly, in contrast to previous suggestions, KMS is not associated with simple haemangiomas.

Kaposiform haemangioepitheliomas can be distinguished clinically, histologically and radiologically from haemangiomas. Both may be seen congenitally, but haemangioepitheliomas tend to have equal gender incidence, and are more often seen outside the head and neck, sometimes in the retroperitoneum. Traditional therapeutic options have been similar to those for haemangiomas, although high-level evidence for these treatments in this context is lacking. In practice, given the high risk of KMS and other serious complications, multimodality treatment is often used, including corticosteroids, chemotherapy, embolization and/or excision, together with parallel treatment of coagulopathy. Propranolol has also been used with some success in a small number of cases, prescribed long-term after a brief initial course of chemotherapy.[25] It is important that heparins should not be used to manage the thrombocytopaenia of KMS, as they may lead to increased FGF release, itself associated with increased tumour proliferation.

Tufted angiomas

Tufted angiomas – also known as angioblastomas – are very similar to kaposiform haemangioepitheliomas. Indeed, these lesions may represent a spectrum of pathology rather than separate entities. KMS may complicate tufted angiomas in the same fashion, and treatment options are similar.

Pyogenic granulomas

Pyogenic granulomas are acquired vascular lesions which are very similar in appearance to haemangiomas but are typically seen in older children and young adults. In contrast to popular belief, they tend to arise suddenly and without a history of trauma. Treatment options include surgical excision, laser ablation and chemical or electrocautery.

Haemangiopericytomas and angiosarcomas

Congenital haemangiopericytomas are very rare tumours, found in the extremities of newborns. Biopsy and surgical excision may be required.

Angiosarcomas are uncommon malignancies in children. They typically arise in the liver and behave aggressively, metastasizing to the lungs. Prognosis is very poor.

VASCULAR MALFORMATIONS

Vascular malformations, in contrast to vascular tumours, have normal endothelial mitotic activity and are errors of morphogenesis.[4] They are present at birth, although some may not initially be obvious, and they grow with the child. They do not involute, but may vary in size with time according to inflation with fluid and/or blood and subsequent deflation. At a molecular level, the markers of proliferation (such as VEGF and FGF) and endothelial proteins (GLUT-1, merosin, Fcγ receptor II), seen frequently in association with vascular tumours, are not usually elevated in vascular malformations.

The clinical impact of these lesions is very variable, depending on location, size, subtype and shunts, ranging from mild cosmetic deformity to life-threatening airway obstruction or haemorrhage. Several varieties are described, according to their cellular components and flow characteristics (**Box 42.1**). These distinctions greatly influence appropriate management. Vascular malformations are associated with skeletal abnormalities in up to 35% of cases and other malformations and syndromes.

SLOW-FLOW VASCULAR MALFORMATIONS

Capillary malformations

Capillary malformations (CMs) occur in 0.1–0.3% of live births,[26] although they may be overlooked in the neonatal period as a result of generalized plethora and/or anaemia. Most involve the head and neck, particularly in the distribution of the trigeminal nerve (**Figure 42.4**). They consist of postcapillary venules within the papillary and superficial reticular layers of the dermis, hence the alternative term **venular malformations**. Initially presenting as flat, pink areas, they have a tendency to darken in colour with age (port wine stain) and to thicken, with a cobblestoned surface in two-thirds of affected adults. Some will develop associated pyogenic granulomas. This evolving appearance is believed to result from abnormal neural modulation of the sympathetic papillary plexus, with vessel thickening and dilatation in the absence of proliferation. Lesions may be graded I–IV (the Waner classification) according to the degree of vessel ectasia, thought to be related to the degree of sympathetic denervation.[27] This system correlates well with clinical severity and treatment outcomes.

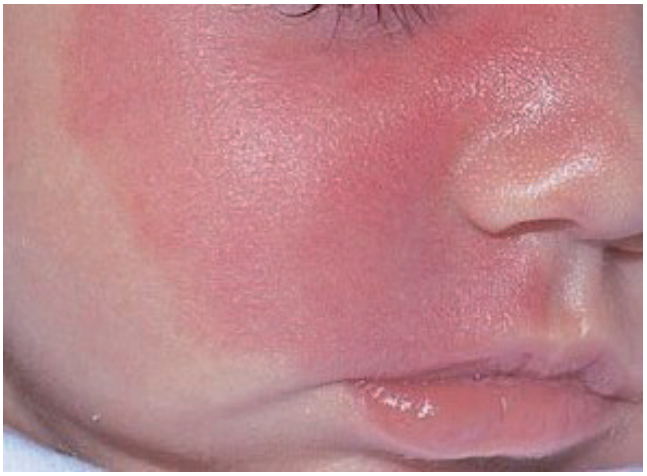


Figure 42.4 Capillary malformation in the distribution of the maxillary division of the trigeminal nerve. Even in an infant, the skin in this affected area is slightly thickened and raised. Without treatment, this thickening is likely to progress with time.

Although most cases are isolated, some may be associated with syndromes and/or other vascular malformations. These include Sturge–Weber syndrome: CM in the distribution of the ophthalmic branch of the trigeminal nerve (CN V1), seizures of neonatal onset, cataracts, learning difficulties and ipsilateral leptomeningeal angioma. Importantly, patients with large facial CM in the distribution of V1 may have ocular involvement, including glaucoma, and/or central nervous system involvement without other features of Sturge–Weber syndrome. Klippel–Trénaunay syndrome (CM, varicose veins, central visceral varices, lower limb hemihypertrophy) is rarer, with complications including variceal haemorrhage and thromboembolic events. These features together with the addition of an arteriovenous malformation (AVM) comprise the Parkes Weber syndrome, presenting in childhood with an enlarged, warm extremity.

Rarer associated syndromes are also described, such as Cobb syndrome (CM overlying the spine, with associated spinal meningeal vascular malformations) and Wyburn-Mason syndrome (facial CM with associated unilateral AVM of the retina and intracranial optic pathway).

In keeping with other vascular malformations, CM may be associated with skeletal and limb abnormalities, even in the absence of other syndromic features.[28] This is particularly the case for lesions overlying the spine, especially if these are multiple and lumbar, for which MRI is indicated.

TREATMENT

In the first instance, careful clinical assessment should confirm the diagnosis, although further investigations (including imaging) may be necessary to exclude associated pathology. For example, suspected syndromic cases should undergo MRI (with gadolinium enhancement) to exclude cerebral and spinal lesions, although these may not always be evident in early life, such that serial scanning may be necessary. A supportive, multidisciplinary approach to treatment and follow-up is essential in these cases, often requiring parallel ophthalmological and neurological/neurosurgical input.

At a simple level, cosmetic cover-up creams may be beneficial. Tattooing with skin-coloured pigments has also been used, albeit not in routine practice. Neither of these approaches, however, will alter the lesions' natural history. Any specific treatment of CM must take into account a typically progressive deterioration in appearance, which may be accelerated by trauma and puberty,

and its associated psychosocial impact. Earlier intervention is therefore now considered in some centres, even before 1 year of life, although the relative benefits of such early therapy are likely to be more psychosocial than physical, and have not been unequivocally demonstrated.

Treatment options depend to some extent on vessel diameter. Pulsed dye laser is widely accepted as the treatment of choice for CM,[29] targeting the oxyhaemoglobin chromophore in abnormally dilated superficial vessels to allow selective thermolysis. Ultra-short laser pulses are used, particularly at wavelengths of 577 nm or 585 nm, limiting lateral thermal injury and related risks of scarring. Some lesions, particularly those which are thicker and more cobblestoned, may not respond well to pulsed dye laser, in which case other lasers (KTP, copper, argon) may be used, although scarring, hyper- and hypo-pigmentation are more likely.

Multiple treatments are typically needed, between two and six on average. Reviews of various studies suggest that the response will vary according to depth, colour and location of the lesion (best on the neck, then torso and face, worst on the hand and arm), as well as the extent of previous therapy and the age of the patient, although the optimum treatment age is not known. Recurrence of CM is common in these circumstances, up to 50% at 4–5 years, most probably representing persistence of vessels innervated by the abnormal papillary plexus. Interval treatments which touch up areas of residual vessel ectasia are therefore an alternative strategy. Depending on forthcoming clinical trials, future options might include laser speckle and photoacoustic imaging to allow more precise assessment of the local effect of laser treatment, or alternatively treatment with anti-angiogenic compounds such as imiquimod (used primarily, or just after laser therapy).[30, 31]

OTHER VARIANTS OF CAPILLARY MALFORMATIONS

Telangiectasias, visible dilated vessels in the skin or mucosal surfaces, are very common in the population, increasing in incidence with age. The great majority are **primary** or **essential**, with no obvious precipitant. In many cases, telangiectasias are found in a symmetrical malar distribution. Alternatively, **generalized essential telangiectasia** affects a smaller number, typically seen first on the distal lower limbs, then more proximally. The pathophysiology is unknown. Treatment options include active monitoring, cover-up creams, topical agents (including ketoconazole), systemic treatments (such as tetracyclines and acyclovir) and pulsed dye laser. **Secondary telangiectasias** are seen in systemic disorders such as hereditary haemorrhagic telangiectasia and chronic liver disease.

Angiokeratomas are vascular ectasias which involve the papillary dermis. Several variants are described, with elements of papillomatosis and hyperkeratosis in addition to vascular dilatation. Like other CMs, some have associations including Klippel–Trénaunay syndrome and Cobb syndrome. Importantly, some variants including **angiokeratoma circumscriptum** may be mistaken for melanoma; excision biopsy is indicated in these circumstances. Appropriate treatment depends on the subtype, with options including observation, laser therapy or excision.

Venous malformations

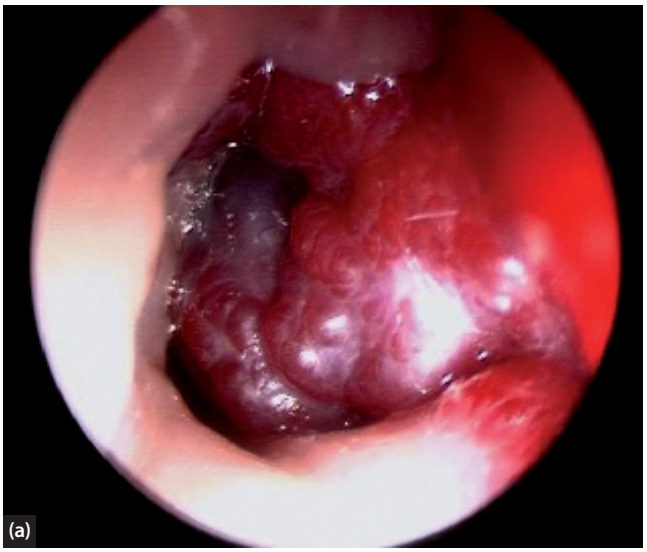
Venous malformations (VMs) are characterized by abnormal collections of veins, typically without a uniform smooth muscle layer, which have no demonstrable endothelial or pericyte mitotic activity and no increased expression of VEGF or FGF.[32–34] They are usually solitary and sporadic (**common sporadic**), but some patients have multiple lesions which may have an inherited basis, and a thorough family history should be sought. An autosomal dominant form results in a subtype termed **multiple glomangiomas**, and a number of other rare familial forms exist. These include Bean syndrome (blue rubber bleb naevus syndrome, BRBNS), characterized by multiple cutaneous VMs in association with visceral VM, particularly affecting the gastrointestinal tract and occasionally the airway (**Figure 42.5**). These carry a risk of life-threatening haemorrhage and often require endoscopic treatment. Patients with Turner syndrome may also have intestinal or lower limb VM. Recent work suggests that an abnormal gene on chromosome 9p coding for an endothelial receptor may be responsible for some familial disease.

All VMs are congenital, although again some are not initially apparent. Presentation is variable, depending upon size, depth and anatomical location. They most often involve the skin of the face, limbs and trunk, but they may also be found in viscera, including the aerodigestive tract, muscle and bones, particularly the mandible. Clinical manifestations therefore vary accordingly, but in general VMs increase in size as the child grows, do not regress, and may swell as a result of raised venous pressure (Valsalva manoeuvre, straining or crying, or when placing the patient with the affected area below the level of the heart, increasing venous drainage to the lesion). Thrombotic events and local infection, with resulting phleboliths, may alter their consistency with time, from soft and compressible to tender, lumpy lesions, especially as more blood flows in but cannot easily drain out. Pain from venous stasis and thrombosis is a strong diagnostic pointer to VM, rather than other vascular malformations. Associated bleeding may occur, in addition to low-grade consumptive coagulopathy.

TREATMENT

The diagnosis of VM is typically clinical, with biopsy undertaken only if there is any doubt. Imaging is usually warranted, both to determine the extent of lesions and to assess relations to large vessels and other hazardous structures. MRI is the most informative modality for deeper lesions, but CT and ultrasound are also helpful.

Many VMs are managed by reassurance and monitoring. Aspirin and compression may be used to limit thrombotic events.[35] Pain is one of the commoner indications for



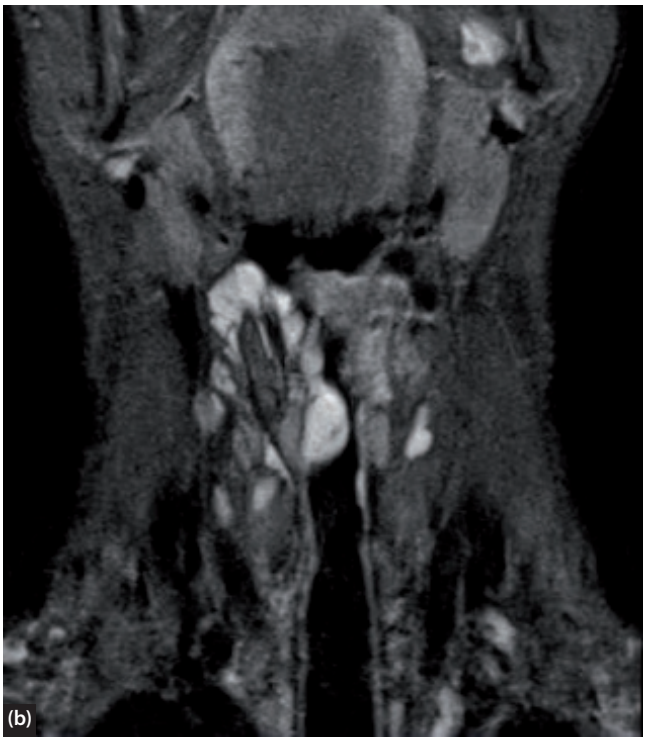


Figure 42.5 Venous malformation. **(a)** Large venous malformation of the upper trachea. This 15-year-old patient recently developed cutaneous venous malformations of the feet, suggesting the diagnosis of blue rubber bleb naevus syndrome. **(b)** Coronal T2-weighted MRI of the same patient, demonstrating numerous venous malformations of the upper aerodigestive tract.

active treatment, although this may also be considered for bleeding, cosmetic and functional reasons, depending on lesion location and size. Once again, a multidisciplinary approach should be adopted, as combinations of treatment, repeated visits and psychosocial support are often necessary.

Sclerotherapy is the primary non-surgical treatment for VM, performed by interventional radiologists under general anaesthesia. Typically, 3% sodium tetradecyl sulphate (STS), instilled as a foam under fluoroscopic guidance, is used. Alternatives at other centres include 95% ethanol and Ethibloc® (ethanol and cornflour), although the risks of tissue necrosis and neurological injury (e.g. the facial nerve branches) have been relatively high in our experience.[36] No controlled trials have assessed the relative efficacy of these agents. Single treatments, with post-injection compression and observation, may be suitable for smaller lesions, but repeated injections and compression are often required for larger VMs. With all forms of sclerotherapy, patients and parents should be aware of significant risks to local soft tissues and nerves, post-operative swelling, secondary infection and the additional risks of communication with deeper structures via fistulous channels, hence the need for prior assessment and imaging.

Superficial components of VM, or entirely superficial lesions, may be treated with laser. Nd:YAG is preferred, owing to the size of the vessels. This may be used in isolation, but it also offers the option of reducing vessel bulk in the skin, thereby facilitating surgical access to deeper components of extensive lesions.

Surgical excision is often extremely challenging. In addition to the friable, vascular nature of excised tissue, VMs often have large communications with major veins, particularly in the head and neck. Complete excision is required to eliminate the risks of recurrence, but the merits of this have to be balanced against major risks. As a result, surgery is often staged and/or combined with sclerotherapy and laser treatment, highlighting the importance of a long-term team approach to management.

Lymphatic malformations

Lymphatic malformations (LMs) are low-flow vascular malformations resulting from abnormal embryologic development of regions of the lymphatic system, although the precise mechanisms are uncertain. The overall result is a collection of varying-sized lymphatic spaces and channels, instead of the normal regular network of fine channels in the dermal papillae which travel to deeper lymphatics, with one-way valves to limit backflow. LMs are found in the head and neck in 75% of cases, from where they may extend into the thorax.

With an overall incidence of some 1:5000, LM accounts for 6% of all paediatric soft-tissue masses.[36, 37] Around half are diagnosed at birth and 90% by 2 years of age, although presentation is variable. This, together with eventual treatment options, depends on the extent of disease and its location, but also upon the size of cysts within it. **Macrocystic** refers to disease with a few large cysts (volume >2 cm^3) and **microcystic** to disease with smaller cysts, but in reality most lesions contain a mixture. Common presentations include cystic masses in the neck and face, but sublingual and tongue base disease may lead to macroglossia, progressive airway obstruction and mandibular distortion. As with other vascular malformations, LMs exhibit commensurate growth with the child. However, although they are usually initially soft and fluctuant, they tend to become firm and lumpy

with time, particularly after respiratory tract infections. Interestingly, these events may also lead to sclerosis within the lymphatics and eventual reduction in size, although the disease does not regress *per se*.

Several classification systems exist based on location. We prefer the dichotomous type 1 and type 2. Type 1 lesions are found below the level of the mylohyoid muscle, in the anterior and posterior triangles of the neck (Figure 42.6). They are more often predominantly macrocystic, and have a better prognosis. Type 2 lesions are found above the mylohyoid, involving the oral cavity, cheek and parotid regions (Figure 42.7). They are more microcystic, responding less well to treatment. In reality, a number of patients have cervicofacial disease of both types.

Alternatively, the De Serres staging proposal has been used.[38] LMs are staged I–IV:

- **Stage I:** unilateral infrahyoid
- **Stage II:** unilateral suprahyoid
- **Stage III:** unilateral suprahyoid and infrahyoid
- **Stage IV:** bilateral suprahyoid.

These stages correspond to the cyst size, functional deficits and treatment complexity associated with the distribution of disease. Low and lateral disease is generally macrocystic, relatively easily managed by surgery or sclerotherapy, with cosmetic but less significant functional deficits. High and medial disease is typically microcystic, involves the face and/or upper aerodigestive tract, and may require tracheostomy and long-term, multimodality treatment.

The diagnosis is usually obvious clinically, although single large cysts may be mistaken for other pathology in particular areas. These include the floor of mouth (ranula) and the lateral neck (branchial cyst, thymic cyst), for example. Imaging (particularly T2-weighted MRI) is useful in these circumstances, especially when treatment is considered, although the diagnosis may remain in doubt in some cases (see Figure 42.7). MRI will certainly help to differentiate macro- and microcystic disease, as well as demonstrating relations to surrounding structures, informing further management.

TREATMENT

As in the case of other vascular malformations, we manage LMs in a multidisciplinary setting. The most appropriate treatment options will be directed by age, the nature of the disease, related symptoms and the wishes of the parents and child. Some smaller, asymptomatic LMs may require no treatment at all, and are simply monitored, but the majority will require some form of therapy, because of relentless increase in size.

In terms of active treatment, our main options are sclerotherapy and surgery, used in isolation[37] or in combination.[36] In broad terms, surgical excision is the only means of achieving complete elimination of disease and cure, thereby offering a one-stop treatment option in selected cases (see Figure 42.6). In reality, the mixed cystic nature of many LMs and their complex anatomy means that they often require multimodality management, delivered in multiple stages. It should also be borne in mind that LM may cause significant bulk-related complications, such as airway obstruction, particularly in the neonatal period. Urgent interventions, such as tracheostomy and debulking surgery, may be required in advance of attempts at definitive treatment.

Sclerotherapy is performed by interventional radiologists under general anaesthesia, with fluoroscopic control. This form of treatment may be used at any time, including the neonatal period, as required. OK-432 (Picibanil, an inactive strain of group A *Streptococcus pyogenes*) was commonly

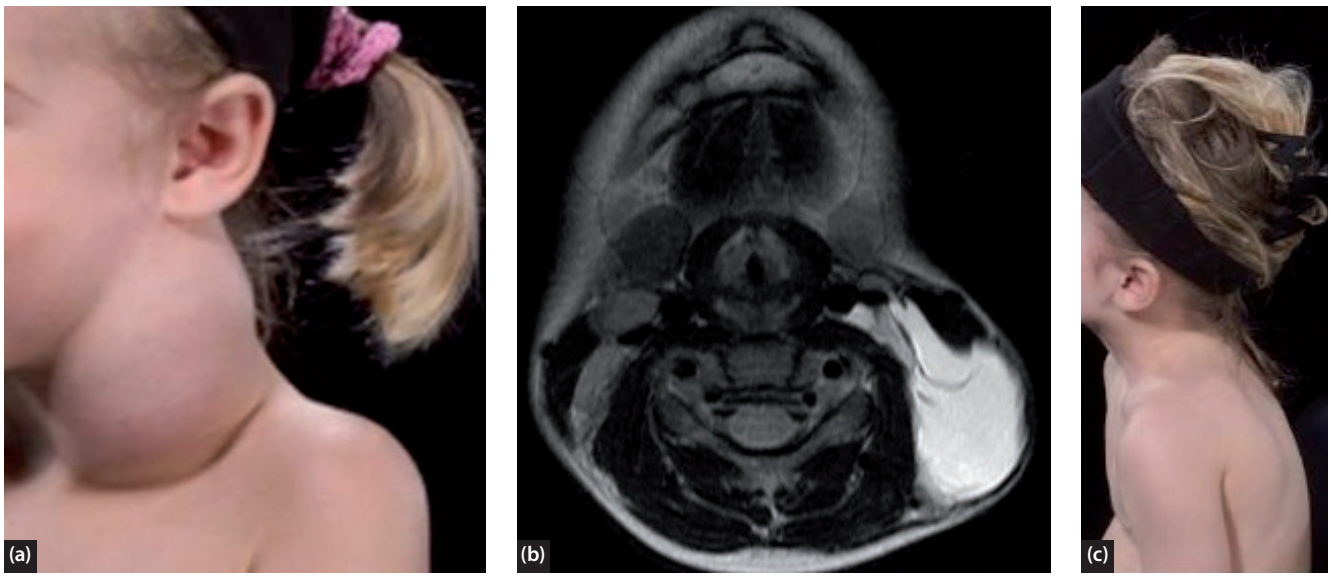


Figure 42.6 Lymphatic malformation: macrocystic, cervical disease (type 1). (a) Clinical appearance, aged 3 years. **(b)** Axial T2-weighted MRI of the same patient. The lesion consists of a few large fluid-filled cysts, of high-signal intensity, in the posterior triangle of the neck. **(c)** Appearance 3 months after uncomplicated surgical excision.

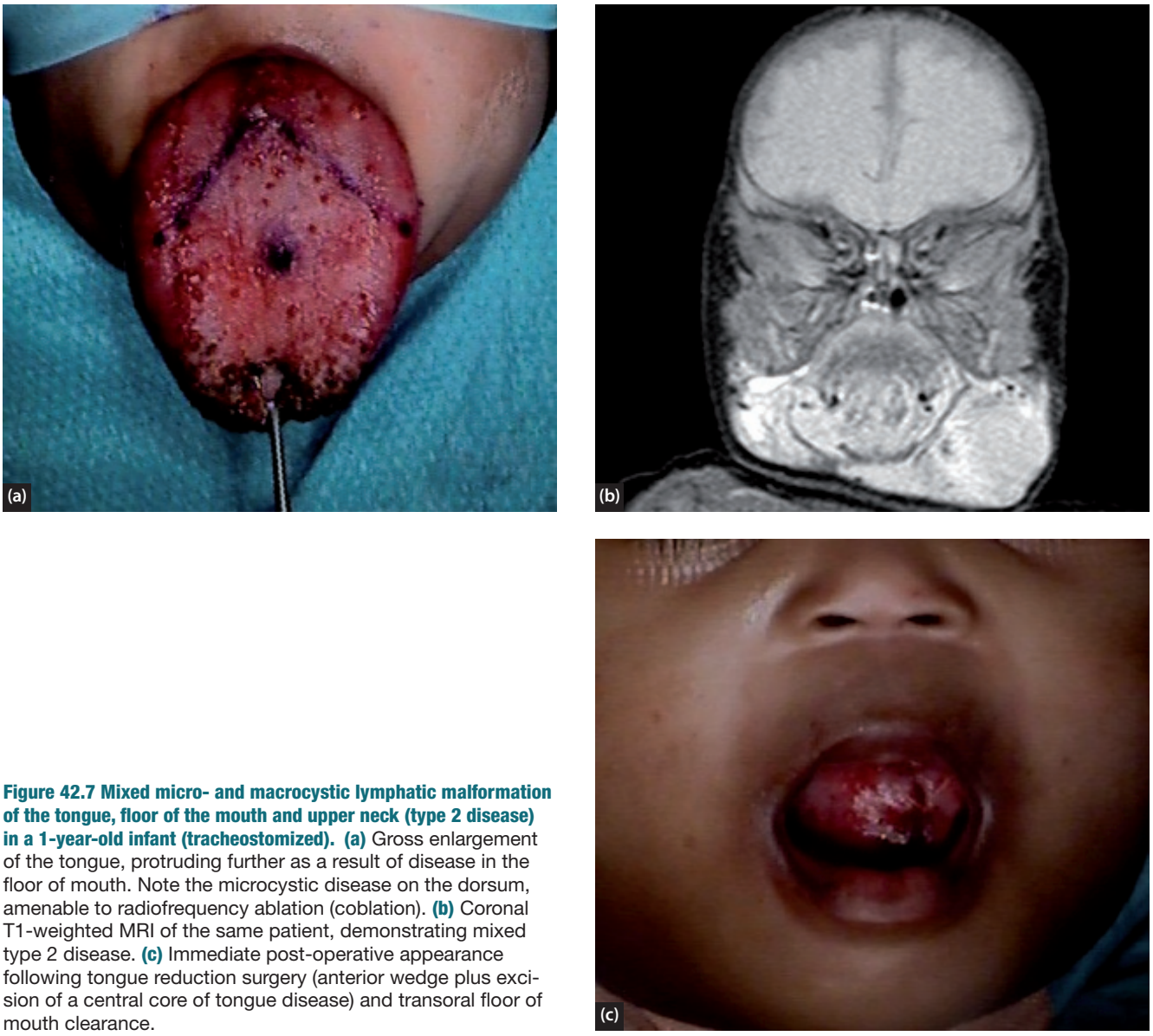


Figure 42.7 Mixed micro- and macrocystic lymphatic malformation of the tongue, floor of the mouth and upper neck (type 2 disease) in a 1-year-old infant (tracheostomized). (a) Gross enlargement of the tongue, protruding further as a result of disease in the floor of mouth. Note the microcystic disease on the dorsum, amenable to radiofrequency ablation (coblation). **(b)** Coronal T1-weighted MRI of the same patient, demonstrating mixed type 2 disease. **(c)** Immediate post-operative appearance following tongue reduction surgery (anterior wedge plus excision of a central core of tongue disease) and transoral floor of mouth clearance.

used until recently,[36] but has been discontinued owing to a lack of supply and withdrawal of USFDA approval for any indication. Our agent of choice is now 3% STS, injected as a foam. This is injected directly into larger cysts after aspiration of fluid, resulting in an inflammatory response with subsequent fibrosis and sclerosis. Multiple treatments are usually required, at intervals of a few weeks or months, since deeper parts of the malformations are difficult to access reliably. Such treatment is generally not beneficial for microcystic disease, as the penetration into adjacent areas is poor. Similar possible side effects may occur as for sclerotherapy to venous malformations. Parents and clinicians should be particularly aware of the likelihood of gross swelling of the injected areas after treatment, risking airway obstruction and worsening deformity.

Surgery may be performed with different objectives in mind. In some circumstances, particularly in the context of localized macrocystic disease of the neck, a single excision procedure may be straightforward and curative. Alternatively, debulking procedures, including in the neonatal period, will allow removal of an area of relatively accessible disease in order to preserve function. In our practice, the anterior cervical portion of large cervicofacial LMs may be cleared in this way within the first few days of life, with limited risk of neurovascular injury. This may obviate the need for tracheostomy, leaving the facial/parotid disease component to be addressed when the child is older and larger, such that the risks to the facial nerve and other structures are reduced. Transoral approaches may be necessary for disease of the tongue and sublingual regions, which is typically microcystic. Mucosal incisions through the floor of mouth, preserving the submandibular ducts and lingual nerves, allow safe access to sublingual disease. Tongue base and mucosal lesions have been treated with partial glossectomy (see **Figure 42.7**), laser or monopolar diathermy in the past, although we now favour Coblation® (radiofrequency ablation), which avoids lateral thermal injury and allows rapid recovery.[39]

For extensive, mixed disease, a combination of surgery for microcystic areas and sclerotherapy for larger cysts is usually undertaken. The relative merits of the different modalities at each stage of life will vary according to the patient and their disease. Apart from a comprehensive multidisciplinary approach, it is essential that parents are fully aware of the scope of each treatment, risks, prognosis and the long-term management entailed.

FAST-FLOW VASCULAR MALFORMATIONS

This group of lesions, like other vascular malformations, are congenital but may go unrecognized for several years, typically presenting in childhood or adolescence. They are distinguished by characteristics related to high blood flow, such as palpable thrills, audible bruits, warmth and redness.

Arteriovenous malformations

Although the ISSVA classification distinguishes a number of fast-flow malformations,[4] the majority have connections between arterial feeders and draining venous systems, centred on a nidus, and are therefore arteriovenous malformations (AVMs) rather than purely arterial lesions (Figure 42.8). Although far rarer in the head and neck than their slow-flow counterparts, AVMs are 20 times commoner within the cranial cavity. Growth is typically relentless but steady, with periods of acceleration in response to trauma, infection and hormonal changes of puberty. Many patients remain asymptomatic for some time, even into adulthood, but given their typical location, these lesions may rapidly produce significant sequelae and life-threatening complications including neural compression and high output cardiac failure. Schobinger in 1990 proposed a clinical staging classification for AVM, illustrating their natural history:[40]

- **Stage I:** Quiescence. Pink-bluish stain, warmth, AV shunt on Doppler
- **Stage II:** Expansion. As per stage I, with enlargement, pulsation, thrills/bruits and tense, tortuous veins
- **Stage III:** Destruction. As per stage II, with dystrophic skin changes, ulceration, necrosis, bleeding, pain
- **Stage IV:** Decompensation. As per stage III, plus cardiac failure.

MANAGEMENT

Owing to their location and possible complications, AVMs particularly demand a multidisciplinary approach to management at a specialist centre. Initial imaging is essential, typically involving ultrasound and colour Doppler to determine flow characteristics and fistulae, and MRI to evaluate extent. In contrast to the situation for slow-flow malformations, angiography is very useful to further delineate vascular anatomy, while also allowing access for embolization if required.

Asymptomatic AVM may be monitored, although the clinicians and family should be aware of the risks of accelerated growth, making the clinical picture and its management more hazardous.[41, 42] The development of symptoms, both local and distal, will often prompt active treatment although this may itself be extremely challenging. The only reliable cure is complete excision of the central nidus and network of vessels, although in the head and neck and especially intracranially this may prove impossible. Benefits of surgery must be assessed against major risks, including death in some cases. Pre-operative embolization may be undertaken 24–72 hours pre-operatively to reduce blood loss.

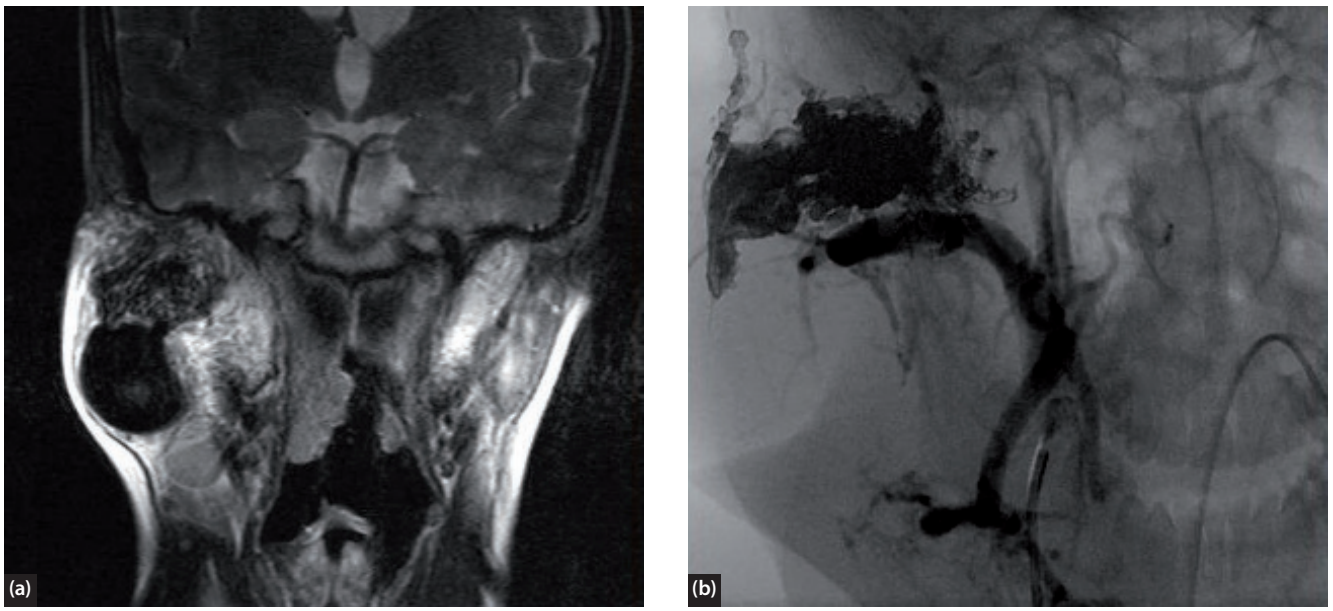


Figure 42.8 Large right arteriovenous malformation in a 15-year-old male. **(a)** Coronal T2-weighted MRI, demonstrating a large flow void (the nidus), and numerous interconnections with other vessels. **(b)** Angiographic appearance at the time of embolization. The nidus is clearly seen, along with multiple arteriovenous anastomoses with intra- and extracranial vessels.

Partial excision is ineffective, as new vascular channels will almost certainly develop. This is also true for embolization with curative intent. However, repeated trials of embolization may be used to palliate symptoms such as recurrent major epistaxis although this treatment carries risks including cerebrovascular thromboembolism and blindness. The relative merits of the various active therapies, as well as palliative options, must be communicated effectively with the patient and family.

COMPLEX COMBINED VASCULAR MALFORMATIONS

A number of complex malformations are possible, comprising various slow- and fast-flow subtypes and combinations of the two. Although the lesions themselves may differ in terms of presentation and behaviour, the principles of investigation and management are similar.

KEY POINTS

- Vascular anomalies, comprising vascular tumours and vascular malformations, are congenital lesions with complex underlying pathology, which account for a variety of presentations.
- Recent advances in histopathology and histochemistry, together with an evolving appreciation of their varied biological behaviour, have enabled precise classification of these lesions, replacing previous redundant and ambiguous nomenclature.
- A comprehensive understanding of these lesions is fundamental to accurate diagnosis and successful multidisciplinary management.

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CHAPTER 43

DROOLING AND ASPIRATION

Haytham Kubba and Katherine Ong

SEARCH STRATEGY

Data in this chapter may be updated by an Ovid Medline search using the keywords: sialorrhoea (and its American spelling), drooling, saliva, hypersalivation and aspiration, supplemented by articles from the authors' own libraries.

DEFINITIONS

Sialorrhoea or **drooling** is the involuntary loss of saliva from the mouth. It is a normal feature of infancy but becomes rare in normal children as they develop oral motor control, sensory awareness and appreciation of social norms. Drooling beyond the age of 4 years is considered abnormal.

Anterior drooling, which is just another term for sialorrhoea, can be distinguished from **posterior drooling**, which is the spillage of saliva into the pharynx. Posterior drooling leads to an increased risk of aspiration. Aspiration of saliva typically presents with coughing and choking, often most obvious when the child is lying supine in bed, as well as recurrent pneumonias and concurrent evidence of aspiration of food and drink.

Drooling is distinct from **hypersalivation**, which is the excessive production of saliva. The majority of children who drool do not hypersalivate so the terms are not interchangeable.

CAUSES

Drooling may be a normal feature in young children up to the age of 4 years, and occasionally slightly older than this in children whose development is otherwise normal. Some children have a delay in achieving this particular motor milestone, perhaps due to a lack of awareness of social niceties but without any obvious physical deficit. The prognosis for these children is good and few require more than simple reminders and cues.[1]

Generally speaking, drooling is the result of a swallowing disorder, due to an impairment of the oral phase of the swallow. Inability to maintain lip closure, altered tone in the oral musculature, impaired oral sensation and difficulties controlling tongue movements all can lead to reduced frequency and efficiency of the swallow.[2–5]

Drooling accompanied by unclear speech (dysarthria) and difficulty chewing solid food may be labelled **oromotor dyspraxia**. The oromotor problems may be quite significant, with some children unable to manipulate food in the mouth with the tongue, resorting to pushing the food around their mouths with a finger. However, the problem is specific to the oral cavity and these children typically have no other developmental issues.

The majority of children who drool also present with other associated disorders affecting general development and muscle control, typically cerebral palsy. The drooling is primarily a motor issue. The drooling is not associated with any structural difference in the saliva glands[6] or in the amount of saliva produced.[2–4] Aspiration is a feature in those with bulbar palsy.

Some children (such as those with autistic spectrum disorders and intellectual disability) will drool because of a lack of awareness that saliva is pooling in the mouth or that the chin is wet, and that this is not socially acceptable. This is primarily a sensory issue.

In fact, most children who drool present with some combination of both a sensory issue and a motor impairment affecting their swallow.

PREVALENCE

Drooling is a common problem in children with neurodisability, although most do not receive any medical attention for this. Parents do not always know that effective treatments are available, or it may be that the family doctor, paediatrician or otolaryngologist does not know enough about the problem to make a recommendation. In 2005, we conducted a survey of 358 children in the 17 special schools for children with complex disability in the city of Glasgow. Twenty-six per cent suffered from sialorrhoea, most of moderate or severe degree, and this was most common in those with cerebral palsy. Only 21% had previously sought medical attention for the problem (J. Leonard and H. Kubba, unpublished data). Other studies have found prevalence figures of 40–58% specifically in children with cerebral palsy.[2, 7–9]

IMPACT ON THE CHILD AND FAMILY

Drooling might be seen as a trivial problem, especially for children with complex disabilities. Speaking to families, however, it becomes apparent that it has a surprisingly large impact on their day-to-day life. Children who are aware of their problem are very embarrassed and sialorrhoea is a very visible sign that they are 'different'. They may suffer discomfort from skin excoriation on the face or from having wet clothes. They are often avoided by their peers in school or nursery and they receive fewer physical displays of affection from their family members such as hugs and kisses. Families often restrict social activities such as visiting relatives or going out to eat. Frequent changes of clothes are a major time burden, and there is a significant cost associated with frequent washing and replacement of clothes. The impact of drooling is obvious and measurable[10–12] and treatment of the drooling, whether medical or surgical, can result in substantial improvements in quality of life for both child and family, and in the child's social interactions with their peers.[13–15]

THE MULTIDISCIPLINARY CLINIC

In most places, no coordinated care exists for saliva control problems and paediatricians see too few children with drooling to build up any useful experience.[16] A child with sialorrhoea can potentially seek help from a number of different specialists, each of whom might have only limited treatment options available. Treatment would depend on which specialist saw the child rather than which treatment would be best for the child. Thus, if the child sees a speech and language therapist, only exercises would be offered. If the child sees a paediatrician, only anticholinergic drugs would be offered. If the child sees a neurologist, only Botox injections would be offered, and if the child sees a surgeon, only surgery would be offered. There is a saying, 'When all you have is a hammer, everything looks like a nail.'

As a response to this problem, many children's services have set up multidisciplinary clinics for saliva control,[17, 18] mostly modelled on the service set up in the early 1970s at the Toronto Hospital for Sick Children.[19] Various specialists may be involved including developmental paediatricians, speech and language therapists, otolaryngologists, orthodontists and dentists. All benefit from having a variety of skills available so that all treatment modalities can be discussed and offered, including behavioural therapies, drugs, botulinum toxin injections, oral appliances, orthodontics and surgery, along with assessment of swallowing and dental health. Treatments are offered in a stepwise, progressive fashion starting with the least invasive options and tailoring the treatment to the specific circumstances of the child (**Figure 43.1**).[18–21]

HISTORY AND EXAMINATION

Look for evidence of aspiration

About a third of the children seen in the clinic aspirate as well as drool. This may be evident from a history of coughing and choking (often most evident at night) or frequent chest infections, or it may be evident on a clinical swallow assessment. If there is any doubt, a videofluoroscopic swallowing study (VFSS, also known as a modified barium swallow), or a fibre-optic endoscopic evaluation of swallow (FEES) should be performed (see below). The presence of aspiration makes a difference to almost all of the decision-making in the clinic. Children who do not aspirate can be safely observed, and there is plenty of time to see the effects of general growth and development on oral motor skills therapy: non-invasive treatments may be reasonable but surgery should not be performed until the child is at least 6 years old. If the child aspirates, however, intervention should not be delayed and the best chance of preserving lung function in the long term comes from aggressive management of the aspiration before 4 years of age.[22]

Assess general development

Most children with sialorrhoea will have general developmental delay often associated with a neurological disorder such as cerebral palsy. Cerebral palsy is a diagnosis that includes children with a very broad range of abilities and prognoses so it is good to ask a few questions about feeding, mobility, speech and communication.

For children with no known underlying neurological diagnosis, it is worth asking a few questions about speech, chewing, swallowing, social interaction and general developmental milestones. In young children there may be early signs of an autistic spectrum disorder or a specific oromotor dyspraxia that are only now becoming evident.

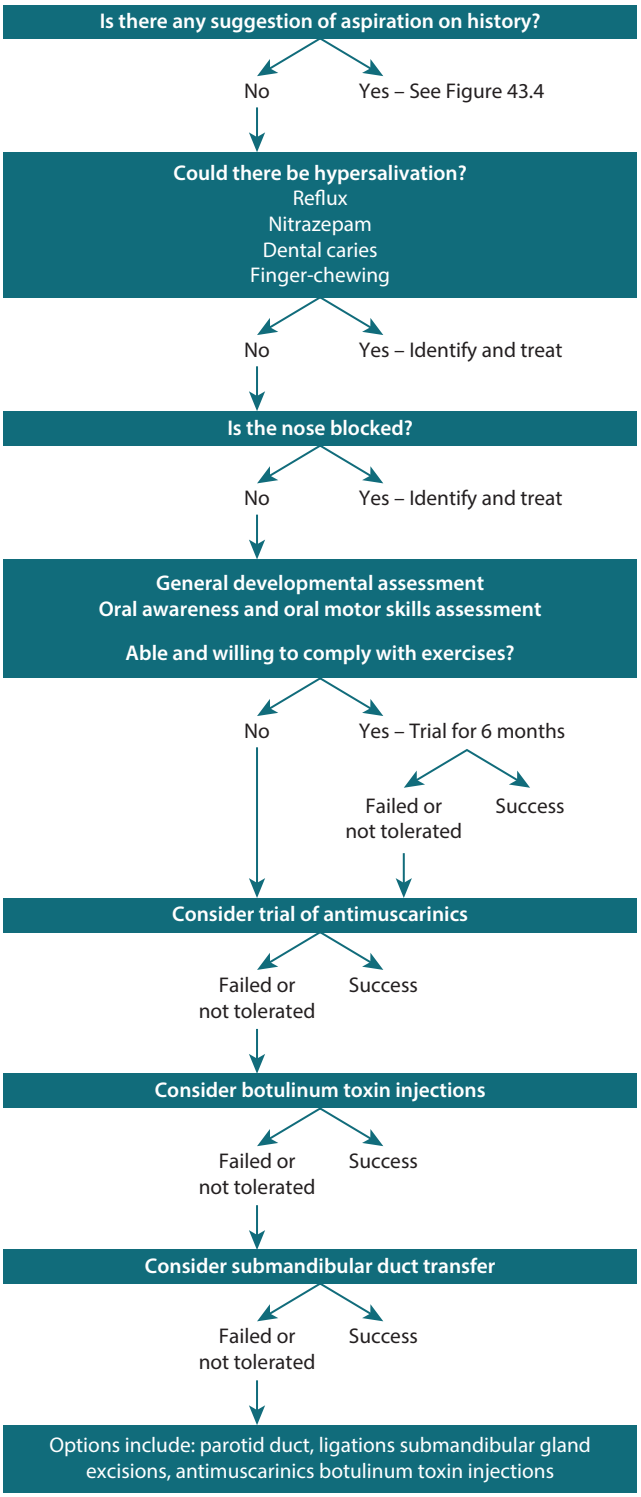

Figure 43.1 A suggested protocol for assessment and stepwise, progressive management of drooling in children.

Look for causes of hypersalivation

Most children with drooling produce a normal volume of saliva; the problem is in controlling it. There are some children, however, who genuinely produce too much saliva (true hypersalivation). This includes children with dyskinetic cerebral palsy, where hyperkinetic oral movements increase saliva production.[3] Other causes include habitual finger-chewing, dental decay, gastro-oesophageal reflux and drugs (particularly nitrazepam, often used for seizures). Where possible, these issues should be addressed before embarking on specific treatments for the sialorrhoea, otherwise success is unlikely. If the child requires nitrazepam for seizure control, there is not much we can do except to warn the family that interventions for saliva control are unlikely to control the problem completely, although they may still be worthwhile. If dental caries are found on examination, a referral for dental care should be the first step before any specific measures are undertaken for the saliva. With regard to reflux, there is a randomized controlled trial of cisapride and ranitidine therapy in children with drooling and proven reflux oesophagitis[23] that did not show any benefit for the drooling. Whether more modern drug treatments (specifically, proton pump inhibitors) would be beneficial is unknown, and there are anecdotal reports of reflux surgery (fundoplication) curing drooling that had been refractory to other measures.[18]

Look for causes of an open-mouth posture

The inability to form or maintain a lip seal is one of the most important factors producing a tendency to drool.[2, 5] Nasal obstruction will, of course, lead to a persistent open-mouth posture and this alone can lead to a significant drooling problem in young children. It should be straightforward to identify features of adenoid hypertrophy or perennial rhinitis on history and examination, and these should be treated on their own merits. In the Glasgow saliva control clinic series, 12% of children had adenoidectomy (with or without tonsillectomy) as the only treatment required for drooling.[18]

An open-mouth posture can also be caused by dental malocclusion, typically an anterior open bite, and the advice of an orthodontist can be very useful.

Many children seen in the clinic (particularly those with quadriplegic cerebral palsy who are in a wheelchair) have very poor posture due to inadequate support of the trunk and head (**Figure 43.2**). Poor trunk support leads to poor

Figure 43.2 Child with cerebral palsy showing poor posture due to poor trunk support in the wheelchair.

head control, which in turn leads to poor jaw control. No progress will be made with salivary continence until the trunk and neck are stable. The wheelchair may need to be modified or replaced. For children with a specific problem of drooling onto schoolbooks or a computer keyboard when they lean forward, use of a slant board is a very simple and effective way to lift and angle the book or computer to encourage a more upright head posture.

INVESTIGATIONS

In routine clinical practice, it is not common for clinicians to measure the severity of the drooling issue although there are certainly a few ways to do this. The simplest is to ask about frequency of bib changes or changes of clothing, but this is very subjective. The Teacher's drooling scale rates frequency of drooling on a scale of 1 to 5. The Drooling Severity and Frequency Scale (DSFS) takes this concept a little further by rating severity of drooling 1–5 and frequency 1–4 and then adding the two together.[24] The drooling quotient (DQ) measures the frequency of drooling in two standardized periods of 5 minutes (one at rest, one at play) with the child sitting up and at least 1 hour after meals. Every 15 seconds, the rater scores whether new saliva has appeared at the lips and the proportion of positive 15-second episodes is converted to a scale of 0–100.[25] This is obviously more time-consuming and difficult to measure than the simple rating scales mentioned above and it appears the DSFS correlates well enough with the DQ to be a good proxy in clinical practice.[26]

Symptom questionnaires and quality of life (QOL) scores have been developed in an attempt to capture the wider impact of the drooling on the child and family.[11, 12]

Various techniques exist to measure salivary flow including weighing cotton swabs that have been placed in the floor of mouth, or technetium scintigraphy, but salivary flow is rarely a useful measure in the context of the drooling child.

The most important area for investigation is in the context of aspiration. The presence or absence of aspiration has a big influence on decision-making and therefore it is crucial to complete a clinical assessment of the swallow (including neck auscultation) by an experienced speech and language therapist whenever aspiration is suspected, supplemented by either VFSS or FEES. VFSS involves X-ray screening while the child swallows various fluid or solid food textures mixed with barium. FEES uses transnasal flexible fibre-optic nasopharyngoscopy to achieve similar results, namely an assessment of the pharyngeal phase of swallow, in particular the presence of preswallow pooling, laryngeal penetration and/or aspiration, and post-swallow residue.

In most cases where aspiration is identified, a neurological cause will be evident. Where no neurological cause is known and an anatomical issue is suspected microlaryngobronchoscopy under general anaesthetic is mandatory to rule out laryngeal cleft or H-type tracheo-oesophageal fistula since it would be tragic to miss such treatable causes of aspiration and lung damage.

ROLE OF THE SPEECH AND LANGUAGE THERAPIST

It is very useful to have the opinion of an experienced speech and language therapist in clinic. They can assess oral motor skills appropriate for the child's age and development, and can judge likely ability and motivation to comply with behavioural therapy. They can also assess the safety of the swallow and risk of aspiration. Associated issues with speech and chewing can also be addressed.

Activities to increase oral awareness include water play to teach the concepts of 'wet' and 'dry' and the use of a mirror to provide visual feedback. Parents can incorporate exercises into play, such as blowing bubbles or toy trumpets. They can also encourage straw drinking, ensuring the straw is held in the lips only (not in the teeth) and progressively lengthening the straw over a period of weeks and using thicker drinks such as fruit smoothie or milkshake.

Issues with jaw strength and stability can be addressed through graduated strengthening exercises such as holding a chewy tube between the molar teeth against resistance as the therapist tries to gently pull the tube out of the mouth. Lip strength can be improved by holding a wooden tongue depressor between the lips for increasing lengths of time.

Behavioural modification may involve giving verbal cues to swallow or wipe, together with positive and negative reinforcement. So, for example, the child may enjoy reading a bedtime story and may be cued to swallow and/or wipe at the end of every page. Towelling sports wristbands can be very practical for wiping but also serve as a visual reminder of the need to wipe or swallow. Auditory cues to wipe and swallow, such as the timer on a microwave oven or the phone app 'Swallow Prompt' can also be used.

All these interventions rely on a degree of cooperation from the child and so are only of use in cognitively able children. With children who are able to comply, it is essential to have at least 6 months of speech and language therapy intervention before considering invasive treatment such as surgery.

There is no strong evidence base for any of these interventions, with clinical practice based on theory and experience rather than any controlled clinical studies.[27]

ROLE OF DENTAL AND ORTHODONTAL SERVICES

It can be very helpful to have the advice of a dentist. Dental caries can be a cause of salivary stimulation leading to hypersalivation. Restorations, extractions and advice on dental hygiene should precede any other interventions for drooling if this is the case.

Drooling does not itself predispose to dental caries[28] but all forms of saliva reduction treatment do, including drugs, botulinum toxin injections and surgery.[29, 30] Saliva has a protective effect for the teeth so families should be warned that treatment for drooling puts the child at greater risk for dental caries. Teeth should be brushed

twice a day with a fluoride toothpaste and there should be dental check-ups every 6 months, with preventative treatments such as fissure seals if appropriate.

Orthodontists can assess those children for whom malocclusion is a contributory factor to persistent open-mouth posture. In addition, there are some enthusiasts for the use of intraoral appliances, such as the ISMAR (Innsbruck Sensory Motor Activator and Regulator) to treat drooling. The device looks much like a dental retainer with an acrylic plate covering the hard palate, held in place with wires around the teeth. A projection is added to the posterior edge with a rotating bead which stimulates the soft palate and tongue to initiate a swallow. Only about a third of children with cerebral palsy will tolerate such a device but, in those who do, significant improvements are seen in eating and drooling.[31]

PHARMACOLOGICAL TREATMENTS

Antimuscarinic (less accurately known as anticholinergic) medication is by far the most common treatment used for drooling. These drugs stop acetylcholine from binding to receptors in nerve cells and therefore have wide-ranging effects on the central and peripheral nervous systems. In the context of saliva control, the effect of the drugs is to reduce the volume of salivary secretions. In doing so the saliva is also thickened and this can be unpleasant. Side effects are common and include dry eyes, dilated pupils with intolerance to bright light and impaired vision, constipation, urinary retention, worsening of seizure control, hallucinations and changes in sleep and behaviour. Anyone prescribing these drugs should be aware of their side-effect profile and should be able to discuss the recognition and management of side effects with the family. Some of these side effects are quite serious. As examples, impaired bladder emptying may lead to frequent urinary tract infections and any suspicion of this should be investigated with a post-micturition ultrasound of the bladder and measurement of residual volume. Constipation is common and sounds trivial but antimuscarinic treatment has been associated with toxic megacolon requiring defunctioning colostomy.[32] Optometry and sometimes ophthalmology advice may need to be sought for visual problems.[33]

Various drugs are in use and their names can be confusing. The most commonly used are hyoscine hydrobromide (also known as scopolamine hydrobromide but distinct from hyoscine butylbromide, which is not used for this indication), glycopyrronium bromide and trihexyphenidyl hydrochloride (also known as benzhexol hydrochloride). There are also anecdotal reports of atropine eye drops being used sublingually for drooling.[34]

A UK survey of paediatricians showed that hyoscine hydrobromide transdermal patches are the first-line treatment for most, with oral (or gastrostomy) glycopyrronium bromide second-line.[16] Hyoscine hydrobromide patches have the advantage of effectiveness and ease of use.[35] They can be applied to any area of thin, hairless skin and changed every 3 days. They are waterproof enough to survive showering. Their main drawback is their high incidence of significant side effects, up to 71% in one series.[36] Skin reactions to the adhesive are common and cessation of patch therapy is required. The other significant drawback is that it is awkward to adjust the dose for the age and size of the child. A full patch every 3 days is appropriate for most children of high school age but this would be too much for younger children, for whom half or even a quarter of a patch would be more appropriate. The patches can be cut with scissors but the dose release mechanism then becomes very unpredictable. Placing the patch over an occlusive dressing so that only half is in contact with the skin may lead to more controlled dosing but it is fiddly for parents to do this. Oral hyoscine hydrobromide seems anecdotally to be much less effective than the patch.

Trihexyphenidyl hydrochloride has the advantage of availability in syrup form, which makes for convenient dosing via the oral or gastrostomy route. The dose can be easily adjusted according to response up to a maximum of 2 mg/kg/day in two or three divided doses.

Glycopyrronium bromide is available as an oral solution and is very effective.[37] It has the distinct advantage of not crossing the blood–brain barrier unlike atropine, hyoscine and trihexyphenidyl. This should lead to significantly fewer central side effects although peripheral effects (on bladder, bowel, sweat glands and eyes) will still be seen and 20% of children will have to stop using the drug due to side effects.[38]

Our own experience in the Glasgow saliva control clinic has been that 45% of children discontinue transdermal hyoscine due to side effects, compared with 15% for trihexyphenidyl and 6% for glycopyrronium.[18] About half the adverse reactions to hyoscine patches were skin reactions to the adhesive: the remainder were visual problems, behaviour change and hyperactivity, constipation, urinary retention and sleep disturbance. Overall, only half the children who commenced antimuscarinics continued to use them as their definitive long-term therapy, the remainder moving on to more invasive options as outlined below.

BOTULINUM TOXIN INJECTIONS

Botulinum toxins are neurotoxic proteins produced by *Clostridium botulinum* bacteria. There are seven types of toxin but only A and B are used medically. The toxins produce their effect by blocking acteylcholine release from axons at the neuromuscular junction causing muscle paralysis. Their use in saliva control comes from their ability to block release of acetylcholine from parasympathetic secretomotor nerves in the salivary glands.

There is a variety of different brands of botulinum toxin available on the market and they are not interchangeable. Dosing is specific to each manufacturer and cannot easily be extrapolated from one brand to another as each has a protein of a slightly different molecular weight and with different diffusion and pharmacokinetic profiles. Botox is the brand of botulinum toxin A made by Allergan. It is now referred to by the generic name onabotulinumtoxin A. Dysport now has the generic name abobotulinumtoxin A. Myobloc and Neurobloc have the generic name

rimabotulinumtoxin B. Onabotulinumtoxin A (Botox) is the most common agent used for saliva gland injections as it has the largest molecular weight: although this gives it the slowest onset of action, it may also help limit its radius of diffusion and therefore should, in theory, reduce the incidence of side effects from spread of the drug. In reality, no convincing difference in effect has been seen between the various preparations.[39,40] Clinicians should familiarize themselves with the dosing, administration and side-effect profile of one formulation of toxin (in this context, probably onabotulinumtoxin A) and only use alternatives if the child has developed antibodies to the toxin as shown by reduced clinical effect over time. Switching to an alternative toxin type can restore effectiveness very well when this occurs.

No consensus exists on which glands should be injected or on how much toxin should be put into each gland. Many clinicians will inject an equal amount (25% of the total dose) into each of the submandibular and parotid glands,[41] others will inject mostly the submandibular glands (66% of total dose) with the remainder into the parotids[42] and others even inject either the submandibular or parotid glands exclusively. Since the majority of resting saliva secretion is from the submandibular glands it makes sense to direct the injections there to some degree.

There is a little more agreement about total dose. For most children the optimal dose is 80–100 units of onabotulinumtoxin A (Botox)[43] or around 4 units/kg bodyweight for those less than age 4 years, with larger doses causing more side effects but not any increase in effectiveness.[42] The same is true for rimabotulinumtoxin B (Myobloc): increasing the dose above 3000 units causes increasing side effects without any benefit in success rate.[44]

Success is somewhat subjective but a worthwhile response usually occurs in 50–80%[45,46] with most large series reporting success in around two-thirds of cases.[36,41,42,47] The toxin can take 2–6 weeks to take maximum effect. The effect of the toxin is often detectable clinically up to 6 months from injection to some extent but the median duration of a worthwhile response, when it occurs, is around 4 months.[41,42,45,46] Very occasionally, repeated injections cause gland atrophy with prolonged responses up to 18 months reported.[42]

Side effects from botulinum toxin injections are less common than with antimuscarinics.[36] The most common and worrying is dysphagia. This is most often a transient phenomenon, lasting just a few days and only apparent if specifically asked about. More severe dysphagia can last for weeks or months and require tube feeding. Reported rates are 7% for transient dysphagia with no intervention required and 3% for severe dysphagia requiring tube feeding.[42,48] Children undergoing botulinum toxin injections often have an abnormal swallow to start with but, if they are only just managing to feed orally, botulinum toxin has significant potential to tip them over into a situation where nasogastric feeding is required. Oral feeding may then be difficult to re-establish. Recent international guidelines urge caution in the use of botulinum toxin in children with swallow impairment.[20] The ideal candidate for botulinum toxin is the child who is already tube-fed, in which case any transient worsening of swallow is unlikely to have a major impact. For those who are orally fed, the decision to use botulinum toxin is one that should be approached with caution and a full discussion of the potential risks.

Botulinum toxin thickens the saliva[49] but this is uncommon as a clinical issue, seen in only 1.5% of one large series.[42] Spread to cervical muscles may cause torticollis, seen in 0.5% of a series of injections done without ultrasound,[42] or even total head instability requiring hospitalization, seen in 4% of another series done with ultrasound.[48]

In most centres, botulinum toxin injections are done under ultrasound guidance. There is no doubt that ultrasound allows more accurate placement of injections but, since the toxin is known to spread through fascial planes up to 4.5 cm from the injection site,[50,51] it is unclear how much difference this actually makes in practice. When injection is done by anatomical landmarks alone (**Figure 43.3**),[42] the success rate is no different to that in series where ultrasound guidance is used.[36,41,45–47] The use of ultrasound has been reported to produce impressively few side effects in one series[52] but, in general, most series report similar rates of complications regardless of whether ultrasound is used.[42,48]

There is a drawback to using ultrasound, namely the time required to do the procedure and the consequent need for general anaesthesia or sedation. If injections can be achieved quickly and effectively by anatomical landmarks alone, skin anaesthesia with local anaesthetic cream is usually all that is required and general anaesthesia can be avoided in 75% of cases.[42] Obviously, careful patient selection is required to achieve rates as high as this, but the very children who are ideal for botulinum toxin injection on the grounds of being tube-fed are also more likely to be tolerant of (and possibly less aware of) awake injection. This makes repeated, regular injections a viable long-term treatment option for this select group of children. For those children who would not be tolerant of awake injection, serious consideration must be given as to whether it is reasonable to give a general anaesthetic to a child three times a year for salivary botulinum toxin

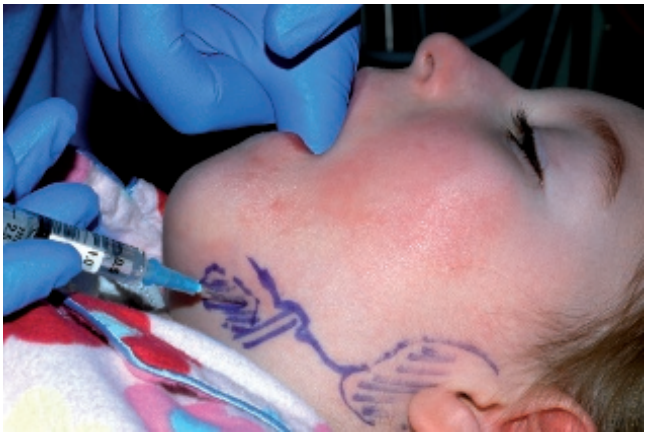

Figure 43.3 Botulinum toxin injection into the left submandibular gland by palpation of landmarks, in this case under general anaesthesia.

injections on a long-term basis. Some clinicians do this but many would judge it inappropriate. There are those who perform botulinum toxin injections just once as a way to select candidates for a permanent surgical procedure, on the assumption that a response to botulinum toxin predicts a good response from surgery.[53] There is no evidence for this assumption and in fact many children with a poor response to botulinum toxin injection will go on to have surgery with good effect.[18]

In order to minimize complications, it is important to consider which botulinum toxin preparation to use (small molecules spread further) and to place the injections accurately. Also very important is the dilution of the toxin. More dilute preparations spread further[54] so the toxin should be made up with no more than 2 mL of saline in total.

There is a group of children, about a third of all those injected, who do not seem to respond to the toxin very well. Children who respond well to the first injection tend to respond well to subsequent ones, whereas those who do not respond well to the first injection tend not to respond well to subsequent injections, suggesting there are features intrinsic to the child which affect response.[42] The effectiveness of the botulinum toxin is not related to cerebral palsy subtype or clinical features[55, 56] and we do not yet understand why some children respond and others do not.

SURGERY

Anything from 22% to 47% of patients attending a multidisciplinary drooling service will end up undergoing surgery at some point in their treatment, usually once more conservative options have been exhausted.[17, 18] Surgery, of course, includes adenoidectomy for nasal obstruction and fundoplication for intractable reflux, but in this section we will consider specific salivary procedures only. Surgery has an advantage over botulinum toxin in that it is a one-off intervention with long-lasting results,[57] but obviously surgery comes with risks and discomforts and the need for a general anaesthetic.

The most important distinction to make is whether or not the child is at risk of aspiration. A swallowing assessment by a speech and language therapist is invaluable and, if there is any doubt, VFSS or FEES should be completed. For children who are not at risk of aspiration, the best long-term results come from bilateral submandibular duct transfer. The operation requires no external incision and is done entirely intraorally. The submandibular ducts are dissected free and tunnelled submucosally to the inferior border of the tonsil fossa where they are sutured in place behind the anterior pillar. The operation causes considerable pain and discomfort and it is not unusual for children to require 3–4 days in hospital for post-operative analgesia. Recovery usually takes 3 weeks. Families and children need to have a full and frank discussion of the likely post-operative pain before agreeing to surgery. This surgery should not usually be done in children who still have time to develop oral continence on their own, i.e. it would rarely be offered below the age of 6 years. Success from surgery is quite subjective to measure, but substantial or complete resolution of drooling can be expected in 80–88% of cases[18, 29, 58–61] and the results are well maintained when assessed 5–15 years later.[29, 58, 61–63] The main determinant of outcome is the severity of the child's underlying neurological disability[59, 60, 64] so the ideal candidates are those with reasonable swallow function, such as those with milder cerebral palsy (diplegic or hemiplegic) or oromotor dyspraxia.[65]

The most common complication of submandibular duct transfer surgery is ranula formation due to obstruction of drainage from the sublingual glands. This affects 4–20% of children after surgery.[59, 60, 61, 63] and on that basis many surgeons elect to excise the sublingual glands at the same time as the duct transfer. This prevents the ranulas but at the expense of longer operating times, greater blood loss, more pain and longer hospital stay.[66] Excision of the sublingual glands makes no difference to the control of drooling.[64, 66]

Another common complication from submandibular duct transfer is swelling of the submandibular gland, which may be transient or persistent. It occurs in 2–22% of cases[59, 60, 61] and the gland may need to be excised if the swelling is troublesome. Careful handling to prevent injury or twisting of the duct during surgery helps to reduce the incidence. Dry mouth is rare in most series but has been reported to occur in 10% by one author who also reported dental caries in 3% after surgery.[29] Aspiration pneumonia after surgery can be disastrous but should be rare if patient selection has been appropriate and aspiration excluded, although it certainly does still occur.[62, 63] Tongue swelling, lingual nerve injury and troublesome bleeding have also been reported.[62]

The morbidity from duct transfer has led to various alternative procedures being popularized. Four-duct ligation (parotid and submandibular ducts bilaterally) is very easy and very quick with little immediate post-operative morbidity.[67, 68] The initial results are similar to those of duct transfer (success 81%, ranula 10%, submandibular gland swelling 15%)[69] but the long-term results are poor, as the ducts tend to recanalize.[70, 71] Submandibular gland excision (with or without concomitant ligation of the parotid ducts) is effective for drooling[72, 73] and is a reasonable alternative to duct transfer. Surgeons have probably avoided it due to concerns about leaving two visible scars in the neck, but carers don't seem to mind the scars as much as we might think.[74] Tympanic neurectomy (transtympanic sectioning of Jacobson's nerve and the chorda tympani) has largely been abandoned due to poor results,[75, 76] as has cervical sympathectomy.[77] Parotid duct ligation has a role for salvage if initial submandibular duct transfer fails.[78]

CHRONIC ASPIRATION

Symptoms of aspiration should be actively sought in the history in all cases, particularly recurrent episodes of pneumonia or coughing and choking on secretions or drinks. A clinical swallowing assessment by an experienced speech and language therapist may be supplemented by VFSS or FEES to confirm the diagnosis. If no neurological cause

is obvious, a structural cause such as laryngeal cleft or H-type tracheo-oesophageal fistula should be actively excluded by means of microlaryngobronchoscopy under general anaesthesia (Figure 43.4).

Mild cases of aspiration can be managed by the speech and language therapist with advice on head positioning during swallow, modifications to food and drinks and other simple strategies. More severe cases will require restriction or complete cessation of oral intake with tube-feeding, usually by means of gastrostomy. If aspiration of gastric refluxate is an issue, fundoplication will often be performed at the same time as gastrostomy insertion. The role of the otolaryngologist in this context is to advance the case for fundoplication with the upper GI team, emphasizing that reflux could be contributing to the drooling and aspiration.

If aspiration of oral feed and gastric refluxate have been dealt with already, or if saliva is the obvious cause of coughing and choking, then saliva reduction becomes important. The younger the child is when saliva reduction is commenced, the more effective it is likely to be in reducing the frequency of pneumonia and preserving lung function.[22]

Management should occur in a stepwise fashion, starting with behavioural strategies and/or antimuscarinic drugs as the least invasive option. Botulinum toxin injections have been shown to reduce the symptoms of aspiration and to reduce the number of episodes of pneumonia and hospital admissions.[79, 80] If surgery is required, duct transfer would be disastrous and the only safe and effective option is bilateral submandibular gland excision with parotid duct ligation. This has been demonstrated to be effective in reducing episodes of pneumonia and hospital admissions.[81]

A small number of children with intractable aspiration have failed all other treatment modalities. In this circumstance, a permanent procedure to separate the air and food tracts can be truly life changing, albeit at the cost of a rather drastic operation and the loss of the ability to make voice. Most children with aspiration of this severity are non-verbal anyway and voice is not an issue. Laryngotracheal separation involves transecting the cervical trachea and bringing out the lower end as a permanent end-stoma. The upper end of the trachea can be closed off as a blind pouch or anastomosed end-to-side to the oesophagus. The procedure produces good results and may allow the resumption of oral feeds.[82, 83]

Total laryngectomy is technically simpler and heals predictably with few complications in the well child but has the disadvantage of being irreversible. Whether this matters in reality is debatable.

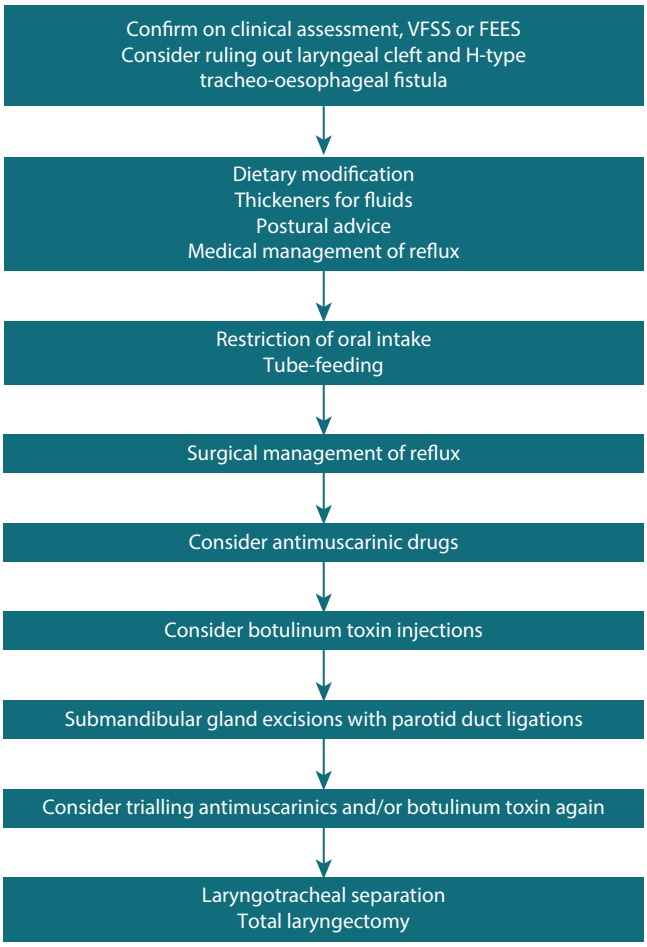

Figure 43.4 Progressive steps in the management of chronic aspiration.

BEST CLINICAL PRACTICE

- ✓ Assessment for aspiration is crucial in management and the advice of a speech and language therapist is invaluable.
- ✓ Causes of nasal obstruction and open-mouth posture should be sought and treated on their own merits.
- ✓ Drooling should be seen in the context of the child's overall development. If development is otherwise normal, the prognosis for the drooling is good.
- ✓ Speech and language therapy exercises require motivation and cooperation on the part of the child.
- ✓ Drugs, botulinum toxin and surgery all have drawbacks as well as potential benefits. The clinician should be able to discuss these with the family to help them make informed choices about treatment.

FUTURE RESEARCH

- ➤ None of the treatment options currently available is perfect and new therapies would be very welcome, particularly to reduce adverse effects.
- ➤ Reasonable evidence exists for the effectiveness and side-effect profile of each treatment modality in current use but studies are needed on treatment philosophies, pathways and decision-making.

KEY POINTS

- Drooling is common in children with neurodisability and it has a significant effect on quality of life.
- It is usually caused by poor swallowing.
- Oral exercises, antimuscarinic drugs, botulinum toxin injections and surgery each have a role in management.

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CHAPTER 44

REFLUX AND EOSINOPHILIC OESOPHAGITIS

Ravi Thevasagayam

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: laryngopharyngeal reflux, gastroesophageal reflux, eosininophilic esophagitis, pediatrics and otolaryngology.

INTRODUCTION

The appreciation of the role of reflux in the genesis and propagation of head and neck conditions in the child is a relatively new phenomenon. Over the last 35 years there have been a large number of papers published on the subject. Eosinophilic oesophagitis is an even more recent clinical entity. As gastro-oesophageal reflux disease and allergic disease increase in prevalence among the general population, it stands to reason that we would encounter both these entities more commonly in clinical practice. This and increased awareness have, indeed, led to this increase. Unfortunately, despite the recent large volume of literature, there remains significant confusion. There is as yet no clear robust causality demonstrated for any otolaryngological condition although there is plenty of evidence of association. There remains no 'gold standard' diagnostic test for extra-oesophageal reflux disease. Dual pH/impedance manometry seems the most helpful relatively objective test available, although normative data is lacking and agreed thresholds for pathology elude us.

That said, it is important to remember that we are relatively early in the understanding of the condition although huge strides have already been made. The evidence for the association of reflux in a large variety of conditions of the head and neck is compelling. There is also very encouraging clinical data that antireflux therapy is helpful, particularly in reflux-mediated airway disease.

This chapter attempts to pull together the current evidence in what is a rapidly evolving field. The challenges are explained and hopefully a working understanding of the field as it stands is presented.

TERMINOLOGY

Gastro-oesophageal reflux occurs when stomach contents travel in a retrograde direction above the level of the lower oesophageal sphincter. The 'refluxate' will usually contain hydrochloric acid and pepsin and may include bile and pancreatic enzymes. This may occur to some extent physiologically in which case it is known as gastro-oesophageal reflux (GOR). At the point at which the patient develops symptoms, signs or histological changes, the term gastro-oesophageal reflux disease (GORD) is used. This refluxate may travel the length of the oesophagus and emerge from the upper oesophageal sphincter and result in disease within the realm of the otolaryngologist, particularly at the level of the larynx. The term in widespread use for this phenomenon is laryngopharyngeal reflux (LPR). However, there is now a greater appreciation that this may impact not just the laryngopharynx but also areas such as the lingual tonsil, pharyngeal tonsils, sinuses,

Eustachian tubes and trachea. Hence a more appropriate term is extra-oesophageal reflux (EOR). The term extra-oesophageal reflux disease (EORD) may be used when this reflux causes symptoms and pathology. For reasons that will be explained, patients may have EORD in the absence of GORD.

Note: As there are regional variations to the spelling of oesophagus/esophagus, GER, GERD, EER and EE (eosinophilic esophagitis) are synonymous with GOR, GORD, EOR and EO (eosinophilic oesophagitis).

PHYSIOLOGY AND MECHANISM OF INJURY

It has been known for many years that the pharynx and particularly the glottis and subglottis are sensitive to the injurious effects of reflux. In a classic study from the 1960s, intermittent application of gastric acid on canine vocal cords produced granulomas which were histologically similar to that of subglottic stenosis.[1]

In another famous study Little[2] created a standard mucosal lesion in canine subglottic larynges, which were then exposed to gastric contents, over 3–4 weeks. This resulted in a nine-fold increase in subglottic stenosis when compared to saline controls. This occurred despite the fact that the exposure to gastric contents was only for 1 minute every other day.

This would suggest that, especially in the presence of mucosal trauma, even minimal reflux exposure might result in significant pathology. Mucosal trauma to the subglottis might occur after endotracheal intubation.

Both the pepsin[3] and the acid probably cause the deleterious effects to the mucosa although bile acids may also play a role. As pepsin works optimally in a low pH environment, acid suppression has been a mainstay of therapy. While pepsin is generally thought to be inactive at high pH levels, there is some evidence that it may be active up to pH 6.5 and may alter the stress protein response which protects epithelium from damage.[4] Cellular damage in cultured hypopharyngeal cells is seen after pepsin exposure at a pH of 7.4.[5]

Low pH causes a reduction in ciliary motility,[6] which may increase the exposure time and potentiate the inflammatory effects of reflux. This may promote cough or throat clearing which may increase the inflammation. Acidification of the lower oesophagus and micro-aspiration may lead to bronchospasm and pulmonary disease.[7]

In addition to direct mucosal effects, there are also chemoreflexic effects on cord mobility. Acid applied to the glottis of piglets causes fatal apnoeas.[8] This chemoreflexive apnoea seems to be vagally mediated. Stimulation of the lower oesophagus produces laryngeal adduction and laryngospasm in puppies.[9] There has been an awareness of reflux-induced awake apnoea for 30 years.[10]

There are therefore many local effects and chemoreflexic effects of EOR. The presence of GORD makes EORD more likely but, of course, not inevitable. However, due to the differences in the sensitivity of the substrate, EORD can and often does occur in the absence of GORD. These differences have led to confusion, especially when using parameters for GORD in the assessment of EORD.

HISTORY AND EXAMINATION

As with all conditions, a full history provides key clues to nature of the disease. If an infant has the typical symptoms of reflux such as emesis, regurgitation, burping, feed refusal and back arching, then the connection is generally easily made. Sandifer syndrome occurs in children with GORD and causes irritability, and regurgitation after feeds with episodes of arching, crying and torticollis. Older children may complain of heartburn, abdominal pain, hoarseness, throat clearing or chronic cough. It is important to recognize that the child with reflux may have none of these symptoms. The key is to have a high index of suspicion that the child's symptoms are related to reflux.

Signs of increased work of breathing such as a history of tracheal tug, subcostal or intercostal recession should be inquired about if not detected in the examination.

A sleep history should be taken. Apnoeic and cyanotic spells are always significant. Apparent life-threatening events (ATLEs) should also be noted.

Chronic cough, especially if it is nocturnal, may be related to reflux. An abnormal voice or cry may be a manifestation of reflux laryngitis.

The frequency and severity of emesis should be noted. A temporal relationship of airway symptoms to meals where present is suggestive of reflux (and/or aspiration). Wet-sounding respirations, cough or 'wet burps' are often present. Irritability and increased noisy breathing after feeds may be seen. The duration of feeds is an important marker of the severity of airway compromise. Infants with airway issues tend to take a long time to take a feed and feeds taking over 30-40 minutes are considered significant.

A history of recurrent pneumonias or croups with multiple hospitalizations or antibiotic courses is very relevant. Signs of neurological impairment could potentiate the effects of reflux. This is because pharyngeal hypotonia and uncoordinated swallowing will lead to pooling of secretions in the hypopharynx. This will increase the exposure time of the larynx to refluxate and increase the risk of aspiration.

The infant should be examined with regard to the airway. Stridor or stertor may not be present at rest but may become apparent if the infant becomes agitated during the examination. Tachypnoea should be noted and in infants may be associated with head bobbing. Signs of increased work of breathing, which includes sternal and subcostal recession, may be seen. A pectus excavatum should be noted. There may be a 'wet sound' heard from the throat. Examination should include examination of the oral cavity to assess tonsil size.

BOX 44.1 Possible symptoms of extra-oesophageal reflux in children[4]

Airway symptoms	Feeding problems	General ear, nose and throat symptoms
Cough	Dysphagia	Nasal obstruction/congestion
Throat clearing	Odynophagia	Nasal pain
Recurrent croup	Gagging	Snoring
Wheezing	Choking	Snorting
Cyanotic spells	Globus sensation	Postnasal drip
Noisy breathing – stertor/stridor	Failure to thrive	Drooling
Hiccups		Oral sores
Recurrent pneumonia		Halitosis
Hoarseness		Taste/tongue problems
Tracheostomy problems, e.g. stomal granulations		Otalgia
Gurgly respirations		
Apnoea		
Sleep-disordered breathing		

The child's height and weight should be noted and plotted on a centile chart to assess failure to thrive, which may serve as an indication to intervene.

The examination in the neonate and potentially in the older child is usually completed with an awake flexible fibre-optic nasopharyngoscopy. This will provide information about the nasopharynx and the larynx. It is the investigation of choice to assess cord mobility and is excellent at visualizing laryngomalacia. In order to assess the area below the glottis, a microlaryngotracheobronchoscopy (MLTB) is performed in a spontaneously breathing infant under general anaesthesia. This allows better optical examination as well as offering the opportunity to perform endoscopic interventions.

Possible symptoms of EOR in children are listed in Box 44.1.

INVESTIGATIONS

Within the realm of gastroenterology clear guidelines exist for what constitutes GORD[11] and what reflux index (RI) scores (see below) are pathological. It is clear that certain levels of reflux exposure to the oesophagus are physiological and not associated with pathology. In view of differences described earlier between the oesophagus and the pharynx and airway, it seems likely that lower levels of reflux exposure may cause disease in the pharynx than would cause disease in the oesophagus. Early authors suggested than any reflux exposure in the pharynx was abnormal[3, 12] although there is increasing awareness that this is likely not the case. In neonates, it is clearly recognized that a certain degree of reflux is both physiological and common. That said, normative data are still not available for this. A threshold figure for pathological EOR does not exist as yet. In view of the variety of substrate tissue and the spectrum of disease, it is possible that a threshold figure for reflux exposure in any of the tests will never be achievable. What is clear is that the threshold figures for GORD do not apply to EOR although a diagnosis of GORD makes EOR more likely.

There is no one 'gold standard' test for EOR. Each of the tests described provides supporting information towards or against a diagnosis of EOR. A diagnosis of GORD will, however, make EOR more likely and treatment should be considered. Likewise, a reduction in the RI below threshold for GORD will not necessarily mean successful treatment of the EOR.

Contrast swallow

A contrast swallow has the advantage of demonstrating anatomical abnormalities such as a tracheo-oesophageal fistula, a hiatus hernia and achalasia. It may detect aspiration especially when used as part of a videofluoroscopic examination of swallow. It is a brief study and so is not a good investigation to detect reflux events. It is not routinely done in reflux unless an underlying anatomic abnormality is suspected.

pH monitoring

Ambulatory 24-hour pH monitoring has been the mainstay of diagnosing GORD in children. This is usually done passing the probe nasally, attempting to site the electrode 5 cm above the gastro-oesophageal junction. The position of the electrode can be determined directly if passed as part of an upper GI endoscopy or can be ascertained via a chest X-ray and repositioned. A wireless capsule can also be used, which has the advantage that it cannot be pulled out by the child. The probe remains in place for 24 hours and patient position, meals and symptoms are documented. pH monitoring provides excellent information regarding lower oesophageal acid exposure but does not provide evidence of non-acid reflux or about extra-oesophageal reflux. Dual probe pH monitoring attempts to provide more information about pH at the upper oesophagus and pharynx and has been widely used in the literature. Achieving a consistent position for the upper electrode has been difficult and drying has led to inaccuracy in pH reading.

A pH drop below 4 is considered significant and the reflux index (RI) refers to the percentage of the entire time of the study that the reading is below this. Within the realms of GORD a reflux index of less than or equal to 4% is considered normal or physiological. As explained, this may not apply to extra-oesophageal reflux but a high RI makes it more likely.

Multichannel oesophageal intraluminal impedance testing

For multichannel oesophageal intraluminal impedance testing a probe is passed like a pH probe which has several sensors along its length and measures changes in electrical resistance when a liquid, semi-solid or gas bolus passes between the electrodes. A combined impedance and pH probe can detect and distinguish acid and non-acid reflux as well as aerosolized, liquid or mixed reflux. Interpretation of the 24-hour study is time-consuming and subject to interobserver variability. Normative data are still lacking. Despite these limitations, pH/impedance monitoring is currently the most valuable investigation in refractory EOR.

As with pH monitoring, the symptom correlation remains difficult. This may be because symptoms such as hoarseness are not paroxysmal and airway symptoms caused by EOR may not occur within any 24-hour period.

Gastric emptying scintigraphy

This investigation may be useful to detect GORD and aspiration, but it is particularly helpful for delayed gastric emptying. It is not an investigation that is routinely done in the investigation of reflux.

Biopsy

Oesophageal biopsy is the mainstay of making a histopathological diagnosis of oesophagitis and eosinophilic oesophagitis. It may also be helpful in inflammatory bowel disease, coeliac disease and Barrett's oesophagus. Multiple biopsies are usually taken, as oesophagitis may be patchy. Absence of histological changes does not rule out GORD. Biopsies of the postcricoid and pharynx have been used to detect inflammation but clinical application is limited.

ENDOSCOPIC FINDINGS

When examining the laryngopharynx and trachea, various appearances have come to be associated with reflux. Many challenges exist, especially as the changes may represent inflammation and not specifically indicate reflux. Another issue is that the findings may exist on a spectrum and may be open to the interpretation of the operator, leading to some degree of interobserver variability. The value and specificity of the findings is therefore contested although there seems to be an evolving consensus that some findings are suggestive of reflux. Care must be taken in the interpretation of these findings in isolation without clinical correlation.

Posterior laryngitis was described by Delahunty[13] in 1972 as a sign of reflux laryngitis in adults (**Figures 44.1** and **44.2**). As the posterior larynx is in close proximity to the oesophageal inlet, it seems likely that this would be the most vulnerable extra-oesophageal site to reflux exposure (**Figures 44.3** and **44.4**). This relates to postglottic oedema and arytenoid oedema with loss of the normal arytenoid contour. It is suggested that severe arytenoid oedema, postglottic oedema and enlargement of the lingual tonsil may be pathognomic for GORD (**Figures 44.2**, **44.3** and **44.5**).[14]

The laryngeal 'pseudosulcus' refers to the appearance of a fold parallel to the free edge of the vocal cord. This may involve just the posterior cord or extend the length of the cord. It is thought to be a manifestation of infraglottic oedema (**Figure 44.6**). This finding appears to have a high sensitivity for reflux[15, 16] although its specificity is lower.

Other findings that have been described include generalized erythema, ventricle effacement and cord nodules.

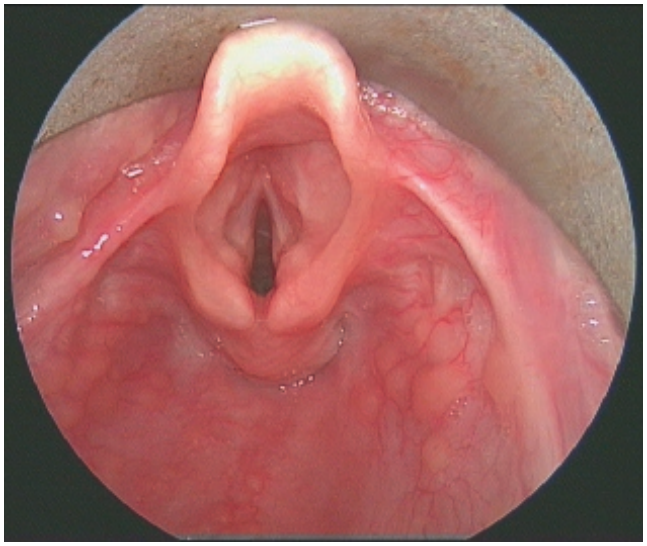

Figure 44.1 Larynx showing generalized erythema and ventricular effacement – a so-called 'active larynx'.

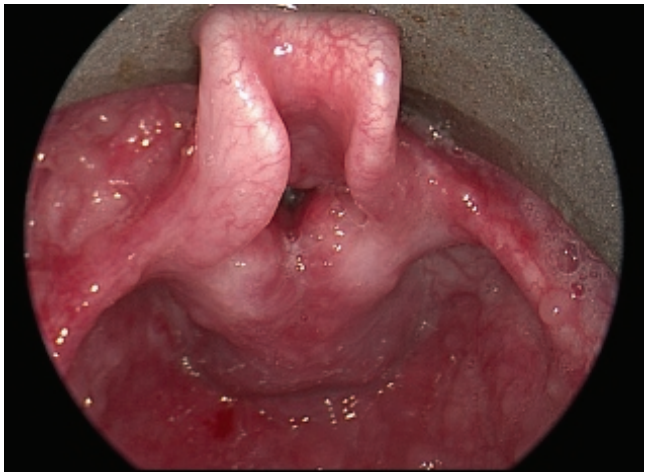

Figure 44.2 Laryngeal view of severe posterior inflammation.

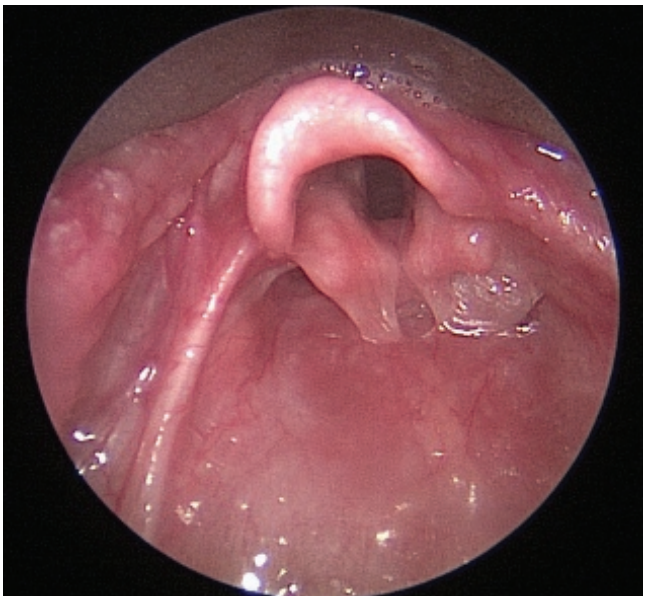

Figure 44.3 Larynx showing arytenoid inflammation and redundancy.

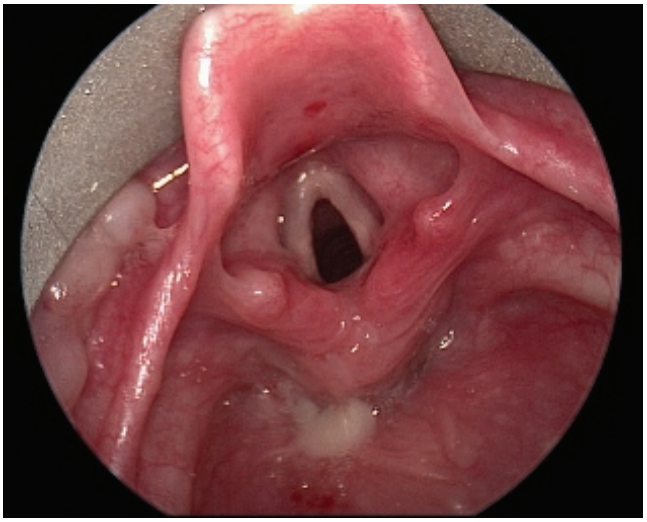

Figure 44.4 Laryngeal view showing an acute reflux episode bathing the posterior glottis.

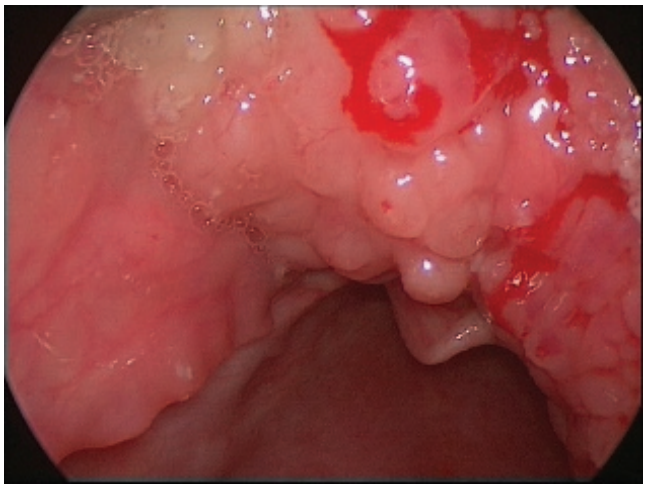

Figure 44.5 View of the valleculae demonstrating lingual tonsil enlargement.

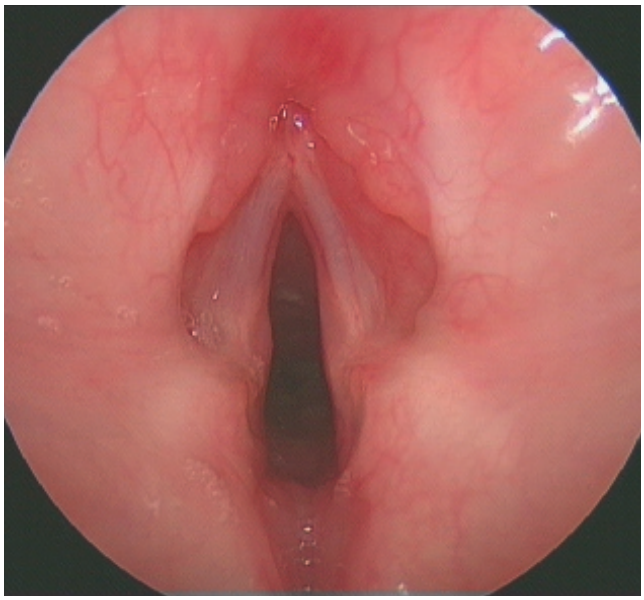

Figure 44.6 Vocal cords demonstrating vocal cord 'pseudosulcus'.

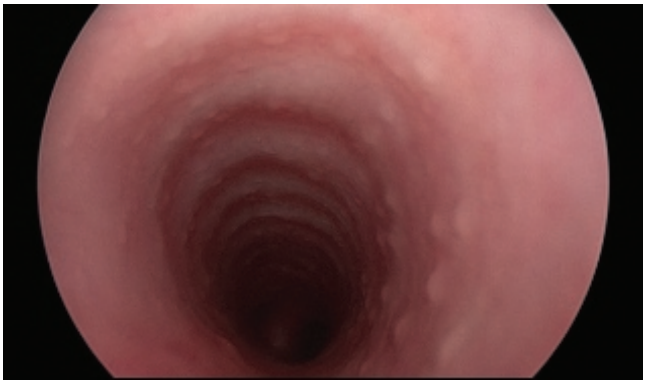

Figure 44.7 Tracheal view showing 'cobblestoning'.

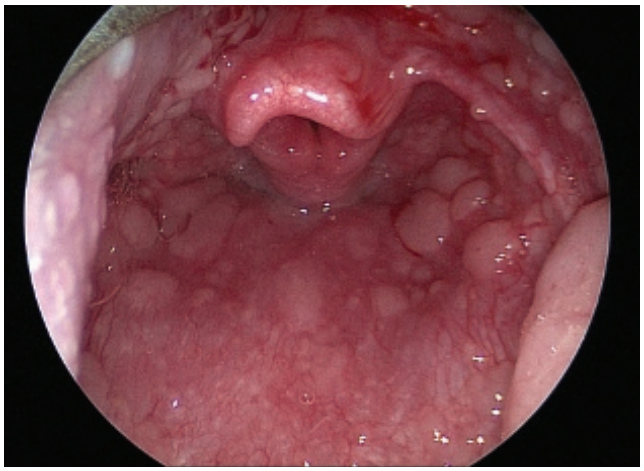

Figure 44.8 Laryngeal view demonstrating posterior pharyngeal wall 'cobblestoning'.

Findings seen in the pharynx and trachea include general oedema, erythema, indistinct tracheal rings and mucosal 'cobblestoning' (Figures 44.7 and 44.8). Blunting of the carina with loss of the normal sharp contour is also suggested to be significantly associated with reflux.[14]

The utility of these findings remains contentious. In addition to the issues raised earlier, all the mucosal changes have been demonstrated in the absence of reflux.[17] The findings appear to represent inflammation and reflux is a common source of non-acute inflammation. The findings should therefore alert the clinician to the possibility of reflux and direct the history and investigation. The clinician must be mindful that, in isolation, these findings have limitations.

THE PAEDIATRIC AIRWAY

It appears that EOR will impact the airway in different ways. Many of the typical endoscopic signs of mucosal change are seen in the airway although these are manifestations of inflammation, which may be the result of exposure to reflux or other irritant or inflammatory process. These may result in coughing or throat clearing, which may create more irritation and irritability. Coughing or increased work of breathing may worsen reflux, which may further exacerbate the problem. Aspiration of refluxate may cause or exacerbate pulmonary disease, the manifestations of which may promote multilevel airway pathology such as tracheobronchomalacia. This confluence of digestive, pulmonary and laryngotracheal involvement may have reflux as a unifying factor. This may be as cause or effect or both. It is the amalgamation and evolution of these effects that have rendered scientific study so difficult. In many ways, breaking down the airway manifestations into specific diagnosis may be unrealistic as reflux has been implicated in hoarseness,[18] laryngomalacia, subglottic stenosis, croup, ALTEs and chronic cough.[19] These conditions may of course coexist in the same patient and impact each other. The more general term of 'reflux-induced airway disease' may be helpful in thinking about these conditions more broadly.

Laryngomalacia

Laryngomalacia is the commonest cause of neonatal stridor. Children typically present within the first few days of life with high-pitched inspiratory stridor. The mainstay of assessment is awake flexible fibre-optic nasopharyngoscopy. The fibre-optic features may reveal foreshortened aryepiglottic folds with the classical 'omega'-shaped epiglottis. The other common finding is redundancy of the arytenoid mucosa, which prolapses forwards causing the obstruction (**Figure 44.9**). The appearances echo the findings of posterior laryngitis seen in reflux. This area is in close proximity to the oesophageal inlet and potentially most at risk from EOR.

Reflux appears to be found in the majority of patients with laryngomalacia[20–23] although it is not entirely clear whether it is causative. The increased work of breathing will result in increases in negative intrathoracic pressure, which will promote reflux. At this point the conditions may become self-perpetuating.

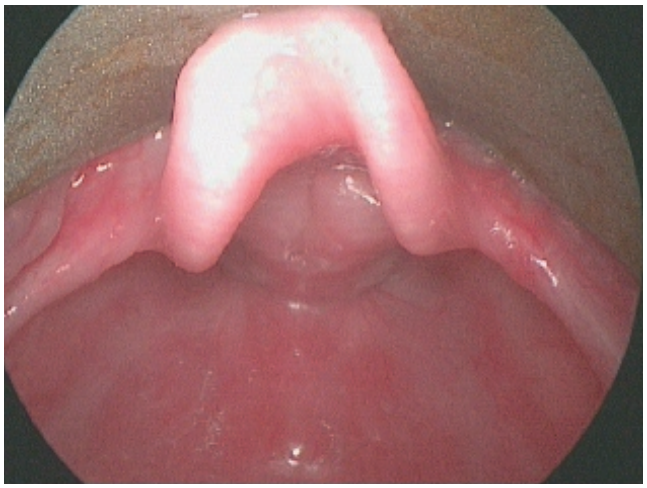

Figure 44.9 Laryngomalacia with arytenoid redundancy with prolapse into the glottis on inspiration.

Children with reflux tend to have more severe laryngomalacia, which is more likely to require surgical intervention.[21] Surgical treatment of laryngomalacia tends to reduce the severity of reflux if present pre-operatively.[24]

In view of the high incidence of reflux in infants with laryngomalacia, this diagnosis should always be sought and excluded in these cases. Infants with laryngomalacia who have coughing, choking, regurgitation and feeding difficulties may be considered candidates for empiric acid reflux suppression,[20] especially in the presence of emesis. A certain number of infants will clinically improve and acid suppression should be weaned based on symptom resolution. However, if responses to empirical therapy are poor, or the infant requires prolonged acid suppression, then the reflux status of these infants should be investigated in the usual manner.

It may be prudent to use antireflux therapy in all patients who have aryepiglottoplasty and supraglottoplasty surgery in the immediate post-operative period. This is to mitigate the risk of reflux on the raw surfaces created by the surgery.

Subglottic stenosis

Subglottic stenosis (SGS) and its treatment continues to be a challenge to the paediatric airway surgeon. In children the stenosis may be congenital or acquired. Acquired SGS generally occurs after some kind of trauma to the subglottis, the most common being endotracheal intubation.[25] Acquired SGS became recognized in the 1960s with the introduction of long-term intubation for the management of neonates needing ventilatory support.[26]

Animal models demonstrate that gastric acid in the presence of mucosal trauma such as might occur during endotracheal intubation may lead to stenosis.[2] Children with SGS seem to have high rates of GOR.[27, 28] In adults the clinical entity of idiopathic SGS, a condition of young adult women, is recognized, and there is intriguing

evidence that reflux plays a role.[29] While the role of reflux in the genesis of SGS remains somewhat unclear, it seems to be a significant cofactor.

GORD has been seen in over 80% of children undergoing laryngotracheal reconstruction (LTR).[30] The appearance of the so-called 'active larynx' (see **Figure 44.1**) has been recognized as a concern for the clinician contemplating performing an LTR. A cause for this finding of which reflux would be commonest should be sought and treated prior to reconstruction. The exposed mucosal surfaces and prolonged endotracheal intubation could serve as an environment in which reflux exposure could affect wound healing. This could lead to failure.[31] Reflux therapy has been seen to improve outcomes of endoscopic treatments for SGS and possibly reduce the number of children requiring surgery.[27]

Reflux certainly seems to occur in SGS and may well sometimes be causative and/or a cofactor in its genesis. Every attempt should be made to identify it. While it has been suggested that all LTR patients should have blanket empirical therapy, others have questioned its utility.[32] There is an evolving consensus that, where reflux is present and especially in the context of the 'active larynx', aggressive treatment is advisable. In view of the complexity and morbidity of surgery, the potential for the presence of reflux should be actively sought. The threshold for antireflux measures may be commensurately lower in this group of patients.

Apparent life-threatening events

An apparent life-threatening event (ALTE) is an episode of apnoea, choking or gagging that to the caregiver appears to be a near-death episode. Over half may be associated with reflux[33] although the significance of this is uncertain.

The mechanism may be multifactorial with both central and local factors at play. When the ALTE occurs suddenly in a well child, vocal cord closure may be occurring. A mechanism for reflux mediation through direct contact,[8] vagally mediated via the oesophagus,[9] or indeed via aspiration-associated reflux events[34] have been suggested. There is also evidence that short non-pathological central apnoea is associated with reflux[35] and it may be that this is a protective phenomenon. While causation has not been proven, where reflux is present, it may well be a cofactor. Fundoplication in children with ALTEs and reflux may be universally effective in eradicating the events when the fundoplication succeeds in stopping the reflux.[36]

Recurrent croup

Croup (acute laryngotracheobronchitis) is usually a viral illness characterized by a prodrome of an upper respiratory tract illness followed by hoarseness, a barking cough and various degrees of inspiratory and expiratory stridor. The illness is usually self-limiting and responds to supportive therapy although it can occasionally result in significant airway compromise. Croup is unusual before 6 months of age and in older children. As croup is usually self-limiting, a child requiring admission, particularly if requiring high-dependency or intensive care, should be viewed as atypical. Recurrent croup (i.e. more than two cases in a year) is also atypical and in all these clinical scenarios an underlying cause should be sought. There is some evidence that reflux may be present in this clinical scenario.[37–39] The exact mechanism is unclear but may relate to high rates of SGS in this group as well as other airway lesions. Convincing causative data are lacking at this time.

Recurrent respiratory papillomatosis

There is limited evidence that reflux may play a role in recurrent respiratory papillomatosis (RRP) control. Where present, it may affect the rate of recurrence and in some cases reflux control may hasten resolution.[40] There is also evidence that reflux control may reduce anterior commisure web formation.[41] The numbers of cases in the literature are too small to draw definitive conclusions but certainly in cases of RRP where there is demonstrable and symptomatic reflux antireflux therapy would seem to be sensible in view of the creation of raw epithelial surfaces that often accompany surgery.

NASOPHARYNX AND OROPHARYNX

Rhinosinsitis

The role of EOR in rhinosinusitis is extremely contentious. Nasopharyngeal reflux exposure obviously occurs during emesis. There is some limited evidence that reflux may adversely affect choanal atresia repair.[42] A significant proportion of children with nasal symptoms appear to have histologically proven GORD.[43, 44] Increased exposure times to low pH have been seen in children with chronic nasal disease.[45] In children with sinus disease and GORD there is some evidence that antireflux therapy may reduce the need for sinus surgery.[46]

In adults with refractory sinus diseases, increased nasopharyngeal altered pH and increased rates of gastro-oesophageal reflux have also been demonstrated.[47, 48] Early results demonstrating pepsin in nasal lavage seem encouraging and may represent a possible means of detecting reflux involvement in sinus disease.[47]

While definitive causative data are lacking, there is emerging evidence to suggest that reflux may have an impact in some cases of sinus disease. There is insufficient evidence to recommend routine screening of asymptomatic children with sinus disease. However, it seems sensible to take a reflux history in these patients and, if suggestive, investigate and treat, particularly if the sinus disease is proving refractory to conventional treatment.

Otitis media

As mentioned above, EOR appears to impact the nasopharynx and sinuses. In 2002, pepsin/pepsinogen was

detected in middle-ear effusions at much higher concentrations than were present in serum.[49, 50] The source of this could only be gastric and raised the possibility that reflux might play a role in otitis media with effusion (OME).

Low pH reduces ciliary motility in respiratory epithelium.[6] In animal experiments acid and pepsin instilled into the nasopharynx increased the opening and closing pressures of the Eustachian tube (ET) as well as the mucociliary clearance times.[51] These impact the ability of the ET to equalize middle ear pressure during swallowing and, in addition to impaired ciliary motility, may explain reflux-induced ET dysfunction. Potentially, this may represent a model for the role of reflux in acute otitis media (AOM), recurrent acute otitis media (RAOM) and OME.

Assessing the role of GOR/EOR in otitis media (OM) is challenging as both have a high incidence, particularly in younger children. Multiple studies have suggested that the prevalence of GORD in children with OM is higher than overall prevalence.[52] The prevalence of GORD in OME ranges from 17.6% to 64% and in RAOM from 61.5% to 64.3%.[52] Small studies have suggested that, where GORD is present, antireflux therapy may reduce the incidence of RAOM.[53]

Unfortunately, despite initial excitement about the reflux–otitis link, no cause-and-effect relationship has been demonstrated satisfactorily. While it remains an area of research interest, there is insufficient existing evidence to support antireflux therapy in OM.[52]

Adenotonsillar hypertrophy

The effect of reflux within the nasopharynx may also impact on the adenoidal pad as well as the ET and sinuses. Children under the age of 2 years undergoing adenoidectomy alone appear to have much higher rates of GORD than their counterparts having grommets alone.[54] Children under 18 months having adenoidectomy also have higher rates of GORD and synchronous airway lesions.[55] Whether this is cause or effect remains to be demonstrated. There is anecdotal evidence that treatment of GORD has resulted in reduction of adenotonsillar size and resolution of obstructive sleep apnoea (OSA).[56]

When assessing children who remain symptomatic post-adenotonsillectomy for OSA, reflux should be considered.[57] Children with a history of GOR appear also to have a higher rate of post-operative complications after adenotonsillectomy.[58]

More recently there has been interest in the presence of *Helicobacter pylori* (HP) in adenotonsillar tissue. Infection with the agent has been shown to be a significant factor in peptic ulcer disease.[59] The evidence seems contradictory, with some studies showing PCR detection of HP in the removed adenoid in impedance-demonstrated EOR.[60] Other studies have not found adenoidal HP despite a strong history of EOR.[61]

Some studies, particularly those using the rapid urease test, failed to demonstrate significant HP involvement in tonsil tissue.[62, 63] Using PCR techniques, HP detection in tonsils has led to the hypothesis that the tonsil is an extragastric reservoir for the organism.[64, 65] It is further postulated that HP may play a role in tonsillitis. While the findings are interesting, their true significance is unclear. This area may prove clinically relevant but as yet remains within the realm of research interest.

MANAGEMENT

The diagnosis of EORD disease is made on an individual basis based on history, clinical findings, pathology and investigations and sometimes on response to therapy. It is often helpful to enlist the aid of a paediatric gastroenterologist.

Other diagnoses for the symptoms should be considered, especially cows' milk protein intolerance. Elimination should be tried. This may involve maternal dietary modification if the child is breastfed.

Limited literature exists to determine the efficacy of therapy for EOR. Most of the literature deals with response of GORD to therapy and we may extrapolate the results to EOR although it is by no means clear that it is appropriate. Certainly, when GORD is established, therapy is indicated and there is a large body of evidence supporting pharmacological therapy. Where there is EOR but no GORD, the evidence for the efficacy of therapy is less clear.

Simple lifestyle changes are often tried in the first instance. Neonates are fed upright with feeds 'little and often'. Feed thickening may help with emesis. For adolescents smoking cessation, alcohol avoidance and weight loss if obese are recommended. Cessation of habitual throat clearing and vocal hygiene advice may be of benefit.

In patients with a strong clinical picture, an empirical antireflux therapy trial is not unreasonable. This is done on the basis that investigations such as pH/impedance are unpleasant for children and antireflux therapy is relatively benign. That said, it should be borne in mind that therapy is not always tolerated and that there are risks.

Pharmacological agents include barrier agents, prokinetic therapy, histamine-2 receptor antagonists and proton pump inhibitors (PPIs).

Barrier agents tend to contain either an alginate or sucralfate. These treatments act to create a barrier between the mucosa and the gastric content. They are generally well tolerated although constipation and diarrhoea may be seen. There may be a risk of aluminium toxicity with prolonged sucralfate use.

Prokinetic agents attempt to reduce reflux by hastening gastric emptying, however there is currently insufficient evidence to support the routine use of these drugs in view of the significant risks.[11]

Histamine-2 receptor antagonist therapy is a well-established therapy usually used twice daily. It has been shown to increase gastric pH for 9–10 hours in infants.[66]

The main issue with use is tachyphylaxis, which is a drawback to long-term use.

Proton pump inhibitor therapy is probably the most widely used therapy for EOR and is more effective at treating oesophagitis and GORD symptoms than H2 receptor antagonists.[11] In contrast to H2 receptor antagonists, the effect of PPIs does not diminish with time. The main risks of therapy of both groups of drugs are an increased rate of community-acquired pneumonia and gastroenteritis. While empiric trials of therapy are useful, treatment should be maintained on as low a dose as possible. If there is failure to show a rapid response to therapy, more detailed investigations should be sought, such as impedance/pH studies.

Consideration to surgical intervention is limited to patients refractory to maximal medical and lifestyle modifications. Certainly in this group it is important to have as much supporting evidence of reflux as possible and to have ruled out a non-reflux diagnosis prior to consideration of surgery. The chief mainstay of surgical intervention is fundoplication, with laparascopic techniques now largely replacing open techniques.

EOSINOPHILIC OESOPHAGITIS

Eosinophilic oesophagitis (EO) is a relatively new clinical entity. It was first described in the literature in the 1990s and over the past 20 years has become an increasingly diagnosed condition in gastroenterology. It first entered the otolaryngology literature in 2002 with a description of a child with the condition who had failed multiple laryngotracheal reconstructive procedures despite effective antireflux therapy.[67] The association between SGS and EO has been seen in other studies[68] with possibly as many as 10% of EO patients being affected.[69]

The condition itself is an inflammatory oesophagitis related to eosinophilia that appears to be immune-mediated. In adults it is known to be a cause of dysphagia and lower oesophageal food impaction and hence the need for biopsy of the oesophagus in this clinical scenario. Children more commonly manifest choking, gagging, nausea, vomiting, diarrhoea and food refusal. GORD-type symptoms including heartburn and regurgitation are common and EO may commonly be mistaken for this. Reflux may coexist with the condition, which may further confuse the picture. A poor or limited response to antireflux therapy should alert the clinician to this potential diagnosis.

Within the realm of otolaryngology a wide variety of airway symptoms have been described particularly cough, stridor, croup and dyspnoea.

The diagnosis is based on a finding of more than 15 eosinophils per high-power field on oesophageal biopsy.[70] The oesophageal appearances are typically of mucosal oedema, erythema and furrowing. The mucosa may also appear normal in almost a third of cases.[70] Multiple biopsies should be taken from different oesophageal sites. There does not appear to be any value in pharyngeal biopsy of affected individuals.[71]

There is a strong male preponderance. The majority of patients have evidence of atopy, particularly allergic rhinitis, asthma and atopic eczema. There may be evidence of food allergy and a strong family history of atopy.

Once the diagnosis is suspected, it is helpful to enlist the aid of a gastroenterologist. A pH/impedance study is helpful, as are multilevel oesophageal biopsies. The current treatment consists of swallowing topical corticosteroids. If food allergy is identified, food elimination or ultimately an elemental diet may be beneficial.

CONCLUSIONS

The true role of reflux in the genesis and propagation of disease within the head and neck remains hugely challenging and controversial. There is good causative evidence for its role in GORD and consensus exists for both its diagnosis and treatment. Unfortunately, no such evidence or consensus exists for EOR. The variety of substrate tissue and function located in such a small area, as well as the interaction of disease processes in each of these with each other, makes the picture even more confusing. Symptoms such as cough or voluntary mechanisms such as throat clearing may increase inflammation, irritability and indeed reflux itself that may in turn exacerbate the problem. This complexity and variability may render robust data and consensus some way off, especially within the realm of reflux-mediated airway disease.

Ultimately, the diagnosis of EORD is a clinicopathological one. Each patient must be viewed as an individual. The diagnosis is made, taking into account the available information from the history, examination, investigations and possibly response to trials of therapy. This will usually be a collaborative effort between gastroenterologist, otolaryngologist, pulmonologist and paediatric surgeon.

Both EO and EORD require a high index of suspicion. Care must be taken to assemble as much information to support or refute the diagnosis as possible. If therapy is instituted, this should be regularly reviewed and the patient weaned off as soon as practical. Parents and clinicians should be aware of the potential complications of therapy. If the initial response to therapy is poor, a re-evaluation should be undertaken.

EORD remains a hugely challenging and controversial area in paediatric otolaryngology. It is clear that reflux plays some role in either the genesis or propagation of a variety of conditions in some children. It is helpful for all clinicians to have an awareness of the condition as well as the limitations of the evidence. It seems likely that our knowledge and understanding will continue to advance exponentially.

FUTURE RESEARCH

- To establish normative values for extra oesophageal reflux using impedance testing.
- To establish a casual link for EOR and airways disease, sinus disease, ear disease and adenotonsillar disease.
- To determine if H Pylori plays a significant role in paediatric reflux mediated otolaryngological disease.

KEY POINTS

- Extra-oesophageal reflux is implicated in the genesis and propagation of various paediatric airway disorders. There is possibly an association with Eustachian tube disorders, rhinosinusitis and adenotonsillar hypertrophy but the evidence is weaker.
- Extra-oesophageal reflux is a clinicopathological diagnosis based on history, examination, investigations, endoscopic findings, exclusion of alternate diagnoses and response to therapeutic trials.
- There is no one definitive investigation that proves or excludes extra-oesophageal reflux disease.
- Extra-oesophageal reflux disease can occur in the absence of gastro-oesophageal reflux disease although it is more likely if oesophageal reflux disease is present.
- Eosinophilic oesophagitis is an immune-mediated inflammatory oesophagitis. It is more common in atopic individuals and there is a male preponderance. There are airway manifestations. It is diagnosed by histological appearance of oesophageal biopsy. It is treated by swallowing topical corticosteroids and by food allergen avoidance.

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CHAPTER 45

OESOPHAGEAL DISORDERS IN CHILDREN

Graham Haddock

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: congenital anomalies of the oesophagus, acquired disorders of the oesophagus, achalasia, caustic oesophageal injury, other oesophageal injury, neonates, infants and children.

CONGENITAL ABNORMALITIES OF THE OESOPHAGUS

Introduction

Congenital abnormalities of the oesophagus are fairly common in paediatric surgical practice. Many of these arise during fetal foregut development when the oesophagus separates from the trachea, and many present early in the neonatal period, require prompt complex surgery and can have long-term sequelae. Some of the rare oesophageal abnormalities present later in life with symptoms which are often difficult to understand.

Oesophageal atresia with or without tracheo-oesophageal fistula

Oesophageal atresia (OA) with or without an associated tracheo-oesophageal fistula (TOF) (OA +/- TOF) is one of the most common conditions which present to neonatal surgeons. It is thought to affect between 1 in 2000 and 1 in 5000 live births.

The embryonic origin of OA and TOF is thought to be similar to that seen in laryngotracheal clefts. If the separation of the developing oesophagus and the trachea by the lateral mesodermal ridges fails, the result is an isolated TOF. The embryologic origin of the more complex OA + TOF is less clear.[1, 2]

There are a number of variants of OA + TOF. The commonest form, which accounts for approximately 85% of cases, comprises a blind-ending proximal oesophageal pouch with a fistula from the trachea or bronchus to the distal oesophagus. Isolated or long-gap OA accounts for approximately 10% of cases in most published series. Isolated TOF without OA (known as an H- or N-type TOF), OA with a TOF to both distal oesophagus and proximal oesophageal pouch, and OA with a TOF to the upper oesophageal pouch are much less commonly seen variations of this anomaly (Figure 45.1).

Antenatal maternal polyhydramnios, which can affect approximately half of pregnancies with the various forms of OA, may give a clue to the presence of this abnormality.

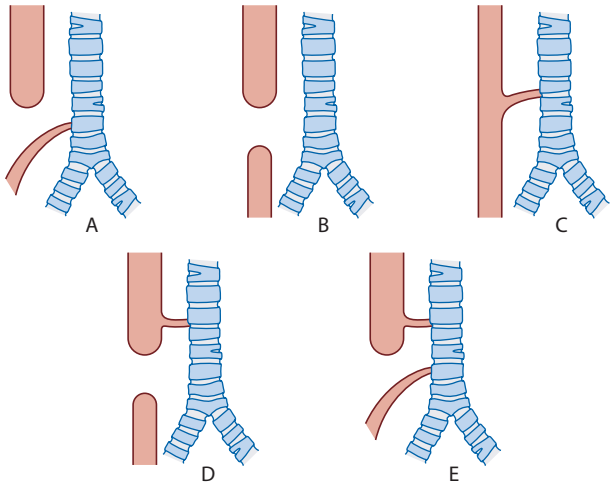

Figure 45.1 Types and incidences of oesophageal atresia with or without a tracheo-oesophageal fistula. Type A (OA with distal TOF): 85%; Type B (isolated OA): 8%; Type C (isolated H or N type TOF): 4%; Type D (OA with proximal TOF): 2%; Type E (OA with proximal and distal TOF): <1%.

A failure to identify the fetal stomach on antenatal ultrasound after 20 weeks' gestation may prompt a diagnosis of isolated OA, although this finding is not completely reliable. Either of these antenatal features should prompt the passage of an orogastric tube immediately after delivery of the newborn.

The newborn affected by any of the common variants of OA (but obviously not the baby with an isolated TOF) will present clinically with frothing at the mouth, choking episodes, cyanosis and respiratory distress. Attempts at feeding will clearly precipitate such symptoms and may cause aspiration and severe respiratory distress. Infants with an isolated TOF may present later in life with recurrent chest infections, symptoms of chronic respiratory disease and bronchospasm. Many will have been thoroughly investigated for cystic fibrosis. Some of these will present in the ENT clinic, hence otolaryngologists need to be aware of the clinical features so they can arrange appropriate investigations, including tracheobronchoscopy when indicated.

Many babies with OA will have associated anomalies. These might include vertebral anomalies, extra or missing ribs, anorectal malformations, cardiac abnormalities, renal or radial anomalies and limb deformities. These are often grouped together and are known as the VACTERL association. The aetiology of these associations is not clear.

The inability to pass an oro- or nasogastric (NG) tube in the newborn is virtually diagnostic. The tube should be a relatively large bore (at least 10 Fr) to avoid missing the diagnosis (**Figures 45.2a-b**). Thinner tubes may be seen to be curled up in the upper oesophageal pouch on a chest X-ray, which also confirms the diagnosis (**Figure 45.3**). Contrast studies or other imaging modalities are not required. The presence of gas in the abdomen on a plain abdominal or chest X-ray will indicate that the baby with OA has an associated TOF. Associated vertebral and rib anomalies can be detected on abdominal and chest X-rays (**Figure 45.2b**).

A comprehensive physical examination of the baby should be supplemented by a number of imaging modalities. An ultrasound scan of the kidneys is required to exclude associated renal anomalies. A cardiological assessment including echocardiography is essential pre-operatively to identify any life-threatening cardiac lesion and to locate the position of the aortic arch,[3] which can be on the right side in 2% of cases. A right-sided aortic arch may make the surgery even more challenging than usual.

In the older child suspected of having an isolated TOF, a pull-back ('tube') oesophagogram with the patient prone or in the left lateral position may make the diagnosis clear (**Figure 45.4**). Contrast may be introduced via an NG

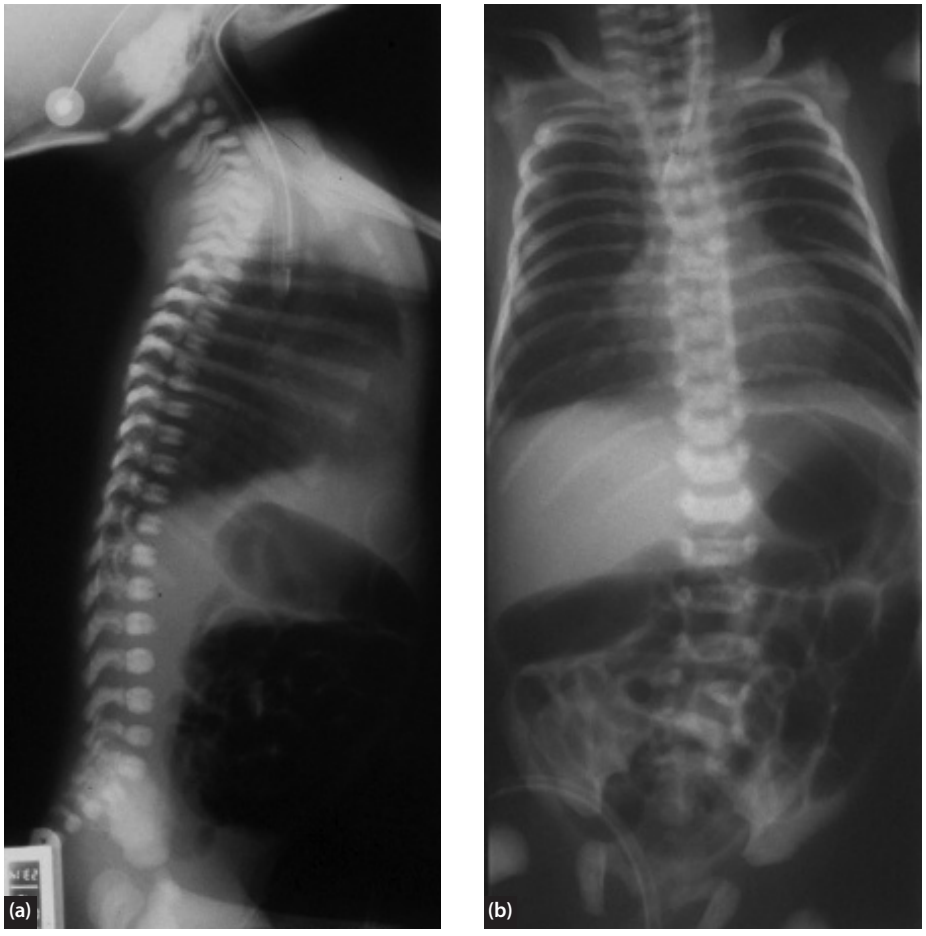

Figure 45.2 Lateral (a) and AP **(b)** chest and abdominal X-rays of a newborn with OA and TOF. A large-bore tube has been placed under tension in the upper pouch. The stomach and intestine contain air which indicates the presence of a TOF. Vertebral anomalies can be seen in the mid thoracic spine.

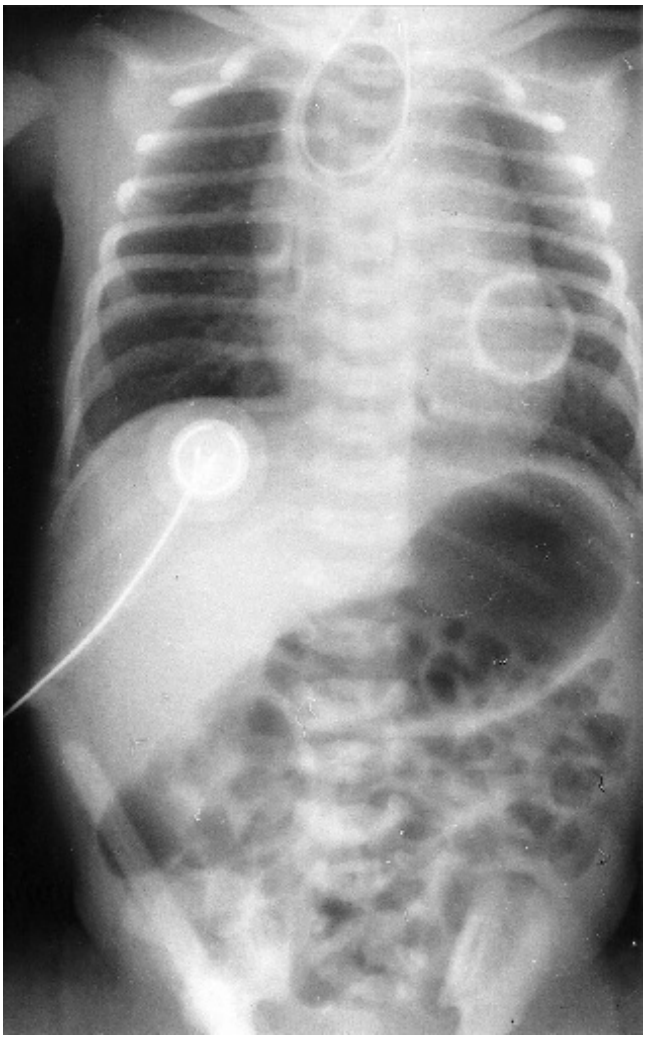

Figure 45.3 Thin nasogastric tube curled up in the upper oesophageal pouch in a newborn with OA and TOF.

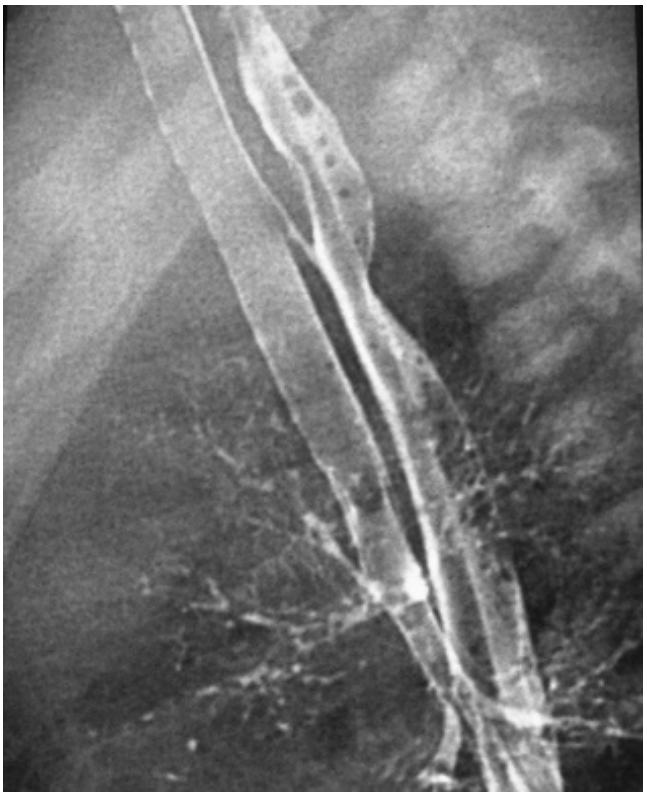

Figure 45.4 H or N-type fistula study demonstrating an isolated fistula between the oesophagus and the trachea.

tube. A tracheobronchoscopy may be needed to identify an isolated TOF and occasionally the fistula is concealed in a mucosal fold, making diagnosis difficult.

Early patient management should focus on maintaining a patent airway and preventing the aspiration of saliva and upper pouch secretions. The baby should be nursed prone with a sump suction (Replogle) tube in the upper pouch set on continuous aspiration. This tube should be injected regularly with air to prevent blockage. Endotracheal intubation and ventilation should be avoided if possible. Positive pressure ventilation in the presence of a TOF may result in large amounts of gas passing into the stomach and intestine. This trapped gas may have no easy route of escape, especially if the baby has an associated intestinal abnormality, like an atresia or anorectal malformation. Abdominal distension due to gaseous distention may impair ventilation and result in hypoxia, hypercapnia and acid-base upset. Gastrointestinal perforation in such cases can have a devastating outcome.[4]

Management of OA and TOF is ligation of the fistula and end-to-end anastomosis of the oesophagus. Prior to surgery, most paediatric surgeons will request that a bronchoscopy be performed to identify any upper pouch fistula and confirm the exact position of the TOF. This may allow the anaesthetist to position the endotracheal tube past the fistula to limit the passage of ventilated gas into the stomach.

Repair can be achieved through an open extrapleural thoracotomy[5, 6] or by using a minimal access thoracoscopic approach.[7–9] The site of the fistula is identified and dissected from surrounding structures. The fistula is divided and sutured closed as flush as possible with the trachea. A large-bore tube passed into the upper oesophageal pouch by the anaesthetists will help identify the pouch. Careful dissection will ensure that the trachea is not damaged during upper-pouch mobilization. A single-layer all-coats anastomosis of the ends of the oesophagus over a transanastomotic feeding tube is probably the most common form of primary surgical repair.

In cases where the gap between the ends of the oesophagus is too far apart for primary repair, there are a number of options for treatment. Ligation of the TOF with creation of a feeding gastrostomy may be the preferred approach initially. This would be followed by a delayed primary repair at a later stage. This approach would require long-term use of a sump suction tube in the upper oesophageal pouch to prevent aspiration of secretions and may require a period of long-term inpatient care. The creation of an open oesophagostomy (or spit fistula) may avoid the need for inpatient care and allow the infant to sham feed but

almost always precludes delayed primary repair at a later date as the length of the upper oesophagus is lost.

The Foker technique of lengthening of the oesophagus by applying traction using two lengths of thread attached to each end of the oesophagus has been reported to achieve delayed primary anastomosis in a shorter timeframe.[10, 11]

In cases of isolated or long-gap OA without a TOF, delayed primary repair remains the preferred approach for treatment.[12] If this is not possible, replacement of the distal oesophagus with a colonic, jejunal or gastric interposition may be required.[13–18] Occasionally, oesophageal lengthening procedures may have a role to play in achieving a safe primary or secondary oesophageal anastomosis.[19]

Complications of surgery to repair OA include anastomotic breakdown and leak, anastomotic stricture, refistulation and gastro-esophageal reflux. If the fistula is not sutured flush with the trachea, a blind-ending pouch can be left behind. Occasionally, this causes problems with intermittent airway obstruction. Most children without other associated congenital anomalies grow and develop normally. Associated very low birth weight and the presence of associated major cardiac defects have been shown to be good markers of poorer outcome in OA.[6, 20]

Congenital oesophageal stenosis

Congenital stenosis of the oesophagus is thought to represent the mild end of the spectrum of conditions caused by problems during the separation of the fetal trachea from the foregut tube during development. The majority of these anomalies affect the middle and distal oesophagus. Three types are described: those containing remnants of cartilage,[21] those with fibromuscular thickening and those with membranous webbing.[22] Stenoses in other parts of the oesophagus have other causes including peptic strictures at the lower end secondary to acid reflux.

Minor degrees of oesophageal stenosis may be completely asymptomatic. Failure to thrive and regurgitation of feeds may be seen when the narrowing is more severe. Sometimes the symptoms do not become apparent until the infant starts to eat solid foodstuffs.

Investigations include an upper gastrointestinal contrast swallow, which will reveal the area of narrowing, and upper gastrointestinal endoscopy. Oesophageal biopsy, particularly if deep, may reveal cartilage.

Dilatation of congenital oesophageal strictures rarely succeeds, especially if there is cartilage in the stenosis. Surgical resection of the area of narrowing and the cartilaginous tissue is usually required in severe cases. Reports of successful minimally invasive surgery for these abnormalities have been published.[21]

Oesophageal webs and rings

In addition to the more commonly encountered OA, a rare, membranous, mucosal atresia of the oesophagus has been reported which is indistinguishable from OA if the membrane is complete.[23] Some cases have been associated with a TOF. A mucosal membrane occludes the oesophageal lumen. In cases where the membrane is perforate, symptoms may be minimal or absent.

The diagnosis of an oesophageal web causing complete obstruction by failure to pass an oro- or nasogastric tube necessitates surgical intervention. The perforate or crescentic membrane usually presents later in life and can be identified on a contrast swallow examination or at upper gastrointestinal endoscopy.[24]

Resection of the membrane at thoracotomy is usually the only possible treatment for the complete membrane. In incomplete membranes, dilatation[24] or endoscopic incision of the membrane by cautery or laser with or without balloon dilatation should be considered.[25] Associated gastro-oesophageal reflux may require vigorous treatment, including possibly surgery, to prevent further stricture formation.

Oesophageal duplication and bronchogenic cysts

Oesophageal duplications appear as tubular or cystic structures in the posterior mediastinum (**Figures 45.5** and **45.6**). They are similar in many respects to other gastrointestinal duplications: they are all lined by gastrointestinal epithelium, have a well-developed smooth muscle wall, and are attached to the normal gastrointestinal tract at some point through their length.

Duplication cysts of the oesophagus, while rare, are the most common of the foregut duplication cysts. Their embryology is not clear. Associated vertebral anomalies might support the 'split notocord' theory of development.[26] This theory suggests that abnormal adhesion between

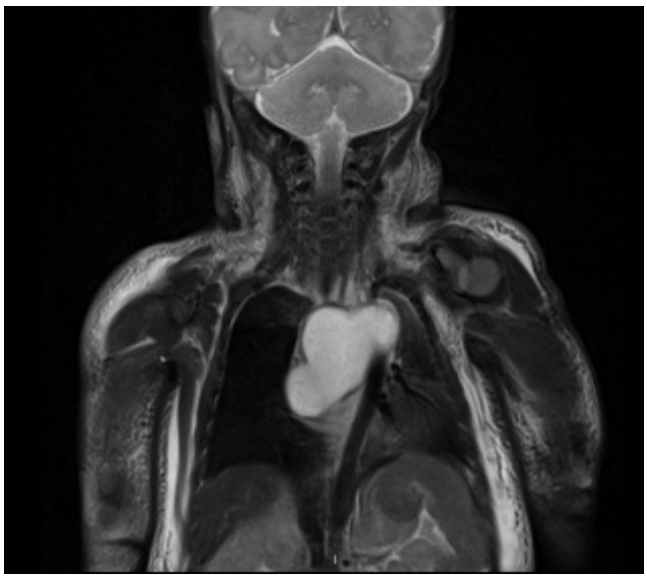

Figure 45.5 Coronal section of a T2-weighted MRI scan on a neonate with an antenatally diagnosed thoracic duplication cyst. The oesophagus and heart have been pushed to the left. The cyst was resected thoracoscopically. Histopathological examination confirmed the classical features of a foregut duplication cyst. It was lined by specialized gastric mucosa and otherwise comprised submucosa and well-formed muscularis propria.

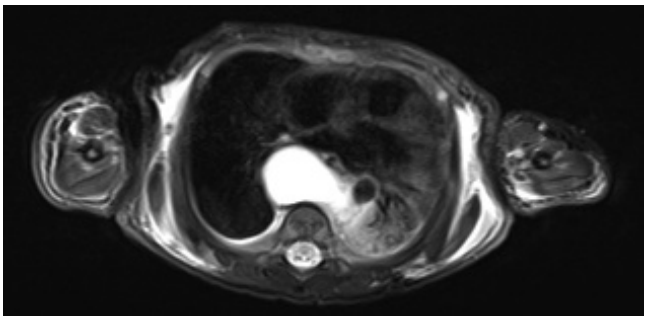

Figure 45.6 Transverse section of a T2-weighted MRI scan of the patient in Figure 45.5. Again the oesophagus can be seen pushed to the left.

ectoderm and endoderm prevents ventral notochordal fusion. Herniation of the yolk sac develops between the halves of the split notochord, resulting in foregut duplication and an associated vertebral anomaly. Alternatively, in those cases without associated vertebral anomalies it has been suggested that some oesophageal duplications occur due to incomplete recanalization after its solid phase of development.[27]

Bronchogenic cysts occur due to abnormalities in the budding process seen during the development of the tracheobronchial tree. Most of these mainly benign lesions are found within the lung parenchyma, but approximately 30% present as mediastinal masses. Occasionally, they are found in the oesophageal wall although they more usually compress the oesophagus from the outside. They are difficult to distinguish from oesophageal duplication cysts and may have a common embryological origin.[28, 29]

Oesophageal duplication cysts present most commonly in the neonatal period with respiratory distress caused by the cyst compressing the lungs and airways, but antenatal diagnosis of a thoracic cyst is becoming more common. Dysphagia can occur in older children. Smaller cysts may be asymptomatic and be detected on a routine chest X-ray. Erosion of the wall of the cyst by acid secreted by the gastric mucosa that can line these lesions can cause serious bleeding.

The diagnosis is usually suspected from the appearance seen on a chest X-ray. A contrast swallow may reveal a communication with the cyst or an indentation of the oesophagus. Chest CT or MRI are the most useful investigative tools (**Figures 45.5** and **45.6**).[30]

Excision of the duplication is the most appropriate treatment option. Excision may not be possible if the oesophagus and the cyst share a common wall. Excision of the bulk of the cyst with removal of the oesophageal mucosa may be an option in such circumstances. Open surgery is gradually being replaced by minimal access approaches to resection of these lesions.[31, 32] Percutaneous drainage under ultrasound guidance prior to definitive surgery may be helpful in newborns where the cyst is causing severe respiratory distress.[33]

Bronchogenic cysts should also be excised. This is usually fairly easy if the cyst is not part of the oesophageal wall but much more difficult if the cyst is within the oesophageal wall.

Oesophageal diverticula

True congenital oesophageal diverticula, which contain all layers of the wall of the oesophagus, are uncommon.[34] False or pulsion diverticula, which are herniations of the oesophageal mucosa between defects in the oesophageal muscular wall, are more common.

The symptoms caused by an oesophageal diverticulum depend on the size and position of the abnormality. Dysphagia can occur as a consequence of compression of the oesophagus from the diverticulum and is the most common presentation. Bad breath from debris retained in the diverticulum may also be obvious.

The diagnosis is usually made on contrast radiology or by endoscopic examination. Treatment requires resection of the diverticulum and repair of the resultant defect in the oesophageal wall and may require thoracotomy or thoracoscopy for lesions in the mid oesophagus.

Oesophageal bronchus

Oesophageal bronchus, where a bronchus takes its origin from the oesophagus, is the most common congenital bronchopulmonary foregut malformation and may be associated with OA and TOF.[35] It can present in different ways including with respiratory symptoms and signs with recurrent sepsis or from the consequence of the consolidated or collapsed lung. It may be found incidentally during investigation for other conditions.

A chest X-ray may reveal an opacity in the lung fields and a contrast or radioisotope study of the gastrointestinal tract for reflux may show contrast or tracer in the lung. An upper gastrointestinal (GI) endoscopy may reveal the fistula, usually in the middle or lower thirds of the oesophagus, and bronchoscopy will demonstrate the absence of a major bronchus. Angiography should be undertaken to demonstrate that the lung associated with the bronchus has an appropriate blood supply. A recent study has reported prenatal MRI findings in a patient with a fetus with an oesophageal bronchus.[36]

Resection of the bronchus and associated lung tissue is usually the treatment of choice. Anastomosis of the bronchus to the trachea may be possible in some cases.[37]

Congenital short oesophagus

Congenital short oesophagus is a rare anomaly that was first described clearly in 1958.[38] Since then, there has been considerable debate as to whether it is a true entity in itself; it has sometimes been described as a congenital hiatus hernia.

In this anomaly the oesophagus is short with an intrathoracic stomach and a hiatus hernia. Affected babies present with failure to thrive in the first few months of life.

Treatment options are very limited and may be technically extremely challenging.[39] A surgical procedure to treat gastro-oesophageal reflux may be possible.

ACQUIRED DISORDERS OF THE OESOPHAGUS

Achalasia of the cardia

Achalasia of the cardia is an uncommon motility disorder of the distal oesophagus in children which causes a functional obstruction at the level of the lower oesophageal sphincter. It tends to affect teenagers. In children it presents with vomiting, difficulty swallowing, respiratory symptoms, weight loss and occasionally chest pain. It can also cause night-time regurgitation. The swallowing difficulty usually starts with solid foodstuffs but can progress on to liquids. Bad breath may also be a feature.

The aetiology of this condition is poorly understood. An upper GI contrast study will reveal the classical appearance of a dilated, baggy oesophagus with a beaked appearance at the lower end (Figure 45.7). An upper GI endoscopy will reveal a baggy, dilated oesophagus which may contain food debris. This investigation may be important to exclude other even more uncommon conditions and allows an assessment of the presence or absence of inflammation. Affected patients have a high resting lower oesophageal sphincter pressure, failure to relax the lower oesophageal sphincter and poor oesophageal peristalsis on manometry studies.

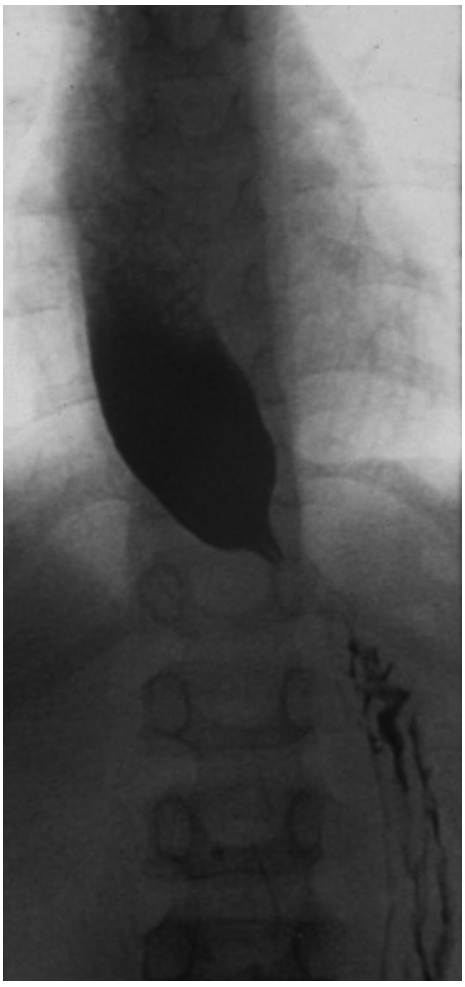

Figure 45.7 Upper GI contrast study in patient with achalasia of the cardia demonstrating massive dilatation of the oesophagus.

Given our poor understanding of this condition, there is no general consensus of how best to treat it. Drugs (including anticholinergics, calcium channel blockers and nitrates) have little to offer in affected children due to the high incidence of side effects and lack of sustained benefit. Pneumatic balloon dilatation under imaging control may have a place. Repeated dilatations are usually required and complications, including oesophageal rupture, are not uncommon. More recently, botulinum toxin (botox) has been successfully used in several centres.

The surgical management usually involves a myotomy of the lower oesophagus, which is extended onto the stomach, protected by an antireflux procedure performed at the same time. The commonest combination is a Heller cardiomyotomy and a partial fundoplication. This can be achieved laparoscopically.[40] More recently, peroral endoscopic myotomy has been described with comparable results to laparoscopic cardiomyotomy.[41, 42]

Oesophageal injury

Injuries to the oesophagus in children are usually due to the ingestion of noxious substances or foreign bodies. Iatrogenic injuries from instrumentation of the oesophagus during endoscopy or surgery are less common. Prompt identification of the problem is essential if perforation or fistulation to an adjacent structure is to be avoided.

SWALLOWED FOREIGN BODIES

Ingested foreign bodies are not uncommon in children. The nature of the swallowed item varies with the age of the child. Coins, batteries and parts of, or whole, small toys are common in infants and younger children. In older children inadequately chewed foodstuffs are more common, especially in the presence of an underlying oesophageal abnormality including a previously repaired OA or a peptic oesophageal stricture. Children with learning or behavioural difficulties are particularly prone to swallowing foreign bodies.[43]

In the majority of cases the history of ingestion will be known and prompt attendance at an emergency department by anxious parents likely. In some cases, where the history is not known, an inability to swallow food or liquids, drooling, respiratory difficulty, wheeziness, hoarseness or chest discomfort may be the presenting symptom.[44]

Initial assessment should include an evaluation of the airway. A chest and abdominal radiograph will reveal radioopaque foreign bodies. Where the swallowed item is a coin (Figure 45.8), a metal detector can be used to determine whether the coin is lodged in the chest or has passed into the stomach. Foreign bodies which pass into the stomach do not usually require treatment. One exception to this rule is in situations where mini magnetic toys or button batteries have been swallowed. In such cases fistulization between loops of small intestine and subsequent perforation can occur due to the magnets adhering across bowel loops,[43] and leakage of the contents of a battery can cause heavy metal poisoning. Button batteries are now extremely

powerful and can cause rapid and severe ulceration, with a risk of catastrophic erosion of the mediastinal great vessels. NHS England has published an important Patient Safety Alert, *Risk of death and serious harm from delays in recognising and treating ingestion of button batteries*, highlighting the seriousness of swallowing these batteries.[45] See also Chapter 34, Foreign bodies in the ear, nose and throat.

Of greater concern are those items which lodge in the oesophagus. They can get stuck at the level of the thoracic inlet, the cricopharyngeus muscle, the mid-oesophagus behind the heart at the level of the aortic arch and the oesophagogastric junction. Items which get stuck in the proximal oesophagus can obstruct the airway. Items which get stuck more distally are more at risk of causing perforation and mediastinitis. Damage to the oesophagus is caused by direct contact in the case of coins and contact, the release of electrical current and leakage of their contents in the case of batteries. Foreign bodies which are impacted in the oesophagus for some time can cause oesophageal perforation,[46] fistulization into adjacent structures including the great vessels and the trachea, with sometime catastrophic consequences.[46, 47]

Rigid or flexible oesophagoscopy under general anaesthetic and endotracheal intubation to protect the airway is usually the preferred treatment option where the foreign body is impacted in the oesophagus. Different types of graspers and basket devices for use with endoscopes have been developed specifically to remove coins. This is usually fairly straightforward, especially when the coin has a raised rim. Batteries are more difficult to remove due to their smooth edges. A catheter with a balloon on the end is sometimes successful when other techniques have failed.[44] Open safety pins are a particular challenge. These are best pushed into the stomach if the open end is proximal. Once in the stomach, the hinge end of the pin can be grasped and the pin removed, using an oesophageal overtube if one is available.

CAUSTIC INJURY

Ingestion of caustic substances by infants and toddlers is becoming increasingly common. Alkali, or less commonly acid, household cleaning or other agents contained in lemonade bottles stored under the sink are frequently implicated. Newer formulations of clothes and dishwashing liquid in tablet and 'liquitab' form are also implicated (**Figure 45.9**).[48] Impulsive behaviour and attention deficit hyperactivity disorder have been shown to be risk factors for such ingestion.[49]

A child who has swallowed a caustic substance usually presents immediately with symptoms of crying, spitting, coughing and stridor. Potential airway compromise is a serious concern in all such cases. Later symptoms include chest pain, dysphagia and vomiting. Signs of burn injury may be seen on the lips and in the mouth, although the absence of such signs does not exclude ingestion. Fever and tachycardia may also be obvious.

As in swallowed foreign bodies, the first concern in such cases should be the integrity of the airway. Oedema of the larynx caused by the caustic substance might occlude the airway. Prompt endotracheal intubation may be required.

The injuries caused by the ingestion of such substances can be severe. Mucosal slough and necrosis are common. Deeper injury and liquefaction of all layers of the oesophagus can also be seen even after brief exposure to a caustic substance. Attempts to wash the caustic substance away by drinking water may result in an exothermic chemical reaction which may only serve to worsen the injury. Other attempts to neutralize the ingested caustic substance may fail if the pH of the ingested substance is not known, and again may result in an unwanted exothermic chemical reaction.

Children suspected of ingesting caustic agents should be admitted for evaluation. A chest X-ray may be useful. Early intubation may be needed if the airway is at risk. All affected

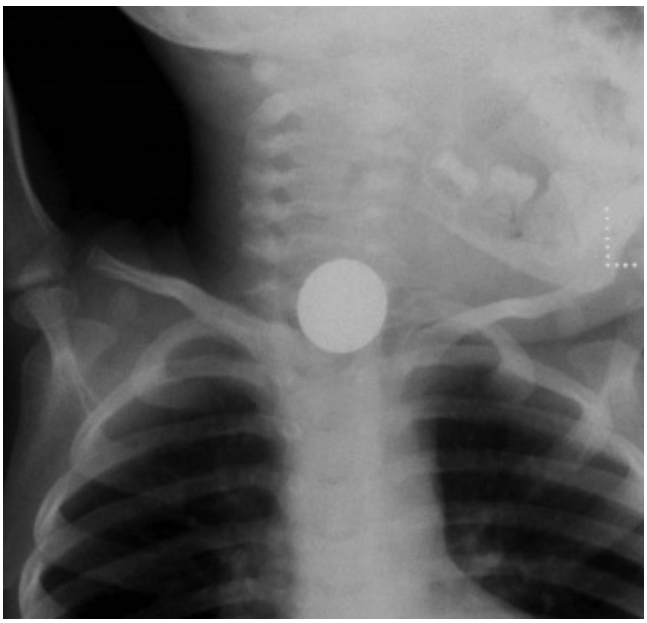

Figure 45.8 Coin impacted in the upper oesophagus in a toddler. The airway is at risk in this patient and prompt removal of the coin is required.

Figure 45.9 'Liquitabs' are increasingly implicated in caustic injuries.

children should be fasted and intravenous fluids administered. Early endoscopy is usually indicated in all cases to assess the extent and severity of the injury. The markers of superficial injury include mucosal erythema, oedema and mild mucosal damage. Deeper injuries will result in haemorrhage, exudates, mucosal sloughing, pseudomembrane formation and the development of granulation tissue. The deepest injuries will exhibit luminal narrowing or obliteration, severe oedema, eschar formation. Perforation and mediastinitis is possible in severe cases.

Blind passage of an NG tube is contraindicated in these patients. Placement of such a tube during the endoscopy is indicated to facilitate enteral nutrition and to maintain the integrity of the oesophageal lumen. The end of a blind-ending NG tube should be cut off to allow passage of a guidewire in the future. This may be helpful if the NG tube needs to be replaced or if a stricture develops (**Figure 45.10**) and might benefit from balloon dilatation under imaging control (**Figure 45.11**).[50]

The use of antibiotics and steroids to limit the effects of the injury and prevent stricture formation is controversial. Conflicting studies have shown both benefit and none. Serial balloon dilatations are the preferred treatment of a fibrous structure. Clearly, there is a risk of oesophageal perforation during this procedure. Placement of oesophageal stents is less well established. Oesophageal resection and replacement with a colonic or gastric tube may be required in long and the most resistant strictures.

In general terms, acid ingestion is less damaging to the oesophagus than alkali ingestion. Acid causes more damage to the stomach and the pylorus.

DRUG-INDUCED INJURY

Drug-induced oesophageal injury is very rare in children, and is most commonly seen in patients with an underlying structural abnormality. It usually only occurs where tablet or capsular formulations of the medication are used. The tablet or capsule gets stuck above a stricture and the release of its active agent causes oesophageal injury. Implicated drugs include non-steroidal analgesics, aspirin, slow-release potassium and the cycline family of antibiotics.

Symptoms of retrosternal chest pain and dysphagia may be reported. Endoscopic assessment is usually indicated.

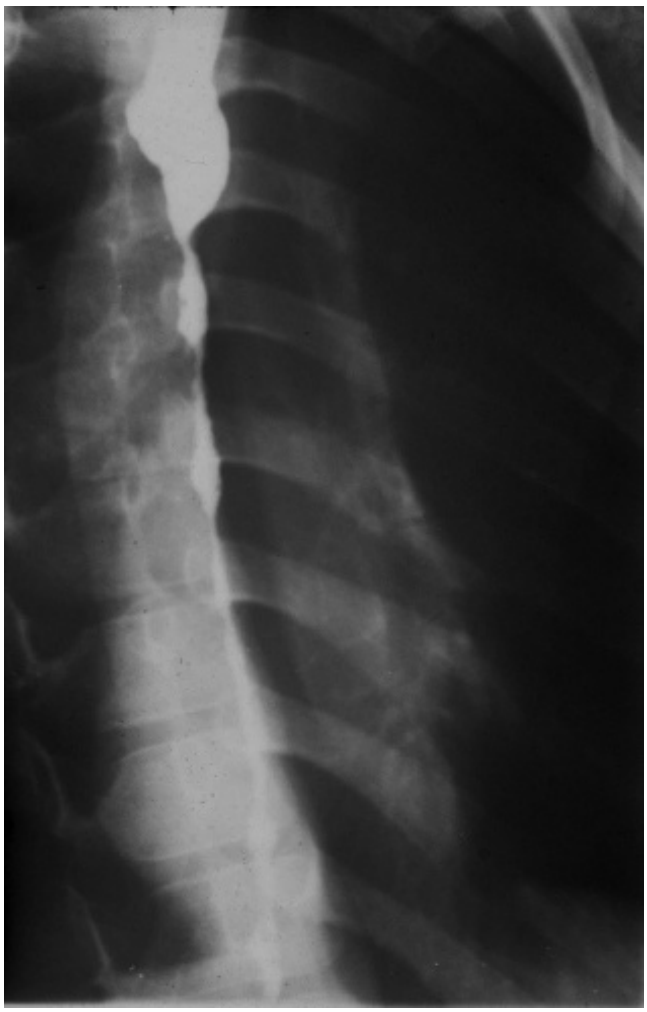

Figure 45.10 Upper GI contrast study in patient with a long oesophageal structure caused by the ingestion of a caustic substance.

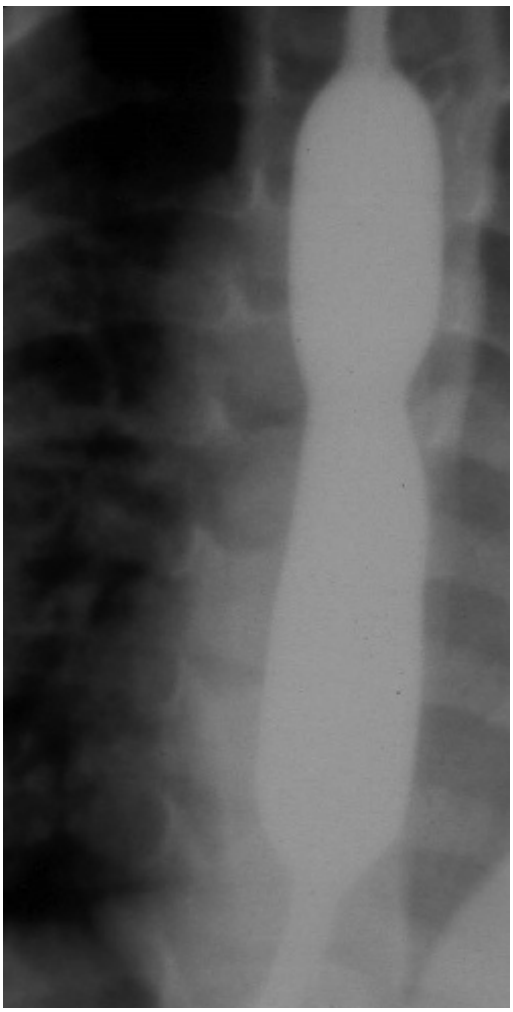

Figure 45.11 Balloon dilatation of a short stricture in the mid-oesophagus. The stricture can be identified where the balloon narrows.

Stricture formation is rare and, when it occurs, should be treated on its merits. The offending medication should be discontinued.

RADIATION-INDUCED INJURY

Radiation-induced injury of the oesophagus in children is extremely rare but can occur when radiotherapy for thoracic tumours is necessary. It is more common when chemotherapy is administered alongside the radiotherapy. Symptoms include dysphagia and chest pain. Endoscopy may reveal mucosal oedema and aphthous ulceration. Treatment is largely symptomatic.

Mallory Weiss tear

The classical Mallory Weiss tear of the lower oesophagus after a severe bout of vomiting is not common in children. However, the more frequent use of upper gastrointestinal endoscopy in paediatric practice has resulted in its more frequent recognition as an entity in children. The vomiting causes a mucosal tear to develop at the oeosphagogastric junction which bleeds.

The presenting features are usually a protracted period of vomiting followed by a haematemesis. Bleeding is usually self-limiting and acid suppression therapy using either proton pump inhibitors or H2 receptor blockers is usually indicated to encourage healing of the tear. In severe cases, often in the presence of an underlying coagulopathy, use of oesophageal balloon tamponade or pharmacological agents may be required to stop bleeding.

Oesophageal perforation and rupture

In neonates and children, the most common cause of oesophageal perforation or injury is nasogastric intubation, upper gastrointestinal endoscopy or other instrumentation. Swallowed foreign bodies may also be implicated.[51] In some cases where the history is unclear, non-accidental injury may need to be considered.

The risk of mediastinitis should be considered in all such cases and appropriate intravenous antibiotic and antifungal therapy initiated. The child should be fasted and parenteral nutrition may be necessary. Contrast or cross-sectional imaging studies may be helpful in determining the extent of the injury.

In the majority of cases, the oesophagus will heal without direct intervention, although clearly foreign bodies should be removed.

BEST CLINICAL PRACTICE

- ✓ The inability to pass a naso- or oro-gastric tube in the newborn is virtually diagnostic of oesophageal atresia.
- ✓ In oesophageal atresia, otolaryngologists need to be aware of the clinical features so they can arrange appropriate investigations, including tracheobronchoscopy, in most cases,
- ✓ Cross-sectional imaging (CT or MRI) is the most useful investigation for cysts associated with the oesophagus,
- ✓ Ingested coins or similar items lodged in the upper oesophagus can cause airway obstruction – urgent removal is indicated,
- ✓ Ingested button batteries which lodge in the oesophagus should be removed as a matter of some urgency to prevent oesophageal injury,
- ✓ The ingestion of caustic substances can cause laryngeal and airway oedema, inflammation and obstruction,
- ✓ Attempts to wash or neutralize an ingested caustic substance can result in an undesirable exothermic reaction and injury.

FUTURE RESEARCH

- ➤ The development of thoracoscopic surgical techniques and instruments is likely to result in more of the congenital anomalies of the oesophagus being managed thoracoscopically.
- ➤ Basic science and genetic research into the causes and the embryology of congenital anomalies of the oesophagus continues to improve our understanding of these complex conditions.

KEY POINTS

- Antenatal maternal polyhydramnios, which can affect approximately half of pregnancies with the various forms of OA, may give a clue to the presence of this abnormality.
- The newborn affected by any of the common variants of OA (but obviously not the baby with an isolated TOF) will present clinically with frothing at the mouth, choking episodes, cyanosis and respiratory distress. Clearly, attempts at feeding will precipitate such symptoms and may cause aspiration and severe respiratory distress.
- True congenital oesophageal diverticula, which contain all layers of the wall of the oesophagus, are uncommon. False or pulsion diverticula, which are herniations of the oesophageal mucosa between defects in the oesophageal muscular wall, are more common.
- Button batteries are now extremely powerful and can cause rapid and severe ulceration, with a risk of catastrophic erosion of the mediastinal great vessels.
- In general terms, acid ingestion is less damaging to the oesophagus than alkali ingestion. Acid causes more damage to the stomach and the pylorus.

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Section 2
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CHAPTER 46

ANATOMY AND EMBRYOLOGY OF THE EXTERNAL AND MIDDLE EAR

Peter Valentine and Tony Wright

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: external ear, middle ear, ossicles, facial nerve, Eustachian tube AND anatomy OR embryology OR development.

INTRODUCTION

The ear functions as an early warning system by detecting and locating potentially threatening environmental sounds. It is crucial for survival by accurately and rapidly detecting head movement so that the eyes can stay fixed on prey or predator. The ear plays a major part in the balance system, giving important information about sudden changes in the environment, both external and self, to avoid falls and injury. In addition, in many animals, and especially in humans, the ears form a major part of a communication system.

A three-dimensional appreciation of the complex temporal bone anatomy is crucial for the understanding of both the pathophysiology and surgery of the ear. Traditionally, the microscope has been used as the main tool to examine and operate on the temporal bone. In more recent years, endoscopic techniques have enhanced the visualization and magnification of vistas previously unseen.

Both convention and convenience have separated the ear into its three parts – external, middle and internal – for descriptive purposes. The structure of the internal ear is described in detail in Chapter 47, Anatomy of the cochlea and vestibular system: relating ultrastructure to function. This chapter deals with the external ear and the adult middle ear cleft including the mastoid air cell system and Eustachian tube. Finally, the embryology of the ear and subsequent development of the temporal bone, external ear and mastoid process are outlined.

THE EXTERNAL EAR

The auricle

The auricle (or pinna) projects at a variable angle from the side of the head and has some function in collecting sound. The lateral surface of the auricle has characteristic prominences and depressions (**Figure 46.1**), which are different in every individual, even identical twins. This unique pattern is comparable to fingerprints and can allow the identification of persons on the physiognomy of their auricles.[1] The curved rim is the helix, which often has a small prominence (Darwin's tubercle) at its posterosuperior aspect. Anterior to and parallel with the helix is another prominence, the antihelix. Superiorly, this divides into two crura, between which is the triangular fossa; the scaphoid fossa lies above the superior of the two crura. In front of the antihelix, and partly encircled by it, is the concha. This is divided into two portions by the descending limb of the anterior superior portion of the helix, known as the crus of the helix, which rests just above the external auditory meatus. The smaller superior portion is the cymba conchae and is the direct lateral relation to the suprameatal triangle of the temporal bone. The larger inferior portion is known as the cavum conchae. Below the crus of the helix and overlapping the external auditory meatus is the tragus, which is a small blunt triangular prominence pointing posteriorly. Opposite the tragus, at the inferior limit of the antihelix, is the antitragus. The intertragic notch separates the tragus from the antitragus. The lobule

lies below the antitragus and is soft, being composed of fibrous and adipose tissue. The medial (cranial) surface of the auricle has elevations corresponding to the depressions on the lateral surface, and possesses corresponding names, for example the eminentia conchae.

The body of the auricle is formed from elastic fibrocartilage and is a continuous plate except for a narrow gap between the tragus and the anterior crus of the helix, where it is replaced by a dense fibrous tissue band. This gap is the site for an endaural incision which, properly performed, should not damage cartilage or its perichondrium and which by splitting the soft-tissue ring surrounding the bony ear canal allows wide exposure of the deeper parts.

The cartilage extends about 8 mm down the ear canal to form its lateral third. The cartilage of the auricle is covered with perichondrium from which it derives its supply of nutrients, as cartilage itself is avascular. Stripping the perichondrium from the cartilage, as occurs following injuries that cause haematoma, can lead to cartilage necrosis with crumpled up 'boxer's ears'. The skin of the pinna is thin and closely attached to the perichondrium on the lateral surface. On the medial (cranial) surface, there is a definite subdermal adipose layer that allows dissection during pinnaplasty surgery. The skin of the auricle is covered with fine hairs and, most noticeably in the concha and the scaphoid fossa, there are sebaceous glands opening into the root canals of these hairs. On the tragus and intertragic notch coarse, thick hairs may develop in the middle-aged and older male.

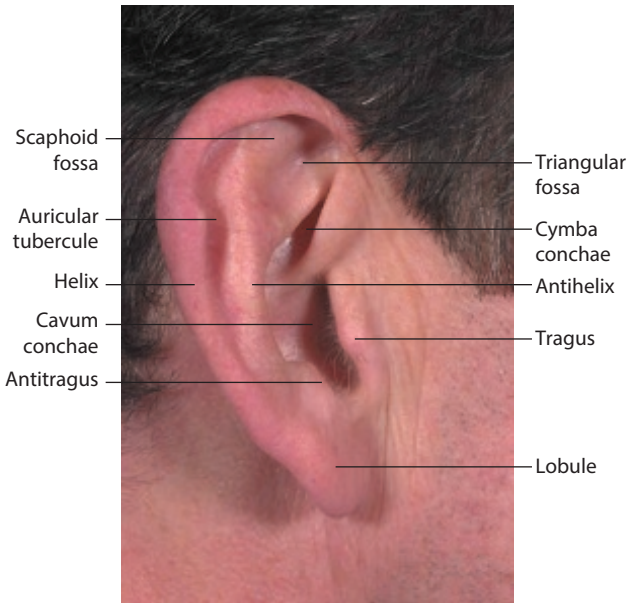


Figure 46.1 Right auricle.

The cartilage of the auricle is connected to the temporal bone by two extrinsic ligaments. The anterior ligament runs from the tragus and from a cartilaginous spine on the anterior rim of the crus of the helix to the root of the zygomatic arch. A separate posterior ligament runs from the medial surface of the concha to the lateral surface of the mastoid prominence. Intrinsic ligaments connect various parts of the cartilaginous auricle; that between helix and tragus has already been described and another runs from the antihelix to the posteroinferior portion of the helix. Extrinsic and intrinsic muscles are attached to the perichondrium of the cartilage. Temporal and posterior auricular branches of the facial nerve supply the extrinsic muscles and, while being functionally unimportant, they do give rise to the postauricular myogenic response following appropriate auditory stimulation.[2] There are three extrinsic muscles: auricularis anterior, superior and posterior, the last being supplied by the posterior auricular branch of the facial nerve. All three radiate out from the auricle to insert into the epicranial aponeurosis. The intrinsic muscles – six in number – are small, inconsistent and without useful function.

Arterial branches of the external carotid supply the auricle. The posterior auricular appears to be the dominant artery and supplies the medial surface (except the lobule), the concha, the middle and lower portions of the helix and the lower part of the antihelix. The anterior auricular branches of the superficial temporal supply the upper portions of the helix, antihelix, triangular fossa, tragus and lobule.[3] The superior auricular artery has a constant course and connects the superior temporal artery and the posterior auricular artery network. This branch can provide a reliable vascular pedicle for retroauricular flaps.[4] A small auricular branch from the occipital artery may assist the posterior auricular in supplying the medial surface.

Both cranial branchial nerves and somatic cervical nerves supply the auricle. Their distribution is heterogeneous and the overlap may be extensive; however, the greater auricular nerve prevails on the lateral and medial surfaces.[5] The essential features are described in Table 46.1.

The lymphatic drainage from the posterior surface is to the lymph nodes at the mastoid tip, from the tragus and from the upper part of the anterior surface to the preauricular nodes, and from the rest of the auricle to the upper deep cervical nodes.

TABLE 46.1 Sensory innervation of the auricle

Nerve	Derivation	Region supplied
Greater auricular	Cervical plexus C2, 3	Medial surface and posterior portion of lateral surface
Lesser occipital	Cervical plexus C2, 3	Superior portion of medial surface
Auricular	Vagus X	Concha and antihelix Some supply medial surface (eminetia concha)
Auriculotemporal	Vc mandibular	Tragus, crus of helix and adjacent helix
Facial VII		Probably supplies small region in the root of concha

The external auditory canal

The external auditory canal extends from the concha of the auricle to the tympanic membrane and is approximately 2.4 cm long. The supporting framework of the canal wall is cartilage in the lateral one-third and bone in the medial two-thirds. The diameter of the canal varies greatly between individuals and between different races. In adults, the cartilaginous portion runs inwards, slightly downwards and forwards. The canal is straightened, therefore, by gently moving the auricle upwards and backwards to counteract the direction of the cartilaginous portion. In the neonate, there is virtually no bony external meatus as the tympanic bone is not yet developed, and the tympanic membrane is more horizontally placed so that the auricle must be gently drawn downwards and backwards for the best view of the tympanic membrane.

In the adult, the lateral cartilaginous portion is about 8 mm long and is continuous with the auricular cartilage. The medial border of the meatal cartilage is attached to the rim of the bony canal by fibrous bands. There are two horizontal fissures, described by Santorini, that lie anteroinferiorly in the cartilaginous portion that possibly increase flexibility but allow passage of infection or tumour into the parotid gland. The bony canal wall, about 1.6 mm long, is narrower than the cartilaginous portion and itself becomes smaller closer to the tympanic membrane. The medial end of the bony canal is marked by a groove, the tympanic sulcus, which is absent superiorly. Although the tympanic bone makes up the greater part of the canal, and also carries the sulcus, the squamous bone forms the roof. Therefore, there are two suture lines in the canal wall with the tympanosquamous anteriorly and the tympanomastoid posteriorly. These suture lines may be more or less developed; they project into the canal with overlying closely adherent skin, which can make raising an intact tympanomeatal flap a challenge. The tympanomastoid suture is a complex suture line between the anterior wall of the mastoid process, a portion of the squamous bone and the tympanic bone.

Apart from these intrusions into the canal, there are two constrictions: one at the junction of the cartilaginous and bony portions and the other, the isthmus, 5 mm from the tympanic membrane where a prominence of the anterior canal wall reduces the diameter. Deep to the isthmus, the anteroinferior portion of the canal dips forwards forming a wedge-shaped anterior recess between the tympanic membrane and the canal. This recess can be a difficult spot for access either in the clinic or at surgery.

The external canal is lined with keratinizing stratified squamous epithelium, which lacks the rete pegs and skin appendages in the thin skin of the bony canal. Body skin normally grows directly from the basal layers towards the surface where it is shed into the surroundings. Excess proliferation in the scalp trapped by the hair is dandruff. If this pattern of growth were to occur in the external ear canal, the canal would soon become filled with desquamated skin. Instead of maturation taking place directly towards the surface, there is outward, oblique growth of the epidermis of the canal skin[6] and pars flaccida so that the surface layers effectively migrate towards the external opening of the canal. The normal rate of migration is about 0.1 mm/day,[7] although this range is hugely variable and in some conditions there is complete failure of migration with a consequent build-up of shed keratin in the ear canal. It has been postulated that patients who are prone to cerumen impaction may lack a 'keratinocyte attachment destroying substance' (KADS) based on the observation they have much longer sheets of desquamated keratin which are in continuity with the stratum corneum, when compared to patients with no issue.[8,9]

The skin of the pars tensa has a different derivation from that of the deep canal and cell divisions occur randomly within the layer of basal cells. The effect of this, in a circular sheet with the handle of the malleus forming a central boundary extending halfway down the membrane, is to create outward mass migration of the skin of the pars tensa. Ink dots applied to the surface have an outward pattern of movement. However, if a hole is made in the tympanic membrane and a graft laid underneath the membrane (an underlay graft), migration of the skin from the outer edge of the perforation is directed centrally to cover the graft. This occurs because the boundary conditions have altered and fortunately provides the basis for the healing of grafts and for the re-epithelialization of mastoid cavities. Even a small piece of pars tensa skin has this ability and so is a precious material and needs to be preserved during ear surgery if a bare area needs covering. However, the property of canal skin to migrate can also bring problems with the formation of cholesteatoma if the skin becomes displaced into the middle ear cleft.

At the outer limits of the ear canal are some short hairs that project towards the opening of the canal. There are fine vellus hairs and larger terminal hairs called tragi (Greek: 'goat'), which tend to be more prominent in males in whom they are a second sexual characteristic. These hairs are oriented with their tips laterally and increase in number and length from the bony-cartilaginous junction laterally, so helping to prevent the entrance of foreign bodies. In the skin of the cartilaginous canal are clusters of ceruminous and sebaceous glands. The ceruminous glands are modified apocrine sweat glands that open into the root canal of the hair follicles and produce a watery, white secretion that slowly darkens, turning semi-solid and sticky as it dries. Since these glands are apocrine sweat glands, they respond to many stimuli such as adrenergic drugs, fever and emotion which, along with direct mechanical stimulation, can all produce an increase or altered secretion.

The sebaceous glands produce an oily material (sebum) from the breakdown of their fat-containing cells which is usually excreted into the root canals of the hair follicles. The mixture of desquamated cells, cerumen and sebum forms wax. Human earwax is a Mendelian trait consisting of wet and dry forms. Dry wax, lacking cerumen, is yellowish or grey and brittle, while wet wax is brownish and sticky. The wet phenotype is dominant over the dry type, and is frequently seen in populations of European and African origins. East Asians show the dry phenotype and there are intermediate frequencies among the Native American and Inuit of Asian ancestry. A single-nucleotide polymorphism in the *ABCC11* gene is responsible for the determination of earwax type, with the *AA* genotype corresponding to dry wax and *GA* and *GG* to wet wax.[10] There is dispute with regard to the specific antibacterial activity of cerumen in

in vitro studies.[11,12] However, the areas of skin that take part in cerumen production have all the components of an active local immune system and probably protect the canal by an antibody-mediated local immune response.[13]

Wax is not usually found in the deep ear canal and a lump of 'wax' overlying the upper portion of the tympanic membrane (pars flaccida or attic region) is rarely true wax, but is nearly always associated with an underlying cholesteatoma as it is, in fact, dried-up, oxidized keratin. The sense of the old adage 'beware the attic wax' is still just as true today as it was in the past.

The arterial supply of the external meatus is derived from branches of the external carotid. The auricular branches of the superficial temporal artery supply the roof and anterior portion of the canal. The deep auricular branch of the first part of the maxillary artery arises in the parotid gland behind the temporomandibular joint, pierces the cartilage or bone of the external meatus and supplies the anterior meatal wall skin and the epithelium of the outer surface of the tympanic membrane. Finally, auricular branches of the posterior auricular artery pierce the cartilage of the auricle and supply the posterior portions of the canal. The veins drain into the external jugular vein, the maxillary veins and the pterygoid plexus. The lymphatic drainage follows that of the auricle.

The external auditory canal receives its sensory innervation from the trigeminal, facial, glossopharyngeal and vagus nerves. Frequently, patients can cough when undergoing microsuction of the canal which is caused by stimulation of the vagus nerve via Arnold's nerve, its auricular branch.

The relationships of the external canal are depicted in Figure 46.2 and a coronal section through the external canal and middle ear are shown in Figure 46.3.

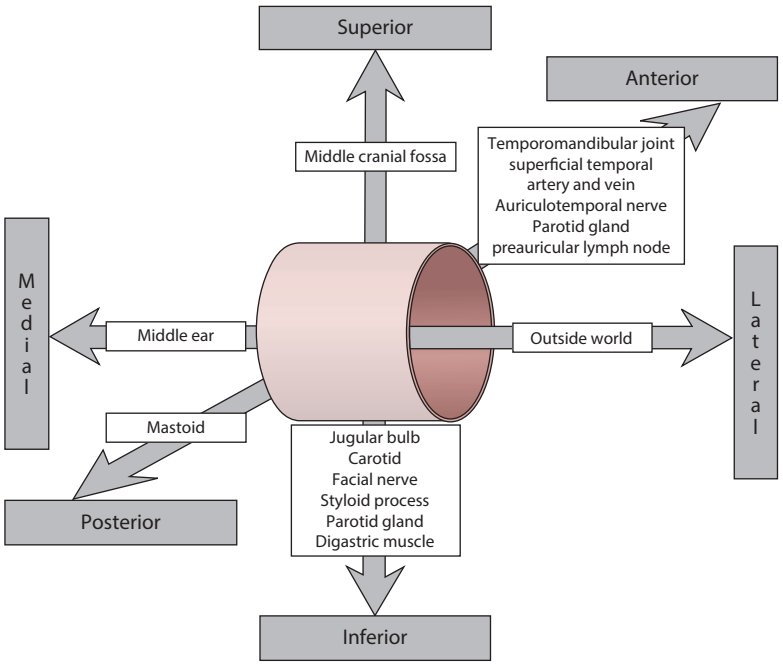
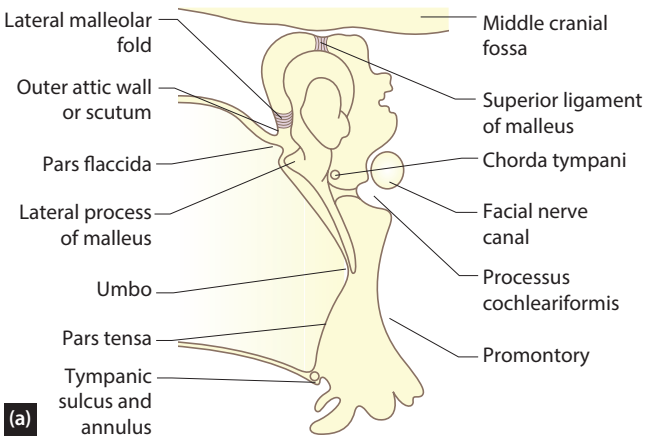


Figure 46.2 Relationships of the right external auditory canal.



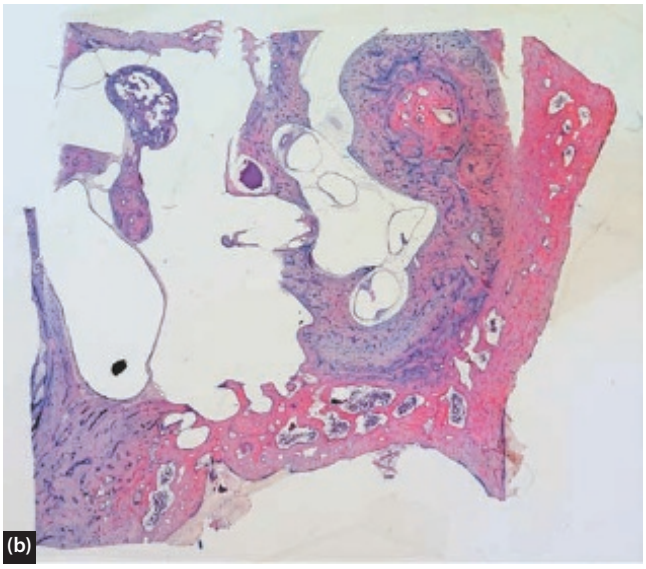


Figure 46.3 (a) Diagram of a coronal section through the external canal and middle ear at the level of the malleus handle. **(b)** Photomicrograph of a more posterior coronal section, including the malleus and the stapes.

THE MIDDLE EAR CLEFT

The middle ear cleft consists of the tympanic cavity, the Eustachian tube and the mastoid air cell system. The tympanic cavity is an irregular, air-filled space within the temporal bone between the tympanic membrane laterally and the osseous labyrinth medially. It contains the auditory ossicles and the tendons that attach them to the middle ear muscles. Other structures, including the tympanic segment of the facial nerve, run along its walls to pass through the cavity.

The tympanic membrane

The tympanic membrane lies at the medial end of the external auditory meatus and forms the majority of the lateral wall of the tympanic cavity. It is slightly oval in shape, being broader above than below, forming an angle of about 55° with the floor of the meatus. Its longest diameter from posterosuperior to anteroinferior is 9–10 mm, while perpendicular to this the shortest diameter is 8–9 mm. Most of the circumference is thickened to form a fibrocartilaginous ring, the tympanic annulus, which sits in a groove in the tympanic bone, the tympanic sulcus. The sulcus does not extend into the notch of Rivinus at the roof of the canal, which is formed by part of the squama of the temporal bone. From the superior limits of the sulcus, the annulus becomes a fibrous band which runs centrally as anterior and posterior malleolar folds to the lateral process of the malleus, the handle of which is clearly visible within the tympanic membrane. This leaves a small, triangular region of tympanic membrane above the malleolar folds within the notch of Rivinus, called the pars flaccida, which does not have a tympanic annulus at its margins. The pars tensa forms the rest of the tympanic membrane and is concave towards the ear canal but each segment is slightly convex between the lateral attachment of the annulus and the centre of the membrane where the tip of the malleus handle is attached at the umbo (Figure 46.4).

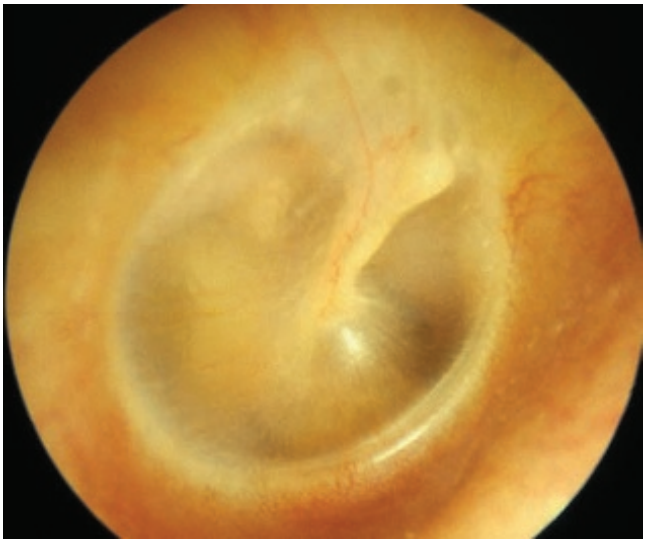


Figure 46.4 Endoscopic photograph of the right tympanic membrane.

Both the pars tensa and pars flaccida comprise three layers. There is an outer epithelial layer, the epidermis, which is continuous with the skin of the external meatus; a middle, mainly fibrous layer, the lamina propria; and an inner mucosal layer continuous with the lining of the tympanic cavity. The lamina propria of the pars tensa has radially oriented fibres in the outer layers and circular, parabolic and transverse fibres in the deeper layer. This arrangement probably accounts for the complex pattern of tympanic membrane displacement during sound stimulation. In the pars flaccida, the lamina propria is less marked and the orientation of the collagen fibres seems random.

The arterial supply of the tympanic membrane arises from branches supplying both the external auditory meatus and the middle ear. These two sources interconnect through extensive anastomoses within the connective tissue layer of the lamina propria. The epidermal vessels originate from the deep auricular branch of the maxillary artery coming from the external auditory meatus, whereas the mucosal vessels arise from the anterior tympanic branches of the maxillary artery, the stylomastoid branch of the posterior auricular artery and probably from the middle meningeal artery.

Branches of the auriculotemporal nerve (Vc), the auricular branch of the vagus and the tympanic branch of the glossopharyngeal nerve supply the tympanic membrane. These also run in the lamina propria and, while variations and overlap are considerable, both the vascular supply and innervation are relatively sparse in the middle part of the posterior half of the tympanic membrane.

The tympanic cavity

The tympanic cavity is traditionally divided into three compartments: the epitympanum (upper), the mesotympanum (middle) and hypotympanum (lower). The epitympanum, or attic, lies above the level of the malleolar folds and is separated from the mesotympanum and hypotympanum by a series of mucosal membranes and folds. The hypotympanum lies below the level of the inferior part of the tympanic sulcus and is continuous with the mesotympanum above. With the advent of endoscopic ear surgery, the mesotympanum may be considered as that part of the middle ear visible through the external canal with a microscope. The retrotympanum lies posterior to it and includes both the posteriomedial and posterior walls of the tympanic cavity, whereas the protympanum is anterior to the promontory and is contiguous with the tympanic portion of the Eustachian tube.

THE LATERAL WALL

The lateral wall of the tympanic cavity is formed by the bony lateral wall of the epitympanum superiorly, the tympanic membrane centrally and the bony lateral wall of the hypotympanum inferiorly. The lateral epitympanic wall is wedge-shaped in section and its sharp inferior portion is also called the outer attic wall or scutum (Latin: 'shield'). It is thin and easily eroded by cholesteatoma, leaving a telltale sign on a high-resolution coronal CT scan.

Three holes are present in the bone of the medial surface of the lateral wall of the tympanic cavity. The petrotympanic fissure is a slit about 2 mm long which opens anteriorly just above the attachment of the tympanic membrane. It receives the anterior malleolar ligament and transmits the anterior tympanic branch of the maxillary artery to the tympanic cavity. The chorda tympani, which carries taste sensation from the anterior two-thirds of the same side of the tongue and secretomotor fibres to the submandibular gland, enters the medial surface of the fissure through a separate anterior canaliculus (canal of Huguier) which is sometimes confluent with the fissure. It then runs posteriorly between the fibrous and mucosal layers of the tympanic membrane, across the upper part of the handle of the malleus and then continues within the membrane, but below the level of the posterior malleolar fold (**Figure 46.5**). The nerve reaches the posterior bony canal wall just medial to the tympanic sulcus, enters the posterior canaliculus and then runs obliquely downwards and medially through the posterior wall of the tympanic cavity until it reaches the facial nerve. The point of entry of the chorda tympani into the facial nerve bundle is quite variable. Usually this is at the level of the inferior third of the facial canal on its anterior wall, but on occasions the chorda can leave the skull base by a separate foramen before it joins the facial nerve.[14] During cortical mastoidectomy, the fibrous strands of the tympanomastoid suture line can often be confused with the chorda tympani although the angle of the white strands of the suture line is different from the angle of the chorda.

THE ROOF

The roof of the epitympanum is the tegmen tympani, a thin bony plate that separates the middle ear space from the middle cranial fossa. Both the petrous and squamous portions of the temporal bone form it; and the petrosquamous suture line, which does not close until adult life, can provide a route of access for infection into the extradural space in children. Veins from the tympanic cavity running to the superior petrosal sinus pass through this suture line. There is a bony crest, known as the cog, which projects from the tegmen tympani caudally to lie anterior to the head of the malleus and can be of variable size. This structure divides the larger posterior epitympanic space from the smaller anterior epitympanic space, where residual cholesteatoma may be left if not formally explored in canal wall-up surgery (**Figure 46.6**).

THE FLOOR

The floor of the tympanic cavity may consist of compact or pneumatized bone with spines and trabeculae. It separates the hypotympanum from the dome of the jugular bulb and its thickness can vary according to the height of the jugular fossa. Occasionally, the floor is deficient and the jugular bulb is then covered only by fibrous tissue and a mucous membrane. This should be kept in mind when raising the inferior portion of a tympanomeatal flap. At the junction of the floor and the medial wall of the cavity there is a small opening, the inferior tympanic canaliculus, that allows the entry of the tympanic branch of the glossopharyngeal nerve or Jacobson's nerve into the middle ear from its origin below the base of the skull. This also carries preganglionic parasympathetic fibres from the inferior salivary nucleus on their course to the otic ganglion.

THE ANTERIOR WALL

The anterior wall of the tympanic cavity is rather narrow as the medial and lateral walls converge. The lower third of the anterior wall consists of a plate of bone covering the carotid artery as it enters the skull and before it turns anteriorly. This plate, which can be wafer thin or up to 3 mm thick, is perforated by the superior and inferior caroticotympanic nerves carrying sympathetic fibres to the tympanic plexus and by tympanic branches of the internal carotid artery. In around 2% of cases, the bone

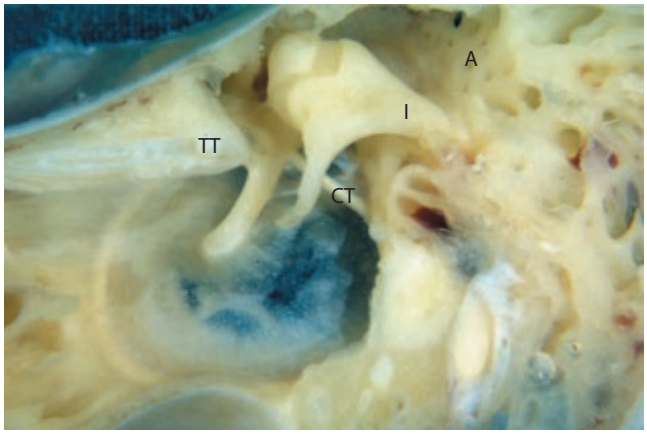


Figure 46.5 The tympanic membrane viewed from the middle ear. The corda tympani (CT) runs superior to the tensor tympani (TT) in its passage across the tympanic membrane, and lies medial to the anterior malleolar ligament in the anterior attic. The aditus to the mastoid antrum (A) lies posterosuperior to the short process of incus (I).

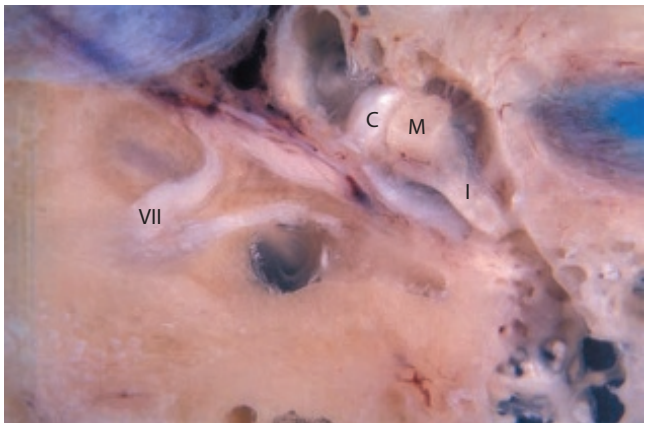


Figure 46.6 A specimen cut axially at the level of the labyrinthine and intratympanic segments of the facial nerve (VII), showing a small cholesteatoma (C) lying between the head of the malleus and anterior epitympanic space. The ossicular heads resemble a scoop of ice cream in a cone, which can be readily seen on a high-resolution axial CT scan. I, incus; M, malleus.

is dehiscent so that the artery is exposed in the protympanum.[15] The middle third of the anterior wall comprises the tympanic orifice of the Eustachian tube which can be irregular, rectangular or triangular in shape and average 5 × 4 mm in diameter.[16] Just above this is a canal containing the tensor tympani muscle that subsequently runs along the medial wall of the tympanic cavity enclosed in a thin bony sheath. The upper third is usually pneumatized and may house the supratubal recess, a small niche that can be separated from the anterior epitympanic space by the tensor fold.

THE MEDIAL WALL

The medial wall separates the tympanic cavity from the internal ear. The promontory is a rounded elevation occupying much of the central portion of the medial wall. It covers part of the basal coil of the cochlea and usually has small grooves on its surface containing the nerves which form the tympanic plexus. Sometimes the groove containing the tympanic branch of the glossopharyngeal nerve may be covered by bone, thereby forming a small canal (**Figure 46.7**). The promontory gently inclines forwards to merge with the anterior wall of the tympanic cavity in the protympanum but is more steeply sloped posteriorly.

Behind and above the promontory is the oval window. This is a nearly kidney-shaped opening that connects the tympanic cavity with the vestibule, but which in life is closed by the footplate of the stapes and its surrounding annular ligament. Its size naturally varies with the size of the footplate, but on average it is 3.25 mm long and 1.75 mm wide. The oval window lies at the bottom of a depression or niche that can be of varying width depending on the position of the facial nerve superiorly, and the prominence of the promontory inferiorly (**Figure 46.8**).

The round window niche lies below and a little behind the oval window niche from which it is separated by a posterior extension of the promontory forming a bony ridge called the subiculum. Another ridge of bone – the ponticulus – leaves the promontory above the subiculum and runs to the pyramid on the posterior wall of the cavity. Occasionally, this structure can resemble a bridge with a medial communication between the sinus tympani and posterior sinus, a space lying behind the posterior crus of the stapes. The round window niche is most commonly triangular in shape, with anterior, posterosuperior and posteroinferior walls. The latter two meet posteriorly and lead to the sinus tympani. The round window membrane is usually out of sight, obscured by the overhanging edge of the promontory forming the niche and mucosal folds within it. The membrane is roughly oval in shape, about 2.3 × 1.9 mm in dimension and lies in a plane at right angles to the plane of the stapes footplate. It tends to curve towards the scala tympani of the basal coil of the cochlea, so that it is concave when viewed from the middle ear, and it appears to be divided into an anterior and posterior portion by a transverse thickening. A further ridge of bone inferiorly running between the basal helix of the cochlea and the bone over the jugular bulb can used as a convenient landmark to separate the retrotympanum from the hypotympanum. Although first identified by Proctor,[17] this has been renamed by Marchioni et al.[18] as the finiculus (Latin: 'borderline').

The facial nerve canal (or Fallopian canal) runs above the promontory and oval window in an anteroposterior direction. It has a smooth, rounded lateral surface that often has microdehiscences and when the bone is thin or the nerve exposed by disease, there are two or three straight blood vessels clearly visible along this line of nerve. These are the only straight blood vessels in the middle ear and indicate quite clearly that the facial nerve is very close by. The facial nerve canal is marked anteriorly by the processus cochleariformis, a curved projection of bone, concave anteriorly, which houses the tendon of the tensor tympani muscle as it turns laterally to the handle of the malleus. Behind the oval window, the facial canal

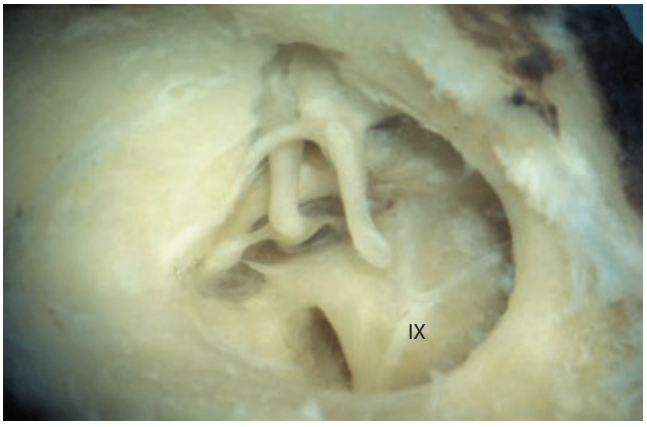


Figure 46.7 The medial wall of the mesotympanum seen after removal of the tympanic membrane. The tympanic branch of the glossopharyngeal nerve (IX) can be seen crossing the promontory. Note the notch of Rivinus in the roof of the canal.

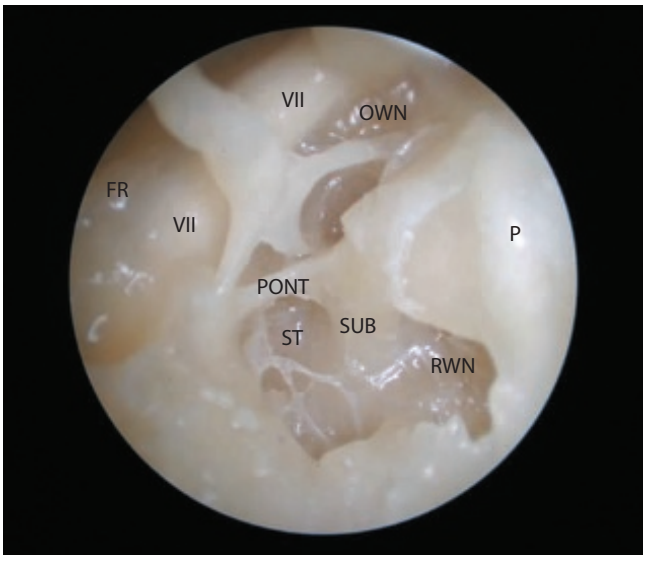


Figure 46.8 Endoscopic view of the retrotympanum showing the relationship between the oval window niche (OWN), round window niche (RWN), promontory (P), facial nerve (VII) and facial recess (FR). The sinus tympani (ST) lies medial to the facial nerve between the ponticulus (PONT) and subiculum (SUB).

starts to turn inferiorly as it begins its descent in the posterior wall of the tympanic cavity (Figure 46.9).

The region above the level of the facial nerve canal forms the medial wall of the epitympanum. The dome of the lateral semicircular canal is the major feature of the posterior portion of the epitympanum, lying posterior and extending a little lateral to the facial canal. During a cortical mastoidectomy, the triangular relationship of the lateral semicircular canal, the short process of the incus and the seventh nerve is often quite helpful. In well-aerated mastoid bones, the labyrinthine bone over the superior semicircular canal may be prominent, running at right angles to the lateral canal and joining it anteriorly at a swelling which houses the ampullae of the two canals. In front and a little below this, above the processus cochleariformis, may be a slight swelling corresponding to the geniculate ganglion, with the bony canal of the greater superficial petrosal nerve running for a short distance anteriorly.

THE POSTERIOR WALL

The posterior wall is wider above than below and has in its upper part a large irregular opening – the aditus ad antrum – that leads back from the posterior epitympanum into the mastoid antrum (Figure 46.10). Below the aditus is a small depression, the fossa incudis, which houses the short process of the incus and its suspensory ligament. Below the fossa incudis and medial to the opening of the chorda tympani nerve is the pyramid, a small hollow conical projection with its apex pointing anteriorly. This houses the stapedius muscle and tendon, which inserts into the posterior aspect of the head of stapes. The canal within the pyramid curves downwards and backwards to join the descending portion of the facial nerve canal.

The facial recess is a groove which lies between the pyramid and facial nerve and the annulus of the tympanic membrane (Figure 46.11). This is shallower lower down where the facial nerve canal forms only a slight prominence on the posterior wall. The facial recess is, therefore, bounded medially by the facial nerve and laterally by the tympanic annulus, with the chorda tympani nerve running obliquely through the wall between the two. The chorda always runs medial to the tympanic membrane, which means that the angle between the facial nerve and the chorda allows a posterior tympanotomy to be cut, thereby accessing the middle ear from the mastoid without disruption to the tympanic membrane (Figure 46.12). This angle can be small or large depending on the site of origin of the chorda from the facial nerve.

The sinus tympani is a posterior extension of the mesotympanum into the posterior wall and lies deep to the facial nerve, pyramid and stapedius muscle. It varies in size and, when extensive, is probably one of the most inaccessible sites in the middle ear when operating with the microscope. A surgical view can be enhanced using a 45° endoscope introduced from the opposite side of the ear being observed. The medial wall of the sinus tympani becomes continuous with the posterior portion of the medial wall of the tympanic cavity in the retrotympanum, and it is bounded superiorly by the ponticulus and inferiorly by the subiculum. Its importance is that cholesteatoma which has extended here from the mesotympanum is extremely difficult to eradicate. As the sinus can extend as far as 9 mm

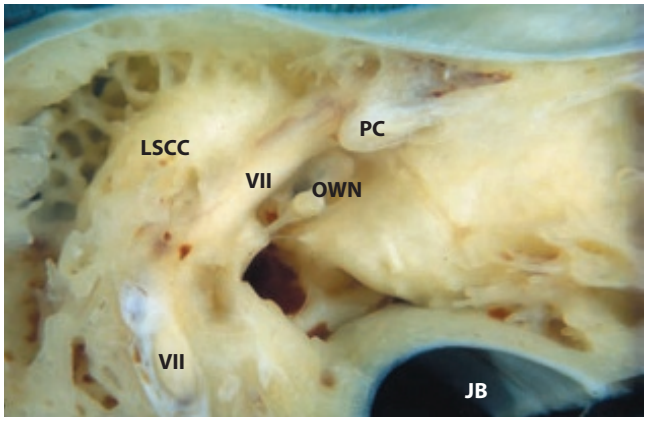


Figure 46.9 A specimen cut to show the medial wall of the tympanic cavity. The processus cochleariformis (PC) marks the anterior position of the intratympanic portion of the facial nerve, which passes between the lateral semicircular canal (LSCC) and oval window niche (OWN). Note the jugular bulb (JB) in the floor of the tympanic cavity.

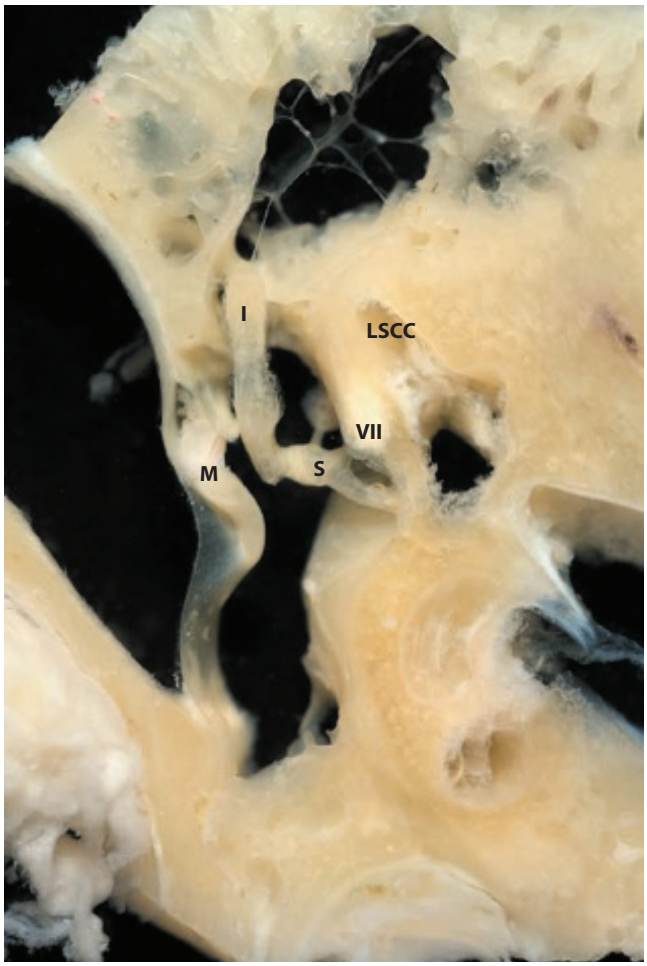
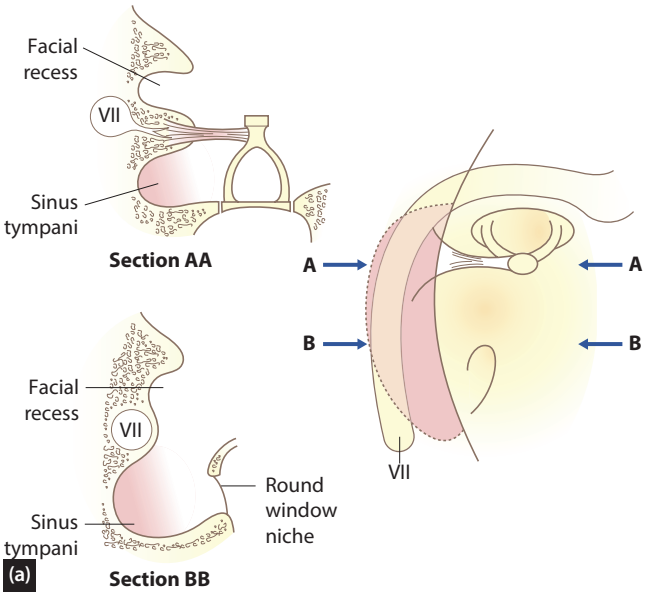


Figure 46.10 A specimen cut coronally at the level of the long process of incus. The aditus to the mastoid antrum lies posterosuperiorly to the incus (I). LSCC, lateral semicircular canal; M, malleus; S, stapes; VII, facial nerve.



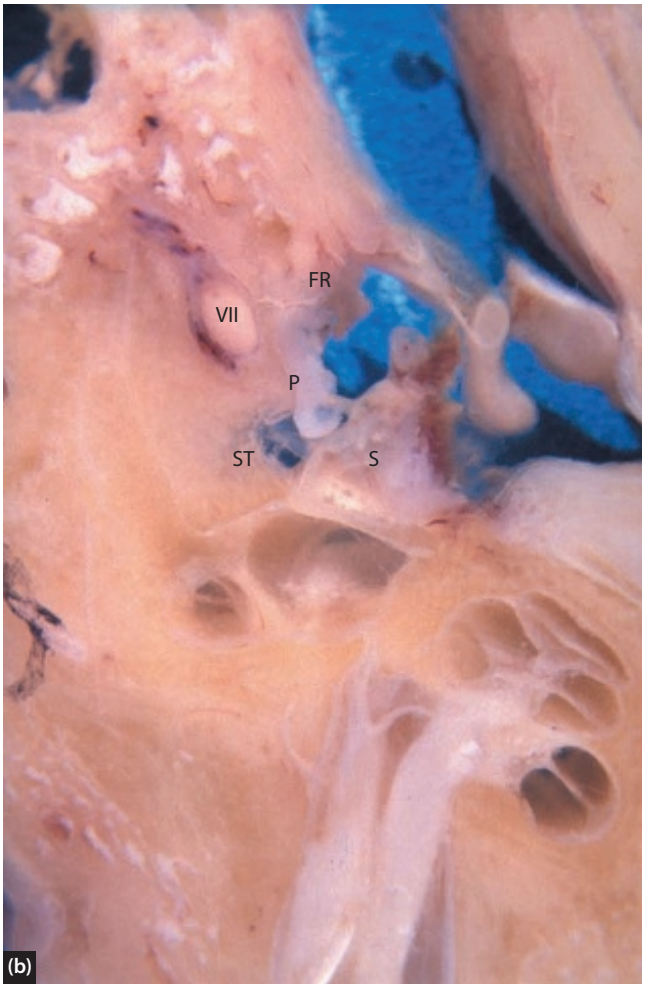


Figure 46.11 (a) The facial recess and sinus tympani at different levels in the middle ear. Section AA is at the level of the pyramid where the facial recess is relatively deep. In section BB, at the level of the round window, the facial recess is quite shallow. The extent of the sinus tympani, deep and posterior to the facial nerve is variable. **(b)** A specimen in section AA at the level of the pyramid (P). S, stapes; VII, facial nerve FR, facial recess; ST, sinus tympani.

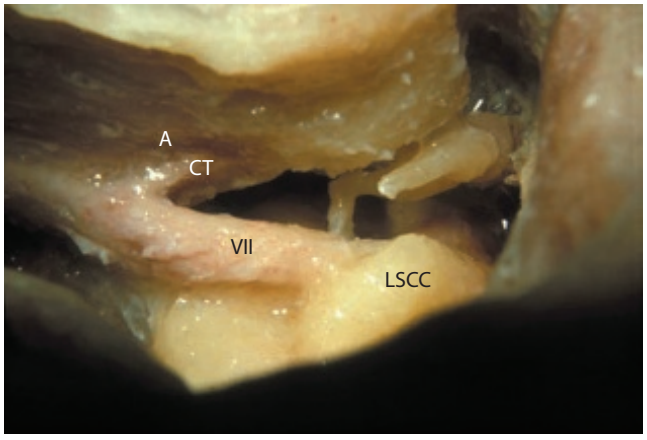


Figure 46.12 Posterior tympanotomy in a left ear, showing the relationship of the facial nerve (VII), corda tympani (CT), annulus (A) and lateral semicircular canal (LSCC). The promontory is readily accessible via this approach in cochlear implant surgery.

into the mastoid bone when measured from the tip of the pyramid,[19] a retrofacial dissection inferior to the posterior semicircular canal may be required should the disease be out of reach using a transcanal endoscopic approach.

The relationships of the middle ear space are shown diagrammatically in Figure 46.13.

The contents of the tympanic cavity

The tympanic cavity contains the ossicles, two muscles, the chorda tympani and the tympanic plexus. The ossicles are the malleus, incus and stapes that form a semi-rigid bony chain for conducting sound. They can be seen photographed with a scale in Figure 46.14. The malleus is the most lateral and is attached to the tympanic membrane, whereas the stapes is attached to the oval window.

THE MALLEUS

The malleus is the largest of the three ossicles, measuring up to 9 mm in length. It comprises a head, neck and handle or manubrium. The head lies in the epitympanum and is suspended by the superior ligament, which runs upwards to the tegmen tympani. The head of the malleus has a saddle-shaped facet on its posteromedial surface to articulate with the body of the incus by way of a synovial joint. Below the neck of the malleus, the bone broadens and gives rise to the lateral process, the anterior process and the handle. The lateral process is a prominent landmark on the tympanic membrane and receives the anterior and posterior malleolar folds from the tympanic annulus. The chorda tympani crosses the upper part of the malleus handle on its medial surface above the insertion of

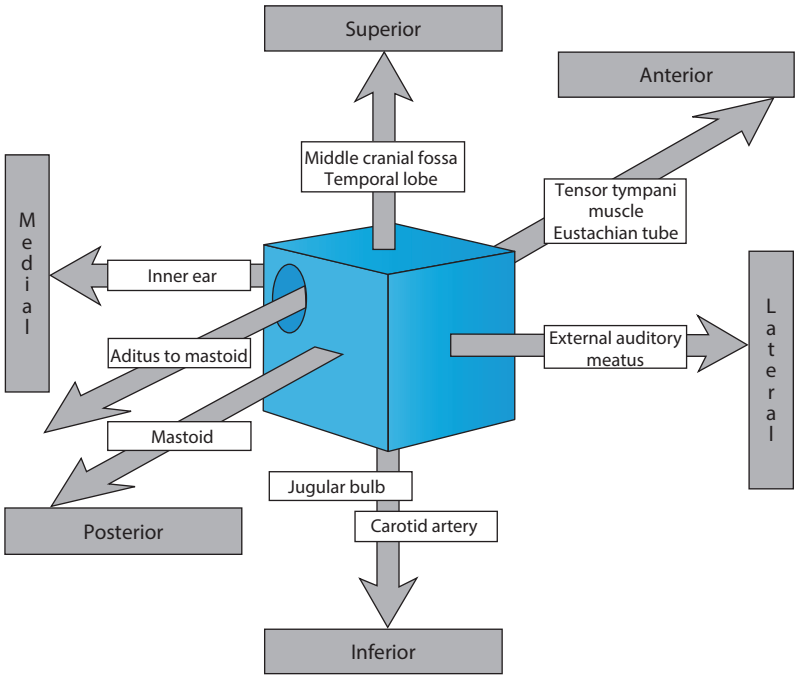


Figure 46.13 The relationships of the right middle ear.

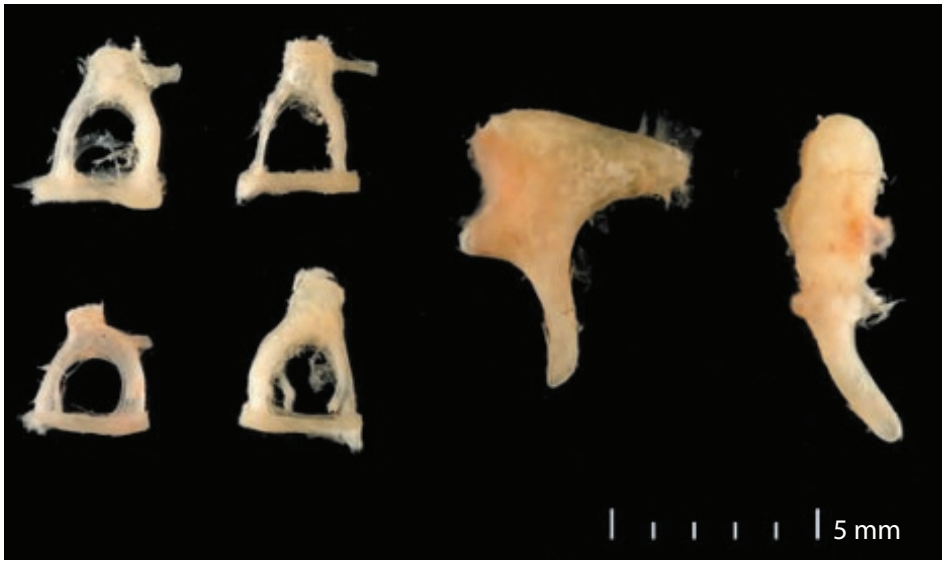


Figure 46.14 Stapes, incus and malleus with scale.

the tendon of tensor tympani, but below the neck of the malleus itself. The neck of the malleus connects the handle with the head and amputation of the head by cutting through the neck leaves both chorda tympani and tensor tympani intact. A slender anterior ligament arises from the anterior process to insert into the petrotympanic fissure. The handle runs downwards, medially and slightly backwards between the mucosal and fibrous layers of the tympanic membrane. While it is very closely attached to the membrane at its lower end, there is a fine web of mucosa separating the membrane from the handle in the upper portion before it becomes adherent again at the lateral process. This can be opened surgically to create a slit without perforating the membrane to allow a prosthesis to be crimped around the malleus handle in certain types of ossicular reconstruction. On the deep, medial surface of the handle, near its upper end, is a small projection into which the tendon of the tensor tympani muscle inserts.

THE INCUS

The incus articulates with the malleus and has a body and two processes. The body lies in the epitympanum and has a cartilage-covered facet corresponding to that on the malleus. The body of the incus is suspended by the superior incudal ligament that is attached to the tegmen tympani. The short process projects backwards from the body to lie in the fossa incudis to which it is attached by a short suspensory ligament. The long process descends into the mesotympanum behind and medial to the handle of the malleus, and at its tip is a small medially directed lenticular process. This has sometimes been called the fourth

ossicle because of its incomplete fusion with the tip of the long process, thereby giving the appearance of a separate bone or at least a sesamoid bone. The lenticular process articulates with the head of the stapes.

THE STAPES

The stapes is shaped like a stirrup and consists of a head, neck, the anterior and posterior crura and a footplate. The head points laterally and has a small cartilage-covered depression for a synovial articulation with the lenticular process of the incus. The stapedius tendon inserts into the posterior part of the neck and upper portion of the posterior crus. The two crura arise from the broader lower part of the neck and the anterior crus is thinner and less curved than the posterior one. Both are hollowed out on their concave surfaces, which gives an optimum combination of strength and lightness. The two crura join the footplate, which usually has a convex superior margin, an almost straight inferior margin and curved anterior and posterior ends. The average dimensions of the footplate are 3 mm long and 1.4 mm wide, and it lies in the oval window where it is attached to the bony margins by the annular ligament. The long axis of the footplate is almost horizontal, with the posterior end being slightly lower than the anterior. There is great variation in the shape of the two crura.

THE STAPEDIUS MUSCLE

The stapedius arises from the walls of the conical cavity within the pyramid and from the downward curved continuation of this canal in front of the descending portion of the facial nerve. A slender tendon emerges from the apex of the pyramid and inserts into the stapes. The muscle is supplied by a small branch of the facial nerve.

THE TENSOR TYMPANI MUSCLE

This is a long, slender muscle arising from the walls of the bony canal lying above the Eustachian tube. Parts of the muscle also arise from the cartilaginous portion of the Eustachian tube and the greater wing of the sphenoid. From its origins, the muscle passes backwards into the tympanic cavity where it lies on the medial wall, a little below the level of the facial nerve. The bony covering of the canal is often deficient in its tympanic segment where the muscle is replaced by a slender tendon. This enters the processus cochleariformis (see **Figure 46.9**) where it is held down by a transverse tendon as it turns through a right angle to pass laterally and insert into the medial aspect of the upper end of the malleus handle. The muscle is supplied from the mandibular nerve by way of a branch from the medial pterygoid nerve.

THE CHORDA TYMPANI NERVE

This branch of the facial nerve enters the tympanic cavity from the posterior canaliculus at the junction of the lateral and posterior walls. It runs across the medial surface of the tympanic membrane between the mucosal and fibrous layers and passes medial to the upper portion of the handle of the malleus (see **Figure 46.5**) above the tendon of tensor tympani to continue forwards and leave by way of the anterior canaliculus, which subsequently joins the petrotympanic fissure.

THE TYMPANIC PLEXUS

The tympanic plexus is formed by the tympanic branch of the glossopharyngeal nerve (Jacobson's nerve) and by caroticotympanic nerves, which arise from the sympathetic plexus around the internal carotid artery. The nerves form a plexus on the promontory and provide the branches to the mucous membrane lining the tympanic cavity, Eustachian tube and mastoid antrum and air cells. The plexus also provides branches to join the greater superficial petrosal nerve and the lesser superficial petrosal nerve that contains all the parasympathetic fibres of the glossopharyngeal nerve.

THE MUCOSA OF THE TYMPANIC CAVITY

The middle ear mucosa is essentially mucus-secreting respiratory mucosa bearing cilia on its surface.[20] The extent of the mucociliary epithelium varies in normal middle ears, being more widespread in the young. Three distinct mucociliary pathways can be identified – epitympanic, promontorial and hypotympanic, the latter being the largest. Each of these pathways coalesces at the tympanic orifice of the Eustachian tube.[21] The mucous membrane lines the bony walls of the tympanic cavity, and it extends to cover the ossicles and their supporting ligaments in much the same way as the peritoneum covers the viscera in the abdomen. The mucosal folds also cover the tendons of the two middle ear muscles and carry the blood supply to and from the contents of the tympanic cavity. These folds separate the middle ear space into compartments. As a result, the only route for ventilation of the epitympanic space from the mesotympanum is via two small openings between the various mucosal folds – the anterior and posterior isthmus tympani. Likewise, the Prussak space is found between the pars flaccida and the neck of the malleus, bounded by the lateral malleolar fold. This space can play an important role in the retention of keratin and subsequent development of cholesteatoma. The mucosal folds have been described in detail by Proctor[22] and are depicted in **Figure 46.15**.

THE BLOOD SUPPLY OF THE TYMPANIC CAVITY

Arteries supplying the walls and contents of the tympanic cavity arise from both the internal and external carotid system. The overlap between branches is extensive and there is great variability in the supply between individuals. **Table 46.2** outlines the general distribution of the arterial supply although the anterior tympanic and stylomastoid arteries are the biggest.

The Eustachian tube

The Eustachian tube is a dynamic channel that links the middle ear with the nasopharynx. In adults, it is about

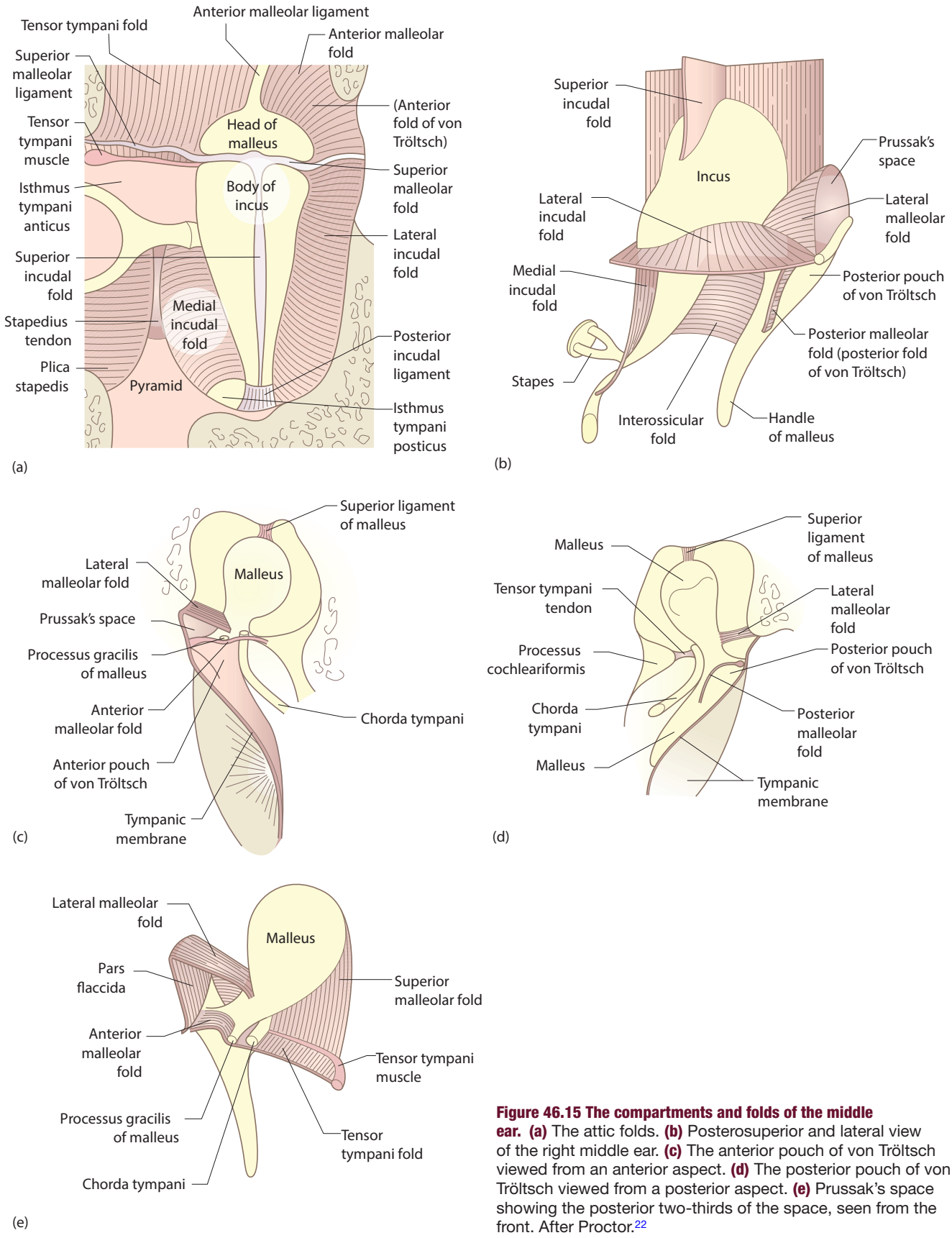


Figure 46.15 The compartments and folds of the middle ear. **(a)** The attic folds. **(b)** Posterosuperior and lateral view of the right middle ear. **(c)** The anterior pouch of von Tröltsch viewed from an anterior aspect. **(d)** The posterior pouch of von Tröltsch viewed from a posterior aspect. **(e)** Prussak's space showing the posterior two-thirds of the space, seen from the front. After Proctor.[22]

TABLE 46.2 Blood supply to the middle ear

Branch	Parent artery	Region supplied
Anterior tympanic	Maxillary artery	Tympanic membrane Malleus and incus Anterior part of tympanic cavity
Stylomastoid	Posterior auricular	Posterior part of tympanic cavity Stapedius muscle
Mastoid	Stylomastoid	Mastoid air cells
Petrosal	Middle meningeal	Roof of mastoid Roof of epitympanum
Superior tympanic	Middle meningeal	Malleus and incus Tensor tympani
Inferior tympanic	Ascending pharyngeal	Mesotympanum
Branch from artery	Artery of pterygoid canal	Meso- and hypotympanum
Tympanic arches	Internal carotid	Meso- and hypotympanum

36 mm in length, a size that is normally reached by the age of 7 years. It runs downwards from the middle ear at 45° and is turned forwards and medially. The tube can be considered to consist of two unequal cones, connected at their apices. The lateral third is bony and arises from the anterior wall of the tympanic cavity. This joins a medial cartilaginous part, which makes up two-thirds of the tubal length, just after its narrowest portion, called the isthmus (Figure 46.16). The tube is lined with respiratory mucosa containing goblet cells and mucous glands, having a carpet of ciliated epithelium on its floor. At its nasopharyngeal end, the mucosa is truly respiratory; however, in passing along the tube towards the middle ear, the number of goblet cells and glands decreases, and the ciliary carpet becomes less profuse.

The bony portion is about 12 mm long and is widest at its oval-shaped orifice in the anterior wall of the tympanic cavity. It runs through the squamous and petrous portions of the temporal bone, gradually tapering to the isthmus, where the diameter is only 0.5 mm or less. A thin plate of bone forms the roof, separating the tube from the tensor tympani muscle above. The carotid canal lies medially and can impinge on the bony Eustachian tube. In cross section, the tube is triangular or rectangular with the horizontal diameter being the greater (Figure 46.17).

The cartilaginous part of the tube is about 24 mm long and consists of a fibrocartilaginous skeleton to which are attached the peritubal muscles. At its upper border, the cartilage is bent over to resemble an inverted 'J', thereby forming a longer medial cartilaginous lamina and shorter lateral cartilaginous lamina. The cartilage is fixed to the base of the skull in a groove between the petrous part of the temporal bone and the greater wing of the sphenoid, which terminates near the root of the medial pterygoid plate. Thus, the back (posteromedial) wall is composed of cartilage and the front (anterolateral) wall comprises cartilage and fibrous tissue. The apex of the cartilage is attached to the isthmus of the bony portion, while the wider medial end protrudes into the nasopharynx, lying directly under the mucosa to form the torus tubarius. In the nasopharynx, the tube opens 1–1.25 cm behind

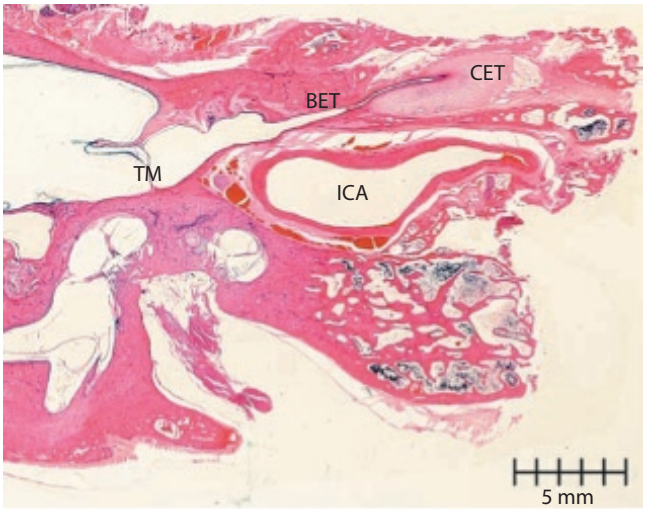


Figure 46.16 Photomicrograph of the left Eustachian tube in axial section, showing its bony (BET) and cartilaginous (CET) portions. The tympanic membrane (TM) is retracted towards the Eustachian orifice and note the adjacent position of the internal carotid artery (ICA).

and a little below the posterior end of the interior turbinate. The opening is almost triangular in shape and is surrounded above and behind by the torus. The salpingopharyngeal fold stretches from the lower part of the torus downwards to the wall of the pharynx. The levator palati, as it enters the soft palate, results in a small swelling immediately below the opening of the tube. Behind the torus is the pharyngeal recess or fossa of Rosenmüller. Lymphoid tissue is present around the tubal orifice and in the fossa of Rosenmüller and may be prominent in childhood.

MUSCLES ATTACHED TO THE EUSTACHIAN TUBE

The tensor palati muscle arises from the bony wall of the scaphoid and from along the whole length of the lateral cartilaginous lamina that forms the upper portion of the front wall of the cartilaginous tube. From these broad

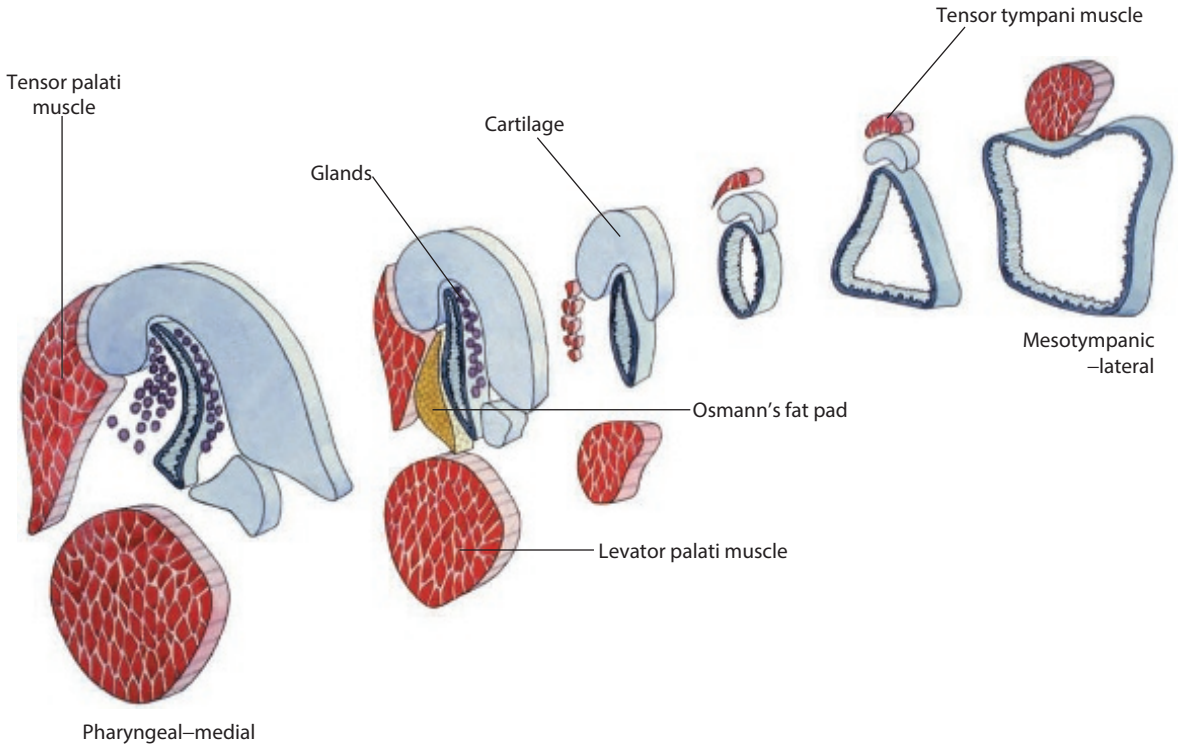


Figure 46.17 Schematic view of the right Eustachian tube. Redrawn from Sade and Ar.[23]

origins the muscle descends, converges to a short tendon that turns medially around the pterygoid hamulus and then spreads out within the soft palate to meet fibres from the other side in a midline raphe. The tensor palati separates the tube from the otic ganglion, the mandibular nerve and its branches, the chorda tympani nerve and the middle meningeal artery. It is supplied by the mandibular nerve.

The salpingopharyngeus is a slender muscle attached to the inferior part of the cartilage of the tube near its pharyngeal opening, and it descends to blend with the palatopharyngeus.

The levator palati contains a few fibres that arise from the lower surface of the cartilaginous tube and originates from the lower surface of the petrous bone, just in front of the opening for the entrance of the carotid, and from fascia forming the upper part of the carotid sheath. It first lies inferior to the tube, then crosses to the medial side and spreads out into the soft palate. Both the salpingopharyngeus and the levator palati are supplied from the pharyngeal plexus.

The ascending pharyngeal and middle meningeal arteries supply the Eustachian tube. The veins drain into the pharyngeal plexus and the lymphatics pass to the retropharyngeal nodes. The nerve supply arises from the pharyngeal branch of the sphenopalatine ganglion (Vb) for the ostium, the nervus spinosus (Vc) for the cartilaginous portion and the tympanic plexus (IX) for the bony part.

The mastoid air cell system

The mastoid antrum is an air-filled sinus within the petrous part of the temporal bone. It communicates with the middle ear by way of the aditus and has mastoid air cells arising from its walls. The antrum, but not the air cells, is well developed at birth and by adult life has a volume of about 2 mL. The roof of the mastoid antrum and mastoid air cell space form the floor of the middle cranial fossa, while the medial wall relates to the posterior semicircular canal. More deeply and inferiorly is the dura of the posterior cranial fossa and the endolymphatic sac. The latter emerges through the operculum on the posterior surface of the petrous bone and derives from the endolymphatic duct, which has passed through the vestibular aqueduct. Posterior to the endolymphatic system is the sigmoid sinus, which curves downwards only to turn sharply upwards to pass medial to the facial nerve and then becomes the dome of the jugular bulb in the middle ear space. The posterior belly of the digastric muscle forms a groove in the base of the mastoid bone. The corresponding ridge inside the mastoid lies lateral not only to the sigmoid sinus but also to the facial nerve and is a useful landmark for finding the nerve itself. The periosteum of the digastric groove on the undersurface of the mastoid bone continues anteriorly and part of it becomes the endosteum of the stylomastoid foramen and subsequently of the facial nerve canal.

The outer wall of the mastoid lies just below the skin and is easily palpable behind the pinna. Macewen's triangle is a direct lateral relation to the mastoid antrum and is formed by a posterior prolongation of the line of the zygomatic arch and a tangent to this that passes through the posterior border of the external auditory meatus. The relationships of the mastoid antrum are shown in Figure 46.18.

In most of the population, the mastoid air cell system is fairly extensive with air cells extending into the mastoid tip,

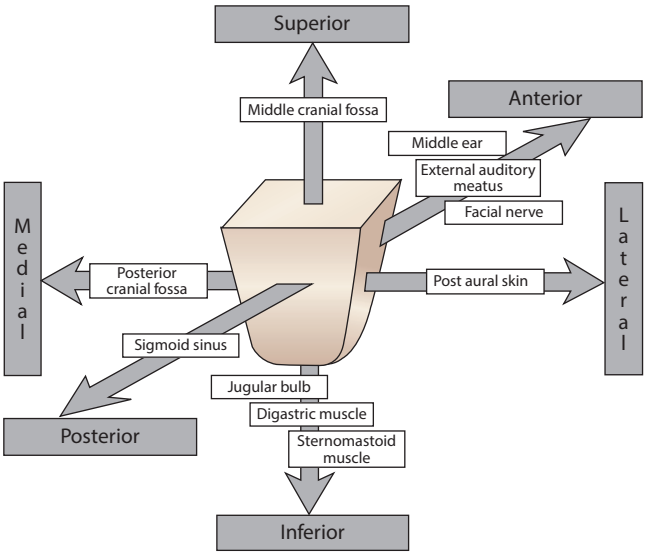


Figure 46.18 Relationships of the right mastoid antrum.

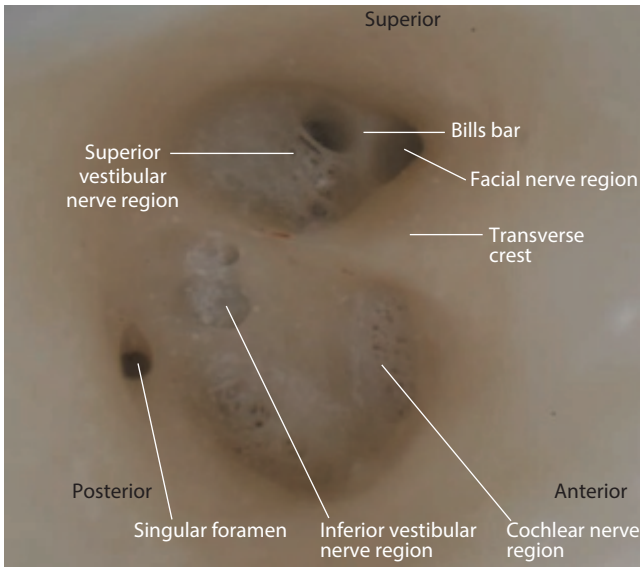


Figure 46.19 Endoscopic view of the apex of the left internal auditory meatus.

the retrofacial region, the sinodural angle and anteriorly into the petrous apex and arch of the zygoma. Alternatively, the mastoid antrum may be the only air-filled space in the mastoid process when the name acellular or sclerotic is applied. This condition occurs in perhaps 20% of adult temporal bones and is seen in individuals with chronic ear disease. In normal ears, the lining of the mastoid is a flattened, non-ciliated epithelium without goblet cells or mucus glands.

The petrous apex lies at the most medial aspect of the temporal bone and is shaped like a foreshortened pyramid, pointing anteriorly and medially. The posteromedial surface of the petrous apex is part of the posterior cranial fossa, while the superior aspect of the bone forms the floor of the middle cranial fossa. The internal carotid artery and the internal auditory meatus run through the bony petrous apex. At the apex of the petrous bone is the trigeminal nerve running into Meckel's cave with the abducent nerve passing close to its roof. Gradenigo's syndrome is the result of infection at the petrous apex and comprises a lateral rectus palsy, facial pain and discharging ear. Historically, the petrous apex has been the most difficult to access surgically but this has been advanced by the development of endoscopically assisted trans-sphenoidal techniques.

The internal auditory meatus

This is a short canal, nearly 1 cm in length and lined with dura, which passes into the petrous bone in a lateral direction from the cerebellopontine angle. It transmits the facial, cochlear and vestibular nerves and the internal auditory artery and vein. The meatus is closed at its outer lateral end, or fundus, by a plate of bone that is perforated for the passage of nerves and blood vessels to and from the cranial cavity.

The bony plate separating the fundus from the middle and internal ears has a transverse crest – the crista falciformis – on its inner medial surface, which separates a small upper region from a larger lower area (**Figure 46.19**). Above the crest and anteriorly is the opening of the facial canal carrying the facial nerve (VII). This is separated, by a small vertical ridge known as Bill's bar, from the posterior region that transmits the superior vestibular nerve through several small foramina to the superior and lateral semicircular canals, to the utricle and a part of the saccule. Below the transverse crest, the cochlear nerve lies anteriorly and leaves the meatus through the cochlear area, which comprises a spiral of small foramina and a central canal. The inferior vestibular nerve passes through one or two foramina behind the cochlear opening to supply the saccule. Just behind and below the inferior vestibular foramen is the foramen singulare, which contains the singular nerve. This runs obliquely through the petrous bone close to the round window to supply the sensory epithelium in the ampulla of the posterior semicircular canal.

DEVELOPMENT OF THE HUMAN EAR

The outer and middle ears

The 9 months from implantation of the fertilized and dividing egg – the blastocyst – to birth is divided into three periods, namely, pre-embryonic, embryonic and foetal. The pre-embryonic stage lasts 21 days, the embryonic stage 35 days and the foetal stage is the longest phase at 210 days.

During the embryonic phase there is rapid growth and differentiation of the ecto-, meso- and endoderm, so that by the end of this period all the major organ systems have been formed and the late embryo has an external shape that is obviously human. In the foetal period there are changes in the shape, size and orientation of the various structures, as well as rapid overall growth, but no new tissues develop.

During growth from the fertilized egg into the fully formed foetus, animals pass through phases that represent, to a certain degree at least, their evolutionary precursors.

The phrase 'ontogeny recapitulates phylogeny' has been used to express this reflection of earlier forms. In mammals, a phase is reached during early embryonic life when the mesenchyme surrounding the primitive foregut and pharynx differentiates into a maxillary and mandibular swelling on each side of the midline just above and below the buccopharyngeal membrane. This membrane then breaks down and a space, which will later become both nasal and buccal cavities, is formed. Further down the embryo and in the mesenchyme surrounding the pharynx, five or six parallel thickenings develop as bands that surround the pharynx. These are the branchial arches, which are numbered 1 to 5 from head to tail. They are formed anterior to the 40–43 paired somites that subsequently give rise to the trunk and limbs. On the external surface a groove develops between each branchial arch and this is matched by a cleft or pouch on the inner pharyngeal surface. In each branchial arch a bar of cartilage, a group of muscles, an associated artery and a cranial nerve, supplying these structures and their derivatives, all develop. The cranial nerve is called the post-trematic nerve. In addition, a nerve from the arch lower down supplies the inner endodermal surface of the arch above and is called the pretrematic nerve.

The first arch has the trigeminal nerve (V), the second arch the facial (VII) and the third arch the glossopharyngeal (IX). These are the post-trematic nerves. The pretrematic nerves are the chorda tympani (from VII) running to the first arch (V) and Jacobson's nerve (the tympanic branch of IX) running to the second arch (VII).

DERIVATIVES OF THE FIRST AND SECOND BRANCHIAL ARCHES

The innervation of the lower arches and indeed their derivation are much less clear (**Table 46.3**). In fish, the layers between the arches break down to form the gill clefts, but in mammals this does not occur although grooves on the external surface of the embryo do develop and for a very short time come into contact with the endoderm lining the pharynx. However, mesoderm rapidly intervenes and develops into the normal adult structures. Occasionally there is failure of this system when the various branchial arch defects can occur as sinuses (blind-ended tracts opening onto an epithelial surface) as a cleft or groove fails to regress, or less commonly as fistulae (a tract running from one epithelial surface to another) when the ecto-endodermal junction breaks down.

The first pharyngeal pouch on the inside expands due to the rapid growth of the surrounding mesenchyme and, after dragging in some of the second pouch endoderm, results in the formation of the Eustachian tube, middle ear and mastoid antrum. In creating these large spaces the neural structures are forced to take a convoluted path to stay within mesenchyme and yet remain bound to their original arch structures and the derivatives. The facial nerve is a good example as it turns posteriorly from the geniculate ganglion, then inferiorly and then anteriorly in order to leave the skull.

The endoderm of the slit-like sac that is the precursor of the middle ear lies against the ectoderm of the first pharyngeal groove by the fourth week. Mesenchyme grows in between these two layers to form the middle layer of the future tympanic membrane. The underlying sac expands and as it reaches the developing ossicles and labyrinth, the epithelium is draped over these structures and their associated muscles, tendons and ligaments, so that a complex series of mucosal folds is formed.

The future Eustachian tube lumen and middle ear spaces are formed by 8 months' gestation and the epitympanum and mastoid antrum are developed by birth. A few mastoid 'air cells' may be present at birth, albeit filled with amniotic fluid. However, development of the mastoid air cell system does not occur until after birth, with about 90% of air cell formation being completed by the age of 6 with the remaining 10% taking place up to the age of 18.

The ossicles develop from the outer ends of the first arch (Meckel's) and second arch (Reichert's) cartilages that lie above and below the first pharyngeal pouch. The process begins at 4 weeks and adult shape, size and ossification are present by 25 weeks. The muscles attached to the ossicles

TABLE 46.3 Derivatives of the first and second branchial arches

Cartilage	Post-trematic nerve	Pretrematic nerve	Artery
First arch derivatives			
Meckel's Malleus Incus 'Mandible' Anterior malleolar ligament Sphenomandibular ligament	Mandibular V	Chorda tympani VII	
Second arch derivatives			
Reichert's Stapes superstructure Styloid process Lesser cornu of hyoid Stylohyoid ligament	Facial VII	Tympanic branch IX	Stapedial

arise from the arches that give rise to that part of the ossicle to which the muscle attaches.

Thus the tensor tympani is attached to the upper part of the handle of the malleus, which is derived from the first arch and is, therefore, supplied by a branch of the Vth (mandibular) nerve. In a similar way the stapedius muscle is supplied by the VIIth (facial) nerve. The chorda tympani, which is the pretrematic nerve of the second arch that supplies endodermal structures of the first arch (i.e. taste to the anterior two-thirds of the tongue and submandibular gland secretomotor fibres) has to run through mesoderm since it cannot run through air. This mesoderm subsequently becomes the middle layer of the tympanic membrane and is the physical connection between the first and second arches.

The external ear canal develops from the first pharyngeal groove in a complex fashion. A complete description is beyond the scope of this chapter and may be sought from Michaels and Soucek.[24] It is sufficient to say that the meatus deepens by proliferation of its ectoderm and that an anteriorly placed bud of epithelial cells expands vertically to form the skin, which will cover the future tympanic membrane. This clump of cells then opens up as a slit to form the canal lumen and produce the pars tensa and deep external canal epithelium. These two types of skin both have migratory properties so that the ear canal becomes self-cleansing.

The external auricle or pinna develops from a series of small cartilaginous tubercles that surround the first pharyngeal groove. These enlarge and coalesce, although it seems that the majority of the auricle is derived from the second arch cartilages and that the tragus is the only contribution from the first arch. The rudimentary pinna has formed by 60 days although it apparently continues to grow throughout life.

Failure of formation of the first and second branchial arch structures gives rise to problems which range from failure of adequate skin migration with 'ear canal cholesteatoma' (which are very rare) through bat ears, accessory auricles and preauricular sinuses, to complete failure of formation of the external ear canal and middle ear. There are also the rare first arch fistulae (collaural fistulae), which comprise a tract between the external ear canal and the skin of the cheek, with the fistula path passing through the parotid gland and frequently between branches of the facial nerve.

The internal ear (labyrinth)

The internal ear initially develops independently of the middle and external ears, although the two become interconnected by the stapes superstructure, becoming attached to the stapes footplate, thereby giving continuity to the auditory pathway.

The development of the labyrinth can be thought of as the initial development of the generalized structure of the membranous labyrinth, followed by a period of encasement by the bony labyrinth and the production of a further series of spaces within this bony shell that in turn become the perilymphatic spaces of the complete structure. These different activities are happening at different times in different parts of the labyrinth so that damage or derangements at specific times give rise to many peculiar and varied abnormalities.

Within the first few days of embryonic life (i.e. at about day 22 or 23) ectodermal thickening forms on the side of the head end of the embryo close to that part of the developing neural tube and neural crest cells, which will later become the brain and brainstem and the cranial nerves, respectively. The ectodermal thickening is the otic placode, which deepens and then sinks below the surface as the sides close in to form an otic pit which eventually loses connection with the surface and forms the otocyst (Figure 46.20).

Associated with the otocyst is the cluster of neural crest cells that later become the separate facial (geniculate), auditory (spiral) and vestibular (Scarpa's) ganglion cell bodies. The otocyst then undergoes a series of spectacular changes, which result in the full-sized outline of the adult membranous labyrinth by 25 weeks' gestation.

The semicircular canals start to develop at around 35 days as three flattened pouches that grow out at right angles from each other from the utricle. At the centre of each semicircular ridge, the opposing epithelial surfaces meet, fuse and then coalesce to be replaced by mesoderm. The superior canal is the first to be fully formed by 6 weeks.

As these developments are taking place, the cochlea starts to be formed. The saccule, which has separated from the utricle, starts to put out a single pouch-like process that grows and then begins to coil from base to apex to reach its full 2.5 coils by 25 weeks.

Within the membranous labyrinth the sensory cells of the three cristae, two maculae and the organ of Corti are beginning to develop from areas of ectodermal specialization. This is encouraged either by the ingrowth of nerve endings from the cochleovestibular ganglion, which was originally outside the otocyst, or by the development of the sensory cells encourages neural ingrowth (Figure 46.21).

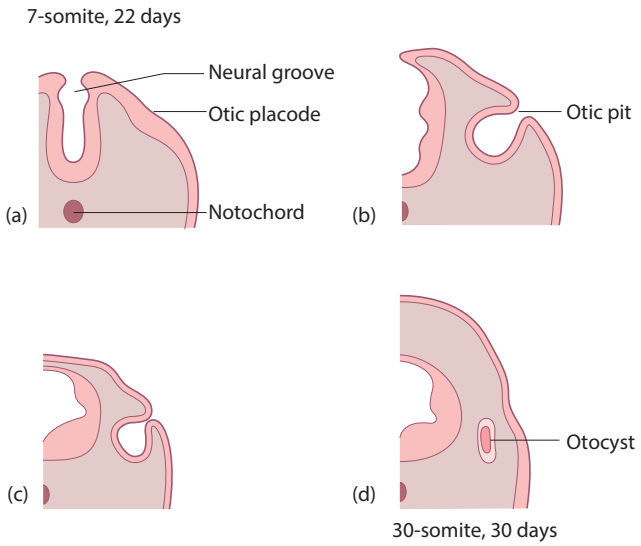


Figure 46.20 Development of an otocyst.

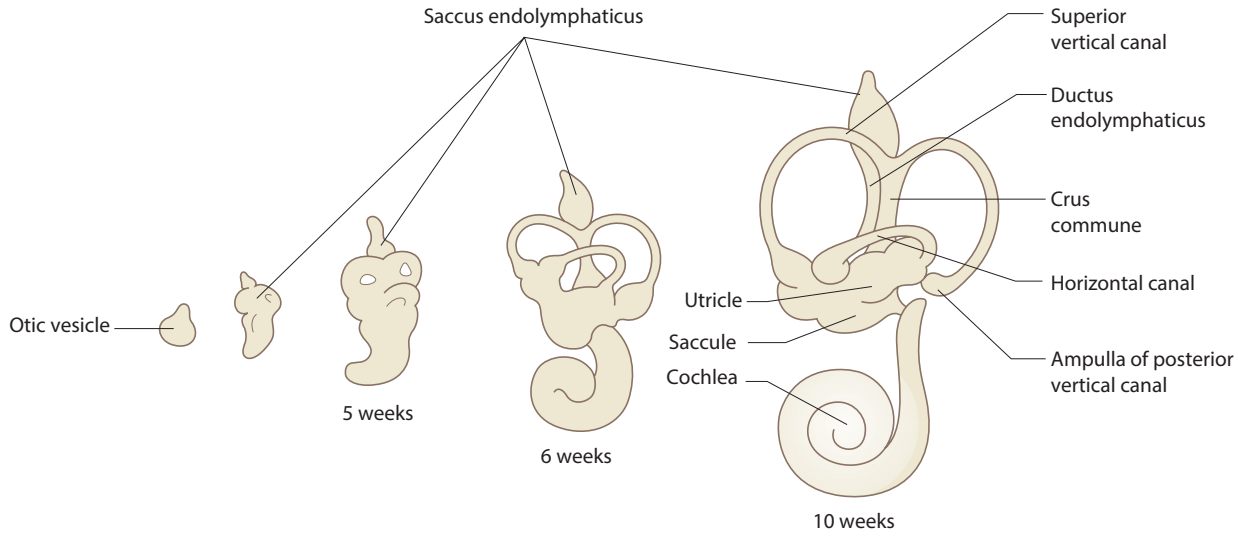


Figure 46.21 Development of the membranous labyrinth.

TABLE 46.4 Development of communication channels passing through labyrinth

	Channel
Internal auditory meatus	Persisting channel in cartilage model around VII and VIII nerves
Subarcuate fossa	Persisting vascular channel
Vestibular aqueduct	Fifth and sixth ossification centres fuse around the endolymphatic duct
Cochlear aqueduct	Resorption of precartilage
Fossula ante fenestram	Resorption of precartilage
Fossula post fenestram (inconstant)	Resorption of cartilage
Oval window	Otic capsule becomes footplate of stapes and annular ligament
Round window	Persisting cartilage becomes round window niche and membrane

The organ of Corti starts developing as a single block of heaped up ectodermal cells at about 11 weeks. Within this mass develop inner and outer hair cells and then specialized supporting cells. The tunnel of Corti appears between inner and outer pillar cells as clusters of stereocilia and a single kinocilium are developing on each hair cell. The cochlear kinocilium regresses, leaving the adult configuration of stereocilia, and the spaces between the outer hair cells open up as the supporting cells (the Deiters cells) change shape. Differentiation progresses from base to apex so that at any one time various stages of development can be seen in appropriately prepared material.

Epithelium close to the sensory regions develops into the specialized cell groups that maintain the ionic and electrical stability of the endolymph. These regions are the stria vascularis of the cochlear duct and the 'dark cell' regions of the vestibular sensory epithelium.

The bony labyrinth

The mesenchyme enclosing the otocyst becomes chondrified to form the otic capsule. As the membranous labyrinth expands, the otic capsule remodels and in places undergoes dedifferentiation to form fluid-filled spaces that eventually become the perilymphatic spaces. This dedifferentiation does not occur where nerves enter the sensory cell regions. Elsewhere, the perilymphatic spaces become continuous and a communication with the cerebrospinal fluid is formed by the development of the cochlear aqueduct, which runs to the posterior cranial fossa from the scala tympani in the base of the cochlea.

Ossification of the cartilaginous otic capsule begins in or around week 16 from a variable number of centres that finally fuse without leaving telltale suture lines. This dense bony mass is the petrous bone. Interestingly, this is frequently the last part of a whale to decompose and is sometimes the only remains of those eaten by sharks.

There are certain channels that remain within the otic capsule with one of the most important being the oval window where part of the otic capsule becomes the stapes footplate and the annular ligament, thereby allowing sound from the middle ear to enter the labyrinthine fluids (Table 46.4).

The temporal bone

Four separate elements eventually fuse to form the temporal bone, which is one of the most complex and interesting parts of the bony anatomy of the body. These four parts are the petromastoid complex, the squamous portion, the tympanic bone and the styloid process.

The petromastoid is derived from petrous bone described above and the continuing growth of its outer layers which form the roof of the middle ear, the lateral wall of the Eustachian tube, the floor of the middle ear, the canal of the facial nerve and the petrous apex.

The squamous bone develops in mesenchyme and starts to ossify from a single centre close to the roof of the zygoma as early as 8 weeks. The posteroinferior portion grows down behind the tympanic ring to form the lateral wall of the foetal mastoid antrum.

The tympanic bone also forms in mesenchyme, but from several centres around the external meatus. These form the major part of a ring with a groove on the inner aspect that becomes the sulcus for the tympanic membrane. Even by late foetal life the bony ear canal is unformed and only after birth do anterior and posterior protuberances grow to form the floor of the canal. These crescentic swellings eventually fuse laterally leaving a gap in the middle of the floor. This is the foramen of Huschke, which is usually closed by adolescence. The tympanic bone fuses with the mastoid process of the petromastoid and with parts of the squamous and petrous bones as the tympanomastoid, tympanosquamous and petrotympanic sutures. The petrotympanic suture has a canal for the chorda tympani nerve.

The styloid develops from two centres at the cranial end of the second arch (Reichert's) cartilage. The part close to the base of the skull starts to ossify before birth, but the styloid process itself does not start to ossify until after, and fusion of the two parts may not occur until after puberty.

Much of the growth of temporal bone occurs after birth with enlargement of the whole structure and major growth of the mastoid process so that the stylomastoid foramen, which was initially close to the surface, becomes buried by the development of the mastoid tip. At the same time there is generalized downwards rotation of the petrous bone so that the tympanic membrane moves from being almost horizontal in the neonate to an angle of about 55° with the horizontal in the adult. With these changes, the floor of the middle cranial fossa flattens and the relations of the geniculate ganglion, the semicircular canals and the internal auditory meatus change so that middle cranial fossa surgery in the baby is anatomically a different experience from that in the adolescent.

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CHAPTER 47

ANATOMY OF THE COCHLEA AND VESTIBULAR SYSTEM: RELATING ULTRASTRUCTURE TO FUNCTION

Jonathan Gale and Andrew Forge

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: structure, anatomy, cell biology; inner ear, endolymph, perilymph; cochlea, vestibular hair cell, supporting cell, organ of Corti, inner hair cell, outer hair cell, spiral ganglion, stria vascularis, spiral ligament, basilar membrane, tectorial membrane, Reissner's membrane , utricle/utricular, saccule/saccular, crista, macula/maculae, type1 hair cell, type 2 hair cell and dark cells.

INTRODUCTION

The inner ear (Figure 47.1a,b) collects, packages and delivers sensory information relating to hearing via the cochlea, and balance via the vestibular system. It is responsible for mechanoelectrical transduction, the conversion (transduction) of movements – initiated by sound waves in the cochlea or by changes in the position of the head in space in the vestibular system – into electrical signals that can then be passed to the brain along the auditory or vestibular nerves. It is formed of a series of bony channels that enclose interconnected fluid-filled tubes (the membranous labyrinth), the inner walls of which are lined by epithelial tissues (Figures 47.1a,c and 47.2). In humans and higher primates, the bony channels are in the temporal bone (Figure 47.1c), the hardest bone in the body, which is fused with the skull. In other mammals, the inner ear is contained within a bony auditory bulla which is not fused with the skull but fills a recess in it and which can be isolated relatively easily.

The bony channels are filled with perilymph, which surrounds the membranous canals (Figure 47.1a). Perilymph is essentially a typical extracellular fluid, similar, but not identical, to cerebrospinal fluid (CSF) or serum; it has a high sodium ion (Na^+) and low potassium ion (K^+) concentration.[1] The perilymphatic compartment connects with the arachnoid space of the brain via the cochlear aqueduct so there is potential continuity between cochlear perilymph and CSF, although the exact compositions of the two fluids are different from each other and also from serum, indicating that perilymph is produced or at least significantly modified locally in the inner ear and is not derived directly from CSF (or serum).

The fluid inside the lumen of the membranous canals is **endolymph** (Figure 47.1a). This has an unusual composition for an extracellular fluid. It is high in K^+ (~140 mM) and low in Na^+ (~1 mM). In the cochlea, endolymph also has a high positive electrical potential of around +80 mV, the endocochlear potential (EP), but although the compartments are interconnected a similar electrical potential is not observed in the vestibular system. The boundary between perilymph and endolymph lies at the level of the junctions between the epithelial cells that surround the endolymphatic spaces. These junctions form a permeability barrier, the maintenance of which is essential for the function of the inner ear.

Three types of epithelium surround the endolymphatic compartment: sensory epithelia, ion-transporting epithelia, and relatively unspecialized non-sensory epithelia (Figure 47.2a,b). The vestibular system of mammals contains five sensory epithelial patches or sheets: the **maculae** of the **utricle** and **saccule**, and the three **cristae**, one

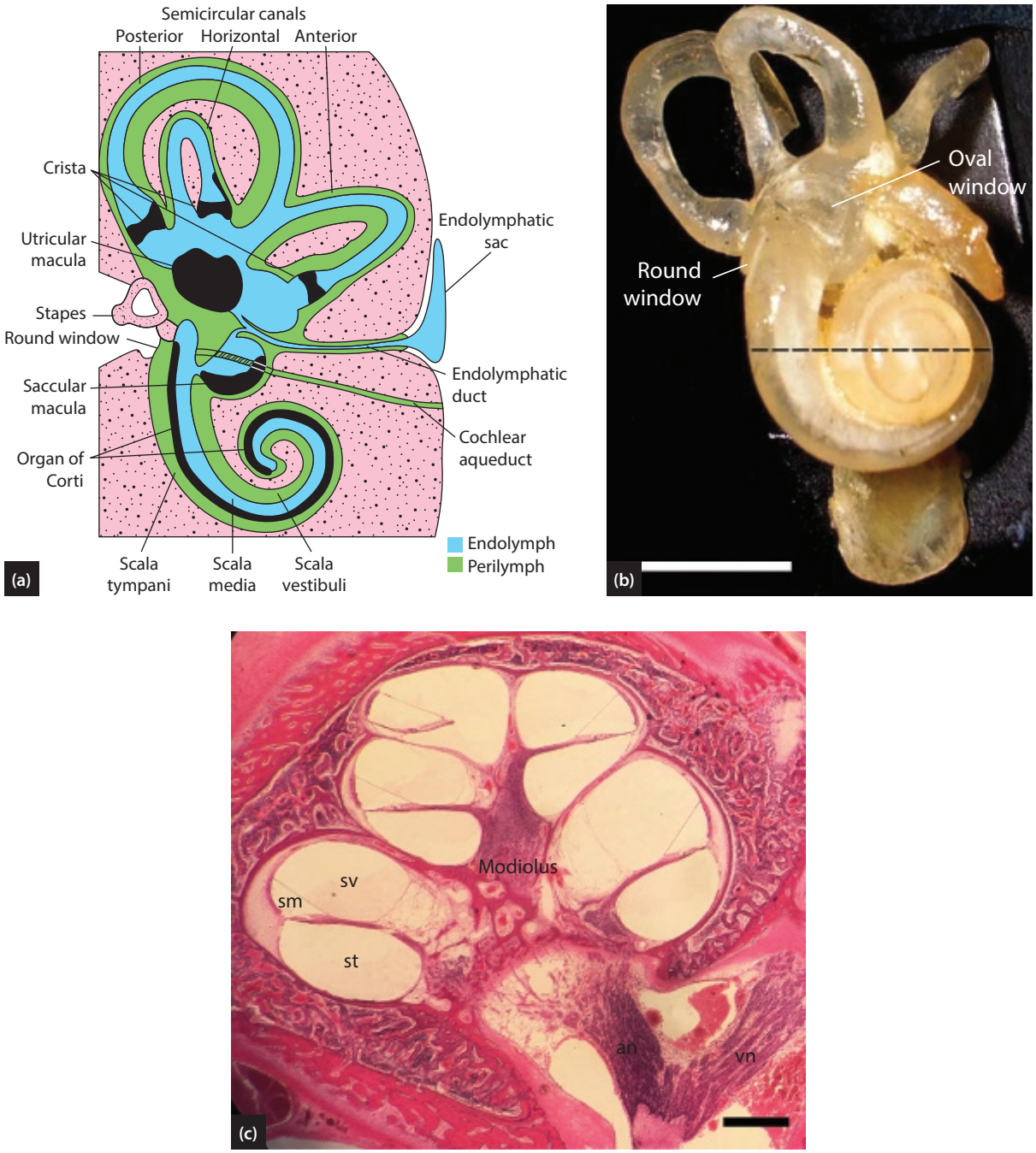

Figure 47.1 **(a)** Diagrammatic representation of the human inner ear showing the different compartments. **(b)** Human inner ear. Plastic injection moulding of the membranous labyrinth, with the temporal bone removed. Scale bar: 5 mm. Dashed line defines plane of section shown in panel (c). **(c)** Section through human temporal bone at approximately the mid-modiolar level of the cochlea. sm = scala media, st = scala media; sv = scala vestibuli; an = auditory nerve; vn = vestibular nerve. Scale bar: 1.5 mm.

in each of the **semicircular canals** (SCCs) (Figures 47.1a, 47.2a, 47.3). The sensory epithelium of the cochlea is the **organ of Corti**, named after the Italian anatomist Alfonso Corti. It comprises a relatively narrow strip of cells running along an acellular basement membrane and coiled in a spiral (Figures 47.2b and 47.4a,b,c). All of the sensory epithelia are composed of two main cell types: sensory hair cells and non-sensory supporting cells (Figures 47.3d and 47.4b,c). Each hair cell is surrounded and separated from its neighbours by supporting cells so that hair cells do not come into direct contact with each other. Viewed from above, each sensory epithelium appears as a more or less regular mosaic of cells at the apical (luminal [endolymphatic]) surface of the epithelium, sometimes referred to as the **reticular lamina**, with each hair cell surrounded by and thus in contact with several supporting cells, and each supporting cell contacting several other supporting cells (Figures 47.3e,f and 47.4d,e,f). The bodies of the supporting cells also intervene between the basal ends of the hair cells and the acellular basement membrane underlying the

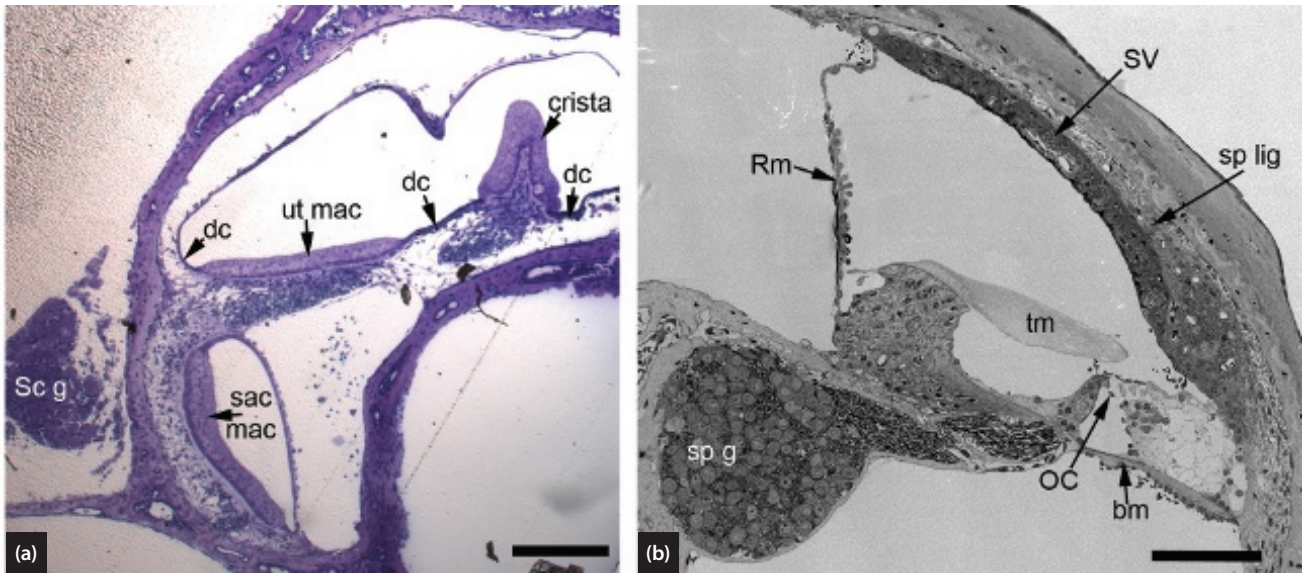

Figure 47.2 **(a)** Cross section through the vestibular labyrinth showing the relationship of the vestibular organs. ut mac = utricular macula; sac mac = saccular macula; crista = crista ampullaris; dc = dark cells; Sc g = Scarpa's ganglion. Scale bar: 100 µm. **(b)** Cross section of a single turn of the cochlea. OC = organ of Corti, tm = tectorial membrane; bm = basilar membrane; sp g = spiral ganglion; SV = stria vascularis; sp lig =spiral ligament; Rm = Reissner's membrane. Scale bar: 100 µm.

epithelium (which is known as the 'basilar' membrane in the organ of Corti) so that only the supporting cells and not hair cells are in contact with the basement membrane (Figures 47.3d and 47.4b,c). The sensory epithelia thus have the appearance of a pseudostratified epithelium. Each sensory epithelium is also covered by a specific acellular extracellular matrix structure: the **otoconial membrane** in macular organs (Figure 47.3g,h); a **cupula** overlying each the crista (Figure 47.3j); and the **tectorial membrane** in the cochlea (Figures 47.4b,g). The hair cells derive their name from the organized bundle of rigid projections at their apical surface (Figures 47.3f and 47.4d,e). Mechanical deflection of the hair bundle caused by either sound waves or changes in head position results in the opening and closing of cation-permeable **m**echanoelectrical **t**ransduction (**MET**) channels that modulate the flow of K^+ ions from endolymph into the hair cells, altering the hair cell's resting electrical potential and so its excitability. Thus, the hair cells are the mechanotransducers that convert auditory or vestibular-evoked mechanical stimuli into electrical signals.

The ion-transporting epithelia, the dark cell regions of the vestibular system and the stria vascularis of the cochlea (Figure 47.2a,b) are involved in active (energy-consuming) ion transport that is necessary to maintain the unusual endolymph composition and positive charge. The comparatively less specialized epithelia, including Reissner's membrane in the cochlea and those which constitute the 'roof' and linings of the saccule, utricle and ampullae of the semicircular canals (Figure 47.2a,b) and the membranous semicircular canals themselves, form important permeability barriers separating the perilymph from endolymph. If these membranes rupture or break down, the permeability barriers are disrupted, leading to fluid mixing and physiological dysfunction. It is thought such an event may occur to Reissner's membrane in Ménière's syndrome.

GENERAL CHARACTERISTICS OF HAIR CELLS

The hair bundle and cuticular plate

The hair bundle is composed of rows of **stereocilia** that increase in height in one particular direction across the apical surface of the hair cell, and a single kinocilium located behind the row of longest stereocilia (Figures 47.5a and 47.6a), but which is absent from the hair bundles of mature hair cells in the cochlea (Figure 47.5b). Stereocilia are really giant microvilli, plasma membrane-bound projections from the apical surface of the hair cell that enclose a packed array of filaments of the cytoskeletal protein, actin[2–4] (Figure 47.5d–f). The kinocilium is composed of microtubules similar in form to motile cilia but they are not motile.[5] In cochlear hair cells, the kinocilium is present only during development, reducing down as the cochlea matures to remain only as the basal body in the apical cytoplasm at one side of the stereociliary bundle (Figure 47.5c).[6] The position of the kinocilium (or the basal body) and the longest row of stereocilia define the polarity of the asymmetric hair bundle (Figures 47.3f, 47.4d,e and 47.5a,b). Deflection of the stereocilia towards the longest ones opens MET channels, K^+ enters and the hair cell becomes depolarized. Deflection in the opposite direction closes the transducer channels and the hair cell becomes hyperpolarized. The transducer channels are located at the tips of the stereocilia of the shorter rows but not in the longest stereocilia.[7]

The parallel actin filaments in the stereocilia (Figure 47.5e,f) are closely packed and are cross-linked by a number of different proteins such as espin, fimbrin, fascin and plastin 1, the last being the second most abundant protein in stereocilia after actin.[2, 8–13] The high

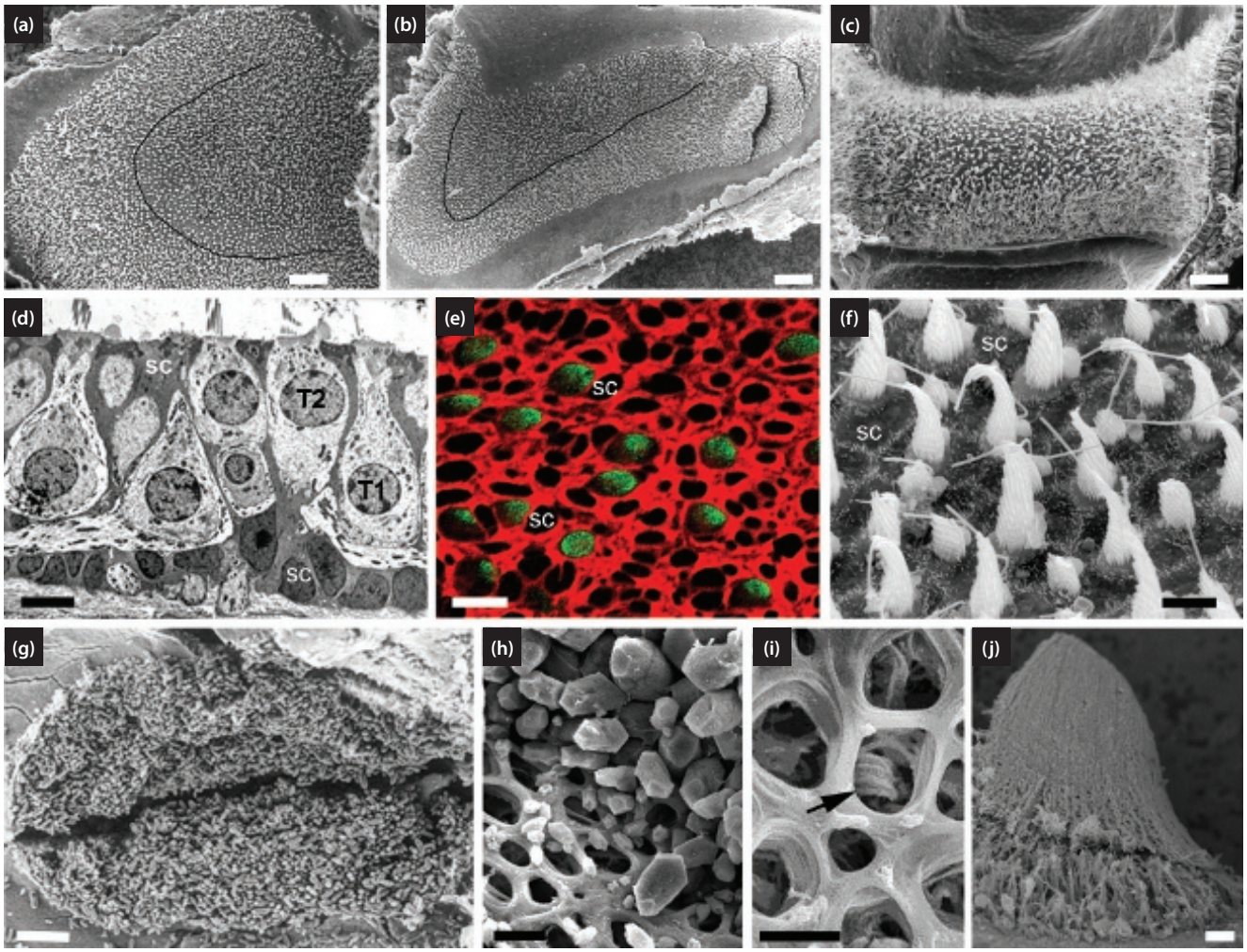

Figure 47.3 Vestibular sensory epithelia. (a) Utricular macula. Scanning electron microscopy of the entire intact utricular macula viewed from above after removal of otoconial membrane. Curved line indicates approximate location of line of hair bundle polarity reversal in the striolar region. Scale bar: 100 µm. **(b)** Saccular macula. As above for the utricular macula. Scale bar: 100 µm. **(c)** Crista ampullaris. Scanning electron microscopy of the upper surface of the crista 'saddle'. Scale bar: 100 µm. **(d)** Transmission electron microscopy of a thin section from a vestibular sensory epithelium (utricular macula of guinea pig). T1 = Type 1 hair cell; T2 = Type 2 hair cell; sc = supporting cell. Note that nuclei of each cell type are at different levels in this pseudostratified epithelium. Scale bar: 5 µm. **(e)** Human utricular macula labelled for filamentous actin (f-actin) with fluorescent-phalloidin (red) and an antibody to calretinin (green, labelling hair cells). Apical surface view to show reticular lamina. Phalloidin labels f-actin in the unusually wide junctional complexes around each cell. Each hair cell (green) is separated from its neighbours by intervening supporting cells (sc). Scale bar: 10 µm. **(f)** Apical surface of utricular macula. Hair cells are easily identified by the hair bundles that project out of the surface of the epithelium. Each hair cell is separated from its neighbour by intervening supporting cell (sc). Scale bar: 5 µm. **(g)** Scanning electron microscopy of the surface of the utricular macula with the otoconia still in situ covering the surface. Scale bar: 100 µm. **(h)** Higher magnification view of the utricular macular surface showing the perforated sheet of extracellular matrix component of the otoconial membrane beneath crystal-like otoconia. Scale bar: 5 µm. **(i)** Hair bundle (arrowed) projecting up into the otoconial matrix. Note that the hair bundle is aligned with a perforation in extracellular matrix component of otoconial membrane (utricle). Scale bar: 5 µm. **(j)** Cupula overlying a crista ampullaris. Scale bar: 10 µm.

density of actin filaments and the extensive cross-linking between them imposes rigidity on the shaft of the stereocilium, which tapers significantly at its proximal end (Figure 47.5a,g) where it is embedded into the **cuticular plate** (Figure 47.5a,c,d), a rigid platform formed of a meshwork of actin filaments and other proteins in the apical cytoplasm of the hair cell (Figure 47.5a,c,d).[14–17] As a result, when pushed at its tip, the stereocilium pivots at the taper like a stiff rod. The fundamental nature of this stereociliary rigidity for all hair cells is evidenced by the hearing impairment and vestibular disorders that result from mutations in genes that encode for such actin-cross-linker proteins. Mice with such mutations are often recognized by erratic and/or circling behaviours, for example the 'jerker' mouse strain, which has a mutation in the gene for the cross-linking protein espin, and in which stereocilia are thinner than normal.[10–13] Loss of plastin 1 results in progressive hearing loss and balance dysfunction and progressive thinning of stereocilia.[9, 12] Actin filaments descend from the stereocilium into the cuticular plate as a rootlet, which is cross-linked into the actin meshwork (Figure 47.5h).[15] The rootlet is formed of densely packed

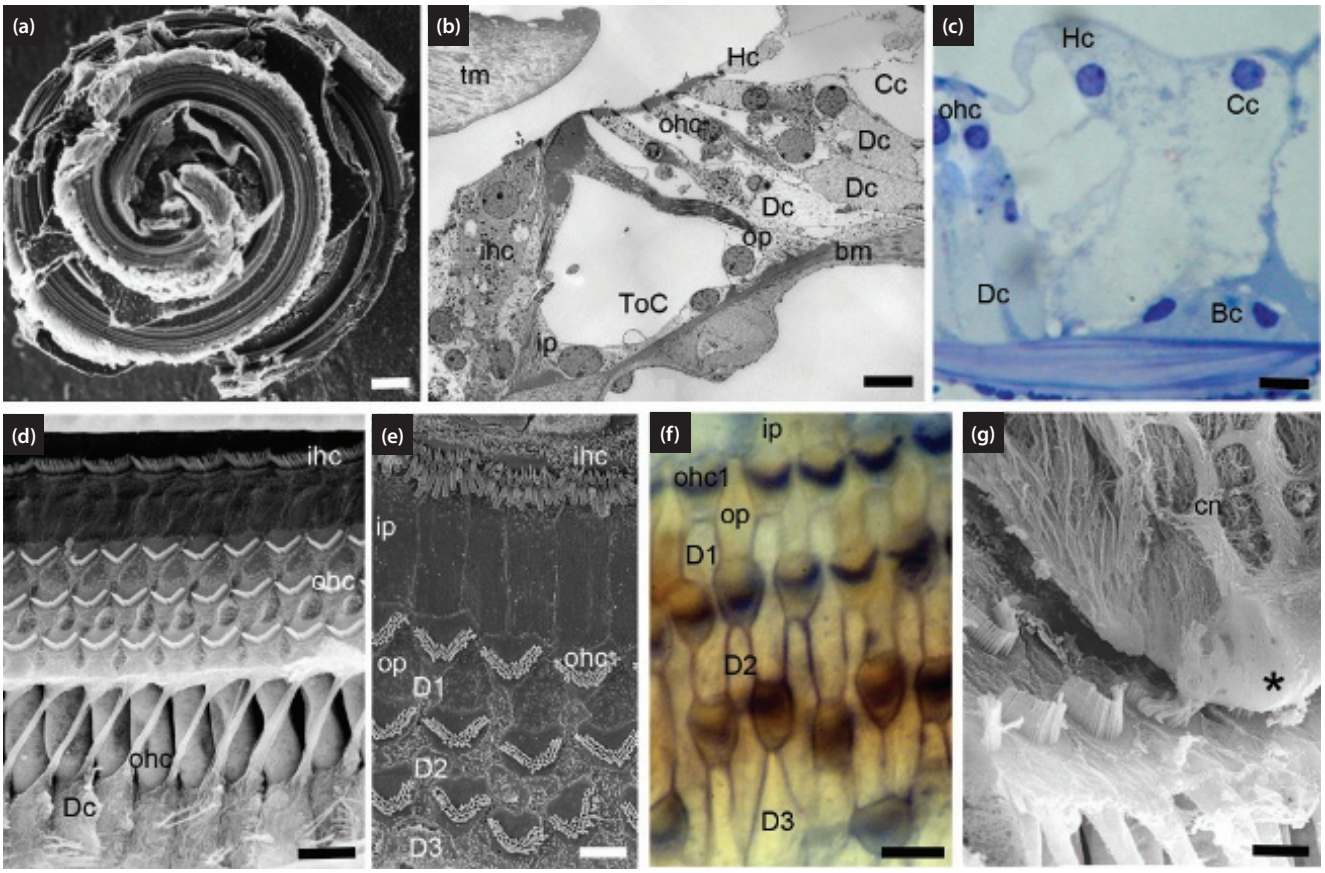

Figure 47.4 **(a)** Whole cochlear modiolus. Scanning electron microscopy showing the organ of Corti spiralling down from the apex for two and a half turns. Scale bar: 100 µm. **(b)** Cross section of the organ of Corti. Transmission EM of a thin section of the organ of Corti. The tectorial membrane (tm) retracts away from the surface of the organ of Corti during processing (see panel (g)). The tunnel of Corti (ToC) is created by the arch formed by the phalangeal processes of the inner and outer pillar cells. Scale bar: 10 µm. **(c)** Supporting cells to the outer, lateral side of the organ of Corti. Scale bar: 10 µm. **(d)** Surface and underside of the organ of Corti (gerbil): scanning electron microscopy of the apical surface with outermost (lateral) supporting cells removed to expose the outermost (third) row of Deiters' cells (Dc) and the outer third row of outer hair cells (ohc). The body of the Deiters' cell surrounds the base of the ohc and its phalangeal process ascends at an angle to the apical surface where the head expands. The hair bundles of the inner hair cells (ihc) in a single row. Scale bar: 10 µm. **(e)** Luminal surface of organ of Corti (mouse). Hair cell/supporting cell mosaic formed when the apical surfaces/heads of various supporting cells that join with and intercalate between individual hair cells. The head of the inner pillar cell (ip) and outer pillar cell (op) are indicated. Scale bar: 5 µm. **(f)** Human organ of Corti: reticular lamina at apical surface across the outer hair cell region (ohc1 = first row outer hair cell). Heads of various supporting cells surrounding each hair cell are indicated. Scale bar: 10 µm. **(g)** Tectorial membrane in situ over the organ of Corti. Radial filaments comprise the body of the tectorial membrane which has a greater density at the outer tip (*). The upper surface is covered by the densely packed fibres forming the covernet (cn). Scale bar: 5 µm. For all panels: Ihc or ihc = inner hair cell; ohc = outer hair cell; ip = inner pillar cell; op = outer pillar cell' Dc = Deiters' cell; HC or Hc = Hensen cell; Cc = Claudius cell; bm = basilar membrane; tm = tectorial membrane; Bc = Boettcher cells; D1, D2, D3 = heads of the three rows of Deiters' cells.

actin filaments (Figure 47.5e). The actin bundling protein TRIOBP plays a key role in the formation and maintenance of the rootlet.[18] In addition to actin, the cuticular plate contains spectrin,[19] another actin cross-linking protein that has elastic, deformation-resisting properties, and tropomyosin,[16, 17] a protein that binds around actin and stiffens it. Around its lateral margin, the cuticular plate is linked to the lateral plasma membrane at the level of the intercellular junction[15, 16] with which, on the supporting cell side, actin and other cytoskeletal proteins are also associated (Figures 47.6b,c,d and 47.7e,h). This may provide a means of support for the cuticular plate so that the stereocilia themselves are supported on a rigid platform, enhancing their ability to respond to small displacement forces.

Various members of the myosin family of motor proteins (types 1c, 6, 7a and 15 – all unconventional, non-muscle isotypes) are also localized in the cuticular plate region and the stereocilia. In addition, immunolabelling for myosins 6 and 7a shows these two proteins to be highly expressed throughout the hair cell cytoplasm, providing a distinguishing marker label for hair cells from their earliest differentiation during development and into adulthood (Figure 47.6e). Mice with mutations in the genes for myosins 6, 7a or 15 all show deafness and balance disorders and abnormalities in their stereociliary bundles.[20] In the mouse mutant where myosin 6 is defective (Snell's waltzer), stereocilia are fused and greatly lengthened.[21] Interestingly, a similar anomaly is seen in the human organ of Corti and

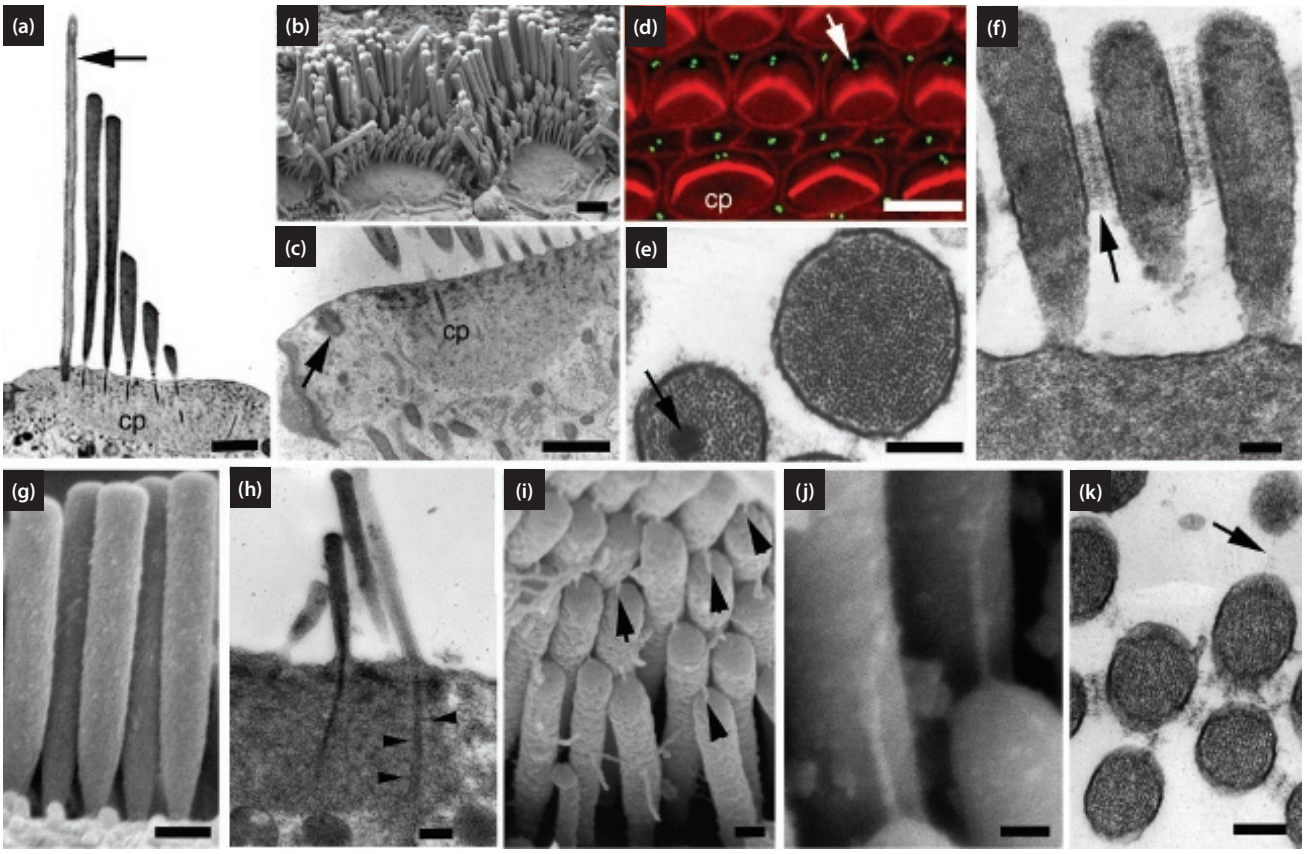

Figure 47.5 The hair bundle. **(a)** Hair bundle from utricular macula (TEM) shows stereotypical features. Rows of stereocilia of increasing height with a longer kinocilium (arrowed) behind the longest stereocilium. The stereocilia embed into the cuticular plate (cp) at their bases. Scale bar: 1 µm. **(b)** Hair bundle of outer hair cell in the human cochlea. Stereocilia in rows of increasing height, but no kinocilium. In humans, there are typically more stereocilia in the hair bundle than in most other mammals. Scale bar: 1 µm. (Preparation courtesy of Prof. Tony Wright, UCL Ear Institute.) **(c)** Apical end of inner hair cell in mature organ of Corti. The kinocilium has retracted to leave the basal body (arrow) to the side of the bundle with the tallest stereocilia in a region of cytoplasm outside of the cuticular plate (cp). **(d)** Labelling for f-actin with fluorescently tagged phalloidin (red) shows the stereocilia and the cuticular plate (cp) are composed of f-actin. Labelling for a protein that is present in basal bodies (Alms1; green) shows basal bodies located behind the stereocilia in a region free of the actin-labelled cuticular plate (arrow). Scale bar: 5 µm. (Figure courtesy of Dr Dan Jagger, UCL Ear Institute.) **(e)** Stereocilia in cross section showing closely packed filaments of actin. Filaments in rootlet are more densely packed (arrow). Scale bar: 100 nm. **(f)** Parallel closely packed filaments of actin in stereocilia. Lateral cross-links between the shafts of adjacent stereocilia in the same row appear to interdigitate at the midpoint of the space between them (arrow). Scale bar: 100 nm. **(g)** Individual stereocilia taper at their proximal end where they embed into the cuticular plate. Scale bar: 500 nm. **(h)** Stereociliary rootlets are cross-linked (arrowheads) before they descend into the filamentous meshwork that constitutes the cuticular plate. Scale bar: 250 nm. **(i)** Tip links (some arrowed) from the top of a short stereocilium to the shaft of the adjacent longer one in the direction of line of polarity in saccular macula of newt. Scale bar: 100 nm. (Figure courtesy of Dr Ruth Taylor, UCL Ear Institute.) **(j)** Higher-power view of tip links between stereocilia on outer hair cells showing branching at their ends. Scale bar: 50 nm. **(k)** Lateral cross-links between neighbouring stereocilia in the same row and adjacent rows. Arrow indicates apparent tip link. Scale bar: 100 nm.

vestibular system from elderly people and may be related to age-related hearing loss and balance dysfunction.[22, 23] It has been suggested that myosin 6 may be involved in holding the apical plasma membrane of the hair cell onto the cuticular plate in the regions between the stereociliary bases so that individual stereocilia can be maintained and, when it is defective, that membrane region becomes detached. In mice where myosin 15 is mutated (shaker-2) stereocilia are greatly reduced in height.[24, 25] Myosin 15 is thought to form a complex with other proteins including whirlin and Esp8 that regulates the height of stereocilia.[26–29] Mutations in the myosin 7a gene are responsible for Usher syndrome type 1B.[30] The mutant mouse strain carrying this mutation (shaker-1) shows hair bundles in which groups of stereocilia are separated from each other at the hair cell apex and the kinocilium is misplaced, suggesting an effect on maintenance of orientation and inter-stereociliary stabilization.[25] Myosin 7a may have a role in the various cross-links that are present between stereocilia (see below).

The stereocilia in an individual hair bundle are connected by a variety of fibrillar extracellular cross-links (**Figure 47.5**).[31] The most critical of these is the 'tip link' which runs from the top of one stereocilium to the shaft of an adjacent longer one along the line of morphological polarity and thus generating the line of functional

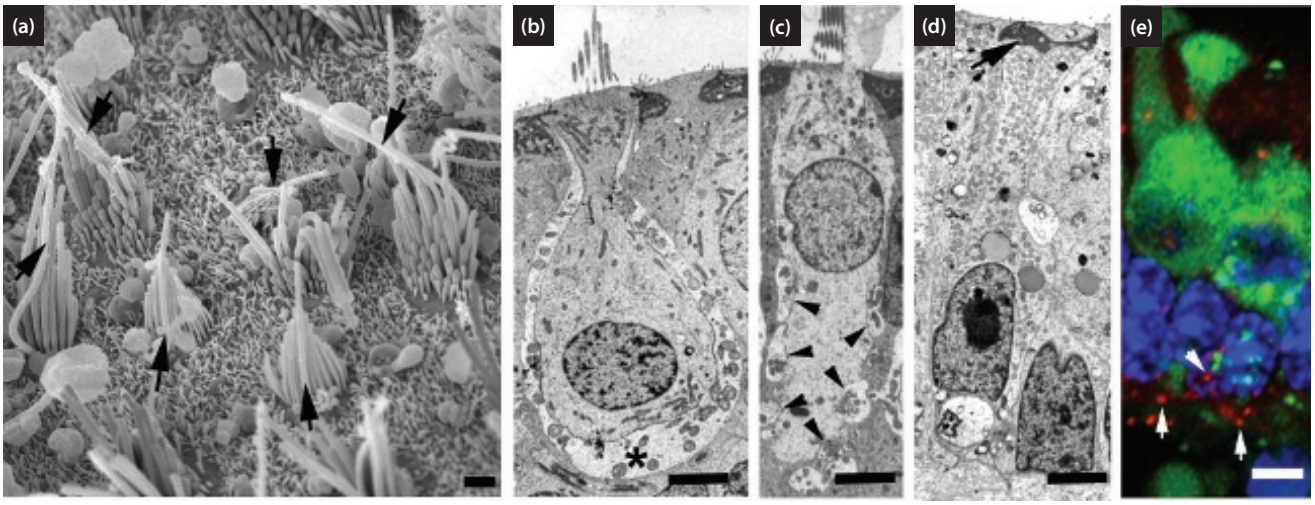

Figure 47.6 Hair cells and supporting cells in vestibular sensory epithelia. **(a)** Hair bundles across the line of polarity reversal in the striolar region of utricular macula. Kinocilia (arrowed) behind row of longest stereocilia. The polarity of the bundles changes by 180° (indicated by the direction of arrows) in the striolar region. Scale bar: 1 µm. **(b)** Type 1 hair cell. The flask-shaped cell body is entirely enclosed within the calyx terminal of a single afferent nerve (asterisk). Scale bar: 2 µm. **(c)** Type 2 hair cell. The cylindrical cell is contacted by several afferent nerve bouton terminals (arrow heads). Scale bar: 2 µm. **(d)** Supporting cell, with cell body basally resting on the basement membrane has a thinner process through the mid-region of the epithelium and a wide, dense cytoskeletal complex (arrow) at the apical head region at the level of the junctions with adjacent supporting cells. Scale bar: 2 µm. **(e)** Human utricular macula. Hair cells labelled for myosin VIIa (green). Punctate labelling for connexin 30 (red) reveals numerous large gap junction plaques (arrows) between the cell bodies of adjacent supporting cells. Nuclei labelled blue (DAPI). Scale bar: 5 µm. (Figure courtesy of Dr Ruth Taylor, UCL Ear Institute.)

polarity (**Figure 47.5i,j**).[32, 33] The tip link is thought to be the gating element that controls the opening of the MET channel.[34–37] As the bundle moves in the excitatory direction, tension on the tip link opens the channel; when the bundle moves in the opposite direction, tension is relieved and the channel closes. The tip link is composed of two coiled filamentous proteins that are adherent end-to-end: cadherin 23 (cdh23) and protocadherin 15 (pcdh15).[38–40] Unsurprisingly, mutations in the genes that encode for either of these proteins cause both hearing impairment and vestibular disorders: mutations in the cdh23 gene result in Usher syndrome type 1D in humans and are responsible for the 'waltzer' mouse strain; mutations in the gene encoding pcdh15 are associated with Usher syndrome type 1F and the 'Ames waltzer' mouse (the names of the mouse strains indicate the movement abnormalities resulting from defects in the vestibular system). At its upper end, around the point of its insertion into the membrane of the shaft of the longer stereocilium, the tip link is associated with a complex of proteins that may regulate tip-link tension thereby controlling transduction channel opening, as well as 'adaptation', the closure of the channel that occurs with sustained excitatory deflection of the stereocilia, of particular relevance in vestibular hair cells. Proteins involved in maintaining tip-link tension include myosin 7a, Sans and harmonin,[41] and again defects in these are associated with hearing impairment and vestibular dysfunction: Usher type 1B in humans and the shaker 1 mouse strain in the case of myosin 7a; Usher type 1C from defects in harmonin; and Usher type 1G from mutations in *Sans*.[38] In addition, myosin 1c localizes to the region near the upper insertion point of the tip link and is thought to be involved in adaptation.[42]

In addition to the tip link, there are 'lateral links' that connect the shaft of one stereocilium to all its neighbours. There are thought to be at least three different types of lateral link between stereocilia.[31] Ankle links, which are present in the hair cells of mammalian vestibular organs and the auditory and vestibular hair cells of non-mammalian vertebrates but not in those of the organ of Corti, connect stereocilia at their proximal ends. Shaft connectors are present along the mid-region of the stereociliary shaft (**Figure 47.5f,k**). Top-connectors link stereocilia just below the level of the tip links. The different types of lateral link were initially identified through the use/generation of antibodies that specifically label each subpopulation separately.[31] This indicates significant differences in protein composition between the links. Mice with defects in the genes for these different stereociliary cross-linking proteins also have hearing impairment and balance dysfunction. Lateral links may have a role in holding the bundle together, thereby stabilizing it and aiding the mechanical coupling of deflections of the stereocilia, such that the stereocilia in a hair bundle all move as a single unit. In agreement with this, mice with mutations in genes that encode lateral link proteins exhibit splaying of the stereocilia and thus loss of efficient MET, indicating the critical role for lateral cross-links in maintaining hair bundle cohesion.[31]

The basolateral plasma membrane

The basolateral membrane of a hair cell is characterized by the presence of a variety of ion channels essential for shaping the response of the cells to mechanical excitation.[43] Outwardly rectifying K^+ channels open when the hair cell is depolarized by the MET current that is generated

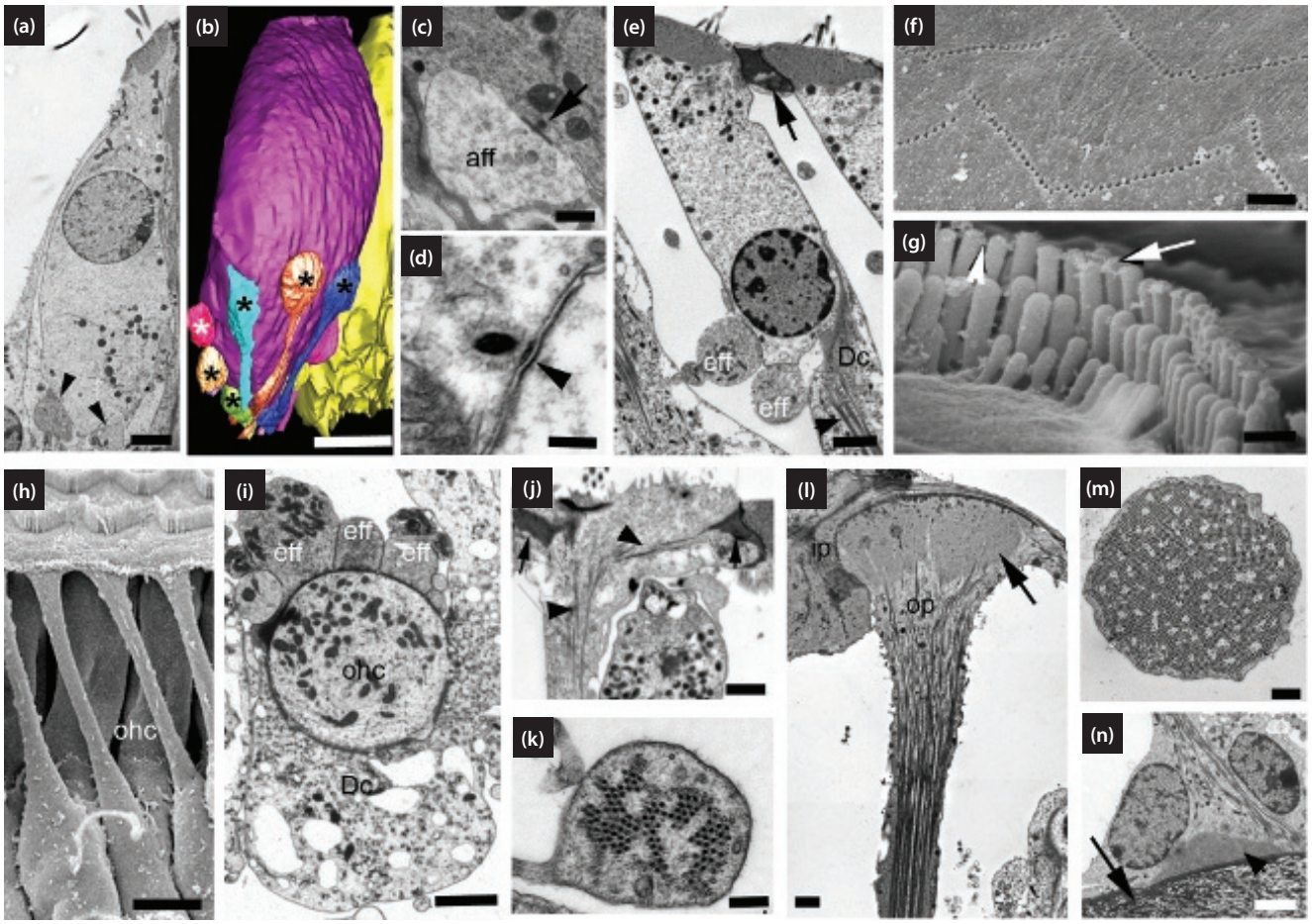

Figure 47.7 Ultrastructure of hair cells and supporting cells in the organ of Corti. **(a)** Inner hair cell. Flask-shaped cell closely surrounded by supporting cells. Terminals of afferent synapse at the base of the cell (arrowheads). Scale bar: 2 µm. **(b)** 3D reconstruction from serial sections of an inner hair cell and its innervation. Several different afferent terminals (coloured and indicated by asterisks) contact around the basolateral surface of the inner hair cell (purple). Scale bar: 5 µm. (Figure courtesy of Dr Anwen Bullen, UCL Ear Institute.) **(c)** Afferent nerve terminal and synapse. A TEM section through the postsynaptic terminal and the presynaptic ribbon in the inner hair cell side (arrowed). The circular ribbon opposes the postsynaptic density of the membrane of the afferent nerve terminal (aff). Scale bar: 1 µm. **(d)** Ribbon synapse. Higher power view showing the ribbon surrounded by neurotransmitter vesicles. Arrowhead indicates postsynaptic density of the membrane of the afferent terminal. Scale bar: 100 nm. **(e)** Outer hair cell. Efferent nerve terminals (eff) around the basal pole of the outer hair cell. The lateral surfaces of the outer hair cell bodies are surrounded by extracellular space (the space of Nuel). There is contact with a Deiters' cell (Dc) around the basal pole and with the head of a Deiters' cell at the apical surface (arrow). The head of the Deiters' cell contains a wide, deep cytoskeletal assembly at the level of the intercellular junctions and the hair cells' cuticular plates. Arrowhead indicates a microtubule bundle in the body of a Deiters' cell below the outer hair cell. Scale bar: 2 µm. **(f)** Underside of tectorial membrane showing indentations of the insertions of the tips of the longest stereocilia of each outer hair cell stereociliary bundle. Scale bar: 1 µm. **(g)** Outer hair cell stereociliary bundle. The tips of the longest stereocilia are crowned with fibrillary material (arrows) that attaches each stereocilium into its indentation in the underside of the tectorial membrane, probably composed of stereocilin. Scale bar: 0.5 µm. **(h)** Deiters' cell: consists of a main cell body region that at its upper end encloses the base of an outer hair cell (ohc); a phalangeal process that ascends at an angle to the apical surface; and an expanded head region at the apical end that contacts an outer hair cell, two cells away along the row from that which the cell body encloses. Scale bar: 5 µm. **(i)** Horizontal/oblique section through the Deiters' cell (Dc) body where it encloses the base of outer hair cell (ohc) in a cup-like fashion, open on the side towards the modiolus. Efferent nerve terminals (eff) contact the basal pole of the outer hair cell at the opening. Scale bar: 2 µm. **(j)** Deiters' cell head. Wide, deep cytoskeletal assemblies (arrow) attached at intercellular junctions with outer hair cells. Microtubule bundle (arrowheads) run across the head parallel to the apical surface and down phalangeal process. Scale bar: 2 µm. **(k)** Deiters' cell phalangeal process in horizontal cross section. The process encloses bundles of microtubules. Scale bar: 200 nm. **(l)** Outer pillar cell (op). The phalangeal process is filled with parallel microtubules. The expanded apical head region forms a buttress beneath the widening head of the inner pillar cell. The junction between the outer and inner pillar cells is supported by a dense, wide cytoskeletal assembly in the outer pillar cell (arrow) into which the microtubule bundles terminate. Scale bar: 2 µm. **(m)** Outer pillar cell phalangeal process in horizontal cross section. The process is filled with many closely packed microtubules in seemingly regular arrays. Scale bar: 1 µm. **(n)** Inner pillar cell, base. The cell body rests on a thin bony lip (arrow) extending out from the modiolus. Microtubules bundles descend from the phalangeal process to the very base of the cell and are associated with a dense triangular-shaped cytoskeletal assembly (arrowhead) that anchors the cell to the underlying bone. Scale bar: 2 µm. *(Continued)*

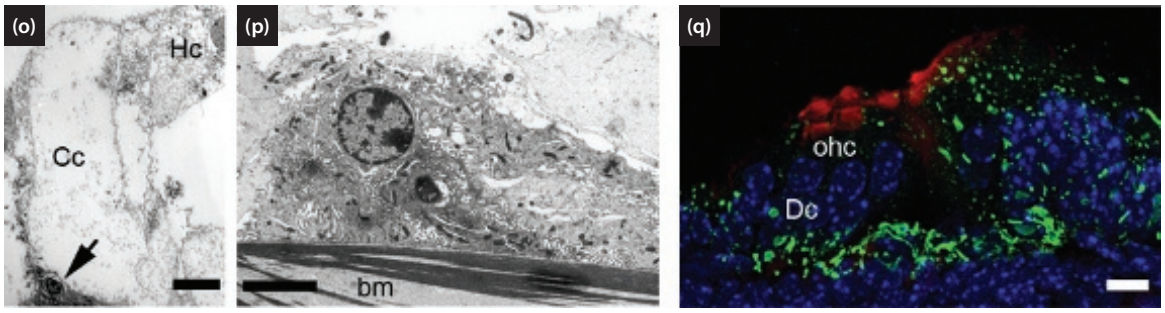

Figure 47.7 (Continued) Ultrastructure of hair cells and supporting cells in the organ of Corti. **(o)** Hensen's (Hc) and Claudius (Cc) cells. Hensen's cell covers the outermost extracellular space of the organ of Corti and does not reach the basilar membrane. Claudius cells are unusually devoid of organelles. They cover the Boettcher cells (arrow). Scale bar: 10 µm. **(p)** Boettcher cells sit on the basilar membrane (bm). They have a dense cytoplasm and numerous interdigitating infoldings. Scale bar: 5 µm. **(q)** The organ of Corti contains many gap junction complexes. Immunohistochemical labelling for connexin 26 (green) reveals gap junction plaques. F-actin is labelled using fluorescent phalloidin (red) and cell nuclei using DAPI (blue). There are numerous large gap junctions between adjacent supporting cells across the entire organ of Corti. Scale bar: 10 µm.

by hair bundle deflection. The resulting outward flow of K^+ through these channels repolarizes the hair cell membrane. The same depolarization also leads to the opening of voltage-gated Ca^{2+} channels and thus an influx of Ca^{2+} that triggers the fusion of intracellular vesicles with the plasma membrane and release of neurotransmitter at the synapses on to the primary afferent nerve endings. In this way, stereociliary deflection opens MET channels, causing depolarization in the hair cells, release of neurotransmitter onto afferent nerve fibres and thus activation of action potentials in neurons, i.e. neural discharge. In addition, hair cells in some rodent species also possess inwardly rectifying K^+ channels that are opened by cell hyperpolarization to restore hair cell resting potentials. Ion channels with these general properties can have different physiological characteristics in terms of their voltage dependence, the speed with which they respond (fast or delayed) and the size of the current that flows through them.[44] Although the general features of a hair cell are well conserved across many species, different types of hair cell are recognized depending on their location (auditory or vestibular), innervation pattern (afferent or efferent) and species of origin. The different types and numbers of ion channels expressed are characteristic features of particular types of hair cell.[44] In addition to the expression of different ion channels, hair cells in the organ of Corti show other specializations of their basolateral plasma membrane that are associated with particular unique functions that these cells perform (see 'Outer Hair Cells' below).

GENERAL CHARACTERISTICS OF SUPPORTING CELLS

The supporting cells provide mechanical support to the epithelium and thus to the hair cells. Their cell bodies contact each other and rest on the basement membrane that underlies the sensory epithelium (Figures 47.3d and 47.4b,c). Rod-like **phalangeal processes** extend from the cell body, interdigitating between the hair cells, to the luminal surface where they expand to fill the spaces between hair cells (Figures 47.3d,e,f and 47.4d,e,f). Supporting cells possess a fairly extensive cytoskeletal system that is particularly well developed in the cells of the organ of Corti. These phalanges contain bundles of microtubules, which can act like scaffolding poles/suspension struts to provide structural support (described in more detail later). At the apical, luminal poles, there are cytoskeletal assemblies that contain actin arranged in filamentous bundles running parallel to the luminal surface of the cell, anchoring to an adherens-like region within the intercellular junction that joins it to the adjacent hair cell (Figure 47.3e). Actin bands that run circumferentially around the neck or cortex of an epithelial cell are present in all epithelial cells and are thought to provide structural support at the points of adhesion between adjacent cells. These cortical actin bands are unusually wide in sensory epithelia of the inner ear (Figure 47.3e), indicating the importance of rigidity at the apical surface of these tissues.[45]

Supporting cells are functionally coupled to each other by substantial numbers of large **gap junctions** (Figures 47.6e and 47.7o).[22, 46–48] Gap junctions are sites of direct cytoplasmic communication between adjacent cells where clusters of pore-forming channel proteins in the membrane of one cell are in direct register with clusters of pore-forming channel proteins in the membrane of its neighbour. When these clusters of proteins dock together, they can form continuous aqueous pores that connect the cytoplasm of the adjacent cells. The protein subunits that form gap junction channels are members of the **connexin** protein family. At least 20 different types, or isoforms, of connexin have been identified. Six connexins form a **hemi-channel** or **connexon**, and the connexons of two adjacent cells align symmetrically to form the communication pathway between the cells. Gap junction channels are clustered in the plane of the membrane to form 'plaques' that can contain up to several thousand connexons. The channels allow the passage of small metabolites (up to 1.2 kDa in size), ions and second messengers, coupling the cells both electrically and chemically. Numerous gap junctions are present at points of contact between adjacent supporting cell bodies and between the head regions of adjacent cells, but there are

no gap junctions associated with hair cells.[22, 47] The large size and number of gap junction plaques between all supporting cells mean that the supporting cell population can be regarded as a functional syncytium, from which hair cells are functionally isolated.[22, 47] In all vertebrate classes from fish to mammals, gap junction plaques in inner ear sensory tissues are typically enormous, among the largest in the whole body, covering several square micrometres (μm^2) in area and containing several thousand channels.[46] One suspected role for supporting cells is thought to be the removal of excess K^+ ions from the intercellular spaces of the sensory epithelium during hair cell repolarization events.[48] Such a mechanism could thereby maintain the low K^+ environment around the body of the hair cell necessary for transduction and sensitivity to stimulation. It has been proposed that the gap junctions provide a means to ferry the K^+ away, preventing local accumulation. Gap junctions in the organ of Corti and in mammalian vestibular sensory epithelia contain two connexin isoforms, Cx26 and Cx30.[46, 48] Mutations in the genes for these connexins have been identified as causes of hereditary sensorineural hearing loss.[49] Those mutations in the gene encoding for Cx26 (*GJB2*) are the most common cause of non-syndromic hereditary deafness. There is increasing evidence that gap junctions with particular connexin composition, in particular Cx26, are important during development of the organ of Corti.[48] However, connexin mutations appear to have much less effect on the vestibular system.

THE VESTIBULAR SYSTEM

The vestibular system can be generally divided into two parts: the **saccule** is anatomically a separate chamber from the **utricle** and the three **semicircular canals** which arise from and terminate in the utricle and run in orthogonal planes – horizontal (lateral), posterior and superior (anterior) (**Figures 47.1a** and **47.2a**). Not only is there anatomical separation; the utricle and semicircular canals are evolutionarily and developmentally separate from the saccule. In the evolutionarily most primitive extant vertebrates (e.g. hag fish), the inner ear is composed of only two semicircular canals that are continuous with a single utricle-like chamber with a macula.[50, 51] During ontogenetic development, the utricle and semicircular canals arise on one side of the embryonic otic vesicle, opposite to that of the saccule which develops close to the site at which the cochlea is defined.[52] There is thus an anatomical and developmental relationship between the saccule and the cochlea, and in fish and some amphibia, the saccule does have an auditory function.[53, 54] This biological relationship may be an underlying factor in the sound-induced vertigo and dizziness characteristic of Tullio syndrome.

Sensory epithelia

The maculae of the utricle and saccule are flat sheets of epithelium that are oriented at right angles to each other (**Figure 47.2a**), the utricle in the anterior–posterior plane, the saccule in the superior–inferior. The utricular macula is approximately U-shaped and the saccular macula, in mammals, is almost S-shaped (**Figure 47.3a,b**). The **cristae ampullares** of the semicircular canals are saddle-shaped epithelial mounds (**Figure 47.3c**) contained within swellings, the ampullae, which open to the utricle at one end. The cell bodies of the nerves that innervate the sensory cells of the vestibular system are collected together in **Scarpa's** or vestibular **ganglion**, which is just external to the medial wall of the inner ear (**Figure 47.2a**).

OTOCONIAL MEMBRANES AND CUPULA

The utricular and saccular maculae are each overlaid by an 'otoconial membrane' which consists of a large number of otoconia (Greek: 'ear dust') (**Figure 47.3g**), crystalline particles composed of calcium carbonate surrounding a proteinaceous core that sit on a honeycomb-like perforated sheet of non-collagenous fibrillar extracellular matrix (**Figure 47.3h,i**). This matrix is composed of proteins unique to the inner ear including otogelin, α- and β-tectorins and ceacam 16 (carcinoembryonic antigen-related cell adhesion molecule 16).[55, 56] In fish, rather than numerous small particles, there is a single, large calcium carbonate particle, the otolith (Greek: 'ear stone'), hence the term 'otolithic organs' is sometimes used (incorrectly) to describe the saccule and utricle of mammals. Hair bundles of the utricular and saccular hair cells appear to align with the perforations in the sheet of extracellular matrix with the longest stereocilia, possibly in contact with the edge of the hole (**Figure 47.3i**). The utricular and saccular maculae detect translational motion of the head in the horizontal and vertical planes. With a linear motion, because of its mass, movement of the otoconial membrane lags in relation to the movement of the epithelium itself, which follows the head movement without any inertia. As a result, the stereocilia are deflected and hair cells stimulated. With a head tilt, the force of gravity acts on the otoconial membrane to produce a relative displacement between the membrane and the tilting surface of the epithelium that deflects the stereocilia. In the semicircular canals, the extracellular structure overlying a crista, known as the **cupula**, is a dense fibrous mass with no otoconia that extends to the roof of the ampulla (**Figure 47.3j**). The principal proteinaceous component is otogelin; neither tectorins nor collagen are are present in the cupula.[55] The longest stereocilia of hair cells of the cristae appear to contact the underside of the cupula. The cristae detect rotational acceleration of the head. When the head rotates, movement of endolymph through the semicircular canals lags behind that of the crista epithelium because of the fluid's inertia. The consequent differential movement displaces the cupula, leading to deflection of the stereocilia.

HAIR BUNDLES AND THEIR ORIENTATIONS

Hair bundles of vestibular hair cells have a stereotypical morphology consisting of stereocilia arranged asymmetrically in a staircase pattern of increasing height in one particular plane, that of activation or sensitivity, and a single kinocilium located behind the tallest stereocilia (**Figures 47.3f**, **47.5a** and **47.6a**). At least four different

arrangements of the stereocilia have been described for the hair bundles on macular hair cells.[57] Although these differences suggest divergent physical and biophysical properties of hair bundles, the functional significance has not been clarified.

In the cristae the orientation of the hair bundles, i.e. the alignment of the staircase pattern which defines morphological and functional polarity, is the same for all the hair cells in an individual crista. In the cristae of the horizontal and superior canals the shortest stereocilia of all hair cells are on the side of the bundle towards the utricle, while in the cristae of the posterior canal the bundles are oriented the opposite way, with the longest stereocilia (and kinocilium) on the side facing the utricle. Because of the uniform orientation of hair bundles across the cristae, a rotation in a particular direction will produce excitatory deflections of all stereociliary bundles of the cristae in one ear and inhibitory deflections of the hair bundles of the cristae in the same semicircular canal in the opposite ear, the integration of signals thereby providing information on the direction of rotation.

In the saccule and utricle there are opposing orientations of the hair bundles across the maculae: all the hair bundles located on one side of a region running across the epithelial sheet are oriented the same way with respect to the periphery, and at 180° to those on the other side of that region (**Figure 47.6a**). In the utricular macula, the shortest stereocilia face the centre (the bundles are oriented 'front-to-front' across the line of polarity reversal) so that excitation of the hair cells occurs with deflections of the stereocilia towards the periphery of the macula, whereas hair bundle orientations in the saccular macula are the reverse of those in the utricle: the longest stereocilia, and excitatory hair bundle deflection, are towards the centre. The line of hair bundle polarity reversal in a macula is located in the middle of the 'striola', a delineated strip, approximately 50–100 µm wide within the body of the macula and shaped to follow its contour.[58] The opposing orientations of the hair bundles, coupled with the asymmetric shape of the maculae and orientation of the saccular and utricular maculae in orthogonal planes, means that as head position changes differing patterns of hair cell excitation are elicited, providing fine-grained information on translational motion.

HAIR CELL TYPES

The basic cellular composition of all vestibular sensory epithelia is essentially the same (**Figure 47.3d**). There are two types of hair cell and these are both surrounded by non-sensory supporting cells. Type 1 hair cells are flask-shaped with a single large afferent nerve ending, a calyx, enclosing the entire basolateral surface of the cell (**Figures 47.3b** and **47.6b**). The endings of efferent nerves (i.e. those that carry signals from the brain to the sensory epithelium) contact the afferent calyx but not the hair cell itself. Type 2 hair cells are cylindrical with several small bouton-like afferent endings that form synapses towards the basal end of the cell (**Figure 47.6c**). In type 2 hair cells the efferent endings contact the hair cell directly. The nuclei of type 2 hair cells are generally located higher (closer to the luminal surface) in the cell than those of type 1s (**Figures 47.3d** and **47.6b,c**) and since the nuclei of the surrounding supporting cells are located beneath the hair cells, cross sections of vestibular sensory epithelia can appear to have three layers of cells (**Figure 47.3d**). There are other morphological features that distinguish the two hair cell types: for example, the stereocilia of type 1 cells are thicker (i.e. they contain more actin filaments) than those of type 2 hair cells. The physiological properties of the two hair cell types, as defined by ion channel expression in the basolateral membrane, are also different.[59] The calcyeal nerve terminals around type 1 hair cells express high levels of a calcium-binding protein, calretinin, which is not expressed in the afferent endings that synapse with type 2 hair cells.[58, 60] Accordingly, immunolabelling for calretinin provides a means for distinguishing and exploring the number and distribution of type 1 hair cells.[61] Use of this and other assays of hair cell morphology combined with dye tracing of the nerves,[62] has shown that the two hair cell types are differentially distributed across the organs. Type 1 cells predominate across the striolar region of the maculae and at the crest of the cristae. Type 2 hair cells are mainly confined to the extrastriolar regions of the maculae and the skirts of the cristae.[58, 60, 62] It is worth noting that the hair cells with a type 1-like innervation pattern are not present in fish or amphibians, rather they appear in vertebrates with necks which initially evolved as terrestrial animals. Thus, type 1 hair cells are likely to be providing information such as detecting rapid and/or smaller incremental head movements that are independent of whole body movements, and necessary for life on land.

PATTERNS OF INNERVATION

The patterns of afferent innervation of the different types of hair cells, often revealed following injection of a tracer dye into a single neurone,[62] are quite complex. An individual afferent neuron usually branches to innervate more than one hair cell. The neurons that innervate hair cells in the striolar region of the maculae and the crest of the crista form calcyeal nerve endings with only a single type 1 hair cell. In the peripheral regions of those organs a few individual afferent nerves form only bouton endings with several type 2s, but the majority of the afferent nerves are 'dimorphic', innervating both type 1 (≥1) and type 2 (typically >1) hair cells.[58, 60, 62] As a result, individual 'dimorphic' afferent fibres carry signals to the brain that result from the integration of convergent inputs from a number of different hair cells. Neurons innervating the striolar regions of the macula and the crest of the cristae do not cross into the extrastriolar regions of maculae or the skirts of the cristae, nor do they cross from one side of the striolar to the other so that the innervations in different regions of the sensory epithelia are anatomically separate. Moreover, there is some evidence from rats that, while afferent neurons from one side of the utricle project to the vestibular nuclei in the brain, those from the opposite side project to the cerebellum.[63] This indicates that there is significant integration and processing of information derived from vestibular sensory periphery that is carried up to higher centres in the brain.

SUPPORTING CELLS

The supporting cells of the vestibular sensory epithelia (Figure 47.6d,e) conform to the general pattern outlined above. They are relatively much less specialized than their counterparts in the organ of Corti and are little different from supporting cells in the sensory epithelia of the inner ear in all other vertebrates. Given that they form the reticular lamina (Figure 47.3e), they play critical roles in the barrier function of the epithelium and are also thought be important in phagocytosing and removing dead or dying hair cells.[64–66]

Ion-transporting epithelia of the vestibular system

The ion-transporting epithelium of the vestibular system is the region of 'dark' cells, so named because in histological sections the cells stain much more intensely (i.e. darker) than any others (Figure 47.8a). Dark cell epithelia are confined to the utricle and semicircular canals; there are no dark cells in the saccule (Figure 47.2a). In the utricle the dark cell epithelium forms a band all around the periphery of the macula separated from the sensory epithelium by transitional cells, a strip of relatively unspecialized cuboidal epithelial cells of as yet undefined function. A band of dark cell epithelium is also located all along the bottom of the skirts of each crista, again separated from the sensory region by a strip of transitional cells. The dark cell is a specialized cuboidal epithelial cell, in which the basolateral membrane is extensively infolded to create a large surface area. These infoldings house numerous large mitochondria likely to be critical for the function of these cells (Figure 47.8a).

Dark cells are crucial to maintaining the ionic concentration of endolymph. Lying underneath the dark cell epithelium is the mesenchyme of the connective tissue, the intercellular spaces of which are part of the perilymphatic compartment (Figure 47.8a). Unusually, there is no basement membrane or permeability barrier between the dark cell epithelium and the connective tissue, so the basolateral surfaces of the dark cells are exposed directly to perilymph. During the ongoing process of MET K^+ is shunted from the endolymphatic to the perilymphatic compartment. The basolateral membranes of the dark cells contain high levels of the Na^+/K^+-ATPase pump,[67] which use ATP to 'pump' two K^+ ions into and at the same time three Na^+ ions out of the cell against their respective ion concentration gradients. The presence of numerous large mitochondria within the basolateral infoldings is likely a specialization necessary for provision of the local energy supply required for this energetically expensive active ion transport. In addition, the dark cells' basolateral membranes contain an Na^+–K^+–Cl^- cotransporter NKCC1 (or SLC12A2).[68] This membrane protein uses energy derived from the Na^+ concentration gradient to cotransport the other two ions into the cell. Entry of Na^+ stimulates activity of Na^+/K^+-ATPase to return Na^+ equilibrium, thereby further enhancing K^+ uptake into the cell. The apical surfaces of the dark cells which face endolymph contain ion channels selective for K^+.[69] K^+ entering the dark cell at the basal side exits through the K^+ channels at the apex, into endolymph.

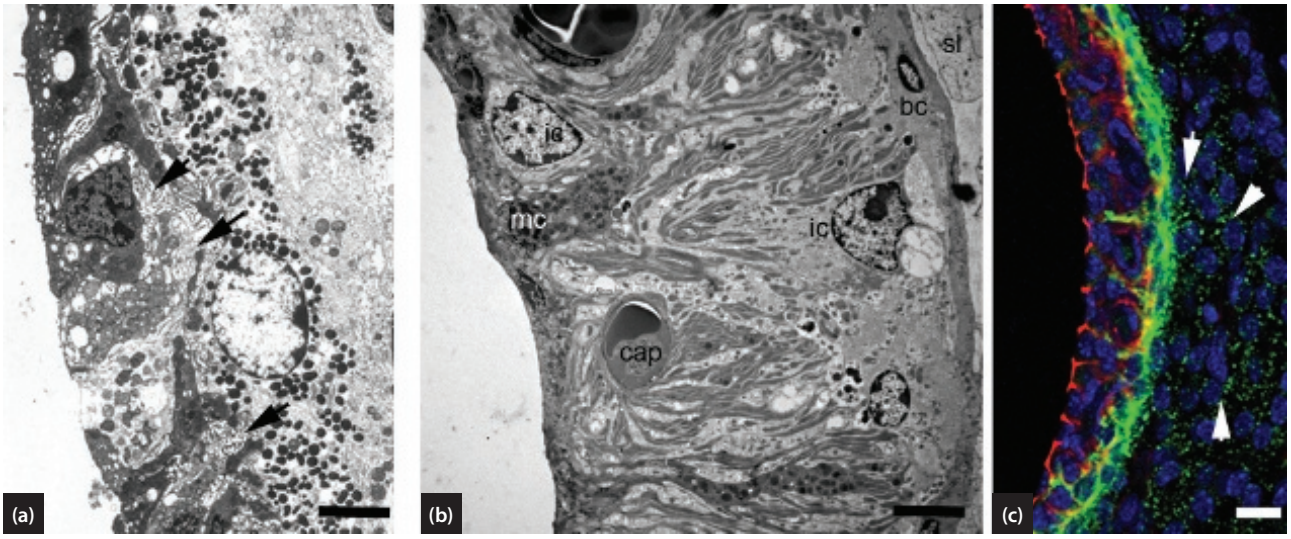

Figure 47.8 Ion-transporting epithelia. (a) Vestibular dark cell layer. The dark cells have numerous basal infoldings (arrows). A layer of pigmented cells containing melanin granules underlies the dark cells with mesenchyme beneath. Scale bar: 5 µm. **(b)** Stria vascularis. mc = marginal cells; ic = intermediate cells; bc = basal cells; cap = capillary; sl = spiral ligament underlying the stria vascularis. Marginal cells line the endolymphatic space and have numerous basal infloldings that extend down to the level of the basal cells. Intermediate cells, which contain melanin pigment granules, are entirely enclosed within the body of the stria. Elongated basal cells in one to two layers separate the stria from the underlying spiral ligament. Capillaries enclosed within the body of the stria are contacted by marginal cell processes and by intermediate cells. Scale bar: 5 µm. **(c)** Stria vascularis. Basal cell layer delineated by intense labelling for connexin 26 (green), indicating numerous gap junction plaques associated with basal cells. Gap junctions are between adjacent basal cells, between basal cells and intermediate cells and basal cells and fibrocytes in the spiral ligament. There are also numerous gap junctions between adjacent fibrocytes in the spiral ligament, indicated by green labelling for Cx26 in puncta (arrows) in tissue below the stria. Scale bar: 20 µm. (Figure courtesy of Dr John Kelly.)

In this way, K^+ ions are transported into endolymph and ion homeostasis in the vestibular system is maintained.

THE COCHLEA

Gross anatomy

The **cochlea** is formed of three parallel canals (or **scalae**, Latin: 'ladders'), coiled in a spiral around a central 'stalk', the **modiolus** (Figure 47.1c). The axons of the central projections of the auditory nerves that innervate the sensory epithelia, and the vessels of the cochlear blood supply, the cochlear artery and cochlear vein, run through the length of the modiolus. There are 2.5 turns in the human cochlea. The number of turns varies between different mammalian species but at present this is not known to have any specific functional significance. The central canal, the **scala media**, is lined by epithelia (part of the membranous labyrinth) and is filled with endolymph. In cross sections of the cochlea, the scala media is bounded by three 'walls' and appears approximately triangular in shape (Figures 47.1c and 47.2b). The sensory epithelium, the **organ of Corti,** running along the **basilar membrane**, forms the 'floor' of the triangle. The primary ion-transporting epithelium, the **stria vascularis**, runs along the lateral side and **Reissner's membrane** forms the 'roof' of the scala media (Figure 47.2b). Above Reissner's membrane is the **scala vestibuli**, and underneath the basilar membrane is the **scala tympani**. These two scalae are filled with perilymph. Reissner's membrane acts as the barrier between endolymph and perilymph in the scala vestibuli. Perilymph from both the scala vestibuli and scala tympani is freely permeable into the intercellular spaces of the spiral ligament that underlies the stria vascularis but, unlike the vestibular system, there is a barrier to direct diffusion of ions from the spiral ligament into the ion-transporting epithelium (see below).

The height and width of all the three scalae decrease systematically from base to apex of the spiral (Figure 47.1c). At the basal end, the scala tympani terminates at the **round window** (Figure 47.1a,b), a flexible membrane formed of two epithelial sheets sandwiching connective tissue, containing collagen and blood vessels.[70, 71] The apical surface of the outer epithelium is exposed to air in the middle ear; that of the inner epithelium is bathed in perilymph. The scala vestibuli at its basal end is continuous with the vestibule and the perilymphatic compartment of the vestibular system. The **oval window**, opening over the vestibule, is covered by a membrane and is filled with the footplate of the stapes. The gap between the border of the stapes footplate and the edge of the oval window is sealed with a ligament. At the apical end of the cochlea, the scala media is closed by epithelial tissue, arising partly by extension of Reissner's membrane, leaving a small opening, the helicotrema, through which the scala vestibuli and scala tympani are connected. Sound-induced movements of the tympanic membrane drive piston-like 'in–out' movements of the stapes footplate displacing incompressible perilymph along the scala vestibuli, through the **helicotrema** and down the scala tympani leading to 'out–in' movements of the round window. As fluid is displaced, the pressure difference across the scala media between the scala vestibuli and scala tympani, produces vibrational movement of the basilar membrane, described by Von Békésy. This 'travelling wave' stimulates the sensory cells housed in the organ of Corti that sits on the vibrating basilar membrane.

Organ of Corti

The mature organ of Corti is a ridge of cells resting on the basilar membrane and overlain by the tectorial membrane (Figure 47.4b,c). The length of the coiled basilar membrane and attendant organ of Corti varies with species; in humans it is about 35 mm long (range, 28–40 mm),[72] ~12 mm in mice, ~20 mm in guinea pigs and ~40 mm in whales. The widths of the basilar membrane and the organ of Corti increase systematically from the base to the apex of the cochlea. The thickness of the basilar membrane and the height (and mass) of the organ of Corti also both increase systematically from base to apex.[73] The consequent changes in the inherent mechanical properties of the basilar membrane, combined with changes in the mass on the membrane, result in sounds of different frequencies producing maximum vibrations at different locations along the cochlea; high frequencies are detected at the basal end and low frequencies at the apex. This frequency-place, or '**tonotopic**' relationship is preserved along the neural pathways in the brain: nerves that innervate the hair cells at the high-frequency, basal end of the cochlea project to a specific place in the cochlear nucleus, and those that innervate hair cells in the apical low-frequency region project to a different but specific place in the cochlear nucleus, i.e. there is a tonotopic map projected onto the cochlear nucleus and this tonotopicity is carried on up the auditory pathway.

There are two hair cell types in the organ of Corti, the **inner** and **outer hair cells** (IHCs and OHCs) (Figure 47.4b,d,e). In most mammals these are regularly arranged into a single row of IHCs on the medial or inner side of the spiral and three, sometimes four, rows of OHCs (Figure 47.4b,d,e) on the lateral or outer side. The human organ of Corti, however, appears less well ordered than the cochleae of lower mammals, with regions containing two ranks of IHC and areas where the rows of OHCs are less clearly definable, less evenly spaced and with occasional discontinuities (Figure 47.4f).[74] Within the body of the organ of Corti are large extracellular spaces (Figure 47.4b,c): the **spaces of Nuel** around the OHCs, and the **tunnel of Corti** between the OHC region. Both of these spaces are created during late stages of developmental maturation of the organ of Corti as a result of morphological specializations of the supporting cells, during which the phalangeal processes between the cell body region and expanded head at the apical (lumenal) end become reduced in width. The spaces are filled with perilymph as the basilar membrane is not a permeability barrier. The actual border and permeability barrier between the perilymph of the scala tympani and endolymph in the scala media is created by the intercellular junctions at the lumenal side of the organ of Corti and lies at the level of the reticular lamina. Mutations in the proteins that

comprise the tight (occluding) junctions in the organ of Corti, result in hearing impairment,[75–77] emphasizing the essential nature of the junctions and the barrier that they form.

BASILAR MEMBRANE

The basilar membrane (BM) is a sheet formed predominantly of extracellular matrix (**Figure 47.4b,c** and **47.7n**). It is composed of filaments within a ground substance, with a discontinuous layer of thin, elongated tympanic border cells on the underside facing the perilymph of the scala tympani.[17] The fibrils of the BM run predominantly radially, and are composed of collagen, mostly collagen type IV α1–α5 chains (COL4A1–COL4A5).[78] In addition, fibronectin[79] and laminin type 11,[80] adhesive-type molecules common to extracellular matrices, are localized to the BM and presumably compose the ground substance in which the collagen fibrils reside. The composition of the BM does not appear to be unique in comparison with basement membranes elsewhere in the body, except for a novel extracellular matrix protein (named 'usherin')[38, 81] that has been identified through the genetic mutation which is associated with Usher syndrome type 2A, in which there is high-frequency hearing loss. Mutations in the genes for the proteins composing the BM might be expected to affect the mechanics of the organ of Corti in response to sound and thereby cause hearing impairment. X-linked Alport syndrome has been attributed to mutations in the *COL4A5* gene. It has been suggested that it is the loss of this protein from the BM that results in the high frequency hearing loss associated with this condition.[82]

TECTORIAL MEMBRANE

The tectorial membrane (TM) is the structured sheet of extracellular matrix material that overlies the organ of Corti (**Figures 47.1b** and **47.4b,g**). At its inner edge it is attached to the interdental cells of the spiral limbus, a bony prominence to the inside of the organ of Corti (**Figure 47.1b**). It appears not to be attached to the surface of the organ of Corti at its outer edge. The longest stereocilia of each OHC are embedded in the underside of the TM (further described below). The TM is not merely a fibrous mass but it is quite highly structured, with a defined shape (**Figure 47.1b**). Its thickness decreases and its radial length increases systematically from base to apex. Over the top surface densely packed fibres are arranged in a network, the 'covernet' (**Figure 47.4g**), that is not unlike the perforated sheet of the otoconial membrane. The outermost tip is also distinguished by a higher density of fibre packing (**Figure 47.4b,g**). On the underside – facing the apical surface of the organ of Corti – there is a thickened ridge known as Hensen's stripe located just lateral to the position of the IHC stereocilia which is thought to contribute to the fluid-coupled deflection of the IHC stereocilia.

The body of the TM is formed of fibre bundles running approximately radially, embedded within a matrix composed of striated sheets formed of fine cross-linked fibrils.[83] The fibre bundles are formed of collagen types II, V and IX,[84, 85] different types to those found in the BM. Associated with the collagen bundles are the glycoproteins otogelin,[86] and α- and β-tectorin[87, 88] and ceacam 16.[89, 90] Otogelin, α- tectorin and β-tectorin are unique and essential to the inner ear, since mutations in the genes that encode for them are associated with non-syndromic hearing loss in humans.[86, 91, 92] Expression of mRNA for otogelin and the tectorins is detected only during development of the cochlea;[93, 94] they are not expressed in the organ of Corti of adults. The cessation of mRNA production indicates that there is no turnover of these key proteins, suggesting that the TM is a lifelong structure produced only during cochlear development. The implication is that damage to the TM (e.g. by disease or noise trauma) would not be repaired and would result in permanent hearing loss.

INNER HAIR CELLS

Rather than being positioned on the flexible BM, the IHCs reside above a thin and inflexible bony extension from the bone that surrounds the modiolus (**Figure 47.2b**). They are roughly flask-shaped (**Figure 47.7a**) and the shape of their hair bundles approximates to a straight line or a shallow 'U'-shape so they appear to form an almost continuous 'fence' along the medial or inner aspect of the organ of Corti (**Figure 47.3d,e**). Unlike the tips of OHC hair bundles, the IHC hair bundles do not appear to contact the TM directly. IHCs are innervated exclusively by **afferent nerve fibres** and 90–95% of all the afferent fibres from the cochlea to the brain arise from IHCs,[95, 96] making them the principal receptor cells that send auditory information to the brain. **Efferent nerve fibres** that terminate in the IHC region arise from the ipsilateral lateral superior olive in the mid-brain. Rather than contacting the IHCs, the efferent fibres contact the afferent fibres that terminate on the IHCs. These **lateral olivocochlear efferent nerve fibres** constitute approximately 20% of the efferent innervation to the organ of Corti.

Each IHC forms synapses with several (up to around 20) different afferent nerve endings that surround its basolateral membrane[97] (**Figure 47.7a,b**) but crucially a single auditory nerve fibre (ANF) innervates only a single IHC. The synapses between an IHC and its innervating afferent nerve endings are specialized **'ribbon' synapses** (**Figure 47.7c,d**). On the pre-synaptic, IHC side of the synapse adjacent to the membrane there is an elongate or rounded structure, the ribbon, surrounded by tethered **secretory vesicles** containing the **neurotransmitter** (glutamate), which release the glutamate into the synaptic gap or cleft when the hair cell is stimulated. The neurotransmitter binds to receptors on the post-synaptic membrane to initiate action potentials in the synapsing ANF. The 'ribbon' specialization provides for a constant pool of neurotransmitter at the site of neurotransmission to allow rapid and sustained release of glutamate and so rapid and sustained firing of the ANFs necessary for audition. Physiological recordings combined with dye tracing of individual ANFs have uncovered different response characteristics within the group of afferent fibres that innervate an individual IHC.[95, 98–101] At least two subpopulations have been identified: afferent fibres with low spontaneous firing rates

(i.e. the numbers of action potentials fired per second in quiet conditions) and high thresholds (i.e. requiring a relatively high sound intensity input to elicit a change in that firing rate); and fibres with high spontaneous rate and low thresholds. This diversity in the firing characteristics of the nerves innervating a single IHC provides a means to enhance the dynamic range of a single IHC that allows it to accurately encode a wide range of sound intensities. There is now increasing evidence that the subpopulations of afferent fibres that innervate an individual IHC are differentially sensitive to the effects of noise and ageing and the loss of a subpopulation of the afferent terminals under these conditions results in what has become known as 'hidden hearing loss'.[101, 102] In this situation, since the IHCs still have some neural connections, the auditory thresholds measured by standard audiological pure tone tests appear normal, but there are deficits in more subtle but critical aspects of audition, for example the ability to discriminate sounds (such as speech) in noise.

OUTER HAIR CELLS

OHCs are located across the most flexible part of the BM (**Figure 47.4b**). They are cylindrical cells with a basally positioned nucleus (**Figures 47.4b** and **47.7e**). Their hair bundles form a characteristic 'W'-shape (**Figure 47.4d,e**) and contact the underside of the overlying TM in which impressions of the longest OHC stereocilia can be seen (**Figure 47.7f**). A fibrous protein, stereocilin, appears to link the tips of the longest stereocilia to the insertion into the TM (**Figure 47.7g**).[103] Mutations in the gene for stereocilin are associated with hearing impairment.[104] Coupling between the longest stereocilia and the TM provides the mechanism by which OHCs are stimulated. The up-and-down movements of the travelling wave that is generated along the BM in response to the sound-induced fluid displacements along the scala vestibuli and scala tympani translate into radial (medial to lateral) movements at the apical surface of the organ of Corti. The TM mass remains static, so there is a relative shearing motion between the reticular lamina (the apical surface of the organ of Corti) and the TM. Since the longest stereocilia of OHCs are embedded in the underside of the TM, this differential movement results in the deflection of the hair bundle along the line of functional polarity resulting in opening and closing the MET channels. Deflection of OHC stereocilia generates a change in membrane potential in the cell, a receptor potential. In the case of the OHCs this generates a motile response (as described below).

OHCs increase in length systematically from the base of the cochlear spiral to the apex.[73, 105] In addition, the longest stereocilia on OHCs also increase in height systematically along the base-to-apex length of the cochlea, in humans increasing from around 2.5 µm in the basal coil to around 7.0 µm at the apex.[106] These systematic, or tonotopic, changes mean that the length of the cell body and height of the stereocilia for a particular OHC are precisely defined for its particular position on the BM. OHCs, in contrast to IHCs, are directly innervated at their basal ends, by several large bouton-like efferent endings (**Figure 47.7e**). About 80% of the efferent cochlear innervation terminates on OHCs.[95, 96] These **medial olivocochlear efferent nerves** that synapse with the OHCs arise primarily from the medial portion of the contralateral superior olive. Afferent nerve fibres that synapse with OHCs, which constitute only 5–10% of the total cochlear afferent innervation,[95, 96] branch considerably within the organ of Corti so that an individual neurone synapses with many OHCs in all three rows. The afferent innervation pattern suggests that OHCs may signal more global, large displacements of the BM, i.e. at high sound pressures, and recent research supports this.[107] The extensive efferent innervation, on the other hand, strongly indicates that OHCs have a modulatory role in the cochlea.

In experiments in which OHC function is disrupted or OHCs are destroyed, in the continued presence of functioning IHCs, there are hearing threshold shifts of 40–60 dB and a loss of fine-tuning of ANF responses (i.e. the sharpness of tuning, whereby an individual nerve fibre is especially sensitive to a specific or **characteristic frequency**).[108] Thus OHCs are critical for the exquisite frequency discrimination of which the cochlea is normally capable. These and other data have suggested the OHCs are the cellular basis of the 'cochlear amplifier'.[109, 110] A particularly unusual feature of OHCs is that they exhibit a unique form of motility. Isolated OHCs maintained in short-term culture undergo fast reversible axial length changes at up to auditory frequencies (at least 20 kHz) when stimulated electrically. It is thought that, *in vivo*, changes in OHC-membrane potential deriving from the normal MET mechanism drive the length changes.[43, 109, 110] Thus motion of the BM induces these motile responses, which are thought to feedback into the BM motion, thereby removing local damping and enhancing the movements. The end result of this cochlear amplification process is to fine-tune and amplify the signal before it reaches the IHCs, which as described do not sit on the flexible BM. Interestingly, as predicted by Thomas Gold in 1948[111, 112] and shown by David Kemp in 1978,[113] the excess energy released by this active process generates sound waves that are emitted from the ear as an **otoacoustic emission** (OAE).[114, 115] These OAEs can be recorded from probe microphones fitted in the external ear canal and they form the basis of the now routine audiological screening test for hearing impairment that can be performed in newborns or adults, and that provides an objective measure of the 'health' of the OHCs.[116–118] The fast motile responses of the OHCs, and the concomitant OAEs, are driven by a motor protein called **prestin,**[119] which is unique to OHCs and which is densely packed all down the lateral plasma membrane of the cell.[120, 121] Mutation or functional absence of the gene encoding prestin causes hearing impairment due to loss of cochlear amplification.[122]

The activity of OHCs upon stimulation is thought to generate a radial flow of endolymph across the surface of the organ of Corti which deflects IHC stereocilia and stimulates IHC responses. In essence, at lower sound pressure levels (below about 60 dB) OHC activity 'drives' IHC responses, but at higher sound pressure levels the larger movements of the organ of Corti produce fluid flow sufficient to deflect IHC stereocilia, and stimulation of the cell, directly.[109]

SUPPORTING CELLS

Several different morphologically recognizable types of supporting cell are present in the mature organ of Corti (Figure 47.3b,c). The **Deiters' cells** that intercalate between OHCs have cell bodies that contact with each other at their basal end and rest on the BM (Figures 47.4b,d,e and 47.7h). Each one forms a cup-shaped enclosure around the very base of an OHC and its nerve endings (Figure 47.7h, i). Deiters' cells extend a thin phalangeal process up through the space of Nuel (Figure 47.7h) so that the entire lateral membrane of each OHC is free from contact with another cell (Figures 47.4b and 47.7e). Contact between the OHC and its surrounding supporting cells is only at the apical junctional complex (Figure 47.7e,j) and at the basal cup around the base of hair cell (Figures 47.4b and 47.7e,h,i). The OHCs and IHCs are separated in the radial plane by the **outer and inner pillar cells** (Figure 47.4b) 'phalangeal cells' that are similar in general morphology to the Deiters' cells, the phalangeal processes of which form the **tunnel of Corti**, the outer pillar cell buttressing against the underside of the head of the inner pillar cell (Figures 47.4b and 47.7l).[123] Unlike OHCs, IHCs are closely surrounded by columnar supporting cells, the inner border cells to the medial side and the phalangeal cells to the lateral side, between the body of the IHC and the inner side of the inner pillar cell (Figures 47.4b,c and 47.7a). Lateral to the outermost (third) row of Deiters' cells are **Hensen's cells** (Figure 47.4b,c and 47.7o) which, in some species contain large lipid droplets that are thought, among other things, to provide additional mass. Additional epithelial cell types including the relatively unspecialized and uncharacterized **Claudius cells** that form the outer skirt of the organ of Corti ridge (Figure 47.4b,c and 47.7o), and lateral to these are the cuboidal epithelial cells of the outer sulcus that extend to the tissues on the lateral wall of the cochlea. In the basal cochlear coils, sitting on the basilar membrane and covered by the Claudius cells are a group of **Boettcher cells** (Figure 47.4c and 47.7p) that have a densely staining cytoplasm and multiple infoldings at their cell–cell interfaces. In most species these cells are absent from the apical coils. The function of these cells is still ill-defined but their morphology suggests some role in maintaining the physiological environment in the cochlea. There is also a suggestion they have a role in the maintenance of the BM.[124]

The Deiters' and pillar cells are thought to provide mechanical support to the organ of Corti that is essential for normal sound-evoked movements of the BM that lead to stimulation of the hair cells. They contain large numbers of microtubules in parallel arrays running from the base to apex of the cell (Figure 47.7k–n).[85, 123, 125] These arrays are some of the largest microtubule bundles in the entire body.[123] The microtubules are packed closely in regular arrays, filling almost the entire phalangeal process (Figure 47.7l,m); they would act like scaffolding poles or suspension struts to provide rigidity. The inner pillar cell lies on the thin bony lip, which extends from the bone covering the modiolus providing a rigid support (Figures 47.4b and 47.7n). The stiffness of the inner pillar cell, anchored on the rigid support provided by the bone and extending to the apical surface, will minimize movement of the reticular lamina on the medial, IHC side of the tunnel of Corti in response to sound-induced basilar motion thereby optimizing sensitivity to deflection of the IHC stereocilia by the fluid motion. In contrast, the rigidity of the outer pillar, anchored to the flexible region of the BM (Figure 47.4b), together with the rigid phalangeal processes of the Deiters' cells, could enable it to act as a stiff rod maximizing transfer of BM motion to movement of the reticular lamina; translation of that movement into the relative shear motion with the TM results in deflection of OHC stereocilia. In this way, pillar cells are crucial elements in the biomechanics that result in detection of sound. Any loss of supporting cell rigidity would, therefore, upset the mechanics by which stereociliary deflection is normally achieved, resulting in loss of hearing acuity. The microtubules of these supporting cells are composed of a form of tubulin that is resistant to depolymerization, which would indicate that the microtubules are long-lived structures,[125] but it has been suggested that changes in the tubulin isoforms may occur with ageing,[126] thereby impacting rigidity and function.

In addition, these cells are thought to play a crucial role in cochlear homeostasis. They take up K^+ from the extracellular spaces around the hair cells[127–129] and ferry it out of the sensory epithelium by an intracellular route through the intercellular coupling provided by the large gap junctions (Figure 47.7q).[48] Removal of K^+ from the spaces around the hair cell bodies is crucial, not only to prevent accumulation of K^+ that would disrupt ionic gradients and thus normal transduction, but also because high extracellular K^+ is toxic to the cells and OHCs are especially sensitive. Consistent with this model, mutations in the genes that encode the K^+-transporting proteins present in the membranes of the Deiters' cells, KCC4 and Kir4.1 (KCNJ10), cause hearing impairment and death of hair cells.[127, 130]

INNERVATION

The afferent ANFs that innervate the inner and outer hair cells arise from two distinct neuronal populations.[95, 96] The majority (90–95%) are myelinated **type 1 neurons** that innervate IHCs. The remaining 5–10% are unmyelinated, thin **type 2 neurons** that innervate OHCs. The cell bodies of both these types of neurons are collected together in the **spiral ganglion** (hence the designation 'spiral ganglion neurones' that is sometimes used) which is enclosed in Rosenthal's canal and located within the bony lip of the modiolar wall just medial and below the organ of Corti itself (Figure 47.2b). The central axonal projections of these bipolar neurons collect together in the modiolus (Figure 47.1c), the number of axons and the width of the nerve (and the modiolus itself) systematically increasing from apex down to the base of the cochlea as the centrally projecting axons from the cell bodies of neurones at successive locations are incorporated. The large bundle of neurons exits the inner ear via the internal auditory meatus as the VIIIth cranial nerve. The peripheral neurites from the cell bodies access the sensory epithelium through a series of holes, the **habenula perforata**, through the thin bone that separates the organ of Corti

from the ganglion and over which the IHCs are located (Figure 47.2b). The type 1 neurons lose their myelination as they reach the habenula, and so are unmyelinated in the organ of Corti as they project directly to the base of the IHCs. The peripheral neurites of the type 2 cells, after crossing through the habenula, turn to run between the bodies of the inner pillar across the floor of the tunnel of Corti, then between the bodies of the outer pillar cells into the region of OHCs. Here they branch, each one sending projections between the Deiters cell bodies to an average of nine (though sometimes many more) OHCs, their terminals mostly synapsing at the very base of the cell.

The innervating efferent neurons have their cell bodies in the mid-brain regions from which they project. The peripheral axons of these neurons also enter the organ of Corti through the habenula perforata. Those projecting from the contralateral medial superior olive in the brain that innervate the OHCs contribute about 80% of the total efferent innervation of the organ of Corti.[95, 96] They pass between the phalangeal processes of adjacent inner pillar cells, cross the tunnel of Corti at a level about the middle of its height, and then pass between phalangeal processes of the outer pillar cells into the OHC region where each individual nerve branches, sending projections to OHCs in each of the three rows. Axons of the efferent nerves arising from the ipsilateral medial superior olive, after passing through the habenula perforata, project directly to the region of the IHCs, branch and form terminals that synapse with the terminals of the type 1 afferent neurons beneath the IHCs.

Ion-transporting epithelia

The **stria vascularis** (SV) is a strip of tissue 150–300 µm wide (depending on location and species) lining the lateral wall of the scala media and running along its entire length (Figures 47.1a and 47.2b). It is responsible for the production and maintenance of both the high endolymphatic K^+ concentration and the EP.[1] The SV encloses a complex capillary network and is composed of three cell types (Figure 47.8b):

- **marginal cells** that line the endolymphatic compartment
- **intermediate cells** in a discontinuous layer enclosed entirely within the body of the epithelium
- **basal cells** that separate the SV from the underlying spiral ligament.

The SV is reputed to have the highest rate of oxidative metabolism (i.e. where oxygen is used to generate energy from carbohydrates) in the entire body, most likely due to the huge energy demand resulting from the mass of active ion transport that takes place in this tissue. The EP provides a source of energy or 'battery' to drive the cochlear amplifier.[131] As would be expected, any loss of EP therefore results in significant hearing impairment.

MARGINAL CELLS

The marginal cells of the SV are primarily involved with the transport of K^+ and are essentially the same as the dark cells of the vestibular system. Their basolateral membranes are extensively infolded, enclosing numerous large mitochondria and they contain high levels of Na^+/K^+-ATPase, both α- and β-isoforms[67, 132] and the $Na^+/K^+/Cl^-$-cotransporter NKCC1 (SLC12A2).[68] NKCC1 is the therapeutic target of action for loop diuretics in the kidney and loop diuretics have rapid, acute ototoxic side effects through an action on the cotransporter in the strial marginal cells[133, 134] inhibiting ion transport, which results in accumulation of ions in the extracellular spaces of the stria and a consequent oedema. The apical membranes of the marginal cells (like the dark cells) contain a K^+ channel which is formed of two subunits, the KCNE1 regulatory protein and the KCNQ1 channel proteins[130, 135] that provide the pathway through which K^+ is secreted into endolymph.[69] Mutations in the *KCNE1* gene disrupt endolymph production, leading to collapse of Reissner's membrane and deafness. In the vestibular system they cause collapse of the epithelia of the roof of the utricle, saccule and ampullae and shaker/waltzer-type behaviours in mice, indicating dysfunction of the vestibular sensory organs.[130, 135] During development, high levels of K^+ are found in cochlear endolymph, and strial marginal cells show high Na^+/K^+ ATPase activity, before an EP can be recorded.[136, 137] These, and other physiological data,[1] indicate that strial marginal cells, like dark cells, are primarily concerned with active transport to maintain the endolymphatic K^+ concentration, but the generation of EP is a separate phenomenon. The absence of any other cell type from the ion-transporting tissue of the vestibular system suggests that the strial intermediate and basal cells play a role in EP generation. During cochlear development the onset and rise in EP coincide with the incorporation of intermediate cells and blood vessels into the body of the stria and the formation of the limiting basal cell layer.[138]

INTERMEDIATE CELLS

The intermediate cells are a type of melanocyte – melanin pigment-containing cells – that arise during development from cells that migrate from the neural crest. They are entirely enclosed within the corpus of the stria, interdigitating with the other two cell types (Figure 47.8b). They contain a variety of enzymes that enable energy production from alternative substrates such as lipids as well as enzymes that detoxify oxidative wastes.[139] In addition, melanin can act as a free radical scavenger. These cellular properties suggest that one role for intermediate cells is to protect the stria under conditions of stress and perhaps also to provide alternative energy sources to maintain activity during periods of reduced blood supply. A population of intermediate cells also sends thin processes to contact the capillaries and express a number of proteins that are found in macrophages, further indicating the role of these cells in protecting the stria from damage. These cells have been termed perivascular macrophage-type melanocytes.[140]

The crucial role of intermediate cells, however, is in the generation and maintenance of EP. In the *viable dominant spotting* mouse mutant, there is a neural crest defect resulting in a highly reduced number or absence of intermediate

cells and no EP is generated,[141] but other than the absence of intermediate cells, the stria appears normal and the marginal cells possess ATPase activity.[132] In wild-type mice, measurement of EP from electrodes inserted into the lateral wall of the cochlea, which pass first through the spiral ligament and then into SV, has shown that under normal conditions a high positive potential is present within the body of SV, i.e. before the electrode actually penetrates into the endolymphatic space, locating the site of EP generation at the intercellular spaces of SV.[142] The intermediate cells are characterized by very high levels of the K^+ transporter protein Kir4.1 in their plasma membranes facing the intercellular spaces and the basolateral infoldings of the marginal cells.[143] Thus EP is considered to be generated by rapid and extensive passage of K^+ via Kir4.1 across the intermediate cell membrane into the intercellular space, followed by immediate uptake of K^+ by marginal cells such that a high positive potential is generated in that space. The basal cell layer provides an insulating seal that prevents dissipation of the potential into the perilymph in the intercellular spaces of the spiral ligament.

BASAL CELLS

The basal cells are flattened and elongated, forming between one and three layers delimiting the basal aspect of SV (**Figure 47.8b**). They arise during development from the mesenchymal cells that also form the spiral ligament. Basal cells closely appose each other and there is extensive sealing of the intercellular spaces between them by tight junctions.[137, 144] This creates an impermeable barrier between the perilymph in the underlying spiral ligament and the body of SV. During development, the initial formation of these tight junctions and the increase in their complexity coincides with onset of EP,[137] suggesting that these junctions are necessary to provide the electrical insulation required for the potential difference to be generated and maintained within the body of SV. Mutations in the gene for the protein claudin 11, which is present in the basal cell tight junctions, cause the loss of EP and so hearing impairment.[145]

Large numbers of gap junctions are also associated with basal cells (**Figure 47.8c**).[46, 144] They are present between adjacent basal cells, between basal and intermediate cells and between basal cells and fibrocytes in the spiral ligament.[46, 144] Thus, basal cells appear to be the central element in a functionally coupled unit or **syncytium**, connected together by intercellular gap junctions, consisting of basal cells, intermediate cells and spiral ligament fibrocytes. Marginal cells are excluded from this syncytium; they do not form gap junctions either with each other or with either basal or intermediate cells[46, 144] and are thus separated, functionally, from each other and from the basal cell/intermediate cell/ligament fibrocyte syncytium.

The gap junction-mediated intercellular communication between basal cells and ligament fibrocytes can provide a pathway for access of ions into SV cells from the ligament that bypasses the tight junctional sealing.[48] Fibrocytes of the spiral ligament possess Na^+/K^+-ATPase activity[67] and thus probably function to take up K^+ from the perilymph in the intercellular spaces of the ligament. The gap junctions between fibrocytes would, therefore, provide an intracellular route for K^+ to those fibrocytes beneath the SV, which are coupled to strial basal cells and which in turn are coupled by gap junctions to the intermediate cells. This gap junctional system, therefore, provides a route for recycling K^+ from endolymph, through hair cells to perilymph in the spaces in the organ of Corti and into supporting cells; out to the intercellular spaces of the spiral ligament and into fibrocytes; then into strial basal cells; into intermediate cells out to the intrastrial spaces and back to endolymph via the marginal cells.[48] The intercellular communication provided by gap junctions may, therefore, be vitally important for the maintenance of EP. During development, the onset and subsequent rise in EP corresponds not only with the formation of the permeability barriers that isolate the SV from the surrounding tissues but also with the initial formation and subsequent increase in size and number of gap junctions associated with basal cells.[137] The gap junctions in the cochlear lateral wall – the SV and spiral ligament – in rodents are all composed of both Cx26 and Cx30,[46, 146] but only functional disruption of Cx30 is associated with loss of EP.[147]

CAPILLARIES

The functional isolation of the SV from the surrounding tissues created by the permeability barriers at the level of the basal cells means there is little or no access of oxygen and nutrients required for the active processes necessary for EP maintenance. These are supplied by the network of intrastrial capillaries that run predominantly longitudinally along the SV (i.e. in an apicobasal direction along the cochlea, so that they are cross-sectioned in sections cut parallel to the modiolus in **Figure 47.8b**) with short interconnecting branches running across the strial thickness. The capillaries are often closely surrounded by extended processes from marginal cells. While allowing passage of oxygen and essential nutrients, the walls of the capillaries form a 'blood labyrinth barrier'[140] that controls exchange between the intrastrial spaces and the blood supply. The capillaries are supplied from branches of the cochlear artery that run from the modiolus through the connective tissue over the roof of the scala vestibuli and further branch into the spiral ligament and SV where the network of capillaries forms. They drain through capillaries that run in the connective tissue beneath the scala tympani to the cochlear vein in the modiolus. The strial capillaries are unfenestrated and the junctions between the endothelial cells that surround the lumen are connected by tight (occluding) junctions that establish a tight seal between the vessel lumen and the intrastrial space.[140] This tight sealing of the capillary lumen from the body of the stria in addition to the tight junctions between marginal cells and the extensive tight junctional sealing between basal cells are crucial to the functional isolation of stria from the surrounding tissues that prevents dissipation of EP as it is generated.

The endothelial cells are surrounded by a basement membrane. Pericytes discontinuously cover the basement membrane extending long, thin processes along the capillary wall. Where these cells are present the basement

membrane thickens to cover them. It has been suggested that macrophage-like melanocytes (the intermediate cell subpopulation), pericytes, BM and endocytes act as a complex to monitor and regulate exchange between the intrastrial spaces and the vessel lumen and maintain the blood-labyrinth barrier.[140] There is increasing evidence that ageing, noise and some genetic mutations may cause disruption of the barrier, leading to dysfunction of the stria, loss of EP and hearing impairment, but further work in this area is needed.

Reissner's membrane

Reissner's membrane is a thin epithelial sheet formed of two cell layers (**Figure 47.2b**).[148–150] A continuous layer of epithelial cells lines the scala media side and, since their apical surfaces face endolymph, they have tight junctions sealing the spaces between adjacent cells. The basal side of the epithelium, in the scala vestibuli, is covered with mesenchymal cells that are bathed in perilymph. The primary role of Reissner's membrane, to maintain the electrical and chemical separation of endolymph and perilymph, is achieved at the level of the tight junctions between the epithelial cells. There is also some evidence that the epithelial cells may have a phagocytic function taking up and then breaking down cell debris released into the endolymphatic compartment. Reissner's membrane also appears to have some elasticity as it can accommodate by swelling outwards into the scala vestibuli quite large increases in endolymph volume – endolymphatic hydrops – such as occurs with ion imbalance that results in water influx into the scala media, before it ruptures (as in Ménière's syndrome).[151, 152] How this is achieved, and whether Reissner's membrane has additional roles, remains to be determined.

FUTURE RESEARCH

- Molecular characterization of the transduction channel and its accessory components.
- Proteostasis (turnover, breakdown and re-synthesis) of hair cell proteins in particular stereociliary components.
- Effects of ageing and stress on tissues, cells and accessory structures other than hair cells, e.g. supporting cells and their microtubule bundles, the tectorial membrane, cells of stria vascularis.
- Detailed structural analysis and determination of the functional and permeability properties of Reissner's membrane and its potential role in clearing debris when cochlear tissues are damaged.
- Understanding of the roles of various glial and glial-like cells in the cochlea.
- The structure and permeability properties of the round-window membrane in relation to delivery of therapeutics to the inner ear fluids.

KEY POINTS

- The cochlea and the vestibular system contain sensory epithelia and ion-transporting epithelia.
- The sensory epithelium of the cochlea is the organ of Corti, a strip of cells coiled in a spiral.
- There are five sensory epithelia in the vestibular system: the utricular macula, saccular macular and 3 cristae, one in each of the three semi-circular canals.
- Sensory epithelia consist of sensory cells – 'hair' cells – and supporting cells, each hair cell separated from its neighbour by intervening supporting cells.
- Hair cells derive their name from the organised bundle of hair-like projections from their apical surface.
- The hair bundle is formed of stereocilia organised in rows of increasing height across the apical surface of the hair cell defining both a morphological and functional polarity.
- In vestibular hair cells, a single true cilium – the kinocilium – is positioned behind the row of longest stereocilia.
- In mature cochlear hair cells there is no kinoclium; the kinoclium is present during cochlear hair cell-development but retracts as the hair cell matures to leave only the basal body.
- There are crosslinks of various types between stereocilia in an individual hair bundle.
- Lateral cross-links produce a cohesive unit of stereocilia in the hair bundle.
- Tip-links are found between the tip of a shorter stereocilium and the adjacent longer stereocilium in the line of functional polarity; these gate the transduction channel at the tip of the shorter stereocilium.
- Each sensory epithelium is overlaid by an acellular extracellular matrix, that provides direct input for the deflection of the stereocilia that stimulates the hair cell.
- There are two types of hair cell in the organ of Corti: inner hair cells and outer hair cells.
- Inner hair cells are the primary receptor cells innervated by 95% of the cochlear afferent nerves that take information to the brain.
- Outer hair cells respond actively to basilar membrane motion to amplify the micromechanics and thus the signal reaching the inner hair cell.
- The cochlea is 'tonotopically' organised; different frequencies are detected at systematically different places along the basilar membrane: high frequencies at the basal end and low frequencies at the apical end.
- There are systematic changes in the basilar membrane and organ of Corti dimensions in line with the systematic tonotopic variation.
- There are two types of hair cell in vestibular sensory epithelia: type 1 hair cells and type 2 hair cells.
- Type 1 hair cells are innervated by a single afferent 'calyceal' nerve ending that enclose the entire baso-lateral surface of the hair cell.
- Type 2 hair cells that are innervated by several afferent nerve bouton endings.
- The stria vascularis is the ion-transporting epithelium of the cochlea.

- The stria vascularis is formed of three cell types and is highly vascularized; it is physiologically and electrically isolated from the rest of the cochlea.
- The stria vascularis generates and maintains the high positive electrical potential of cochlear endolymph – the endocochlear potential – as well as the high potassium ion composition characteristic of endolymphatic fluid.
- The ion-transporting epithelium of the vestibular system is the dark-cell region at the base of each crista and around the utricular macula; there is no dark cell region in the saccule.
- The dark-cell region is a single layer of ion-transporting epithelial cells responsible for maintaining potassium levels in vestibular endolymph, but it is not electrically isolated from the rest of the inner ear tissue, and there is no equivalent of endocochlear potential in the vestibular system.

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CHAPTER 48

PHYSIOLOGY OF HEARING

Soumit Dasgupta and Michael Maslin

SEARCH STRATEGY

The data may be updated by a PubMed search using the keywords for 'Fundamentals of sound': soundwaves, measuring sound, decibel scales and acoustic impedance. For 'Applied physiology of Hearing', use the following keywords: pinna, external auditory canal, ossicles, tympanic membrane, cochlea, outer hair cells, inner hair cells, auditory nerve and cochlear efferents.

INTRODUCTION

This chapter consists of two parts. The first (Fundamentals of Sound) will discuss properties of sound and important concepts related to hearing; the second part (Applied Physiology of Hearing) will discuss the applied physiology of the peripheral ear correlated to normal functioning of the ear from the hearing point of view and the aftermath of an affliction by a disease.

FUNDAMENTALS OF SOUND

Michael Maslin

A SOUND WAVE

For something to be a source of sound it must vibrate. Sound is vibratory energy that is transmitted from the source through surrounding media in the form of pressure waves. Sound waves cannot therefore travel through a vacuum; a physical medium is required to convey the vibratory energy. In the context of otolaryngology, the most relevant physical medium is air since most sounds reach the ear by the vibrations of air molecules. Vibratory energy that arrives at, and is detected by, the ear gives rise to hearing. Hence, some understanding of the physical properties of sound is required in order to understand the way in which sound is detected by the ear.

As a starting point one might consider a scenario whereby no force is applied to a region of air. In such a scenario, the air molecules are said to be at ambient (or atmospheric) pressure. When an object in the region vibrates, a force is applied to those air molecules that are in contact with the object, causing their displacement. For example, take the loudspeaker shown in Figure 48.1. As the diaphragm of the loudspeaker moves to the right of its centre position, the air molecules at the surface of the diaphragm are displaced to the right. This movement causes the air molecules to be pushed closer to adjacent air molecules that are further over to the right. Relative to the ambient pressure, a localized pressure increase is produced and this pressure increase is known as compression. Next, when the diaphragm of the loudspeaker moves back through its centre position and over to the left, those air molecules that were displaced to the right are now drawn to the left. When the displaced molecules reach their centre (equilibrium) position, the pressure will momentarily be equal to ambient pressure, but as the molecules move further to the left they are drawn increasingly further apart from their adjacent air molecules. The pressure will now drop below the ambient pressure and this decrease in pressure is called rarefaction. As each molecule vibrates

backwards and forwards around its equilibrium position, alternating regions of compression and rarefaction arise. If these pressure variations can be detected by the ear, they can be described as sound. (It is worth noting that the variations in density of the air molecules shown in Figure 48.1 have been exaggerated for the purposes of illustration. In reality, pressure fluctuations associated with sound are only a small fraction of the overall atmospheric pressure.) Since air is a continuous and elastic medium, the pressure variations will propagate away from the source such that sound generated by the source can be detected in regions of air that are remote. This is known as acoustic radiation.

The air molecules move about their equilibrium position, so there is no permanent displacement of the air. Rather, it is the vibratory pattern (i.e. mechanical disturbance) that is transmitted. Since the air molecules move in the same axis as the sound wave, it is known as a longitudinal wave.

There are two key properties of a sound wave:

- the frequency of the sound wave, which is linked to the perception of pitch
- the intensity of the sound wave, which is linked to the perception of loudness.

Frequency, velocity, period and wavelength of sound

As the air molecules vibrate about the equilibrium, their velocity is greatest as they pass through the equilibrium position and is momentarily zero when at the extreme displacement (where direction of movement reverses). The movement of air molecules from equilibrium to maximum displacement in one direction, back through equilibrium to the maximum displacement in the opposite direction, and back to equilibrium, is one complete cycle of vibration. Frequency (f) is the number of cycles per second (usually expressed in Hertz (Hz) (named in honour of the German physicist Heinrich Rudolf Hertz). The simplest type of sound wave is a sinusoidal (or sine) wave, where the cycles of vibration occur at a single frequency. A concept related to frequency is the period (T), the time required for a vibration to complete one cycle. The higher the frequency, the less time it takes a vibration to complete one cycle. Hence, frequency and period have an inverse relationship which can be expressed as follows:

$$T = 1/f \text{ or } f = 1/T$$

Please note that while the velocity of the displacement of the air molecules relates to the frequency of the sound, there is also the velocity of the sound wave to consider, as it progresses away from the source (i.e. the speed of sound, c). This is not an absolute value. Sound travels more quickly in warm air than in cooler air. Therefore as temperature drops with altitude or in colder climates the speed of sound becomes lower. The velocity of sound waves radiating from a source at sea level is about 344 metres per second (ms^{-1}). Furthermore, at least in air, the velocity is the same irrespective of the frequency of vibrations. The velocity of a sound wave and the frequency of that wave are related by wavelength (λ), which is the distance between corresponding points of displacement in successive cycles (see Figure 48.1). We therefore have four quantities that are related to one another: the frequency, the period, the velocity and the length of a sound wave. The relationship between these quantities is described in the following equations:

$$\text{Wavelength} = \text{velocity} \times \text{period}$$

$$\text{Velocity} = \text{frequency} \times \text{wavelength}$$

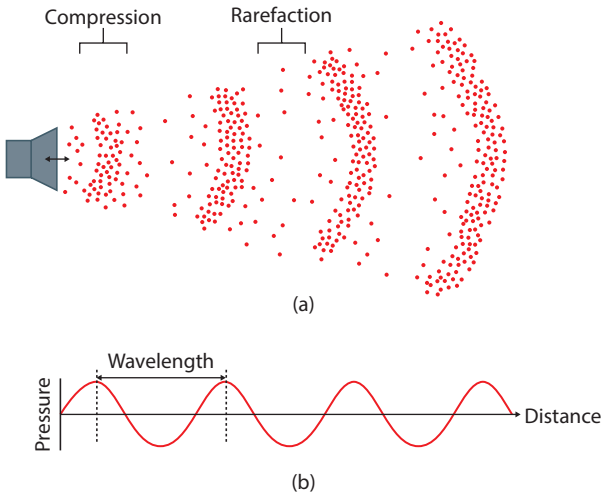

Figure 48.1 **(a)** A schematic of a sound wave propagating away from source via alternating regions of compression and rarefaction of (air) molecules. **(b)** The (air) pressure variations plotted as a function of distance. This example shows pressure varying at a single frequency, to produce a sinusoidal waveform. The distance between two consecutive points on the waveform is the wavelength.

Pressure, impedance, particle velocity and intensity of sound

As we have discussed, as a sound wave radiates from a source, the air pressure fluctuates in cycles of compression and rarefaction as air molecules are displaced about their equilibrium. Let us consider a 'plane progressive' sound wave, i.e. a sound wave with an advancing wavefront that is treated essentially as a flat surface, as it moves unperturbed through a sound field. (In reality a progressive wavefront is almost spherical as it expands from a point source, but at the point of measurement, which might be some distance away, the wavefront will appear flat. Furthermore, there are often objects in a sound field that produce reflections, all of which means that peak pressure and velocity do not necessarily coincide in reality.) The pressure variations about the ambient pressure that occur are directly proportional to the velocity of the particles as they vibrate. That is, the greater the peak particle velocity, the greater the peak pressure of the sound wave. Pressure and particle velocity are therefore said to be in

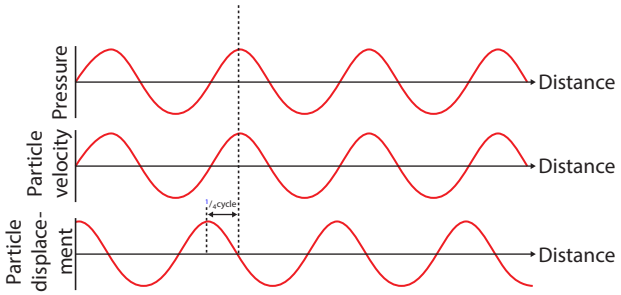

Figure 48.2 The relationship between pressure, velocity and particle displacement. **(a)** Pressure variations plotted as a function of distance. **(b)** Particle velocity plotted as a function of distance. Note that (air) pressure and (air molecule) particle velocity vary in phase with one another. **(c)** Particle displacement plotted as a function of distance, showing a 90° phase lag in relation to particle velocity and pressure variation.

phase, as illustrated by the upper and middle traces shown in Figure 48.2. However, while peak particle velocity and peak pressure are in phase, the displacement of the air molecules shows a one-quarter cycle, or 90-degree, phase lag, illustrated in the lower trace in Figure 48.2.

Phase relates to the temporal relationship between two (or more) oscillatory components that are present simultaneously. In this case, pressure, particle velocity and displacement. One cycle is defined as 360 degrees. If the two components vary together over the cycle, there is no timing difference between then, and they are said to be in phase. However, the second component can lead or lag the first according to its starting point relative to the first, i.e. there is a timing difference. The actual timing difference for a given phase lead or phase lag will depend on the frequencies of the two components, with higher frequencies producing shorter timing differences.

As air molecules become compressed, we also have to consider acoustic impedance, or more specifically characteristic impedance ($\rho_o c$) when referring to a plane progressive wave. The concept of impedance may be illustrated by drawing analogy to electrical circuits, where impedance behaves rather like the resistance to electricity in a circuit. It acts to dissipate energy and so if the sound wave is to radiate out from the source then it must overcome the acoustic impedance of the medium. Impedance depends on the stiffness and density of the medium (in this case air), and so the acoustic impedance at a particular frequency will contribute to defining how much sound pressure is generated by a sound wave. The greater the impedance of air molecules at a given displacement velocity, the lower the sound pressure level. Peak pressure can be related to peak velocity and characteristic impedance (which is independent of frequency), according to the equation:

$$\text{Peak pressure} = \text{characteristic impedance} \times \text{peak velocity}$$

Impedance varies greatly according to the media, especially between gases and liquids. Liquids, being much denser than gases, have a higher acoustic impedance. Therefore, they will convey sounds with much lower intensities for a given pressure variation than if that pressure variation were to occur in a gas.

To continue the analogy drawn with circuits of electrical current, where sound pressure is analogous to voltage (volts) and acoustic impedance is analogous to resistance (ohms), particle velocity is analogous to current (amps), but there is a further component still to consider: power.

The energy of sound and how this is transferred (dissipated) is referred to as the intensity of sound and, in electrical circuitry, this is analogous to power (measured in watts). The more energy that is supplied by the source, the greater the intensity of the sound. Since pressure variation is the means by which sound energy is transmitted, and pressure is force per unit area, then intensity is the power transmitted by the wave through a unit area (watt/metre^2). For a sinusoid, the relationship between intensity, pressure and particle velocity and impedance is expressed using these equations:

$$\text{Intensity} = \frac{\text{Peak pressure}^2}{2 \times \text{impedance}}$$

$$\text{Intensity} = \frac{\text{Peak velocity}^2 \times \text{impedance}}{2}$$

At this point the importance of root mean square (RMS) values becomes apparent. The equations that are shown above relate to the **peak** pressure and **peak** velocity, yet pressure and velocity are continually varying throughout the cycle of vibration hence the intensity of sound will vary throughout the cycle. A solution is therefore to consider the average intensity (kinetic energy) across a complete cycle of vibration. Simple averaging will not suffice, since the mean values will be zero (see Figure 48.3).

One solution is to consider the distance between the most positive peak and the most negative points in the cycle. Alternatively, the square root of the average squared value for pressure (known as RMS pressure and expressed in Pascals or Nm^{-2}) and velocity (known as RMS velocity or ms^{-1}) are perhaps the most common way to overcome this challenge. The equation can now be read as:

$$\text{Average intensity} = \frac{\text{RMS pressure}^2}{2 \times \text{impedance}}$$

$$\text{Average intensity} = \text{RMS velocity}^2 \times \text{impedance}$$

It is also important to note that sound waves spread in all directions, and as the wavefront moves away from the source it spreads over a larger area. Sound intensity

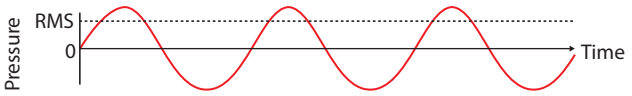

Figure 48.3 A sinusoidal wave. When measuring sound, the time-varying pressure variations would average to zero, which is not representative of the peak pressure. Root mean square (RMS) can be used instead, where RMS pressure = $\frac{1}{\sqrt{2}}$ = ≈ 0.7 of the peak pressure.

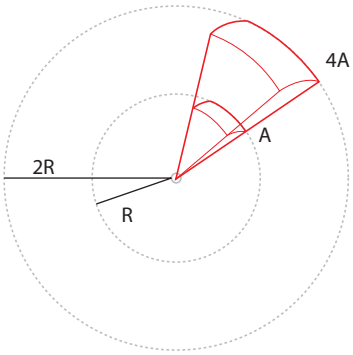

Figure 48.4 Schematic of a point source of sound. Sound waves would spread equally in all directions to produce a spherical wavefront. Due to the expanding area of the wavefront with distance from the source, the energy of the wavefront will progressively attenuate with distance. Sound is attenuated by distance from the source and the amount by which this occurs is given by the inverse square law; intensity falls as the inverse square of the distance. Other factors that influence attenuation with distance in real-world scenarios include, for example, reflections from, and interactions with, obstructions in the sound field, interactions with other sound waves, heat dissipation and net flow of air (wind).

decreases with distance from the source. The total area increases with the square of the distance, so intensity falls as the inverse square of the distance. This relationship is known as the inverse square law, as depicted in Figure 48.4 for a point source of sound in a free field, i.e. with no objects reflecting or blocking the path of the sound.

PERCEPTUAL CORRELATES OF FREQUENCY AND INTENSITY

The two key properties of a sine wave, frequency and intensity, each have a perceptual correlate. The subjective correlate of frequency is pitch and of intensity, loudness.

The bandwidth of human hearing (at least for a young person with normal hearing) is typically from around 0.02–20 kHz. Vibrations of around 20 times per second correspond to a low pitch whereas vibrations of 20 000 times per second correspond to a much higher pitch. Each time the frequency of a sine wave is doubled, the pitch increases by an octave, so human hearing spans around 10 octaves. A sound which has one frequency is known as a 'pure tone' although, in reality, typical sounds are made up from many frequencies and are therefore complex sounds.

As intensity increases above the threshold of hearing, a sound becomes louder. For a 1 kHz sine wave, a young and normal-hearing human listener can detect pressure fluctuations in the air from as little as 0.00002 Pa (the quietest sounds) and increases in pressure become progressively louder to the listener up to as much as 200 Pa (where the threshold of pain is approached). Hence the relationship between the softest audible pressure variation and the maximum tolerable one (known as the dynamic range) is around one million times.

It is important to note that perceived loudness is in fact dependent on both frequency and intensity. The ear is less sensitive to very low frequencies and very high frequencies, and maximally sensitive to frequencies around the 2–4 kHz range. Typically, pure-tone audiometry, as performed in the test battery for diagnosing hearing loss, covers the frequency range 0.25–8 kHz (five octaves) that is most clinically relevant since this corresponds to the frequency range where normal speech occurs. The intensity of pure tones used in pure-tone audiometry is normalized according to the different sensitivities of the ear as a function of frequency in order to plot a pure-tone audiogram. More on this will be described below.

THE INFLUENCE OF A SOUND'S DURATION

In addition to frequency and intensity, a third dimension of sound is its duration. The duration of a sound interacts with frequency and intensity to influence pitch and loudness sensations. For example, a sound must exceed a certain minimum duration before its pitch characteristics become apparent. Below this point, about 200 ms, and the sound will have a click-like sensation regardless of its duration. Similarly, loudness increases as a function of intensity over time, a phenomenon known as temporal integration. Below durations of about 200 ms the sound intensity will need to increase progressively in order to maintain the same sensation of loudness. Therefore, audibility reduces as sounds become briefer below 200 ms (although the perception of duration does not). Paradoxically, despite this reduction in audibility with sound duration, sounds with extremely short duration can become more audible again, at least when close to threshold. We can think of pure-tone sounds used in hearing tests as being comprised of three segments: an onset period when the intensity increases (also known as the rise time), an offset period where the intensity reduces again (also known as the fall time) and between these two extremes there may be a steady period where the sound intensity is maintained. Imagine the steady-state period getting shorter, so that the volume of the pure tone is reducing as the overall duration drops below 200 ms. Eventually, there would be no steady-state period, and so the intensity of the sound would ramp up and immediately down again. Now the only way to make the sound shorter is to reduce the duration of the onset and offset periods themselves. As the onset and offset periods get shorter, the frequency spectrum of the sound becomes progressively broader (the so-called 'spectral splatter'); sound duration and bandwidth are inversely proportional. It is these additional frequencies that may be heard, causing the paradoxical increase in audibility for very short duration signals. Clinically, this is especially relevant in audiological applications where short duration signals are required, such as auditory evoked potential testing. Here, the need for brief stimuli such as a transient click, producing a more synchronous discharge of neural energy (and greater signal strength), must be weighed against the need for frequency-specific analysis of hearing sensitivity (i.e. minimizing spectral splatter) in order to diagnose hearing loss accurately where hearing at some

frequencies is different from others. However, it is also relevant with regards to understanding the way in which normal everyday sounds such as speech, not just audiological test sounds, are heard.

MEASUREMENT OF SOUND

The three dimensions of sound that we have encountered so far (frequency, intensity and duration) can each be described according to principles that have parallels with the way in which sound is detected and processed by the ear (the mechanisms of which will be described in detail later in the chapter). The amplitude of a sound (either in terms of the intensity or resulting pressure fluctuations) can be described by the decibel scale, and the frequency composition of a sound can be shown by spectral analysis of the signal. The influence upon both of these quantities by the duration of the signal will also be described.

The decibel scale

As described, when the energy of a sound wave increases, the pressure fluctuations become greater. A common way to describe the average variation of these quantities is by referring to an increase in the amplitude of the sound.

Given the dynamic range of hearing described above, if sound was routinely described in Pascals (using the most common and practical way to measure sound by observing the electrical output of a pressure-sensitive device or transducer), calculations for the amplitude of sound would soon become cumbersome and unmanageable. To overcome this, a compressed scale which produces a more manageable range of values for describing amplitude is used: the decibel scale. The basic unit of measurement is the bel, named in honour of Alexander Graham Bell, inventor of the telephone. Even this is somewhat large for convenience and so the decibel (dB), one-tenth of a bel, is typically used. Compression of a large-scale dynamic range (either intensity or pressure) to the decibel scale is achieved by finding the logarithm (to the base 10). Importantly, the decibel is not an absolute unit of measurement. It is a ratio. This means that the bel is the logarithm of intensity of sound divided by some agreed reference intensity. Zero dB therefore simply indicates that the measured sound is the same as the reference; it doesn't mean silence. A negative dB value means that the measured sound is less than the reference, and a positive dB value means that the measured sound is greater than the reference. Multiplying the bel by 10 produces the decibel such that a sound's intensity in dB can be calculated using the following equation:

$$\mathrm{dB} = 10\,\mathrm{Log}_{10}\frac{\mathrm{Intensity}_{\mathrm{measured}}}{\mathrm{Intensity}_{\mathrm{reference}}}$$

Sound pressure as measured in Pascals can also be expressed in decibels. This is the logarithm to the base 10 of a measured pressure relative to some agreed reference pressure, multiplied by 20 (to reflect the fact that intensity is related to the square of the pressure). A value very close to the threshold of human hearing for a 1 kHz pure tone at sea level (0.00002 Pa) commonly serves as such a reference pressure, and in this case the scale is referred to as decibel sound pressure level (dB SPL) according to the following equation:

$$\mathrm{dB\,SPL} = 20\,\mathrm{Log}_{10}\frac{\mathrm{Pressure}_{\mathrm{measured}}}{\mathrm{Pressure}_{\mathrm{reference}}}$$

The dB SPL scale is convenient because 0 db SPL is close to the threshold of hearing. The threshold of pain, near the top of the dynamic range of hearing, is 140 dB SPL, i.e. when the pressure in Pascals is multiplied by 10, 20 dB is added to the dB level.

Note that, in addition to convenience of calculation, a second advantage of using a logarithmic scale is that the response of the ear is also logarithmic. This means that loudness is not spaced linearly across the dynamic range, so linear increments in the amplitude of sound do not produce even increments of loudness (e.g. 100 Pa is almost as loud as 200 Pa). However, logarithmic increments in amplitude do produce even increments of loudness; a 1 dB change in amplitude (approximately the minimum detectable change) gives almost the same relative change in loudness across the whole dynamic range.

An important consideration when discussing the relationship between the amplitude and loudness of sound is that the ear is not equally sensitive to sounds of different frequencies, as mentioned earlier. Further complications are that the difference in sensitivity to sounds across frequencies is more pronounced closer to threshold, and less at high SPLs well above threshold. Loudness is also strongly affected by the duration of sounds. That is, sounds of short duration (below approximately 200 ms) will sound less loud than a sound of longer duration with the same sound pressure level. (For further information on the interaction between acoustics and perception, please refer to Moore.[1]) Consequently, this means that, while 0 dB SPL is (close to) the threshold of hearing for a 1 kHz pure tone, the same is not the case for pure tones of other frequencies. Bear in mind also that 'threshold', the quietest sound one can hear, is variable and depends on the way it is defined, the method of measurement and psychological factors such as attention and motivation.

Figure 48.5 shows the threshold, in dB SPL, for a range of pure tones of different frequencies as measured under

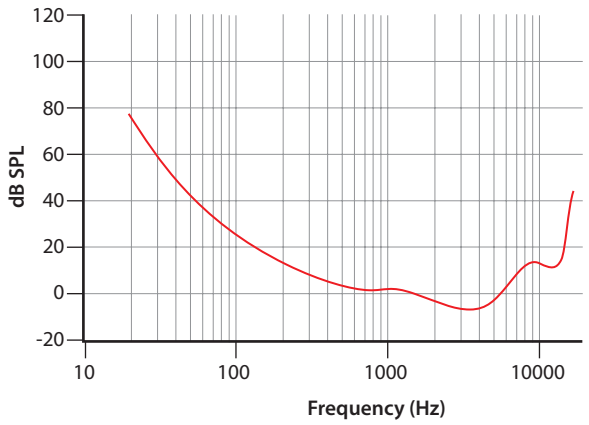

Figure 48.5 Reference threshold of hearing, in dB SPL, based on a group of ontological normal, young adults in binaural listening conditions (ISO 389-7[2]).

binaural free-field listening conditions (ISO 389-7).[2] Hearing sensitivity declines at very low and very high frequencies, and it is not the same even within the central frequencies that comprise the audiometric range. For clinical purposes these differences in hearing sensitivity according to sound frequency present some complications when describing the extent of hearing loss; the same degree of hearing loss across different frequencies produces a different threshold in dB SPL. For example, an individual whose hearing threshold was 40 dB worse than the average threshold at 1 kHz would have a hearing threshold slightly higher than 40 dB SPL. However, if the same individual had a 40 dB reduction in hearing sensitivity at 4 kHz, their hearing threshold would be around 35 dB SPL.

To bypass this complication, audiology uses different reference sound pressures. Perhaps the most important among these is for pure tones in which the reference is the threshold of hearing for normal listeners; this is the decibel hearing level (dB HL). The reference sound pressures for pure tones therefore change in a frequency-specific way to allow a convenient comparison of an individual's hearing thresholds compared to normal, i.e. the amount of hearing loss. The resulting audiogram (see **Figure 48.6**) shows normal hearing (0 dB HL) towards the top of the chart whereas increasing amounts of hearing loss are plotted downwards. For an interesting historical account of the why the audiogram is upside down, the reader is referred to Jerger.[3]

There are other decibel scales used in audiology such as Sensation Level (dB SL), which uses the individual's own threshold of hearing as the reference. For example, a 1 kHz sound presented at 50 dB HL to a patient with a threshold of 10 dB HL would be 40 dB SL. However, to a patient with a threshold of 20 dB HL the same sound would be 30 dB SL. Presentation at the same sensation level may therefore produce different intensities of sound according to alternative scales such as dB HL. Another scale that is in common use is decibel normal Hearing Level (dB nHL). In the strictest sense dB nHL denotes a reference for a sound that is either the mean or the median threshold of hearing for ontologically normal young adults, the same concept as dB HL for pure tones. However, in practice dB nHL usually refers to the level of short-duration sounds as used in auditory evoked potentials. Other important decibel scales in audiology are the peak Sound Pressure Level (pSPL) and peak-to-peak equivalent Sound Pressure Level (ppeSPL). Both of these scales have audiological applications in the measurement of short-duration sounds. Peak sound pressure level is the greatest sound pressure (be it condensation or rarefaction) over the duration of a signal. Peak-to-peak equivalent sound pressure level is the sound pressure level of a long-duration signal (such as a 1 kHz pure tone) that produces the same peak-to-peak sound pressure as a short-duration sound typically used in measuring auditory evoked potentials. The need for these alternative scales arises because, in a similar way in which there is a minimum duration of perception, the ability to measure sound acoustically with a microphone has a lower limit of duration. This limit arises because the measuring device (e.g. a sound level meter) is usually incapable of responding quickly enough to produce an accurate and stable reading of the sound pressure level.

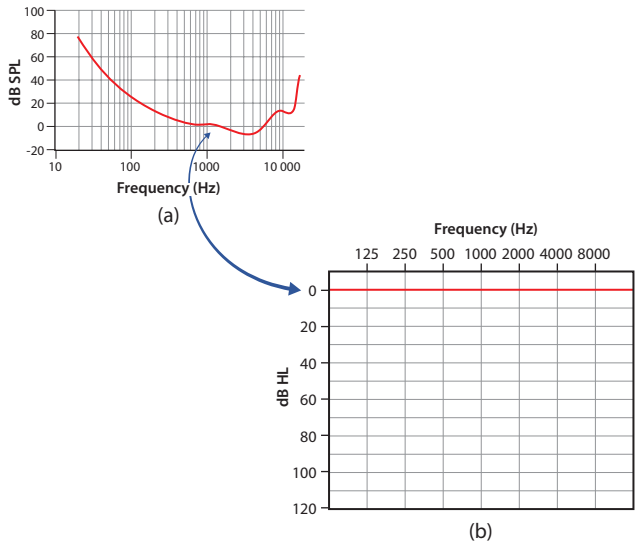

Figure 48.6 Schematic showing the relationship between dB SPL and dB HL. Note that the actual reference equivalent sound pressure levels (RETSPLs) used for audiometric zero in the calibration of audiometers and other diagnostic equipment are specific to transducer type in a specific coupler.

Spectral analysis of sound

So far we have considered sounds in the time domain, where the summed pressure variances as a function of time (or distance) are drawn. It is possible to represent sound in the frequency domain, where the spectral (or frequency) content of the sound is considered irrespective of the temporal relationship between different frequency components. As mentioned earlier, most everyday sounds are complex sounds so, by breaking down such a sound into its individual frequency components one might more easily describe the behaviour of a system in operation (such as the ear in sound detection) and infer the behaviour of that system to more complex sounds. Another reason for considering sounds in the frequency domain is that the ear itself acts as a spectral analyzer. As will be described in more detail later, a filtering action arises within the cochlea that allows sounds of different frequencies to be separated and then transduced into neural energy at different places within the cochlea, known as tonotopicity. Therefore, an understanding of the spectral content of a complex sound can give insight into the way in which that sound will produce activity within the auditory system.

The primary means of decomposition of a complex sound into its constituent frequency components is called Fourier analysis (for a continuous signal), or Fourier transform for any signal (devised by the French mathematician Fourier in the 1820s). A useful starting point is to consider a pure tone, since the spectral content of such a signal will consist of just a single frequency component, as illustrated in **Figure 48.7** for a 0.1 kHz pure tone. **Figure 48.7a** shows the temporal pattern of amplitude fluctuations for the signal (i.e. it is in the time domain); **Figure 48.7b** shows the spectral content of the signal (i.e. it is in the

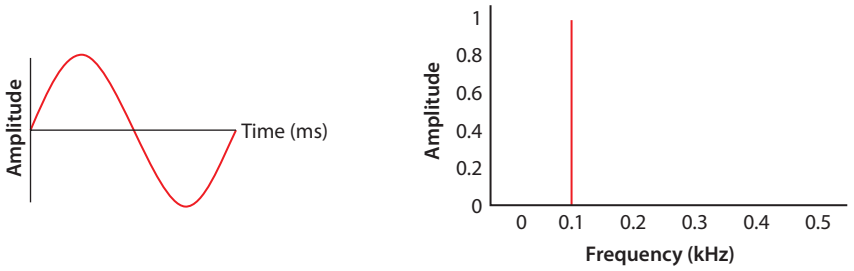

Figure 48.7 A 0.1 kHz sinusoid shown in the time domain (a) and in the frequency domain **(b)**.

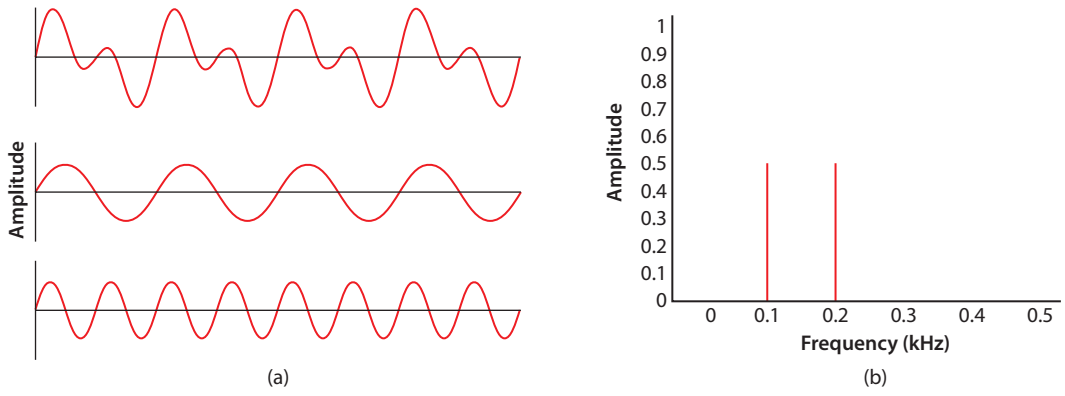

Figure 48.8 (a) The upper row depicts a complex tone in the time domain, comprising 0.1 kHz and 0.2 kHz sinusoids depicted in the middle and lower rows, respectively. The two components are in phase. **(b)** The components of the complex tone are displayed in the frequency domain where the frequencies and amplitudes of the two components are apparent.

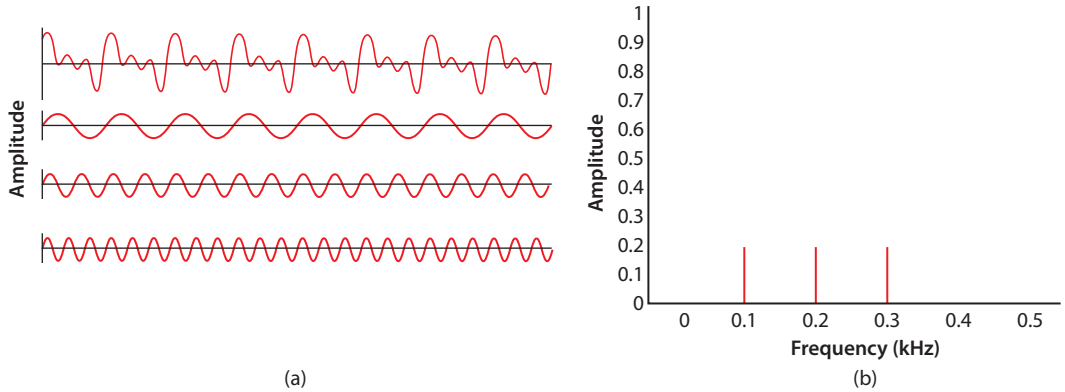

Figure 48.9 (a) The upper row depicts a complex tone in the time domain, comprising three components at 0.1 kHz, 0.2 kHz and 0.3 kHz (second, third and fourth rows, respectively). **(b)** The components of complex tone, displayed in the frequency domain.

frequency domain). Three-dimensional displays may be used to show both amplitude and timing of the different frequency components of a complex sound simultaneously.

A complex tone can be similarly decomposed to produce line spectra at the various different components. For example, the upper trace in Figure 48.8a illustrates a complex tone in the time domain, made up from two components, 0.1 kHz and 0.2 kHz, that are of the same amplitude and both starting from a zero degree phase angle. There are four cycles of the 0.1 kHz component (middle trace), and in the same period eight cycles of the 0.2 kHz component arise (lower trace). Figure 48.8b provides the line spectra corresponding to the complex tone formed by these two components.

In a further example shown in Figure 48.9, a complex sound comprising three pure tones is displayed in the left column (a) (upper trace) with constituent pure tones of 0.1 kHz, 0.2 kHz and 0.3 kHz all at zero degrees phase and of equal amplitude (second, third and fourth traces respectively). The corresponding line spectra are displayed in Figure 48.9b.

The above examples show the effect of adding sinusoids that are in phase. Since sinusoids are periodical sounds, their summation will produce a repeating pattern, the frequency of which (repetition frequency) is known as the fundamental frequency (F_0). In the above examples, 0.1 kHz is the highest common factor between each of the constituent components (i.e. the highest integer that

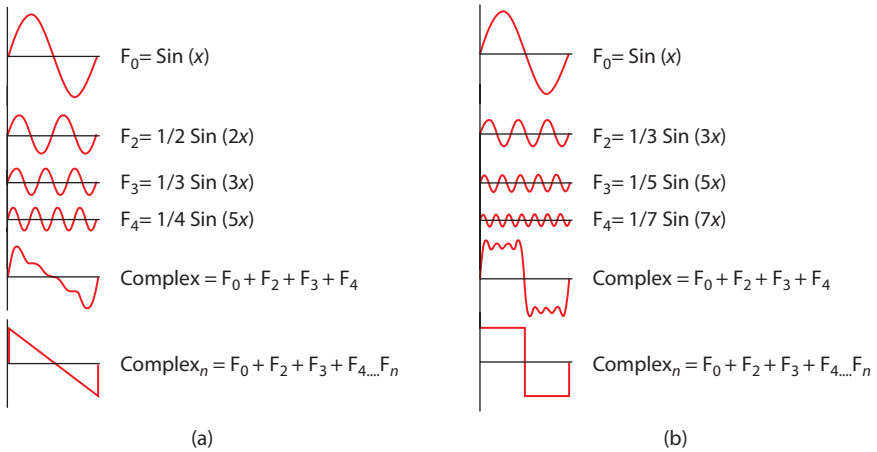

Figure 48.10 **(a)** The upper row shows a sinusoid, beneath which are odd- and even-numbered harmonics which, when added indefinitely, will form a sawtooth wave. **(b)** The same sinusoid with only odd-numbered harmonics added will form a square wave.

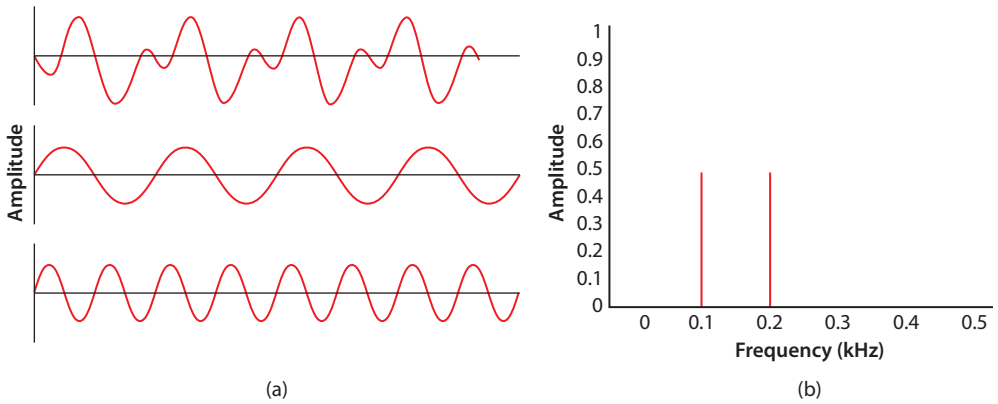

Figure 48.11 **(a)** The upper row depicts a complex tone in the time domain, comprising 0.1 kHz and 0.2 kHz sinusoids depicted in the middle and lower rows, respectively. The 0.2 kHz component has a 90° phase lead over the 0.1 kHz tone. **(b)** The two components are shown in the frequency domain, which does not display the timing relationship between components.

all components will divide into). The period (and therefore the repetition frequency) of the complex periodical sound is equal to the highest common factor. The higher-frequency components, which are exact integer multiples of the fundamental frequency, are known as harmonics.

Continuing the pattern illustrated in Figure 48.9 indefinitely would produce a 'sawtooth' pattern: sine waves with odd and even multiples of the fundamental. However, there are other combinations. For example, a square wave contains only the fundamental and an indefinite number of odd-numbered (or odd-order) harmonics. Sawtooth and square waves are shown in Figure 48.10 a and b respectively.

So far, all of the complex sounds have comprised components of different frequencies, but all with the same phase. Figure 48.11 shows the effect of complex sound that results from combining two pure tones as before, 0.1 kHz and 0.2 kHz of the same amplitude, but this time with a different phase. The 0.2 kHz component has a 90-degree phase lead over the 0.1 kHz component. The result is a different pattern of interaction, resulting in a different complex wave pattern (a) from that shown in Figure 48.8, although both examples have the same fundamental frequency. Note the line spectra (b) are unchanged because the temporal relationship between frequency components is not reflected in the frequency domain. The ear itself is relatively insensitive to phase. What the ear detects are the amplitude and frequency characteristics of the components that made up the complex signal. (The auditory system does respond to phase characteristics of sound, such as phase differences between sounds presented binaurally, and this is achieved by interaural comparisons within the central auditory system. For further information, see the review by Moore.[4])

For a complex sound to be periodic, the sinusoidal components must have a harmonic relationship; each component is an integer multiple of the fundamental. An aperiodic sound is the opposite of this as it does not repeat over time. It is therefore impossible to predict what such a waveform will look like from one moment to the next. While sounds that are (at least nearly) periodic are common in some forums, such as the sounds produced by pitched musical instruments, the majority of sounds in nature are aperiodic and therefore cannot convey pitch. Aperiodic sounds include wind noise, traffic noise and percussive instruments. Spoken speech contains both periodic and aperiodic sounds. The spoken vowel sounds are typically periodic, while consonant sounds are aperiodic.

Since there is no fundamental or harmonic structure, the spectra of aperiodic sounds cannot be a series

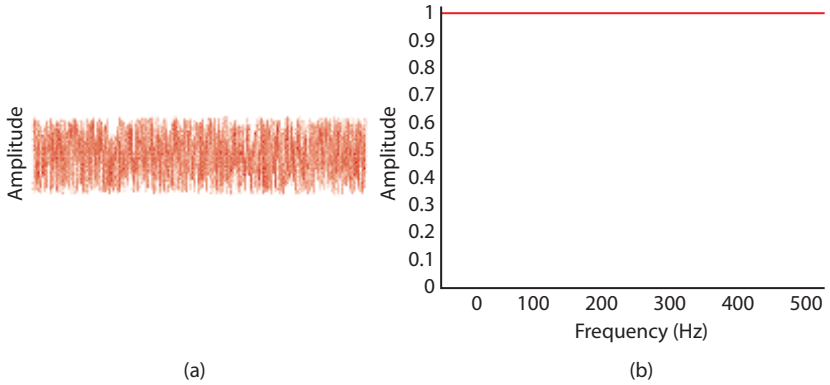

Figure 48.12 A sample of white noise, an aperiodic sound with equal energy at different frequencies, in (a) both the time domain and **(b)** the frequency domain. The relevant frequency range for white noise is 0.02–20 kHz, i.e. the range of human hearing.

of vertical lines. They are a continuous line, with differences in height corresponding to the differences in amplitude across the frequency range of the sound. Perhaps the simplest example is white noise, which is an aperiodic waveform with equal energy in every frequency band (1 Hz wide), as shown in Figure 48.12.

The name 'white noise' is analogous to white light, which has energy in all light wavelengths. Following this convention, different 'colours of noise' typically refer to noise whose energy levels across the spectrum reflect the colour of light with a similar spectrum, such as pink noise (where power density decreases with frequency) and blue noise (where power density increases with frequency).

TRANSMISSION OF SOUND BETWEEN DIFFERENT MEDIA

Earlier we briefly discussed the speed of sound through the medium of air, i.e. the rate at which sound propagates through the air. The speed of the propagation and the extent to which a sound may propagate at all are determined by physical properties of the medium such as the stiffness and density. Air is low density, and low stiffness. This means that vibratory energy from the source is passed from one molecule to the next relatively easily but relatively slowly. As the density of the medium increases, so does the speed of sound. For example, the speed of sound in water is around 1500 metres per second. The speed of sound is calculated using the following equation:

$$c = \sqrt{\frac{\text{Stiffness}\,(K)}{\text{Density}\,(\rho)}}$$

However, as density increases so does the stiffness of the medium. For example, air is far more elastic, and compressible, than fluid. This means that, when an object vibrates in air, the sound waves can propagate relatively 'easily', i.e. small pressures are required to produce a given velocity of movement of the air molecules. However, as the density of the medium and therefore the stiffness increase, such as with a fluid, then the same pressure will produce a smaller velocity of movement. This is the effect of acoustic impedance. The closer the impedances of two media (such as air and fluid), the more acoustical energy will be transmitted between them. The relationship between acoustic impedance (Z) of any substance, sound pressure and velocity of vibration is provided in the following equation:

$$z = \frac{\text{Sound pressure}\,(P)}{\text{Velocity of vibration}\,(\nu)}$$

The effect of different acoustic impedances of media such as air and fluid is relevant because, while sound typically reaches the ear via propagation through air, the physiologically vulnerable structures of the ear within the cochlear are filled with (and bathed in) fluid. Therefore, if the sound waves of a given pressure were to arrive directly at the cochlea from the remote source, the resulting velocity of vibration within the fluid-filled cochlea would fall due to the increased acoustic impedance; most of the energy would instead be reflected back into the air. That this does not happen is a result of the outer and middle ears, which act as an impedance matcher, so that a large proportion of acoustic energy is transmitted into the cochlea. The way in which this happens will be outlined below.

KEY POINTS

- Sound is variations in the pressure of the air (or other medium).
- Key dimensions of a sound wave are its frequency, intensity and duration.
- Each of these three dimensions of a sound can be detected and processed by the cochlea.
- The outer and middle ears match the acoustic impedance of the air in the external environment and the fluid of the cochlea, allowing efficient transmission of sound.

APPLIED PHYSIOLOGY OF HEARING

Soumit Dasgupta

This section looks at the applied physiology of how sounds or acoustic stimuli behave in the ear as well as what happens to the detection of these stimuli in diseases of the ear.

The peripheral ear consists of the pinna, the external auditory meatus and canal, the middle ear with the

tympanic membrane, the ossicles, the middle ear ligaments and the mucosal folds, the ossicles, malleus, incus and stapes, the Eustachian tube opening, the oval and the round windows, and the inner ear with the cochlea and the early part of the auditory nerve. Each component is crucial for normal functioning (i.e. audition) and it follows that any mechanism or process interfering with normal functioning will lead to a decrease in the perception of the auditory signal, generating a hearing loss.

THE PINNA

The pinna is vestigial in man, with non-functional auricular muscles. In lower groups of mammals, especially predators, these muscles are well developed and can move the pinna to localize and concentrate acoustic energy to the external auditory meatus, hence participating in spatial resolution of sound as well as focusing the energy to a relatively smaller area to be incident on the tympanic membrane.

The pinna and the external auditory meatus and the canal develop from similar morphological structures *in utero*. Therefore a dysmorphic pinna might reflect a dysmorphic external auditory canal and middle ear. Simple preauricular tags can indicate an underlying problem further down in the auditory pathway. Indeed, simple pinna deformities may be associated with an inner ear disorder.[5] It has been shown that in Down syndrome 3.5 pinna defects are observed, on average, in each ear as compared to 2.5 defects in the non-Down population; all of these are associated with conductive hearing loss in the former.[6] A pinna deformity is therefore clinically significant and demands an audiovestibular workup and, if necessary, monitoring. Since a pinna deformity may be a part of certain craniofacial syndromes, a genetic workup may be essential.

In terms of acoustic function, although the pinna is vestigial, when coupled with the external auditory meatus and canal, the unit acts to provide frequency specific resonance of sound incident on the ear to make up for the impedance encountered at the air–fluid interface between the cochlea and the middle ear. The applied importance of this is considered below.

The role of the pinna in localization of sound cannot be underestimated.[7] It has been postulated that the unique position of the pinna on the head and its relative size to the craniofacial skeleton transform the incoming sound signal with delay paths dependent on the wavelengths of the acoustic waveform to provide localization clues for the listener to an incoming signal. The head shadow, i.e. the intervening head and the pinna on either side, is an important factor for auditory localization, with interaural time and interaural intensity differences generated by the same acoustic signal impinging on the pinna with different temporal and intensity values at each side.[8]

There are numerous anatomical ridges and convolutions in the pinna. Sound waves from either the horizontal or the vertical direction are reflected from these ridges and enter the ear canal with the original non-reflected incident sound (see below). Then, via the fixed external auditory canal, they are transferred to the eardrum, further modifying the transfer function. The different changes of transfer function from the pinna to the external auditory canal when delivered to the cochlea through the middle ear are encoded accordingly to be finally perceived by the cognitive cortex as directionality of sound or a spatial representation of sound.[9] A pathology in the pinna may therefore interfere with this localization and directionality process.

It is logical to consider the pinna as a funnel to collect sound. As mentioned earlier, however, it can also be a reflector of sound and works best above 1 kHz. Some of the reflected waves enter the canal and may interfere with the original waves if they are out of phase, noted particularly between 7 kHz and 10 kHz where they produce a pinna notch.[10] The frequencies at which the reflected and incident waves boost each other are 2–3 kHz, roughly at frequencies which possess wavelengths of four times the length of the pinna.

The postauricular myogenic response (PAMR) is a measurable compound action potential generated in response to an electrical or acoustic stimulus.[11] The reflex magnitude is a large one and the afferent substrate is the cochlea rather than the vestibular system with the efferent pathway being the facial nerve.[12] The reflex is a bipolar compound action potential with typical latency of 12.5–15 ms and can be elicited by either tone-burst or click stimuli. The reflex is obtained at 20 dB SL and can be detected in 80% of the population.[11] The PAMR has been reported to be inconsistent and variable, with significant test–retest variations. It is also difficult to measure with standard auditory brain stem response (ABR) settings and therefore does not find much clinical use. However, there is evidence that, when measured, it can still be clinically useful to screen for hearing loss, especially in difficult-to-test children,[13] in facial nerve function monitoring for intracranial facial nerve palsies[8] and in auditory neuropathy (AN now called auditory neuropathy spectrum disorder where there is an abnormality in sound conduction and propagation from the inner hair cell synaptic junction all the way up to the brain stem and includes the auditory nerve) where it can be abolished.[14] Given the observation that the acoustic reflex is useful to test for AN in the clinical setting, PAMR can augment suspicion before an ABR for confirmation due to its potential ease of use.

The pinna is an important landmark for taking an impression of the ear, an important step in hearing aid fittings. The antihelix and the concha are anchors for hearing aid retention,[15] and a dysmorphic pinna lacking important landmarks may preclude standard behind-the-ear hearing aid fitting.

The pinna is made of fibrocartilage except at the region of the lobule and an area just above the tragus. These anatomical features provide areas for potential surgical accessibility. The lobule can be used as a fat graft and the supratragal notch can be used in endaural incisions, thereby not injuring the tight cartilage mucoperichondrium of the external auditory canal (see next section).

THE EXTERNAL AUDITORY CANAL

The external auditory canal (EAC) commences at the conchal opening called the external auditory meatus (EAM), includes the ear canal itself and ends at the tympanic membrane lateral surface, which separates it from the middle ear. It is made up of an outer cartilaginous part

and an inner bony part with two constrictions, one at the junction of the distinct anatomical parts and one 5 mm before the tympanic membrane in the bony part. Thus, it can be considered as a tube which is open at one end. The typical length is 25–26 mm in the adult human.

The EAC has acoustic and non-acoustic functions and pathologies of the ear canal will therefore interfere with both of these functions.

Acoustic physiology of the EAC

The most important physiological function of the EAM and the EAC is to 'transfer' the acoustic signal from a sound field to a much smaller area, i.e. the tympanic membrane. The EAC transfer function is a mathematical representation of the output of the external ear in dB SPL plotted against an input of sound in db SPL at different frequencies. The resultant acoustic energy delivery to the tympanic membrane is thus a modified and amplified signal which undergoes resonance amplification and provides directional/localization cues.

The ear canal can be considered as a resonating tube following the quarter-wave principle for resonance; i.e. at a frequency with a wavelength four times the length of the canal, the canal and the pinna together will resonate and vibrate with the incoming signal to augment or magnify the incident acoustic signal given by the equation:

$$f = c/4l.$$

where f is the frequency, c is the speed of sound and I is the length of the canal.[16] The resonant frequency which amplifies the incident sound by 10–20 dB is generally 2.7 kHz with a range of 2–7 kHz.[17] Signals below 1 kHz are generally resonated by the head and the torso whereas frequencies above 3 kHz are augmented by the pinna.

It follows, therefore, that the length of the ear canal plays a significant role in modifying the incident sound signal before its delivery to the tympanic membrane. This amplification is essential to overcome the air–fluid impedance at the oval window.

The EAC and the pinna acting as a unit are also involved in providing monoaural and binaural cues for localization of sound (see 'The pinna' above). The EAC pressure gain and transfer factor changes with directionality of the incident signal especially above its resonant frequency and can be as much as 30 dB in both the horizontal and vertical planes.[18]

The EAC canal is subject to variation in size and may grow from the neonate until the age of 7–9 years.[17] The transfer function may change during this period, with important amplification issues in fitting hearing aids, and must be calibrated accordingly by referring to the normal range. The resonant frequency remains more or less constant from the age of 2 years.[19] However, the resonance amplitude changes at old age.[16] Since prescribed hearing aid function is significantly dependent on external ear canal function, this change of resonance must be taken into account to prevent inappropriate amplification.

In some frequencies the EAC generates a standing wave phenomenon. A standing wave is defined as being created when two sounds of the same frequency travel in opposite directions in the canal (e.g. when the same sound is reflected by the tympanic membrane) and cancel each other out. For sounds of high frequencies, a standing wave may be produced which may interfere with circum or supra aural head phones measured hearing threshold at 8 kHz, which might generate a spurious hearing deficit.[20] Another reason why a spurious threshold may be obtained is because in adults supra aural headphones may collapse the soft cartilaginous part of the external auditory canal. This consideration also becomes important when performing real-ear measurements.

In disorders of the EAC ranging from dysplasia to occlusive pathologies (e.g. wax or tumour), the effect on the external canal resonance gain is real and tangible and some conductive hearing loss (a hearing loss which is caused by any factor interfering with the conduction of sound in the external auditory apparatus i.e., the meatus, canal and pinna and the middle ear) is expected. This hearing loss is usually concentrated around the area of maximum resonance, i.e. at about 2.7 kHz. In cases of occlusive hearing aid moulds, this loss must be incorporated in the prescription.

Morphology of the EAC

The EAC is characterized by its skin and by the production of wax, each of which serves its own functions.

The skin is tightly adherent to the underlying perichondrium without any subcutaneous tissue. It is thicker in the cartilaginous part than in the bony part.[15] Minor trauma to the skin may directly involve the perichondrium, potentially leading to serious infection. A skin breach may damage the mucoperichondrium too, therefore due care must be taken not to damage the skin. Surgical incisions utilize the cartilage-free supratragal notch and the superior wall of the canal which spare the cartilage. Earrings are recommended to be worn in the lobule which is devoid of cartilage.

The migration of dead skin is towards the meatus, i.e. lateral. A blind pocket in the ear canal will trap this skin and prevent its migration, leading to infection and finally to a cholesteatoma if it affects the posterosuperior region of the canal.

The skin of the canal is supplied profusely by nerves. Irritation of the canal may provoke a cough reflex or even a vasovagal spell by stimulating the vagus nerve, which serves the canal by way of the nerve of Arnold. Paraesthesia or anaesthesia of the posterior meatus wall may be a feature of a vestibular schwannoma, which is supplied by the nerve of Arnold.

The canal skin is lined in the outer third by two different types of secretory glands: the sebaceous glands and the modified apocrine ceruminous glands. Sebum and cerumen from the glands mixed with dead skin, dust and shed hair form wax. Therefore wax is a product of secretions from both sebaceous and apocrine glands. It turns brown on oxidation in air. There are two types of wax, dry and wet, which are genetically determined. The functions of ear wax are to lubricate and clean the canal, to act as a vehicle for carrying migrating dead skin from the canal skin in the lateral direction and a protective function due to its bactericidal effects against some bacteria and the antimicrobial effects of the lysozyme, immunoglobulin A (IgA) and fatty acids which it contains.[21]

The ear canal is sometimes called the 'greenhouse of the human body', being warm, dark, humid and moist.[21] It is a perfect culture medium for microbes, especially fungi. The wax provides some protection by trapping these microbes, by virtue of its antimicrobial properties and by providing an acidic milieu. Sodium bicarbonate drops to soften wax in the canal disturb the acidic pH and may lead to infection. It is therefore best to use a neutral agent for this purpose (e.g. olive oil).

Impacted wax generates morbidity. Complete occlusion of the ear canal leads to a hearing loss of 40 dB in addition to possible tinnitus and cough.[21] There is usually a high-frequency shift on lesser occlusions starting from 2 kHz, probably due to the compromise of the resonant gain of the ear canal. Wax may irritate Arnold's nerve to cause a vagal-induced cough reflex, especially during microsuction. Superadded infection may lead to social isolation and even a frank otitis externa.

THE MIDDLE EAR

The middle ear in the human acts as an efficient passive and linear transformer to conduct acoustic energy from the tympanic membrane to the stapes footplate at the oval window and to the cochlea. The middle ear apparatus consists of the tympanic membrane, the ossicular chain of the malleus–incus–stapes complex along with the middle ear muscles. Its fundamental function is to provide critical modifications to the sound energy by providing mechanical advantages to overcome the impedance encountered by the acoustic signal when it is conducted from an air-filled medium (the middle ear cavity) to a fluid-filled medium (the perilymphatic and the endolymphatic fluid in the cochlea). Essentially, therefore, acoustic energy is transferred from a low-impedance, high-velocity medium to a high-impedance, low-velocity medium through this ossicular coupling (**Figure 48.13**). The impedance difference is mainly matched by the ratio of the surface area of the tympanic membrane to the stapes footplate and by the lever action of the ossicles and the membrane. The Eustachian tube links the nasal cavity to the middle ear. This tube supplies air to the middle ear for the air particles to vibrate and also equalize pressure across the tympanic membrane between the EAC and the middle ear.

Middle ear function is assessed by impedance audiometry which measures compliance and pressure of the system by tympanometry, which, in addition, also measures volume of the external auditory canal and the stapedial reflex tests. Tympanometry is essentially a measure of admittance (i.e. the reciprocal of impedance) of the middle ear system. The EAC volume can indirectly verify a tympanic membrane perforation or a patent grommet where the canal volume is higher than the average range of the normal and the stapedial reflex tests provide information about the auditory nerve pathways (see 'The middle ear muscles' below). Middle ear function tests are discussed further in Chapter 51, Psychoacoustic audiometry.

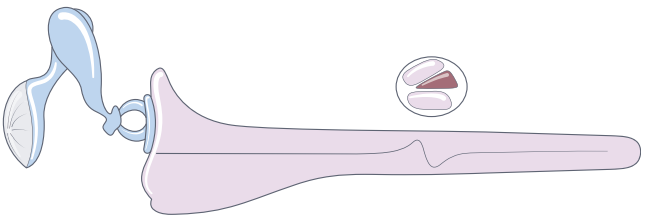

Figure 48.13 Ossicular coupling.

The middle ear space

The middle ear is a closed cavity consisting of the medial surface of the tympanic membrane, the ossicles, the oval window, the Eustachian tube and the middle ear muscles and the ligaments with mucosal folds. The greatest transfer function of the middle ear is at the resonant frequency between 1 and 3 kHz and is determined by the mass and the stiffness of the system. In other words, the middle ear may be considered to be a system with a band pass filtering action.[22] The stiffness or elasticity of the middle ear is determined by the tympanic membrane, the ossicular ligaments and the middle ear cavity compression of the air column while the mass is governed by the ossicles. The stiffness factor limits passage of low-frequency sounds while the opposite is true for the mass factor.

The tympanic membrane

Like the EAC, the middle ear mechanism delivers acoustic energy from a relatively large area of the tympanic membrane to the much smaller area of the stapes footplate. The ratio is about 18:1.[23] This disproportionality contributes to overcoming the acoustic impedance mismatch at the air-fluid interface between the middle and the inner ear. The process begins at the lateral or outer surface of the tympanic membrane which, strictly speaking, is a part of the EAC. The canal side of the membrane exhibits a uniphasic response with little pressure variation and is relatively uniform[24] while the middle ear side is multiphasic with significant pressure variations. This can be explained by the consistency and the structure of the membrane which is non-uniform and provides a multiple integrated multilever mechanical advantage.[25] There is also a destructive interference due to reflection of the sound waves by the membrane, which is important to create a pressure difference across the membrane.

The incident sound from the EAC hits the membrane and sets up a travelling wave, which is mainly collected at the rim of the membrane. This is then conducted to the umbo and coupled to the manubrium of the malleus.[26] At lower frequencies, the membrane transfers all its energy by uniform movement to the malleus; at higher frequencies, the movement is more complex and part of the vibration is shunted by the middle ear.

The reflectance of the membrane is high at the lower frequencies below 1 kHz while it is lowest between 1 kHz and 4 kHz, which means that between these frequencies maximum energy is delivered to the cochlea and the middle ear is most efficient.[27] This range of frequencies happens to be where the middle ear apparatus resonates to the incident stimulus and amplifies the signal to overcome the impedance at the stapes oval window interface.

At higher frequencies up to 15 kHz, the reflectance rises to near total again, which suggests that the middle ear limits sound wave propagation at higher frequencies.[28]

In disorders of the tympanic membrane (e.g. tympanic atelectasis or perforations) the multiple lever action is compromised, leading to a hearing loss, and a myringoplasty cannot restore this feature of the membrane in all cases. A unique case is tympanosclerosis where hearing is preserved in spite of a loss of action of the membrane, presumably because the preferential distribution of the acoustic energy to the oval window from the middle ear is intact due to preservation of some structural integrity.[29] Therefore, structural integrity is crucial for the middle ear transformer mechanism. Note that, when the rim of the membrane is intact (i.e. central perforations), hearing is better preserved than when the margins are affected as energy transfer from the canal to the membrane is via the rim of the membrane.

In perforations, the volume velocity of the sound waves (the volume of vibrating air particles conducting the sound per unit time) is not preferentially distributed to the stapes–oval window interface as normal displacement of the membrane is precluded, but a part of it is absorbed or shunted by the middle ear cavity. Sound transmission may still occur but in a perverted and unnatural way. The main reason for a hearing loss is the reduction in pressure across the tympanic membrane due to this shunt and preclusion of the multilever action.[27] The degree of the loss is proportional to the size of the perforation and inversely proportional to the frequency, i.e. the greatest loss is at lower frequency. This is because reflectance of the membrane, which is an important factor for the pressure difference across the membrane, is lost or diminished at lower frequencies, which does not aid compliance and transfer of energy to the oval window.[30]

The Eustachian tube

The Eustachian tube opens to supply air into the middle ear cavity and is controlled by the muscles in the tube, which are under tonic control and follow the nasal cycle. The tubal opening is best demonstrated at 6–8 kHz, i.e. high-frequency sounds. An evolutionary hypothesis can be proposed to account for this. Since high-frequency sounds are the most important consonant-containing sounds, the middle ear must act in the most efficient way to conduct these sounds, which should be close to its resonant frequency and unaffected by the damping effect of reduced air supply. In other words, maximum air entry from the tube needs to occur at high frequencies to facilitate sound conduction. In Eustachian tube dysfunction where the middle ear cavity is deprived of air, as in early stages of otitis media with effusion (OME), the stiffness of the system is augmented, which leads to a low-frequency hearing loss. With further progression, fluid collection in the middle ear cavity increases the mass of the system, which generates a high-frequency hearing loss.[22] This model may be useful to prognosticate one of the commonest causes of hearing loss in children, i.e. glue ear. It is important to bear in mind that, unlike perforations, which do not affect eventual transmission of sound, OME physically disrupts transmission.

The middle ear cavity

The reflections of the acoustic signal from the walls of the middle ear cavity may contribute to pressure differences across the tympanic membrane[31] and may provide an additional drive to the membrane function.

The transfer function of the middle ear is linear. If stapes velocity which is proportional to acoustic frequency is considered the output of the middle ear mechanism, then it has been shown that there is a peak function at 3 kHz and the shape is that of a shallow band pass cut off.[32] The stapes velocity drives the cochlear fluid movement. Once again, note that the transfer function is most efficient around the resonant frequency range of the middle ear. The cochlear impedance itself makes the middle ear highly damped, which is essentially the impedance the middle ear needs to overcome in order to preserve acoustic stimulus characteristics.

The middle ear mucosal folds

The mucosal folds in the middle ear, which thicken in some instances to form ligaments, divide the middle ear cavity into a superior epitympanum and an inferior mesotympanum and hypotympanum. The ligaments in this epitympanum diaphragm are formed by malleal folds, with the lateral malleoincudal fold posteriorly and the tensor fold anteriorly.[33] The connection between the two is the tympanic isthmus, which is the only conduit for a ventilation stream in the epitympanum from the Eustachian tube, unlike the mesotympanum, which is flooded by air at all times. Congenital defects in the folds, or folds affected by inflammatory processes (e.g. mucosal disease or cholesteatoma), can block the narrow isthmus, leading to loss of air from the epitympanum and provoking further inflammation.[34, 35]

The middle ear muscles

There are two middle ear muscles with function in man: the tensor tympani and the stapedius. They both participate in a reflex contraction, thought in part to protect the delicate sensory epithelium of the cochlea by attenuating high amplitude sounds. Of these, the tensor tympani is less efficient and active than the stapedius, which is the dominant muscle driving the reflex. The muscles are also important for eliciting a prevocalization reflex, i.e. a reflex when someone is about to speak.[36] Given the bony continuity of the human skeleton, vocalization leads to cochlear stimulation via the bony EAC, the ossicles and the skull bones. The middle ear muscles modulate this acoustic signal so that the ear is protected from one's own voice. In the evolutionary sequence, if we consider bats, the acoustic reflexes completely disarticulate the ossicular chain when the bat emits a high-frequency and otherwise very loud echolocating pulse.

The tensor tympani supplied by the Vth nerve has very low electrical activity in response to sound. It attaches to the malleus manubrium and pulls the malleus anteriorly. However, it is active in the following situations: tactile stimulation of the EAC and face, pneumatic pressure on the eyelids, sudden forced opening of closed eyelids or forced closing of the eyelids, swallowing, head movements, anticipation of loud sounds and a startle.[37] It is

interesting that these movements all entail some movement of the bony skull which can stimulate the cochlea. Disorders of the tensor tympani may generate the 'tensor tympani syndrome', which manifests as an audible thump in the ear; the condition is rare.[37]

The stapedius muscle supplied by the VIIth nerve is the dominant muscle in the middle ear and attaches to the stapes neck. Its contraction pulls the annular ligament in the footplate. The stapedius responds primarily to high-intensity low-frequency sounds – about 0.8 kHz[38] –which tend to overpower the high frequencies to preserve high-frequency consonant-containing speech sounds (see below). The middle ear system at lower frequencies therefore generates the maximum impedance to incident sounds. Stapedius contraction is responsible for the stapedial reflex which moves the stapes about 50 microns, increases the stiffness of the ossicular chain and can attenuate the sound transmission to the inner ear by as much as 30 dB.[39]

At the 80–90 dB SL intensity range, the reflex is elicited. However, the stapedius tendon takes about 100–200 ms to contract fully, which implies that it will be unable to protect the cochlea from intense short-impulse noise such as a gunshot, although a noise primer just before the gunshot may address this latent period and may be otoprotective.[37] Although the role of the reflex is controversial, it is thought to serve three important functions:

- Protection of the cochlea to high-intensity sounds to preserve a dynamic range of the auditory system.
- Reduction of output of the middle ear from high-intensity low frequency sounds – these high-intensity low-frequency sounds may mask the high-frequency speech consonant sounds at the base of the cochlea due to the forward propagating cochlear wave (see 'Cochlear travelling wave' below), thereby aiding speech recognition.
- Modulation of self-monitoring of voice and preserving high-definition, high-frequency ambient sounds when one is speaking or by self-generated noise.

The neuronal circuitry of the reflex crosses over to the other side and therefore the reflex can be elicited by both ipsilateral and contralateral stimuli delivered to one ear. As a result, there are several possible response patterns that reflect conductive, sensory and neural hearing losses. The author [SD] believes that the most important utility of measuring the stapedial reflex is to screen for auditory neuropathy spectrum disorder (ANSD) in case of hearing/listening problems with preserved otoacoustic emissions[41] and in cases of spurious hearing losses, for example third windows (see 'The middle ear windows' below) where, in the presence of a significant air–bone gap in pure-tone audiometry (the difference between air conduction and bone conduction thresholds), the reflex may be preserved (the reflex is usually unobtainable in middle ear disease). The reflex may be abolished in brainstem lesions although the response cannot be used to diagnose such a lesion. The reflex itself may be audible, generating an objective tinnitus in the ear which is due to a stapedial tendon myoclonus.

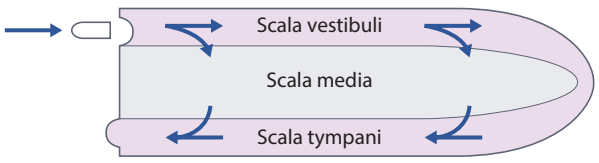

Figure 48.14 The oval window–round window pressure difference for the cochlear travelling wave.

The middle ear windows

The middle ear is characterized by two natural windows or real connections between the middle and the inner ear. The oval window articulates with the stapes footplate while the round window is covered by the secondary tympanic membrane.

The pressure difference between the oval and the round windows is fundamental for the cochlear travelling wave (see below) which drives cochlear function (**Figure 48.14**).[42] Cochlear fluid is not compressible and therefore, to allow a cochlear travelling wave while protecting the sensory epithelia from excessive movement, a mechanism must be present to dissipate part of the mechanical vibration-induced pressure through a channel in the opposite phase. The oval window is the site of the preferential distribution of sound energy although, at higher frequencies, this preference is occasionally shunted by the middle ear cavity.

Disorders of the oval window or in the vicinity (e.g. stapedial or cochlear otosclerosis), congenital absence of the oval window or X-linked gusher syndromes will lead to a loss of this preferential distribution and have a significant effect on auditory sensitivity.

In addition to providing the integrity of the cochlear travelling wave, the round window also participates in absorption and secretion of the perilymph by virtue of a semipermeable membrane.[43] This has opened up possibilities for intratympanic drug delivery through the round window to achieve effective intralabyrinthine concentrations. The round window approach is also used as an alternative to a standard cochleostomy approach for insertion of cochlear implants to minimize operative trauma and subsequent intracochlear fibrosis.[44]

In addition to the two natural windows, virtual third windows may exist for some absorption of the sound from the middle ear thereby affecting the preferential stapes-oval window sound distribution. This includes the vestibular aqueduct and the bony skull itself as well as the ossicular inertia, all of which may shunt away some of the energy, with variable cochlear effect. A pathological third window which can be a real one (perilymph fistula, X-linked gusher i.e., real connection between the inner and middle ear) or a virtual one (dilated vestibular aqueduct or semicircular canal dehiscence i.e. no direct communication between the inner and middle ear) also absorbs or shunts part of this preferential distribution. The cochlea might in part be directly stimulated by the vibrations in the third window itself. Measured air-conduction thresholds therefore decrease and bone-conduction (BC) thresholds increase, generating a spurious conductive hearing loss or 'false' or air–bone gap.[45] The improved BC can also be explained by the fact that the third window generates a pressure drop across the two natural windows. However, it must be noted that third window pathology may directly damage

the cochlear or the vestibular sensory epithelia. As a result, it is very difficult to accurately estimate auditory sensitivity in patients with the disorder and consequently prescriptive fitting of digital amplification which is based on pure-tone thresholds may not give a favourable outcome.

Bone conduction

Apart from being stimulated by the stapes–oval window interface acoustic energy transfer and the round window effect, the cochlea can be directly stimulated by the bony skull composed of canal, ossicles and bony cochlea within which the whole inner ear apparatus is enclosed. Airborne and internally generated sound produces vibrations in the hard bony skull which in turn can lead to endolymphatic movement of the cochlear basilar membrane (BM), bypassing the middle ear and the external ear mechanisms. In addition, there is a non-osseous pathway for stimulation by the acoustic energy which is conducted through the brain and the cerebrospinal fluid (CSF) and transmitted to the cochlea by its fluid channels.[46]

The cochlea is directly stimulated by factors including the sound pressure level in the bony canal vibrating the skull, the ossicular inertia, the cochlear fluids and the cochlear space vibrations.[47] Thus, there are three methods of bone stimulation:[48]

- vibration-induced compression and distortion of the cochlear space consisting of the intralabyrinthine bony skeleton which causes distortion of the BM due to the flexibility of the vestibular aqueduct
- vibration-induced inertia of the ossicles transferring to the bony labyrinth
- particle vibrations leading to vibrations of the EAC, the tympanic bony sulcus and directly transmitted to the cochlea.

The middle ear has a resonant frequency around 1–3 kHz considering both air and bone conduction. If this resonance is reduced or damped by a mechanical problem in the ossicular chain (e.g. adhesion, fixation or sclerosis), the ossicular component of bone conduction as outlined above is jeopardized and generates a drop in the pure-tone thresholds as measured by BC of about 5–10 dB. This classically appears at 2 kHz as Carhart's notch in the BC thresholds in stapedial fixation; however, in any pathology involving the ossicles, a Carhart's effect may be present between 1 kHz and 4 kHz with dips in BC thresholds. Occlusion of the EAC to a significant degree may improve bone-conduction thresholds as the vibrations from the bone travel through the skull and on re-entering the external ear are contained within the canal to directly stimulate the inner ear by the osseotympanic route and do not escape to the outside.

The ossicles

The three ossicles (the malleus, the incus and the stapes) are connected together by synovial joints for transmitting the acoustic stimulus from the tympanic membrane. The geometric length of the malleus is approximately 2.1 times that of the incus and thus the lever action multiplies by 2.1 times; with velocity decreased by a factor of 2.1, the net mechanical advantage or impedance ratio is therefore 4.4. Further, the lever action changes with frequency with its most efficient at 2 kHz.[49]

The malleus and the incus rotate around an anterior–posterior axis of the malleus–incus complex that passes through the centre of gravity of the ossicles.[50] At low frequencies there is relatively less motion between the malleus and the incus; however, at higher frequencies the motion becomes more complex, allowing some slippage between the two to conduct higher-frequency sounds more efficiently.[27] The stapes shows a similar pattern of movement, i.e. simple piston-like movements at low frequencies and more complex spatial movements in higher frequencies along the long and short axes of the footplate.[51]

In ossicular discontinuity, whether congenital or acquired, the ossicular coupling-led preferential distribution of sound to the oval window is lost and the cochlear partition pressure between the round and the oval windows, which drives the cochlear travelling wave, is compromised.[52] The total expected conductive loss is about 60 dB, but much less if there is incomplete discontinuity or when there is a pathological bridge between the ossicles (e.g. a cholesteatoma). In ossicular fixation, such as in chronic adhesive otitis media involving ossicular joints or their ligaments, especially the anterior malleolar ligament, continuity is present but mobility is restricted and leads to a high impedance in the system. This is offset to a certain extent by inbuilt redundancy mechanisms in the middle ear. Thus, the hearing loss which is generated is less than that obtained with ossicular disruption. Otosclerosis is one type of ossicular fixation where the output substrate of the EAC and the middle ear concentrated on the stapes footplate affect forward propagation to the cochlea, thereby generating a significant conductive hearing loss proportional to the mobility of the stapes affected by the disease.

Tympanoplasty and ossicular chain reconstruction surgery attempts to re-establish the broken ossicular bridge either using soft tissue or by synthetic or autologous grafts.

Middle ear impedance match

The two primary mechanisms to match loss of acoustic energy at the stapes–oval window interface due to change of acoustic transmission from an air to a fluid medium, i.e. the surface area ratio of the tympanic membrane to the stapes footplate and the lever actions of the tympanic membrane and the ossicular levers, are responsible for a pressure gain in the middle ear conducted sound. Ossicular coupling, which is mainly contributory to the pressure gain, is frequency-dependent;[53] between 0.25 and 0.5 kHz it is 20 dB, reaching to 26.6 dB at 1 kHz and then decreasing by about 8.6 dB per octave until near zero above 7 kHz. The cochlear impedance is less at higher frequencies than at lower frequencies.

The effectiveness of impedance matching varies according to sound frequency. At 2 kHz, when the external canal and the middle ear transfer the acoustic energy most efficiently, the average sound pressure loss at the cochlea is 39.5 dB, which is partially compensated for by an external canal gain of 9 dB and a middle ear gain of 26.6 dB for a total gain of

35.6 dB factoring in some loss due to frequency-dependent middle ear function. In humans, at 2.7 kHz (i.e. the resonance of the canal) the sound pressure loss is approximately 35 dB, which is very closely matched by the external and the middle ear transfer function.[54] Note the difference in the impedance match at 2 kHz and at the resonant frequency of 2.7 kHz; the latter is a closer match than the former.

THE COCHLEA

The stapes–oval window interface delivers the mechanical and kinetic energy of the incident acoustic signal to the cochlea. The cochlea is a 2.5-turn coil in humans resembling a snail in the anterior compartment of the bony inner ear labyrinth. Sound introduced to the cochlea undergoes two major processes: a biological and active compression/amplification by the outer hair cells (OHCs) and an electrochemical transduction by the inner hair cells (IHCs), both contained in the scala media of the cochlea. The resulting neural output is a coded and gated signal conveyed by the auditory nerve via the spiral ganglion cells to the brainstem, which preserves frequency information, the amplitude and the phase of the sound by cochlear tonotopicity (frequency specificity), auditory nerve firing rate, phase locking and synchrony.

The cochlea is characterized by amplification to make hearing more sensitive, tuning to make it sharply frequency-selective and compressive non-linearity so that relatively large stimuli are translated to proportionally lesser systematically encoded mechanical functions to maintain integrity.[56] Cochlear mechanisms for the above actions are therefore responsible for the essential functions of the cochlea that include frequency analysis, loudness discrimination, temporal resolution, and the spectral analysis of the incoming signal. This is a highly complex process and interference with any of the component processes will lead to a hearing disorder.

Cochlear OHC function is measured by otoacoustic emissions that include transient emissions in response to a broadband click and distortion product emissions in response to frequency-specific pure tones. It can also be measured by electrocochleography and cochlear microphonics, the latter being incorporated in the software for auditory brainstem response (ABR) testing (see Chapter 9, Hearing tests in children).

Cochlear travelling wave

The mechanical displacement of the stapes–oval window junction is conducted along the cochlea, impinging on the base first and then travelling all the way up to the apex (**Figure 48.15**). In its wake, it causes mechanical movement of the BM which divides the cochlea into two compartments: the scala vestibuli above and the scala tympani below with a small connection between the compartments at the helicotrema in the apex. In addition, there is a third component called the scala media between the scala vestibuli and the scala tympani separated from the scala vestibuli by the Reissner's membrane and the scala tympani by the basement membrane. There are therefore three different travelling waves generated: the wave as a result of the pressure difference of the two compartments, the wave as a result of the mechanical displacement of the BM, and the acoustic energy wave which displaces the cochlear fluids.[56] The displacement wave is by far the most important wave for cochlear function.

The travelling wave propagates aided by the gradual diminution of the thickness and stiffness of the basement membrane from base to apex. As it propagates, it is acted upon by numerous critical oscillators, the characteristic frequency of which is specific to a particular region of the BM. These oscillators move the BM in addition to the travelling wave by expending active energy and are coupled with OHCs in the organ of Corti. The mechanical travelling wave propagates from the base to the apex, so there is a biological need to maintain signal strength at a relatively stable state due to gradual changes in thickness and stiffness of the BM along its length. The oscillators become active when they compress or modify this signal and passive when they allow the signal to pass. There is a critical point at which these may cancel each other out called the Hopf bifurcation.[57] In order to prevent this, the oscillators must possess an autoregulation process or a self-tuning property which, as can be seen later, generates a very important attribute of the cochlea in the form of a cochlear tuning curve.

Given that the critical oscillation function and the compressive function of the OHC (see below) are responsible for tuning the BM in response to an acoustic signal, which is variable along the length of the BM and is spatially represented, it can be inferred that the acoustic output, which is the end result of the BM function, is a non-linear output. In pure tones with frequencies well below the characteristic frequency (see below 'Cochlear tuning curve'), the function is linear and passive. In disease processes, the non-linearity may become linear and can be measured in the growth function of distortion-product otoacoustic emissions. Pathologies such as ototoxicity and possibly age-induced hearing loss will interfere with the non-linear function of the cochlea.

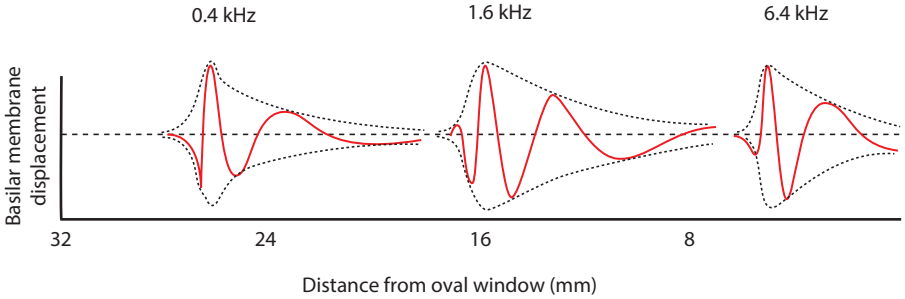

Figure 48.15 The cochlear travelling wave.

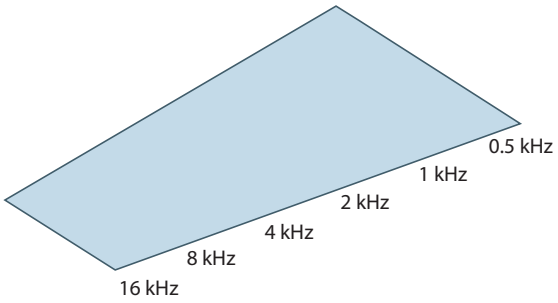

Figure 48.16 Tonotopic representation of the cochlear BM.

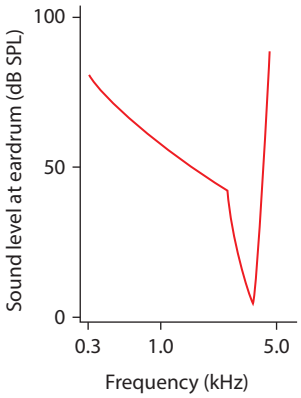

Figure 48.17 The cochlear tuning curve.

Cochlear tuning curve

The cochlear travelling wave in response to an acoustic stimulus reaches a maximum displacement somewhere along the BM following which it starts to dissipate. High-frequency sounds produce peak displacement towards the base of the cochlea whereas the peak moves progressively towards the apex as sound frequency decreases. There is therefore a clear relationship between frequency and displacement in the BM. The frequency at which the maximum displacement occurs is also called the characteristic frequency[58] at a specific place in the BM making it highly frequency-specific or tonotopic (Figure 48.16).

A cochlear tuning curve is the response of the cochlear BM to changing intensities to achieve a maximum amplitude response and is plotted as a function of intensity with frequency (Figure 48.17). A psychophysical tuning curve is the plotting of the amplitude of a narrow band masker required to mask a fixed pure tone as a function of the masker signal.[59]

The human ear has a dynamic range up to 120 dB which inherently dictates that signals of very high intensity must undergo modification at the cochlear level without damaging the cochlea and need to be compressed. The cochlea does this via the OHCs and their non-linear function, and depends on the frequency specificity or the tonotopicity of the BM.

Compression is achieved by the OHCs to generate the tuning curve. For example, a 50 dB SPL tone will result in a 10 dB SPL equivalent change in BM displacement, which inherently implies that the dynamic range is maintained with relatively lesser displacements of the BM.[58] This compression is essential for maintaining the integrity of the BM and increasing its stability in the presence of high-intensity stimuli. For lower-intensity signals, the OHCs amplify the BM response by mechanical elongation/compression of their cell bodies which sharpen the tuning curve; again, this is variable across the response, preserving non-linearity.

Another property of the cochlea is its filtering action. This is indirectly dependent on the tonotopicity. In simplified terms, the characteristic frequency is where other neighbouring frequencies are filtered so as not to interfere with the frequency selectivity i.e., the characteristic frequency is best resolved at a given point in the BM in preference to other frequencies. In other words, these neighbouring frequencies undergo some sort of a filtering action. It has been proposed that this filtering also explains the attribute of perceptual streaming.[59] This is essentially a central auditory function contributed by the ability of the cochlea to discern a rapid sequence of sounds coming from a single or a multiple source (i.e. whether the single sound is an overlap of multiple sounds or whether multiple sounds can be perceived on their own). When the sounds are close together in frequency, fusion may occur and the perception will be of a single sound as the filtering action becomes less in neighbouring frequencies. However, factors other than this overlapping of exciting frequencies may interfere.[59]

The dynamic range is significantly lost and reduced in cochlear pathologies. The tuning curve loses its sharpness and frequency selectivity is compromised along with perceptual streaming. Different pathologies may affect the shape of the tuning curve in different ways: for example, some genetic losses involve the lower-frequency sensitivity while ototoxicity affects the high-frequency sensitivity. Cochlear hearing loss therefore may show some characteristic features, including loss of frequency selectivity leading to difficulties to understand speech and appreciate music, loudness recruitment due to reduced dynamic range and a compromise of perceptual streaming which manifests itself as an inability to perceive or segregate multiple sounds at a given time. (see 'Pathophysiology of cochlear hearing loss' later in the section). These pathologies lead to a perceived hearing loss.

Cochlear fluid

The cochlea contains perilymph in the scala vestibuli and scala tympani. This is an ultrafiltrate of blood plasma and the CSF, rich in sodium and low in potassium and calcium. The scala media or the cochlear partition consists of the endolymph which is actively pumped by the stria vascularis in the scala media. This, in contrast, is rich in potassium, low in sodium and has negligible calcium. The stereocilia of the hair cells are bathed in the endolymph while the hair cell bodies are bathed in perilymph. There is another compartment called the intrastrial space which is the space between the extracellular matrix of the stria vascularis.

The cochlea is supplied by the spiral modiolar artery, which is a branch from the vestibulocochlear artery (VCA) from the anteroinferior cerebellar artery. The VCA is an end artery. The microcirculation of the cochlea, especially the stria vascularis, has certain characteristic features.

The capillary network is arranged in a parallel fashion in the lateral wall of the cochlea; there is an abundance of pericytes and fibrocytes in the network, and the cochlear blood flow is autoregulated by multiple factors which are exquisitely sensitive to changes in the internal environment.[60] These factors include local metabolites such as lactate, nitrous oxide and potassium, the pericytes and the fibrocytes, and the blood vessel smooth muscle cells. Cochlear microcirculation ensures the integrity of the cochlear fluids and there exists a blood–labyrinth barrier which is responsible for ultrafiltration and abundantly supplied with enzymes and protein subunits, for example the Na^+ - K^+ ATP subunit so important for ionic transport. The objective is to deliver energy and provide processes for ionic transport for the cochlear internal milieu. Cochlear microvasculature is affected in a number of disease processes with secondary involvement of cochlear fluid hydrodynamics which in turn lead to impaired cochlear functions. These include noise-induced hearing loss, endolymphatic hydrops and possibly age-induced hearing loss. In addition, the artery is an end artery, which implies that a blockade or obstruction to it (e.g. an embolus) if it persists beyond a certain period of time (about 15–30 minutes[61]) will lead to irreversible damage (ischaemia) to the organ it supplies, which is the cochleovestibular apparatus.[61]

The highly intricate cochlear microvasculature ensures nutrition in the cochlear compartment and also provides the internal environment for cochlear function. The main driving ion for cochlear function as furnished by different cochlear processes is potassium. The way it is recycled is called a potassium cycle, responsible for the endocochlear potential. This potential is the resting potential kept at a constant level in the scala media. From the teleological point of view, potassium is the chosen cation as the other cellular ion, sodium, entails far more cumbersome active transport systems between different media which would crowd up the BM, precluding highly sensitive hair cell function. Potassium, on the other hand, simply utilizes a concentration gradient.[62] However, the role of Na^+ for maintaining the endolymphatic potential cannot be ignored as the Na^+Cl^- ATP cotransporter in the marginal cells and in the fibrocytes of the spiral ligament ensures further potassium efflux and influx by coupling with the potassium.[63] The endocochlear potential results in a dynamic flux of ion transport in the cochlear endolymphatic space in the scala media. The stria vascularis has four cell types:[64] the marginal cells related to the medial scala media, responsible for maintaining a low potassium composition in the intrastrial space by continuous active uptake of the ion from the endolymphatic space; the intermediate cells, which have the marginal cells medially and the basal cells, laterally, are connected to the basal cells by gap junctions regulated by the connexin family genes and where the endocochlear potential is generated; and the basal cells, with the intermediate cells in their medial end and laterally connected to the spiral ligament in the lateral wall of the cochlea by gap junctions as well. potassium from the blood is actively taken up by the fibrocytes of the spiral ligament and pumped to the basal, cells which in turn deliver the ion to the interstitial cells. These cells present the ion to the intrastrial space from where they are taken up by the marginal cells. The scala media receives its ions from the marginal cells. All the active processes are regulated by various enzymatically driven potassium channels and Na–K ATP systems; the end result is maintenance of a high potassium ionic composition in the scala media which is vital for hair cell function by virtue of the endocochlear potential. Some potassium finds its way back by basolateral potassium channels in the perilymph.[65] The whole process is shown schematically in **Figure 48.18**.

Hyperacoustic stimulation depresses the potassium cycle for protecting the cochlea and actually leads to a drop in the endolymphatic potential[66] and stimulation of the P2X by the ATP pathway, which inhibits OHC motility (see below), while beta adrenergic stimulation as a part of sympathetic stimulation swings the cycle to the opposite side.[64]

Genetic mutations in the connexin family or the potassium transport family interfere with maintaining endocochlear potential and therefore sensory epithelia function. Examples include connexin 26/30 hearing loss, the commonest genetic autosomal non-syndromic prelingual genetic hearing loss, and Jervall–Lange–Nielsen syndrome with long QT interval where the *KCNQ1* ionic transport gene in the stria vascularis and cardiac conductive system is deficient.

Cochlear sensory epithelia and supporting cells

The mammalian cochlea is characterized by the presence of two distinct subtypes of sensory epithelia which differ in orientation, morphology and function. The OHCs number about 12 000 in humans; are arranged in three rows;

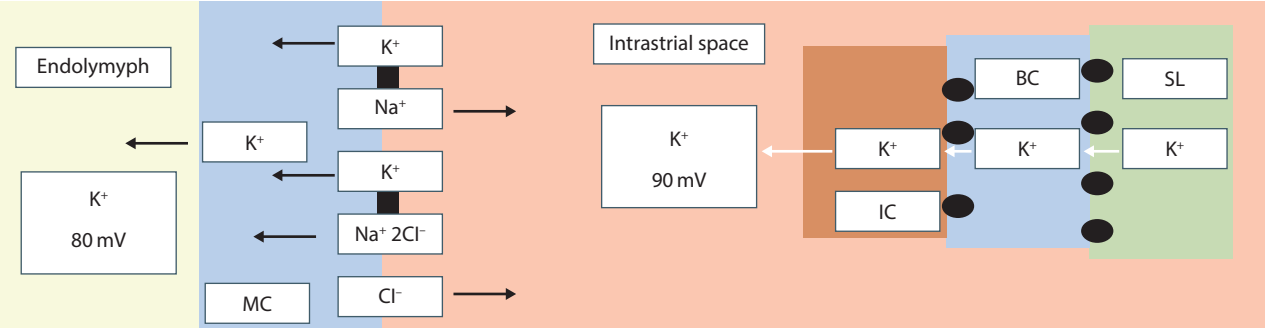

Figure 48.18 Endolymphatic fluid dynamics for generating the endocochlear potential. SL, spiral ligament; BC, basal cells; IC, interstitial cells; MC, marginal cells.

participate in electromotility leading to cochlear tuning, amplification, compression and frequency selectivity; and are innervated by type 2 spiral ganglion afferents and cochlear efferents from the medial olivocochlear bundle. IHCs are arranged in one row; number about 3500 in humans; participate in cochlear transduction of the incoming acoustic signal; largely generate the cochlear afferents to the spiral ganglion type 1 cells from where the auditory nerve commences and also receive efferents from the lateral olivocochlear bundle. Both these cells form the sensory epithelium in the organ of Corti with their apical or stereocilia side bathed in the endolymph of the scala media and their bases bathed in the perilymph of the scala tympani.

Undulations or mechanical vibrations from the BM lead to a shearing force in the tectorial membrane which in turn moves the stereocilia of the hair cells in the endolymph. Following this initial mechanical displacement, the behaviour of the OHCs and the IHCs differ and will be considered separately.

As will become apparent below, cochlear hair cell integrity depends on enzymatically driven functions to maintain structural stability. Thus mutations in the protein-encoding genes are likely to cause a sensory hearing loss.

THE OUTER HAIR CELLS

The OHCs are cylindrical with bundles of stereocilia composed of actin filaments which project at their apical ends in the scala media. BM-led tectorial membrane displacements in response to acoustic stimuli result in movement of these stereocilia in a plane parallel to their plane of orientation: depolarization when the movement is towards the tallest stereocilia and hyperpolarization/repolarization when the movement is towards the smallest stereocilia. Displacement opens up the cation-selective ionic gates responsible for transduction and generation of an action potential. A displacement of just 0.3 nm can displace the stereociliary bundle.

An action potential thus generated happens within 10 ms, which is a graded action potential (AP) mediated through the tip links between adjacent stereocilia which regulate ionic flow in this case potassium from the potassium-rich endolymph. The OHC itself is more negative than the endolymph, which facilitates movement of potassium without any energy expenditure, and it appears that, given the overall metabolic rate of the OHC with its specialized energy-expending function in modulating the acoustic signal, is nature's way of conserving energy. Potassium entry through the transduction channels then generates voltage-gated calcium channels and results in the influx of Ca^{2+} ions in the cells which participate in synaptic transmission and 10% of the depolarizing voltage.[67] The entry of potassium constitutes the depolarization stage. Repolarization occurs in two distinct processes: by the efflux of cell-rich potassium to the potassium-poor perilymph across the concentration gradient through the cation-selective ionic channels in the basolateral portion of the OHC, and by the influx of the Ca^{2+} mentioned above. There is a fine balance between the two and, if this balance is lost (i.e. if there are fundamental problems with either the potassium or the Ca^{2+} delivery or gated controls), then the cochlea OHC loses its tuning curve and therefore part of its function.[68]

The action potential is transmitted to the type 2 spiral ganglion cells, which are essentially non-myelinated and smaller than their IHC counterparts and not as developed. They show reciprocal synapses with their OHC counterpart, i.e. the type 2 cells feed back to the OHC providing a pathway for a closed loop neuronal circuit for bidirectional signalling and reverse transduction.[69] It should be noted that the action potential in the OHCs does not carry auditory information to the auditory nerve. Its job is to provide a motor for altering OHC physical dimensions for further displacement of the BM. The force contributed by this motor is sufficient to drive the acoustic signal through the entire length of the cochlea as an additional travelling wave as well as providing enhanced modulation at a local, site-specific area of the BM[70] (see also 'Cochlear travelling wave'). It also leads to movements of the tectorial membrane itself to open up further ionic gates and augment the AP and amplification process. Note that some type 2 cells are carried through the auditory nerve (only 5%) to synapse at the cochlear nucleus.

The OHC exhibits the special feature of electromotility, which is a highly sensitive attribute as cochlear motility translates frequency specificity and amplification and is responsible for fine-tuning of the acoustic signal. In response to acoustic stimulation of the BM, this motility is driven by two forces: a voltage-dependent mechanotransduction (MET – see last paragraph) that moves the hair bundle with an active movement[68] and a somatic non-linear capacitance prestin-mediated motility[71] which modulates the stiffness of the stereocilia and makes them alter their sizes. Prestin is a crucial component, abundantly located in the lateral membrane of the OHC, which belongs to the SLC26A family and participates in selective anion transport and binder, in this case chloride and carbonate. The action of prestin is voltage-dependent and results in either contraction or elongation of the OHC necessary for augmenting the acoustic signal incident on the BM. Cochlear electromotility is sensitive to frequencies and intensities of the signal.

The OHC in addition receives efferents from the medial olivocochlear bundle in the brainstem which synapse with the spiral ganglion type 2 nerves, offering a regulation of the reverse transduction process.

THE INNER HAIR CELLS

The IHCs are the true sensory end organs for hearing and are responsible for generating the action potential which then is conducted to the type 1 spiral ganglion cells to be delivered to the auditory nerve. The spiral ganglion type 1 nerve endings are myelinated and synapses here are well developed with ribbons and glutamate activity, unlike the OHC synapses.[72] The IHCs are non-actively motile and receive the output from the OHCs through the modified movement of the BM at a given region of the BM.

The IHCs are depolarized as a result of BM movements causing deflection of the stereocilia. The depolarization is mediated by cations potassium and Ca^{2+}, the latter being crucial for synaptic action through chemical neurotransmitters

especially glutamate.[73] The IHC synapses do not exhibit any reciprocal arrangement, unlike the OHC. Ca^{2+} release is mediated by voltage-dependent depolarization mediated by potassium of the IHC apical membrane, i.e. the stereociliary deflections.

Since it delivers the eventual output of cochlear function, the IHC needs to contain all the information amassed so far in the form of coding to the cochlear nerve. There are two types of coding, namely frequency coding and intensity coding.[74] The IHCs phase-lock with the stimulation frequency under 5 kHz while, above this frequency, the frequency-specific depolarization/repolarization is too fast for the IHCs to phase-lock. Intensity coding is by way of an increasing number/rate of action potentials proportional to stimulus intensity (see also 'The auditory nerve').

THE COCHLEAR SUPPORTING CELLS

Increasing evidence is emerging as to the important function served by the cochlear supporting cells (i.e. Hansen cells, Deiters cells, pillar cells, interphalangeal cells and border cells). In addition to providing a scaffold for anchoring the hair cells, these cells also participate in cochlear function and stability.

The supporting cells contribute to the development, differentiation, patterning and synaptogenesis of the hair cell sensory epithelia. From a common precursor, cellular differentiation and their mosaicism dictate variable cell line maturity and feed into each other by the process of autoregulation: if this enzyme-driven process is disrupted, then supporting cell populations might be converted to hair cells and vice versa.[75] Another important function of the supporting cells is that they contribute to the planar cell polarity (PCP) of the hair cells, which essentially is the stable plane of orientation of the basal and apical ends of the hair cells which expose them to the right environment for mechanotransduction. In fact, the supporting cells are abundant, with a PCP regulator which has been shown to regulate the orientation of the stereocilia.[76]

In the mature cochlea, the supporting cells provide the anchor and the platform for tight adherence of the sensory epithelia to the BM at the basal surface and form the reticular lamina at the apical surface where it separates the endolymph from the perilymph and helps maintain the endocochlear potential. They provide proteins for maintaining the extracellular matrix of the BM and thus maintain rigidity and stability of the hair cell population. They further contribute importantly to the homeostatic process by serving four functions:

- By virtue of being endowed with Na^+ gates, they take up Na^+ from the endolymph, ensuring a low concentration of the ion in the scala media.
- They assist in the potassium cycle, especially in the basolateral part of the BM.
- They influence glutamate activity at the hair cell synaptic regions.
- By virtue of their gap junctions (which are regulated by connexin 26), they are involved in the passage of ions and compounds either across the concentration gradient or actively by the ATP mechanism. This ATP-mediated energy-expending process also leads to Ca^{2+} coupling in the hair cells;[75] Deiters cells have an internal Ca^{2+} store which can be readily available in cases of need.[77]

Supporting cells may play a role in the eventual repair and regeneration of the hair cells in response to damage, as they are shown to do particularly in birds.[78] At the moment, mammalian hair cells show no evidence of regeneration although there might be low-level repair in vestibular hair cells.[79]

Curiously, there is nerve innervation of the supporting cells which implies that these cells can generate an action potential. These nerve endings do not synapse with the cochlear efferents or contribute to the formation of the cochlear nerve; they are considered to be a part of the internal neural circuitry which characterizes OHC afferents and participates in OHC non-linear fine-tuning of the acoustic signal through BM activity.[80]

Mutations in genes encoding for supporting cell proteins will lead to cochlear sensory loss. For example, in addition to maintaining gap junctions in the stria vascularis, connexin 26 is also expressed in the supporting cells and a mutation will lead to the loss of structure, stability and integrity of the hair cells through the supporting cell mechanism. *DFNB29*, a cause of autosomal recessive hearing loss, is characterized by a mutation in the gene containing claudin, which is a structural protein of the reticular lamina responsible for tight junctions. A loss of this tightness leads to increased potassium permeability from the scala media to the hair cells, resulting in a drop of the endocochlear potential and loss of function.[81]

Pathophysiology of cochlear hearing loss

Loss of cochlear function for any reason will result in a drop in auditory sensitivity; a drop in complex sound appreciation and analysis due to the loss of frequency selectivity; loss of fine-tuning of the acoustic signal with narrowing of the dynamic range of hearing due the loss of non-linearity, amplification and compressive properties; loss of perceptual streaming due to the loss of frequency selectivity; and loss of temporal pattern of sounds due to the loss of spatial discrimination and the ability of the cochlea to distinguish between closely following frequencies and intensities.

- **Structural abnormality:** A cochlear dysplasia of any kind leads to ill-formed or absent cochlear components. This can follow a congenital maldevelopment, trauma or a space-occupying lesion and will lead to a cochlear hearing loss.
- **Abnormal metabolic activity:** Since ionic transport dictates cochlear function, it follows that a metabolic abnormality (systemic or otherwise) that interferes with cochlear ionic transport as a result of either a genetic syndrome or an acquired condition (e.g. problems with glucose metabolism or thyroid metabolism) will lead to changes in the endolymphatic potential and affect cochlear function.

- **Vascular changes:** Cochlear vascular afflictions (either systemic or local) will lead to a compromise in stria vascularis function; a diminution in cochlear nutrition and hypoxia; sluggish vascular flow or complete obstruction of the cochlear arterial blood flow. Examples include pressure effects due to any cause, noise trauma and ototoxicity, transient ischaemic attacks (TIAs) and hyperviscosity for any reason. Endolymphatic hydrops, i.e. an expansion of the endolymphatic space for any reason including a lack of integrity of the stria vascularis (e.g. Ménière's disease or endolymphatic fluid disturbances such as third window syndromes) will lead to a compromise in function of the stria vascularis.
- **Overloading the BM:** A crowded or loaded BM due to local or systemic causes (e.g. a metabolic syndrome such as diabetes, hyperlipidemias, iron overload, inflammation or autoimmune conditions) will prevent OHC motility and IHC loss of transduction.
- **Infection and inflammation:** An inflammatory involvement in the cochlea leads to the disruption of the biochemical pathway of cochlear function (see below) and the accumulation of toxic lipid-derived substrates which hamper cochlear function.
- **Genetic mutations:** As indicated earlier, a genetic mutation in the genes encoding for numerous proteins involved in cochlear function, from ionic transport to structural proteins, will lead to a cochlear hearing loss. The different genes expressed in the cochlea are given in a seminal publication by Nishio et al.[82] The Hereditary Hearing Loss home page lists genetic hearing losses with phenotypes and genotypes and is updated continually.[83]
- **Biochemical pathway abnormalities:** In response to noise trauma, ototoxicity and due to cumulative wear and tear action in presbycusis, a biochemical cascade for cochlear hair cell integrity loses its balance leading to apoptosis and subsequent cell death. This cascade suggests that, theoretically at least, pharmacological intervention aimed at various steps in the cascade can reverse the process. Figure 48.19 illustrates this.

Otoprotective endogenous compounds play an important role in preserving the delicate cochlear structures and influence the biochemical cascade, although in a rather heterogeneous way. These include heat shock factors (HSFs) and heat shock proteins (HSPs), both abundantly expressed in the cochlea, which can modify the apoptosis response;[84]

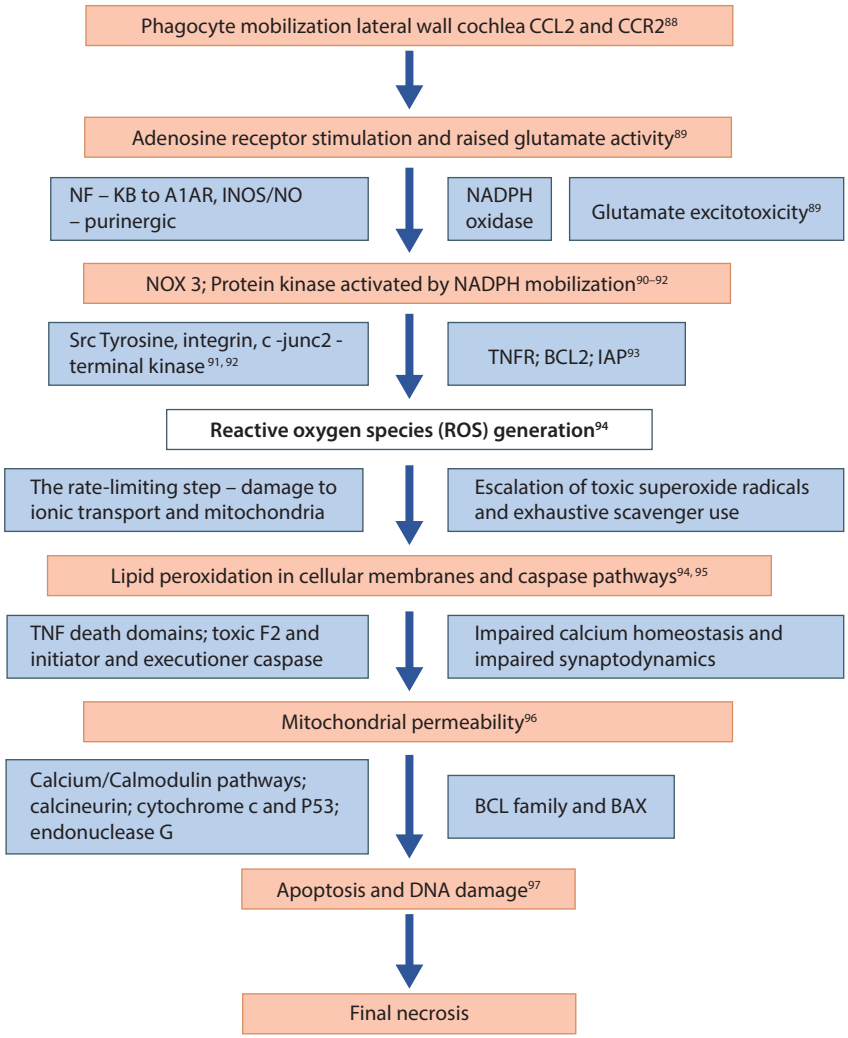

Figure 48.19 Biochemical pathway/enzymatic cascade for hair cell damage.

downregulation of some growth factors;[85] neurotrophin, mainly glial cell-derived neurotrophic factor (GDNF) regulation,[86] to modify the end result of apoptosis for recovery of function and the coenzymes Q9 and Q10.[87]

THE AUDITORY NERVE AND COCHLEAR EFFERENTS

The auditory nerve

The auditory or cochlear nerve, cranial nerve VIII, originates from the joining of the spiral ganglion cells in the cochlea where their cell bodies lie. There are two types of nerve fibres originating from the spiral ganglion cells: type 1, which have large diameters, innervate the IHCs constituting 95% of the nerve fibre population and are myelinated, and type 2 fibres, which are smaller diameter, innervate the OHCs and are unmyelinated. The nerve traverses the internal auditory canal and joins with the vestibular nerve forming the vestibulocochlear nerve. One type 1 fibre innervates one IHC but one IHC may synapse with several nerve fibres. The cochlear nerve fibres terminate at the cochlear nuclear complex located in the medulla of the brainstem.

The synaptic architecture of the hair cells and the spiral ganglions is discussed in detail in 'The cochlea' above. The cochlear nucleus synapses with the cochlear nerve and is represented tonotopically, which implies that frequency encoding by the cochlea is carried up to the central nervous system to be further analyzed.

The action potential of the cochlear nerve in response to acoustic stimulation entails a release of bundle synaptic receptors proportional to the stimulus, which results in spike potentials which are short-lived and attain their peaks quickly. The rates of the spikes vary depending on the intensity and the frequency of the incident sound. Each fibre fires most at a given frequency (called the characteristic frequency) like the spatially represented characteristic frequency in the cochlear BM which facilitates transfer of the tonotopicity to the nerve from the cochlea. For example, fibres from the base of the cochlea will lead to increased firing of the fibres with a high characteristic frequency.

The discharges of the fibres to low-frequency sounds occur at particular times, in other words, there is a phase-locking mechanism which occurs up to 5 kHz.[98] Phase-locking is important to convey temporal information of the incoming signal.[99] A two-tone suppression model is also present in auditory nerve function which dictates that a second stimulus close to the characteristic frequency of the first one will suppress the first, facilitating the representation of complex and multiple stimuli in the nerve which is a non-linear function.[100]

Intensity coding also occurs in the nerve fibres. Nerve fibres possess spontaneous firing activity without sound stimulation. Fibres with high spontaneous firing rates have a low threshold for intensity while fibres with intermediate and low spontaneous firing rates have a high threshold.[101] Stimulus intensity thus influences the firing rate of the nerve fibre: the higher the stimulus intensity, the higher the firing rate, with a saturation point where it plateaus off,[102] which is important for adaptation as explained below. Thus, the fibre codes for intensity as well.

The auditory nerve is the beginning of central processing of the acoustic stimulus delivered from the periphery. This is in the form of auditory nerve adaptation which entails a spike frequency adaptation where the spike in response to a stimulus quickly adapts and reaches a plateau that is more pronounced in high-frequency fibres than the lower ones.[103] Adaptation, which is found in neurons elsewhere, is crucial in the auditory context as it provides vital cues to the brain regarding timing of the signal. Adaptation gets progressively complex and sophisticated in the brainstem and the cortex.

The auditory nerve can be affected by a variety of disease processes which include pressure effects by space-occupying lesions such as a VS; the demyelination processes such as in multiple sclerosis; granulomatous lesions; head trauma; viral illnesses; congenital dysplasias and autoimmune disorders. Essentially, the tuning curve and the phase-locking properties are affected and lead to a failure in encoding time, frequency and intensity information. This is a classical neural deafness. ABRs are a robust way of measuring auditory nerve function and may be used for prognosticating a demyelinating lesion.[104]

The condition auditory neuropathy spectrum disorder (ANSD) deserves special mention. This is defined as a disorder with abnormal auditory brainstem morphology but preserved cochlear OHC function (although measured cochlear OHC function may disappear with time). Structurally, the nerve is unremarkable, especially on imaging, and most likely the damage is at the molecular level precipitated by a few known risk factors such as hypoxia, hyperbilirubinemia and prematurity. Neuropathies such as Charcot–Marie–Tooth and Mohr–Tranebjaerg syndromes or mitochondrial syndromes can cause ASND.[105] Metabolic conditions such as diabetes have a theoretical risk of causing it, especially those which are complicated.[106]

ANSD can be inherited as an autosomal recessive disease, now called *DFNB9* due to the mutation in the gene otoferlin, and presents with profound behavioural neural hearing loss.[107] A second autosomal recessive gene pejvakin has been identified as well which causes ANSD named as *DFNB59*.[108] This may respond to cochlear implants. Previously thought to be a condition involving only the auditory nerves after it has been formed, i.e. beyond the spiral ganglion level, it is now thought to extend to the IHC spiral ganglion synaptic junction and may include the IHC itself. It gets picked up by the newborn hearing screening programme but can affect adults also. The auditory sensitivity as measured by a pure-tone audiogram may be normal but the patient has significant processing problems or the sensitivity might be significantly decreased (e.g. up to severe hearing loss on the PTA). Aiding these patients is difficult as augmenting amplification at the cochlear level may not lead to any benefit in the nerve dysfunction, although it may improve some phase-locking; in addition, providing excessive amplification to a normal cochlea may

be damaging to the cochlea itself. The effect of implantation is also variable; however, theoretically, patients whose condition is limited to the inner ear (the IHCs or the IHC–spiral ganglion synaptic junction) have a better outcome than patients with the problem once the nerve is already formed.

Cochlear efferents

The cochlear efferent system consists of projections from both the lateral olive and the medial olivary complex which synapse mostly with type 1 spiral ganglion cells and type 2 spiral ganglion cells respectively and thus connect to both the IHCs and the OHCs.[109] The efferent fibres are carried by the inferior vestibular nerve and meet at the anastomosis of Oort through the saccular branch of the nerve to join up with the cochlear nerve.[110]

The ratio of efferent to afferent fibres in the OHC is 1:2 whereas those in the IHCs is 1:7,[111] suggesting that the biological amplifiers are the main substrates of efferent function which in turn inherently implies that the signal modulation is primarily a function of the OHC. The medial system innervates both ears while the lateral system supplies only the ipsilateral cochlea. Both project to the different parts of the ventral cochlear nucleus.

The cochlear efferents serve an important function by virtue of their modulation of inhibitory and excitatory neurotransmitter release in the cochlear processes thereby offering cochlear protection from loud noise. The activation of the efferent system modifies frequency-specific gain at the tonotopic BM by acting on the voltage-dependent OHC motility and attempts to linearize the signal with a damping effect.[109] Other functions include fine perception of the acoustic signal for localization, improving the signal-to-noise ratio and supporting adaptation and frequency selectivity. Their function may be compromised in acoustic trauma, ototoxicity, tinnitus and ANSD.[109] The medial olivocochlear bundle function can be measured by contralateral suppression of otoacoustic emissions.

KEY POINTS

- The pinna and EAC participate in localization of sound and, acting as a unit, contribute to add resonance to the incident sound which in turn aids in matching impedance encountered when sound travels from an air-filled medium in the middle ear to a fluid-filled medium in the cochlea.
- The middle ear by its mechanical processes contributes to match the impedance as described above.
- The cochlea receives the oncoming acoustic signal from the middle ear and a cochlear travelling wave is generated which traverses the BM of the cochlea stimulating cochlear OHC function which acts non-linearly as a biological amplifier/compressor and modifies the incident signal.
- The BM of the cochlea is highly frequency specific.
- The IHCs in the cochlea transduce the mechanical or kinetic energy of the OHC influenced cochlear travelling wave to an electric action potential and synapse at the spiral ganglion to form the auditory or cochlear nerve.
- The cochlea participates in frequency resolution, intensity discrimination and temporal ordering of incident sound.
- The auditory nerve phase locks and synchronizes with the IHCs and processing of sounds commence.
- The cochlear efferents originate from the brain to synapse with the cochlear hair cells regulating their function and help in localization and improving signal-noise ratio.

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CHAPTER 49

PHYSIOLOGY OF EQUILIBRIUM

Floris L. Wuyts, Leen K. Maes and An Boudewyns

SEARCH STRATEGY

Data in this chapter may be updated a PubMed search using the keywords: vestibular system, vestibulo-ocular reflex (VOR), central pathways of VOR, hair cells and mechanoelectrical transduction.

ROLE OF THE VESTIBULAR SYSTEM

Introduction

Many physiological systems and functions have to be interpreted in view of survival of the species. The main function of the mammalian vestibular system is to generate information to the central nervous system with a fourfold purpose:

1. to ensure gaze stabilization
2. to enable balanced locomotion and body position
3. to provide general orientation of the body with respect to gravity
4. to readjust autonomic functions after body reorientation.

To achieve this, several input systems provide information to the brain, such as visual, vestibular and proprioceptive systems (**Figure 49.1**), but also other clues such as hearing are used, although these are of lesser importance.

Central processing of all this information in the brain leads to distinct outcomes:

- the vestibulo-ocular reflex (VOR) to ensure gaze stabilization
- the vestibulospinal (VSR) and vestibulocollic reflexes (VCR) to ensure maintenance of upright position of body and trunk and head stabilization in space
- orientation and, in higher species, navigation and the perception of self-position with respect to the surroundings and gravity mediated by the vestibular cortex
- autonomic function adjustments after alterations of body orientation.

This list of outcomes is certainly not restricted to these four tasks, since, for example, the vestibular system has recently been shown to influence the circadian rhythm,[1] and there are also connections with cognitive function.[2] Circadian influence is most likely due to direct projection of the vestibular nuclei to the Suprachiasmatic Nucleus (SCN). Hormonal connections are to be studied.

Although visual, vestibular and proprioceptive inputs are constantly processed by the brain, this information is heavily weighted by other factors, such as learning, memory, drugs, ageing, as well as environmental conditions. Additionally, the weight of the different inputs is constantly adjusted depending on the circumstances. It is obvious, for example, that when walking in darkness, balance cannot rely so heavily on vision and so reliance on the somatosensory and vestibular senses is increased. For optimal functioning in daily life, all systems are needed and there is little redundancy in the systems.

Motion decomposition and orientation in the head

Every motion in space can be broken down into three rotational degrees of freedom (yaw, pitch and roll) and three translational degrees of freedom (left–right, up–down, fore–aft). No event in one degree of freedom can

be described by the others, hence every movement is uniquely and appropriately described by a combination of all six degrees of freedom. The anatomical design of the motion sensors in the peripheral vestibular system in the inner ear reflects these six degrees of freedom. The semicircular canals (SCCs) measure predominantly rotations whereas the maculae of the utricle and saccule detect mainly translations.

The orientation of the vestibular system in the head is depicted in Figure 49.2. In a first approximation, one can model the left and right canals as parallel systems, i.e. the right anterior (RA) canal is parallel with the left posterior (LP) canal and both lie in a plane denoted as the RALP plane. Together with the right posterior (RP) canal the left anterior (LA) constitutes the LARP plane. Both horizontal canals are also parallel with each other in the lateral plane. The horizontal canal makes an angle of approximately 30° up with the horizontal axis of the upright head. The angles of the vertical canal are approximately 45° with the sagittal plane of the head. When studied in more detail, however, there exists a great variability of orientation within and between subjects.[3] In addition, the canals themselves are often quite curved, as seen in Figure 49.3.

Movement detection

Basic laws of physics are responsible for the detection of movement or orientation by the vestibular system. The first law of Newton states that 'objects in motion will stay in motion until acted upon by a force'. This force can change either the object's direction or speed. The second law states that a force (F) acting on an object equals mass (m) times acceleration (a) ($F = m \times a$). During daily life, body and head are continuously moving (even during each heartbeat, the head and body are shaking a little), and these movements are always related to forces, i.e. accelerations. These movements are sensed in the vestibular organ by a rigid coupling of sensory epithelium to the bony structure. Thus, a fluid-filled system is attached to the skull and the inertial forces drive the fluid. Motion of the fluid lags behind any motion of the head and this relative displacement is the trigger for movement detection. To limit the movement of the hair cells triggered by the accelerations that drive the head movements, the canal system is designed such that the deflection of the hair cells is proportional to the head velocity.

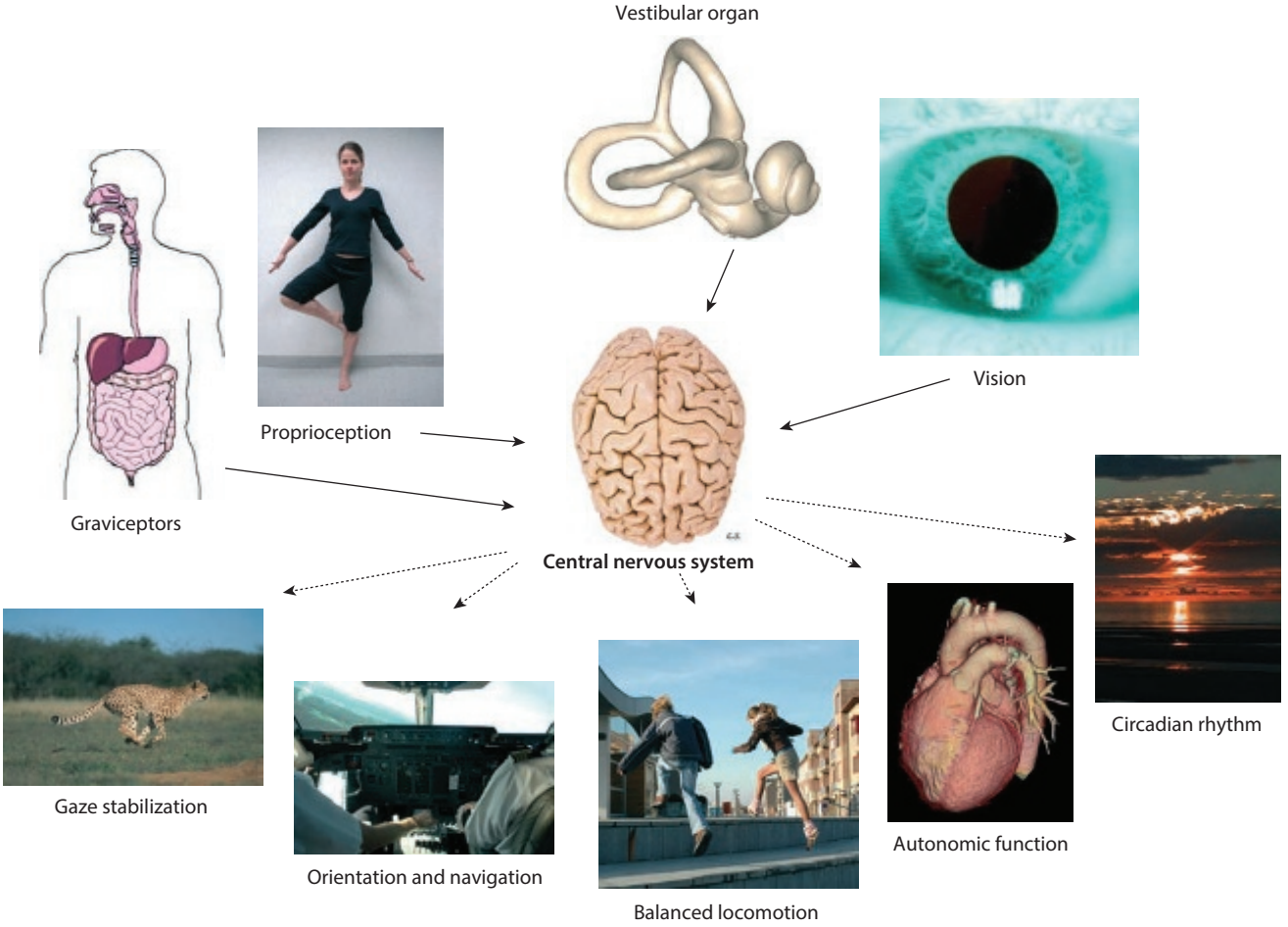


Figure 49.1 Basic input and output scheme of the vestibular system. Main inputs constitute vision, proprioception and information from graviceptors in the body and from the labyrinths. Outputs are gaze stabilization (needed for hunting and food tracking), balanced locomotion, perception of orientation in the surrounding world and autonomic function regulation after altered body position.

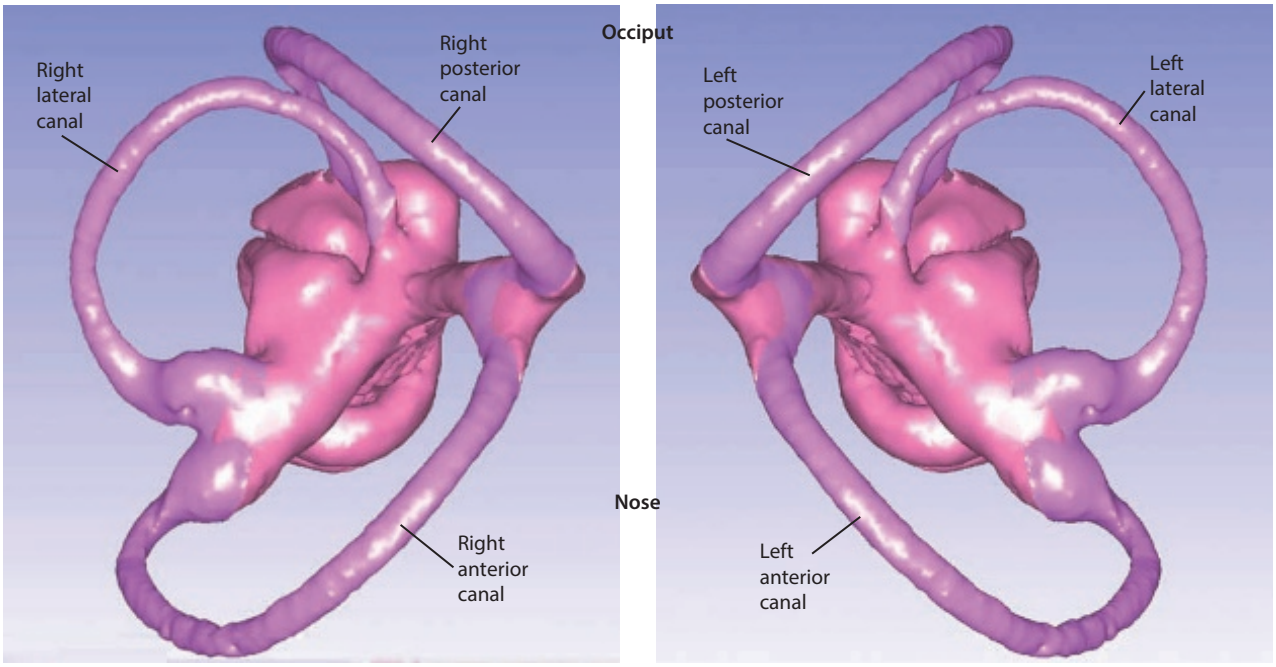


Figure 49.2 Top view of labyrinths as oriented in the human head. The labyrinths are of a gerbil.

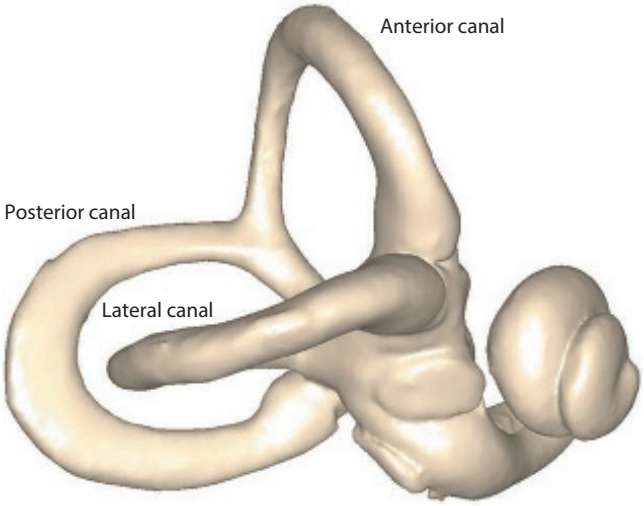


Figure 49.3 Side view of a right human labyrinth (labyrinth filled with resin and bone cut away). The nose is on the right side. The lateral canal makes, in general, an angle of 30° with the horizontal axis of the head.

OTOLITH ORGANS

On Earth, the gravitational force acts on us permanently, hence gravitational acceleration needs to be detected continuously. This is the role of the otolith organs. They additionally detect all linear accelerations. The otolith organs are designed such that they detect the accelerations and send encoded signals to the brain that processes this information. The otolith organs saccule and utricle are relatively orthogonally oriented to each other, with the utricle relatively horizontal and the saccule predominantly vertical (tangential in the head). Consequently, motion in the horizontal plane triggers predominantly the utricle, and vertical movements trigger mainly the saccule. Both organs are, however, quite curved so that any movement is in fact detected by both organs.

Thus, both the saccule and the utricle sense linear accelerations caused by translational movements of the head as well as static tilts of the head. This is enabled by an otolithic membrane, a gelatinous membrane stacked with otoconia (calcium carbonate crystals) characterized by a density about three times higher than that of the surrounding endolymph. Hair cells are embedded at the base of the gelatinous membrane, so that any movement of the membrane results in a deflection of the hair cells, which in turn codes for a signal to the brain. The working of the hair cell is explained under 'Vestibular sensory cells' below.

Einstein's equivalence principle states that no single physical device can distinguish gravity from linear acceleration. This poses a difficulty for the central nervous system, since the otoliths cannot differentiate between linear acceleration and tilt since only the deflection at the base of the hair cells is encoded and sent to the brain. This is illustrated in Figure 49.4. During natural movements (active or passive), the otolith organs sense the sum of all accelerations acting on the head and interpret these signals to initiate postural and eye reflexes mediated by the vestibular nuclei, diverting the appropriate signals either to limb, trunk and neck muscles via the vestibulospinal tract or to eye muscles via the VOR. The interplay of several senses at the same time (visual, vestibular and proprioceptive) enables the central nervous system to cope with the ambiguity of linear accelerations, enabling humans to distinguish tilt from linear translation under normal conditions. In darkness, however, when the system is relying on vestibular cues, Angelaki et al.[4] have shown evidence that an internal model of head orientation exists. This model is presumably constructed in the vestibulocerebellum

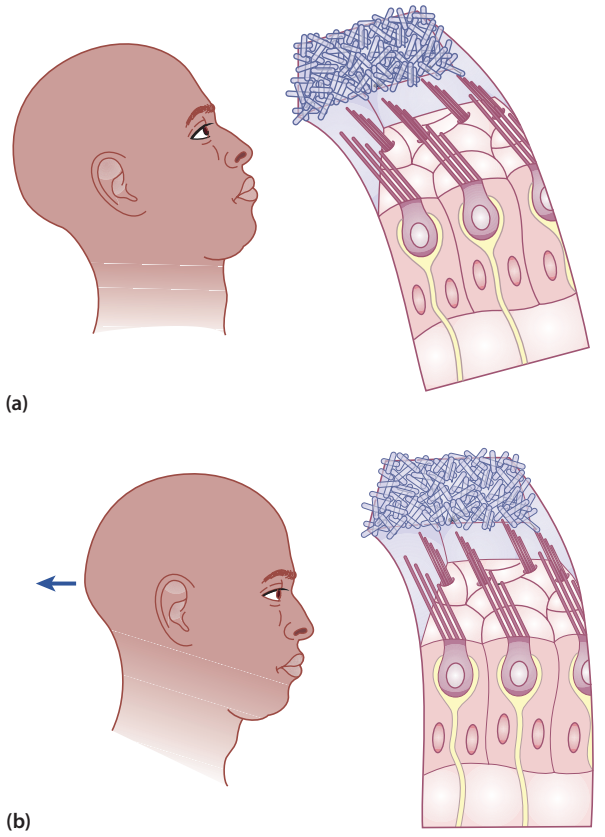


Figure 49.4 Deflection of the otoconial mass causes hair cell depolarization. This deflection is identical when the head is tilted backward **(a)** or when accelerating forward **(b)**.

(floculus and nodulus) and the vestibular nuclei, and it resolves the ambiguous gravitoinertial cues that are measured by the graviceptors, as well as with input from the SCCs. Both sets of information are used to help interpret ambiguous gravitoinertial cues. This implies that the signals from the otoliths and from the canals are not treated separately in the brain, and are continuously combined to optimize the VOR, as can be deduced from the fact that almost all partitions of the vestibular end organs overlap in most of the vestibular nuclei and project to several parts of the vestibulocerebellum.

SEMICIRCULAR CANALS

The moving endolymph in the SCCs is the key trigger for movement detection of the head. Natural movements of mammals consist dominantly of transient rotations, such as during back and forth movements of the head (e.g. nodding), or during walking and running. The SCC system is evolutionarily adapted for these movements. Whereas head accelerations trigger the sensory epithelium, the signal that is transmitted to the brain is proportional with the head velocity. Head accelerations can raise up to several thousands of degrees per second square, while head velocity is limited to several hundreds of degrees per second. Sustained velocity is no longer detected nor perceived after approximately 30 seconds.

Passive forms of motion, such as aeroplanes, merry-go-rounds, cars, rollercoasters or even spaceships, however, generate more intricate movements, and can readily introduce motion sickness since the vestibular apparatus is not adapted to this kind of motion.

The configuration of the SCC allows the movement of the endolymph only in the direction along the cylindrical canalicular cavity. When such a canal is rotated about an axis, three forces act upon the endolymph and cupula in the canal:

- the inertial force, proportional to the mass of the endolymph and cupula
- the elastic restoring force of the cupula that positions the cupula back to the centre position after stimulation
- the viscous forces that act upon the fluid when sliding past the internal wall of the tube. This viscous force is dependent on the speed of relative movement of the endolymph with respect to the wall.

The behaviour of the SCC, referred to as the pendulum model, is governed by the fact that any stimulus (head angular acceleration) provokes a number of reactions within the canal. These include movement of the fluid, determined by its inertial mass, together with its viscous drag along the wall and the restoring force pulling the cupula back to its resting position.

The cupular deflection can be described as a function of the applied stimulus to the head, purely based on physical laws, even without any interference of the central nervous system. The cupular deflection is ultimately the signal that is fed to the brain, because this deflection triggers hair cell depolarization or hyperpolarization. Therefore, it is important to know the specific behaviour of this endolymph–cupular system upon stimulation. Engineers typically approach this kind of system as a transfer function where a given input leads to a specific output. Gain and phase are two quantities that describe very appropriately the behaviour of such a system. Gain expresses the amount of output per input, and phase describes the time difference between output and input.

Given the very small size of the canal ($r \approx 0.15$ mm,[5] the inertial forces that act on the endolymph become very small with respect to the viscous forces that act upon the fluid. Although it is a quite watery substance, endolymph acts as a thick, viscous oil in the small dimensions of the canal. So, rather than being left behind due to its inertia, this fluid is dragged along the walls of the canal, and the relative displacement of the fluid with respect to the wall is of the order of a few microns for very fast head movements. Consequently, the viscous flow 'velocity' of the endolymph becomes proportional to the head's angular 'acceleration'. However, if this holds true for a system, then the flow displacement also becomes proportional to head velocity (after mathematically integrating for time). This is a very important finding, which implies that the message that is sent to the brain, initiated by a deflected cupula which is directly related to the fluid movement, is coding for the head angular velocity (and not its angular acceleration).

The time constant T1, determined by the viscosity and the mass of inertia of the endolymph yields approximately 0.003 s. This means that, when a sudden angular velocity is applied to the head, the cupula reaches 67%, i.e. $(1-e^{-1})$, of its ultimate deflection after just 3 ms. Translated to actual movements, this means that the cupula is deflected almost instantaneously upon movement of the head, signalling the amount of deflection to the brain, which is proportional to the head angular velocity. The design of the SCC enables it to function as an integrator, i.e. inertial force-driven acceleration is reduced to velocity. In normal conditions the head angular accelerations can be very high (in the range of 4–5000 degrees/s^2)[6] so that the time integrator from acceleration to speed limits the deflection of the cupula and presumably prevents it from large excursions that may damage the sensory epithelium.

Many dynamic systems are frequency dependent and yield functionally different kinds of information according to the frequency content of the input stimulus. The frequency region is determined by cut-off frequencies, denoted often by 1/T1 and 1/T2, with T1 and T2 being time constants of the system. Between these frequencies, 0.1–5 Hz, the canal–cupula system is characterized by an appropriate response in amplitude and phase. A gain equal to 1 implies that the output (cupular deflection) matches closely the input (head angular velocity). A phase close to zero indicates an instantaneous reaction. A bode plot (**Figure 49.5**) illustrates this behaviour.

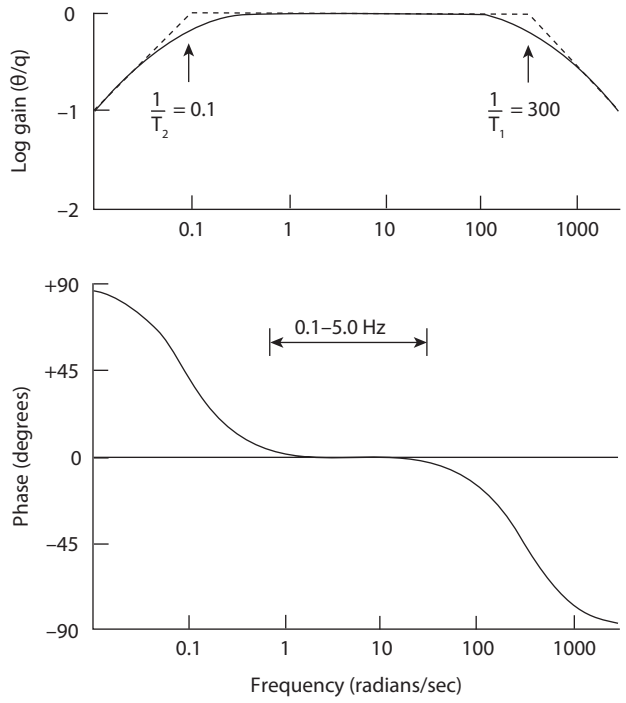


Figure 49.5 Bode plot representing the response of the SCC sinusoidal rotations. The optimal response consists of immediate and appropriate deflection of the cupula what is transmitted to the brain. This optimal situation is characterized by a gain of 1 (log gain = 0) and a phase of zero degrees. Between 0.1 Hz and 5 Hz, this optimal behaviour of the endolymph-filled SCC is achieved in humans, enabling gaze stabilization for these frequencies.

Below or above the frequencies 1/T2 and 1/T1, the gain is reduced and the phase lag is increased. For humans the typical frequencies of natural head movements during walking and running for yaw, pitch and roll are approximately between 0.5 Hz and 5 Hz.[7] Recent work by MacDougall and Moore[8] proves that the 'human resonant frequency for locomotion' is 2.00 Hz ± 0.03 Hz (mean ± s.e.) for vertical head movement, regardless of the activity (e.g. walking, riding a bike uphill, cleaning).

Velocity storage

The above description modelling the deflection angle of the cupula largely explains the behaviour of the vestibular system during laboratory testing, achieved with rotatory chairs. Typical stimulation patterns exist of sinusoidal rotations, usually around 0.05–0.1 Hz, although with more sophisticated equipment higher rotations up to 1 Hz can be achieved. Characteristic for sinusoidal rotations is that the angular velocity and acceleration are varied with sine and cosine functions, respectively. Also used are velocity step tests where a sudden acceleration rotates the subject at a constant velocity and then, after a plateau of constant speed, the chair is suddenly stopped (a ramp test). A variation of this is the test where the speed is gradually increased by applying a constant yet slow acceleration (e.g. 5 degrees/s^2) for 40 seconds to reach a speed of 200 degrees/s, followed by a plateau during which the nystagmus fades away, and then suddenly the chair is stopped.

The SCC system is not designed for sustained rotations, and even rotating at relatively high but constant speeds (> 200 degrees/s) is not sensed by the SCC after approximately 30 seconds. Only the acceleration or deceleration phase is detected. During constant speed rotations, elastic forces pull the cupula again into its centre position. However, after sudden cessation of the rotation (e.g. with a deceleration of 400 degrees/s^2), the endolymph continues to move within the SCC and a nystagmus in the opposite direction becomes evident for another 20–30 seconds. The subject has the impression of being spun around in the opposite direction. After a longer time the nystagmus fades away and may reappear again in the initial direction (post-rotatory nystagmus). Based on mathematical principles and physiological measurements, the time constant during which the cupula repositions itself is determined as approximately 5–7 seconds, which implies that the cupula is almost entirely restored to its central position after 12 seconds. This gradual decrease in cupular deviation results in a decrease in firing rate of the vestibular neurons to the brain, suggesting erroneously a progressively lower head velocity. The fact that the nystagmus outlasts this mechanical phenomenon is due to the so-called 'velocity storage mechanism' (VSM)[9] which is a neurophysiological process, taking place mainly in the nucleus prepositus hypoglossus and the adjacent medial vestibular nucleus. The VSM serves to maintain the VOR at low frequencies (below about 0.02 Hz). The VSM uses principally the peripheral labyrinthine signal and by a process of integration, in the mathematical sense, increases the frequency

response of the VOR, by prolonging the time constant (originally 7 seconds) of the decay of the vestibular nystagmus to approximately 20 seconds. This circuitry is therefore a mechanism that stores neural activity related to head and eye velocity and discharges it over its own time course.

In conditions where visual information of the surrounding rotating world is present during sustained rotations, the optokinetic reflex comes into play and, although slower in response, this takes over the fading performance of the vestibular system. The transition between both reflexes is facilitated by the VSM. Indeed, the VSM not only regulates the dynamics of the VOR but also accounts for optokinetic (after) nystagmus (OKN), i.e. the reflexive eye movements that are induced by a moving background (e.g. while looking outside the window of a moving train). The VSM coordinates these two oculomotor responses that are related to self-motion. Whereas the VOR shows high-frequency behaviour, the OKN reflects low-frequency characteristics. Matching of their time constants in the brain assures smooth transition from the quick-onset vestibular response into the slow-onset optokinetic response. Together, the VOR initially and the OKN subsequently, matched and fine-tuned by the VSM, ensure gaze stabilization.

Interestingly, the time constant of velocity storage is influenced by static inputs from the otoliths. It can be reduced considerably when the head is suddenly tilted (tilt dumping) just after the velocity step, and it is shorter during off-vertical axis rotations.[10–11]

Vestibulo-ocular reflex

The peripheral sensors transmit motion to the brain through frequency encoding. Similar to FM radios, the brain continually receives 'frequency-modulated' signals. A normal resting discharge rate of approximately 90 spikes per second (recorded in the squirrel monkey vestibular nerve)[12] is modulated such that increase of this rate corresponds with an excitation and decrease with inhibition.

The left and right SCCs are oriented in the head such that any movement always induces an antagonistic response in both canals. For example, consider horizontal head movements occurring in the yaw plane. During rightward head rotation, the endolymph in the lateral SCCs on both sides lags behind, bending the cupula of the right SCC towards the vestibulum (ampullo- or utriculopetal) whereas simultaneously the cupula of the left SCC is deflected away from the vestibulum (ampullo- or utriculofugal). A key difference is the polarization of the hair cells. Indeed, since the implantation of the hair cells is opposite for both right and left canals as a mirror image, the deflection on the 'leading' right side induces a movement of the stereocilia towards the kinocilium, whereas on the opposite 'following' ear the movement of the stereocilia is away from the kinocilium. Consequently, the activity of right lateral SCC primary afferent neurons increases, while at the same time the activity of left lateral SCC primary neurons decreases with respect to the normal resting discharge rate. This is called the push–pull principle of the VOR.

The right medial vestibular nucleus in the brainstem receives an increased input from the right lateral SCC primary neurons (no crossing), which excites the activity of type 1 position vestibular pause (PVP) secondary vestibular neurons. These excitatory neurons drive the leftward compensatory eye movements of the VOR, to ensure gaze stabilization. However, commissural disinhibition from the left lateral SCC primary neurons also contributes to the excitation of the PVP neurons. Therefore, both the excitation of the right SCC and the disinhibition of the left SCC are needed for an optimal VOR. In first approximation, the VOR process is a three-arc neuron reflex (first-order vestibular neurons, second-order vestibular neurons and oculomotor plant neurons) as depicted in **Figure 49.6**.

The simplified principle of VOR generation (yaw-plane rotation and horizontal SCC) is as follows:

1. During head rest, hair cells in both SCCs have a resting discharge rate of 90 spikes per second.
2. Head rotation is to the right.
3. Endolymph fluid lags behind, i.e. moves relative to the left within each SCC due to inertia.
4. The cupula bends to the left in each canal.
5. In the (leading) right SCC the stereocilia bend towards the kinocilium.
6. In the (following) left SCC the stereocilia bend away from the kinocilium.
7. The discharge rate increases in the leading right ear (e.g. from 90 to 300 spikes per second).
8. The discharge rate decreases in the following left ear (e.g. from 90 to 20 spikes per second).
9. The vestibular nuclei interpret the difference in discharge rates between left and right SCCs as movement to the right, and therefore trigger the oculomotor nuclei to drive the eyes to the left to maintain gaze stabilization.

Similar to the horizontal canal, a push–pull principle also governs the vertical canal excitatory and inhibitory functions. For example, the left anterior canal is excited while the right posterior canal is inhibited for the same movement. Also, the vertical canals are direction-sensitive, but at this stage ampullopetal movement results in a decreased firing rate. Thus, the ampullar deflection in the vertical canals, corresponding to excitation, is in the opposite direction to the horizontal SCC. For the horizontal canal, excitation is elicited upon ampullopetal endolymph movement (towards the vestibulum–utricle) whereas for both the vertical posterior and anterior SCC ampullopetal flow is inhibitory.

The horizontal canal is involved in pitch movements to only a small extent. The inclination of the vertical canals is more than 90° to the horizontal so that horizontal movements are always detected also by the vertical canals. However, given the antagonistic response of the anterior and posterior SCC on each side, horizontal head movements produce primarily horizontal eye movements.

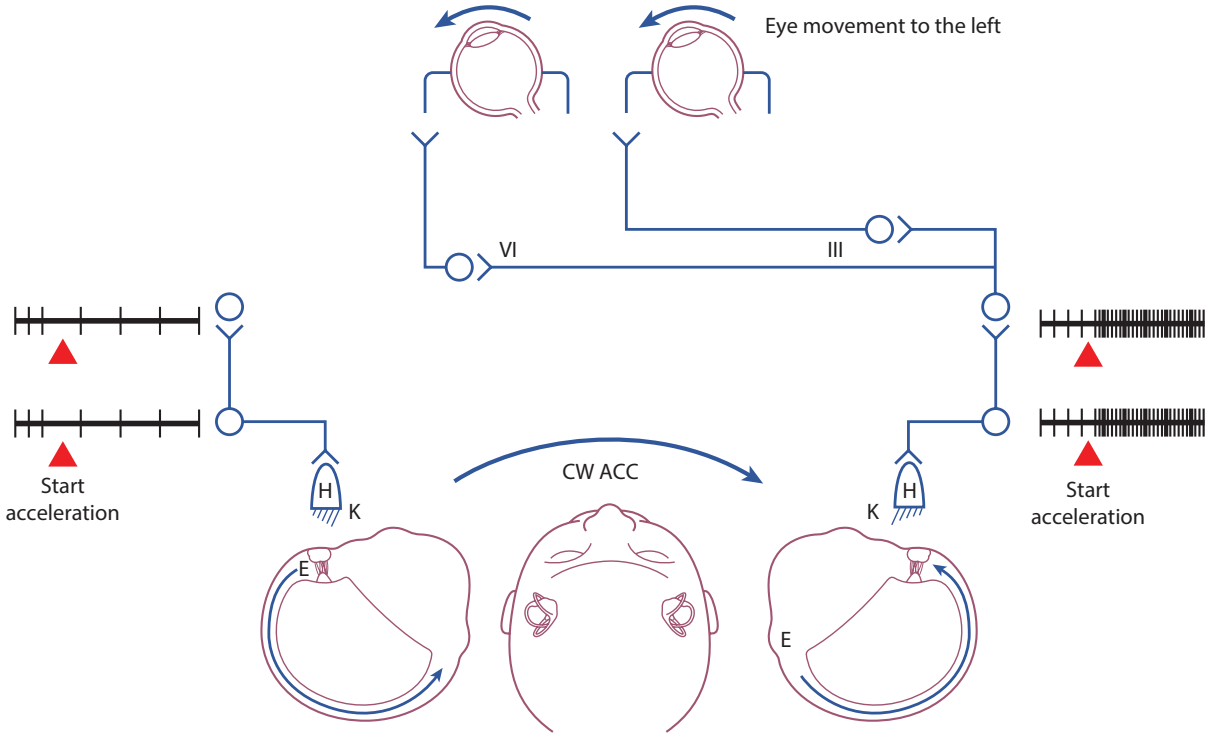


Figure 49.6 Three-arc neuron representation of the VOR. Upon head rotation to the right (CW ACC, clockwise acceleration), the hair cells on the 'leading ear' side are excited and increase their discharge rate, whereas the hair cells on the following ear are inhibited, thereby decreasing the discharge rate. The vestibular nuclei encode the increased discharge rate and redirect the excitation to the ipsilateral ocumolotor nuclei to contract the medial rectus of the right eye, while the contralateral abducens nucleus is triggered generating a contraction of the contralateral lateral rectus. Consequently, the eyes are driven to the left to compensate for the head movement to the right. This is the essence of the VOR. However, only the excitatory pathway is represented here; the actual VOR is much more complex. (E, endolymph; H, hair cell; K, kinocilium; III, oculomotor nucleus; VI, abducens nucleus)

The SCCs and the otolith organs provide the inputs for the VOR. Horizontal VOR compensates for both horizontal rotation and horizontal translation. The former is due to the canal system where the latter due to the utricular system. It is therefore more convenient to use the angular VOR (aVOR) and linear VOR (lVOR). A third type of VOR, the ocular counter-rolling, is provided by the otoliths as a response to, for example, tilting of the head with respect to gravity or a stimulus that results in a shift of the gravito-inertial acceleration (the sum of an acceleration in any direction and gravity).

There are three types of rotationally induced eye movements: horizontal, vertical and torsional. Each of the six pairs of eye muscles must be controlled to produce the desired response. The vertical SCCs and the saccule are responsible for controlling vertical eye movements, whereas the horizontal canals and the utricle control horizontal eye movements. Torsional eye movements are controlled by the vertical SCCs and the utricle.

Stimulation of a single canal results in eye movements that lie in the plane of the canals. To understand the generation of the different eye movements, it is necessary to analyze the stimulation of individual canals and their effect on the eye muscles. Table 49.1 gives an overview of the active and passive eye muscles for each stimulated canal.

TABLE 49.1 Schematic canal stimulation and concomitant eye muscle contraction and relaxation

Canal stimulation	Contracted eye muscle	Relaxed eye muscle
Lateral SCC	Ipsimedial rectus	Ipsilateral rectus
	Contralateral rectus	Contramedial rectus
Anterior SCC	Ipsisuperior rectus	Ipsi-inferior rectus
	Contrainferior oblique	Contrasuperior oblique
Posterior SCC	Ipsisuperior oblique	Ipsi-inferior oblique
	Contrainferior rectus	Contrasuperior rectus

Figures 49.7 to 49.11 represent the effects of single or multiple canal stimulation on the eye muscles and consequently which type of compensatory eye movement is generated.

Figure 49.7 and Figure 49.8 illustrate the stimulation of the anterior and posterior canals. Every stimulation in whichever direction always evokes the push–pull principle. When the head is tilted sidewards (Figure 49.9), a torsional nystagmus is generated, as both posterior and anterior canals are stimulated. When the head is pitched forward (Figure 49.10), both left and right anterior canals are

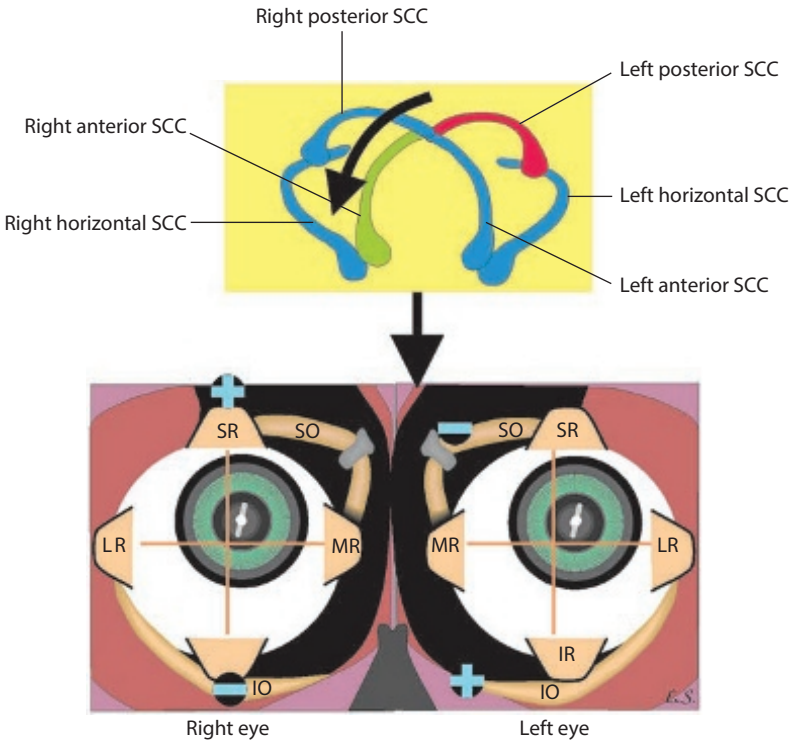


Figure 49.7 Stimulation of the right anterior SCC while the left posterior canal is inhibited occurs during a head movement in the right anterior—left posterior (RALP) SCC plane, i.e. turn the head 45° to the right and move the head downward in that plane. This generates a counterclockwise movement of the eyes (seen from the examiner's view), together with an elevation. The right superior rectus (SR) muscle and the left inferior oblique (IO) muscle are contracted. The right inferior rectus (IR) muscle and the left superior (SO) muscle are inhibited. +, excitation; -, inhibition; LR, lateral rectus muscle; MR, medial rectus muscle. The black arrows show the direction of movement of the head.

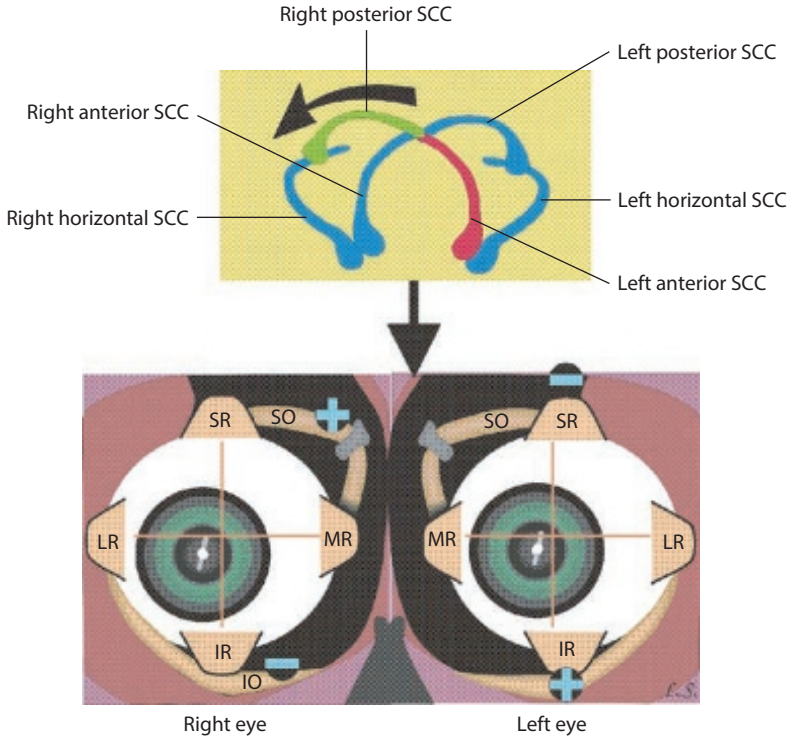


Figure 49.8 Stimulation of the right posterior SCC while the left anterior canal is inhibited occurs during a head movement in the left anterior–right posterior (LARP) SCC plane, i.e. turn the head 45° to the left and move the head upward in that plane. This generates a counterclockwise movement of the eyes (seen from the examiner's view), together with a depression of the eye. The right superior oblique (SO) muscle and left inferior rectus (IR) muscle are contracting, while the right inferior oblique (IO) muscle and the left superior rectus (SR) muscle are relaxing. +, excitation; -, inhibition; LR, lateral rectus muscle; MR, medial rectus muscle. The black arrows show the direction of movement of the head.

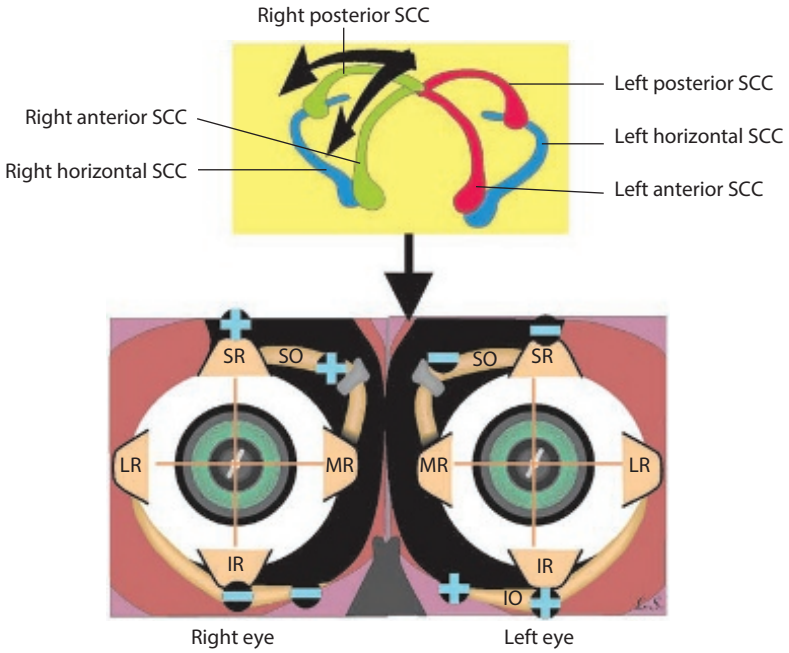


Figure 49.9 Stimulation of the right posterior and right anterior SCCs while the left anterior and left posterior canals are inhibited occurs during a rightward sideways tilting of the head towards the shoulder. This generates a counterclockwise movement of the eyes (seen from the examiner's view). The right superior rectus (SR) muscle and superior oblique (SO) muscle, as well as the left inferior oblique (IO) muscle and inferior rectus (SR) muscle, are contracting while the right inferior rectus (IR) muscle and inferior oblique (IO) muscle and the left superior rectus (SR) muscle and superior oblique (SO) muscle are relaxing. The elevation and depression cancel out and a pure counterclockwise torsional nystagmus is generated. This suggests why during a unilateral lesion, such as a vestibular neuritis that affects the whole peripheral vestibular system, there is never a vertical nystagmus, but only a torsional and a horizontal (not depicted here). Spontaneous vertical nystagmus is therefore almost always due to a central neurological pathology. The black arrows show the direction of movement of the head. LR, lateral rectus muscle; MR, medial rectus muscle.

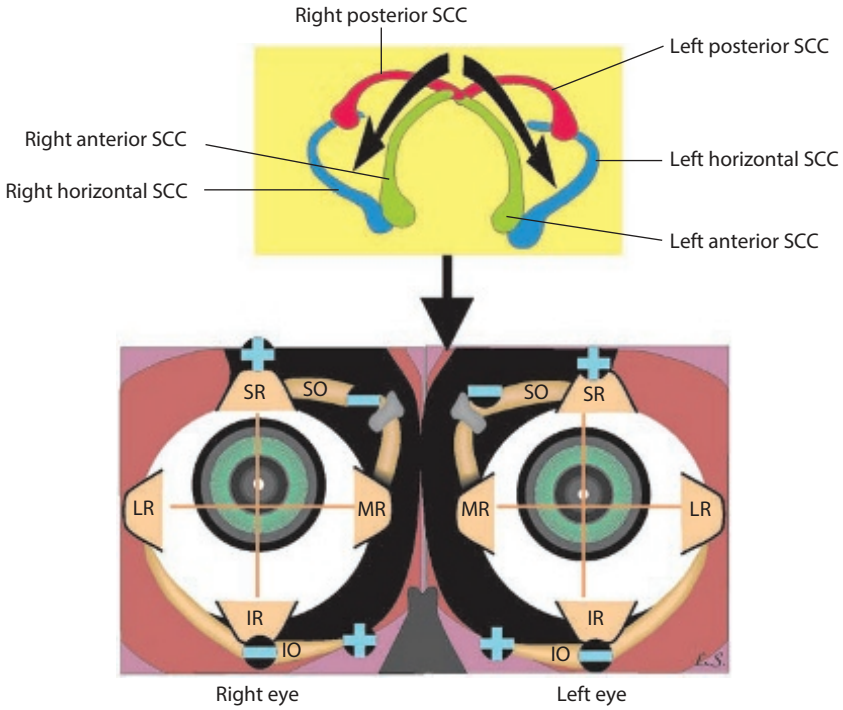


Figure 49.10 Stimulation of the right anterior and left anterior SCCs while the right posterior and left posterior canals are inhibited occurs during a forward bending of the head. This generates an elevation of the eyes or a downbeat nystagmus, depending on the amplitude and speed of bending the head. The right superior rectus (SR) muscle and inferior oblique (IO) muscle, as well as the left inferior oblique (IO) muscle and superior rectus (SR) muscle, are contracting while the right inferior rectus (IR) muscle and superior oblique (SO) muscle and the left superior oblique (SO) muscle and inferior rectus (IR) muscle are relaxing. Given the activity of these muscles, any torsional components are cancelled out. The black arrows show the direction of movement of the head. LR, lateral rectus muscle; MR, medial rectus muscle.

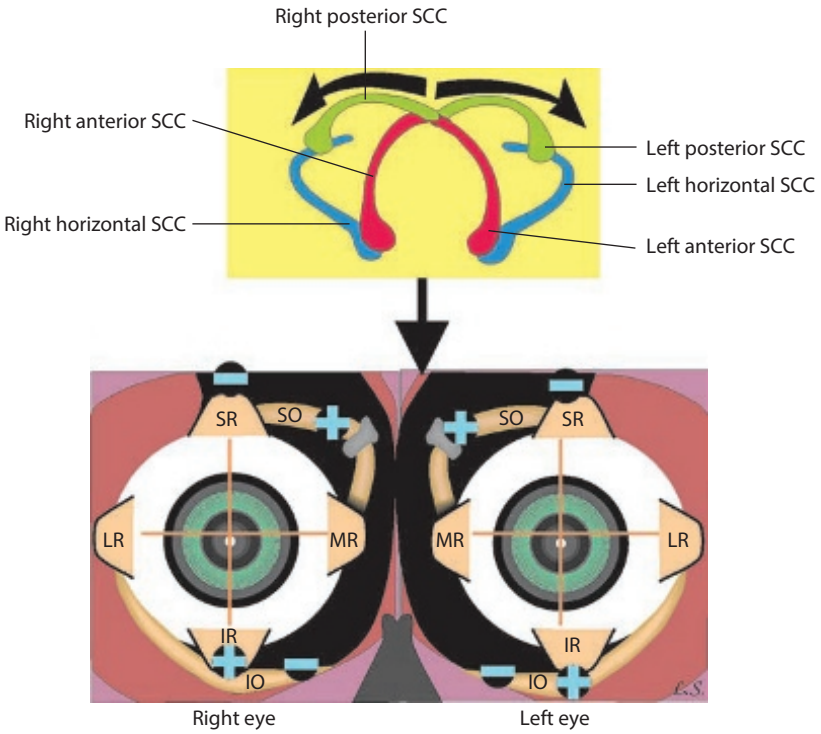


Figure 49.11 Stimulation of the right posterior and left posterior SCCs while the right anterior and left anterior canals are inhibited occurs during a backward bending of the head. This generates a depression of the eyes or an upbeat nystagmus, depending on the amplitude and speed of bending the head backwards. The right inferior rectus (IR) muscle and superior oblique (SO) muscle, as well as the left superior oblique (SO) muscle and inferior rectus (IR) muscle, are contracting while the right superior rectus (SR) muscle and inferior oblique (IO) muscle and the left superior rectus (SR) muscle and inferior oblique (IO) muscle are relaxing. Given the activity of these muscles, any torsional components are cancelled out and a pure vertical nystagmus remains. The black arrows show the direction of movement of the head. LR, lateral rectus muscle; MR, medial rectus muscle.

stimulated, whereas both posterior canals are inhibited. This produces an upward eye movement. Each anterior canal also produces an ocular counter-rolling movement, but as both are in different directions, the counter-rolling is cancelled out. The same applies when the head is tilted backwards (Figure 49.11), but now both posterior canals are stimulated producing a downward compensatory eye movement.

For the horizontal canal stimulation, a more detailed neurological pathway is explained later in this chapter.

Nystagmus

The eye response to a head rotation consists of a combination of a slow phase or drift until the eye reaches the edge of the outer canthus, and a fast phase to reset the eye in its initial position. This pattern repeats itself as long as the head rotation lasts. This saw-tooth pattern is called nystagmus (Figure 49.12). The direction of the nystagmus is defined by the fast reset phase, since that is easiest identified by the clinician. The slow phase, however, represents the actual vestibular output and is quantified. An upward excursion, by convention on electronystagmography or video-nystagmography, represents eye deviation to the right. If the slope of the sawtooth is upward to the right, i.e. a positive slope, this corresponds to a slow drift of the eye to the right, followed by a quick leftward reset saccade, as represented by a steep downward trace. This is defined as a left nystagmus. It is quantified by measurement of the slope of the upward trace, which indicates the speed of the eye movement (degrees/s).

Figure 49.12 Typical pattern of nystagmus to the left. This trace represents the eye movement amplitude in degrees (vertical) as a function of time in seconds (horizontal). Upward deflection denotes rightward eye movement. The trace indicates a series of slow eye deviations to the right (upward) followed by fast beat to the left (downward). This typical behaviour of slow movement followed by a fast reset movement is called nystagmus. Although the slow phase is the vestibular partition of the movement, by convention the nystagmus is called after the direction of the fast beat, since clinically this is more easily discernible. The slope of the slow component represents the velocity that characterizes the VOR.

NYSTAGMUS INDUCED BY ACUTE UNILATERAL DEAFFERENTIATION

The push–pull principle is very convenient to explain the origin of the nystagmus observed during acute peripheral lesions. In the case of an acute unilateral vestibular

deafferentiation (uVD) on, for example, the right side, all three right canals and the otoliths cease spontaneous activity (from 90 spikes per second to zero), while the spontaneous activity of the left SCC remains at 90 spikes per second. Although the head is not moving, the brain perceives an apparent imbalance (R: 0 spikes/second versus L: 90 spikes/second) similar to, for example, when the left system is triggered during head movements towards the left. This tonic imbalance drives the vestibular and, consecutively, the ocular motor nuclei to move the eyes towards the right, as would be appropriate for a head movement towards the healthy side (left).

The brain erroneously interprets the abruptly decreased or absent firing rate of the ipsilateral-affected peripheral system as a relative increase of the contralateral system, resulting in a nystagmus that beats away from the acute lesion.

Additionally, the combination of muscle contraction and relaxation generates not only a pure horizontal nystagmus but also a torsional nystagmus. Indeed, when all the canals are lesioned on the right side, this is interpreted by the brain as a sudden excitation of the contralateral vestibular system, which generates a contraction of the left eye medial rectus, superior rectus and superior oblique muscles. Eye movements may be considered as additive and so, although both superior muscles are on the upper surface of the eye, they have an opposite effect on the eye movement, cancelling any vertical movement. Consider the right eye, activation of the superior rectus results in an elevation, adduction and intorsion, whereas the superior oblique generates a depression, abduction and again an intorsion. When all muscles contract simultaneously, as is the case upon stimulation of all three canals on the same side, the elevation and depression cancel out, as does the abduction and adduction. The torsional movement remains, as well as a horizontal nystagmus due to the contraction of the medial rectus of the left eye (and the lateral rectus of the right eye).

For a left uVD, the torsional nystagmus is counterclockwise (CCW) (from the examiner's perspective) in combination with a horizontal nystagmus beating to the right, whereas a clockwise (CW) and leftward nystagmus is seen for a right-sided uVD. A torsional and horizontal nystagmus is the clinical sign indicating an acute whole labyrinthine deficiency. Conversely, a pure vertical nystagmus is very unlikely to be produced by an acute labyrinthine lesion, and the clinician should in that case firstly consider a central neurological lesion rather than a peripheral vestibular lesion. The sudden onset of this nystagmus is associated with vertigo and disorientation, since the absence of real movement constitutes a conflict between vision, proprioception and the vestibular system.

Vestibulocollic and vestibulospinal reflexes

When they are walking, pigeons move their heads backwards and forwards. This head movement is actually a head nystagmus, meant for gaze stabilization and controlled in an exactly similar manner to the VOR in higher species. In rabbits, however, both eye and head nystagmus are equally present, whereas in the primate eye nystagmus predominates.

The extraocular muscles are the effector organs for the VOR, while the extensor muscles of neck, trunk, arms and limbs are those for the vestibulocollic (VCR) and vestibulospinal reflex (VSR). Similar to the VOR, the same push–pull mechanisms are used for controlling the balance between extensor and flexor muscles.

It is obvious that any change in movement, detected by the vestibular organ, is compensated by a series of contractions and relaxations of several muscles. Since the freedom of motion of the body is much larger than that of the eye, a multitude of muscles are involved in the reaction chain to maintain upright position and stability.

These reflexes are mediated through projections of the vestibular nuclei on to the medial and lateral vestibulospinal tract. These pathways project to the lower limb and neck muscles to maintain an upright position and balanced locomotion. The driving input here is mainly gravity detected by the otolith system. However, proprioceptive and visual information is also necessary to provide the correct body position, given the fact that gravity is only detected in the head, regardless of the position of the trunk and lower body.

Cervico-ocular reflex

In some cases, when the head is fixed but the body is rotated, nystagmus may be observed. This reflex is based on the stimulation of neck receptors, rather than vestibular receptors. However, in humans, this reflex is very unreliable and unpredictable. Only in subjects with, for example, congenital peripheral vestibular loss does this alternative strategy for gaze stabilization become more robust. According to a review by Brandt,[13] the clinical significance of lesions involving the cervico-ocular reflex (COR) are debatable. The fact that voluntary eye movements interfere with the reflex eye movements makes objective measurements very questionable.

Vestibulosympathetic reflex

Moving from a supine to a standing position generates a substantial orthostatic stress on the body, inducing a pooling of blood of approximately 800 mL in the lower limbs and the abdomen. Maintenance of the supply of blood to the brain and other vital organs (orthostatic tolerance) requires the activation of sympathetic outflow in response to such changes in posture, generating increases in heart rate and vascular tone that maintain blood pressure and prevent pooling of blood in the lower body. The otoliths have recently been shown to participate in mediating a vestibulosympathetic reflex that could help maintain orthostatic tolerance when upright.[14–16] The baroreflex is a negative feedback response that buffers short-term changes in blood pressure, with a latency (1.4 s) that, among other factors, depends on the response to pooling of fluid in the legs. The vestibulosympathetic reflex

has a shorter latency (0.4 s) that could provide earlier feed forward excitation to maintain orthostatic tolerance.[14] In addition, recent studies have described an otolith-sympathetic reflex that acts to increase vasoconstriction during nose-up linear acceleration,[14, 16] which may be a short latency mechanism to sustain blood pressure upon standing.

Besides this reflexive sensorimotor control of gaze and balance at the level of the brainstem and cerebellum, the vestibular system is also responsible for the perception of self-motion and sensorimotor control of voluntary movements and balance which are regulated at the cortical/subcortical level. Another important function of the vestibular system is the processing of higher cognitive vestibular functions such as spatial memory, orientation and navigation, where the hippocampus and parahippocampus play an important role.[17]

Vestibular cortex

The insular cortex is a part of the cerebral cortex folded deep within the lateral sulcus and is believed to have a main role in the processing of vestibular signals.[48, 49] Moreover, a predominant role of the right hemisphere in the cortical processing of vestibular afferents has also been proven in the meta-analysis by zu Eulenburg et al.[47] More specifically, zu Eulenburg et al. suggest that operculum parietale 2, a histological defined part of the human parietal operculum in the right hemisphere, is the core region of the human vestibular cortex and possibly processes only vestibular information instead of multisensory input. Recently, changes in the vestibular cortex have been shown in an astronaut returning from space.[50] Space is a unique lab to investigate the effect of unusual physiological stimuli on the human body such as weightlessness. These preliminary findings corroborate the concept of neuroplasticity and may guide further research to find possible causes in the brain of vestibular disorders such as visual vestibular mismatch among others. Until recently, many vestibular dysfunctions were traditionally attributed to peripheral vestibular lesions, but the brain will become more and more important in vestibular physiology.

CENTRAL PROJECTIONS OF THE PERIPHERAL VESTIBULAR SYSTEM

Any movement is detected by several parts of both left and right vestibular organs, and the results converge in the vestibular nuclei after being passed through the ganglion of Scarpa. The different canals and otolith maculae project to different portions of the vestibular nuclei from where they trigger other brain centres so as to maintain gaze stabilization, as well as body stabilization.

Projections to the central nuclei

The vestibular nerve consists of a superior and inferior branch. Afferents coming from the horizontal and anterior canals, as well as from the utricular macula and anterosuperior region of the saccular macula, form the superior vestibular nerve, whereas the inferior vestibular branch contains fibres coming from the posterior canal and the saccular macula. The relative position of these vestibular afferents changes as the vestibular nerve approaches the brain. Fibres coming from the three SCCs are situated at the anterior side of the vestibular nerve, whereas saccular and utricular branches come together at the ventroposterior margin of the vestibular nerve.[18] This knowledge is important for interpreting clinical vestibular tests, i.e. caloric and rotary tests evaluate the horizontal SCCs and thus the superior branch of the vestibular nerve, while the collic vestibular-evoked myogenic potential (cVEMP) test evaluates the saccule and thus the inferior branch.

These vestibular primary afferents mainly project to the vestibular nuclear complex in the pontomedullary region of the brainstem and the cerebellum, with the highest projections to the nodulus and uvula. In the brainstem four classical vestibular nuclei (VN) have been identified: the superior (SVN), lateral (LVN), medial (MVN) and descending vestibular nuclei (DVN). In addition, several small cell groups lie at the periphery of this vestibular complex and also receive vestibular primary afferents. These include, among others, the y-group, the interstitial nucleus of the vestibular nerve (INT8), the parasolitary nucleus (Psol), and the nucleus intercalates.[18–19] Canal and otolith afferents enter the vestibular nuclear complex at the level of the LVN and rostral DVN, and thereafter divide into ascending and descending pathways. The ascending branch mainly projects to the SVN and further on to the cerebellum, whereas the descending branch of all primary vestibular afferents innervates the central region of the vestibular nuclear complex.[18]

Topography within the vestibular complex exists, but it does not conform to the cytoarchitecturally defined boundaries.[19] Several studies have tried to unravel the existence of a topographical map of the single end organ partitions, which confirmed large inconsistencies dependent on the type of test animals and the type of examination technique used.[18, 20–26] This confusion about the topography is not surprising since VN are not simple relay nuclei passing along sensory information to other parts of the brain, but include a mix of complex intrinsic and projection neurons which are responsible for spatial transformation and sensory integration of the incoming head movement signals.[26] In general, it can be concluded that most peripheral systems project to the larger part of all the VN. In early reports[22, 24] common patterns in the central projection of vestibular afferent fibres have been demonstrated, with projections from the canals being prominent in the rostral part of the VN (horizontal and anterior SCC project laterally and posterior SCC medially) whereas otolith fibres terminate more caudally. More recent reports seem to agree more or less on the following findings: the SCCs project to all four VN, with the most heavy projection to the MVN and SVN. Saccular afferents project strongly to the DVN, the INT8, and the y-group, and weakly to the other VN, whereas the utricle mainly projects to the lateral and dorsal portions

of the MVN, the ventral and lateral portions of the SVN and the rostral portion of the DVN.[18, 23, 26]

Besides input from the primary vestibular afferents, non-vestibular systems such as the optokinetic system, the neck-proprioceptive system and the cerebellar Purkinje cells also project to the vestibular nuclear complex,[19] affecting the processing of vestibular signals.

Within the vestibular brainstem nuclei there are commissural projections, which centrally reinforce the differential detection of vestibular signals by commissural inhibition. For signals coming from the SCC, these commissural projections allow push–pull reactions in the VOR, by interconnecting vestibular neurons with bilateral coplanar SCC-related signals. A similar organization exists for the utricular commissural connections, based on spatially aligned bilateral utricular epithelial sectors.[27] This commissural inhibition results in a central amplification which is essential for the detection of small angular and linear head accelerations, and for the prolongation of the dominant time constant of the VOR which is regulated by the VSM.[23, 27–28] In the saccular system this commissural inhibition is present to a lesser extent; however, cross-striolar inhibition enhances here the sensitivity to linear acceleration.[28] This amplification mechanism is based on the fact that neurons in the VN are typically excited monosynaptically by unilateral afferents from the striola of the saccule, whereas they are inhibited disynaptically by afferents from the other side.[28]

From the vestibular nuclear complex, second-order vestibular neurons project to different pathways. These neurons contribute to the control of balance by influencing the discharge of motor and pre-motor neurons. For the **vestibulo-ocular pathways**, the central and dorsal regions of the SVN, the MVN and ventral part of the LVN, as well as the dorsal division of the y-group project heavily to the oculomotor nuclei by means of the medial longitudinal fascicle (MLF) and the ascending tract of Deiters (ATD).[23, 26] The most important **vestibulo-spinal pathways** are the lateral vestibulospinal tract (LVST) and medial vestibulospinal tract (MVST), as well as the lateral and medial reticulospinal tracts (LRST and MRST). Vestibulospinal pathways originate from a wide area in the vestibular nuclear complex including MVN, LVN and DVN.[18] **Vestibulocerebellar pathways** contain neurons coming from all parts of the vestibular nuclear complex, and mainly project to the cerebellar flocculus, paraflocculus, nodulus and uvula.[23] Next, there are also projections found to the nucleus prepositus hypoglossus (NPH), nucleus tractus solitarius, parabrachial nucleus, medullary autonomic centres, the thalamus and even further cortical into the parietoinsular vestibular cortex (PIVC).[18, 23, 29] Most of these projections are beyond the scope of this chapter, but it should be kept in mind that mainly the vestibulocerebellum plays a dominant role in the fine-tuning of the vestibular functions, by adapting and readjusting central vestibular processing if necessary.

A detailed neurological pathway of the horizontal canal stimulation will be explained below.

Two types of neurons have been traced in the MVN, triggered by the lateral SCC input, namely type 1 and type 2 neurons. Their resting discharge rates are approximately 80–90 spikes per seconds. This relatively low resting discharge rate implies that, under specific high accelerations, the discharge rate is blocked to 0 spikes/s. Increased rates, however, can exceed 300 spikes/s. This intrinsic asymmetry is responsible for a limited VOR at higher frequencies when lesions occur. Some type 1 neurons are excitatory (the PVP neurons) and some are inhibitory. Primary vestibular afferents synapse with inhibitory as well as excitatory type 1 neurons (**Figure 49.13**).

Excitatory pathways

Upon head rotation to one side (**Figure 49.14**), denoted as the ipsilateral side, the ampulla of the ipsilateral horizontal canal is stimulated followed by an immediate increase in firing rate of the neurons, proportional to the velocity of the head turn. These signals project mainly on to the ipsilateral MVN, but other parts of the VN are also involved. From there, axons decussate onto the contralateral abducens nucleus which innervates the lateral rectus of the contralateral eye through the VIth nucleus. Additionally, the interneurons of the contralateral abducens nucleus project through the longitudinal medial fasciculus to the ipsilateral medial rectus subnucleus in the oculomotor nucleus (III) that activates the medial rectus muscle of the ipsilateral eye.

There is also an accessory pathway that originates from projections of the ipsilateral horizontal canal ampulla on to the ipsilateral magnocellular part of the MVN (formerly denoted as the ventral lateral vestibular nucleus).[26, 30] From there, increased activity is transmitted via the ATD onto the medial rectus subnucleus of the ipsilateral oculomotor nucleus, activating the medial rectus muscle of the ipsilateral eye. This drives both eyes to rotate towards the side opposite to the direction of the head to stabilize the image on the retina.

It is important to realize that this is not a strict parallel circuit. Although the ipsilateral medial rectus and the contralateral lateral rectus muscles contract simultaneously, the signals coming from the VN neurons are not sent through collateral axons but through different pathways. This separation permits distinct regulation of muscle contraction to combine vergence movements with the VOR, while fixating targets at different distances. Additionally, studies have shown that there is a difference in physiological signals that are conveyed by the abducens internuclear (eye velocity and eye position) and ATD (head velocity) pathways, which suggests that there is a separate control of visuomotor and vestibular functions.[31]

Inhibitory pathways

In addition to the contraction of the appropriate eye muscles (ipsilaterally the medial rectus and contralaterally the lateral rectus), a relaxation of the antagonist eye muscles has to be initiated in the context of the push–pull principle (**Figure 49.15**). This is generated by inhibitory type 1 neurons in the ipsilateral MVN.

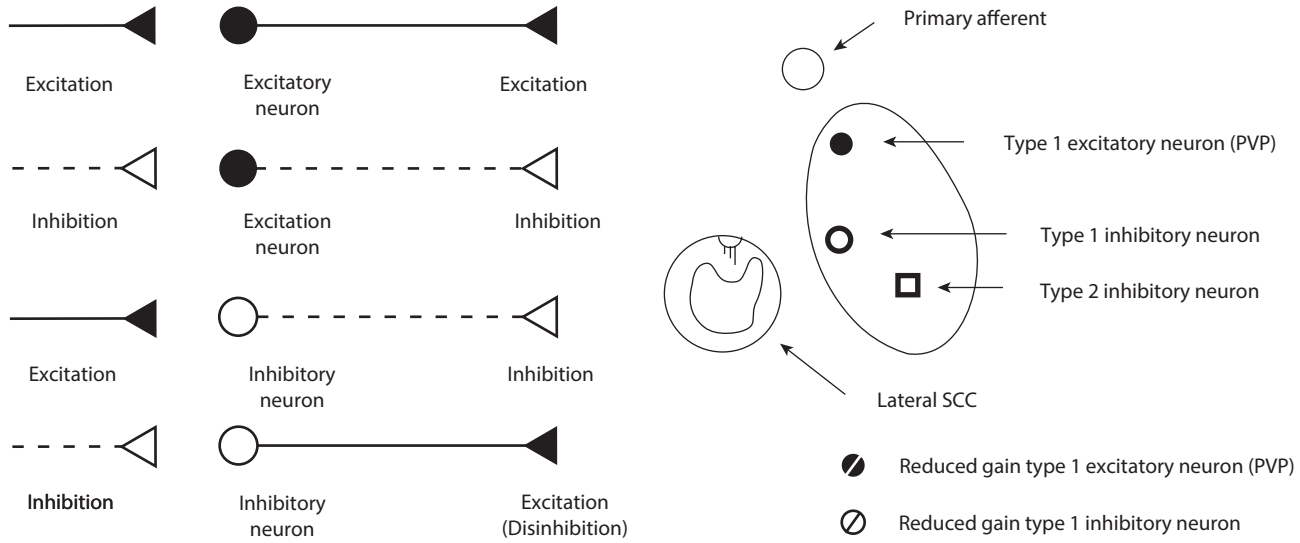
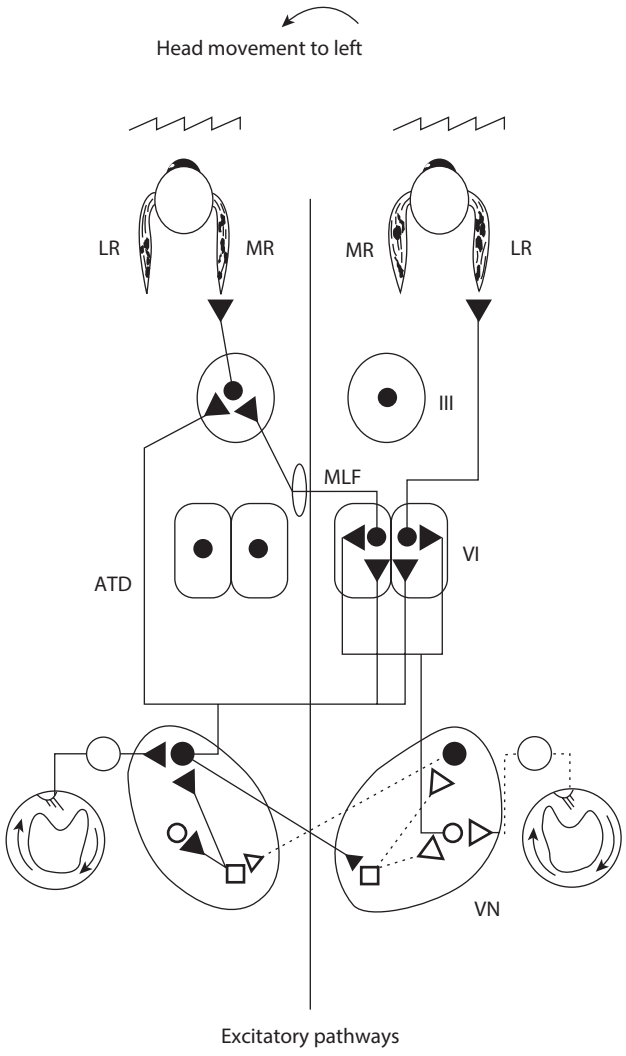


Figure 49.13 Code for excitation and inhibition of vestibular nuclei and oculomotor plants in the brain. Closed symbols represent excitation (full of neurotransmitters). Dashed lines denote inhibitory signal transfer. Solid lines denote excitatory signal transfer. Excitation of an inhibitory neuron will result in further inhibition. Inhibition of an inhibitory neuron results in excitation. This figure provides the key for Figures 49.16, 49.17, 49.18 and 49.19.



These inhibitory type 1 neurons project onto the ipsilateral abducens neurons and interneurons and, by inhibition, relax the lateral rectus on the ipsilateral eye through the VIth nerve. Likewise, the medial rectus of the contralateral eye is relaxed by inhibition of the contralateral oculomotor neurons where the signals come from the ipsilateral superior vestibular neurons and pass through the MLF.

To enhance this mechanism even further, at the same time the contralateral ampulla is deflected such that the firing rate of the primary afferents is decreased. This inhibits the contralateral MVN, resulting in an opposite effect for the antagonist eye muscles, again optimizing the gaze stabilization during movement.

To summarize, the generation of the VOR is mediated through a combination of signals coming from both labyrinths. During rotation to the ipsilateral side, the ipsilateral horizontal SCC with ampullopetal endolymph movement will transmit an increased firing rate to the central VN, whereas the contralateral SCC will transmit a decreased firing rate to the contralateral VN due to the ampullofugal endolymph movement.

Figure 49.14 During head rotation to the left, a VOR is generated to stabilize the eyes, with the concomitant nystagmus to the left. Stimulation of the horizontal SCCs initiates an excitatory pathway through the ganglion of Scarpa on to the vestibular nuclei. Given the projections of the canals and otolith organs to almost all parts of the vestibular nuclei (VN), we did not subdivide the nuclei into superior, inferior, medial and lateral VN. ATD, ascending tract of Deiters; LR, lateral rectus; MLF, medial longitudinal fascicle; MR, medial rectus; III, oculomotor nucleus; VI, abducens nucleus. See Figure 49.13 for key.

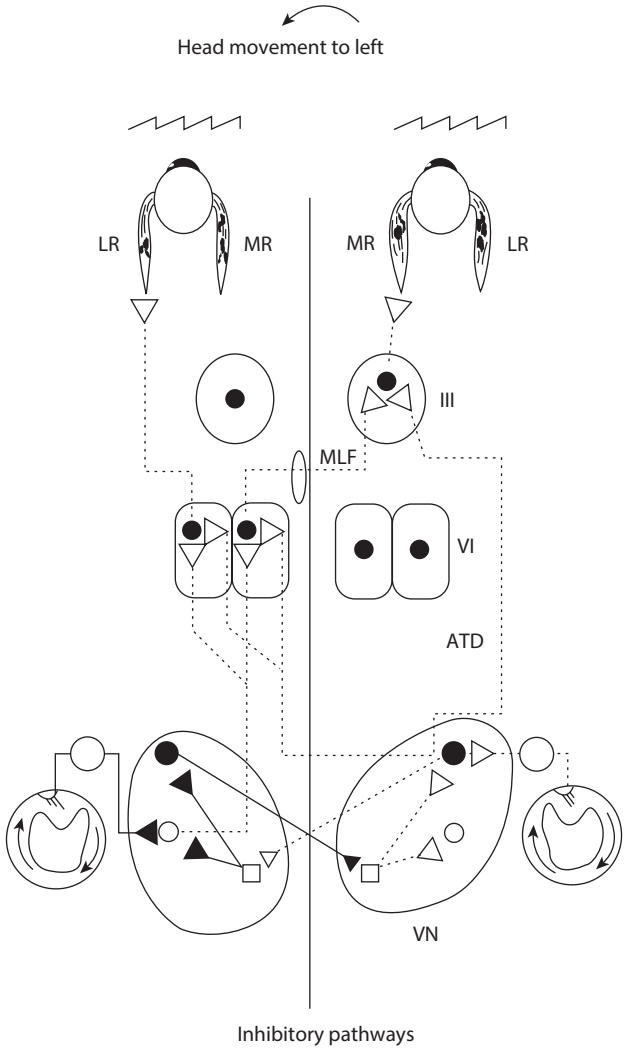


Figure 49.15 During head rotation to the left, a VOR is generated to stabilize the eyes, with the concomitant nystagmus to the left. Stimulation of the horizontal SCCs also initiates an inhibitory pathway. ATD, ascending tract of Deiters; LR, lateral rectus; MLF, medial longitudinal fascicle; MR, medial rectus; III, oculomotor nucleus; VI, abducens nucleus. See Figure 49.13 for key.

Commissural pathways

In the VN, there are also type 2 secondary vestibular neurons, which behave in an exactly opposite manner to type 1 neurons. Activating the inhibitory type 2 neurons silences the neighbouring type 1 neurons. Whereas type 1 neurons increase their discharge rate upon ipsilateral head acceleration, inhibitory type 2 neurons decrease their firing rate. For movement towards the contralateral side, ipsilateral type 1 neurons decrease their firing rate and ipsilateral type 2 neurons increase it.

The VOR-generating mechanism is enhanced in a positive feedback loop by commissural pathways where the excited type 1 neurons in the ipsilateral MVN excite the type 2 neurons on the contralateral side that in turn silence the contralateral type 1 neurons.

Excitation of the ipsilateral type 1 neurons is increased as the silenced type 1 neurons on the contralateral MVN inhibit the ipsilateral type 2 neurons, so that their inhibitory effect is reduced on the ipsilateral type 1 neurons. Therefore, type 1 cells receive direct input from the ipsilateral SCC, as well as indirect input from the contralateral SCC.

The commissural pathway is indicated at the bottom of Figures 49.14 and 49.15. This feedback loop proves to be crucial in the case of unilateral lesions.

Acute peripheral vestibular lesion and central vestibular compensation

As a model for a peripheral lesion, the acute uVD is commonly chosen. After uVD, specific changes occur immediately at the level of type 1 and type 2 neurons in the MVN on the ipsilesioned site. Given the absence of peripheral activity by the SCC afferent neurons, the firing rate of the type 1 neurons decreases.

Due to the decreased inhibitory effect of the ipsilateral type 1 neurons, the contralateral type 2 neurons are less stimulated so their inhibitory effect on the contralateral healthy type 1 neurons is decreased, and thus the healthy type 1 neurons increase their firing rate. This increased type 1 activity on the healthy side in turn activates the inhibitory type 2 neurons on the lesioned side, so that they additionally inhibit the neighbouring type 1 neurons on the lesioned side.

This imbalance generates the typical clinical signs of acute labyrinthine lesions, such as spontaneous nystagmus, i.e. a nystagmus that is present even under static conditions. The direction of the slow phase of the nystagmus is towards the lesioned side, i.e. the fast phase of the nystagmus beats towards the healthy side. The generated nystagmus reflects the situation as if the subject rotates towards the intact side. Indeed, both the absence of the ipsilesioned tonic input from the affected labyrinth and the increased contralesioned activity in the MVN mimic a rotation towards the intact side. This is illustrated in the scheme with acute uVD (Figure 49.16), where a nystagmus is generated by pathways that are very similar to the generation of VOR response upon rotation to the contralateral side. The difference is that no input from the contralateral SCC is present and still a nystagmus is generated. Also the gain of the ipsilesioned type 1 neurons is largely decreased and this will remain that way for a long time.

Stance and gait disturbances, as well as vertigo, are clearly observed in most patients. The postural disturbance often includes head and trunk flexion towards the damaged labyrinth with the head tilted so that the ipsilesioned ear is directed down. The appearance is of the healthy side being pushed towards the damaged side, which lacks the power to counteract the push.

These disturbances also occur under static, immobile conditions. The dynamic alterations yield a dysfunctional VOR, so that gaze stabilization during, for example, locomotion is hampered. Whereas the static symptoms improve within a week, the dynamic disturbances can last much longer, from weeks to years. The static symptoms decrease

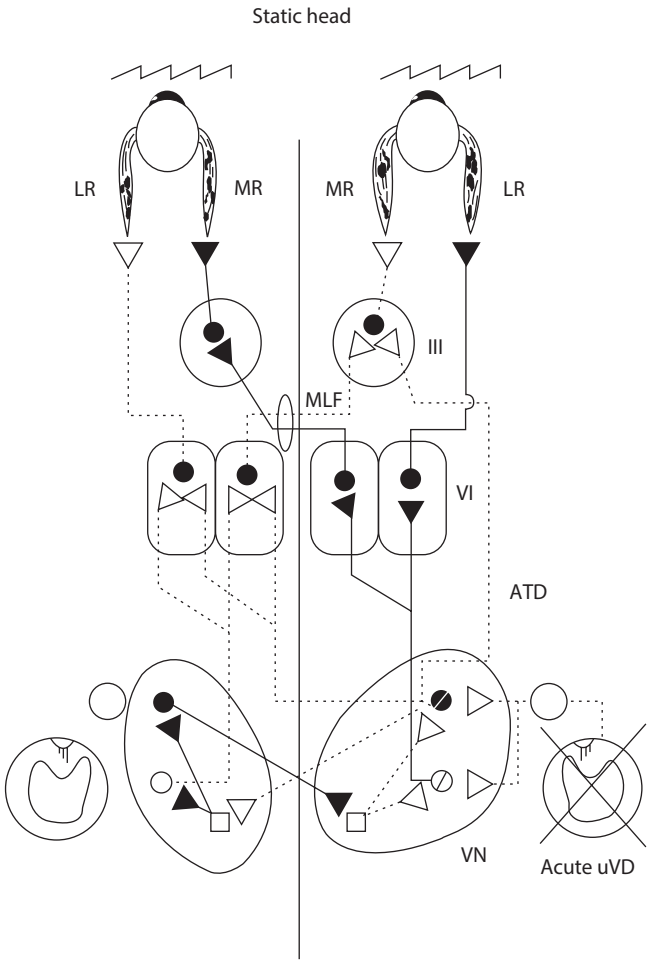


Figure 49.16 Acute stage of a right lesion of the peripheral vestibular system. Only the horizontal pathway is depicted, although a torsional nystagmus can also be observed. No vertical eye movement is seen, since the effect of inhibition of both anterior and posterior canals cancels the vertical eye movements out. Now all excitatory pathways are secondary induced through the commissural pathways and the inhibition of the type 2 inhibitory neurons, generating an excitation. ATD, ascending tract of Deiters; LR, lateral rectus; MLF, medial longitudinal fascicle; MR, medial rectus; III, oculomotor nucleus; VI, abducens nucleus. See Figure 49.13 for key.

over time, as a restoration of the resting discharge rate is affected at the level of the vestibular nuclei. This results in the disappearance of the spontaneous nystagmus: a process called 'vestibular compensation'. In humans, the gain of the VOR is permanently limited to a variable degree, depending on the acceleration of the head movements.

Many VN neurons show convergent input from both canal and otolith systems. The spontaneous activity of otolith afferents arriving in the VN is important for the generation of the oculomotor compensatory responses to SCC stimulation. The consequence of this is that an otolith loss affects not only the lVOR but also the aVOR during angular acceleration. The otoliths are therefore fundamental for the optimal operation of the entire vestibular system.

The imbalance in resting discharge rate between the lesioned vestibular neurons and the healthy vestibular neurons after uVD is the key factor that generates the acute clinical signs of nystagmus and unsteadiness. The short-term restoration of the imbalance of resting activity at the level of the VN results in a recovery of the static clinical symptoms, and the acute spontaneous nystagmus disappears within a week.

Very soon after uVD (within 52 hours), type 1 neurons in the MVN generate a spontaneous firing rate to balance the situation, although this firing rate is not influenced by afferent input from the lesioned side during rotation towards the lesioned side. It is, however, modulated through the ipsilesioned type 2 neurons that receive their input from the intact side type 1 neurons. Therefore, the ipsilesioned type 1 neurons are inhibited when the type 1 neurons on the healthy side are excited during rotation towards the healthy side, and are disinhibited when the contralateral type 1 neurons are inhibited during rotation towards the lesioned side. The responses of the ipsilesioned type 1 neurons are only half of their initial responsiveness, but qualitatively they act in a similar manner as before the lesion. This recovery takes place over a period of weeks to months and parallels the clinical recovery of the patient. The type 1 neurons on the intact side regain a firing rate equal to that before the acute lesion. The sensitivity (gain) decrease of the ipsilesioned neurons explains why the overall VOR gain after a lesion is lower than before the lesion. Even given the commissural network that largely enhances the efficiency of the generation of the appropriate VOR, an optimal VOR is never obtained. At slow accelerations, a relatively normal situation can be obtained, since the VN also receive input from extravestibular systems such as vision and proprioception, and they are not saturated. At higher accelerations, however, even in the physiological range, the intrinsic saturation of the inhibitory neurons (i.e. not being able to inhibit more than to 0 spikes per second), increases the deficiency of the VOR.

Figure 49.17 represents the pathway upon rotation towards a lesioned side. As indicated from the diagram, the only input is the inhibition sensed at the contralateral side. Due to the commissural pathways, a very similar reflex arc is established, generating an appropriate VOR under normal conditions. Nonetheless, the time taken to evoke the appropriate eye movement may be increased, which is demonstrated as an increase in phase during laboratory testing. The clinician may be surprised by the fact that the nystagmus appears symmetrical, i.e. movements to the left and right induce a similar gain (eye velocity/head velocity), but when the phase is too high (>18 degrees), the reaction comes too late, with suboptimal gaze stabilization as a consequence. For the patient, this translates into global unease and unsteadiness, and general fatigue and psychotropic drugs will worsen this.

A clinical bedside test to detect severe unilateral loss of SCC function is the head impulse or head-thrust test, first described by Halmagyi and Curthoys in 1988.[32] The head-thrust test is based on the fact that inhibition of primary and secondary vestibular neurons cannot produce fewer than 0 spikes per second. Excitation can drive the discharge rate from 90 to 300 or more spikes per second. So when the healthy side is excited for a high acceleration

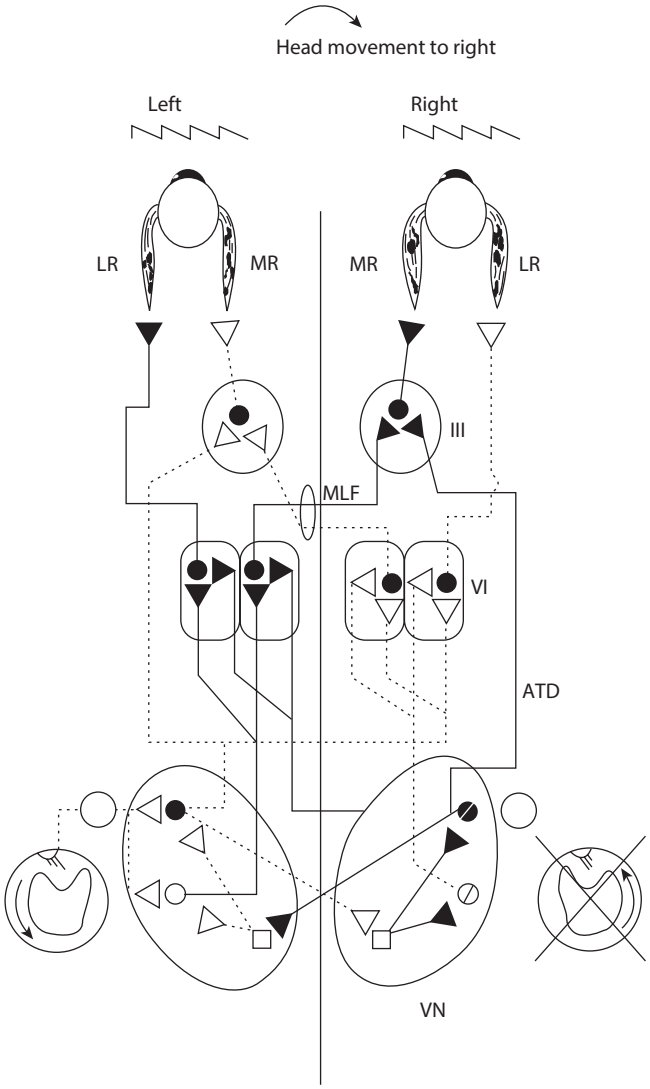


Figure 49.17 Under slow movement, rotating the head towards a stable lesioned side generates conditions for an appropriate nystagmus for gaze stabilization. ATD, ascending tract of Deiters; LR, lateral rectus; MLF, medial longitudinal fascicle; MR, medial rectus; III, oculomotor nucleus; VI, abducens nucleus. See Figure 49.13 for key.

head movement, the healthy side will generate the larger part of the VOR since the disinhibition of the ipsilateral type 1 neurons by the contralateral SCC contributes relatively little to the VOR. When the subjects head is turned to the lesioned side, the VOR is deficient and the eyes move together with the head, so that they no longer fixate. The patient therefore has to make one or more refixation saccades just after the thrust. When the head impulse is imposed in the direction of the healthy side, the VOR is able to maintain the target on the fovea and no refixation saccade is needed. The head-thrust test is positive for the side that causes the refixation saccades upon thrust (**Figure 49.18**). Not only can the lateral SCC be examined, which is in a sense a clinical approximation of the caloric test, but also the other SCC can be investigated. The patient's head has then to be moved in the RALP or LARP planes.

Gaze holding

Not only is it necessary to drive the eyes in the opposite direction to the head movement, but when the head has stopped turning, the eyes should remain in position. This is a complex task as elastic-restoring forces drive the eyes back to their primary position (straight ahead). This gaze-holding system is generated by the neural integrator, which is located in the NPH and the MVN for horizontal eye movements, and in the interstitial nucleus of Cajal (INC) for vertical movements. It is a circuit that integrates the velocity signal over the time the eye movement has occurred and this is mathematically equivalent to a position. In this way, the nuclei that command the eye muscles have input about the position that the eyes have to maintain and receive input mainly from the MVN.

Horizontal or vertical retinal image motion of a target should be held below 5° in order to maintain visual acuity. Torsional movements along the line of sight are much better tolerated. Additionally, it is desirable for optimal vision that the image of the object is directed within 0.5° on the centre of the fovea. This explains the need for an intricate image stabilization system with high gains for horizontal and vertical movement, but much lower gains for torsional movements.

To ensure gaze stabilization during normal movements of head and body, two mechanisms have evolved, namely the VORs and the visually mediated reflexes (optokinetic and smooth pursuit). The first is based on the detection by the labyrinth of the head movements, whereas the latter depends on the ability of the brain to determine the speed of image drift on the retina. Both reflexes work synergistically to maintain gaze stabilization during head movements. The eye movements generated by the VOR have, however, a much smaller latency (<16 ms),[33] whereas the visually mediated reflexes have latencies greater than 70 ms.[34]

During typical head perturbations that occur while walking (1–2 Hz),[8] the main stabilization task is performed by the vestibular system, which explains why patients with a bilateral labyrinthine deficit cannot read street signs when walking. In specific circumstances one system is overridden by the other.

- Watching a tennis match, for example, sitting alongside the court, the head moves from left to right as do the eyes to follow the tennis ball. In this case, the smooth pursuit system is mainly responsible for the image tracking.
- During sustained movements, such as on a merry-go-round, the vestibular system is assisted by the optokinetic system. This is because the vestibular receptors cannot cope with prolonged movements, and the VOR is degraded over time, therefore the optokinetic system takes over to ensure visual stability.

There are also, however, specific systems designed to shift gaze so that new objects of interest can be placed on the fovea. The main functional classes are summarized in **Table 49.2**.[35]

Figure 49.18 Head impulse test for horizontal canals. Hold the subject's head slightly turned to one side ((a) and (c)), and ask them to maintain fixation on a target behind you. Then, turn the head briskly to the opposite side. If the gaze is still focused on the target (as in **(b)**), then the SCC on the side towards which the head was turned (in this picture to the right) is functioning properly, generating compensatory eye movements upon excitation. However, when the eyes rotate together with the head and are no longer focused on the target, the SCC on the side towards which the head was turned is not functioning properly **(d)**. The off-target eye movement is quickly followed by a refixation saccade, so that the target is in sight again. Since this happens quickly, careful observation and handling by the investigator is required to notice abnormalities. When posterior and anterior canals need to be investigated, brisk head movements need to be made in the right anterior–left posterior (RALP) and left anterior–right posterior (LARP) planes while observing the gaze stabilization.

VESTIBULAR SENSORY CELLS

Each response of the peripheral vestibular system starts at the level of the sensory epithelium located in the SCCs and the otolith system. This section describes the functional anatomy of the peripheral vestibular system and its physiological properties related to the processing of vestibular stimuli.

The vestibular sensory epithelium is formed mainly of hair cells, which are very similar to those located in the cochlea. Two types of hair cells (I and II) can be distinguished. Type I hair cells are amphora-shaped, have a spherical nucleus and are surrounded by a chalice-like afferent nerve ending. Efferent nerve buds impinge on the afferent nerve chalice. Type II hair cells are more cylindrical, contain a cylindrical nucleus and have bud-shaped

TABLE 49.2 Functional classes of human eye movements

Class of eye movement	Main function
Vestibular	Gaze stabilization, i.e. holds images of the surrounding world steady on the retina during transient head movements (0.5–5 Hz) (see **Box 49.1**)
Visual fixation	Holds the image of a stationary object on the fovea
Optokinetic	Holds the image of the surrounding world steady on the retina during sustained head movement
Smooth pursuit	Holds the image of a small slow-moving target on the fovea
Nystagmus quick phase	Resets the eyes during sustained head movement and directs gaze towards the oncoming visual scene
Saccades	Bring images of objects of interest onto the fovea
Vergence	Moves the eyes in opposite directions to place targets simultaneously on both foveas

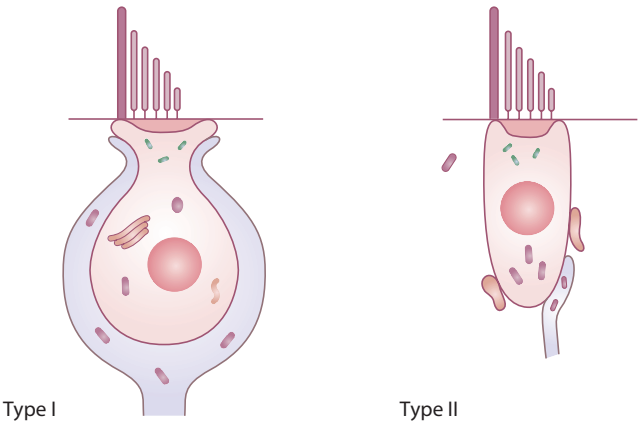


Figure 49.19 **(a)** Type I and **(b)** type II hair cells of the vestibular system.

afferent and efferent nerve endings located at the distal end of the cell. The apex of the hair cells is bathed in endolymph and is surrounded by non-sensory, supporting cells and dark cells (**Figure 49.19**).

The cell's hair bundle serves as the receptor for mechanical stimuli and is located at the apical end of the cell. Each bundle consists of 20–300 stereocilia and a single kinocilium. Hair bundle length varies: from 40–120 µm in vestibular hair cells to 0.5–30 µm in auditory hair cells.[36]

The sterocilia are rigid tubes of plasma membrane with a cytoskeleton of actin filaments, cross-linked by fibrin. They are arranged in a hexagonal pattern and vary in length across the surface of the cell, with the shortest stereocilia at one end and the tallest at the other end of the apical membrane, adjacent to the kinocilium. Consequently, the hair bundle looks like a staircase. The ion channels involved in mechanoelectrical transduction are located in

BOX 49.1 Gaze stabilization and the VOR

Shake your index finger at arm's length left and right, with increasing speed. As soon as you shake it at a frequency above 1 Hz, the eyes are not capable of following the movement and you see a blurred image of your finger. Next, shake your head while you fixate your finger, held stable at arm's length. You'll notice that the image remains sharp even at higher accelerations of your head. Up to frequencies of 5–6 Hz of head movements, many people are able to maintain a clear image of the target. This is the effect of a properly working VOR.

the stereocilia and each stereocilium possesses only one or a few transduction channels.[37]

Stereocilia are connected to each other by tip links, fibrillary strands running obliquely from the distal end of one stereocilium to the side of the longest adjacent stereocilium. The tip links are connected to the molecular gate of the transduction channels and the tension in the tip links controls the opening or closing of the transduction channels. The hair cell bundle is stiffer along its axis of mirror symmetry.[38] This increased stiffness is accounted for by the tip links. The upper end of each tip link is anchored to the stereocilium at a particular structure, known as the 'insertional plate' or 'insertional plaque', an oval disc that joins the plasmalemma of the stereocilium to its actin core (**Figure 49.20**).

The kinocilium is located at the tall edge of the bundle. The kinocilium is a true cilium consisting of an axoneme (nine paired microtubules and sometimes an additional central pair of microtubules). The role of the kinocilium is the transmission of stimulus forces to the stereocilia, but this appears not to be essential for mechanotransduction.

Hair cells are organized differently depending on their location in the SCCs or the otolith organs. Hair cells in the SCCs are located at the crista ampullaris, an elevated sensory area within the ampulla of the SCC. The tips of the cilia are embedded in a gelatinous cupula attached to the membranous labyrinth and functioning like a diaphragm (**Figure 49.21**). Hair cells in the SCCs are sensitive to changes in angular velocity and the output of the sensory cells is proportional to the angular displacement of the cupula, not to its velocity of motion.[39] Displacement amplitude of the cupula due to endolymph flow was found not to exceed 1 µm or 35° in the natural situation.[40] Larger displacement of the cupula is restrained by cupular attachments to supporting cells. As the hair cells located at the crista are all oriented in the same direction, they are all excited or inhibited by endolymph flow in the same direction. Hair cells in the horizontal SCC are excited by flow of endolymph towards the utricle (utriculopetal), whereas hair cells in the vertical SCCs are excited by endolymph flow in the opposite direction (utriculofugal). This organization is the basis of Ewald's first law which states that head and eye movements always take place in the plane of the canal being stimulated and in the direction of endolymph flow.[41]

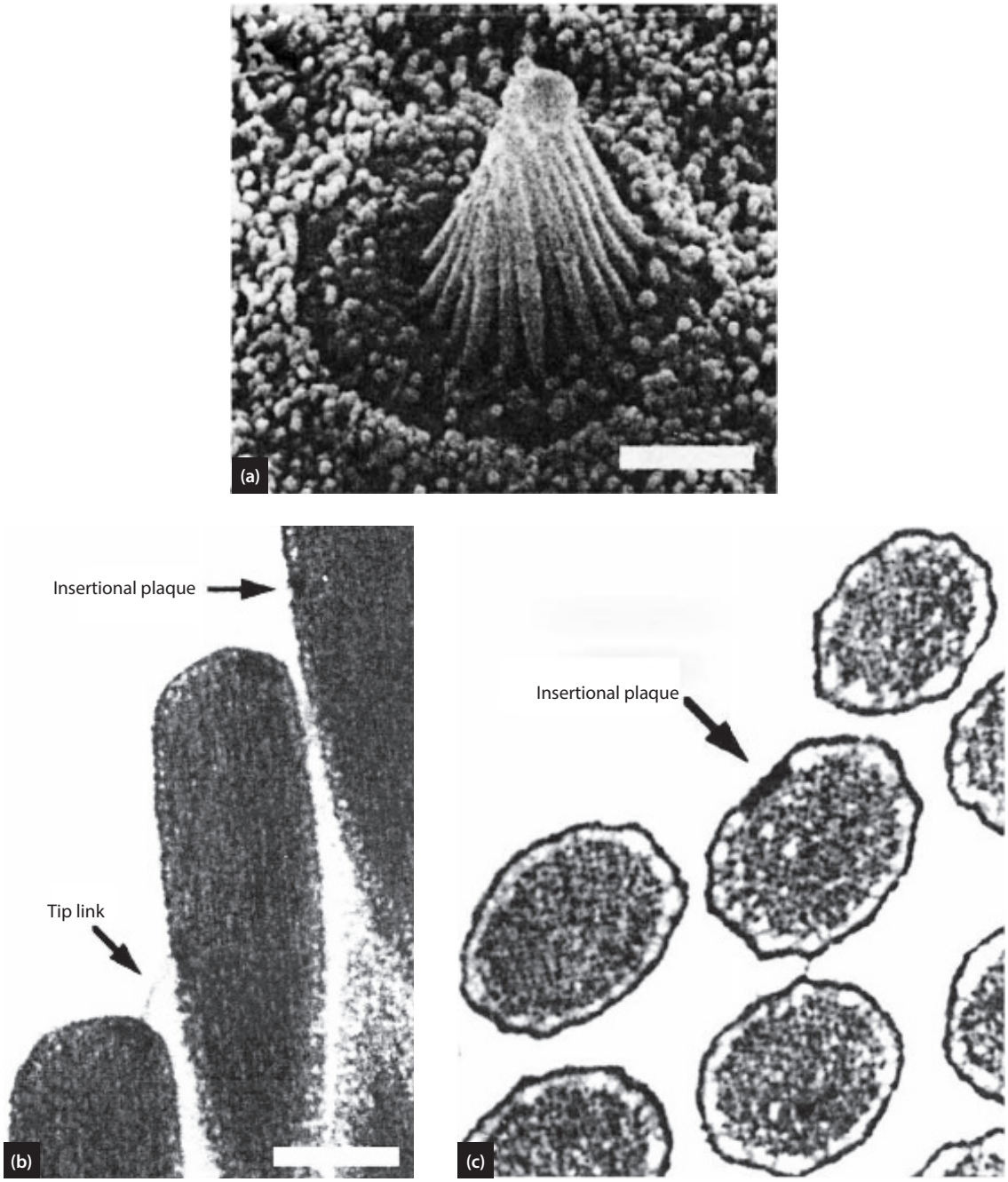


Figure 49.20 The hair cell's transduction apparatus. (a) The hair bundle comprises about 20–300 stereocilia and a single kinocilium surmounted by a bulbous swelling. The stereocilia monotonically increase in length across the mirror-symmetrical bundle. The bar in this scanning electron micrograph of a bullfrog's saccular hair cell represents 2 µm. **(b)** A tip link, a fibre about 160 nm in length and 3 nm in diameter connects the end of each stereocilium to the side of the longest adjacent process. A link often appears to comprise two or more strands, and it may splay into a pair of filaments near its upper termination at the osmiophilic insertional plate. A tip link's lower end is secured to the density capping a stereocilium. Each link is thought to be attached to the molecular gate of one or a few ion channels. **(c)** A section across several stereocilia reveals in one the insertional plaque at which a tip link's upper insertion occurs. The plaque, which interconnects the plasmalemma and the outermost tier of microfilaments in the stereociliary core, is about 50 nm high, 70 nm across and 20 nm thick. Transmission electron micrograph **(b)** is from a bullfrog; **(c)** is from a leopard frog. Scale bar: 200 nm in both. (Reprinted from Hudspeth and Gillespie.[45] Copyright 1994 with permission from Elsevier.)

In the utricle and saccule, hair cells are located in a structure known as the 'macula'. The utricular macula lies on the floor of the utricle and the saccular macula is usually in a vertical plane, on the posterior wall of the saccule. The hair cells of the utricle and saccule are embedded in a gelatinous layer impregnated with crystals of $CaCO_3$ called otoliths or otoconia. A filamentous network, the so-called subcupular meshwork, connects the lower surface of the otoconial membrane to the supporting cells of the sensory epithelium (Figure 49.22).

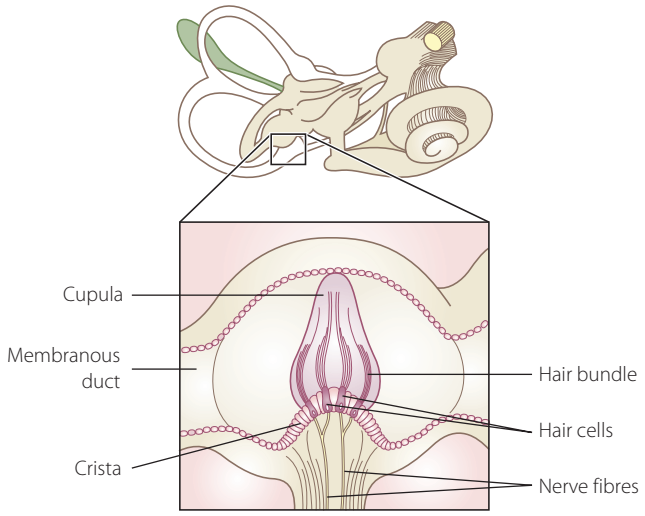


Figure 49.21 Organization of hair cells in the SCC. Hair cells are located at the crista ampullaris. The tips of the hair cells are embedded in the cupula.

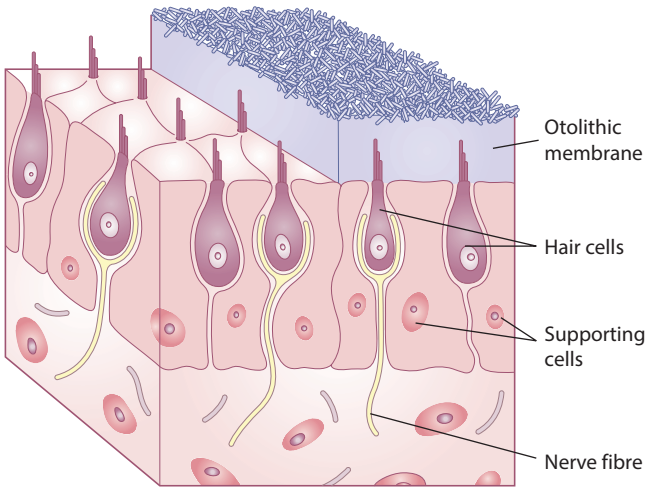


Figure 49.22 Hair cells of the otolith organs are located at the macula. The tips of these hair cells are embedded in the otolithic membrane (a gelatinous mass covered with calcium carbonate crystals, the so-called otoliths or otoconia).

Utricular hair cells are oriented in the shape of a fan with a medial group of cells pointing in an anterior–lateral–posterior direction and a lateral group of cells pointing in the opposite direction. Saccular hair cells can be divided into two parts with opposing orientation (a ventral group and a dorsal group), separated from each other by a virtual central line (the striola). Responses originating from hair cells located at opposite sides of the striola are coordinated in the central vestibular system, thus generating a common excitatory or inhibitory input. The otolith organs are sensitive to linear acceleration or changes in gravitational forces.

The endolymph surrounding the apical pole of the hair cells is characterized by a positive endolymphatic potential which plays an essential role in the transduction process. It was found that the endolymphatic potential in the vestibular part of the labyrinth (the endovestibular potential) is much lower (1–10 mV) in comparison to the endolymphatic potential in the cochlea (the endocochlear potential with values of 80 mV).[42] A more detailed analysis has shown that the ampullar and utricular endolymphatic potentials are respectively generated within the ampulla and utricle and independent of the endocochlear potential. By contrast, the endolymphatic potential of the saccule (with values of 4 mV) depends upon the integrity of the first turn of the cochlea. It is assumed that the presence of an utriculoendolymphatic valve between the saccule and the cochlear duct on one side and the ampullae and utricle on the other side might account for these differences in endolymphatic potential.[42]

Mechanotransduction

Hair cell function can be described in terms of a biological strain gauge; mechanical stimulation opens ion channels (transduction channels) in the cell membrane.[37] Displacement of the stereocilia towards the kinocilium stretches the tip links, which increases the ion permeability of the channel, resulting in an influx of cations (mainly K^+ and Ca^{2+}), thus depolarizing the hair cell. Displacement of the stereocilia away from the kinocilium shortens the tip links. This results in closure of the transduction channels and hyperpolarization of the cell. In a steady state condition, 10–20% of the transduction channels are open. Hair bundle displacement in the positive direction opens transduction channels. Channel opening decreases the stiffness of the hair bundle, which in turn promotes further movement in a positive direction, thus resulting in a positive feedback mechanism. This mechanism is known as 'gating compliance', an intrinsic property of direct mechanoelectrical transduction that enhances hair cell sensitivity.[43] The hair bundle's compliance is similar to other biological systems characterized by a non-linear stress/strain behaviour, i.e. stiffness increases when more tension is exerted on the system.

Adaptation

The extreme sensitivity of hair cells calls for a mechanism to prevent saturation of the mechanotransductor response from large and sustained stimuli (longer than 25 ms). Since mechanotransduction is a direct and fast process without intervening second messenger molecules, a unique mechanism has been developed, known as 'adaptation'. During adaptation, the transducer's sensitivity is maintained but the position at which the hair bundle displays maximal sensitivity changes from the resting position towards that at which the bundle is displaced with sustained stimulation. The stimulus/response relationship of the hair cells shifts in the direction of the applied stimulus and causes a return of the channel open probability to its resting value.[44] In this respect, adaptation in hair cells is completely different from the desensitization process encountered in other cell types. If a second stimulus is imposed during the adaptation process, the cell responds again.[45] In the primary vestibular afferents, adaptation manifests itself as a decay in spike rate during sustained head movement.

During sustained angular head velocity, deflection of the cupula decays so slowly that it does not affect afferent responses in the physiological range of human head movements (0.1–5 Hz). There is no adaptation of otolith movement during linear acceleration.[46]

Adaptation in vestibular hair cells may have at least four different purposes:[43]

- It avoids saturation of hair cell responsiveness by large or sustained stimuli.
- It allows a cell to detect small stimuli in the presence of an enormous background input.
- It places the hair cell bundle in a sensitive region of its operating domain.
- It contributes to high-pass filtering because hair cells with very fast adaptation responses are insensitive to low-frequency stimuli. Cells in the same receptor organ may have different adaptation responses, accounting for differences in frequency responsiveness.

Frequency selectivity

The length of the hair bundle varies from cell to cell in the same receptor organ. Hair cells responding to low-frequency acoustic vibration and acceleration stimuli bear relatively long bundles whereas receptors for the highest-frequency stimuli have the shortest bundles. Shatz et al. suggested that hair bundle length might be related to frequency selectivity and that longer hair bundles, such as those encountered in the vestibular hair cells, contribute to the low-frequency selectivity in the vestibular organs.[36]

FUTURE RESEARCH

- ➤ The development and implementation of vestibular implants, similar to cochlear implants in the past decades.
- ➤ Study of the vestibular cortex and regions of interest relevant for the vestibular system by application of advanced MRI scan methods such as e.g. diffusion tensor imaging (DTI), resting state functional MRI (rsfMRI) and voxel and surface based morphometry (VBM and SBM).
- ➤ The efferent vestibular system and its regulatory characteristics.
- ➤ Study of functional dizziness and its physiological correlates.

KEY POINTS

- The vestibular system ensures gaze stabilization, postural control, balanced locomotion and autonomic function readjustment.
- The geometry of the SCCs is such that head velocity is measured and used for the generation of VOR.
- The optimal efficiency of the SCC is obtained for frequencies of 0.1–5 Hz.
- The typical head frequencies for human behaviour peak around 2 Hz.
- The VOR is essentially a three-arc neuronal reflex, but the central pathways of the VOR generation use multiple inputs from both ipsilateral and contralateral vestibular afferents, through commissural fibres.
- The push–pull principle states that, upon head rotation to one side, the discharge rate in the hair cells in the leading ear increases while it decreases in the following ear. This imbalance generates the appropriate nystagmus for gaze stabilization upon rotation.
- After an acute unilateral vestibular lesion, a spontaneous nystagmus is generated due to the imbalance in discharge rate of the peripheral organs, similar to that induced during head rotation to one side.
- An acute spontaneous vertical nystagmus is more commonly due to a central nervous system disorder than to a peripheral vestibular disorder.
- Conflict between sensory inputs often leads to motion sickness.
- The head-thrust test is a bedside test that investigates directly the efficiency of the VOR.

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CHAPTER 50

PERCEPTION OF SOUNDS AT THE AUDITORY CORTEX

Frank E. Musiek and Jane A. Baran

SEARCH STRATEGY

The data in this chapter maybe updated by a search using the keywords: auditory cortex, auditory pathways, tonotopic maps, cortical mapping, and auditory field maps.

INTRODUCTION

In discussing the auditory cortex (AC) and what it does, one must realize there is probably much more about this structure that is unknown than known. That said, to adequately cover what is known about the AC would require books and not just a single chapter. So in an attempt to provide some meaningful information about the AC we will follow a course that provides glimpses of what this central auditory nervous system (CANS) structure is and does.

The first part of the chapter will discuss the anatomy of the AC, touching on some of the basic principles and findings. Questions to be addressed include: What is the extent of the AC and how do we define it? How is it connected to other parts of the auditory system and brain? Are the ACs in each hemisphere highly similar or different?

The second major area of discussion in the chapter addresses some of the functions of the AC. How does the AC represent the various parameters of sound? How does it respond to sound and how do we measure these responses? The physiology of the AC provides us with much of the meaning that we garner from both simple and complex stimuli – do we know how this happens?

The final section of the chapter will relate information on what happens when the AC is compromised in some way. Some classic animal ablation studies are reviewed and cryoloop cooling will be introduced. Also discussed will be lesion studies in humans. This particular discussion will be clinically oriented. The studies that look at humans with damage to the AC can provide us with some very practical and highly relevant views of what the AC can or cannot do in regard to hearing and related processes.

Many of the questions that have just been posed cannot be answered fully, but hopefully they will provide the reader with some direction and guidance regarding the organization and contents of this chapter. Throughout the chapter, we will stress basic elements of understanding and build upon them as much as the scope of this chapter will allow.

The orientation of the chapter will be one that necessarily utilizes some of the traditional literature for establishing a foundation of knowledge. However, whenever possible we will touch upon some of the newer studies that are garnering attention. Certainly, there has been an explosion of knowledge about the brain recently and, along with this, there have been many advances in our understanding of the structure and function of the AC. We hope that this mixture of information provides a worthwhile learning experience for the reader.

GROSS ANATOMY OF THE AUDITORY CORTEX

It is difficult to fully define the extent of the human AC, mainly because there is considerable variability among the findings in many of the studies on the anatomy of the AC. These variances are reflected in imaging studies, electrophysiological reports and investigations of human cadaver brains.[1,2] Also it is difficult to discern what constitutes primary versus secondary or associative AC.[1] Given these kinds of limitation, this chapter will provide our best deductions regarding the anatomical definition of the AC in humans.

Defining the auditory cortex

Two approaches to defining the AC will be rendered here: one will be what we term the 'traditional approach' and the other the 'core–belt approach'. In the traditional view the primary AC is generally considered to be limited to Heschl's gyrus, which is positioned on the superior temporal plane of the superior temporal gyrus (**Figures 50.1** and **50.2**). This gyrus runs in an anterior–lateral to posterior–medial direction. Heschl's anterior segment is located in the posterior third of the superior temporal gyrus. It is bordered anteriorly by the planum polare and posteriorly by the planum temporale. The medial border is formed by the insular sulcus and the insula. There often are one or two gyri in this auditory structure, but three or more have been reported, although this is quite rare. Depending on the stimulus, recording technique and other variables, additional areas in the vicinity of Heschl's gyrus can be found to respond rather vigorously to sound, making one consider anatomical areas such as the planum temporale, the supramarginal gyrus, the inferior central gyri, the frontal lobule, and the posterior part of the planum polare as part of the AC, and if not a part of the AC itself, at least a 'highly responsive auditory area' in the vicinity of the AC. This roughly defined region is strikingly similar to the auditory areas defined in the classic paper by Celesia based upon recordings from humans[3] – though Celesia[3] and others[2] confine the AC to the planum polare, Heschl's gyrus and the planum temporale. Although there are differing views as to the extent of what may be considered the AC and the auditorily responsive area(s) around it, most would agree that the anatomical region just defined would provide some insight into the general location and extent of the AC in humans.

The core–belt approach to defining the AC has gained popularity recently (**Figure 50.3**). This increased interest is based primarily on non-human primate studies and the subsequent extrapolations of the results of these studies to humans.[2] In non-human primates the AC has a central or 'core' designation, which receives inputs from the medial geniculate body (MGB), mostly from the ventral division of this CANS structure. The core, if adapted from the non-human primate to the human, is estimated to take up about one-half or more of Heschl's gyrus.[2] The 'core' constitutes the primary auditory reception area and is immediately surrounded by a 'belt' region, which then is surrounded by a 'parabelt' area. The concept that is promulgated here is that, at this level, neural activity originates at the core and then spreads to the belt and parabelt

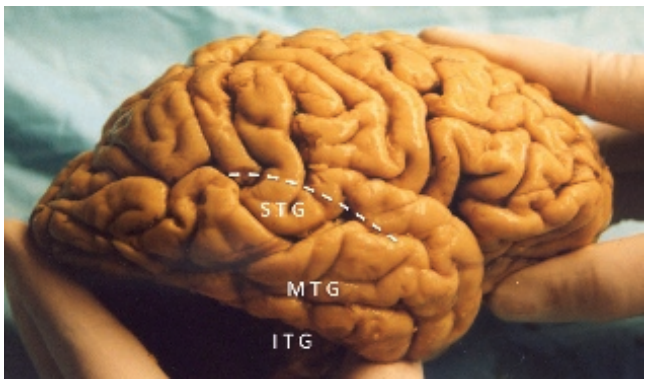

Figure 50.1 Right lateral view of the human brain with focus on the temporal lobe. The white arc signifies the course of the Sylvian fissure. The superior (STG), middle (MTG) and inferior (ITG) temporal gyri are indicated.

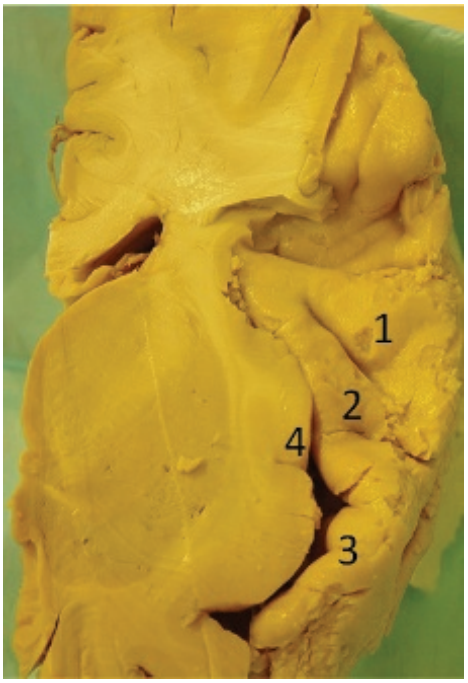

Figure 50.2 View looking down on the left superior temporal plane. The orientation of the numeration is from posterior to anterior. Key: 1 = planum temporale, 2 = Heschl's gyrus, 3 = planum polare, 4 = insula.

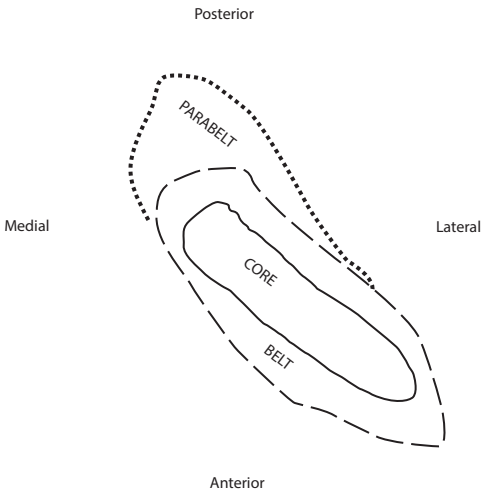

Figure 50.3 Sketch depicting the authors' interpretation of the core–belt anatomy of the auditory cortex. The drawing is aligned at a similar angle as seen in Figure 50.2 with Heschl's gyrus on the superior temporal plane. The core covers most of Heschl's gyrus with the belt and parabelt extending to parts of the planum polare and planum temporale.

regions as part of processing and neural connectivity of the CANS. Beyond the parabelt region there is neural communication with other parts of the brain in a rather non-modular fashion.[4, 5]

The core–belt arrangement makes sense in many ways and certainly there is good evidence that it exists in the non-human primate. However, the existence of a similar anatomical arrangement in humans remains an unsettled argument. Some evidence does exist from imaging data in humans, but it is not convincing to the present authors' interpretation. Moreover, even if there is a core–belt arrangement in humans, a question remains as to what form it may take; i.e. is it highly similar to that which is seen in the non-human primate, or does it vary considerably from the non-human primate model?

Projections to the auditory cortex

Heschl's gyrus receives projections from other cortical areas of the brain, but the present discussion will focus on the inputs that ascend from the thalamus. Neurons arising from the MGB project to the AC via the internal capsule. Specifically, the ventral division of the MGB is the main input to the AC. The dorsal division of this CANS structure also sends fibres to the AC, though not to the extent of the ventral division.[1] In referring to the core–belt model, the core receives input from the ventral MGB and the belt areas receive inputs from the other areas of the MGB.[6]

Projections from the auditory cortex

There are intrahemispheric, interhemispheric and efferent output projections (either direct or indirect) from the AC. Heschl's gyrus has immediate connections within this structure and then connections outside the structure. The key intrahemispheric connection is input to the arcuate fasciculus, which has fibres that connect to the insula and the frontal lobe (Broca's area).[4] The core–belt model has proposed connections from the core to the belt and parabelt regions in the superior temporal gyrus, which is similar to the Heschl's gyrus connections mentioned above.[1, 2, 6] Efferent connections originate in the AC regions and project to the inferior colliculus and MGB forming a loop that feeds back to the AC. The interhemispheric connections leave the AC and likely course around the lateral ventricles and across the midline via callosal fibres. These connections are mostly to similar loci in each hemisphere (i.e. homolateral connections), but some callosal fibres connect to different neural substrate in the opposite hemisphere (i.e. heterolateral connections).[7] Of course, the AC has connections to other parts of the brain as well, making its neural network more of a non-modular than a modular one.[5]

Asymmetries of the auditory cortex

The classic study of Geschwind and Levitsky[8] alerted us to the concept of anatomical differences between the left and right sides of the planum temporale (see **Figure 50.2**). This study and many subsequent studies have shown that in normal brains the left planum temporale is significantly larger than its right-sided counterpart. There is also anatomical evidence that is definitely slanted towards the Sylvian fissure being longer and more horizontal on the left than the right side of the brain.[2, 9] In regard to Heschl's gyrus there is also evidence supporting a left-sided size advantage, but this is not without some exceptions that point to both left and right Heschl's being similar in size.[1, 2, 10, 11] The existence of asymmetries for the core–belt orientation is, at least for the present authors, difficult to glean from the literature and requires more investigation before a definitive determination of the existence of any asymmetries (or lack thereof) can be rendered. This lack of information regarding asymmetries in the core–belt areas is due in part to the lack of understanding of the borders of the core–belt designation as it applies to humans.

It is important when discussing asymmetries of the AC that variations in the contour of the Sylvian fissure be considered. Rubens'[12] classic article brought attention to the concept that approximately the last third of the Sylvian fissure can course horizontally, or it can ascend or descend. Most Sylvian fissures run essentially a horizontal course, but in many instances this fissure ascends – often termed an ascending ramus (**Figure 50.4**). An ascending ramus has been shown to alter the morphology of a number of auditory structures, including Heschl's gyrus, the planum temporale, the angular gyrus and the supramarginal gyrus.[13] This altered morphology obviously has an influence on anatomical interpretations of imaging, lesion and evoked potential studies, rendering interpretations of the structures on the posterior third of the superior temporal gyrus and adjacent regions complex and controversial. Structural asymmetries may well exist if one hemisphere has an ascending ramus and the other does not. However, the impact of brains that have ascending rami compared to brains that do not is not fully understood at this time, but it is anticipated that with more investigation the effects will likely be found to be considerable.

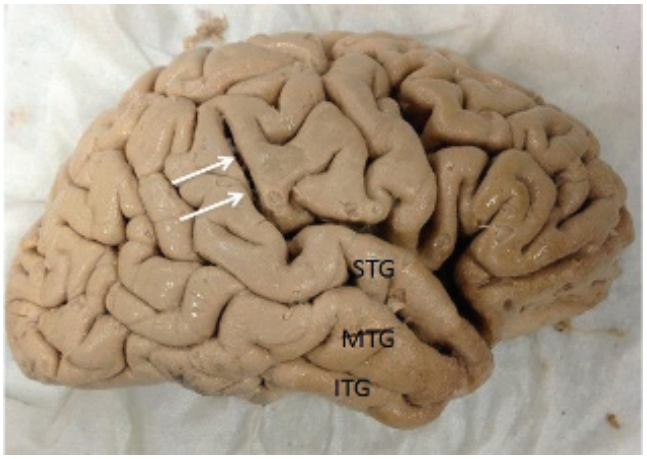

Figure 50.4 Right lateral view of a human brain with the arrows pointing to an obvious ascending ramus. Key: STG = superior temporal gyrus, MTG = middle temporal gyrus, ITG = inferior temporal gyrus.

Vascular anatomy relevant to the auditory cortex

A familiarity with the vascular anatomy of the AC is essential to understanding both its function and dysfunction (Figure 50.5). The key vessel for the AC is the middle cerebral artery (MCA). As shown by Waddington and Ring[14] and related by Musiek and Baran,[1] the MCA is derived from the internal carotid artery deep within the cerebrum. The MCA essentially runs along the Sylvian fissure before sending branches to the frontal, temporal and parietal regions of the brain. The length and morphology of the MCA proper varies greatly before it changes into branches and the MCA can no longer be discerned. Key auditory branches originating from the MCA include two or three temporal branches that infuse the temporal lobe (anterior to posterior) as well as the angular gyrus, and provide the vascular supply for the posterior temporal lobe, the supramarginal gyrus and the angular gyrus. These major arteries then give rise to smaller branches and even arterioles that penetrate the auditory regions.

AUDITORY CORTEX PHYSIOLOGY

The discussion of the physiology or function of the AC will initially focus on the manner in which this structure codes intensity, frequency and temporal information. Much of the available information in this area is a result of animal recordings where the intensity, frequency and/or temporal characteristics of an acoustic stimulus are varied and the effects are measured intracranially. Human physiological data, on the other hand, are generally obtained using functional imaging, evoked potentials, and psychoacoustic paradigms using non-invasive procedures, and although these non-invasive procedures do provide some insights to the physiology of the AC, they do not offer the spatiotemporal resolution that intracranial recordings afford.

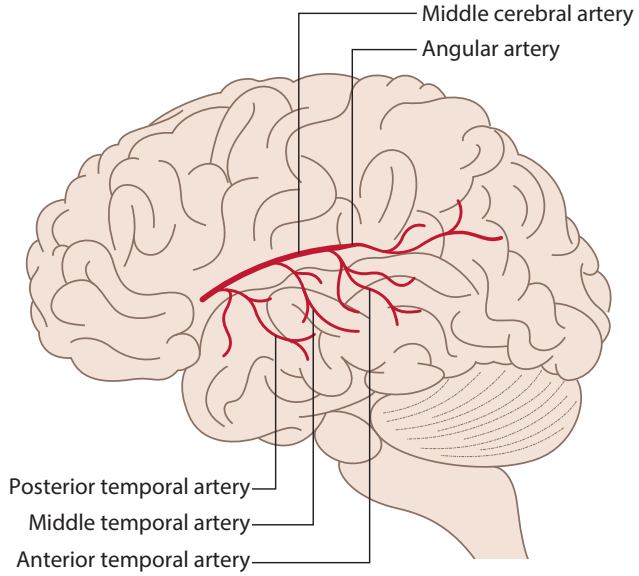

Figure 50.5 Sketch of the key arteries for the auditory cortex and immediate areas around it.

Intensity representation at the auditory cortex

Intensity in the AC is coded in three major ways. One is that as the intensity of the stimulus is increased neurons increase their firing rates.[15] Though this concept is often true, there are some exceptions that are indeed interesting and insightful. It is true that many AC fibres do increase their firing rates in a monotonic fashion, but some neurons will show a different firing pattern, i.e. they will 'roll over'. These neurons increase their firing rates with increases in stimulus intensity up to a certain level and then they actually decrease their firing rates as stimulus intensity increases further, yielding what are called non-monotonic intensity functions. The range of intensities for which there is continuous increase in a neuron's firing rate and the level at which the neuron 'rolls over' varies greatly across neurons.

A second way in which intensity is coded is related to the number of fibres that respond to a stimulus.[16] Generally, as the stimulus intensity increases, more neurons will respond, resulting in a larger neural response area. This increase in the number of neurons firing has been documented in imaging, fMRI and evoked potential studies in humans.[16] In general, as intensity increases, the response area for functional imaging responses becomes larger. Also, with increases in intensity, auditory evoked potentials (AEPs) will become larger in amplitude, likely reflecting changes not only in the number of neurons firing but also their firing rates.[16, 17]

The third way that the AC codes intensity is a complex interaction between excitatory and inhibitory neurons in the cerebrum. For example, a neuron could be non-linear in its amplitude representation and could be inhibited or enhanced in its response to a sound stimulus by activity in other neurons in and around its cortical field.[1, 18]

Changes in the latency of the neural response can also be noted if responses from the AC are recorded for a stimulus that systematically increases in intensity. In such cases, the latency of the neural response will often decrease. Though some of this shortened latency can be attributed to the travelling wave time in the cochlea, this cochlear phenomenon cannot account for all of the decrease in latency. Therefore, it appears that the neurons that respond to higher intensities may be favoured in some way to allow faster neural conduction times. This can be demonstrated by the decrease in late cortical potentials generated from the AC.[16, 17]

As has been discussed above, the AC employs a number of different neuronal mechanisms to process and code intensity information. It is likely that these mechanisms interact in various ways to provide the neural response that forms the foundation for the perception of loudness as well as changes in loudness.

Frequency representation at the auditory cortex

The representation of frequency at the AC depends on whether one is ascribing to the traditional or core–belt view. Early animal studies seemed to indicate that low

frequencies were located rostrolaterally and high frequencies were found in a caudomedial location in the AC. This, at least for present purposes, is referred to as the classic view. This view gained momentum with the functional imaging study performed by Lauter et al.[19] for which results in humans were found to be similar to those in earlier studies conducted in other animals. More recent functional imaging work with humans supported the Lauter et al. findings.[20, 21] However, it has become clear that there was variability surrounding these studies:[21] these studies in general would use only a few frequencies to map the tonotopic representation of the AC and this limitation could have lead to an overinterpretation, if not a complete misinterpretation, of the tonotopic contour in the human AC. For example, the classic investigation by Lauter et al.[19] used only two acoustic stimuli (500 Hz and 4000 Hz). The 500 Hz stimulus resulted in AC activity that was lateral and caudal to that evoked by the 4000 Hz tone. Therefore, these responses, though likely accurate for the specific frequencies studied, may or may not paint a valid picture of the complete tonotopic organization of the human AC as only two frequencies were tested. Certainly, a number of assumptions must be made in studies like those of Lauter et al. to allow an accurate interpretation of frequency contour of the human AC. It seems clear that the frequency arrangement described earlier is what is seen in non-human primates, as more comprehensive mappings of frequency representations in non-human primate studies have been completed. However, this does not mean that this same tonotopic arrangement occurs in humans and caution is recommended before applying non-human primate findings to humans. Moerel et al.[2] tried to reconcile the varying views on the tonotopic arrangement within the human AC. These investigators relate that perhaps the tonotopic arrangement may stretch from the planum polare to the planum temporale with a more general high–low–high representation. This varies from the more concentrated (less area) that has been postulated. This frequency representation has the core area segmented into three regions, each having its own frequency display. The anterior and the posterior segments have a low to high frequency representation coursing medially and maybe slightly posteriorly. The middle segment has essentially the opposite representation.[22]

It seems that perhaps many issues emerge in understanding what the tonotopic arrangement really is in humans, but two will be offered here. One is the adoption of the non-human primate tonotopic findings for human models. The other is the lack of specificity of the frequency representation in the human, and even (to a lesser degree) the non-human primate. These issues, among others, make the clear identification and definition of frequency maps within the human AC an unresolved issue.

Coding of temporal information at the auditory cortex

Frequency-modulated (FM) and amplitude-modulated (AM) signals are often used to gain insight to temporal processing capabilities, and in this case the AC. A basic concept of interest and import is that many neurons in the AC respond to changes in an acoustic signal over time, and a good example of this is the response of cortical neurons to AM and FM signals. Perhaps one of the most insightful concepts in regard to how the AC responds to acoustic signal modulations is that some neurons will only respond to modulated signals and not to steady-state signals.[23] It has long been suggested that modulated tones create more activity in the cortex than steady-state tones. A glimpse of this kind of AC activity was related by Whitfield and Evans[24] over 50 years ago. Notable is research showing that FM modulation depth discrimination thresholds are strikingly better than those derived with static tones.[25] Extending this concept, this could be one reason why complex acoustic stimuli such as FM and AM signals are more appropriate than traditional pure-tone stimuli for evaluating dysfunction of the AC clinically.

Modulation rates of AM and FM signals are an important consideration when reviewing the topic of temporal processing within the AC. Although there is variability in findings as well as in opinions, it appears that lower modulation rates seem to favour activity from the AC as opposed to higher modulation rates, which align better with brainstem and auditory nerve activity. It has been suggested that AM rates of less than 50 Hz are optimal for involving the AC, whereas rates above 50 Hz better suit brainstem neurons and the AC becomes less involved.[26] However, it must be understood that there is considerable overlap of cortical and subcortical neurons in regard to their responses to both high and low modulation rates but that, as modulation rates decrease, the neurons that respond best to the stimuli ascend in their location from the low brainstem to the AC.[23]

Another factor related to AC temporal processing of AM and FM signals is phase locking, which of course is related to overall responses to various modulation rates as just discussed. For AC neurons, phase locking is best for lower rates (again below 50 Hz), but in unsedated animals some phase locking for frequencies of over 100 Hz has been shown.[23, 27]

As recently reviewed,[28] the sweep of FM signals (low to high to low) appears to have a laterality factor in regard to AC activity. For slow sweeps, the right AC seems to respond better than the left, while just the opposite is true for fast sweeps. More fundamentally, however, is the key concept that there are neurons in each AC that are specifically sensitive not only to FM signals but to the direction of the sweep of these signals.[28] These kinds of functions would likely be related to the manner in which the AC processes speech stimuli as speech is represented by rapid changes in its underlying acoustic representation(s).

Gap detection procedures also have been used to measure temporal acuity of the AC as well as other areas of the auditory pathway. As in other regions of the CANS, neurons within the AC synchronize to the offset and onset of the lead and trailing segments within the stimuli. In addition, there is suppression of activity during the silent interval – although some spontaneous activity remains.[29] Accuracy for gap detection perception requires that the neuron array, whether in the cortex or elsewhere, follows the acoustic pattern in the stimulus (**Figure 50.6**).

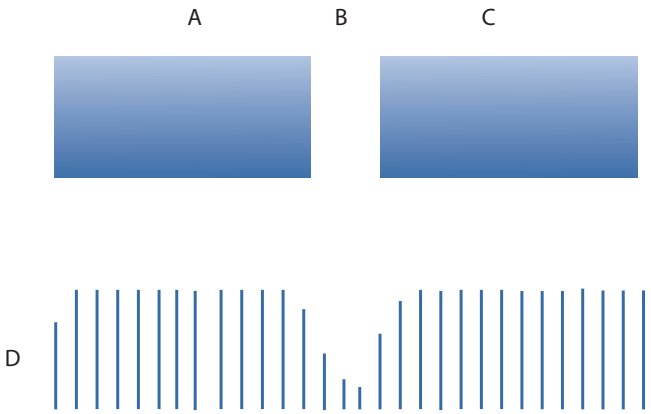

Figure 50.6 Depiction of a gap-in-noise stimulus array. Key: A = lead white noise, B = gap, C = trailing white noise, and D = predicted neural response (firing rate).

That is, when the lead element is 'on', cortical neurons are firing, and when the stimulus stops, the neurons must synchronously shut down quickly (i.e. reduce their activity to their spontaneous firing rate) and then synchronously initiate increased firing rates again when the stimulus (trail element) returns. The available research appears to indicate that the termination of the gap physiologically is of more import than the onset of the gap.[30]

Localization

The AC plays an important role in spatial hearing, which has been shown to underlie two major auditory functions: the ability to identify the location or the source of a sound, and auditory scene analysis or the ability to separate sounds based on their locations.[31–33] Research findings in both other animals[34] and humans[35] have demonstrated that the accurate localization of a sound source is affected if the AC is compromised. In humans, sound localization in the horizontal plan is largely dependent on the neural processing of interaural time differences (ITDs) and interaural intensity level differences (ILDs). Research findings have demonstrated that the perceived location of low-frequency sounds is largely mediated by processing of ITDs, while perception of high-frequency sounds is more heavily weighted on the processing of ILDs.[36,37] The time and intensity differences in these binaural cues are represented by excitatory and inhibitory responses in the cells of the AC.[38] Within the AC, there are two main types of cells, including excitation–excitation (EE) cells and excitation–inhibition (EI) cells. EE cell responses are excitatory to stimulation at each ear, whereas EI cells usually present an excitatory response at the contralateral ear and an inhibitory response at the ipsilateral ear.[38] The identification of the elevation of a sound source is based primarily on monaural spectral cues, although some weak binaural cues may be available due to small head asymmetries that often exist in individual listeners.[33]

Non-human primate studies have suggested the existence of a number of distinct subregions within the AC that are responsible for processing distinct sound properties. For example, a number of investigations have revealed that the tonotopic organization representing frequency that is first seen in the cochlea is maintained in some topographic fashion up to and including the belt regions of the AC.[33] However, investigations of the AC in humans have not yielded consistent findings and, as a result, the existence of similar topographic fields and/or representations in the human AC has not been established.[1,33]

Although the existence of clear frequencies maps within the human AC have not been established, results of fMRI testing in humans have provided evidence for two broad processing areas in humans, an anterior 'what' and a posterior 'where' area.[33] The posterior auditory 'where' pathway in humans is involved in the processing of spatial information and encompasses two non-primary AC areas, the planum temporale and the posterior superior temporal gyrus. These posterior non-primary AC areas have been shown to be strongly activated by horizontal sound direction changes, distance changes and sound movement. However, they are also activated by a wide variety of other stimulus features (e.g. frequency and phonetic stimuli), which suggests that the processing of acoustic information in these areas is not limited to purely spatial information (see 'Complex sounds (speech)' below).[33,39]

Research studies in humans have shown that unilateral lesions interfered with the localization of sound in the contralateral hemisphere of space, suggesting that each cortex preferentially processes acoustic signals on the contralateral side.[40] However, there appear to be some differences between the right and left ACs in their responses to sounds. For example, Spierer et al. found that lesions in the right hemisphere typically affected the localization of sound sources originating from both the ipsilateral and contralateral hemifields, whereas left hemisphere lesions were limited to contralateral sound sources.[40,41] They also found that the deficits noted among their subjects tended to be more severe following right hemisphere compromise than left hemisphere damage, and that greater deficits were noted for the processing of ITD than ILD cues. Based upon their findings, these researchers have proposed that the right hemisphere plays a dominant (but not an exclusive) role in the processing of spatial location, and it has an integrative role in representing sound localization.[41]

The processing of acoustic cues for moving sound sources is different from the processing of acoustic cues for stationary sources,[15] with the available evidence implicating the presence of separate processing mechanisms for stationary and moving sounds. The existence of direction-specific motion sensitive neurons in the non-primary areas of the AC (planum temporale and the posterior superior temporal gyrus) has been suggested in a number of studies.[33,42,43] However, it is not clear if the neural responses to moving acoustic targets are the result of activation of unique 'motion'-sensitive neurons, or whether the perception of auditory movement is based upon the sampling of discrete locations in space as the target moves.[33]

Complex sounds (speech)

In humans, research has documented that a variety of speech sounds activate areas immediately anterior to

Heschl's gyrus in both hemispheres,[44] while others have shown that speech stimuli (syllables and words) activate cortical areas both immediately anterior and posterior to Heschl's gyrus in the left hemisphere.[45] These findings (i.e. that speech stimuli activate areas both anterior and posterior to Heschl's gyrus) are consistent with more recent theories that posit a 'where' area in the non-primary AC as has been discussed above, as well as a 'what' area, which incorporates the anterolateral Heschl's gyrus, the anterior superior temporal gyrus and the posterior planum polare.[39] Recent auditory evoked response findings have suggested that these two processing mechanisms occur in parallel with activation of the 'where' processing pathway, occurring slightly ahead of the activation of the 'what' processing mechanism, which may enable the brain to employ top-down spatial information to assist with the processing of speech sound identity cues.[39]

Dichotic listening studies have shed some light on how the AC processes dichotic stimuli. In 1999, Hugdahl et al. in a positron emission tomography study using dichotic CVs as stimuli found activation in the mid to posterior segment of the superior temporal gyrus, with the most noticeable activation levels occurring around Heschl's gyrus in both hemispheres.[46] However, when the activation patterns of the two hemispheres were compared, the extent of the activation in the left hemisphere was greater than that noted for the right hemisphere, a pattern that is consistent with behavioural findings for dichotic speech materials. In addition, the activation area in the AC appeared to extend beyond the 'core' and possibly even the 'belt' areas. Finally, results from fMRI and magnetoencephalography (MEG) studies have shown that directing attention to one ear or the other during dichotic listening to speech stimuli influences the amount of activation in the primary AC, with increased activity noted in the hemisphere contralateral to the attended ear.[47, 48]

Auditory evoked potentials

AEPs reveal stimulus-related responses that can be measured both near and far field. These responses can tell us, at least to some degree, about the functional integrity of the AC. Of course, the AEPs that are most relevant to AC function are those for which the generator sites are in the AC.

Perhaps the earliest of AEPs that are generated by the AC is the middle latency response (MLR) (**Figure 50.7**).[49]

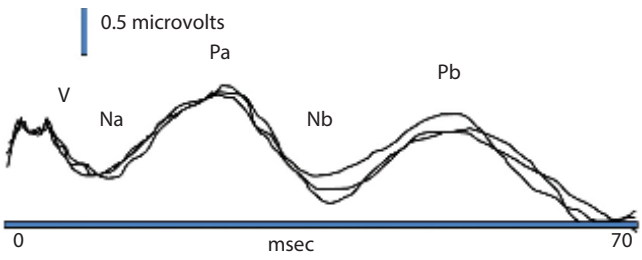

Figure 50.7 Sketch of a normal middle latency response (MLR). V = wave V of the auditory brainstem response (ABR) and Na, Pa, Nb, Pb are the wave components of the MLR.

The MLR is considered a thalamocortical potential, meaning that it is likely generated by the thalamocortical pathway. However, the main wave component of the MLR is the Pa wave, which most would agree is generated by the AC. The Pa wave has a latency of approximately 30 msec in adults for stimuli such as tone bursts and clicks presented at moderately intense levels. It appears to be generated by the medial aspect of Heschl's gyrus.[50]

The N1 and P2 potentials are often considered late and/or cortical AEPs. The N1 and P2 waves occur at about 100 and 200 msec after the onset of the stimulus in adults. The origin of N1 is Heschl's gyrus and possibly the planum temporale.[51] The P2 response also is generated by or in the area of Heschl's gyrus.[51, 52] The N1 appears to demonstrate laterality differences, with earlier latencies and greater amplitudes typically noted for the responses arising from the contralateral hemisphere, and with the right hemisphere showing greater lateralized activity (i.e. greater amplitude) than the left.[53] The P2 component may have laterality differences as well, but this has been debatable for a long time. Hine and Debener[53] relate that, if laterality differences exist for the P2, they are not as great as those noted for the N1. Even as far back as 1977 reports indicated that there was little agreement on laterality differences for AEPs.[54] Lesion effects on AEPs will be discussed in the next section of this chapter, which will provide additional information on AC function.

THE DISORDERED AUDITORY CORTEX

There is a long and respected history of learning about the function of the AC by measuring the effects of damage to it. This approach to learning about the AC can take a variety of forms. In this chapter we will focus on various ablation studies, and a new technique called cryoloop cooling as well as clinically based studies of various disorders of the human AC.

Ablation studies

Ablating the AC in mammals in most cases is related to some depression in performance on auditory tasks. Though cortical damage is generally not associated with changes in tonal thresholds, this may not be entirely true. One of the key investigations was performed on monkeys with bilateral AC ablations.[55] Immediately after these ablations the animals, at least in some cases, were unable to respond to simple stimuli but over a period of time ranging from months to years their detection thresholds improved in some cases to essentially normal levels.

Sound localization is dependent on good AC function. The early work by Neff in the late 1940s indicated that with cortical ablations animals could discriminate left-from right-sided sounds but could not locate these sounds in space with any degree of accuracy.[56] Later work showed that, if one AC was damaged, deficits of localization were often noted in the opposite auditory field.[57] Like most structures along the auditory pathway, damage to the AC compromises consistent and accurate sound localization.

Diamond and Neff[58] performed a series of bilateral AC ablations on cats. They initially measured the animals' intensity and frequency discrimination abilities before surgery and then reassessed these abilities post-surgery. The cats were able to relearn discriminations to near their pre-surgical performance levels. However, when the cats were tested on the discrimination of tone patterns, they did not regain pre-ablation performance levels. Since Diamond and Neff's studies in the late 1950s and early 1960s their findings on intensity and frequency discrimination have been both supported and disputed.[1] It has been shown that, after AC ablation, intensity discrimination suffers, especially for detecting decreases in intensity. Also, after AC ablations, non-human primates cannot distinguish a tone at given frequency from one that is changing in frequency.[55] This finding was consistent with animal research that demonstrated that, after AC ablations, gerbils were not able to accurately discriminate FM tones, while discrimination of steady-state tones was largely unaffected.[59] The findings of impaired pattern perception following AC ablation have been well accepted. In fact, these findings on auditory pattern discrimination influenced the development of two popular clinical tests of central auditory function (frequency pattern sequences and auditory duration patterns).

Cryoloop cooling

A relatively new technique termed cryoloop cooling presents some advantages over ablation procedures and other techniques that create permanent lesions.[60] Lesion effect studies often provide valuable clinical information in regard to disordered auditory systems. Cryoloop cooling involves passing cooled methanol through specially designed tubing directly into the brain. This tubing can be inserted for short-term study or implanted for long-term investigation of the physiology of the AC or other areas of the brain. The cooling has been shown to deactivate areas of the brain in a rather discrete manner, rendering the underlying neural circuitry inactive. However, the cooled area of the brain can then be allowed to warm and resume normal function. This capability provides the investigator with a research design that permits a measure of normal function, impaired function and then a return to normal function. It also allows the animal to retain a healthy system. Recent work with the cryoloop cooling procedure has shed light on a number of functions and dysfunctions of the auditory system, including the underlying mechanisms for localization[61] and effects of impairment in one auditory field on an adjacent field,[62] as well other processes.

Clinical studies

Clinical and clinically relevant studies have provided a significant amount of information on AC function and dysfunction in the human. One of the key findings reported in the mid 1950s was that simple high redundancy stimuli such as pure tones were not highly sensitive to AC damage, but more complex stimuli such as altered (distorted) speech materials were.[63] Low redundancy speech stimuli such as filtered speech, compressed speech, speech stimuli presented in noise and especially dichotic speech often revealed deficits for the ear contralateral to the damaged AC.[64] In addition, deficits in auditory pattern perception have been noted in individuals who suffered damage to the AC, though interestingly many of these patients with unilateral damage revealed deficits in both ears.[65]

Though not as commonly used clinically, studies employing AEPs on patients with AC lesions have often shown deficits. Principally, middle and late potentials (MLR, N1, P2 and P3) have been shown to be compromised in patients with AC pathology.[49] In humans, lesions of the AC can result in extended latencies and reduced amplitudes of cortically generated AEPs. However, in general it appears that changes in amplitudes of AEPs may be a more sensitive index for detecting dysfunction than changes in latency. Key in utilizing AEPs in AC lesion studies are multichannel recordings. Electrodes placed over the auditory areas and midline will allow comparisons of responses between the two hemispheres. Also, each ear can be, and should be, tested independently to allow ear comparisons. These types of comparisons can reveal differences which, if present, can document CANS dysfunction.

KEY POINTS

- The precise anatomical extent of the auditory cortex (AC) is uncertain.
- The auditory cortex codes intensity, frequency and temporal information from acoustic stimuli.
- The key vessel for the AC is the middle cerebral artery (MCA).
- The AC plays an important role in the ability to identify the location or the source of a sound.
- Auditory evoked potentials (AEPs) are clinically useful and can tell us about the functional integrity of the AC.

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CHAPTER 51

PSYCHOACOUSTIC AUDIOMETRY

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: pure-tone audiometry, audiogram, hearing loss, hearing thresholds, degree of hearing loss, type of hearing loss, speech audiometry.

INTRODUCTION

What the mind perceives as sound is not directly equivalent to the physical stimulus that reaches the ear. Psychoacoustics is the science that studies the transformation of the physical signal of sound into a mental percept. In other words, Psychoacoustics studies auditory perception. Psychoacoustic audiometry requires that a person is able to cooperate by giving a suitable response to the auditory stimuli being presented. In general, the methods described in this chapter will relate to adults and children older than approximately 5 years of age. Younger children require adjustments to the test protocol and to the type of response required, depending on age and abilities. These will not be covered here.

Psychoacoustic methods are valuable in clinical practice as their outcomes can give a first indication of the site of a lesion in the auditory system (i.e. external or middle ear, cochlea, or higher levels of the auditory system). Also, these methods provide a basic measure of the impact of ear pathology on communication.

AUDITORY DEVELOPMENT AND DECLINE OVER A LIFETIME

The auditory system in humans is permanently scanning and interpreting sound signals in the environment, moment by moment. The anatomical structures of the ears begin to develop around day 22 of gestation.[1] By weeks 25–30 of gestation, the outer, middle and inner ears are structurally developed, and the auditory system has experience of speech and other physiological sounds.[2] The fetus is capable of auditory learning while still *in utero*, as has been shown in fetuses as young as 33 weeks' gestational age.[3] There is evidence of auditory plasticity elicited by maternal voice and heartbeat before the full period of gestation is completed.[4] Near term, the fetus learns to recognize its mother's voice or a particular melody and is able to discriminate between these sounds after birth.[5]

Input from the peripheral auditory system shapes and drives the development of the central auditory system from the first years of life. Auditory deprivation arising from unidentified hearing loss can result in delays in linguistic,[6] social[7] and cognitive[7] development. The human auditory system continues to develop the capacity to receive, interpret, and respond to complex sound stimuli such as language and music over the first decade of life and well into the teenage years.[8] In later years, the auditory system starts to decline. 'Presbyacusis' (derived from the Greek words *presbys,* meaning 'elder', and *akusis,* meaning 'hearing') describes age-related changes to the auditory system. Four predominant pathological types of presbyacusis have been described: sensory, strial, neural and cochlear-conductive.[9] An individual may have more

than one type of presbyacusis, with age-related changes affecting both the peripheral and central auditory systems. Typically, changes to the periphery are seen in elevated pure-tone thresholds[10] and absent or reduced otoacoustic emissions (OAEs),[11] with decreased speech recognition scores, while changes to the central auditory pathways are demonstrated by even poorer speech recognition scores[12] and low scores on gap-detection tests,[13] which may indicate abnormal temporal processing. In other words, as the threshold for detecting a sound deteriorates with age, it may be paralleled by the reduced ability to discriminate and categorize complex sounds. In other cases, the hearing thresholds may be normal or near-normal, but suprathreshold abilities, such as the ability to use the information about the rapid time changes in sound (temporal fine structure), and some top-down cognitive processes involved in speech processing may deteriorate, which is reflected by poor speech intelligibility in noise.[14]

USEFUL DEFINITIONS

Sound level: Sound levels are measured in decibels (dB). Decibels are used to express the magnitude of a sound relative to a reference. The number of decibels is 10 times the logarithm of the ratio of two intensities, or 20 times the logarithm of the ratio of two amplitudes or pressures. The reference commonly used for sound in the air is 20 µPa, as this is close to the average absolute threshold for 1000 Hz (see Chapter 48, Physiology of hearing). This is defined as 0 dB SPL (sound pressure level). Decibels are a convenient unit, as the human dynamic range of hearing is very wide. The ratio between the intensity of the softest detectable sound and that of the loudest tolerable sound one can hear is vast, being in the order of 1 000 000 000 000:1, which corresponds to 120 dB.[15]

Frequency: The frequency of a sound is the number of times the wave is repeated within 1 second.[15] Each repetition is known as a cycle, and one cycle per second corresponds to 1 Hertz (Hz), which is the standard unit used to specify frequency (see Chapter 48, Physiology of hearing).

Absolute threshold: The level at which a person reliably just detects a signal in the absence of any other sounds is referred to as the **absolute threshold** for that sound. If the sound level were to be increased even slightly, the person would always hear the sound; if the sound level were to be decreased, the sound would be generally inaudible. The absolute threshold is the 'lowest sound pressure level or vibratory force level at which, under specified conditions, a person gives a predetermined percentage of correct detection responses on repeated trials'.[16] In audiology, the absolute threshold is also referred to as the **hearing threshold**. Measuring the absolute threshold for pure tones at different frequencies is standard practice in clinical settings. This is known as 'pure-tone audiometry' (PTA), and it aims to quantify the degree of hearing loss.

Minimal audibility curve: The human ear does not have equal sensitivity for pure tones across frequencies. For example, a pure-tone signal of 100 Hz is just detectable to the normal-hearing person when delivered to the ear via headphones at a level of about 35 dB SPL. However, a 4500 Hz pure-tone signal at a level of about 12 dB SPL will be just audible to a normal-hearing person. Figure 51.1 shows the minimal audibility curve for normal-hearing listeners. The dashed line shows thresholds measured monaurally, usually delivering the sound by headphones. The sound pressure levels at thresholds were measured with a probe microphone placed closed to the eardrum. A threshold measured in these conditions is called the minimum audible pressure (MAP). The solid line shows thresholds measured bilaterally, by delivering the sound through a loudspeaker in an anechoic chamber. The sound pressure levels are thresholds measured in the sound field, at the point where the centre of the head of the listener was placed, after the listener has left the room. A threshold measured in such conditions is called the minimum audible field (MAF). MAP thresholds are about 2 dB higher than MAF thresholds, since the latter are binaural and the former monaural. The MAP and MAF curves also differ in shape, particularly at around 3000–4000 Hz and around 8–9 kHz.[15] This is due to the effect of the head, the pinna, and the ear canal when thresholds are measured in the sound field. Remember that the conditions of measurement for these curves are different. The maximal sensitivity is around 2000–5000 Hz as this is the range where the least sound pressure is required to just detect a sound at threshold. Between 500 Hz and

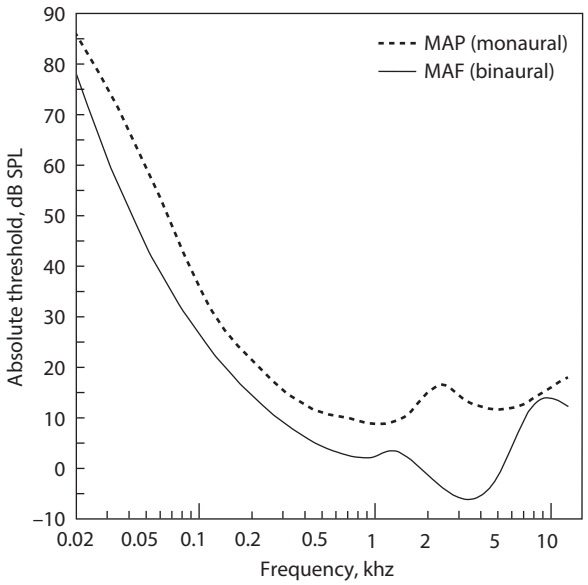

Figure 51.1 The solid line shows the MAF estimates for binaural listening as published in the standard ISO 389-7:1996. The dashed line shows the MAP estimates for monaural listening. Figure courtesy of Brian C.J. Moore. Published in *An introduction to the psychology of hearing*, 6th ed. Emerald Group, 2012.[15]

5000 Hz the variation in sensitivity is less than 10 dB and this is the frequency range that encompasses most speech sounds. Outside this range, hearing becomes increasingly less sensitive. This is partly due to the characteristics of the transmission of vibrations by the middle ear to the cochlea.[17] It is generally agreed that the range of human hearing for typically hearing young adults falls between 20 Hz and 20 000 Hz.

Upper level limit of hearing: The upper limit of hearing before pain and possible damage to the auditory system is in the region of 120–130 dB SPL; the upper limit of comfort for most people is well below this, however, in the region of 100 dB SPL.

PSYCHOACOUSTIC CORRELATES OF SOUND PRESSURE LEVEL AND FREQUENCY

Loudness and sound pressure level: It is generally understood that the higher the level of a sound is, the louder it will sound. In other words, loudness is the subjective psychoacoustic correlate of sound pressure level, although there are additional factors that can influence loudness. Loudness is the term used for the attribute of sensation by which a listener can order sounds on a scale going from quiet to loud,[15] whereas the measured level of a sound is based on the physical properties of the signal. The relationship between loudness and sound level is not straightforward. Two sounds of different frequencies can have different sound pressure levels but lead to the same loudness level. For example, a 40 dB SPL 1000 Hz pure tone may be judged to have the same loudness as a 250 Hz pure tone presented at 50 dB SPL. The unit used to quantify loudness levels is the **phon**. The phon is referenced to a particular level of a 1000 Hz pure tone against which the loudness of all other tones is matched. The 250 Hz tone would therefore have a loudness level of 40 phon. Figure 51.2 shows the equal loudness contours and the lower dashed curve represents the hearing threshold. The shape of the loudness contours changes with increasing level, with contours becoming flatter at high input levels.

The healthy auditory system is able to operate in a very wide range of sound levels, as described above. There are several mechanisms that may be involved in supporting the wide dynamic range of human hearing: the compressive behaviour of the basilar membrane, changes in the firing rate of the auditory nerve, the spread of excitation on the basilar membrane, and the information provided by phase-locking of the responses of the auditory nerve.[15] Although describing these mechanisms and discussing their contribution is beyond the scope of this chapter, they are mentioned here because one of the most common manifestations of cochlear damage in ENT clinics is **loudness recruitment**. Loudness recruitment occurs when the dynamic range of hearing is narrower than normal.

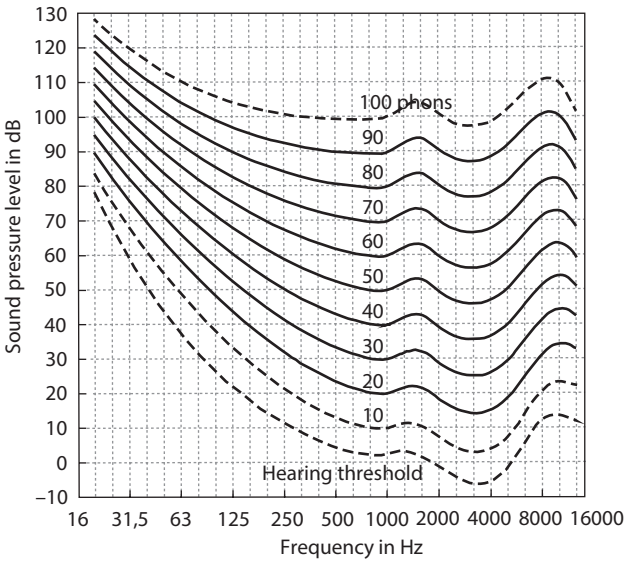

Figure 51.2 Graph showing the equal loudness contours and the lower dashed curve representing the hearing threshold. Figure courtesy of Brian C.J. Moore. Published in *An introduction to the psychology of hearing*, 6th ed. Emerald Group, 2012.[15]

In other words, the range between the sound level that is just detectable and the maximum comfortable level is less than for normal-hearing people.

Pitch and frequency: Pitch is an 'attribute of the auditory sensation in terms of which sounds may be ordered on a scale extending from low to high'.[18] Periodic sounds have pitches, as pitch is related to the repetition rate of the sound. For pure tones, the repetition rate of a sound is given by its frequency. Thus, pitch and frequency are closely related for pure tones. As stated above, frequencies are objectively measured using units of Hertz (Hz). Pitch cannot be measured directly because it is a subjective quality. Pitch is coded in the auditory system using both a place code (given by the distribution of activity across the auditory neurons) and a temporal code (given by the temporal patterns of firing within and across neurons). The relative importance of these codes for a given sound may depend on its frequency range and other characteristics.[15]

The thresholds for sounds of different frequencies are measured in PTA. The frequencies of the tones presented to the patient during audiometric testing are measured at octave intervals, i.e. their frequencies increase by a factor of 2 from tone to tone: 250, 500, 1000, 2000, 4000 and 8000 Hz. Sometimes semi-octave frequencies are tested too, as will be explained later. It should be noticed that pitch perception, as many other suprathreshold abilities, is not explored during PTA. The detection of a sound does not imply the perception of all the qualities of that sound. For example, two patients with identical pure-tone audiograms may have completely different outcomes for speech perception. Similarly, it is not uncommon to find patients who have rather good hearing thresholds but relatively

poor sound discrimination or even speech perception. From a clinical point of view, it is important not to dismiss any functional problems described by the patient solely based on a normal or near-normal audiogram.

PURE-TONE AUDIOMETRY

The purpose of PTA is to determine the hearing thresholds for pure tones, which are sinusoidal signals with a single defined frequency, amplitude and phase (see Chapter 48, Physiology of hearing). While pure tones are rare in nature, they are easily characterized, which makes them suitable for quantitative tests of hearing sensitivity. Pure tones can be considered as the basic components for all periodic sounds generated by the human larynx and many tones from musical instruments, thus having validity for hearing assessment in addition to convenience of use.

There are international and national standards that specify the characteristics and calibration of the equipment used to carry out PTA (e.g. IEC 60645-1:2017[19] and BS EN 60645-1:2017[20]), as well as the characteristics of the test room and the procedure followed for identifying thresholds (ISO 8253-1:2010[21]). These specify the types of signal used, the way in which they are presented and their duration, the type of response expected from the patient, and the presentation mode (air conduction (AC) or bone conduction (BC), as will be explained later). It is crucial to follow these conventions in order to obtain valid, comparable results across sessions and clinicians. Local professional societies usually publish their own guidelines for the procedures, which in turn are in line with the current standards (e.g. American Speech–Language–Hearing Association,[22] British Society of Audiology[23]).

Equipment for pure-tone audiometry

The principal equipment for deriving the clinical audiogram is the audiometer. There are four different levels of complexity of functions and options, classified as: screening, clinical, diagnostic, and more recently, via computer-integrated software applications.[19, 20] **Figure 51.3** shows a clinical audiometer. All types of audiometer generate pure tones at specified levels for standard test frequencies. In addition, there are narrow and broad bands of noise for use in clinical testing, as discussed later. The option of being able to present pure tones as modulated warble tones or pulses can help listeners detect signals in the presence of tinnitus. Warble tones are also crucial for getting around standing-wave artefacts particular to a given booth in the sound field. Some audiometers include options for higher-frequency hearing assessment up to 16 000–20 000 Hz, used, for example, for monitoring the effect of ototoxic drugs on high-frequency hearing thresholds.[24]

The calibration of test equipment is required at least annually and perhaps twice-yearly in some situations. Calibration may drift over time so that the gradual change in signal output is not apparent without systematic daily checks and measurement routines as specified in ISO 8253-1:2010.[21] Changes in the transducer type – for example, between headphone sets, or from headphones to insert earphones – require different calibration settings to be stored within the audiometer. The audiometer, transducers and response buttons (used by the patient to indicate that they hear the stimuli) need to be clean, functioning consistently, and used with the correct calibrated equipment.

Figure 51.3 A clinical audiometer.

Transducers: air-conduction and bone-conduction measurements

When performing PTA, the tester fits the transducers to the patient, and the patient is instructed not to move or hold the transducers. The examiner should check for any discomfort caused by the transducers.

The use of AC and BC transducers seeks to separate the conductive (outer and middle ear) and sensory (cochlear) components of hearing loss. Signals presented from headphones or insert earphones are transmitted by AC. In BC testing, a bone vibrator is positioned on the mastoid behind the pinna, or sometimes on the forehead, with a known force so that mechanical vibrations are coupled to the skull bone to stimulate the cochlea through bone transmission. The sensitivity for detecting these mechanical vibrations depends largely on the inner ear function, with reduced influence of the outer and middle ears. Thus, comparison of results obtained by AC and BC often allows the separation of conductive and sensorineural components of hearing loss. There are, however, caveats in this simple model which have useful diagnostic indications, as described later in this chapter.

AIR-CONDUCTION TRANSDUCERS

The most common headphone type is the Telephonics TDH-39, 49 or 50 headphone, which is a **supra-aural** headphone. These rest on the surface of the pinna, without enclosing the pinna in their cups. Supra-aural headphones can fail to achieve good coupling with the ear. Thus, air

leaks can occur, and the hearing thresholds below 500 Hz may be overestimated as a consequence.[25]

An alternative type is the **circum-aural** headphone, which encloses the pinna in its cups. These are designed to give a close fit to the outer ear to prevent leakage of the test signal or ambient noise from the test environment, and reduce the amount of physiological noise in the ear.[25] Examples include Sennheiser HDA-200 headphones, which have noise-excluding muffs and can be used for high-frequency audiometry (i.e. 8000–20 000 Hz). However, circum-aural headphones, as well as supra-aural headphones, are less reliable at high frequencies due to wave effects in the cavity defined by the headphone and the ear canal, which in turn depend on the positioning of the headphone.[25]

A third type of AC transducers are **insert earphones** (e.g. Etymotic Research EAR-Tone 3A). These consist of two probes (right and left) covered by a disposable foam tip that is placed in the ear canals for testing. Insert earphones give improved attenuation of ambient noise relative to supra-aural headphones, along with reduced likelihood of infection transmission as inserts are single use,[26] and the positioning of the insert reduces the likelihood of the ear canal becoming collapsed in soft or elderly ears.[26] They also reduce the amount of physiological noise in the ear and the occurrence of air leaks even further than circum-aural headphones, and reduce the wave effects associated with the other types.[25] In addition, they are more convenient when testing patients with profound loss at the low frequencies, for whom responses are given to vibrotactile stimulation. Insert earphones reduce vibrotactile stimulation when delivering high-level low-frequency tones.[27] They also have a higher 'interaural attenuation' compared to supra- and circum-aural headphones.[25, 26]

Interaural attenuation (or transcranial transmission loss) is the attenuation of sound delivered by a transducer to one ear as it reaches the opposite ear. While supra-aural headphones typically have 40 dB interaural attenuation, Etymotic Research ER3 or ER5 insert earphones inserted deeply have at least 75 dB interaural attenuation at frequencies below 1000 Hz, and about 50 dB interaural attenuation at frequencies above 1000 Hz.[28] This is relevant when testing the AC hearing thresholds of persons with asymmetric hearing or with bilateral conductive hearing loss, and it will be addressed later in this chapter. However, insert earphones are not recommended when there is excessive earwax in the ear canal, or when obstructions and abnormalities affect the ear canal or in the event of ear infection.[23]

The correct position for supra- or circum-aural headphones is to have the sound opening of the headphone aligned with the ear canal entrance. For insert earphones, the correct position is to have the outer end of the foam tip flush with the ear canal entrance. It is important to use an appropriate-size tip for the earphones. **Figure 51.4** shows the correct placement of supra- and circum-aural transducers. **Figure 51.5** shows correct insert positioning.

Calibration standards are different for supra-aural headphones (ISO 389-1:2017[16]), insert earphones ISO 389-2:1994[29]) and circum-aural earphones (ISO 389-8 2004[30]).

BONE-CONDUCTION TRANSDUCERS

The most commonly used BC transducer for clinical audiometry is the Radioear B-71. The transducer is held at one end of a rigid vertical headband. The opposite end has no transducer attached and serves only as support. When placed correctly, the headband holds the BC transducer against the skull with a given static force. The BC transducer is placed first on the mastoid prominence of the worse-hearing ear.[23] The transducer must be placed so that it is as close as possible to the pinna, without touching it and avoiding the hair (see **Figure 51.6**).

The Radioear B-71 is prone to distortion below 500 Hz[31] and limited above 6000 Hz.[32] Thus, testing is generally done for frequencies between 500 Hz and 4000 Hz. For 3000 Hz and 4000 Hz, especially when testing at relatively high-level, the Radioear B-71 produces airborne sounds. In order to prevent the patient from responding to these, an earplug can be used in the test ear when testing the BC threshold in this ear. It is important to record the use of an earplug during testing on the audiogram form as this causes an occlusion effect. Airborne sounds are reduced when placing the BC transducer on the forehead. However, corrections should be made to the calibration in this case.[23] Recently, it was proposed to adjust the reference equivalent force threshold level (REFTL), especially for 4000 Hz, to reduce observed false air–bone gaps at this frequency.[33] Calibration for BC transducers is specified in the standard ISO 389-3:2016.[34]

Environment for clinical testing

The acceptable level of ambient noise in the test environment is specified by standard ISO 8253-1:2010.[21] It is generally accepted that the ambient noise should not exceed 35 dB(A). Additionally, the examiner should be aware that transient noise (i.e. coughing, furniture noise following movement, etc.) can also affect the test results.

It is crucial that the examiner can see the face of the patient at all times. This helps to detect situations when the patient is confused, or has lost their focus on the task, or feels that the test sounds are unpleasant. It is equally important that the patient is not able to see or hear the examiner manipulating the audiometer controls. Usually, the patient sits in a soundproof booth during the test, and the examiner controls the audiometer from outside the booth (**Figure 51.7**). Soundproof booths used for clinical testing have silent fans, light and a double-glass window or a closed-circuit TV system through which the examiner can see the patient and the patient can see the face of the examiner. The examiner and the patient should be able to talk to one another when needed, thus an intercom system is available in most clinical audiometers.

Audiometric procedure for clinical assessment

BEFORE THE TEST

The following is based mainly on the recommendations of the British Society of Audiology.[23] The examiner relies

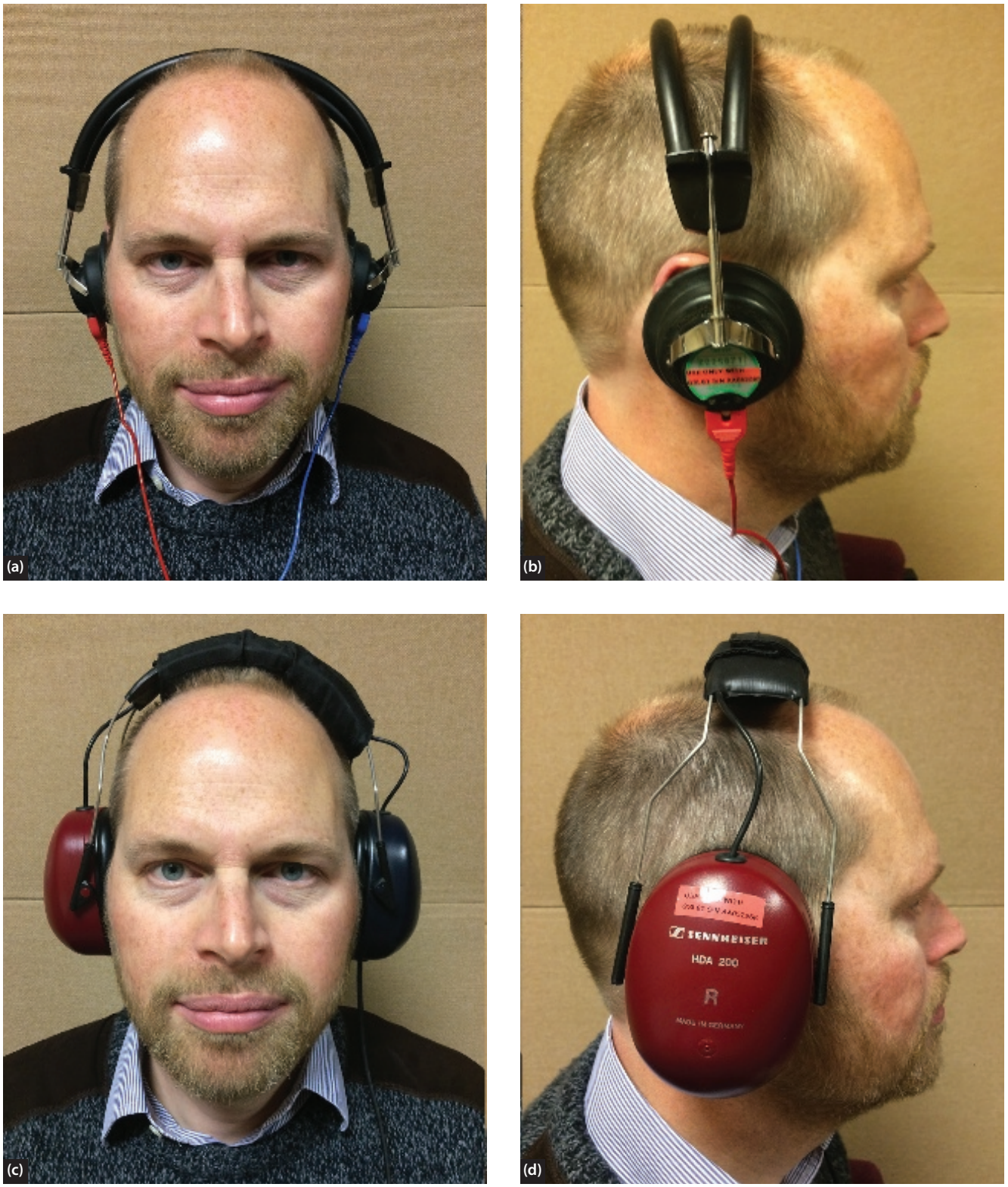

Figure 51.4 Correct position of the supra-aural headphones **(a,b)** and circum-aural headphones **(c,d)**.

on the patient's responses for the accuracy of the test and therefore establishes at the beginning of the test that the patient understands what they are expected to do and that they feel comfortable in the test environment. Several factors about the patient, including age, hearing deficit, language skills and communication problems (whether or not related to their hearing problem), should be taken into account. Important communication difficulties must be recorded as they are likely to affect the outcomes of the test. If the test is carried out in a soundproof booth, claustrophobia will constrain testing for some patients. In this case, the environment should be modified (e.g. by

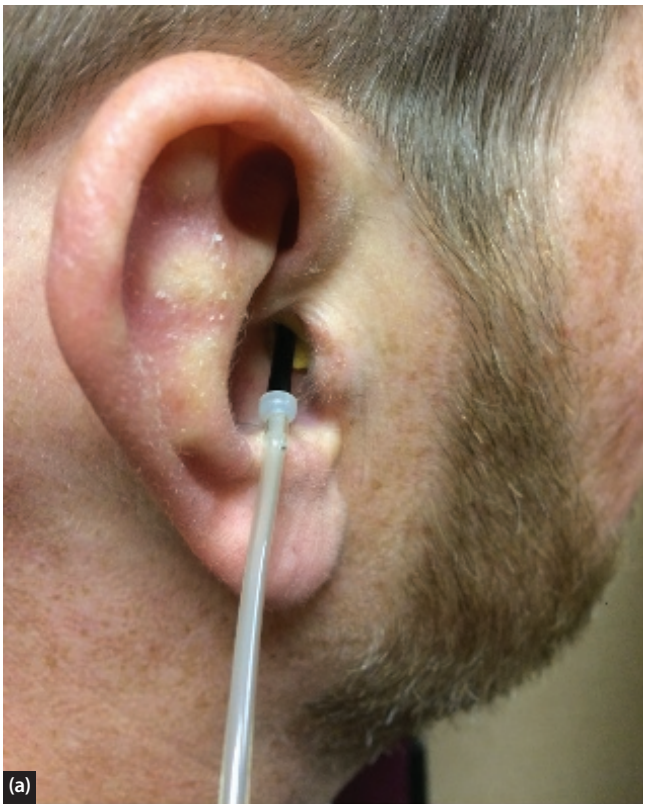

Figure 51.5 Insert earphones. (a) Correct position of earphones. **(b)** View of the inside of the ear canal in an ear model. This illustrates the depth of the transducer into the ear canal when the foam is placed flush with the entrance of the ear canal, as shown in (a).

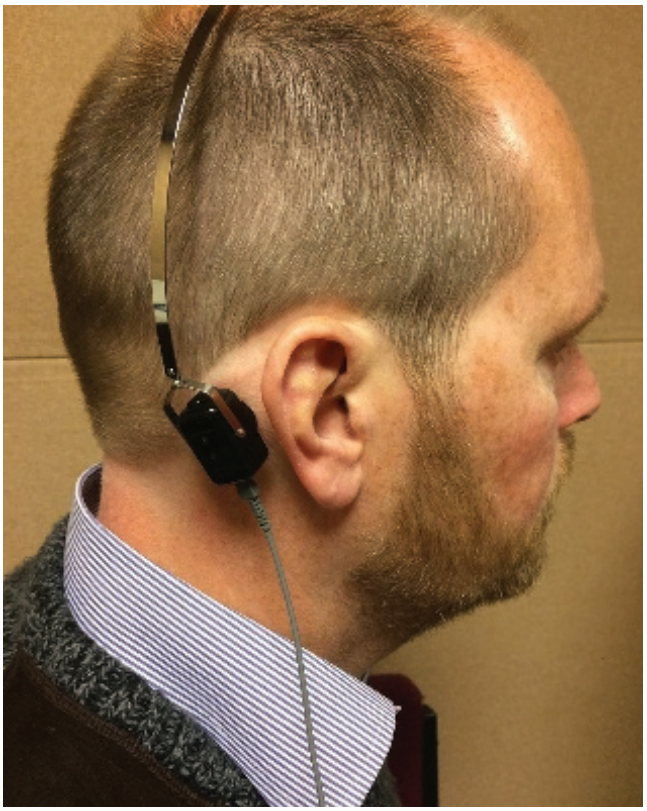

Figure 51.6 Correct placement of the bone-conduction transducer. Note that the transducer is not touching the hair or pinna.

Figure 51.7 A typical clinical audiometric booth. The examiner sits outside and the patient inside the audiometric booth. The booth has a window that allows the examiner to see the patient. Photograph courtesy of Joanna Lemanska.

not closing the door of the booth) to avoid subjecting the patient to undue anxiety, and any modifications to the test procedure should be noted in the outcome form or audiogram.

Typically, the patients are asked about two situations that can interfere with the detection of the test tones:

- **Exposure to loud sounds in the last 24 hours:** In this case, it may be necessary to retest the patient as loud sounds could temporarily shift the hearing threshold.
- **Tinnitus:** In this case, the patient must be asked to ignore their tinnitus as much as possible. The clinician may decide to use warble tone signals to make it easier for the patient to distinguish between their tinnitus and the test stimuli. Frequencies where there was variation in thresholds and any modification in the protocol to measure the thresholds should be recorded.

Patients are also asked whether they have better hearing in one ear, as in this case testing should start in that ear.

It is essential that the PTA is preceded by otoscopic examination, and that the findings are noted on the audiogram. Hearing thresholds will be affected by the presence of occluding earwax so, if occluding earwax is detected, the patient should have earwax removal first. If it is determined that the ear canals are likely to collapse during the test, this should be noted in the audiogram, and insert earphones should be used if possible.

Before carrying out the test, instructions are given to the patient about what they are expected to do during the test. While the wording can be varied, the essential points of the instructions should be kept constant in order to be able to compare test results across sessions and/or examiners. The British Society of Audiology proposes the following instructions to the patient:

> *'I am going to test your hearing by measuring the quietest sounds that you can hear. As soon as you hear the sound (tone), press the button. Keep it pressed for as long as you hear the sound (tone), no matter which ear you hear it in. Release the button as soon as you no longer hear the sound (tone). Whatever the sound and no matter how faint the sound, press the button as soon as you think you hear it, and release it as soon as you think it stops.'*[23]

A printed version of these instructions may be useful. The patients should be asked whether they understood the instructions, and should be told to sit quietly during the test, and that they may interrupt the test in the event of discomfort.

The patient responds by pressing a button or perhaps raising a finger, in the way indicated in the instructions. Every time the button is pressed a light indicator is lit on the audiometer panel, so that the examiner knows that the patient has responded.

MEASURING THE HEARING THRESHOLDS

As discussed above, the procedure for PTA is specified by the relevant standards.[21] For AC audiometry, the test is started in the better ear, and the threshold for each of the pure tones is measured before moving to the next pure-tone test frequency. Traditionally, the order of the pure tones presented to the patient is: 1000 Hz, 2000 Hz, 4000 Hz, 8000 Hz, 500 Hz and 250 Hz. Inter-octave frequencies can be tested if there is a difference of 20 dB hearing loss or more between contiguous frequencies. The threshold at 1000 Hz is then retested for the ear tested first only. If the test–retest difference is within 5 dB, the best hearing threshold is noted. If the test–retest difference is greater than 5 dB, it is necessary to check that the patient understands the procedure, the transducers are still in place, and the response button works properly, together with other possible sources of variation. After testing the first ear, testing is carried out in the other ear. Retesting of the hearing threshold at 1000 Hz is not required for the second ear if there was no significant test–retest difference for the first ear.

Testing is preceded by a familiarization trial. Details of the step-by-step procedures for familiarization and testing are shown in **Figures 51.8** and **51.9**. Each test signal is introduced at an easily audible level, and then systematically attenuated, or reduced in volume, in 10 dB steps until the signal is inaudible. When the patient does not respond, the signal is increased in steps of 5 dB until the signal becomes audible and the patient responds. This can be described as a 'bracketing technique' and it is also called the '10 dB down, 5 dB-up technique'.

The bracketing technique used to determine the hearing threshold is schematized in **Figure 51.9**. This technique is used until two corresponding ascending thresholds have been derived, with the listener responding for the full duration of the signal. The duration of the signal is varied between 1 and 3 seconds. At very short durations, there is a trade-off between time and intensity, with the hearing threshold being higher for shorter sounds. This occurs for sounds shorter than about 200 msec. It is therefore convention that signal durations shorter than 500 msec are not used during the measurement of the audiogram. Duration is usually varied between 1 and 3 seconds.[23] The onset and offset of the pure-tone signal is the most salient feature for detection when listening close to threshold. For accurate assessment of hearing thresholds, the listener is required to respond by pressing the button, or perhaps raising a finger, for the full duration of the perceived signal rather than just at the onset. Effective audiometry requires unpredictable silent gaps (lasting 1–5 seconds) between signal presentations, as rhythmic presentation leads the patient to respond at regular times, even if they did not hear the signal. It is generally accepted that the threshold of hearing is defined as the stimulus level giving rise to 50% or more correct detection responses, or a minimum of two out of two, three or four ascending presentations.[23]

Testing is carried out by AC first and then, if necessary, by BC. Test frequencies for BC are those in the range 500–4000 Hz, with no retest at 1000 Hz required. The mechanism for transmission of sound through BC conduction is more complex than for AC. However, comparison of results for AC and BC generally provides evidence for

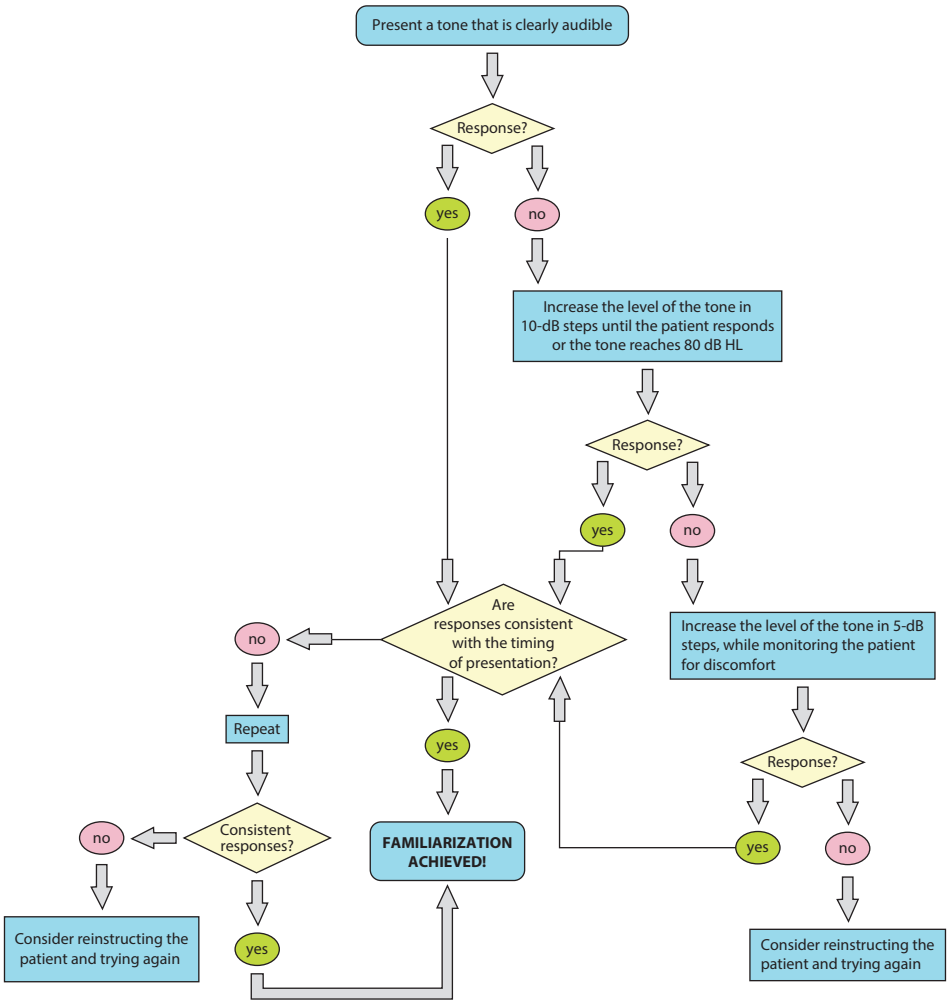

Figure 51.8 Procedure to achieve the familiarization of the patient with the task.

conductive and sensorineural components of hearing loss, although BC thresholds can be increased in the absence of sensorineural loss

The AC pure-tone audiogram is the basic test used to express the degree of hearing loss. BC thresholds provide important information for differentiating between conductive and sensorineural disorders. An equal extent of hearing loss for AC and BC generally indicates a sensorineural lesion whereas a larger loss by AC than BC, referred to as an air–bone gap (ABG), often indicates a conductive lesion. The ABG at a single frequency needs to be at least 15 dB in order to be considered clinically significant, particularly at 4000 Hz where there is a recognized artefact in the BC threshold norms.[33] As mentioned above, it should be noted that BC thresholds can occasionally be increased due to pathology affecting the middle ear and not the cochlea. An example is the hearing loss due to otitis media with effusion. Although in most cases BC thresholds are normal, these can be slightly elevated, especially at lower frequencies. According to Huizing[35] this can occur because: a) The round window is being pressed by a fluid; b) the stiffness of the middle ear is increased by the negative air pressure; c) the resistance of the mass of the middle ear may be increased by the presence of fluid and

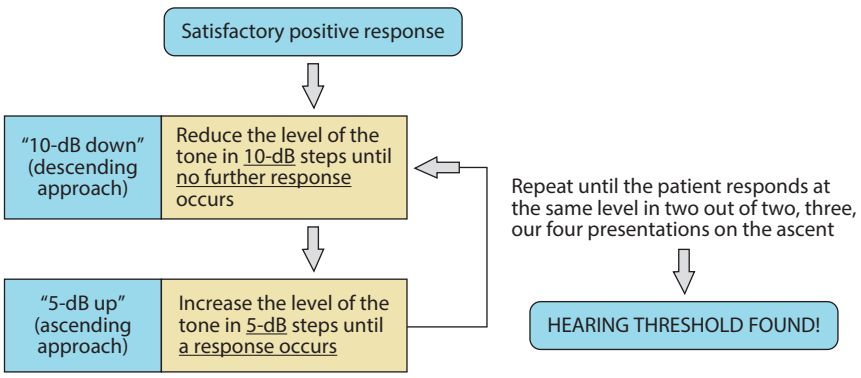

Figure 51.9 Method to measure threshold.

the swelling of the mucosa (which can improve or worsen BC thresholds depending on its point of action on the ossicular chain). Another example is the 'Carhart notch' (originally thought to be present more often at 2000 Hz),[36] described as an increased BC threshold that improves after surgical treatment in cases of otosclerosis.[37]

MASKING

In order to accurately measure hearing in each ear, signals are presented directly to the right and left ears. In the case of poorer hearing in one ear, when a signal is delivered to that ear at a sufficiently high level, it may be perceived in the contralateral ear. This is known as **transcranial transmission** or **cross-hearing**, and it is related to the concept of interaural attenuation introduced in 'Air-conduction transducers' above. If the hearing threshold of the non-test ear is equal to or lower than the level of the stimulus minus the interaural attenuation, then the stimulus may be detected by the non-test ear. Using conservative estimates of interaural attenuation, it is recommended to present a continuous masking noise (or masker) to the non-test ear to prevent cross-hearing of the test tone whenever there is an interaural difference of 40 dB or more when using supra- or circum-aural headphones, or 55 dB or more when using insert earphones.[23] As BC signals are transmitted to both cochleae, regardless of the side on which the transducer is placed, it is necessary to deliver masking noise to the non-test ear to prevent the test signal being detected in that ear. Calibration for the narrow-band noise signals used for clinical masking are specified in the standard ISO 389-4:1994.[39] Masking noises used in clinical masking are calibrated in dB 'effective masking level' (dB EML). Presenting the masking noise at a given EML will raise the threshold for a pure tone of the same frequency as the geometric centre frequency of the noise to that level.[23] For example, if the threshold for a pure tone of a given frequency were taken when presenting (to the same ear) a noise centred at the same frequency and whose level was 50 dB EML, the masked threshold would shift from 0 to 50 dB HL.[23, 28]

A procedure for plateau-seeking for clinical masking is specified in ISO 8253-1:2010.[21] The masking noise is presented continuously to the non-test ear and is introduced first at a level where it is just audible. It is increased in steps of 10 dB and the threshold for the pure tone signal is re-evaluated. When the masking noise level can be increased by three 10 dB steps without changing the detection level of the test tone, this constitutes the masking plateau (See **Figure 51.10**). This is interpreted as the true hearing threshold of the poorer test ear. This method is known as the 'plateau-seeking' method.

There are constraints in the use of clinical masking: sometimes the masking plateau cannot be reached because the level of the masking noise is so high that it reaches the test ear by cross-hearing and it shifts the measured hearing thresholds. This is called 'cross masking', and is likely to occur when testing listeners with a large bilateral conductive hearing loss. Use of an insert earphone reduces the likelihood of cross masking in addition to the necessity for clinical masking. Additionally, special masking techniques may be required in these cases.

Although the plateau-seeking method is the standard procedure for clinical masking, clinicians sometimes use abbreviated procedures in which an initial masking noise level is used, and subsequent increments of this level, if necessary, are adaptively varied depending on the threshold shift in the presence of the masking noise (e.g. see Yacullo).[28] Such procedures have the advantage of using lower masking noise levels in most cases, and the disadvantage of not producing a masking noise level–threshold function. Masking noise level–threshold functions (usually called 'masking functions') can be useful to detect cases of central masking (a usually 5 dB threshold shift that occurs when the tone is presented together with a contralateral masking noise and may be related to central processes)[28] or cases of cross-masking. The clinician should use their judgement to determine which type of procedure is most suitable in each case.

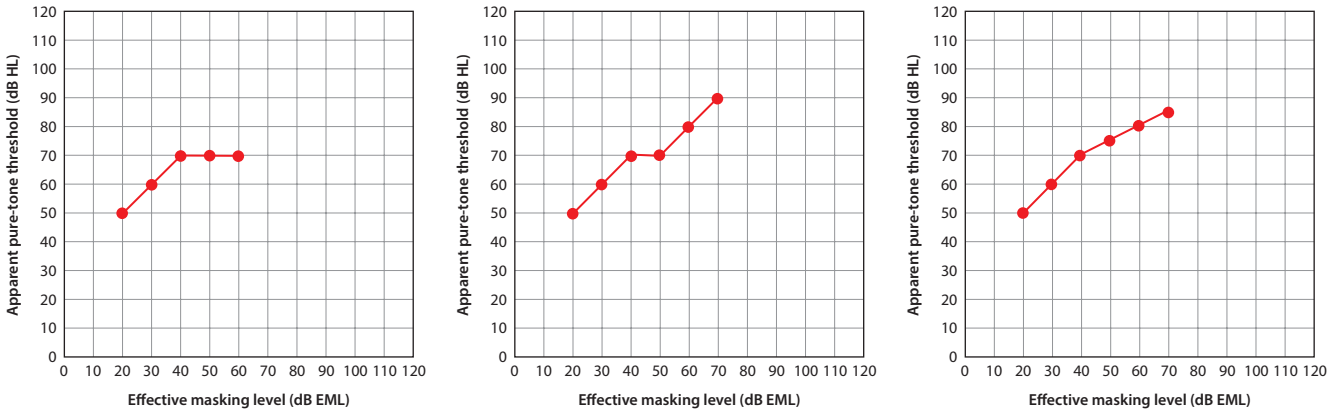

Figure 51.10 Examples of masking functions. The left panel shows a typical shape of the curve when a plateau is reached and the masked threshold is found. In this example, the threshold is 70 dB HL, as this is the level where the plateau is found. The central panel shows an example of cross-masking. Here the plateau is short, consisting only of two points. This is followed by a second 1 dB per dB slope. The right panel shows an example of central masking, where the slope of the function is less than 1 dB per dB. In this example a 5-dB increase of the hearing threshold follows a 10-dB increase in the masking noise, so the slope is 0.5 dB per dB.

TABLE 51.1 Rules or indicators for the use of clinical masking

'Rule'	Situation	What to do
1	The not-masked AC thresholds differ by 40 dB or more when using supra- or circum-aural headphones, or by 55 dB when using insert earphones.	Retest the AC threshold of the worse ear masking the contralateral ear.
2	The not-masked BC threshold of one ear is better than the AC threshold of either ear by 10 dB or more.	Retest the BC threshold of the ear with the worse AC threshold masking the contralateral ear. Use clinical judgement. Is it critical to diagnosis to apply this rule (e.g. when there are only small BC thresholds)? If the masked BC threshold has changed little (i.e. up to 10 dB), it may be necessary to retest the BC threshold of the ear with better AC thresholds masking the contralateral ear.
3	Rule 1 was not applicable, but the BC threshold of one ear (ear A) is 40 dB (for supra- or circum-aural headphones) or 55 dB (for insertion earphones) better than the not-masked AC threshold for the other ear (ear B).	Retest the AC threshold of ear B masking ear A.

Although interaural attenuation varies across individuals, there are some rules or 'indicators' for the use of clinical masking during audiometric testing. These rules are based on typical values of interaural attenuation. Table 51.1 summarizes the rules for the use of clinical masking as recommended by the British Society of Audiology,[23] for AC and BC testing. In clinical practice, there are often cases where it is difficult to obtain accurate masked thresholds.

It is fundamentally important for ENT doctors to have reliably masked audiometric information for discussion and decision-making of surgical options.

DURATION OF TESTING

The total time for testing should be managed with care to avoid fatigue and its subsequent impact on test results. It is recommended that the subject should have a short break if the test exceeds 20 minutes.[23]

INTERPRETING RESULTS

Test–retest difference

The test–retest difference in hearing levels measured on two different occasions is accepted as +/–5 dB without necessarily indicating a real change in hearing levels. If assessing average change in threshold across two or three frequencies, a difference of 10 dB is more likely to be significant.[38] The test–retest accuracy for absolute thresholds derived with BC transducers is poorer than that for AC transducers.[38]

Variability in responses

Variability in hearing thresholds can be influenced by multiple factors including:

- **subject variables**, including physiological noise or tinnitus, attention state, fatigue and motivation, and precise wording of instructions to the subject
- **method of assessment**, including the duration and variation in the intervals between signal presentations, subject positioning in test booth, ambient noise levels in the test environment, method of response (e.g. pressing a button or lifting a hand)
- **type and placement of signal transducer**, including removal of earrings and glasses when needed; relatively small changes in placement over the earphone in relation to the ear canal can affect the sound pressure at the eardrum
- **calibration of test equipment**, monitoring and maintenance of all parts including transducers, plugs and connectors.

Screening audiometry

There are procedures for screening audiometry, for example the one described in ISO 8253-1:2010.[21] The outcomes are either a 'pass' or a 'fail' rather than defined audiometric thresholds. Industrial or occupational hearing screening is often provided using automated audiometry and is not within the remit of this chapter.

The pure-tone audiogram

The results of PTA are plotted on the pure-tone audiogram, which is a graphic representation used to characterize hearing detection thresholds in each ear for clinical assessment.

The pure-tone audiogram is a graph where the *x*-axis shows the frequency of sounds in Hertz and the *y*-axis shows the sound level expressed in decibels hearing level (dBHL), where 0 dBHL represents the average threshold for otologically normal young individuals at each frequency. Thresholds in the minimal audibility curve (see Figure 51.1) are expressed in dBSPL (decibel sound pressure level). As mentioned above, the minimum sound pressure level required for the hearing threshold of a sound varies with frequency. Therefore, if the mean normal-hearing thresholds were plotted in dBSPL, a curve would be obtained. In contrast, in a pure-tone audiogram, the average normal-hearing thresholds across frequency lie on a straight line, as they are expressed in dBHL. Another difference between the graph in Figure 51.1 and

a pure-tone audiogram is that the levels in the *y*-axis are ascending from bottom to top in the former, but they are descending from bottom to top in the latter. Levels are shown in the pure-tone audiogram from –10 to 120 dB HL. Negative numbers mean that the measured thresholds are better than the average.

The *x*-axis, which is logarithmic, represents frequency in the range 125–8000 Hz, thereby covering the frequencies important for understanding speech and the frequencies of many environmental sounds. For example, 250 Hz is close in frequency to middle C on the piano keyboard.

Assessment is performed at each frequency across octave spaces, typically at 250, 500, 1000, 2000, 4000 and 8000 Hz. Inter-octave frequencies (e.g. 750, 1500, 3000 and 6000 Hz) may be included in steeply sloping hearing loss configurations or when the desired frequency resolution is greater (e.g. for the fitting of hearing aids). It is recommended to use forms with an aspect ratio of 20 dB : 1 octave to facilitate the visual reading of the audiometric curve. It is important to register the date of the test, the name of the examiner, the audiometer and transducers used and the date of the last calibration.

Figure 51.11 shows an audiogram chart. Note that the test results for each ear and transducer have different symbols. Outcomes for the right ear are usually plotted in red, and those for the left ear are usually plotted in blue. AC symbols are open circles for the right ear and crosses for the left ear. The thresholds are joined by continuous straight lines. In the UK, BC thresholds are either an open triangle for unmasked thresholds or a square bracket for masked thresholds (see below). BC thresholds are usually joined by broken straight lines. Conventions may vary slightly between countries. It is important to use conventional symbols in order to facilitate the interpretation of test results across institutions.

Figure 51.12 shows a simplified representation of the levels and frequencies of the sounds of speech and of environmental sources on the audiogram. Graphs of this type are used for counselling purposes, and the area where the speech sounds are represented is colloquially known as 'the speech banana'. Although the perception of these sounds should not be thought of as an 'all-or-nothing' event, merely reliant on the audibility at a given frequency/level, it is useful to see where conversational and environmental sounds fall on the audiogram plot. It should be noted that the audiogram is mainly focused on the range of frequencies that are important to understand speech.

Interpreting the pure-tone audiogram

QUANTIFYING THE EFFECT OF HEARING LOSS

Traditionally, hearing loss is characterized by its degree: mild, moderate, severe and profound. These degrees are defined as ranges where the average hearing threshold falls. An example of these categories is the classifications of the British Society of Audiology (2011),[23] which is based on the average of the hearing thresholds for 250, 500, 1000, 2000 and 4000 Hz, and describes four categories:

- Mild: 21–40 dB
- Moderate: 41–70 dB
- Severe: 71–95 dB
- Profound: 96 dB and above.

Classifications based on the average hearing loss originated from the need to have an easy way of describing cases among professionals or from professional to patient.[40] However, they do not describe the implications of hearing loss accurately for several reasons. First, hearing loss often affects hearing thresholds unevenly across frequencies. Examples are shown in Figure 51.13. The hearing losses shown for 'Example 1' and 'Example 2' have the same pure-tone average (60 dB HL) but the audiogram configuration (i.e. the shape of the audiogram, given by the difference in hearing thresholds across frequency) differs considerably across the two. The functional consequences of each hearing loss will vary significantly. These examples, most common in clinical practice, illustrate how inadequate the classification of hearing loss by degree based on hearing thresholds is.

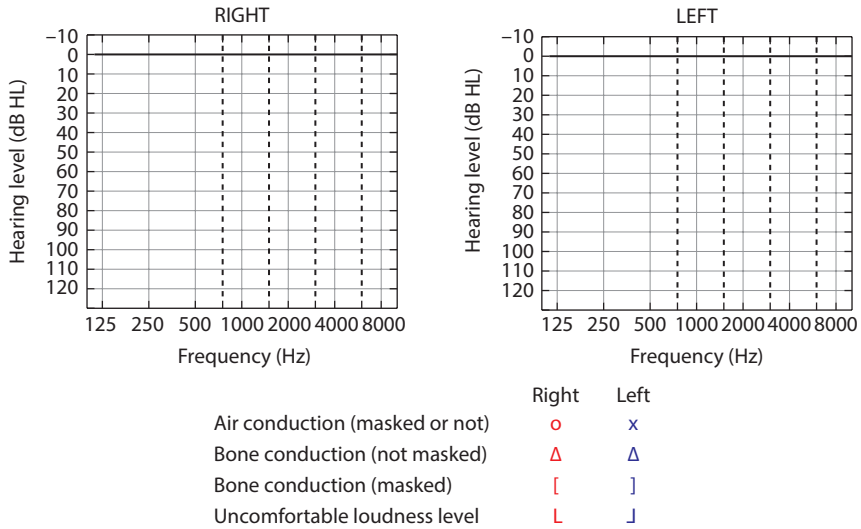

Figure 51.11 Audiogram chart and symbols used in clinical audiometry.

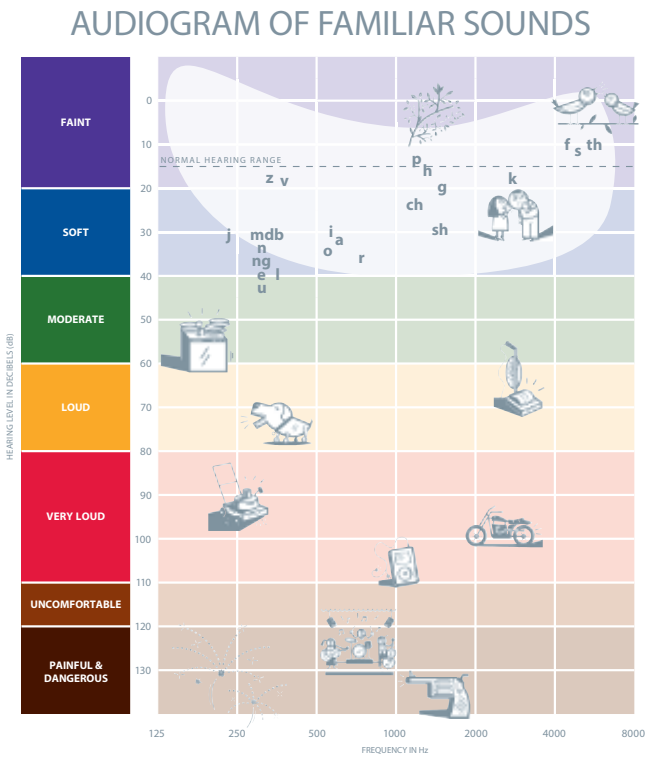

Figure 51.12 Audiogram of familiar sounds by the American Academy of Audiology. Reproduced with the permission of the American Academy of Audiology in the format "Republish in a book" via Copyright Clearance Centre.

It is also worth mentioning that even individuals with the same degree and configuration of hearing loss may have very different outcomes in real-life communication. The impact of hearing loss cannot be appreciated based purely on the audiogram, as characterization of the degree of hearing loss based purely on the hearing threshold does not account for suprathreshold deficits, such as in the mechanisms for frequency selectivity, temporal resolution and integration, etc. Thus, the degree of hearing loss defined by the hearing threshold does not adequately reflect the impact of hearing loss on auditory perception, communication and quality of life. In addition, other factors that can have an influence on the functional implications of hearing loss, such as the existence of other sensory deficits, use of hearing aids, lip-reading abilities, cognitive abilities and family support, among others, are not considered.

FUNCTIONAL IMPACT OF HEARING LOSS ON SPEECH COMMUNICATION

In terms of the functional effect of hearing loss categories, it can be seen that what is categorized as mild hearing loss may reduce half of the audible information in conversational-level speech, or even more for quiet speech or when at a distance. Thus, 'mild' is a misnomer in this context: the communicational impact of mild hearing loss is not mild but significant. For example, a person of school or university age will have trouble following teachers or lecturers, and persons of working age may struggle at company meetings. A moderate loss may make distant speech inaudible and degrade the quieter parts of conversational speech even at close range. A severe hearing loss makes speech inaudible even at close range, though the person may be able to hear some of her own vocalizations. A profound hearing loss prevents a listener from hearing his/her own speech or that of others at all without hearing-aid or cochlear implant use.

TYPES OF HEARING LOSS

As already mentioned, hearing loss can be broadly divided into four types: conductive, sensorineural, mixed or auditory neuropathy (see Figure 51.14).

Conductive and mixed hearing loss

A hearing loss is classified as 'conductive' when there is a difference of more than 10 dB between AC and BC thresholds at any frequency, which, as mentioned in 'Measuring the hearing thresholds' above, is considered a significant ABG. BC thresholds are generally at normal-hearing levels (equal or better than 20 dB HL) in cases of conductive hearing loss. If the BC thresholds are raised above 20 dB HL and there is a significant ABG, this is referred to as a 'mixed' hearing loss. Conductive hearing loss occurs due to the disruption of the transmission mechanisms of

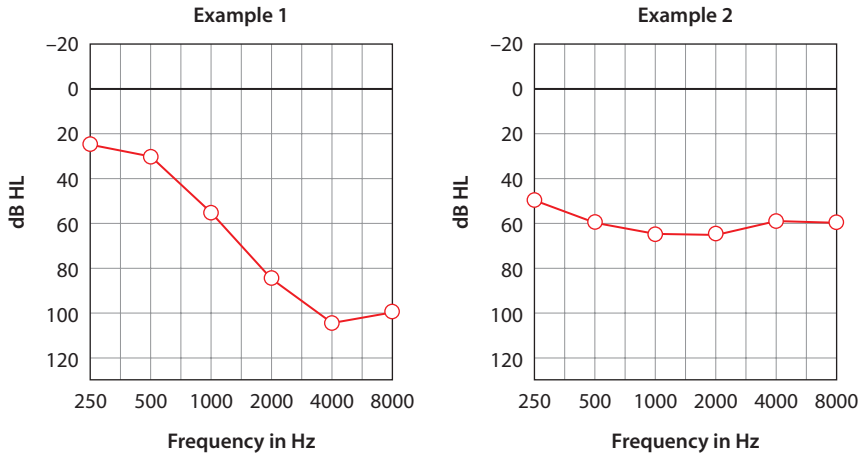

Figure 51.13 The hearing losses shown in the two right-ear examples have the same pure-tone average up to 4000 Hz (60 dB HL). However, the audiogram configuration (i.e. the shape of the audiogram, given by the hearing loss across frequency) is very different for the two ears. The functional consequences of each hearing loss will vary considerably.

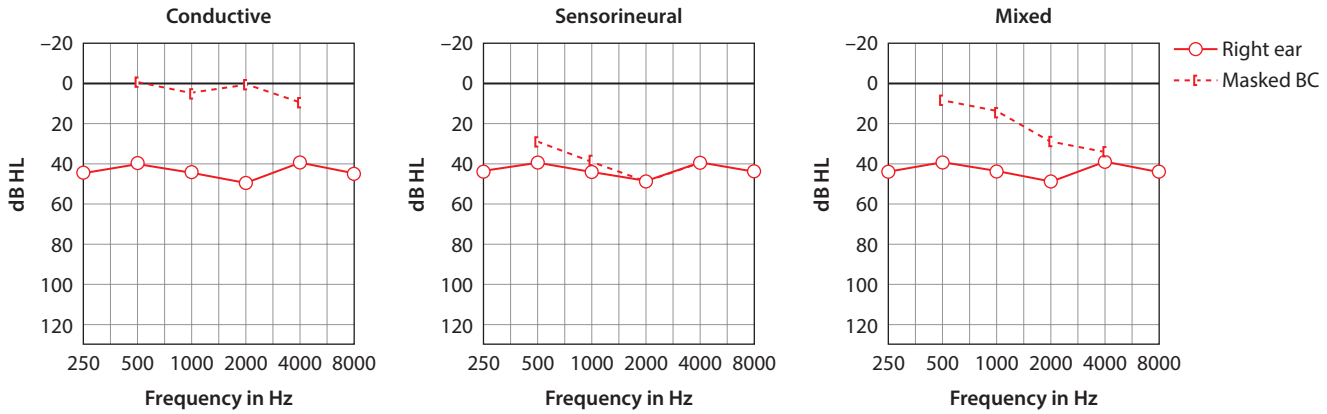

Figure 51.14 Types of hearing loss. **(a)** A conductive hearing loss, where the BC thresholds are normal, the AC thresholds are increased and there is significant ABG. **(b)** A sensorineural loss, where both BC and AC thresholds are increased and there is no significant ABG. **(c)** A mixed hearing loss, where the AC thresholds are increased, at least some of the BC thresholds are increased too and there is significant ABG.

the external and/or middle ear. For example, abnormalities of the tympanic membrane or the ossicles, or presence of fluid in the middle ear, lead to conductive hearing loss. Conductive hearing loss causes reduction in hearing sensitivity that may vary across frequency, but most aspects of sound perception remain generally unaffected as long as the signal is fully audible. This means that conductive hearing loss can be well compensated for by hearing-aid amplification. The maximum possible extent of conductive hearing loss is traditionally deemed to be 60 dB HL. However, all sounds are attenuated (reduced) equally by the extent of the hearing loss, regardless of their input level, so overall auditory deprivation from conductive hearing loss may be greater than for an equivalent level of sensorineural hearing loss with loudness recruitment.

The fluctuating nature of conductive hearing loss means that children with this type of hearing loss may have inconsistent perception of sound patterns and consequently reduced opportunities for recognizing familiar patterns of sound.[41] With the relatively high incidence of middle ear pathology in children, conductive hearing loss is very common and can also overlie cochlear-based sensorineural hearing loss, giving rise to a 'mixed loss'. Medical and surgical treatments are available for many cases of conductive hearing loss, sometimes with the possibility of hearing restoration. When there is a permanent conductive or mixed hearing loss, hearing aids stimulating via AC or BC and BC hearing implants are treatment options.

Sensorineural hearing loss and auditory neuropathy

Sensorineural hearing loss (SNHL) refers to impairment in the cochlea and/or the immediate (primary) nerve connections. The extent of SNHL can range from minimal to total and is usually permanent. The inclusion of 'neural' in 'sensorineural' only refers to the nerve connections from the inner hair cells to the auditory nerve (CN VIII). This is therefore different from auditory neuropathy spectrum disorder (ANSD) in which neural firing may be diminished or out of synchrony across nerve fibres, causing fluctuations and distortion in speech information.

SNHL is shown on the audiogram by both AC and BC thresholds being within 10 dB of each other. Recall that there is an artefact in the standards for BC thresholds at 4000 Hz which means that a discrepancy of 15 dB between AC and BC thresholds is often seen but does not indicate a conductive hearing loss.[33] Be aware that in moderate-to-profound hearing loss some low-frequency BC signals may be felt as vibration, giving the impression of an apparent mixed hearing loss at the low frequencies. The thresholds at which individuals can feel the bone conductor vibration can be as low as 25 dB at 250 Hz, 55 dB at 500 Hz and 70 dB at 1000 Hz.[23]

Options for medical or surgical interventions are very limited in cochlear-based mild or moderate impairment. Most cases of SNHL are treated with hearing aids or hearing implants.

Example audiograms for the different types of hearing loss are illustrated in **Figure 51.14**.

WHAT THE AUDIOGRAM DOES NOT SHOW

Sources of distortion in cochlear hearing loss

Although the measurement of hearing thresholds is the most commonly used method of characterizing hearing status in clinical settings, there are many changes in sound perception that can occur and are not apparent on the audiogram.

These other features of impaired auditory perception may combine to cause reduced clarity of hearing for complex sounds, particularly in understanding speech in noisy listening environments. The interested reader is referred to Moore[42] for a comprehensive analysis of the perceptual effects of cochlear hearing loss. Below is a brief description of the perceptual deficits most commonly associated with cochlear hearing loss.

Loudness recruitment: As stated above, this refers to the reduced dynamic range of hearing between the hearing threshold and the upper limit of loudness tolerance for the listener. A feature of cochlear hearing loss is that loudness grows faster with increasing sound level than for normal hearing. Therefore the dynamic range over which a person

with hearing loss can hear becomes narrower compared to that of a person with normal hearing. In other words, if a person had a hearing threshold of 60 dB HL and a loudness discomfort level of 90 dB HL, their dynamic range of hearing would be 30 dB. This would be about one-third of the dynamic range of someone with normal hearing (when measured in dB) and creates difficulties in providing amplification to make more low-level sounds audible while preventing amplified sounds from being uncomfortably loud. The 'active mechanism' of the outer hair cells (OHCs) on the basilar membrane is believed to be involved in the normally wide dynamic range of hearing. By virtue of this mechanism, the response of the basilar membrane increases in a compressive manner with increasing input level for a wide range of sounds levels between moderate and perhaps very high levels. This means that, for example, a 10 dB increase in sound level leads to only a 2.5 dB increase in the response of the basilar membrane.[43] Damage to the active mechanism in hearing loss cases leads to a reduction or loss of cochlear compression and thus to a narrower dynamic range. Loudness recruitment is addressed by the use of amplitude compression in current hearing-aid design.[42]

Loss of frequency selectivity: Frequency selectivity is the ability of the hearing system to separate out the individual frequency components of a complex sound.[15] Damage to the OHCs in the cochlea leads to a reduction in the sharpness of the basilar membrane response to a narrow-band sound. When the active mechanism of the OHCs becomes damaged, perhaps through noise exposure and/or ageing, the ability to separate the frequency components of complex sounds is degraded. The loss of frequency selectivity makes hearing-impaired people more susceptible to masking.[42] This leads to problems in understanding speech, particularly in a background noise, even when the noise does not have the same spectrum as the speech.[43] The perception of timbre, which allows the listener to distinguish between sounds of the same loudness and pitch (e.g. the same note played by two different musical instruments), is also affected when frequency selectivity is impaired. A reduced ability to perceive differences in timbre can lead to poorer vowel discrimination.[42]

Loss of ability to use temporal fine structure (TFS) information: A complex sound reaching the ear is separated in the cochlea into a series of narrow-band signals. These signals can be characterized by their envelope (the slow changes in the amplitude of sound over time) and their TFS (the rapid changes in the amplitude of sounds, with rate close to the centre frequency of the band). Deficits in TFS perception may result from loss of auditory neurons or loss of synapses between inner hair cells (IHCs) and neurons. These aspects are represented in the timing of neural spikes. TFS information is relevant for pitch perception. Deficits in pitch perception can lead to problems in the identification of the prosodic aspects of speech (i.e. to distinguish a question from a statement), the identification of a speaker, and the discrimination of speech sounds.[42] In addition, impaired TFS perception may reduce the ability for listening in the dips of a fluctuating masker, for example, when listening to a talker in the presence of a competing background talker, and to 'hear out' a target speaker in the presence of a competing talker based on differences in fundamental frequency (the fundamental tone produced by the vibration of the vocal folds).[42, 44] Deficits in the processing of TFS information may also lead to reduced sound localization abilities.[44]

Loss of temporal resolution: Temporal resolution refers to the ability to detect changes in auditory stimuli over time, particularly in their envelope.[15] Temporal resolution may be compromised in cochlear hearing loss due to the partial or complete loss of the compressive mechanism of the basilar membrane. When cochlear compression is reduced or lost, sounds that have fluctuations in their envelope may seem to have even greater fluctuations. This may make it difficult to detect gaps in those sounds.[42] This is relevant to speech perception as one feature of consonants such as /p/, /b/ and /t/ is the presence or absence of a gap between the burst of the consonant and the start of voicing of the following vowel, and this feature is one of the cues for the discrimination of these consonants. Another consequence of a loss of temporal resolution is an increased threshold for detecting a sound preceded by another more intense sound. In speech perception, this can make low-level consonants preceded by more intense vowels more difficult to hear.[42]

Cochlear dead regions: A dead region in the cochlea is a place on the basilar membrane where the IHCs or synapses are not functional or function very poorly.[45] When a signal excites only a region with such IHC damage, such signal would theoretically be inaudible. However, if the sound level is increased, the area of excitation along the basilar membrane spreads to a non-dead region, and the signal may become audible. If a person has a dead region at 4000 Hz, they may hear sounds with a frequency of 4000 Hz using IHCs placed at a neighbouring point along the basilar membrane, tuned to a different frequency. This is known as 'off-frequency listening'.[45] The pure-tone audiogram might show a detection threshold for 4000 Hz, but this would not reflect encoding of the signal by the correct part of the cochlear hearing mechanism. The recognition of speech cues falling well within extensive dead regions is limited.[46–48]

In summary, SNHL is associated with changes in the individual experience of loudness perception, frequency selectivity, pitch perception and speech recognition, especially when listening in noise. It is therefore important to recognize that people with similar pure-tone audiograms may have very different experiences of hearing in everyday life and they may receive very different help from hearing-aid amplification.

Human speech is a great deal more complex than the simple pure-tone signals that are used to define the lowest level of detection across frequencies on the audiogram. The distortions that occur with SNHL are not assessed by the pure-tone audiogram, and are often not acknowledged by professionals working in hearing loss.

Improved hearing for speech is, however, the primary motivation of the patient looking for ENT intervention for hearing impairment.

SPEECH AUDIOMETRY

In the past speech audiometry was an important component of the diagnostic test battery for distinguishing peripheral from central causes of hearing loss, particularly acoustic neuroma. This role has been superseded by imaging techniques.

Speech audiometry is now mainly used for assessing rehabilitation outcomes from both hearing aids and cochlear implants. There are also specialist test applications developed for auditory processing disorders which may have central auditory components.

Speech intelligibility

SPEECH INTELLIGIBILITY INDEX

The speech spectrum for conversational speech can be represented on the audiogram as a shaded area covering the frequencies range 125–8000 Hz and the level range from 20 to 60 dB, as previously shown in **Figure 51.12.** Some of the acoustic information to detect consonants has levels lower than 20 dB, requiring hearing levels below 20 dB in order to hear all the speech sounds. A way of predicting the impact of hearing loss on speech intelligibility is to consider the proportion of speech information that is audible to the patient given their hearing deficit on the audiogram. The Speech Intelligibility Index (SII)[49] is calculated as the product of a band–importance function (the contribution of a frequency band to the intelligibility of speech) and a band–audibility function summed across all the frequency bands. Additionally, the SII takes into account the known sources of distortion in cochlear hearing loss and the impact of these on speech understanding for the listener. However, predictions of the SII for listeners with hearing loss are not always accurate, particularly when hearing loss is greater than 55 dB.[50] It is important to understand that no method of amplification can offset the sources of cochlear distortion or provide 'normal hearing'; it can only improve the audibility of sounds. Additionally, there is usually a period of relearning the new sound patterns of speech through amplification, derived from a consistent period of hearing-aid use over several weeks or longer.[51]

HEARING LOSS AND SPEECH INTELLIGIBILITY

Normal-hearing listeners use multiple cues to understand speech. For sustained vowels, the main cues are the formant patterns (the frequencies of the resonances of the vocal tract, added to the fundamental tone produced by the larynx).[52] For vowels in conversational speech, duration and temporal pattern of the direction of the change of the formant frequencies into and out of the syllable nucleus are more relevant.[52] For consonants, there are several possible cues that can be used for identification. These vary across consonant groups. Because of the redundant nature of speech, there is usually more than one cue available at a given time. In general, features such as the gross spectral shape of a sound and the relationship with the spectral shape of the next sound, the rate of spectral or amplitude change, the presence or absence of periodicity, the presence or absence of a silent gap, the delay in the start of voicing after this silent gap, the formant transitions and envelope cues (given by the relative slow changes in amplitude over time) have all been shown to provide important information.[15] Detecting these features requires the auditory system to perform temporal and spectral analyses of the speech signal. These analyses are disrupted by the perceptual deficits associated with SNHL, and this has an impact on the ability to understand speech in quiet and in noise. The interested reader is referred to Revoile[53] for a review of the use of cues for speech intelligibility by persons with hearing loss. It is extremely common in the clinic to find patients with SNHL who have trouble understanding speech, particularly in situations where the talker they want to hear is not the only speaker, and there are other talkers in the background. This is known as the 'cocktail party problem',[54] and it is an issue to some extent even with the use of hearing aids or hearing implants.

Speech testing in clinical audiometry

Hearing loss impacts greatly on speech understanding in everyday situations in ways that cannot be represented simply by the ability to detect pure tones. This role is fulfilled by the use of speech testing both in identifying the cause of hearing loss and, more importantly, in the potential for improved ease of speech understanding through surgery or applied technology. Speech audiometry methods are specified in the standard ISO 8253-3:2012.[55] They are an important component of hearing assessment which cannot be represented by simpler psychoacoustic testing or assessing the hearing-aid output levels to estimate the audibility of amplified speech. In addition, an important diagnostic and often underutilized role of speech testing is in identifying non-organic or feigned hearing loss, either in isolation or as an overlay to a true physiological hearing deficit.

Historically, speech testing used single words presented at different levels in a defined procedure called 'speech audiometry' to derive an individual's performance-intensity (PI) function. Different features of the PI function were used to infer diagnostic indications. Features such as the optimal discrimination score (ODS) and the corresponding half peak measure were used to characterize and differentiate potential central causes from peripheral hearing loss.[12, 56]

There are a number of terms still used when testing with speech material from these earlier roles. **Speech discrimination** implies an ability to hear a difference between a set of alternative response options. **Speech intelligibility** and **speech recognition** are used interchangeably now,

rather than in the defined circumstances of their original use (as a measure of fidelity of a transmission system, and as defined by the PI function in speech audiometry, respectively).

HEADPHONE OR SOUND-FIELD TESTING

As part of the diagnostic process of hearing assessment, speech material may be presented to each ear through the use of headphones or insert earphones. When the test material is used to assess benefit for speech understanding from use of hearing devices, speech is presented in the sound field, thereby being processed by the hearing aid or hearing implant before being delivered to the patient's ears. As with any ear-specific testing, clinical masking may need to be delivered to the non-test ear to prevent cross-hearing in the non-test ear. When measuring the threshold for speech, contralateral masking is used when the speech presentation level in dB HL exceeds BC thresholds in the better-hearing ear by 40 dB or more at two frequencies. The noise masker used for speech audiometry is a 'speech-shaped noise'. This means that it is the result of having filtered white noise to match the long-term average speech spectrum.

CALIBRATION OF SPEECH TEST MATERIAL

Recorded speech materials should be used for testing, as this increases control of the testing conditions and quality of the stimuli. The recorded speech materials include calibration signals. When testing in the sound field (presenting the stimuli via a loudspeaker), the calibration signal is usually a narrow band of noise or a frequency-modulated tone at 1000 Hz, as defined in ISO 8253-3:2012.[55] The level of this calibration signal is equal to the level of the speech signal derived with a specified frequency- and time-weighting and is expressed as the equivalent sound pressure level, L_{eq} with A-weighting. The silent pauses between words or test items are discarded in the measurement of the equivalent sound pressure level. When speech testing is in the sound field, the calibration method is typically performed using a sound level meter and defined in dB A. Presentation levels need to be checked in the calibration position (corresponding to the position of the listener's head) – on a regular basis.

When speech testing is performed with headphones, the speech signals are usually calibrated by playing the calibration sound (usually a 1000-Hz pure tone) and adjusting the audiometer and so that the VU-meter displays the desired value, usually 0. In computer-based audiometers instructions for calibration vary depending on the options of each device. The presentation level of speech through headphones is typically expressed in dB HL.

EQUIPMENT FOR SPEECH TESTING

The level of presentation of speech is typically controlled through a two-channelled clinical audiometer or computer-based audiometer software. In sound-field audiometry the loudspeaker is typically placed at a distance of 1 m from the listener and at the same height as the head. Competing noise may be presented either from the same loudspeaker or from a pair of loudspeakers located on either side, at a recommended azimuth (i.e. angle relative to the head of the listener) of +/– 45 degrees, 90 degrees or 180 degrees depending on the functional testing required. Multi-speaker configurations can also be used.

SPEECH MATERIAL

The simplest and most commonly used speech material in clinical audiology is lists of monosyllable, real words made up of three speech sounds, or 'phonemes', usually a consonant, a vowel and a consonant, for example 'hat'. Most languages have enough monosyllabic, familiar vocabulary items to develop lists of words in which each list has a similar number of types of phonemes in approximately the same proportion as these speech sounds occur within the given language. Some languages have a small number of monosyllabic words available and use two- or three-syllable words (e.g. Spanish, Finnish, and Arabic).

PRESENTATION METHOD

The typical way that speech tests are delivered is through prerecorded material played from a computer or CD and passed through the audiometer so that the level of presentation can be controlled. As with PTA, the method of presentation, calibration and the acoustic characteristics of the test room need to be specified and consistent for valid and comparable results.

The acoustic characteristics of a test room fulfilling a quasi-free sound field considered adequate for clinical speech testing is specified in ISO 8253-3:2012[55] but the requirements of ambient noise levels are less restrictive than for PTA since the speech signal is presented at suprathreshold levels.

OPEN-SET AND CLOSED-SET TESTING

Responses are typically made by the patient repeating the word they identified. This is referred to as 'open-set testing' as there is no constraint on the options that the patient has in the response that they make. The tester records their response or the number of speech sounds they correctly identified from the target word. For example, response 'cat' for test item 'hat' gives a score of two out of three, although there are many variations on scoring methods for different languages. For open-set speech material to be valid the test material must be novel to the listener. Repeated use of the same material, whether made up of single words or sentence material, in open-set testing makes results invalid due to learning effects. There are therefore practical constraints from the number of speech tests available for patients requiring ongoing speech recognition assessment, such as those with hearing aids, cochlear or brainstem implants.

An alternative method of presenting closed-set speech material gives the listener a selection of items from which to choose a response. This may be from a list of options on a computer screen, a written list of words or a constrained

range of options, for example by repeating spoken numbers between 1 and 100. The benefit of closed-set testing is that one can analyze the individual speech sound confusions that were made between the target word and the response and therefore derive confusion matrices, which can be crucial when adjusting hearing-aid features or fine-tuning cochlear-implant maps for instance. Scoring of responses in closed-set testing does not require clear articulation by the patient, and results can be scored by the computer in many cases.

There are many different types of material that can be used to assess speech detection, discrimination and recognition. In order to assess the functional benefit of a particular hearing aid for an individual, open-set sentences presented in quiet and in different types of noise may be required. For assessing the discrimination potential of a cochlear-implant recipient, one may use closed-set nonsense syllables (such as /aka/, /ubu/, and /isi/) to evaluate consonant discrimination while keeping the vowel context consistent. For assessing whether the frequency-lowering feature in a hearing aid is helpful (a feature intended to increase the access to high-frequency information for people with high-frequency hearing loss), one could use a single word final-s test in closed-set testing; for example, a plural detection test, where the pictures of a 'brick' and a selection of 'bricks' are presented as alternative response options, are used to indicate whether detection of the sound /s/ is improved with the frequency-lowering feature activated.[57, 58]

RESPONSE MEASURES

The speech reception threshold (SRT) is defined as the lowest speech presentation level at which the individual is able to correctly identify 50% of the items.[59] For a given individual, the outcome depends on the type of speech material that is used. In general, the more familiar and meaningful the information that is audible to the listener, the lower the minimum presentation level that is required for them to identify the test item. Thus, meaningful sentences will be correctly identified at lower presentation levels than single words. Familiar single words will be identified at lower levels than nonsense syllables. Cognitive resources are employed when performing intelligibility tasks,[60] especially when not all of the speech cues have been audible or there are competing speakers in the background. In other words, listeners use cognitive resources such as memory and attention to focus on the target speaker and fill in the gaps of missing information. In practice this tends to conspire against patients with high cognitive ability fulfilling criteria for cochlear implantation on the basis of their sentence recognition score, as they are very efficient in working out the spoken message in spite of their poor auditory abilities. However, the increased demand for cognitive resources often leads to fatigue and therefore has an impact on quality of life.

Different types of speech material are shown in Table 51.2. For each of the types of speech material used there is a different level of linguistic and acoustic redundancy and the opportunity for the cognitive and linguistic function of the listener to influence scores, independent of hearing status. Any single test material is a compromise between validity in terms of representing real-life listening experience (e.g. sentences in noise) and repeatability of results in defining audibility (e.g. by using nonsense words in quiet).

The difference in two scores that infers a significant change in the two test conditions is related to the number of test items in the list. The PI function can be quite steep. For example, for normal-hearing listeners, an increase in presentation level from 20 dB to 25 dB may lead to a 20% increase in the score for word recognition.[12] The more the steepness of the slope of the function increases, the more predictable speech material is. Thus, the level at which speech is presented and the consistency in calibrating this level in test sessions is critical in deriving useful comparative information across test sessions and conditions.

SPEECH-IN-NOISE TESTING

Measures of speech recognition in competing noise give a better representation of cochlear distortion and the potential benefit from hearing aids than speech in quiet, which aims to characterize performance in optimal listening environments. Speech-in-noise testing is generally carried out using sentences presented in a specific type of noise, by scoring the number of keywords correct. In adaptive scoring algorithms the signal-to-noise ratio (SNR) is varied (by changing the level of the speech or the noise) depending on how many of the keywords are correctly identified. Typically, tests are performed to find the SRT in noise. This is the SNR required to identify 50% of the test items correctly. An outcome of 5 dB SNR

TABLE 51.2 Different types of speech material commonly used in clinical practice

Speech material	Detection	Discrimination	Recognition	Speech in noise	Clinical uses
Phoneme	Ling six-sound test (/m/ /a/ /u/ /i/ /s/ /sh/)[61]	Repetition of Ling sound	Identification of item containing the Ling sound, e.g. snake for /s/		Setting sensitivity, e.g. hearing-aid gain, cochlear-implant map
Word	Plurals test[57]	AB words lists[62]	McCormick toy test[63]	Adaptive McCormick toy test[64]	Evaluation of frequency-lowering hearing aids, indication or assessment of assistive technology
Sentence		ASL[65] BKB[66]	GASP[67]	HINT[68]	Assessment of hearing aids, cochlear implants and remote mics

means that the speech needs to be presented at 5 dB above the level of the noise for the individual to identify 50% of words correctly. Similarly, an SRT equal to −5 dB SNR, means that the noise level was 5 dB above the speech level and still the words were recognizable 50% of the times. In a clinical setting, the speech-in-noise measure gives an indication of distortion in the hearing mechanism, regardless of hearing level on the audiogram. Aside from the auditory factors involved, the value of the SRT depends on the characteristics of the background noise[69] (e.g. steady noise, competing talker, multi-talker babble), reverberation,[56, 70] as well as linguistic[71] and cognitive factors.[60]

It can be seen from this short section on clinical testing with speech materials that this is an area of rapid development, largely driven by changes in hearing-aid technology and hearing implants and the new testing that is necessary for evaluating individual hearing potential.

OBJECTIVE TESTS OF AUDITORY FUNCTION

Decades ago special tests with pure tones, usually termed 'suprathreshold audiometry', were used to distinguish cochlear and retrocochlear hearing loss. The most popular tests were the Short Increment Sensitivity Index (SISI) test[72] and the tone decay test (TDT).[73] The SISI test is based on the detection of an intensity increment superimposed upon a pure tone. Traditionally, the outcomes of the SISI test have been considered indicative of cochlear pathology if the person was able to detect a critical number of 1 dB increments in a continuous pure tone presented at 20 dB above the threshold. The TDT is based on the phenomenon of adaptation. The TDT outcomes have been interpreted as suggestive of retrocochlear pathology if the person is unable to perceive a pure tone presented at 10 dB above the threshold over 60 seconds, requiring several 5 dB increments of the sound level to maintain perception over this interval. However, some persons with cochlear hearing loss present pathological adaptation and therefore score positive in the TDT probably due to dysfunction of the IHCs/neurons.[74] In addition, some individuals with retrocochlear pathology such as acoustic neuroma score positive in the SISI test and/or negative in the TDT.[75] The consistency of outcomes of the special tests varies within groups classified by audiogram shape (e.g. flat loss, high-frequency hearing loss, low-frequency hearing loss) and with tumour size (smaller tumours leading to greater inconsistencies).[75]

Nowadays, image studies and objective tests have replaced these special tests in the differential diagnosis of cochlear and retrocochlear hearing loss. The most popular objective audiology tests used for topographic diagnosis are briefly introduced below.

Measuring middle ear function

A test-battery approach is used to assess middle ear function and hearing threshold levels. Tympanometry is used to assess middle ear function and the mobility of the eardrum. This test confirms the presence of middle ear effusion when tympanometry shows a flat compliance trace. Additional testing through the use of tympanometry includes measurement of the acoustic stapedial reflex, elicited by brief pure tones or noise bursts. The lowest intensity of sound that triggers the reflex is the acoustic reflex threshold (ART), and this can give an objective measure of loudness recruitment in addition to the subjective uncomfortable loudness level, which can be subjectively measured following the PTA.[76] An absent or abnormal stapedial reflex with normal middle ear pressure is characteristic in cases of otosclerosis.[77] The stapedial reflex threshold and decay have been used in the assessment of cases of acoustic neuroma.[75] However, it emerged in the last decades that its sensitivity is relatively low compared to PTA asymmetry and, most importantly, because of the high levels required in these cases, it poses a hazard on residual hearing.[78] The stapedial reflex can be electrically evoked in users of cochlear implants in order to obtain information about their dynamic ranges.[79] These tests are covered in Chapter 48, Physiology of hearing.

Otoacoustic emissions

Otoacoustic emissions (OAEs) are low-level sounds that are recordable in the external auditory meatus and reflect the active mechanism of the OHCs in the cochlea.[80] These are absent if there is damage to the OHCs. OAEs are an important part of the evolving test battery, particularly when screening for hearing loss in early life. It is advised that the measurement of OAEs is combined with tympanometry, especially in screening cases where the OAEs are absent. The reason for this is that middle ear problems can interfere with the recording of OAEs. Thus, clinicians may misinterpret the absence of OAEs as indicative of sensorineural loss if they are unaware of the existence of middle ear pathology.[81] These tests are covered in Chapter 48, Physiology of hearing.

Electrophysiological tests including ABR

Auditory brainstem response (ABR) testing measures the nervous system activity around the primary auditory pathway which can be affected by tumours of the eighth nerve and neural demyelination. The normal result is a waveform with multiple peaks (known as waves I, II, III, IV and V) that are generated by neurons at different levels of the auditory system from the distal portion of the eighth nerve to the midbrain. The ABR is a test of neural synchrony but is also used to estimate hearing sensitivity, particularly in predicting hearing thresholds in infants.[82, 83] Aside from the analysis of the morphology of the response, the observation of response parameters such as the wave I–V interpeak latency and the interaural latency difference of wave V and others are useful in the functional assessment of the auditory nerve.[84, 85] Electrophysiological tests can be electrically evoked in users of cochlear implants.[86] These tests are discussed in Chapter 48, Physiology of hearing.

FUTURE RESEARCH

- Methods that involve machine learning have been developed to automate audiometric testing and decrease its duration. This approach tends to minimize the number of trials used while achieving outcomes that are close to conventional PTA and some additional information, as testing is not limited to the standard frequency intervals. For example, in the implementation developed by Schlittenlacher et al.,[87] the frequency and level of each signal after the initial stimulus are selected based on the responses to all previous trials in order to maximally decrease the uncertainty of the outcome.
- Systems have been developed lately that perform audiometry with a computer and a special headset composed of insert earphones enclosed by circum-aural cups. These systems monitor background noise and do not require a soundproof booth.[88] This has potential for use in caring for persons unable to attend a clinic, or in surveillance audiology, where workers exposed to noise are screened for hearing loss.
- Internet-based systems have been developed to perform PTA remotely. This is known as 'teleaudiometry'.[89] Some of these systems allow for the storage of results in a 'cloud' format, making them available to the user from any device. They also have potential for the analysis of the large datasets collected.
- Smartphone and tablet apps have emerged recently to perform PTA with domestic headphones. However, the reliability of these systems is usually low.[90]
- Psychoacoustic tests have been developed that test for the dysfunction of the IHCs by detecting and characterizing 'dead regions' in the cochlea.[91, 92] Other tests assess the ability to use temporal fine structure information.[93, 94] Although these tests have been available for some time, most of them are not implemented in clinical equipment. They can be carried out easily with a computer and good-quality sound card and headphones, but it is expected that clinical use will increase once they are integrated in the test batteries included in audiometers.
- Speech audiometry is being complemented with objective measurements of listening effort such as pupillometry[95–97] or EEG[95, 98] in order to increase the sensitivity of the test battery when comparing different hearing devices or evaluating technology features (i.e. algorithms for noise reduction). It is expected that new clinical tools will be developed based on these findings.
- Speech recognition systems are being developed in order to replicate the speech recognition issues associated with ageing. Such systems could assist audiologists, reducing the time needed to optimize hearing-aid selection and fitting.[99]

KEY POINTS

- PTA is often the first functional test of hearing performed in the clinic. It provides basic information about the type and degree of hearing loss.
- However, performance in PTA relies on sound detection and therefore the PTA outcomes do not quantify or characterize other deficits that have a significant impact on communication.
- PTA and speech audiometry must be carried out following standardized procedures, equipment and environment, and the outcomes must be recorded in forms following conventions to facilitate the circulation of clinical information among health professionals.
- Speech audiometry is essential in the assessment of the impact of hearing loss on communication, particularly when assessing candidacy for or the outcome of hearing aids, hearing implants or assistive listening devices. The test battery in speech audiometry is rapidly evolving to adjust to the technological changes of hearing aids and hearing implants, and new measures are emerging that assess listening effort in order to achieve greater sensitivity.

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CHAPTER 52

EVOKED MEASUREMENT OF AUDITORY SENSITIVITY

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: auditory evoked potentials, auditory brainstem response, middle latency response and auditory late response.

INTRODUCTION

Excitation of auditory neurons by an acoustic stimulus presented at the ear results in electrical activity that can be recorded at the scalp using electrodes. Though small in amplitude, this electrical response can be isolated from the background electroencephalogram (EEG) by averaging the auditory electrical activity across many successive presentations of an acoustic stimulus. This averaged auditory electrical response, or auditory evoked potential (AEP), can be used to infer the relative health of various peripheral and central auditory regions. For instance, a reduction in amplitude of the evoked potential or prolongation of its latency may indicate an inability of the auditory neurons to respond efficiently to the stimulus, or it may reflect a reduced ability of the cochlea to respond to the sound and stimulate the auditory neurons. In either case, the AEP would reflect auditory pathology.

There are several obligatory AEPs that are used by audiologists in the diagnosis of hearing disorders. These potentials include the auditory brainstem response (ABR), middle latency response (MLR), and auditory late response (ALR). Historically, much of the clinical interest in AEPs has focused on the ABR. Initially used as a diagnostic measure in the detection of acoustic neuromas, applications of the ABR have expanded to include assessment of cochlear hearing sensitivity (i.e. threshold ABR). Part of the utility of the threshold ABR is a result of this AEP being relatively unaffected by sleep or sedation. Thus, patients who are difficult to test or who are too young to have their thresholds assessed by behavioural audiometry can often have their hearing thresholds quantified using the threshold ABR.

Neural generators for the remaining obligatory AEPs, the MLR and ALR, are situated superior to the ABR generators. Like the ABR, these measures have also been used to identify neurologic dysfunction and/or to establish hearing threshold. Since the MLR and ALR both include cortical contributions, they provide a more comprehensive view of the ability of the central auditory nervous system (CANS) to respond to sound. They are limited, however, by the requirement that the patient remain awake during the procedure. In addition to the diagnosis of neurologic dysfunction and establishing threshold, some of these later AEPs have also been used in the assessment of central auditory processing disorder (CAPD). CAPD occurs as a result of CANS dysfunction and is thought to interfere with the processing of speech when in complex listening situations.

The present chapter will provide a discussion of these three AEPs as they relate to clinical audiology. Given the broad application of the ABR in current audiology practice, the majority of this discussion will centre on this AEP and how it can be used to establish threshold and diagnose neurological issues. However, some consideration will also be given towards the end of the chapter to the MLR and ALR. These latter potentials complement the ABR in many clinical situations and can be used to test some aspects of auditory function that are not assessed by the ABR alone.

EVOKED POTENTIAL BASICS

There are several principles that apply to all of the AEPs discussed in this chapter that we will consider here briefly. AEPs are a reflection of synchronous activity in auditory neural generators resulting from the presentation of an auditory stimulus. Activity in these generators creates an electrical field that has a positive and a negative pole. To measure this activity at the scalp, at least three electrodes must be placed: an inverting, non-inverting and ground electrode. **Figure 52.1** shows electrodes placed on the scalp for acquisition of different AEPs following the 10–20 system.[1] For the ABR, the non-inverting electrode is placed at Fz and the inverting electrode is placed at either A1 (for left-ear stimulation) or A2 (for right-ear stimulation). The ground electrode is also placed on the forehead some distance below Fz. For the MLR and ALR, the location sites for the inverting and ground electrodes are similar to the ABR. However, for the non-inverting electrode, these potentials may utilize Cz or a combination of C3 and C4 instead of Fz.

There are many sources of noise that can interfere with the acquisition of AEPs. These sources may be acoustic, electric or biological in nature. In order to partly reduce the negative influence of these noise sources, AEPs are acquired through a process called physiological averaging. In averaging, the auditory system's electrical responses to many presentations of a stimulus are averaged together. Averaging will tend to enhance the AEP while reducing the effect of noise.[2] This occurs in part because noise is mostly random in its occurrence while AEPs occur at a predictable latency post-stimulus onset.[2] A common exception to this rule is 60 Hz electrical line noise, which can cause sinusoidal-type interference with the evoked potential. This line noise can sometimes be reduced by using special filters, changing stimulus rates or instituting improved grounding precautions.

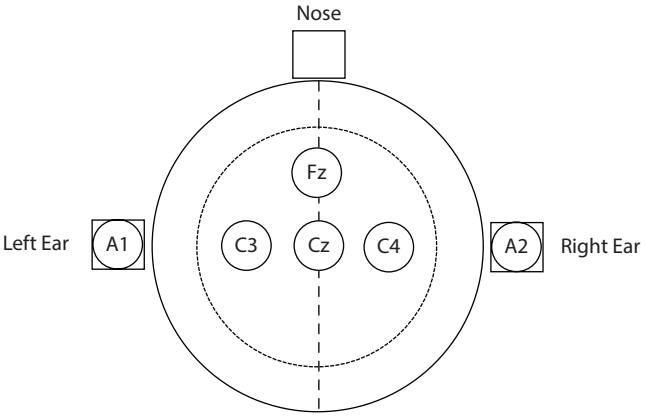

Figure 52.1 Electrode locations following the 10–20 system. The image is a superior view of the top of the scalp. A1 and A2 are located on the earlobes or mastoids. Fz is located on the high forehead and Cz is located at the centre of the scalp. C3 and C4 are located to the left and right of Cz, respectively. A ground electrode (not pictured here) is placed some distance below Fz on the forehead.

AEPs are commonly evoked with a click stimulus, which is a 100 microsecond (msec) rarefaction or condensation square wave pulse. The very rapid acoustic wave front of a click yields an abrupt stimulus onset. As the ABR is a stimulus-onset response, the abrupt onset provided by a click will frequently evoke well-formed ABRs. Spectral energy of the click measured acoustically at the ear canal is broadband but tends to be greatest in the 2000–4000 Hz range.[3] AEPs can be evoked to other stimuli, including tone bursts. Tone bursts are sinusoidal and, relative to a click, can be longer in duration with a more gradual onset and offset. The longest duration tone bursts can be used for the MLR and ALR, while the ABR makes use of shorter duration tone bursts. The spectrum of tone bursts varies by the duration of the stimulus, with longer stimulus durations showing less splatter of spectral energy into bands around the centre frequency.[4]

Stimulus intensity level for AEPs is expressed as dB normal hearing level, or dB nHL. This dB unit uses the average behavioural hearing threshold for normal hearing individuals as its reference. As an example: if calibrating a click stimulus, one would obtain an average behavioural threshold to the click in a sample of normal hearing individuals. This threshold would correspond to 0 dB nHL. Subsequently, any given dB nHL presentation level used in the clinic would reflect how much higher or lower the presentation level was relative to the average behavioural hearing threshold for normal-hearing individuals. If an 80 dB nHL presentation level was used, this would indicate that the level was 80 dB above the average normal behavioural threshold to the stimulus. Sometimes AEP equipment is not calibrated in dB nHL for all stimuli. In such cases, the clinic should make sure to establish their own behavioural calibration so a correction factor can be applied to the presentation level on the equipment display.

DIAGNOSTIC AUDITORY BRAINSTEM RESPONSE

Overview

The ABR is a response to stimulus onset and arises from the auditory nerve and low brainstem. It was first reported by Jewett and Williston,[5] who identified a complex occurring under 10 msec post-onset of an auditory stimulus that was comprised primarily of five potentials. These potentials, or waves, are labelled consecutively from I to V, with the earliest wave occurring near 1.5 msec and the latest around 5.5 msec in the normal auditory system. The waves were subsequently correlated with various neural generators of the peripheral and central auditory system.[6–8] Wave I reflects a neural response which originates from the distal end of the auditory nerve, wave II from the proximal end of this nerve, wave III from the cochlear nucleus, wave IV from superior olivary complex and lateral lemniscus, and wave V from the lateral lemniscus and possibly the inferior colliculus. Frequently, waves IV and V will present as a complex, with wave IV at the peak and wave V as a smaller shoulder to this peak occurring

later in latency. A negativity follows wave V that in many cases is the SN10 wave. The SN10 is a low-frequency negative potential that is most readily apparent when using low frequency stimuli.[9, 10] The negativity following wave V for other stimuli most likely receives some contribution from this potential. The SN10 is thought to arise from the inferior colliculus.[9] **Figure 52.2** shows an ABR with the major peaks identified.

The ABR initially emerged as a tool for diagnosis of retrocochlear pathology, such as acoustic neuromas.[11] More recently, it has found application as an estimate of hearing sensitivity for difficult-to-test patients. The current section discusses uses of the ABR as a diagnostic tool to detect lesions of the auditory nerve and central auditory system. The section that immediately follows this discussion of diagnostic ABRs considers applying the ABR to obtaining electrophysiological thresholds.

Description of diagnostic protocol

Many stimulus and recording parameters can be used in acquisition of the ABR. Subtle changes in these parameters can affect the quality of the electrophysiological response. Presented below is a description of recommended parameter values. The ABR is evoked separately from the left and right ears using these settings.

- **Stimulus:** A 100 msec click stimulus is most commonly used for assessment of retrocochlear function using the ABR. Tone-burst stimuli are sometimes used because they can be less influenced by peripheral hearing loss effects.[12] A tone-burst waveform envelope of 2-cycle onset, 0-cycle plateau, and 2-cycle offset is used. Stimuli are administered through insert earphones for diagnostic ABR testing.
- **Presentation level:** The presentation level of the ABR stimulus varies between 80 dB nHL and 100 dB nHL. If there are not concerns that hearing loss will affect the ABR indices, then 80 dB nHL is an appropriate level to use.

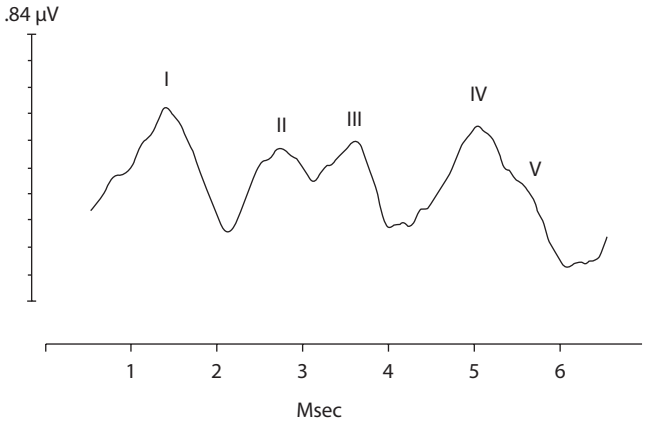

Figure 52.2 ABR with the first five peaks identified.

- **Polarity:** A rarefaction click stimulus will yield slightly earlier latencies than a condensation click.[13] As most normative values utilize a rarefaction click, it is recommended that this polarity by applied in diagnostic ABR protocols. If a tone-burst stimulus is being used, then alternating polarity should be applied.
- **Time window:** The recording time window refers to the duration over which the auditory system's response is recorded following presentation of a stimulus. A recording time window of 10–15 msec is recommended to ensure full view of the ABR response.
- **Filters:** The electrical activity recorded from the scalp is generally filtered out both above and below the frequency range of the ABR response. In adults, ABR electrical energy at the scalp is primarily in the 100–3000 Hz range, and therefore the filter is designed to pass energy in this range only. An exception to this is when the ABR is evoked to 500 Hz tone bursts, which requires the use of a lower high-pass filter setting around 30 Hz. Additionally, in infants the morphology of the ABR can sometimes be improved by using a lower high-pass setting.[14] If electrical artefact is encountered and cannot be resolved by other means, a notch filter option is available in most AEP units. This filter will reduce the amplitude of energy around 60 Hz. This filter should be used only sparingly as it can sometimes negatively affect the ABR morphology.
- **Stimulus rate:** Neurons contributing to the ABR have relatively short refractory periods and, for this reason, the response is acquired at a relatively high stimulus rate of 20–30 clicks per second. A non-integer rate, such as 17.7 clicks per second, should be used to avoid the time locking of periodic noise sources. For fast-rate ABRs, the stimulus rate is increased to 77.7 clicks per second.
- **Number of trials:** As mentioned previously, averaging the ABR across many trials will enhance the AEP and reduce noise. At least 2000–3000 trials per recording are recommended. Another viable option is to acquire a response until a predetermined signal-to-noise ratio has been reached, at which point testing can be stopped.[15] This method can help to reduce test time.
- **Replications:** Clinical analysis of ABRs requires some comment on whether the response was replicable. A replicable response is one that appears morphologically similar across two waveforms. After completing 2000–3000 trials, the ABR is acquired a second time to ensure reliability of the response. If there is concern regarding the consistency of the response, a third waveform may sometimes be acquired.

Diagnostic ABR analysis

The presence of retrocochlear lesions, including unilateral acoustic neuromas, can affect characteristics of the ABR waves, such as latency and amplitude. For instance, the neuroma can prolong the time it takes click energy to reach a particular neural generator, thus delaying the latency of the wave that arises from that generator. Likewise, a neuroma can negatively affect the synchrony of neural firing

and reduce the number of neurons being recruited for the response. In this scenario, amplitude of the wave may also be reduced. Measures of the ABR waves are discussed below and normative values are provided in Table 52.1.

Latency in the context of ABR measurement is defined either as the absolute latency of the wave, which indicates the time it takes for the wave to occur post-stimulus onset, or as the interwave latency difference, which indicates the time it takes for the neural energy to be conducted from one neural generator to the next. Interwave latency differences are calculated as the difference between the absolute latencies of two ABR peaks. This measurement is identified by the waves used in the calculation. Typical interwave latency differences are the I–III, III–V and I–V intervals.

Both absolute and interwave latency measurements can be abnormally delayed by lesions that directly involve the ABR neural generators. Absolute latencies can also be delayed by lesions occurring earlier in the auditory pathway. For instance, an acoustic neuroma can delay the latency of wave V even though the lesion is occurring in the vicinity of where wave II is generated. In addition, interwave latencies can be prolonged by lesions occurring between the two neural generators contributing to the latency measurement. A lesion between the neural generators of waves III and V will increase the latency of the III–V interval even though the generators responsible for III and V may not be directly compromised by the lesion.

Both absolute and interwave intervals have been shown to be sensitive and specific to the diagnosis of retrocochlear dysfunction, particularly in the application of acoustic neuroma detection. Musiek et al.[16] showed that all three interwave intervals had 100% specificity for this type of lesion. They varied, however, in their sensitivity, with the I–III interval showing the largest sensitivity value of approximately 90%, followed by the I–V interval with around 75% sensitivity, and then the III–V interval with the lowest sensitivity of 45%. If one considers just the I–III and III–V intervals, then 100% of the patients with acoustic neuromas in the study failed at least one of these measures and high specificity was still maintained.

TABLE 52.1 Normal limits for diagnostic ABR indices

Index	Normative value (msec)
Absolute latency of wave V	<6.2
Interwave latency I–III	<2.5
Interwave latency III–V	<2.4
Interwave latency I–V	<4.4
Inter-ear latency difference	<0.5
Fast rate shift	<1.0

Source: Values reflect adult cut-offs for ideal test efficiency based on clinical decision analysis and are obtained from Dartmouth Hitchock Medical Center normative data (Musiek). Protocol was click stimulus, monaural presentation of stimuli, presentation level 80 dB nHL, presentation rate of 17.7 clicks per second for slow rate and 77.7 clicks per second for fast rate, a 10 msec time window with 2000 accepted trials, and an online filter of 100–3000 Hz with recordings made from Fz.

Two additional latency measures that can be calculated are the inter-ear latency difference (ILD) and the fast-rate latency shift (e.g. fast-rate ABR). The ILD reflects the difference between the left ear wave V latency and the right ear wave V latency. As acoustic neuromas commonly present unilaterally, the affected side will often show an extended latency relative to the unaffected side. This leads to a larger ILD value for patients with the disorder. Sensitivity and specificity for ILD are 90% or greater.[17]

The fast-rate latency shift quantifies the degree to which the latency of wave V will shift when the click stimulus is presented at higher repetition rates. Presentation of the stimulus at these higher rates can lead to longer latency and smaller amplitude ABR waves even in the normal auditory system. This is a consequence of the stimulus rate more closely approximating the refractory period of the neurons that contribute to the ABR. In the disordered auditory system, increasing the repetition rate can lead to even longer extensions in wave latency and/or the absence of waves.[18] Normal limits on this measure are calculated as follows:[19]

[Normal wave V latency at standard repetition rates] + [0.1 msec for every 10 clicks/second increase in repetition rate] + 0.2

Therefore, if the normal latency is 6.1 msec and the repetition rate is increased from 20 clicks/second to 70 clicks/second, we would expect the new normal limit to be 6.1 + [0.1 × 5] + 0.2, or 6.8 msec. If the latency of wave V is beyond this value when the stimulus rate is 70 clicks/second, it would be considered an abnormal shift in latency.

Amplitude characteristics of the ABR are also sometimes examined to determine the presence of retrocochlear pathology. Amplitude is measured as the wave V to wave I (V/I) ratio. The amplitude of both peaks is measured from wave peak to the nearest negativity that follows the wave. The ratio is computed by dividing the wave V amplitude by the amplitude of wave I, and values less than 1.00 indicate that wave V amplitude is below that of wave I. While the specificity of this measure is relatively high (92%), the sensitivity is low enough to limit the diagnostic utility of this measure (44%).[20] As a result, amplitude is not used as commonly as latency measurements in the diagnosis of retrocochlear pathology.

Related to wave amplitude is the concept of examining wave presence or absence as an indicator of acoustic neuroma. This index does not appear always to be a reliable indicator. For instance, the percentage of patients with known acoustic neuromas who lack a wave I, III or V is 41%, 85% and 33% respectively.[21] Therefore, while the absence of a wave might be cause for follow-up testing, a high number of patients with neuromas will demonstrate the ABR waves.

Middle ear/cochlear hearing loss and test interpretation

Middle ear or cochlear hearing loss can negatively affect the latency and amplitude of the ABR peaks and can

sometimes complicate interpretation of the diagnostic ABR results. These hearing losses can prolong the latency and reduce the amplitudes of ABR waves. In such situations it is not always clear if these abnormal results are obtained because of the middle ear/cochlear hearing loss or because of a retrocochlear lesion.

There are several ways in which hearing loss can be addressed in the diagnosis of acoustic neuromas using ABR. First, if the degree of hearing loss is symmetrical, then the ILD can be used.[17] This is because the wave V latency shift being caused by the decrease in hearing sensitivity should be relatively equal in each ear. Second, interwave intervals can be used instead of absolute latencies to determine dysfunction as hearing loss would be expected to shift all waves relatively equally.[16] This approach can sometimes be limited if one or more waves cannot be visualized due to the severity of the hearing loss, particularly in the case of cochlear hearing loss. Finally, the Selters–Brackmann method yields an adjustment to the expected normal maximum latency of wave V based on the degree of sensorineural hearing loss at 4000 Hz. The new normal limit based on this method is computed as:

[Normal wave V latency] + [0.1 msec for every 10 dB of hearing loss above 50 dB HL at 4000 Hz].

Thus, if someone had a 70 dB HL loss at 4000 Hz, we would expect the new normal limit to be 6.1 + [0.1 × 2], or 6.3 msec. This modification yields reasonably good test efficiency.[22]

Diagnostic accuracy of ABR vs MRI

There has been much consideration in recent years over the diagnostic utility of the ABR when compared to magnetic resonance imaging (MRI). This arises from the observation that MRI has improved detection of acoustic neuromas when compared to ABR.[23] While this has led to the implication that all patients suspected of acoustic neuromas should be referred for MRI,[24] others have advocated for the continued use of the ABR in testing for the disorder. The value of the ABR in this capacity arises from both its very high diagnostic efficiency (e.g. sensitivity and specificity) and its reduced cost relative to MRI.[25, 26] Mangham[27] has suggested determining referral for ABR versus MRI based on the degree of average interaural hearing asymmetry at the octave frequencies of 1000–8000 Hz. If the average asymmetry is 20 dB HL or greater, patients should be referred for MRI, while average asymmetries less than 20 dB HL would warrant referral for an ABR. Using this approach they report about 2% less sensitivity than if all patients had received a diagnosis based on MRI. The cost saving was approximately US$25 000 per tumour diagnosed.

An alternative approach to acquiring ABRs has been proposed which improves the sensitivity of the test to small acoustic neuromas. The stacked derived-band ABR (or stacked ABR) utilizes the presentation of ipsilateral noise during the ABR procedure to derive responses from specific tonotopic regions of the auditory nerve.[28] This approach is based on the observation that standard click ABRs may miss dysfunction in certain frequency regions of the auditory nerve due to the spectral properties of the unmasked click stimulus. By introducing ipsilateral masking noise with different low-pass cut-offs, these various frequency regions can be assessed more directly. This approach has been shown to detect small tumours that are missed by conventional ABR.[28]

It has also been suggested that sensitivity of the ABR to small acoustic neuromas may be improved by comparing patients' ABR click threshold to their behavioural click threshold.[29] The trend witnessed in cases of acoustic neuroma is that ABR threshold tends to be poorer than behavioural threshold. Results in the study showed that patients with acoustic neuromas show approximately a 40 dB mean difference between these thresholds in the affected ear, while unaffected ears tend to yield a much smaller mean difference of 15 dB. Applying an abnormal criteria of >30 dB difference between the thresholds yielded excellent sensitivity and specificity.[29]

THRESHOLD AUDITORY BRAINSTEM RESPONSE

Overview

The ABR is commonly used in the electrophysiological assessment of hearing thresholds. ABR testing can be utilized to estimate hearing sensitivity in many cases where reliable behavioural audiometric results cannot be obtained. The test is commonly used in paediatric populations who are too young for reliable visual reinforcement audiometry or who otherwise would not condition to audiometric tasks. Acquisition of the ABR in this context allows for an estimate of hearing sensitivity that would not otherwise be obtainable.

It should be noted that the morphology of the ABR at threshold levels is different from the suprathreshold response. As the level of the stimulus is decreased, the latency of the ABR waves increases while the amplitudes decrease.[30] This occurs because fewer neurons are recruited at less intense stimulus levels and neuron firing occurs less synchronously. Earlier ABR waves (e.g. wave I) are more affected by these changes in intensity than later waves (e.g. wave V). For this reason it is not uncommon for the ABR to show only a wave V and SN10 at threshold. It is based on detection of these two peaks that ABR threshold estimates are generally made.

Description of threshold protocol

The equipment parameter settings for the threshold ABR are nearly identical to those used for the diagnostic ABR described above. As the lower stimulus levels used in the threshold ABR will increase the latency of the ABR peaks, a slightly longer time window is used, between 15 msec and 25 msec. In addition, unlike diagnostic ABRs, there tends to be a greater variety of stimuli used when completing a threshold ABR protocol. The click provides a good estimation of hearing at 2000–4000 Hz in many

clinical groups[31, 32] and tends to yield a robust ABR waveform. Since the click only assesses this 2000–4000 Hz range, it is recommended that tone bursts also be used in the assessment of hearing threshold via ABR.[31, 33] To this end, low (e.g. 500 Hz) and mid-frequency (e.g. 1000 Hz) stimuli are added to the protocol to provide a more complete evaluation of the patient's hearing. In cases where hearing thresholds demonstrate a sloping configuration for the 500 Hz, 1000 Hz and click threshold, acquisition of responses to 4000 Hz can sometimes provide a better estimate of the severity of a high-frequency loss.[31]

A typical threshold ABR evaluation will begin with assessment of the click ABR at suprathreshold levels (e.g. 70 dB nHL). There are several reasons why the acquisition of the suprathreshold response is advantageous to the clinician. First, except in cases of substantial hearing loss, this provides a well-formed template response to which subsequent click ABR responses can be compared. Second, this suprathreshold ABR should be evoked to condensation and rarefaction clicks to also test for auditory neuropathy (see below). Finally, though the patient was referred for a threshold ABR evaluation, there may be reasons to investigate the integrity of the auditory nerve and/or brainstem in a diagnostic manner, such as in cases of Chiari malformation or neurofibromatosis type 2. Acquiring a suprathreshold response will allow for this evaluation of retrocochlear pathology.

Once the suprathreshold ABR has been established, threshold can be determined for each of the frequencies being evaluated in the ABR protocol. Threshold may be defined as the lowest level at which wave V and SN10 are present. Alternatively, some clinics will only test down to a minimal hearing level (e.g. 15 dB nHL), as a detectable threshold at this level establishes that hearing is normal.

There are several ways in which threshold can be assessed. A modified Hughson–Westlake procedure[34] can be used in a fashion similar to what is done in pure-tone behavioural audiometry. However, it is sometimes more convenient and less time-consuming to test for a response at a minimal normal hearing level first. If a replicable response is not obtained, the presentation level can be increased in 5–10 dB steps until wave V is reliably evoked.

ABR testing must be undertaken when the patient is completely relaxed or asleep in order to minimize recording artefact generated by muscle movement. For newborn infants, ABR testing can be completed without sedation. Sleep deprivation, along with feeding just prior to the appointment, can increase the likelihood of a sufficient period of relaxation or sleep during the test. However, time to complete testing is often limited and testing may be interrupted or terminated early when the patient awakes. Multiple follow-up appointments may sometimes be necessary to obtain complete results in newborns.

An ABR utilizing sedation is often necessary for difficult-to-test patients. ABR can be performed under sedation or anaesthesia without degradation in response morphology. While sedation is generally used as a last resort, it can be valuable in providing the uninterrupted time necessary to perform a thorough audiological examination.

Correlation between AEP and behavioural threshold

The goal of performing the threshold ABR is ultimately to comment on the patient's hearing sensitivity. While the correlation between ABR threshold and behavioural hearing sensitivity is less than perfect, there tends to be a strong relationship between the two measures. ABR thresholds to clicks show a high degree of correspondence with some behavioural thresholds. The strongest correlation is seen between the ABR click threshold and the pure-tone average of 2000 Hz and 4000 Hz, with 89% shared variance.[31] The mean difference between the click ABR threshold and this pure-tone average threshold is approximately 1 dB, with the largest differences being in the vicinity of 35 dB.[31] Other studies have confirmed this high correlation between click ABR thresholds and the pure-tone average of 2000 Hz and 4000 Hz, with 81% shared variance, a mean ABR–behavioural threshold difference of 4 dB and a modal difference of 0 dB.[32]

ABR thresholds to tone bursts also show a relatively high level of association with their respective behavioural thresholds. The 500 Hz and 1000 Hz ABR thresholds share between 86% and 89% of their variance with behavioural measures.[31] The mean difference between the 1000 Hz ABR threshold and the corresponding behavioural threshold is approximately 1 dB, with the largest differences being in the vicinity of 30 dB.[31] In this regard, prediction of threshold at these frequencies using the ABR is as accurate as using the click threshold to predict the average of 2000 Hz and 4000 Hz.

Contralateral masking, conductive hearing loss and asymmetrical hearing

Certain clinical situations may require the use of a contralateral masking stimulus to eliminate the contribution of the non-test ear from the ABR. Testing the poorer ear of a unilaterally deaf subject has been shown to evoke a response from the contralateral ear that can be successfully eliminated with sufficient masking.[35] The presence of contralateral masking does not appear to influence the ipsilateral waveform.[35, 36] For air-conduction testing, the interaural attenuation for using ER-3A earphones and a click stimulus is approximately 70 dB.[37] Since click presentation levels will generally not much exceed 90–100 dB nHL, using a contralateral masking level of 50 dB nHL will eliminate most crossover. A white noise masker is typically provided with commercial ABR units.

Special consideration must be given to administration and interpretation of the threshold ABR in cases of conductive hearing loss and asymmetrical hearing. In cases where unilateral conductive hearing loss is suspected, the degree of hearing loss being contributed by the conductive component can sometimes be determined by obtaining bone-conduction ABR thresholds. Bone-conduction stimuli are elicited in an approach similar to that taken when obtaining behavioural thresholds, with placing a bone vibrator onto the mastoid. The contralateral non-test

ear will require masking during bone-conduction threshold assessment of the test ear.

There are several potential limitations to bone-conduction testing with ABR. First, responses evoked using this type of transducer tends to be more susceptible to stimulus artefact and this can decrease the ABR morphology and detectability. Alternating polarity stimuli must therefore be utilized to minimize the effect. Second, as artefact is sometimes high even at mid-intensity levels, the maximum intensity level at which ABRs can be reliably elicited by bone conduction (i.e. the equipment limits) is often lower than that obtained by air conduction. Finally, the spectrum of the stimulus is different when conducted through earphones as compared to the bone oscillator.[38] While this would imply that it is difficult to equate air- and bone-conduction thresholds, it has been noted that, at least in normal hearing individuals, air- and bone-conducted ABR threshold testing yields similar ABR results despite these spectral differences.[39]

Another approach to determining whether a conductive hearing loss is contributing to an ABR threshold shift is to use a latency–intensity function.[40] The latency of wave V is inversely related to stimulus intensity. Plotting wave V latency as a function of stimulus intensity generates a predictable curve in normal hearing subjects, with wave V latency increasing as stimulus intensity decreases. Conductive hearing impairment causes a latency shift in the curve that is relatively equal at all intensities and which yields no change to the slope of the curve.[41] Conversely, sensorineural hearing loss can cause a greater deviation from normal latency for stimuli closer to threshold and this can contribute to an increase in the slope of the latency–intensity curve.[41] In this way, the latency–intensity function can sometimes be used to discriminate conductive from sensorineural hearing loss.

As with behavioural audiometry, the presence of bilateral conductive hearing loss can pose a masking dilemma for the clinician. Assessment of cochlear hearing using the bone oscillator requires contralateral masking in order to prevent the contralateral cochlea from responding. However, when the masking level in the contralateral ear is raised to an intensity level that exceeds the degree of conductive impairment on that side, the masking signal can cross over to the cochlea in the test ear. This can elevate the bone-conduction threshold in the test ear, with subsequent increases in contralateral masking level further elevating this threshold. This phenomenon creates a situation in which bone conduction thresholds cannot be assessed by standard methods.

Jerger and Tillman's[42] sensorineural acuity level (SAL) technique has been advocated as an approach to measuring ABR bone-conduction thresholds in these cases of bilateral conductive hearing loss.[43] The rationale behind this method is to apply masking via a bone oscillator placed on the forehead and then quantify the degree of air-conduction threshold shift as a function of the masker level. In sensorineural hearing loss, the bone-conducted masker is less effective at shifting air-conduction thresholds since some or all of the masker energy will be below cochlear threshold. In cases of conductive loss, the masking noise is more effective at shifting air-conduction thresholds because the cochlea is unaffected by the conductive pathology. Therefore, the degree of air-conduction threshold shift that presents when a bone-conducted masking signal is introduced can assist in discriminating conductive from sensorineural hearing losses.

Central maturation

Morphology of the ABR changes with age from the perinatal period through the first years of life. The ABR response to high-intensity stimuli emerges at 28–32 weeks conceptual age.[44, 45] A repeatable three-peaked response is present by 35 weeks conceptual age. The ABR gradually becomes better defined with a full five-peaked response emerging in the first months of life. The ABR is similar in morphology to an adult response by 1–3 years of age.[45]

Maturation effects are also seen in ABR latency measures. All components of the ABR show a rapid reduction in latency during the first weeks of life, with wave I of the ABR reaching adult latency by 8–10 weeks postpartum.[40, 45] Waves III and V continue a gradual decrease in latency over the next several years, reaching adult latency by 2–3 years of age.[40, 45]

Perhaps of greater relevance to the clinician interpreting threshold ABRs is the effect of central maturation on threshold detectability. Studies have shown that, in some cases, ABR thresholds are initially elevated in newborns and show a gradual reduction over the first 6 months of life.[46–49] The degree of threshold elevation from suspected immaturity ranges from a few dB to as much as 25 dB. Often the greatest elevation in threshold occurs for higher-frequency stimuli such as 4000 Hz, whereas lower-frequency stimuli such as 500 Hz are more similar to adult levels at birth.[46, 48] ABR thresholds are also more variable in infants and this variability decreases with age.[46, 47]

Due to this trend of elevated thresholds and greater threshold variability in infants, the possibility of overtreatment may present itself when mild–moderate hearing loss is identified with the ABR at a young age. A conservative approach that includes close audiological monitoring through infancy may be warranted in cases where central immaturity is suspected. Follow-up electrophysiological testing or behavioural audiometry can be used to confirm the presence of hearing loss.

Auditory neuropathy

Auditory neuropathy is a condition that is characterized by normal cochlear responses on otoacoustic emissions and/or cochlear microphonic testing, but absent or abnormal suprathreshold ABRs.[50] Hearing loss can occur with the disorder and the site of dysfunction is localized to auditory structures beyond the outer hair cells through the auditory nerve.[51] There is a variety of risk factors associated with the disorder, including hypoxia, prematurity and hyperbilirubinaemia. There may also be genetic causes of the disorder.[51]

The patient is evaluated for the disorder as part of the threshold ABR protocol to eliminate neuropathy as a cause

of their listening difficulties. The disorder is assessed by comparing the presence/absence of the cochlear microphonic to the morphology of the ABR. The cochlear microphonic is an electrical potential that mimics the acoustic properties of the stimulus. It starts at near zero latency and, in some cases of neuropathy, it can also contribute to peaks later in the recording time window. If the cochlear microphonic is present but the ABR is otherwise compromised, auditory neuropathy would be suspected.

To evaluate the AEP for the presence of a cochlear microphonic, the ABR is evoked to a rarefaction and condensation click at suprathreshold levels. The cochlear microphonic will appear as peaks in the ABR waveform that invert in amplitude when the polarity of the stimulus is switched from rarefaction to condensation. Observation of the inversion in these peaks is typically consistent with detection of the cochlear microphonic.

One pitfall to be wary of when evoking the cochlear microphonic is not to misinterpret stimulus artefact as the microphonic response. Stimulus artefact arises from the transducer and is not a physiological potential. This artefact, when present, will show similar morphology to the cochlear microphonic and will sometimes overlap this AEP in time. Artefact will also invert its amplitude with changes in stimulus polarity. At stimulus levels of 80 dB nHL or greater there is an increased risk of stimulus artefact being present in the waveform.[52]

Alternatives to the conventional threshold ABR protocol

AUDITORY STEADY-STATE RESPONSE

The auditory steady-state response (ASSR) is sometimes used to predict hearing thresholds in difficult-to-test populations. Unlike the ABR, the procedure uses a continuous tonal stimulus instead of frequent repetition of a transient stimulus (e.g. click or tone burst). A carrier frequency is presented which is amplitude-modulated at a given modulation rate and depth. If the sound is detected by the cochlea and stimulates the auditory system, the neural generators underlying the ASSR will respond at a rate equal to the modulation rate of the stimulus. When neural firing is detected at this rate, the response is said to be 'phase-locked'.[53] A phase-locked response indicates that the auditory system has responded to the carrier frequency and this information can be used to establish threshold.

A potential advantage of this approach is that multiple frequencies can be assessed simultaneously as long as their carrier frequencies utilize different modulation rates.[53] Another benefit is related to the analysis of the ASSR. While ABR analysis involves the subjective interpretation by a clinician to identify response peaks, the ASSR can be analyzed using statistical methods that are applied and interpreted automatically.[53] This removes some of the subjectivity inherent to the process of obtaining an electrophysiological threshold.

The accuracy of the ASSR in predicting behavioural thresholds is similar to that of the tone-burst threshold ABR.[53, 54] There is some evidence that ASSR may be less likely to underestimate hearing loss in patients with steeply sloping audiometric configurations than is the ABR.[54] The ASSR may also be negatively affected by state of arousal[55, 56] and this could potentially limit its clinical application. This is particularly problematic for difficult-to-test populations where the ABR may be acquired while the patient is asleep or sedated.

ABR CHIRP STIMULUS

The chirp stimulus was developed to achieve greater neural synchrony by compensating for the travel time of the cochlear wave.[57] When a traditional click stimulus is presented, higher-frequency regions of the basilar membrane near the base of the cochlea are stimulated before the lower-frequency regions nearer the apex. This time delay causes different portions of the basilar membrane to respond in succession rather than synchronously. Conversely, chirps are acoustically designed to compensate for the tonotopic arrangement of the cochlea. This is accomplished by using a tone that increases in frequency throughout its duration, so that low-frequency cycles occur earlier than high-frequency cycles. Therefore, low-frequency energy enters the cochlea first and, by the time it reaches the apex, the higher-frequency energy is stimulating the base of the cochlea. The chirp creates a situation in which all regions of the basilar membrane are likely to be stimulated simultaneously. A potential benefit of the higher neural synchrony provided by chirp stimuli includes a larger response that is more easily detectable at lower intensity levels.[58]

MIDDLE LATENCY RESPONSE

Overview

The middle latency response (MLR) was first reported by Geisler and colleagues.[59] It is an AEP that is both larger in amplitude and later in latency than the ABR. It has multiple neural generators in the thalamocortical system, which includes the medial geniculate body, thalamocortical connections, auditory cortex and reticular formation.[60] The MLR comprises four separate potentials, a negativity occurring in the latency range of 12–21 msec (Na), a positivity that occurs between 21 msec and 40 msec (Pa), a negativity that follows Pa (Nb), and a second positivity that follows Nb in the latency range of 50 msec (Pb). MLR indices include the latency of the potentials, as well as the peak-to-peak amplitude (i.e. Na–Pa or Nb–Pb voltage difference). The Na and Pa amplitudes are the only two measured with any regularity in the clinic. This is a result of Pb being more difficult to evoke.[61] **Figure 52.3** shows an MLR with the Na–Pa peaks recorded and identified.

Historically, the MLR was pursued as a measure of hearing sensitivity. Relative to the ABR, this AEP provided an advantage in this regard since its larger amplitude made it more detectable near threshold.[62, 63] This application was limited, however, by the discovery that

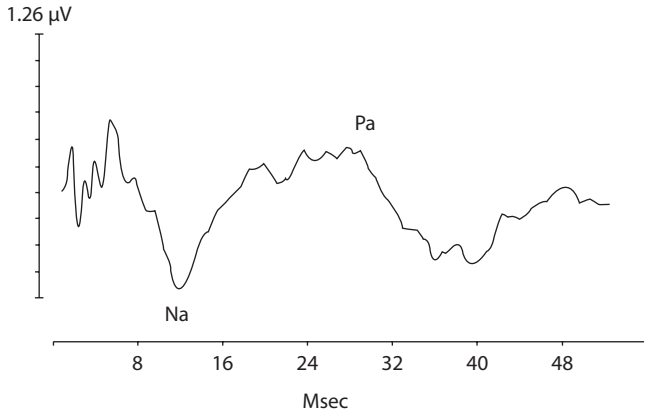

Figure 52.3 MLR with Na–Pa identified. The waves present at less than 8 msec are the ABR.

characteristics of the MLR morphology were negatively affected by degree of wakefulness.[64] Acquiring the MLR during sleep can lead to a reduction in peak amplitude or a complete absence of the complex. This posed a limitation for the use of this potential in the objective assessment of hearing sensitivity as the testing is frequently performed when the patient is asleep or sedated.

Presently, there are two primary applications of the MLR in the clinic: detection of neurological dysfunction of the CANS and diagnosis of CAPD. In regards to the former, patients with lesions that include the generator sites of the MLR will often show abnormalities on this measure. Lesions in the vicinity of the primary auditory cortex can give rise to changes in the morphology of Pa, frequently when measured over the affected hemisphere.[65, 66] Conversely, damage to the midbrain appears to affect the characteristics of the Na peak.[67] MLR abnormalities appear to be more common overall with brainstem lesions than with cortical lesions and this may be because large brainstem lesions are more likely to denervate thalamic projection nuclei.[68]

Applications of the MLR have also been reported in the diagnosis of CAPDs. CAPD refers to dysfunction of the CANS that contributes to significant listening difficulties, particularly when in the presence of background noise.[69] In addition to neurological dysfunction, it has been attributed to ageing-related changes to the CANS in older adults[70, 71] and CANS immaturity in younger populations.[72–74] There exists some controversy related to diagnosing the disorder by using tests that require patients to make a behavioural response (e.g. repeat back what they hear or press a button). For instance, it has been speculated that these types of tests may be susceptible to cognitive issues.[75] In this regard, using the MLR to evaluate for CAPD may be advantageous because no patient response is required and cognitive demands may be reduced as a result.

Description of MLR protocol

The MLR is evoked in a manner similar to the ABR, but there are several key differences. Figure 52.1 shows the electrode montage for recording this potential. Note that the response can be assessed using Cz as the non-inverting site (one-channel recording), or a combination of C3 and C4 can be used as the non-inverting electrodes (two-channel recording). The MLR settings are further characterized below, and differences from the ABR protocol are highlighted.

- **Stimulus:** A click stimulus is used to evoke the MLR for clinical purposes. Tone bursts can also be used and, due to the longer time window and slower stimulus presentation rate, a larger number of cycles can be included in these stimuli when compared to the ABR. Use of low- and mid-frequency tone bursts in this manner may be advantageous when evoking the MLR from patients with high-frequency hearing loss.
- **Presentation level:** The presentation level used for evoking the MLR is 70 dB nHL. This can be increased if there are concerns about sufficient audibility, although postauricular muscle artefact (PMA, see below) may be more likely to be evoked at these higher levels.
- **Polarity:** Rarefaction or condensation clicks may be used to evoke the MLR. If tone bursts are used, the polarity should alternate.
- **Time window:** Stimulation of the neural generators responsible for the MLR occurs only after the ABR neural generators have responded. For this reason, the latencies of the MLR peaks are later than the ABR peaks and a longer time window is needed. If only Na and Pa are being assessed, then a 50 msec time window is usually sufficient. For Nb and Pb, the time window should be extended to 75 msec.
- **Filters:** The frequency range of the MLR is lower than the ABR, extending down to 30 Hz.[76] For this reason a bandpass filter from 30–1500 Hz is used during acquisition of the MLR. Post-acquisition, an offline filter with a bandwidth of 30–300 Hz can be applied to assist in smoothing the MLR peaks. A 60 Hz notch filter should not be applied when acquiring the MLR as a filtering at this frequency could reduce a large proportion of MLR energy.
- **Stimulus rate:** Neurons contributing to the MLR have longer refractory periods than those that contribute to the ABR. For this reason, a slower stimulus rate of 9.7 clicks per second is used to evoke the MLR.
- **Number of trials:** Relative to the ABR, a fewer number of trials need to be averaged together to measure the MLR. Approximately 800–1000 trials are collected in the MLR average.
- **Replications:** As with the ABR, the MLR average is acquired at least twice to confirm response reliability.

MLR analysis

Although the latency and peak-to-peak Na–Pa amplitude of the MLR can be analyzed to determine dysfunction, these measures tend to have high between-subject variability in normal listeners.[77, 78] If normal variability on a

clinical measure is too high, it becomes difficult to establish practical normative values. One way in which MLR between-subject variability can be reduced is to compare MLR amplitude between ears (left vs right) or electrodes (C3 vs C4). Therefore, instead of examining the amplitude at either ear or either electrode individually, the difference between the two ears or two electrodes is calculated and this difference is used to determine normalcy. Sources of individual variation that are common to both ears or electrodes will be subtracted out of the index by computing this difference, and this will decrease between-subject variability on the MLR.[71, 79] In addition, amplitude measures of the MLR tend to be more sensitive to dysfunction than latency measures,[80] so differences in amplitude are used instead of latency.

Between-ear and between-electrode amplitude differences are referred to as ear effects and electrode effects, respectively.[80] They are computed as the absolute value of the difference between the two amplitude measures, or |Left ear Na–Pa amplitude - Right ear amplitude| for ear effects and |C3 amplitude - C4 amplitude| for electrode effects.[79, 80] For patients with neurological lesions, normalizing the difference by dividing by the smallest amplitude can improve the sensitivity of the index.[80] Normative values for ear and electrode effects are included in Table 52.2.

One pitfall to be aware of when interpreting the MLR is to not misinterpret PAM artefact as the MLR. PAM artefact is a myogenic response that can be evoked by the MLR stimulus.[81] The latency of PAM artefact is approximately 10–15 msec and, given its much larger amplitude relative to the MLR, the presence of this myogenic activity makes the MLR difficult to measure accurately. It has been suggested that the presence of PAM artefact is related to the direction of gaze and neck tension.[82] If the artefact is encountered, it can sometimes be reduced by having patients stare directly straight ahead at a picture on the sound booth wall and/or reclining them in a chair so as to relax the neck.

TABLE 52.2 Normal limits for MLR indices

Index	Normative value (μV)
7–8 years (AD)	Ear effect: <0.49 Electrode effect: <0.15
9–10 years (AD)	Ear effect: <0.43 Electrode effect: <0.17
11–12 years (AD)	Ear effect: <0.27 Electrode effect: <0.19
13–14 years (AD)	Ear effect: <0.24 Electrode effect: <0.20
15–16 years (AD)	Ear effect: <0.35 Electrode effect: <0.22
Adult (N)	Ear effect and electrode effect: <20% to 50%

Source: Values reflect upper limit of 95% confidence interval in normal hearing participant and are obtained from Musiek et al.[79] and Weihing et al.[78] Protocol was as follows: click stimulus, monaural presentation of stimuli, presentation level 60–70 dB nHL, presentation rate of 9.8 clicks per second, a 72 msec time window with 1000 accepted trials, and an online/offline filter of 20–1500/20–200 Hz with recordings made from the C3 and C4 electrodes.

Key: AD = Absolute difference: |Amplitude 1 – Amplitude 2|

N = Normalized: (|Amplitude 1 – Amplitude 2| / Smaller amplitude) × 100

AUDITORY LATE RESPONSE

Overview

The auditory late response (ALR), or long latency response, is an AEP that is primarily cortical in origin and was first reported by Pauline Davis.[83] The neural generator system contributing to the ALR is broad but receives important contributions from the Sylvian fissure and the superior aspect of the temporal lobe including Heschl's gyrus.[84–86] A total of six or more neural generators may contribute to the response.[86] The peaks most commonly measured in the ALR are the N1 and P2. The N1 is a negativity that can be observed between 60 and 170 msec, while the P2 is a positivity that is seen between 115 and 290 msec. Amplitude of the ALR waves is larger than the ABR or MLR wave amplitudes. Figure 52.4 shows an ALR with the N1–P2 peaks recorded and identified.

The ALR can be used clinically to diagnose lesions of the CANS. Patients with lesions of the temporal lobe have been shown to demonstrate prolonged ALR latencies, reduced amplitudes and/or absent potentials.[87] The ALR can also be used in the assessment of hearing sensitivity and in auditory rehabilitation applications.[88–92] Stimuli of relatively long duration can be used to evoke the response due to the very slow stimulus repetition rate and long time window of the ALR (see below). This allows for an increased number of cycles in pure-tone stimuli, which may yield better frequency specificity of

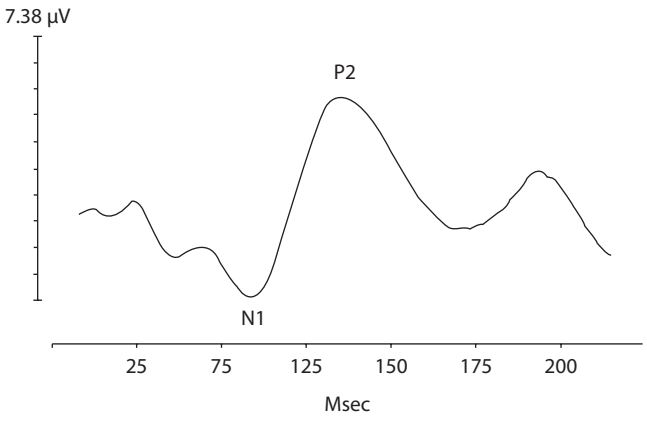

Figure 52.4 ALR with N1–P2 identified.

the evoked response in adults.[88] The ability to use longer stimuli also allows for the inclusion of more complex sounds, such as speech, in the ALR paradigm.[89] The ALR has also been used in rehabilitation contexts for demonstrating that amplification makes sounds audible in infants[90] and to show outcomes from auditory training.[91, 92]

Similar to the MLR, the ALR morphology is affected by sleeping and this can limit its utility as a threshold measure in difficult to test populations.[92, 93] In addition, the amplitude and latency characteristics of the response are affected by whether the auditory stimulus is attended to or not.[94] This may be the result of ALR arising from generator sources that respond to multiple modalities and/or that are responsible for mediating attention.[85, 95, 96]

Description of ALR protocol

Due to the many novel applications for which the ALR is used it is not possible to discuss all configurations the clinician may encounter when attempting to measure this response. However, we present below a minimal protocol that can be used to evoke an N1–P2 to address basic clinical questions. Note that, while the ALR protocol shares similarities with the ABR and MLR protocols, differences exist because of the later latency of the ALR peaks and the longer refractory periods of the cortical neurons. Recording sites include some combination of Cz, C3 and C4, as the N1 and P2 amplitudes are sufficiently large in these regions.[97] The ALR settings are further characterized below, and differences from other AEP protocols are highlighted.

- **Stimulus:** Although a click stimulus can be used to evoke the ALR, the much longer time window and slower stimulus rate allows for long duration tones and complex stimuli to be used in the task. For example, consonant–vowel syllables are frequently used to assess the response of the CANS to speech stimuli.[87, 98]
- **Presentation level:** A presentation of level of 70–80 dB nHL is sufficient for evoking the ALR if there are no concerns about audibility.
- **Polarity:** Rarefaction or condensation clicks may be used to evoke the ALR. If tone bursts or complex stimuli are used, the polarity should alternate.
- **Time window:** The latencies of the ALR peaks are later than the ABR and MLR peaks. For this reason, a much longer time window of 300–400 msec is utilized to acquire the N1–P2.
- **Filters:** The frequency range of the ALR is considerably lower than the ABR and MLR, from 1–30 Hz.[99] A bandpass filter in this range is applied online.
- **Stimulus rate:** ALRs are evoked using a slow rate of 1.1 stimuli/second due to the longer refractory periods of cortical neurons. Given the slow rate of presentation, there is sometimes concern that eye blinks will become time-locked with the AEP unit. To prevent this, an electrode should be placed at the outer canthus to reject trials on which eye blinks occur.
- **Number of trials:** Relative to the ABR and MLR, fewer trials need to be averaged together to measure the ALR. Approximately 100–200 trials are collected in the ALR average.
- **Replications:** As with the other AEPs, the ALR average is acquired at least twice to confirm response reliability.

TABLE 52.3 Normal limits for ALR indices

Index	N1	P2
Amplitude (μV) (male)	<-2.28	>2.99
Amplitude (μV) (female)	<-2.73	>3.83
Latency (msec) (male)	<109.24	<170.53
Latency (msec) (female)	<102.23	<163.35

Source: Values reflect upper or lower limit of 95% confidence interval in young adult normal hearing participants and are calculated based on data from Swink and Stuart.[100] Protocol was as follows: ~750 Hz tone burst with a 10.5–49–10.5 envelope and a duration of 70 msec, binaural presentation of stimuli, presentation level 75 dB peak SPL, presentation rate of 1.1 tones per second, a 500 msec time window with 150 accepted trials, and an online filter of 1–30 Hz with recordings made from the Cz electrode. Amplitude was measured from pre-stimulus baseline.

ALR analysis

ALR indices include the latency of the potentials, as well as a single peak-to-peak amplitude (i.e. N1–P2 voltage difference). Alternatively, N1 and P2 amplitudes are sometimes measured relative to the baseline voltage of the response. In these cases a separate amplitude measure is obtained for the two peaks (see Table 52.3 for example normative values). In neurological cases, ear and electrode effects are not calculated even though the ALR recorded over the affected hemisphere is more likely to show dysfunction.[87]

SUMMARY

The present chapter described basic approaches to acquiring AEPs in clinical populations. Perhaps the most relevant of these AEPs is the ABR, which can be used diagnostically to assess retrocochlear function or as a threshold measure in difficult-to-test populations. The resistance of the ABR to sleep effects and its high reliability make it a valuable tool in this regard. In addition to the ABR, protocols and characteristics of the MLR and ALR were also considered. These potentials assess regions more superior in the CANS and their acquisition provides a more comprehensive description of hearing health in this regard. The MLR has been used in the diagnosis of CAPD, while the ALR has a found a broad range of applications that include assessment of neurological function, validation of hearing aid fittings and quantifying neural benefits from auditory training.

KEY POINTS

- AEP can be used to infer the relative health of various peripheral and central auditory regions.
- Patients who are difficult to test or who are too young to have their thresholds assessed by behavioural audiometry can often have their hearing thresholds quantified using the threshold ABR.
- AEPs are commonly evoked with a click stimulus.
- ABR is a response to stimulus onset and arises from the auditory nerve and low brainstem.
- Auditory neuropathy is a condition that is characterized by normal cochlear responses on otoacoustic emissions and/or cochlear microphonic testing, but absent or abnormal suprathreshold ABRs.

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CHAPTER 53

PREVENTION OF HEARING LOSS

Shankar Rangan and Veronica Kennedy

SEARCH STRATEGY

Data in this chapter may be updated by Medline and PubMed searches using the keywords: hearing loss, deafness, epidemiology, prevention, infection, vaccination, cytomegalovirus, measles, mumps, meningitis, ototoxicity, barotrauma and noise trauma. Epidemiological data from the World Health Organization have been used. Material from previous editions of this textbook on the same chapter has also been used.

EPIDEMIOLOGY

Hearing loss is a very common worldwide problem affecting all age groups and leading to marked disability and handicap. The World Health Organization (WHO) lists hearing loss in the 20 leading causes of burden of disease and as a most common cause of disability globally.[1]

In 2012, the WHO estimated that there are 360 million people worldwide with a disabling hearing loss, which is 5.3% of the world's population.[2] Of these, 91% are adults and 9% children. The prevalence of disabling hearing loss is greatest in South Asia, Asia Pacific and Sub-Saharan Africa both for children and for adults over the age of 65. The prevalence of hearing loss increases with age: in children it is 1.7%, 7% in individuals over the age of 15, and in adults over the age of 65 it is almost one in three. However, a noteworthy point is that half of all cases of hearing loss can be avoided through primary prevention.[3]

In the UK the incidence of children born with a permanent hearing impairment is about 1 in 1000, but this figure nearly doubles in early childhood.[4] In 2011 there were approximately 10 million people in the UK with some form of hearing loss.[5]

DISABLING HEARING LOSS AND ITS PREVENTION

Disabling hearing loss refers to hearing loss greater than 40 dB in the better ear in adults (15 years or older) and greater than 30 dB in the better-hearing ear in children (0–14 years).[3] The majority of people with a disabling hearing loss live in the developing countries.

For any disease or disability, there are three levels of prevention:[6]

- **Primary prevention:** This is prevention of pathology by reduction in the causative factors leading to that pathology.
- **Secondary prevention:** This is prevention or limitation of disability and handicap in those individuals with an impairment. This can be by screening for affected individuals prior to clinical presentation and, when possible, providing treatment to prevent progression of pathology and impairment.
- **Tertiary prevention:** This is prevention or limitation of handicap by early management of the disability.

The three levels of prevention of hearing loss are further subclassified in **Box 53.1**.

PRIMARY PREVENTION OF HEARING LOSS

The effects of primary prevention have markedly altered the profile of the aetiology of hearing loss in the developed countries. The incidence of hearing loss due to chronic suppurative otitis media has fallen dramatically. However, this still remains a leading cause in the developing countries.

BOX 53.1 Subclassification of the three levels of prevention of hearing loss[6]

1. Primary preventable causes of hearing loss
   - Genetic
     - Genetic counselling
   - Infective (congenital or acquired)
     - Immunization
     - Early treatment
     - Avoidance and education
   - Traumatic (noise, physical trauma and barotrauma)
     - Avoidance
     - Early treatment
   - Ototoxic medications
     - Avoidance
     - Monitoring
     - Treatment
   - Prevention of deafness by improving lifestyle to prevent other diseases
2. Secondary prevention
   - Screening
   - Treatment
3. Tertiary prevention
   - Early rehabilitation of hearing loss

Prevention of disease in the developing countries still lags far behind and ongoing efforts to promote uptake of preventive measures is essential. The WHO has developed a programme for the prevention of deafness and hearing impairment (PDH) and has produced guidelines on the prevention of hearing impairment from ototoxic drugs, chronic otitis media and noise-induced hearing loss.[7]

Genetic hearing loss

Around 60% of prelingual deafness is genetic. Of this, about 70% is non-syndromic. Between 75% and 80% of non-syndromic hearing impairment is autosomal recessive, 10–15% is autosomal dominant, and the rest are X-linked, mitochondrial or chromosomal.[8] The most common cause of genetic deafness is mutations in the gap junction beta 2 gene (*GJB2*), located on chromosome 13q and encoding the protein connexin 26.[9, 10] One particular mutation, 35 delG, is the commonest[11, 12] and has been reported to account for more than 80% of the *GJB2* mutation in the Caucasian population.[13]

PREVENTION OF GENETIC HEARING LOSS

Genetic counselling

Identifying the genetic profile of the hearing loss is the first step before any genetic counselling can be given to the individual and the family members. The genetic counsellor can inform a family about the risks of any child being born with a hearing impairment. This is especially applicable when they already have a child with hearing loss. The parents can then make an informed choice whether to have more children. Prenatal counselling would also enable early intervention and provision of support for a child with deafness, thus minimizing the impact of the hearing loss.

Role of consanguinity

With almost three-quarters of genetic hearing loss being autosomal recessive, the role of consanguinity assumes very important proportions. The prevalence of parental consanguinity has been found to be significantly higher in hearing-impaired children than in those with normal hearing. A decline in the prevalence of hearing impairment has been found with restriction of consanguineous marriages.[14] Improved education of the community about the risks involved with consanguinity should help to some extent to prevent deafness.

Infective causes of hearing loss

The role of primary prevention is quite significant and effective in the field of prevention of infective causes of hearing loss. This is true for both congenital and acquired infective causes. In the developing world, the focus on preventing hearing loss due to chronic suppurative otitis media remains as important as ever.

Where possible, the aim should be to prevent hearing loss due to infective causes. This can be through vaccinations, or, the adoption of measures which will prevent the development of chronic suppurative otitis media. If this is not possible, infection should be treated early to minimize the impact of hearing loss.

PREVENTION OF INFECTIVE CAUSES OF HEARING LOSS

Although infective causes of hearing loss may be congenital or acquired, the methods of prevention are the same for both. These include immunization, early treatment, and education and avoidance.

Rubella (or German measles) is a generally mild viral infection occurring mostly in children and young adults. Rubella infection during pregnancy can cause congenital rubella syndrome (CRS) with the classical triad of symptoms of sensorineural hearing loss (SNHL), ophthalmic abnormalities and congenital cardiac defects. There is no effective treatment for rubella, but the disease can be prevented by vaccination. Vaccines have been developed since 1969 and the immunization programmes have nearly eradicated CRS from most developed countries. However, the disease can still be a problem in developing countries. In 2014, the WHO estimated that there were 110 000 babies born worldwide with CRS.[15]

Hearing loss is a known complication following measles. The hearing loss can be sensorineural or conductive or mixed.[6] Prior to widespread vaccination for measles, it was reported to account for 5–10 % of cases of profound SNHL in the US.[16] Atrophy of the stria vascularis and loss of the organ of Corti after measles infection have been proposed to be the cause of SNHL.[17] Encephalitis is a rare complication of measles that can lead to profound SNHL. Measles is also associated with a high incidence of otitis media, which can also lead to hearing loss.[18] In addition, measles virus has been implicated in the aetiopathogenesis of otosclerosis.[19] Immunization against measles

may therefore play a role in reducing the incidence of otosclerosis.

Mumps is a systemic viral illness typically causing symptoms of fever, malaise, myalgia, headache and swelling of one or both parotid glands. Complications of mumps may include SNHL, orchitis, meningitis, encephalitis and pancreatitis. The incidence of SNHL after mumps has been estimated to be 0.5–5 per 100 000, but it has been reported to be as high as 1 in 1000 in Japan where mumps vaccination is optional.[20] The hearing loss is mostly unilateral but can also be bilateral. With the introduction of the Mumps, Measles and Rubella (MMR) vaccination, the incidence of mumps, and thereby hearing loss due to mumps, has reduced significantly.[21]

Effective immunization against mumps, measles, rubella and meningitis has led to a reduction in the incidence of hearing loss due to these conditions. The MMR vaccine was first licensed by the US government in 1971. In the UK it has been available for children between the ages of 1 and 2 years since 1988.[22] After the introduction of the MMR vaccine, the spread of measles was effectively halted in the mid 1990s. However, following adverse publicity, linking it with autism and Crohn's disease, there was a reduction in the uptake of the vaccination. Vaccine uptake levels in UK fell to 80% in 2003 and 2004 from levels of 92% in 1995.[23] This led to an increase in the incidence of these diseases, with 1370 cases of measles reported in England and Wales in 2008.[24] From November 2012 to July 2013, Wales experienced the largest outbreak of measles, with 1202 cases notified.[24] There has been a similar increase in mumps cases. The suggested association between MMR and autism has been proven to be baseless:[25] Public Health England investigated possible links between the MMR vaccine and autism and Crohn's and determined there was no evidence for this.

Meningitis remains the most common cause of acquired severe to profound SNHL in childhood.[26] Likewise, deafness is the most common long-term neurological sequela of the disease.[27] The hearing loss after meningitis can be unstable, with the deterioration occurring many years after the disease.[28] Another important consideration following meningitis is the development of labyrinthitis ossificans in which there is new bone formation within the lumen of the otic capsule. Ossification of the labyrinth can develop within a few days of meningitis.[29] This can make cochlear implantation difficult.[30] Early diagnosis of deafness after meningitis is therefore important. Of the various organisms causing bacterial meningitis, *Streptococcus pneumoniae* is associated with more profound hearing loss.[31] Various vaccinations against meningitis are available. These include the pneumococcal vaccine for *Streptococcus pneumoniae*, meningitis C vaccine for the serogroup C of *Neisseria meningitidis* and vaccination against *Haemophilus influenzae* type B. Quadrivalent vaccines effective against serogroups A, C, W-135 and Y of *Neisseria meningitidis* are also available. By protecting against mumps, measles and rubella, the MMR vaccine also protects against meningitis, which can arise as a complication of these diseases. Vaccination against serogroup B of *Neisseria meningitidis* has also become available, although it is still not available widely. Pneumococcal vaccines also have a role in the prevention of hearing loss arising due to otitis media: use of the 13-valent pneumococcal vaccine has been shown to reduce the incidence of pneumococcal otitis media in childhood.[32]

The use of adjuvant corticosteroid therapy in acute bacterial meningitis due to *Haemophilus influenzae* has been shown to reduce the incidence and severity of SNHL.[33] Its role in preventing hearing loss resulting from meningitis caused by other organisms is less well defined.

Cytomegalovirus (CMV) is the most common cause of congenital infections in humans.[34] Congenital CMV (cCMV) is being increasingly recognized as a leading cause of non-hereditary congenital SNHL,[35, 36] and it has been estimated to be the cause of congenital SNHL in 20–30% of cases.[37] The hearing loss associated with cCMV may be detectable at birth or can be of delayed onset.[38] It could be the only symptom in an otherwise asymptomatic baby. The hearing loss can be progressive. Fowler et al. reported a progression of hearing loss in 50% and fluctuation in around 23% of children with SNHL due to cCMV infection.[39] CMV is a ubiquitous infection and in adults causes mild flu-like symptoms. However, when a pregnant woman acquires the disease for the first time or develops a primary CMV infection, the risk of vertical transmission to the foetus is estimated to be around 30–40%.[40] Only about 13% of children with cCMV exhibit obvious symptoms at birth.[41] These may include permanent neurological sequelae including sensorineural deafness, blindness, seizures and learning disability. Treatment of cCMV with antiviral medications started within 1 month of life,[42] with 6-week therapy of intravenous ganciclovir[43] or 6-month therapy with oral valganciclovir,[44] has been shown to improve the audiological outcome. Recent evidence seems to suggest 6 months of oral valganciclovir produces better outcomes in the long term.[45]

Health education forms an important part of primary prevention for many diseases. Awareness about cCMV infection among the general public is still quite low. Providing health education materials to pregnant women has been shown to increase their knowledge about the infection and may reduce its incidence.[46] CMV is transmitted in body fluids including saliva and urine. It is a very common infection in toddlers and preschool children and exposure to saliva and urine of small children is the commonest cause of CMV spread to pregnant women. Simple hygiene measures adopted by pregnant women, such as avoiding kissing young children on the mouth or cheek, careful hand washing after contact with any bodily fluids and not sharing cutlery or drinks and food, can help to reduce the risks of pregnant women getting CMV.[47]

Toxoplasmosis is an infection caused by the parasitic protozoan *Toxoplasma gondii*. Cats are important vectors in the transmission of the infection. They can become infected by eating infected rodents, birds or other small animals. They then pass the parasite in their faeces. Handling cat litter can spread the infection. It can also be contracted by eating uncooked meat. *Toxoplasma* infection

during pregnancy is often asymptomatic or may present as mild flu-like symptoms. Congenitally infected infants are mostly asymptomatic at birth, but long-term studies have shown that up to 85% may develop sequelae including sensorineural deafness, chorioretinitis, developmental delay and microcephaly.[48] The incidence of *Toxoplasma*-associated hearing loss has been estimated to be in the range of 0–26%.[49] Careful hygiene during pregnancy, avoiding handling cat litter and eating only well-cooked meat can prevent toxoplasmosis during pregnancy. In children with congenital toxoplasmosis who received antiparasitic therapy initiated within 2.5 months of age, the prevalence of SNHL was 0%. The prevalence was 28% in children who did not receive any treatment.[49] However, there is no randomized controlled trial evaluating the benefits of treatment. The optimum duration of treatment is not clear and there are concerns about the adverse effects of treatment in the newborn period. In the UK, routine screening for *Toxoplasma* during pregnancy is not carried out as there is no clear evidence that prenatal treatment reduces maternal to foetal transmission of the infection.

Exposure to tobacco smoke is a known cause of increased ear infections in children, and parental education regarding the effects of passive smoking is vital to reduce the incidence of ear infections in children.[50] Inadequate treatment of acute otitis media, delay in seeking medical treatment, poor housing conditions, poor hygiene and nutrition, unhygienic ear cleaning and swimming in infected ponds and pools are some of the factors leading to chronic suppurative otitis media (CSOM) in developing countries.[51] Public education about the impact of the disease, and improvement in hygiene, nutrition and housing conditions will reduce the global burden of deafness due to CSOM.

Traumatic causes of hearing loss

Traumatic causes of hearing loss include acoustic trauma, noise-induced hearing loss (NIHL), direct physical trauma and barotrauma.

PREVENTION OF TRAUMATIC CAUSES OF HEARING LOSS

Noise

It has been estimated that worldwide about 16% of disabling hearing loss in adults is occupational noise-induced.[52] The risk of developing NIHL is proportional to the duration of noise exposure. Although most developed countries have legislation in place to prevent NIHL, it still remains one of the commonest health problems and one of the most common occupational diseases. Non-occupational noise exposure, such as that resulting from leisure activities, including music, power tools and motor sports, and also daily exposure to noise due to environmental conditions, can lead to NIHL. The formation of free radicals reactive oxygen species (ROS) and reactive nitrogen species (RNS) seems to be the molecular basis for NIHL and ototoxicity. Excessive noise exposure leads to the formation of these free radicals; they trigger cell death pathways through necrosis and apoptosis, resulting in loss of hair cells and neurons, which results in the hearing loss.[53] Apart from using adequate protection to prevent exposure to noise, the role of several antioxidants and therapeutic agents has been studied in the prevention of NIHL in mainly animal models but also in some human studies. These include glutathione,[54] *N*-acetylcysteine,[53] transforming growth factor (TGF)-β1 inhibitor,[55] alpha lipoic acid[56] and hydrogen sulphide[57] among other agents. The topic of NIHL is covered more extensively in Chapter 57 Noise-induced hearing loss and related conditions.

Acoustic shock is another phenomenon which can cause SNHL. This happens when there is exposure to a short-duration, high-frequency and high-intensity sound through a telephone headset. Use of telecommunications with an acoustic limiter reduces the risk of hearing loss associated with acoustic shock.[58]

Physical trauma

Hearing loss can be due to physical trauma to the ear such as temporal bone injuries. The trauma may also be self-inflicted or iatrogenic. A recent study found that, in adults, cotton swabs, first-aid products, hearing aids and other ear-specific accessories were common aural foreign bodies.[59] Public education about the risks of ear cleaning with buds or other materials has to be ongoing.

Iatrogenic trauma includes inexpert attempts at syringing or removal of foreign bodies. In some developing countries 'ear cleaning' services are offered by street vendors which may cause serious damage to the ear. Increasing public awareness about the risks associated with these actions is vital. Iatrogenic trauma can also be caused during ear surgery. Ensuring adequate and appropriate training is given to surgical trainees is necessary to reduce this. Radiotherapy to the head and neck for tumours can cause conductive hearing loss due to middle ear effusion or sensorineural deafness due to cochlear damage. This can be prevented by careful modulation of radiation fields to limit exposure of the cochlea.[60]

Barotrauma

Barotrauma results when there is failure to equalize the pressure between an air-containing space and the surrounding environment. Barotrauma to the ear is most commonly caused by pressure changes encountered in flying and scuba diving. It can result in damage to the middle or the inner ear. Middle ear barotraumas results when there is failure of equalization of pressure between the middle ear and the atmospheric air pressure. This occurs when the Eustachian tube function is compromised.

Inner ear barotrauma is encountered in divers when they force a Valsalva manoeuvre to try to equalize the middle ear pressure and the resultant increase in pressure causes inner ear damage by either the **implosive** or the **explosive** route. In the implosive route, if the forced Valsalva opens the Eustachian tube, there is a significant increase in the middle ear pressure which can cause either

rupture of the round window membrane or disruption of the stapes footplate. If the Eustachian tube remains closed, the increase in intracranial pressure can be transmitted along a patent cochlear duct or the internal auditory meatus, causing disruption of the round window or the stapes footplate. With either route, perilymphatic leak or intracochlear membrane damage may result in SNHL. Decompression sickness in divers occurs when dissolved gas, usually nitrogen, comes out of solution on ascent and forms bubbles in soft tissues and blood vessels, causing various symptoms including sensorineural deafness.

Preventive measures for barotrauma as a result of air travel would include avoidance of flying during or immediately after an upper respiratory tract infection. Frequent swallowing, for example by sucking sweets or sipping drinks during ascent and descent, helps equalization of pressure in the Eustachian tube. Similarly for divers, avoidance of diving during an upper respiratory tract infection is important. Proper training in equalizing pressure plays a major role in preventing barotrauma. Manoeuvres to equalize pressure include the Valsalva (blowing against closed nose and mouth) and Toynbee (holding the nose and swallowing simultaneously). Decompression sickness can be prevented by strictly following existing guidelines on decompression times relating to time and depth of dive.

Ototoxic medications

A wide variety of drugs may have ototoxic effects. Ototoxic medications include aminoglycosides, antimalarials (e.g. quinine), aspirin, anticancer drugs (e.g. cisplatin), diuretics (e.g. ethacrynate and furosemide) and industrial solvents (e.g. toluene). As in the case of NIHL, ototoxic medications may lead to the formation of free radicals which trigger cell death pathways through necrosis and apoptosis, resulting in hearing loss. Ototoxic hearing loss may be prevented by minimizing and controlling the exposure to these medications. There does not seem to be a safe dose with relation to vestibulotoxic effects.

There is a known genetic predisposition to ototoxicity. Individuals with the mitochondrial mutation *A1555G* develop a hearing loss with aminoglycoside exposure which often progresses after the use of aminoglycoside at therapeutic doses has ceased.[61] However, the prevalence of deafness in individuals with the *A1555G* mutation is likely to be high even in the absence of aminoglycoside exposure.[62] Screening individuals due to receive aminoglycoside treatment may lead to prevention of hearing loss from this cause.[63] Similar to NIHL, antioxidants may have a role in preventing ototoxic hearing loss. Aspirin has been shown to attenuate the ototoxic effects of gentamicin.[64] Ototoxicity is discussed in greater detail in Chapter 59 Ototoxicity.

Perinatal factors

The role of preventable perinatal factors in developing SNHL has reduced in the developed countries with better obstetric care, but it can still be a major concern in developing countries. Reduction in morbidity due to hazardous levels of hyperbilirubinaemia has been achieved in developing countries through a variety of preventive measures including better antenatal care, monitoring of serum bilirubin in infants, exchange transfusion, phototherapy and anti-D immunization. Use of other antibiotics and careful monitoring of aminoglycoside levels can prevent incidence of ototoxicity in the perinatal period. Paradoxically, in developed countries, improved neonatal care now enables several very preterm infants to survive and as a result of their extreme prematurity they may have long-term neurodevelopmental sequelae including SNHL. The major preventable perinatal factors which can cause SNHL include hypoxia, hyperbilirubinaemia and aminoglycoside toxicity. Although birth asphyxia is associated with SNHL,[65] it is thought that it is a combination of risk factors which leads to SNHL.[66] Severe neonatal hyperbilirubinaemia is associated with a higher incidence of SNHL.[67] Hyperbilirubinaemia may also be associated with auditory neuropathy spectrum disorders.[68]

Prevention of deafness by improving lifestyle to prevent other diseases

Smoking, obesity and poor gylcaemic control are well-known risk factors for cardiovascular diseases which in turn may increase the risk of hearing impairment.[69] Ongoing public education, especially in developing countries, about the risks of smoking and benefits of healthier diet with regular exercise would help in the prevention of hearing loss by reducing the risk of cardiovascular diseases. Hypertension is also associated with hearing loss. Optimizing blood pressure control should also, therefore, reduce the risk of hearing loss.[70]

SECONDARY PREVENTION OF HEARING LOSS

Screening

Increasing evidence that early identification of deafness and early intervention will result in significantly better outcome for language development[71, 72] led to the development of the Newborn Hearing Screening programme. The World Health Organization[73] recommended that the policy of universal neonatal hearing screening should be adopted in all countries with available rehabilitation services and that this should be extended to other countries and communities as rehabilitation services are established. This has been implemented in several developed countries in the world. Implementing it can be quite a challenge in developing countries due to factors including non-availability of expensive screening equipment and trained personnel to do the screening. In many developing countries, the majority of births may take place away from maternity hospitals so, typically, screening will not be performed by skilled staff and screening equipment will not be available in such settings.[74] In countries which

have adopted universal newborn hearing screening, the age of identification of hearing loss has reduced dramatically. In England, the median age at identification of permanent hearing impairment has come down from 18 months before the implementation of the screening to 10 weeks, with 90% of cases being identified before 6 months of age.[75] In many developing countries, family suspicion remains the main mode of diagnosing childhood hearing impairment.

Hearing loss undiagnosed at birth or during the first few years of life adversely affects speech and language development, academic progress and social and emotional development. In countries without universal newborn hearing screening programmes, a significant number of children with permanent childhood hearing impairment (PCHI) are not diagnosed until well into childhood. Milder hearing loss or unilateral hearing loss may not be identified until 6 years of age. Identification and rehabilitation of PCHI during the first few months of life will result in a significantly better outcome for speech and language development, school performance and social and emotional development.[73]

School screening is an effective method of identification of children with hearing loss. Even in countries with universal newborn hearing screening, school screening identifies those children who may have developed a hearing loss later in life, have a progressive hearing loss or have missed hearing screening at birth.

Regular hearing screening of those at risk of developing NIHL is mandatory in several industries. Early identification and cessation of the noise exposure will prevent the hearing loss from progressing.

Treatment

Early identification of hearing loss and its cause can enable commencement of appropriate treatment in several situations. For instance, in the case of NIHL and ototoxicity, once the hearing loss is diagnosed, cessation of exposure to the noxious agent will usually prevent the hearing loss from progressing. Several agents have also been shown to be effective in improving NIHL and hearing loss due to ototoxicity (see above). Early diagnosis of cCMV as a cause of hearing loss in the neonatal period and treatment with antiviral medication has been shown to prevent the progression of the associated hearing loss.

Hearing loss due to middle ear disease can be very effectively prevented by early identification of the disease and appropriate management. This is all the more important in developing countries where CSOM is still a leading cause of hearing disability.

TERTIARY PREVENTION OF HEARING LOSS

Tertiary prevention involves early rehabilitation of hearing loss. Provision of appropriate amplification is the first step, but ongoing support is equally important. In the case of children, educational support specially tailored for the hearing-impaired child is essential. The use of assistive listening devices, such as hearing loop systems, FM systems and personal amplifiers, are invaluable tools in the management of an individual with hearing loss. The provision of appropriate amplification is an ongoing challenge in the developing world. The WHO has made several efforts at improving the availability of high-quality hearing devices in low- and middle-income countries, where in many cases charitable institutions play a major role in providing hearing aids.[76] The financial aspects of cochlear implantation may be a significant limiting factor in its availability in the developing world. To overcome this, some developing countries produce their own indigenous cochlear implants.[77] However, continuing support for cochlear-implanted children, which is so vital for its success, may not be available. Efforts to improve education and support for the family of a hearing-impaired child or older person across the world must continue.

CONCLUSION

Hearing loss is a leading disability worldwide but there are several preventable causes of hearing loss. Health education and improving awareness about the role of preventive medicine should be an ongoing endeavour by health professionals worldwide to reduce the impact of disabling hearing loss. Although major advances have taken place over the years in preventing deafness, there is still much more work to be done. This chapter gives a broad overview of the various preventable causes of hearing loss. For more exhaustive knowledge the reader is directed to the references listed.

FUTURE RESEARCH

- More clinical trials in humans need to be carried out to establish firmly the role of various therapeutic agents in the prevention of NIHL and ototoxicity.
- Gene therapy has been shown to have a role in preserving inner hair cells exposed to ototoxic agents in animals. Gene transfer and stem cell therapy for the cochlea may become a possible way of treating SNHL, but much more research has to be carried out in this area before it can have any clinical benefits.

KEY POINTS

- The World Health Organization (WHO) lists hearing loss as one of the 20 leading causes of burden of disease and as a most common cause of disability globally.
- Around half of all cases of hearing loss can be avoided through primary prevention.
- The incidence of hearing loss due to chronic suppurative otitis media (CSOM) has fallen dramatically in developed countries but still remains a leading cause in developing countries.
- CMV is the most common cause of congenital infections in humans, and congenital CMV (cCMV) is a leading cause of non-hereditary congenital sensorineural hearing loss (SNHL), which can be progressive.
- Treatment of cCMV started within the first month of life can prevent progression of hearing loss.
- About 16% of disabling hearing loss in adults is occupational noise-induced.
- Formation of the free radicals reactive oxygen species (ROS) and reactive nitrogen species (RNS) seem to be the molecular basis for noise-induced hearing loss (NIHL) and ototoxicity.
- Several antioxidants and other therapeutic agents may have a role in the prevention of NIHL and ototoxicity.
- In babies early identification of deafness and early intervention will result in significantly better outcome for language development.

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CHAPTER 54

HEARING AIDS

Harvey Dillon

SEARCH STRATEGY

The developments and research described in this chapter are in part based on a PubMed search using the keywords 'hearing aid'. To a small degree, they are also based on technical reports provided by manufacturers and on otherwise unpublished measurements and calculations by the author.

INTRODUCTION

Hearing aids partially overcome the deficits associated with a hearing loss. For a sensorineural hearing loss, there are several deficits to be overcome. Some sounds are inaudible. Other sounds can be detected because part of their spectra is audible, but may not be correctly identified because other parts of their spectra (typically the high-frequency parts) remain inaudible. The range of levels between the weakest sound that can be heard and the most intense sound that can be tolerated is less for a person with sensorineural hearing loss than for a normal-hearing person.

To compensate for this, hearing aids have to amplify weak sounds more than they amplify intense sounds. In addition, sensorineural impairment diminishes the ability of a person to detect and analyze energy at one frequency in the presence of energy at other frequencies.

Similarly, a hearing-impaired person has decreased ability to hear a signal that rapidly follows, or is rapidly followed by, a different signal. Hearing-impaired people are also less able to separate sounds on the basis of the direction from which they arrive. This decreased resolution (frequency, temporal and spatial) means that noise, or even other parts of the speech spectrum, will mask speech more than would be the case for a normal-hearing person.

The physiological origins of sensorineural hearing loss include loss of inner hair cell and outer hair cell function, reduced electrical potential within the cochlea and changes to the mechanical properties of the cochlea. The resulting auditory deficits mean that a person with a sensorineural hearing impairment needs a signal-to-noise ratio (SNR) greater than normal in order to communicate effectively, even when sounds have been amplified by a hearing aid. In contrast, a conductive impairment simply attenuates sound as it passes through the middle ear, so the amplification provided by hearing aids comes close to restoring hearing to normal.

To understand how hearing aids work, the physical characteristics of signals must be understood. These characteristics include the rate at which sound fluctuates (frequency), the time taken for a repetitive fluctuation to repeat (period), the distance over which its waveform repeats (wavelength), the way sound bends around obstacles (diffraction), the strength of a sound wave (pressure and sound pressure level), the break-up of a complex

sound into pure-tone components at different frequencies (spectrum), or into several frequency bands (octave, one-third octave or critical bands), and the degree to which a body of air vibrates when it is exposed to vibrating sound pressure (velocity and impedance).

The amplifiers inside hearing aids can be classified as linear or non-linear. For sounds of a given frequency, linear amplifiers amplify by the same amount regardless of the level of the signal or what other sounds are simultaneously present. By contrast, the amplification provided by a non-linear amplifier varies with the amplitude of the signal input to the amplifier. The degree of amplification can be represented as a graph of gain versus frequency (gain–frequency response), or as a graph of output level versus input level (I–O curve). The highest level produced by a hearing aid is known as the saturation sound pressure level (SSPL). The SSPL is usually estimated by measuring the output sound pressure level (OSPL) for a 90 dB SPL input (OSPL90).

The sound output by a hearing aid can be measured in the ear canal of an individual patient, or in a small coupler or ear simulator that has a volume similar to that of a real ear.

Hearing aids are described according to where they are worn. In order of decreasing size these categories are: body, spectacle, behind-the-ear (BTE), in-the-ear (ITE), in-the-canal (ITC) and completely-in-canal (CIC). For behind-the-ear hearing aids, further categorization is needed to distinguish between styles where the hearing aid receiver (the output transducer) is within the hearing aid case (receiver-in-the-aid, RITA) or within the ear canal (receiver-in-the-ear, RITE).

Decreasing size has been a constant trend during the history of the hearing aid. This history can be divided into six eras: acoustic, carbon, vacuum, transistor, digital and wireless. The last of these eras, which we are just entering, promises to hold advances at least as significant as in the eras that preceded it.

HEARING AID COMPONENTS

Hearing aids are best understood as a collection of functional building blocks. The manner in which a signal passes through these blocks in any particular hearing aid is indicated in a block diagram. The first block encountered by an acoustic signal is a microphone, which converts sound to electricity. Modern miniature electret microphones provide a very high sound quality, with only very minor imperfections associated with internal noise and sensitivity to vibration. Directional microphones, which have two entry ports, are more sensitive to frontal sound than to sound arriving from other directions. These enable hearing aids to improve the SNR by several decibels (depending on acoustic conditions) relative to omnidirectional microphones, and hence they can improve the intelligibility of speech in noise. Dual-microphone hearing aids can be switched automatically or by the user to be either directional, or omnidirectional, as required in different listening situations.

The small signals produced by microphones are made more powerful by the hearing aid amplifier. All amplifiers will distort the signal, by peak clipping it, if they attempt to amplify the signal to too high a level. Excessive distortion decreases the quality and intelligibility of sounds. To avoid distortion, and to decrease the dynamic range of sound, compression amplifiers are used in most hearing aids. These amplifiers decrease their gain as the level of the signal put into them increases, in much the same way that a person will turn down a volume control when the level becomes too high.

Amplifiers can represent sound in an analogue or a digital manner. The signals within analogue amplifiers have waveforms that mimic the acoustic waveforms they represent. Digital systems represent signals as a string of numbers. Performing arithmetic on the string of numbers alters the size and nature of the signals these numbers represent. Fully digital circuits may be constructed so that they process sounds in ways specific to each device, or may be able to perform any arithmetic operation, in which case the type of processing they do depends on the software that is loaded into them.

Filtering a signal is a common way in which hearing aids alter sound. Filters can be used to change the relative amplitude of the low-, mid- and high-frequency components in a signal. When the filters are made with variable, controllable characteristics, they function as tone controls operated by the user or the clinician. Filters can also be used to break the signal into different frequency ranges, so that different types of amplification can be used in each range, as required by the hearing loss of the hearing-impaired person.

Receivers are miniature headphones that use electromagnetism to convert the amplified, modified electrical signals back into sound. Their frequency response is characterized by multiple peaks and troughs, which are partly caused by resonances within the receivers, and partly caused by acoustic resonances within the tubing that connects a receiver to the ear canal. Inserting an acoustic resistor, called a damper, inside the receiver or tubing will smooth these peaks and troughs. A damper absorbs energy at the frequencies corresponding to the peaks, and this improves sound quality and listening comfort.

There are several other ways to put signals into hearing aids. A telecoil senses magnetic signals and converts them to a voltage. A radio receiver senses electromagnetic waves and converts them to a voltage. A direct audio input connector enables an electrical audio signal to be plugged straight into the hearing aid.

Users operate hearing aids via electromechanical switches on the case of the hearing aid or via a remote control. The hearing aid performs all its functions by taking electrical power from a battery. These batteries come in a range of physical sizes and capacities, depending on the power needed by each hearing aid and the space available.

HEARING AID SYSTEMS

Components can be combined into hearing aids in an extremely customized manner, such that individual components are selected for each patient and are located in

the position that best suits each ear. At the other extreme are modular aids, including some ITC hearing aids, and all BTE hearing aids, which are prefabricated in a totally standard manner. Many hearing aids fall somewhere between these extremes.

Increasingly, the hearing aids on each side of the head communicate with each other by wireless transmission so that their amplification characteristics (directionality, noise reduction processing, compression characteristics and input source) can remain coordinated as the environment changes or as the user varies a control. In some cases, the complete audio signal is transferred from one side of the head to the other, which enables a telephone signal to be heard in both ears and will enable superdirectional microphones to be developed.

Hearing aid amplification characteristics are programmed from a computer, via a suitable wired or wireless interface, to suit the hearing capabilities of each user. Often, more than one program is put into the hearing aid so that different amplification characteristics can be selected, automatically by the hearing aid or manually by the user, in different listening conditions.

The most effective way to make speech more intelligible is to put the microphone near the lips of the person talking. This markedly decreases noise and reverberation but requires a means of transmitting the signal from the microphone to the hearing aid wearer some distance away. Methods to do this currently include:

- magnetic induction from a loop of wire to a small telecoil inside the hearing aid
- radio transmission of a frequency-modulated or digitally modulated electromagnetic wave
- infrared transmission of an amplitude-modulated electromagnetic wave
- acoustic transmission of an amplified sound wave.

Each of these systems has strengths and weaknesses compared to the others. The first three offer a very large potential increase in SNR, and hence intelligibility. It can, however, be a challenge to adjust the hearing aid and wireless system together so that both the wireless system and the hearing aid individually provide maximum benefit to the wearer without the wireless input and microphone input signals interfering with each other. Increasingly, wireless receivers are being built into hearing aids, considerably improving cosmetic appearance and convenience. A major application of these systems is to make teachers more easily understood in classrooms, but they can be used by children and adults in other situations as well.

Wireless reception is also enabling hearing aids to conveniently accept electrical signals from a range of audio devices, including televisions, MP3 players, computers and mobile phones. In many cases, this connection requires an intermediary wireless relay device, as the current consumption of the ubiquitous Bluetooth receivers and transmitters precludes them from being directly built into hearing aids. While there have been problems with mobile phones causing interference in hearing aids, this problem is decreasing due to improvements in hearing aid design and changes in the mobile phone transmission system. Use of a mobile phone via hearing aids is now often trouble-free. There is the potential for hearing aids to become the audio portal to the world, and possibly not just for hearing-impaired people.

Assistive listening devices enable hearing aid wearers to receive sounds other than just by the amplification provided in a self-contained hearing aid. Assistive listening devices include the transmitter/receiver pairs already described for remotely sensing and sending speech or music, and devices that alter sound at its source (such as a telephone amplifier). Other types of assistive listening devices enable the aid wearer to detect alerting sounds (e.g. the doorbell, a telephone ring, a smoke alarm). Some do this by transmitting the sounds wirelessly to the hearing aids; others convert sound to other sensory modalities (such as flashing lights or vibrating shakers).

The long-established distribution and fitting system for hearing aids is being somewhat challenged by over-the-counter hearing aids, and their more modern cousin, hearing aids sold over the internet, and even by disposable hearing aids.

ELECTROACOUSTIC PERFORMANCE AND MEASUREMENT

The performance of hearing aids is most conveniently measured when the hearing aid is connected to a coupler. A coupler is a small cavity that connects the hearing aid sound outlet to a measurement microphone. Unfortunately, the standard 2 cc coupler is larger than the average adult ear canal with a hearing aid in place, so the hearing aid generates lower SPL in this coupler than in the average ear. This difference is called the real-ear-to-coupler difference (RECD), a quantity that is worth measuring in infants because they have ear canals considerably different from the average adult. A more complex measurement device, which better simulates the acoustic properties of the average adult ear canal, is called an ear simulator.

Test boxes provide a convenient way to get sound into the hearing aid in a controlled manner. These sounds can be pure tones that sweep in frequency, or can be complex, broadband sounds that, like speech, contain many frequencies simultaneously. Broadband sounds are necessary to perform meaningful measurements on many non-linear hearing aids. Increasingly, it is necessary for the test sound to approximate the spectral and temporal properties of speech so that the various signal processing algorithms in the hearing aid alter the gain in a manner representative of actual use. The measurements most commonly performed using test sounds are curves of gain or output versus frequency at different input levels, and curves of output versus input at different frequencies. The curve of output versus frequency when measured with a 90 dB SPL pure tone input level is usually taken to represent the highest levels that a hearing aid can create. Some other test box measurements that are less commonly performed are measures of distortion, internal noise and response to

magnetic fields. These measurements are used to check that the hearing aid is operating in accordance with its specifications.

Test box measurements are but a means to an end. That end is the performance of the hearing aid in an individual patient's ear. This performance can be directly measured using a soft, thin probe-tube inserted in the ear canal. Real-ear performance can be expressed as real-ear aided response (REAR; the level of sound in the patient's ear canal), real-ear aided gain (REAG; the level of sound in the ear canal minus the input level of sound near the patient) or as real-ear insertion gain (REIG; the level of sound in the ear canal when aided minus the level in the same place when no hearing aid is worn). Each of these measures requires the probe to be carefully located, but the requirements for probe placement are a little less critical for REIG than for REAG or REAR.

Both types of real-ear gain are different from coupler gain, partly because of the RECD already mentioned, and partly because the input to the hearing aid microphone is affected by sound diffraction patterns around the head and ear. The changes in SPL caused by diffraction are referred to as microphone location effects. Insertion gain is further different from coupler gain because resonance effects in the unaided ear form a baseline for the insertion gain measurement. This baseline, referred to as the real-ear unaided gain, provides the link between the REAG and the REIG.

Many factors can lead to incorrect measurement of real-ear gain. These include incorrect positioning of the probe, squashing of the probe, blockage of the probe by cerumen, background noise and hearing aid saturation. Fortunately, there are some simple checks one can do to verify measurement accuracy.

Feedback oscillation is a major problem in hearing aids. It happens when the amplification from the microphone to the receiver is greater than the attenuation of sound leaking from the output back to the input. Clinicians must be able to diagnose the source of excess leakage. Other problems that often have simple solutions include no sound output, weak output, distorted output and excessive noise.

HEARING AID EARMOULDS, EARSHELLS AND COUPLING SYSTEMS

An earmould or earshell is moulded to fit an individual's ear and retains the hearing aid in the ear. Premoulded canal fittings, available in a range of standard sizes and shapes, are an alternative way to connect the hearing aid to the ear canal. Whether custom-moulded or preformed, the ear fitting retains the sound bore, which is a sound path from the receiver to the ear canal. In many cases the fitting provides a second sound path, referred to as a vent, between the air outside the head and inside the ear canal. Where no vent exists, as in high-gain hearing aids, the fitting is said to be occluding. Where the cross section of the ear canal remains largely unfilled for its entire length, the hearing aid is said to be an open fitting, or an open-canal fitting. The three functions of an ear fitting are thus physical retention, transmission of amplified sound to the ear canal, and control of the direct sound path between the ear canal and the air outside the head.

There is a wide variety of physical styles of both earmoulds and earshells. These styles vary in the extent of the concha and canal that they fill. These variations affect the appearance, acoustic performance, comfort and security of retention of the hearing aid.

One unwanted consequence of a hearing aid can be an occlusion effect, in which the aid wearer's own voice is excessively amplified by bone-conducted sound. For many hearing aid fittings, vent selection is a careful juggle between choosing a vent that is big enough to avoid an unacceptable occlusion effect, but not so big that it causes feedback oscillations or limits the ability to achieve sufficient low-frequency gain and maximum output. For patients with mild or moderate hearing loss, the choice will often be an extremely open fitting comprising a BTE connected to thin tubing, or a wire connection for an ITE style, terminating in a preformed, flexible, perforated, dome-shaped canal fitting.

For any ear fitting with a vent or other direct path to the outside air, the speech range of frequencies can be subdivided into the vent-transmitted frequency range, the amplified frequency range and the mixed frequency range that is intermediate to these. Hearing aids perform very differently in each of these ranges.

The shape of the sound bore that connects the receiver to the ear canal affects the high-frequency gain and output of hearing aids. Sound bores that widen as they progress inwards (horns) increase the high-frequency output. Conversely, those that narrow (constrictions), whether by design or as a consequence of poor construction technique, decrease the high-frequency output. Horns have to exceed a certain length if they are to be effective within the frequency range of the hearing aid.

Dampers are used within the sound bore to smooth peaks in the gain–frequency response. Careful choice of the placement and resistance of the damper can also control the mid-frequency slope of the response.

The key to a well-fitting earmould is an accurate ear impression. This requires an appropriate material (medium viscosity silicone is good for most purposes), a canal block positioned sufficiently deeply in the canal and smooth injection of the impression material.

Tighter earmoulds or shells that reduce leakage of sound from the ear canal can be achieved by a variety of techniques. These techniques include taking an impression with the patient's jaw open, patting down the impression material before it sets, using viscous impression material and building up the impression in the patient's ear.

Earmoulds are made from a variety of materials. The most important difference between materials is hardness. Soft materials provide a better seal to the ear, but they deteriorate more rapidly, can be more difficult to insert and are more difficult to modify and repair. Earmoulds and earshells are routinely constructed by computer-aided

manufacture in which lasers guide the 'printing' of plastic based on a scanned image of the ear impression.

COMPRESSION SYSTEMS IN HEARING AIDS

The major role of compression is to decrease the range of sound levels in the environment to better match the dynamic range of a hearing-impaired person. The compressor that achieves this reduction may be most active at low, mid or high sound levels. More commonly, it will vary its gain across a wide range of sound levels, in which case it is known as a wide dynamic range compressor. Compressors can be designed to react to a change in input levels within a few thousandths of a second, or their response can be made so gradual that they take many tens of seconds to react fully. These different compression speeds are best suited to different types of people.

The degree to which a compressor finally reacts as input level changes is best depicted on an input–output diagram or on an input–gain diagram. The compression threshold, which is the input level above which the compressor causes the gain to vary, is clearly visible on such diagrams. The compression ratio, which describes the variation in output level that corresponds to any variation in input level, is related to the slope of the lines on these diagrams.

Simple compression systems can be classified as input-controlled, which means that the compressor is controlled by a signal prior to the hearing aid's volume control, or as output-controlled, which means that the compressor is controlled by a signal subsequent to the volume control. This classification is irrelevant for hearing aids with no volume control and inadequate for hearing aids with multiple, sequential compressors.

Compression systems have been used in hearing aids to achieve the following more specific aims, each of which requires different compression parameters. Output-controlled compression limiting can prevent the hearing aid ever causing loudness discomfort or the signal being peak clipped. Fast-acting compression with a low compression threshold can be used to increase the audibility of the softer syllables of speech, whereas slow-acting compression will leave the relative intensities unchanged but will alter the overall level of a speech signal. Compression applied with a medium compression threshold will make hearing aids more comfortable to wear in noisy places, without any of the advantages or disadvantages that occur when lower level sounds are compressed. Multichannel compression can be used to enable a hearing-impaired person to perceive sounds with the same loudness that would be perceived by a normal-hearing person listening to the same sounds. Alternatively, it can be used to maximize intelligibility, while making the overall loudness of sounds (rather than the loudness at each frequency) normal. Compression can be used to decrease the disturbing effects of background noise by reducing gain most in those frequency regions where the SNR is poorest. Gain reduction of this type increases listening comfort and with some unusual noises may also increase intelligibility. Finally, compression can be applied by using the combination of compression parameters that patients are believed to prefer, irrespective of whether there is a theoretical rationale guiding the application. Although these rationales are different, they have various aspects in common. Furthermore, many of them can be combined within a single hearing aid.

Despite the complexity, the benefits of compression can be summarized simply, but accurately, as follows. Compression can make low-level speech more intelligible, by increasing gain and hence audibility. Compression can make high-level sounds more comfortable and less distorted. In mid-level environments, compression offers little advantage relative to a well-fitted linear aid. Once the input level varies from this, of course, the advantages of compression become evident. Its major disadvantages are a greater likelihood of feedback oscillation and excessive amplification of unwanted lower level background noises.

DIRECTIONAL MICROPHONES AND ARRAYS

Other than the use of a remote microphone located near the source, directional microphones (which work by sensing sound at two or more locations in space) are the most effective way to improve intelligibility in noisy environments.

Directivity is most commonly achieved in hearing aids with first-order subtractive directional microphones, in which the output of one omnidirectional microphone is delayed and subtracted from the output of the other. This internal delay, relative to the physical spacing between the two microphone sound ports, largely determines the polar sensitivity pattern of these microphones. The head itself also affects the polar pattern.

These subtractive directional microphones inherently cause a low-frequency cut in the frequency response, for which the hearing aid signal processing often compensates by a low-boost characteristic, but which also causes greater internal noise in the hearing aid. Split-band directivity, which combines a directional response for the high frequencies with an omnidirectional response for the low frequencies, avoids this problem but, of course, provides no noise reduction for the low frequencies. Irrespective of the frequency range over which the microphone is directional, the complete hearing aid fitting will have directivity only over the frequency range for which the gain of the amplified sound path exceeds that of the vent sound path. In open fittings, this will likely be only half the speech frequency range. Whether achieved by split-band processing or by the acoustics of an open fitting, the resulting pattern of high-frequency directivity and low-frequency omnidirectional processing simulates the directivity pattern of normal hearing.

Additive directional arrays create directivity by adding together the output of two or more omnidirectional microphones. They do not create additional internal noise. To be effective, however, the microphones have to be separated by distances larger than a quarter of the

sound's wavelength. They are therefore less suitable for hearing aids, but are suitable for accessories such as handheld microphones.

These simple fixed subtractive and additive arrays have a fixed pattern of sensitivity versus direction of the incoming sound. Adaptive arrays, by contrast, have directional patterns that vary depending on the location, relative to the aid wearer, of background noises. Adaptive arrays automatically alter the way they combine the signals picked up by two or more microphones so as to have minimum sensitivity for sounds coming from the direction of dominant nearby noise sources. The multiple microphones that provide the input signals can be mounted on one side of the head or on both sides of the head.

The most sophisticated directional microphone arrays apply complex, frequency-dependent, adaptive weights to the outputs of each omnidirectional microphone before combining them. Like all directional microphone arrays, complex adaptive arrays work most effectively in situations where there is a low level of reverberant sound.

Directional microphones are effective when either the target speech or the dominant (rearward) noise source(s) are closer to the aid wearer than the room's critical distance (at which the reverberant and direct sound fields have equal intensity). In the special case of a close frontal talker and many distant noise sources, the improvement in SNR will approximate the directivity index of the hearing aid averaged across frequency.

The disadvantages of directional microphones include insensitivity to wanted sounds from the sides or rear, increased internal noise if used in quiet places, reduced localization accuracy if the two hearing aids act in an uncoordinated manner, and increased sensitivity to wind noise. These disadvantages can be minimized by intelligent switching (automatically or manually) between directional and omnidirectional modes, on the basis of noise levels and apparent SNR at the output of the omni and directional microphones.

All hearing aid wearers are candidates for directional microphones because all hearing aid wearers need a better SNR than people with normal hearing. Adaptive directional arrays that combine (via a wireless link or a cable) the outputs of microphones on both sides of the head produce a superdirectional response that should enable people with mild hearing loss to hear better than people with normal hearing in many social situations.

ADVANCED SIGNAL PROCESSING SCHEMES

Adaptive noise-reduction schemes, such as Wiener Filtering and Spectral Subtraction, progressively decrease the gain within each frequency region as the SNR deteriorates. Although they generally improve sound comfort and the overall SNR, these schemes do not change the SNR in any narrow frequency band. Consequently, they do not generally improve intelligibility. Other types of noise reduction include wind noise reduction, achieved by a low-frequency cut, and transient or impulsive noise reduction, achieved by limiting the rate at which the waveform changes.

Feedback oscillation can be made less likely by several electronic means. One simple technique is to decrease the gain only for those frequencies and input levels at which oscillation is likely. A second technique is to modify the phase response of the hearing aid so that the phase shift needed for oscillation does not occur at any frequency for which there is enough gain to cause feedback oscillation. A third technique involves adding a controlled internal negative feedback path that continuously adapts to maintain the gain and phase response needed to cancel the accidental leakage around the earmould or shell. A final technique involves making the output frequency different from the input frequency. Often, a combination of these techniques is used.

High-frequency components of speech can be made more audible by lowering their frequency. This can be achieved by transposition: moving sections of the spectrum to lower frequencies and superimposing them on the spectrum already in the lower frequency range. Alternatively, frequency compression is used to compress a wide frequency range into a narrower (and lower) one. While both frequency transposition and frequency compression can guarantee audibility of high-frequency sounds, they do not necessarily guarantee better intelligibility, as the speech components shifted down in frequency may interfere with perception of the speech components that were originally dominant in this lower frequency range. The range of possible frequency-lowering methods, frequency transformation maps and gain characteristics is large. Finding the best combination is made more difficult by the time it takes people to adapt to a highly altered spectrum and by our present uncertainty over how best to evaluate success.

There are various theoretically appealing methods for enhancing features of speech that have been tried in research experiments. These include exaggerating the peaks and troughs in the spectrum of a speech sound, increasing the amount of amplification whenever a consonant occurs, increasing the amplitude at the onset of sounds, lengthening and shortening the duration of particular sounds, simplifying speech down to a few rapidly changing pure tones, and resynthesizing clean speech based on the output of an automated speech recognizer. On the evidence available so far, however, none of these techniques will produce a worthwhile increase in intelligibility compared to conventional amplification, so there is as yet little motivation to include the processing within commercial hearing aids.

Various other signal processing algorithms have already been implemented in commercial hearing aids, or could readily be implemented. Reverberant energy that does not overlap other speech sounds can be removed, giving a crisper sound quality. Hearing aids can automatically categorize the listening environment they are in, and select amplification characteristics that have been preprogrammed into the hearing aid for each type of environment. Their data-logging systems can record how often each environment is encountered, and how the user

adjusts the hearing aids in each environment. Trainable hearing aids can learn from the adjustments the aid wearer makes, and infer how the aid wearer likes the hearing aid to be adjusted as the acoustics of the listening situation vary. Fine-tuning is therefore carried out by the hearing aid and the client together, rather than by the clinician. Active occlusion reduction processing enables a hearing aid to sound like an open-canal hearing aid, despite the ear canal being completely blocked. In addition to cancelling the occlusion-induced sound, active occlusion reduction cancels the vent-transmitted sound, enabling directional microphones to work over the entire frequency range, increasing their efficacy.

ASSESSING CANDIDACY FOR HEARING AIDS

Although the decision to try hearing aids is ultimately made by the patient, many patients will be in doubt as to whether they should acquire hearing aids and so will look to the clinician for a recommendation. This recommendation must take into account many factors other than pure-tone thresholds.

Initial motivation to obtain hearing aids has been shown to be a key determinant of whether patients continue to use them. This motivation reflects the balance of all the advantages a patient expects hearing aids will provide offset by all the expected disadvantages, irrespective of whether all these positive and negative expectations are realistic. The advantages expected by the patient are affected by the degree of disability they feel they have. Disability includes how much difficulty the person has hearing in various situations, referred to as activity limitation, and the extent to which a person is unable to participate in activities because of the hearing loss, referred to as participation restriction. The advantages and disadvantages expected by the patient are affected by what the patient has been told about hearing aids by others. Disadvantages potentially include the impact on a patient's self-image of wearing hearing aids. The clinician must attempt to discover a patient's expectations and modify those that are unrealistically low or unrealistically high. Although hearing aids help in quiet and in noise, they help much more in quiet, so hearing aids are more likely to be valued and used if the patient needs help hearing in quiet places.

When a clinician encounters a hearing-impaired patient who does not want hearing aids, the clinician should find out whether this is because the patient is not aware of the loss and/or the difficulty that he has compared to others, or because the patient, although acknowledging the loss, does not wish to wear hearing aids. If the latter is true, the patient's reasons should also be discovered.

Difficulty managing a hearing aid can greatly affect use, so the clinician must consider likely manipulation difficulties when determining candidacy and aid type. People with tinnitus often find that hearing aid use diminishes their problems, so tinnitus positively affects candidacy. The presence of central processing disorders and extreme old age can both affect candidacy, but not in a manner sufficiently predictable to affect the clinician's recommendation. People who are not worried that hearing aids will stigmatize them are more likely to acquire them, and people who more readily accept the presence of noise while listening to speech are more likely to use them. Several personality characteristics also make hearing aid acquisition, use and/or benefit more likely.

People with a severe to profound hearing loss are likely to receive more benefit from cochlear implants than from hearing aids. The most useful indicator of which device will be better for them is the speech score they receive for well-fitted hearing aids after some years of becoming accustomed to them. For infants, this is not possible so the decision to implant has to be based primarily on aided or unaided hearing thresholds (as well as requiring no medical or psychological contraindications). Cochlear implants and hearing aids generally provide complementary cues, whether they are worn in the same ear, or in opposite ears.

Vibrotactile or electrotactile aids are a worthwhile alternative for those with too much hearing loss to receive useful auditory stimulation from hearing aids but who do not wish to receive a cochlear implant, or for whom a cochlear implant is not suitable on medical or psychological grounds. Training in integrating the tactile information with visual information is essential.

Hearing aids should not be withheld just because speech scores obtained under headphones fall below some arbitrarily determined criterion. There are, however, several audiological/medical indications that should cause hearing aid fitting to be delayed until the cause of the problems has been resolved.

A clinician therefore has to consider a large number of factors that may affect candidacy for hearing aids, none of which has such a strong effect that the remaining factors can be ignored.

PRESCRIBING HEARING AID AMPLIFICATION

Amplification can be prescribed using a formula that links some characteristics of a person to the target amplification characteristics. Prescription formulae most commonly used are based on hearing thresholds, but some are based on suprathreshold loudness judgements.

Popular procedures for linear hearing aids include prescription of gain and output (POGO), National Acoustic Laboratories (NAL) and desired sensation level (DSL). For all of these, gain can be prescribed based on hearing thresholds alone. These formulae all contain variations of the half-gain rule (in which gain equals half of hearing loss, in dB), but the variations are so different that the resulting prescriptions differ greatly, especially for people with a sloping hearing loss.

For non-linear hearing aids, all available prescription procedures include some aspect of normalizing the loudness of suprathreshold sounds. Procedures such as loudness growth in octave bands (LGOB), International Hearing Aid Fitting Forum (IHAFF), DSL[i/o] curvilinear, the Cambridge method for loudness restoration (CAMREST)

and FIG6 aim to normalize loudness at all frequencies, at least for sounds with levels above the compression threshold of the hearing aid. Other procedures vary from loudness normalization in some way. ScalAdapt decreases the loudness of low-frequency sounds; CAM2 and NAL-NL2 normalize only the overall loudness. CAM2 aims to equalize the contributions that different frequency regions make to loudness, whereas NAL-NL2 aims for the sensation levels across frequency that will maximize calculated speech intelligibility. As each of the formulae has been revised, their prescriptions have become more similar to each other, but marked differences still occur.

There are some issues related to prescription that are not yet resolved, although there is considerable information available about each issue. How much do patients' preferences and performance with hearing aids change following weeks, months or years of experience with amplified sound? How loud (a perception, not a physical quantity) do patients like sound to be? Should tests of dead regions in the cochlea routinely be conducted? How severe does hearing loss need to be before it is considered unaidable? As signal level decreases, down to how low a level should gain keep increasing? How accurately must prescription targets be met? What is the best combination of fast and slow compression?

Maximum output (OSPL90) has to be prescribed so that loudness discomfort is prevented, but so that enough loudness can be obtained without the hearing aid becoming excessively saturated. In many procedures, the target OSPL90 is assumed to just equal the loudness discomfort level (LDL), in others it is predicted from threshold, in which case it may fall above or below an individual patient's LDL as measured in the clinic. For patients with mild to severe hearing loss, an acceptable sound quality is more likely if compression limiting controls maximum output than if peak clipping controls maximum output. Many patients with a profound loss, however, will benefit from the additional SPL that is achievable with a peak clipper.

People with conductive and mixed hearing loss require greater gain and OSPL90 than people with sensorineural loss of the same degree. For a variety of reasons, the gain needed to compensate for a conductive loss seems to be less than the amount of attenuation that the conductive loss causes in the middle ear. Consequently, the same is true of OSPL90.

Multimemory hearing aids can have a different prescription for each memory. These alternatives can be prescribed as variations from the baseline response prescribed for the first memory. The variations are designed to optimize specific listening criteria or for listening to different types of signals, such as music. People who wear their hearing aids in many environments, have more than 55 dB high-frequency hearing loss and require more than 0 dB low-frequency gain are most likely to benefit from multiple memories.

Neither gain nor OSPL90 should be any higher than is necessary for a patient. Otherwise, a hearing aid may increase hearing loss because of the resulting high-level exposure to sound. The risk of temporary or permanent noise-induced loss is greatest for patients with a profound loss and can be minimized by using non-linear amplification.

SELECTING, ADJUSTING AND VERIFYING HEARING AIDS

The first decision to be made when a clinician and patient select a hearing aid is whether a CIC, ITC, ITE, BTE–RITE, BTE–RITA (with standard tubing and earmould, or thin tube and earmould or instant-fit dome), spectacle, body, or a subvariety of any of these would be most suitable. For each style there are advantages relating to ease of insertion, ease of control manipulation, visibility, amount of gain, sensitivity to wind noise, directivity, reliability, telephone compatibility, ease of cleaning, avoidance of occlusion and feedback, ability to assess and fit in the same appointment, and cost. The weight given to each factor will vary greatly from patient to patient.

The need for specific features, such as a volume control, a telecoil and switch, a direct audio input and a directional microphone, must be determined on an individual basis. These needs will also influence the style of hearing aid selected. BTEs have more advantages than the other styles for a majority of patients.

Next, signal-processing options appropriate to the needs of the patient must be selected. Compression limiting is a more appropriate form of limiting than peak clipping if it can provide a high enough maximum output. In addition to compression limiting, a low compression ratio, active over a wide range of input levels, is appropriate for most patients. This low-ratio compression will provide advantages whether it is single- or multichannel, and whether it is fast- or slow-acting. Multichannel compression will provide greater speech intelligibility and/or comfort for patients with moderately or steeply sloping hearing loss, and the multichannel structure facilitates other features such as adaptive noise suppression and feedback suppression. The comfort advantages of adaptive noise reduction are greatest for patients who wear their hearing aids in a range of environments and who also require amplification across a wide range of frequencies. These same considerations apply to multimemory hearing aids, the only difference being that the patient, rather than the hearing aid, chooses the response variations. Feedback cancellation is most beneficial for patients with a severe or profound hearing loss, patients with a severe loss in the high frequencies but near-normal hearing in the low frequencies, any patients fitted with open canal devices, and any patient who wishes to use the telephone without using telecoil input. This combination makes it useful for nearly every client. Frequency lowering is advantageous for some patients though it is not yet possible to predict which patients will benefit. Trainability enables patients to take responsibility for fine-tuning their hearing aids.

Hearing aid fitting software provides a first approximation to the prescribed gain–frequency response target. The software must appropriately allow for the

acoustic configuration of the earmould shell or dome fitting. The approximation can be made even more accurate by incorporating the individual patient's RECD in the prescription. This increased accuracy in the precalculation is probably only worthwhile for hearing aids intended for infants, where measurement of the final real-ear gain is difficult.

Any signal-processing scheme that requires adjustment for each patient must also be supported by an appropriate prescription method. Measurement of real-ear gain is necessary unless the hearing aid has been adjusted in the coupler using the individual's (or at least an age-appropriate) RECD.

Because it is not possible to prescribe OSPL90 with complete precision, the suitability of maximum output should be subjectively evaluated before the patient leaves the clinic. A variety of intense sounds should be presented to the patient to ensure that the hearing aid does not make sounds uncomfortably loud. Maximum output must, however, be great enough for the patient to experience intense sounds as being loud. This can be assessed by presenting speech signals at a high level and asking the patient to report their loudness.

PROBLEM SOLVING AND FINE-TUNING

Many hearing aid fittings need to be fine-tuned, either electronically or physically, after the patient has had a week or two to try the hearing aids. When a patient has trouble managing hearing aids (inserting, removing, using the controls, changing the battery), reinstructing the patient may solve the problem. If not, the hearing aid should be physically modified or, if necessary, a different style chosen. Physical modification will also be necessary when a patient is suffering discomfort from the earmould, shell or case, or when the hearing aid works its way out of the ear.

Feedback oscillation has several potential solutions: reducing gain at selected frequencies; reducing the vent size; making a tighter earmould or shell; or changing the hearing aid to one that has more effective feedback cancelling and management algorithms.

Complaints about the patient's own-voice quality are particularly common. The most common cause is physical blocking of the ear canal, so the best cure is to add a vent, or increase the size of an existing vent, including using an open-fitting. Where feedback oscillation precludes that, the earmould or shell can be remade with the canal stalk extended down to the bony canal, preferably using a soft material. Own-voice problems are sometimes caused, and cured, by electronic variation of the gain–frequency response for high-level sounds.

Complaints about the tonal quality of amplified sounds are fixed by changing the balance of low-, mid- and high-frequency gain. The hard part is knowing when to ask the patient to persevere with a gain–frequency response in the expectation that it will eventually become the preferred response and confer maximum benefit to the patient.

When a patient complains about the clarity or loudness of speech, or the loudness of background noise, he/she must be questioned particularly carefully so that the acoustic characteristics of the sounds causing the problems can be identified. The clinician's first aim is to identify whether it is the gain for low or high frequencies, and the gain for low, mid or high levels, that should be adjusted. Only then can the appropriate hearing aid controls be adjusted.

In those cases where it is not clear which control should be adjusted, or by how much it should be adjusted, a systematic fine-tuning can be performed using one of two general methods. The first of these is paired comparisons, in which the patient is asked to choose between two amplification characteristics presented in quick succession. Multiple characteristics can be compared by arranging them in pairs. Paired comparisons can be used to adaptively fine-tune a hearing aid control if the settings compared in each trial are based on the patient's preference in the preceding trial.

The second general method for fine-tuning relies on the patient making an absolute rating of sound quality. The best amplification characteristic (out of those compared) is simply the characteristic that is given the highest rating by the patient. The absolute rating method can also be used to adaptively alter a chosen hearing aid control. This is achieved by deciding on a target rating (e.g. just right) and adjusting a control in the direction indicated by the patient's rating (e.g. too shrill or too dull).

The paired comparisons and absolute rating methods are best carried out while the patient listens to continuous discourse speech material, or other sounds they are complaining about. Depending on the complaint being investigated, this can be supplemented with recordings of commonly encountered background noises. The paired comparisons method is more sensitive when the differences between the conditions are small. Fine-tuning is usually carried out only for patients dissatisfied with the prescribed response, but it can be used for all patients if desired.

PATIENT EDUCATION AND COUNSELLING FOR HEARING AID WEARERS

People with a hearing impairment benefit from patient education and may benefit from communication training and counselling. These activities may be aimed at giving patients information about their hearing loss, developing skills needed to operate and care for their new hearing aids, improving listening skills, or changing patients' beliefs, feelings and behaviour relating to their hearing and communication. Providing appropriate education and counselling increases the likelihood that hearing aids will be fully used and that residual communication difficulties will be minimized.

It is difficult to help patients understand the variety of hearing aid styles and performance features that may be suitable for them. The benefits and cost implications of

each (including ongoing service costs, warranty and trial periods) have to be presented in a suitably simple manner.

Once they start using their hearing aids, first-time hearing aid users experience a new world of amplified sound and may benefit from guidance about how to gradually increase their range of listening experiences. The aim is to provide them with the best experiences first and to avoid having them become overwhelmed by sound. Patients need to know that their brains may take some time to adapt to hearing parts of speech and other sounds around them that they have not heard for some time.

A major part of educating the new hearing aid user has nothing to do with hearing aids! A wide range of hearing tactics and strategies can help the hearing-impaired person understand more in difficult listening situations. The first group of hearing strategies requires the listener to look carefully at the talker and the surroundings. The second group requires the listener to alter the communication pattern in some way. The final group requires the listener to manipulate the environment to remove or minimize sources of difficulty. Patients will benefit if family members and/or other frequent conversation partners participate in education sessions on these topics.

Patients will more easily appreciate and learn this material if it can be taught in a patient-centred, individual problem-solving method, rather than as a set of rules disconnected from their everyday lives. Communication training comprises training in the use of these hearing strategies, plus practice in listening to speech (synthetic training) or to the basic sounds from which speech is built (analytic training), especially in difficult listening conditions. Increasingly, communication training is being provided in packages that patients can use on their computer or DVD at home. Patients should be advised about protecting their remaining hearing and be made aware of where they can obtain support (from peer groups or other professionals) beyond that which the clinician can provide.

Hearing aids do not provide an adequate solution to all hearing problems, so patients must be made aware of other assistive listening devices that may help them. Clinicians should be aware that different people learn in different ways. Consequently, the same material should be taught in different ways to different patients, and clinicians should develop the flexibility needed to accomplish this.

Clinicians must be flexible regarding how and when they present information and carry out other procedures. It is, nonetheless, useful to have in mind a standard programme from which variations can be made as required.

ASSESSING THE OUTCOMES OF HEARING REHABILITATION

Clients and clinicians both benefit when the outcomes of the rehabilitation process (i.e. changes in the patients' lives) are measured in some way. Systematic measurement of outcomes can help clinicians learn which of their practices, procedures and devices are achieving the intended aims. Some measures can also help determine how the rehabilitation programme for individual patients should be structured and when it should be ended.

Outcome assessment can be based on an objective speech recognition test (the results of which depend hugely on the measurement conditions) or on a subjective self-report and/or the report of a significant other person. Speech test scores show the increase in the ability to understand speech in specific situations, whereas self-report measures more generally reflect the patient's views about the impact of rehabilitation.

Many self-report measures have subscales so that outcomes can be separately assessed for different listening environments. Outcome measures can assess the domains of benefit, defined as a reduction in disability (comprising activity limitation and participation restriction), device usage, listening effort, quality of life or the satisfaction that the patient feels.

Self-report measures that assess benefit can be grouped into various classes. First, patients can be asked to make a direct assessment of the benefit of rehabilitation. Alternatively, patients' views of their disability can be assessed both before and after the rehabilitation programme. The change in score provides a measure of the effects of rehabilitation. Measures obtained both before and after rehabilitation provide a more complete view of disability status and change. These difference measures probably assess change less accurately than those that directly assess benefit because they involve subtracting two scores.

The second way in which self-report measures differ from each other is the extent to which the items are the same for all patients or are determined individually for each patient. Results can more easily be compared across patients if a standard set of items is used for all patients. When the items are individually selected for each patient, however, the questionnaires become shorter and can more easily be incorporated within interviews with the patient. They are also more relevant to each patient.

There are thus four types of self-report measures: standard questionnaires that directly assess benefit (e.g. Hearing Aid Performance Inventory (HAPI); standard questionnaires that compare disability before and after rehabilitation (e.g. Hearing Handicap Inventory for the Elderly (HHIE); Abbreviated Profile of Hearing Aid Benefit (APHAB)); individualized questionnaires that directly assess benefit (e.g. Client Oriented Scale of Improvement (COSI)); and individualized questionnaires that compare disability before and after rehabilitation (e.g. Goal Attainment Scaling (GAS)).

Self-report measures also commonly assess hearing aid usage (which can now also be measured objectively with data logging) and are the only viable way to assess satisfaction. Some measures contain questions that address only one domain (benefit, use or satisfaction) whereas others address more than one domain. One comprehensive questionnaire, the Glasgow Hearing Aid Benefit Profile (GHABP), addresses all three dimensions, contains standard and individualized measures, and assesses benefit both directly and by comparing disability before and after rehabilitation. A very simple and widely used

questionnaire that assesses several domains with a single question each is the International Outcomes Inventory for Hearing Aids (IOI-HA).

Some questionnaires are designed to assess problems experienced with the hearing aid, although freedom from problems with the hearing aid is more properly viewed as a means to an end rather than a life-changing outcome.

While outcomes can be assessed any time after hearing aid fitting, the extent of benefit does not appear to stabilize until about 6 weeks after fitting. Hearing loss is associated with a decrease in many aspects of quality of life (such as increased depression) and use of hearing aids is associated with general improvements in health and quality of life. Causal relationships between these quantities are difficult to establish, however. Generic measures of health outcome are not efficient means by which a clinician can assess the outcomes of rehabilitation.

BINAURAL AND BILATERAL CONSIDERATIONS IN HEARING AID FITTING

Sensing sounds in two ears (binaural hearing) makes it possible for a person to locate the source of sounds and increases speech intelligibility in noisy situations. Wearing two hearing aids (a bilateral fitting) instead of one hearing aid (a unilateral fitting) increases the range of sound levels for which binaural hearing is possible. Bilateral fitting is thus more important when hearing loss is severe than when it is mild or moderate.

Accurate horizontal localization is possible because sounds reaching the two ears differ in level and in arrival time, and hence in phase. These cues are also present, but altered, when people wear hearing aids. Most hearing-impaired people, once they become used to the effect of their hearing aids on these cues, can localize sounds accurately to the left and right in the horizontal plane. Vertical localization and front–back localization, which are based on very high-frequency cues created by the pinna, are extremely adversely affected by hearing loss and are not significantly improved by hearing aids.

When speech and noise arrive from different directions, head diffraction causes the SNR to be greater at one ear than at the other. Further, the auditory system can combine the different mixtures of speech and noise arriving at each ear to effectively remove some of the noise. This ability is known as binaural squelch. Even presenting identical sounds to the two ears provides a small improvement in speech intelligibility over listening with one ear, a phenomenon known as binaural redundancy.

Wearing a second hearing aid will improve speech intelligibility in noise whenever it causes speech to become audible in the previously unaided ear. Achieving audibility of speech in both ears is a prerequisite to attending to the ear with the better SNR, and to benefiting from binaural squelch and binaural redundancy. Bilateral fitting of hearing aids has several other advantages. These include improved sound quality, suppression of tinnitus in both ears and greater convenience if one hearing aid breaks down or when one battery dies. A bilateral fitting may help prevent a problem sometimes associated with unilateral fittings: a unilateral fitting can lead to decreased speech processing ability in the unaided ear if this ear is deprived of auditory stimulation for too long, a phenomenon referred to as late-onset auditory deprivation.

The advantages of bilateral fittings also apply to patients with asymmetrical hearing thresholds. If such patients must receive a unilateral fitting, it may be generally advisable to fit the ear with thresholds closest to about 60 dB HL.

Bilateral fittings also have disadvantages: they cost more, are more susceptible to wind noise and are more difficult for some elderly people to manage. Also, some people regard two hearing aids as an indication of severe hearing loss and do not wish to be perceived in this way. For some people, binaural interference causes speech identification ability to be better when unilaterally aided than when bilaterally aided. The causes of this interference may lie in differences between the two cochleae, differences between the two hemispheres of the cortex or distortions in transfer of information from one hemisphere of the cortex to the other.

Because of the variability associated with speech intelligibility testing, conditions have to be chosen carefully to reliably demonstrate bilateral advantage or detect binaural interference on an individual patient. To best demonstrate bilateral advantage, loudspeaker positions for speech and noise should be chosen to maximize the effects of head diffraction and binaural squelch. To best detect binaural interference, speech and noise should emanate from a single, frontal loudspeaker, so that the effects of head diffraction and binaural squelch are minimized. In either case, speech tests with steep performance–intensity functions should be used. A method for predicting whether individual patients will benefit more from a unilateral or bilateral fitting is urgently needed.

SPECIAL HEARING AID ISSUES FOR CHILDREN

When a child is born with a hearing loss, early provision of hearing aids is essential if he or she is to learn to speak and listen with the greatest possible proficiency. Hearing aids should be provided by 6 months of age. If cochlear implants are a better option, these should be implanted by 12 months of age. Children with bilateral loss should receive bilateral hearing aids. There is some uncertainty over optimal treatment for children with unilateral loss, mild loss or auditory neuropathy.

For the hearing aids to be optimally adjusted, frequency-specific hearing thresholds must be determined separately for each ear. No matter what type of transducer is used, the small size of a baby's ear complicates the interpretation of hearing threshold. This difficulty is overcome either by expressing threshold in decibels sound pressure level (dB SPL) in the ear canal, or by expressing it as equivalent adult hearing threshold in decibels hearing level (dB HL).

BTE hearing aids are most likely to be provided, in conjunction with soft earmoulds, until the child is at least 8 years old (and possibly much older). The hearing aid should contain features that will enable the child to receive the best possible signal. This is likely to include an audio input socket and/or telecoil and/or internal wireless receiver, so that there is some means to receive wireless transmission. Ideally, the wireless device should be able to automatically attenuate the local microphone whenever the person wearing the transmitter talks.

To communicate effectively, normal-hearing children learning language need a better SNR than do adults. They also understand speech less well than adults at very low sensation levels. These observations may lie behind the empirical finding that hearing-impaired children prefer more gain than adults with the same hearing loss. Compared to adults, they almost certainly do not need any more real-ear gain for high-level sounds, they probably prefer more gain for medium level sounds, and they almost certainly need more gain for low-level sounds.

There is an even greater need for wide dynamic range compression in hearing aids for children too young to manipulate the volume control than there is for adults. Similarly, infants have an even greater need than adults for directional microphones and adaptive noise-reduction systems. These algorithms also have potential disadvantages but they should be provided if the clinician has confidence in the automated manner in which the hearing aid selects them.

To achieve a certain real-ear gain, young children need less coupler gain than do adults, because children have smaller ear canals. An efficient way to allow for small ear canals is to measure RECD before prescribing the hearing aid, and to calculate the coupler gain that will result in the target REAG. A faster but less accurate way is to use age-appropriate values of RECD.

The maximum output that has been prescribed should be evaluated by observing the child when intense sounds are made and, for those over approximately 6 years of age, by assessing the loudness of these sounds.

Hearing aid fittings can be evaluated by speech testing (for those over 3 years of age), paired-comparison preference testing (for those over 6 years of age), and subjective reporting by the child, the parents or the teachers, whether informally or using systematic methods such as Parents' Evaluation of Aural/Oral Performance of Children (PEACH) and Meaningful Auditory Integration Scale (MAIS). The audibility of speech can be estimated by calculating the articulation index (also known as the speech intelligibility index (SII)) or assessed by measuring the presence, latency and perhaps morphology of the cortical responses elicited by speech sounds. The availability of speech to the child can be indirectly assessed by measuring the child's language development.

Effective amplification for young children is not possible without the support and understanding of parents. The audiologist must therefore inform and support the parents in a variety of ways. One way to provide ongoing habilitation is to base the service activities around goals determined jointly by the audiologist and the parents (and by the child when old enough). Information provided to parents includes safety aspects of amplification and hearing loss. Hazards include battery, earmould or hearing aid ingestion, excessive exposure to noise, physical impact and failure to detect warning signals if amplification is not functioning correctly.

CROS, BONE-CONDUCTION AND IMPLANTED HEARING AIDS

In the CROS (contralateral routing of signals) family of hearing aids, hearing aid components on opposite sides of the head are wirelessly linked. Basic CROS aids are most suitable for people with unilateral loss. CROS aids consists of a microphone on the side of the head with a deaf ear, combined with an amplifier, receiver and open earmould or shell on the side with a normal-hearing ear. Adding a microphone to the side of the better ear converts it to a BICROS hearing aid, which is suitable for patients with loss in both ears. A transcranial CROS has all the components in one ear, but sends a signal across the head by bone conduction. CROS hearing aids must be carefully fitted to ensure the aid wearer receives, in a single cochlea, an appropriate balance of sounds reaching the two sides of the head.

Bone-conduction hearing aids output a mechanical vibration instead of an airborne sound wave. They are most suited to people who, for medical or anatomical reasons, cannot wear a hearing aid that occludes the ear in any way, or for those who have a large conductive loss in either ear. For patients with normal external and middle ears, bone-conduction hearing aids cannot stimulate the cochlea as effectively as do air-conduction hearing aids because of the relative inefficiency of the bone conduction pathway. For patients with maximal conductive hearing losses, whether or not there is also a sensorineural loss, bone-conduction hearing aids can stimulate the cochlea as strongly as air-conduction hearing aids. Prescriptions for air-conduction hearing aids can be converted into bone-conduction prescriptions by using available standards for the thresholds of hearing for air- and bone-conducted sound. Bone-conduction output is specified in terms of output force level instead of OSPL and in terms of acoustomechanical sensitivity instead of gain.

Disadvantages of non-implanted bone-conduction hearing aids include their wearing comfort and the limited sensation level they can provide. A commonly used form of bone-conduction hearing aid is the bone-anchored hearing aid, in which the vibrations are transmitted to the skull via an embedded titanium screw, thereby increasing stimulation of the cochlea by about 15 dB compared to a bone conductor applied to the skin. Bone-anchored hearing aids have been used successfully for patients with unilateral or bilateral conductive or mixed loss. They are also routinely being fitted to people with unilateral sensorineural loss, referred

to as single-sided sensorineural deafness. The output levels they can achieve make them suitable for people with cochlear loss up to about 45 dB HL for head-worn devices and up to about 60 dB HL for body-worn devices. Bone-anchored hearing aids can provide greater cochlear stimulation than air conduction hearing aids for patients with air-bone gaps greater than about 30 dB.

A variety of other middle-ear implants have been researched, and several have been approved for routine use. Middle-ear implants may have only the output transducers surgically implanted or may be combined with implanted microphones and batteries to form completely implanted hearing aids. Four types of output transducers have been used: magnets enclosed by a coil that rely on the inertial mass of the magnet, magnets mounted on the middle ear chain driven by a remote coil, and piezoelectric or electromagnetic stimulators anchored to the mastoid bone and vibrating the middle ear chain. Three types of microphones have been used: external microphones, microphones implanted under the skin on the scalp or in the ear canal, and transducers that are driven by the vibration of the middle ear chain.

Several implanted hearing aids are now commercially available. For some clients, particularly those with mixed hearing loss, middle ear implants may have advantages related to freedom from occlusion, amplification gain and bandwidth, stimulation level and invisibility of the device. Fully implanted devices have additional advantages arising from there being no external parts. Candidacy criteria are still developing.

FUTURE RESEARCH

- Research is needed to better understand the barriers preventing many people with hearing loss from seeking rehabilitation through acquiring and wearing hearing aids. Equally important, psychological research is needed to find effective ways to overcome those barriers and so reduce the time that hearing loss adversely affects quality of life. Related to this, knowledge is needed on the minimal degree of hearing loss at which hearing aids become effective, and how this minimal aidable loss is also determined by the cognitive, psychological, psychoacoustic and lifestyle characteristics of each patient.
- At the other end of the hearing loss spectrum, prediction tools that take account of individual characteristics are needed to indicate which patients are likely to function better were they to receive one or more cochlear implants, rather than continue to wear hearing aids. Fully implantable hearing aids require a method of implanting microphones that enables them to achieve the same sensitivity and low internal noise levels that hearing aids mounted outside the head currently achieve.

KEY POINTS

- Hearing aids have become sophisticated devices, the amplification characteristics of which are adjustable to optimize listening over a wide range of hearing loss configurations and degrees.
- Digital signal processing has largely solved the previous major problem of feedback oscillation (whistling) even when the hearing aid is fitted to the ear with an acoustically open connection. Such open fittings leave the patient's own voice sounding more natural.
- Although nothing can reverse the reduced precision of signal analysis that inevitably accompanies sensorineural loss, hearing aids can restore audibility, and in many listening situations can improve the signal-to-noise ratio of the signal delivered to the ear, so that good speech understanding occurs despite the reduced analysis ability of the damaged auditory system.
- Wireless technology is increasingly being built into hearing aids, and in situations where a remote microphone can be positioned near the talker or source, speech understanding in noise can be superior to that enjoyed by someone with normal hearing.
- Compared to the number of people with significant hearing loss, hearing aids are an under-utilized solution. This applies even in developed countries, but much more so in the developing world.

ACKNOWLEDGEMENT

The material in this chapter is a slightly edited version of synopses of each of the chapters in the chapter author's book *Hearing aids*.[1] The reader is referred to that book, which is comprehensively referenced and elaborates on all the information covered in this chapter.

REFERENCE

1. Dillon H. *Hearing aids*. 2nd ed. New York: Thieme; 2012.

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CHAPTER

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BEYOND HEARING AIDS: AN OVERVIEW OF ADULT AUDIOLOGICAL REHABILITATION

Lucy Handscomb

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: aural rehabilitation, hearing therapy, hearing assistance technology and language service professionals.

INTRODUCTION

Hearing aids are often seen as the mainstay of adult audiological rehabilitation, and their benefits are undeniable. However, they are far from being a panacea. While some patients attend hearing services seeking hearing aids and are satisfied with the help they provide, others have needs which cannot be met by amplification alone. This chapter gives an overview of approaches to aural rehabilitation other than hearing aid fitting and provides guidelines about when they may be needed.

NON-TECHNOLOGICAL REHABILITATION

Hearing therapy

Hearing therapists provide one-to-one support to people with hearing loss and related problems (particularly tinnitus). The term aural rehabilitation specialist may also be used, and in some countries this kind of service is provided by clinical psychologists. Hearing therapy involves counselling and supporting patients as they adjust to living with hearing loss. For many people, the experience of losing hearing goes far beyond the frustration of mishearing speech, although this in itself is a significant problem. Hearing loss can necessitate changes in lifestyle, both at work and at leisure. It can change the way one interacts with others, making conversation effortful and tiring, and profoundly alter one's sense of identity.[1] An in-depth interview study found that people felt their hearing loss held them back in life, made them feel 'left out' and caused considerable emotional distress.[2] Personal relationships are also negatively affected, with couples in particular feeling that hearing loss places a strain on their interactions.[3, 4] People who are having difficulty adjusting to life with hearing loss may well benefit from an opportunity to discuss their feelings and explore ways of coping, whether or not they are also fitted with hearing aids (or cochlear implants). A group in particular need of urgent referral to rehabilitation services are those who develop sudden hearing loss, who often report feelings of utter bewilderment and confusion. In a medical emergency, it is easy for emotional needs to be neglected, but timely emotional support is just as important as prompt medical treatment.

Specialist rehabilitative support can also be beneficial to people who feel ambivalent about using hearing aids. There are many reasons why people feel unsure about using amplification including perceived stigma and lack of confidence.[5, 6] An opportunity to spend time discussing one's ambivalence in a supportive environment is likely to be more cost-effective than fitting hearing aids that are likely to remain unused.

A hearing therapy appointment is likely to consist of counselling and joint goal-setting, using a collaborative approach between patient and therapist. Hearing assistance technology may also be demonstrated (see 'Types

of technology' below). Most patients are seen for several appointments over a period of weeks or months as they develop and practise new coping strategies.

Access to specialist aural rehabilitation services is usually via ENT and may require a referral form or letter.

Aural rehab groups and lip reading classes

Some audiology clinics offer rehabilitation through an aural rehab group. As well as being cost-effective for clinics, groups have the advantage of bringing people with hearing loss together to share experiences and ideas and to support each other. Many encourage the participation of partners too. There are many different group formats, but typically participants meet weekly for five or six sessions of around 2 hours each. Groups usually follow a problem-solving format, with a facilitator encouraging participants to generate ideas themselves about how to manage difficult communication situations and then to role-play them with each other. A review of research into aural rehab groups found fairly consistent evidence that they are effective in reducing the amount of restriction people feel in relation to their hearing loss (as measured on self-report scales) and in improving use of communication strategies.[7] The author also points out that participants' comments after attending a group are overwhelmingly positive; people enjoy group sessions and perceive them to be very worthwhile.

Outside the healthcare system a number of groups and classes exist for people with hearing loss. Perhaps the most popular are lip-reading classes, often held in community centres and adult education colleges. These are usually run by trained lip-reading teachers and involve a mixture of lip-reading exercises and communication tips. Although effects of class attendance on lip-reading ability are equivocal, qualitative research indicates that people value their classes very highly.[8] Hard-of-hearing groups or clubs are also available in some areas which offer peer support and an opportunity to take part in social activities without being restricted by hearing problems.

The UK charity Hearing Link offers week-long residential rehabilitation courses for adults with acquired profound hearing loss and their families. Such courses are hugely beneficial to families struggling to adjust to the far-reaching changes that profound deafness brings. Referral from a medical professional – such as an ENT doctor – is normally required in order to secure funding to attend a course.

Auditory training

Auditory training attempts to improve speech discrimination in people with hearing loss by presenting a variety of listening tasks involving phonemes, words and sentences. Exercises such as listening in background noise or attending to sound in one ear and not the other might be included. Traditionally, auditory training was conducted one-to-one in clinics, but now a number of computer-based auditory training programs are available, enabling users to practise regularly at home with minimal intervention from clinicians. A systematic review of 13 computerized auditory training studies found firm evidence that performance on auditory training tasks improves significantly with practice.[9] Some (but not all) studies also showed generalization of learning to untrained tasks, which of course has more real-world benefit. The authors of the review conclude that better-quality evidence is needed, but computerized auditory training is already an increasingly popular option for motivated individuals who are willing to put in the practice time required.

The voluntary sector

A great deal of support for people with hearing loss and related problems (such as tinnitus and balance disorders) is provided by charities and voluntary organizations. Charities are very often an invaluable source of information; many produce fact sheets about a range of hearing-related topics and some have telephone and email helplines available. Regular magazines for members can help people with hearing loss feel better informed and connected to others with similar problems. There are also several forums available via the internet and social media through which people can share information and offer support. These are perhaps particularly helpful to younger people with hearing loss, who may otherwise feel rather isolated.

TECHNOLOGY OTHER THAN HEARING AIDS AND COCHLEAR IMPLANTS

The need for additional technology

While both hearing aids and cochlear implants are capable of providing great benefit, there are situations in which many users find them inadequate. In spite of recent advances in digital signal processing, interference from background noise is still a primary cause of dissatisfaction among hearing aid users and, in some cases, a reason for giving up with hearing aids altogether.[10, 11] Distance can also cause difficulties; many hearing aid users complain that, while they hear well in their own living room, they struggle to understand a speaker in a large church or hall. The two problems of intrusive background noise and distance are combined when, for example, fellow students cough and shuffle in a lecture theatre. Telephone use can also be problematic, particularly as many people experience interference when a mobile phone is placed close to their hearing aid. People with more severe hearing loss may find television unclear, even when using hearing aids, and disputes over TV volume have been found to be among the most frequent sources of irritation when one half of a couple has hearing loss.[12] Moreover, there are situations in which most people take their hearing aids or speech processors off (particularly while bathing or in bed) but still need to be aware of signals such as smoke alarms or alarm clocks. Additional technology goes some

way towards solving all of these difficulties but, as will be discussed, its use is not widespread.

Types of technology

Additional technology can broadly be divided into two categories: assistive listening devices (ALDs), which are designed to improve audibility, and alerting devices, which use visual or tactile signals as a substitute for sound. Collectively they are sometimes known as hearing assistance technology (HAT).

Connectivity

There are three ways in which hearing aids or speech processors can be linked with audio equipment and ALDs.

- **Telecoil:** A telecoil is a small receiver fitted as standard in most behind-the-ear (BTE) and many in-the-ear (ITE) hearing aids. When active, it picks up signals from an electromagnetic field created by an induction loop, which itself can be linked to a range of amplifiers and audio devices. The telecoil can be switched on and off by the hearing aid user, but it first needs to be activated by the person fitting the hearing aid. Switching the telecoil on normally disables the hearing aid microphone, thus reducing background noise substantially. A neckloop can be plugged directly into a standard headphone socket, essentially allowing hearing aids to function as headphones.
- **Direct audio input:** Some BTE hearing aids can have a small electric cable plugged into them either directly or via an adapter which clips onto the bottom of the hearing aid; this is sometimes known as a 'shoe' or 'boot.' The other end of the cable can be plugged into a standard headphone socket, enabling the user to receive the sound directly into the hearing aid without interference from surrounding noise.
- **Bluetooth:** In recent years a number of Bluetooth-compatible hearing aids have become available. Most of these require an intermediary device called a streamer (worn round the neck) to enable the hearing aid to pick up signals from paired Bluetooth-enabled devices such as smart phones and tablets. At the time of writing, some hearing aids which use Bluetooth technology without the need for a streamer are also available.

All of the options above enable users to connect their hearing aids directly to a range of standard audio devices and also to specialized ALDs.

Personal listening equipment

A number of devices exist which are designed to improve sound quality, increase amplification and reduce interference from background noise when listening to live speech, television, radio or music. All of the devices described below allow people direct control of the volume of sound going through their hearing aids, meaning that companions without hearing aids can listen alongside them comfortably.

FM SYSTEMS

These consist of a receiver connected to the user's hearing aids by means of direct audio input or a neckloop, and a transmitter (with an in-built microphone) which can be placed close to any sound source or clipped onto a speaker's clothing. The transmitter converts sound into a radio signal which is then picked up by the receiver. When linked to the FM system, hearing aids will only pick up signals from the receiver and not extraneous noise. FM systems are particularly valuable in classrooms and lecture theatres, where the speaker tends to be at a distance from the listener and may be moving about, and they are often used by hearing-impaired children in school. The sound quality is excellent.

LOOP SYSTEMS

A less expensive option than an FM system for those purchasing equipment privately is a portable loop system. At their most basic, these consist of a neckloop, an amplifier 'box' with volume control and a hardwired microphone which can be placed close to any sound source. Wireless microphones are also available. Portable loops tend to perform less well at a distance than FM systems but are useful in domestic environments and when travelling. Listening to a driver or travelling companion in a car or bus via the amplifier and neckloop cuts out interference from engine and road noise.

A convenient option for TV listening is a room loop. An amplifier is connected to the television (usually by means of a SCART lead) and a loop wire emerging from it is fixed to the skirting board around the room. Once installed, the user only needs to switch the amplifier on and activate the telecoil in the hearing aids in order to be able to listen through the loop from anywhere in the room.

INFRARED SYSTEMS

Sound can be converted to an infrared signal which is then transmitted wirelessly to a receiver worn by the hearing aid user with a neckloop attached. This is another neat and convenient option for TV watching, but it has the disadvantage that the signal can easily be interrupted if the user moves around.

STREAMERS

As well as giving access to Bluetooth, streamers can be used with compatible hearing aids as portable amplifiers with wireless microphones or plugged into personal music players. An additional adapter is needed in order for a streamer to be used as a TV listener.

Using personal listening equipment without hearing aids

Many personal amplifiers and FM systems can be used with headphones as an alternative to neckloops or direct

audio input. These make them accessible to non-hearing aid users and to people who need or prefer to be without their hearing aids temporarily, perhaps due to an ear infection.

An inexpensive personal amplifier with headphones can be particularly helpful as a communication device in hospital. Many hearing-impaired patients on a ward will not have their hearing aids in, either because they were left behind during an emergency admission or because they are uncomfortable to wear in bed. This sometimes results in confidential and sensitive information being spoken at high volume by hospital staff and being clearly audible to all those around. Speaking to the patient via a simple amplifier with headphones slipped over the ears can make all the difference to confidentiality and dignity.

ALDs in public places

Commercial loop systems have been installed in many public buildings such as theatres, cinemas, meeting halls and places of worship. Loops can also be found at reception desks, ticket counters, banks, post offices and in taxis. Where a public loop system has been installed, the user only needs to switch their hearing aid to telecoil to be able to benefit from clearer sound. The presence of a loop system is normally indicated by an ear symbol with the letter T (for telecoil).

Some theatres use infrared listeners instead of a loop system and will loan receivers to hearing-impaired customers at the box office.

Telephones

LANDLINES

Many conventional telephones available from mainstream suppliers have a small inductive coupler fitted into the receiver, which enables the hearing aid user to listen via the telecoil and thereby reduce ambient noise. If this does not provide adequate volume, a range of portable amplifiers is available, which either strap onto the receiver or can be connected to a corded phone between the handset and the base.

A wide range of telephones, both corded and cordless, is available with amplifiers built in, some of which are very powerful. Many have tone control as well, which can improve clarity. A selection of additional features are also available, such as large buttons for people with visual impairment, extra receivers to allow another person to assist with the conversation and adapted handsets which can be held against the mastoid bone to allow hearing via bone conduction.

Adapters can be bought to enable landlines to be heard via a streamer.

MOBILE PHONES

For many years the majority of hearing aid users found it impossible to use a mobile phone with a hearing aid, due to an unacceptably high level of interference. While interference continues to be an issue, more recently manufacturers have taken the needs of their hearing-impaired customers into account and a universal rating scheme has been introduced (although its use is not compulsory). Mobile phones can be given a rating of 1 (poor) to 4 (excellent) depending on how well they perform with hearing aids set to microphone (M) or telecoil (T). The very best mobile phone for hearing aid users would be rated M4/T4.

Even better clarity can still be obtained by the use of a mobile phone-compatible neckloop or a Bluetooth streamer (discussed above). These enable the phone to be held right away from the hearing aid and have the added advantage of making the ringtone audible in the hearing aid itself.

Some older people may be put off by additional gadgetry but want to use a mobile phone for security. A range of basic mobile phones is available with amplified speech and large buttons but with a minimum of extra features.

TEXTPHONES

People with severe or profound hearing loss can communicate using a textphone – sometimes known as a Minicom – which can send and receive typed messages over a phone line. Two people with textphones can communicate directly with each other or a textphone user can communicate with a conventional phone user via an operator. This system predates the internet and has been a lifeline to many, but its use is now in decline owing to the multiple methods of mainstream text communication available via computers and smart phones.

Alerting devices

STAND-ALONE EQUIPMENT

There are many quite simple and inexpensive devices which can be used to alert people with hearing loss to telephone ringers, door bells, alarm clocks, smoke alarms and baby monitors. Most use a loud sound accompanied by a flashing light. Some devices can be supplied with a vibrating pad which can be placed under the pillow to wake the user at night.

PAGERS

A practical option for many people is a pager, which can be linked to several devices at once. Normally, a small unit clipped onto clothing or worn on the wrist will vibrate when any device it is linked to makes a sound, and a small light indicates which device has been activated. Larger vibrating units can be supplied for night-time.

WIRED-INSYSTEMS

It is possible for an electrician to connect doorbells and telephones to the house lights so that they flash on and off in response to sound. However, this is a less popular option now that pagers are widespread.

HEARING DOGS

People with severe or profound hearing loss can apply to have a hearing dog. Such dogs are specially trained to alert their owners and lead them to the source of the sound when the doorbell, phone or other device is activated. They are also taught a 'danger' signal in response to a smoke alarm. Like other assistance dogs, hearing dogs wear a special coat and can accompany their owners in public places. Many deaf people feel more confident with a hearing dog by their side.

Research into HAT use and benefit

There is a paucity of research into the use of HAT and its benefits. However, when ALD users have been asked about their impressions, responses have been largely positive. An internet survey of 356 ALD users reported that the majority rated their ability to understand speech as 'better' or 'much better' when using a personal listening device as compared to when using their hearing aids or cochlear implants alone.[13] Ratings were particularly high for listening through an ALD when part of an audience. A qualitative interview study conducted by the charity Action on Hearing Loss also cites several very positive comments about the clarity of listening via a loop system.[14] FM systems have been subject to more rigorous investigation than other technology and a consistent finding is that their performance is superior to hearing aids alone when listening to speech in noise.[15–17] A smaller-scale study also showed use of a more basic listening device with headphones to result in fewer communication breakdowns in informal discussion.[18]

Despite these benefits, it appears that the use of any type HAT is not very widespread. A large survey of almost 3000 Australian adults aged 49 and over found that 11% owned hearing aids but only a quarter of these had used any kind of ALD over the past year.[19] The most commonly used type of ALD was a telephone amplifier, while only a tiny proportion had used a personal listening device. A survey of around 500 adults over 65 in the US found that only 5% of those with hearing loss used any kind of ALD, as compared to 26% who used hearing aids (notably, of those who did use ALD, all but two reported high levels of satisfaction).[20] In the UK, the aforementioned study conducted by Action on Hearing Loss found that only a few interviewees had ever used HAT of any kind. This study gives lack of awareness as a principle reason for non-use of HAT; most people simply did not know that technology other than hearing aids was available. A similar theme emerged from an earlier qualitative study in Canada.[21] Other potential barriers to HAT use which were identified by this study were concerns over adapting to new technology and lack of confidence. Previous research has found that ALDs may be rejected because of the extra effort required to set them up.[15] For personal listening systems particularly, a further possible barrier is that people may feel awkward about asking others to speak through a microphone on their behalf.

Chisolm et al. noted that, in previous trials of FM systems, most participants have not continued to use their devices afterwards despite clear benefits to hearing.[17] These authors tried a different approach, offering intensive support with FM systems over five visits which included discussion and role-play of difficult listening situations in addition to instructions for use. They found that 30 out of 36 of their participants were continuing to use their FM system a year later. Further research in this area is needed, but it seems that successful use of ALDs could potentially be increased by seeing them as an integral part of aural rehabilitation rather than an 'add-on'.

LANGUAGE SERVICE PROFESSIONALS

In certain situations where communication is difficult, a person with severe or profound hearing loss may find that even additional equipment is inadequate. In such cases, communication support is available from specially trained people known as a language service professional (LSP). LSPs are most often used to enable participation in meetings, conferences and training courses. They can also provide support in court rooms and at medical appointments. Different types of LSP are listed below.

- **Sign language interpreter:** Interpreters translate what is being said into sign language in real time and also 'voice over' what a deaf person is signing. Interpreting usually happens live but is sometimes provided by video link. Hands-on interpreters are available to deaf–blind people and 'relay' interpreting is possible for deaf people who use sign language from another country.
- **Lip speaker:** Lip speakers repeat exactly what a speaker is saying but without voice. They use clear lip patterns and always face the front to enable people to lip-read.
- **Speech-to-text:** A speech-to-text operator either types an instant summary of what is being said or converts speech to text verbatim using a special keyboard, with text appearing on a screen. Increasingly, this service is being provided over the internet, making it more widely available.
- **Notetaker:** A notetaker's role is to support a deaf student by taking lecture notes on their behalf, thus enabling them to look up and lip-read the lecturer.

OBTAINING HAT AND ACCESSING LSP

Unlike hearing aids, HAT is not provided by the UK National Health Service. Devices can often be purchased from private hearing aid dispensers or directly from the companies which supply them by mail order or online. However, some equipment and services are available free of charge to the user.

Domestic equipment

In the UK, equipment for home use by both adults and children can usually be supplied by the local social services. A referral can be made by the audiology department or an individual can refer themselves (or their child). Normally, an assessment of needs will be arranged before equipment is supplied. The range of equipment provided by social services is generally quite limited, but a major advantage is that help with set-up is available and faulty devices can be replaced.

The UK fire service offers domestic fire safety assessments on request. It is able to provide smoke alarms with flashing lights and vibrating pads free of charge to individuals with hearing loss.

Equipment for work

It is an employer's responsibility to supply additional equipment or support necessary for an employee with hearing loss to perform his role. This might be an amplified telephone, a loop system for meetings or a speech-to-text operator for a training course. In the UK, help with funding can be applied for through the government's Access to Work scheme.

Equipment for education

In the UK, FM systems for school children with hearing loss are provided by the Local Education Authority. In higher and further education, students with hearing loss can apply for a Disabled Students Allowance. A certain amount of money is allocated per year, depending on the level of disability, and the student is able to spend this on either equipment, communication support or a combination of both.

CONCLUSION

The consequences of hearing loss are far-reaching. Many people with hearing loss could benefit from a range of rehabilitation services, either as an alternative or as a supplement to hearing aids or cochlear implants. While it is not the responsibility of ENT doctors to provide such services, it is important to be aware of what is available in the local area and to be able to make appropriate referrals and recommendations.

KEY POINTS

- Hearing therapists provide one-to-one support to people with hearing loss and related problems (particularly tinnitus).
- In a medical emergency, it is easy for emotional needs to be neglected, but timely emotional support is just as important as prompt medical treatment.
- Auditory training attempts to improve speech discrimination in people with hearing loss by presenting a variety of listening tasks involving phonemes, words and sentences.
- A telecoil is a small receiver fitted as standard in most BTE and many ITE hearing aids. When active, it picks up signals from an electromagnetic field created by an induction loop, which itself can be linked to a range of amplifiers and audio devices.
- In recent years a number of Bluetooth-compatible hearing aids have become available.
- FM systems are particularly valuable in classrooms and lecture theatres, where the speaker tends to be at a distance from the listener and may be moving about, and they are often used by hearing-impaired children at school.
- There are many quite simple and inexpensive devices which can be used to alert people with hearing loss to telephone ringers, door bells, alarm clocks, smoke alarms and baby monitors.

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CHAPTER 56

AGE-RELATED SENSORINEURAL HEARING IMPAIRMENT

Linnea Cheung, David M. Baguley and Andrew McCombe

SEARCH STRATEGY

Data in this chapter may be updated by Medline searches using the keywords: age-related hearing loss, presbyacusis and presbycusis. The search strategy included the keywords diagnosis and management for sourcing the relevant subsections. Some references have been hand-sourced from the authors' personal collections on this subject.

DEFINITION, BACKGROUND AND PATHOPHYSIOLOGY

DEFINITION

Age-related hearing loss may be defined as a progressive bilateral sensorineural hearing loss of mid to late adult onset, where underlying causes have been excluded. Strictly speaking, age-related hearing loss is a diagnosis which excludes hearing loss caused by primary factors including loud noise exposure, intrinsic otological disease (e.g. otosclerosis, chronic otitis media and Ménière's disease), head injury, ototoxic drug therapies and underlying medical conditions (e.g. atherosclerosis, diabetes, hypertension, Paget's disease of bone, myxoedema). 'Age-related hearing loss' is used interchangeably with 'age-associated hearing loss' and these are now terms in widespread use, replacing 'presbyacusis' (presbycusis in US spelling). Presbyacusis was originally derived from 'presbyacusia', used to describe a loss of high-frequency hearing acuity in the elderly observed when tested with tuned whistles designed by Sir Francis Galton for testing hearing.[1, 2] Age-related hearing loss is associated, in the majority of cases, with an audiogram that reveals greatest hearing loss at higher frequencies. Indeed, the definition of age-related hearing loss is also somewhat arbitrary; there is no agreed age above which an individual suffers from age-related hearing loss and below which one does not.

BACKGROUND

It would appear that auditory acuity is at its best in the late teenage years and into one's early twenties.[3] From then on there is a progressive decline,[4] which is greater for men[5] and for manual workers.[6]

It has generally been believed that at the extremes of life, there is relatively little progression of hearing loss, with most deterioration taking place in between. However, as the number of people surviving to extreme old age increases, there are emergent indications that the rate of progression of hearing loss in the 10th decade increases.[7]

Whilst the rate of deterioration tends to increase with age, the timing of onset is variable, with the greatest variability in the middle years (40–60 years). It appears that once a certain amount of hearing loss has occurred (approximately 75–80 dB HL), further progression is very slow,[8] particularly in the higher frequencies.[9] The variability of onset in the middle years can be explained by the concept of accelerated ageing.[10] In all likelihood this represents some form of hereditary/genetic degenerative process[11, 12] or some alternative process causing a sensorineural hearing loss. Table 56.1 summarizes the causes of sensorineural hearing loss.

TABLE 56.1 Causes of sensorineural hearing loss, shown in order of prevalence and with approximate values where available

Cause	Prevalence (%)
Age	Ultimately 100?
Noise	<5
Idiopathic	5–30
Ear infections	
Ménière's disease	
Head injury	> 0.004
Ototoxicity	
Non-syndromic genetic	0.7 (probably greater)
Syndromic genetic	0.3
Systemic illness (e.g. meningitis, renal failure, diabetes)	
Others (e.g. autoimmune, otosclerosis, acoustic neuroma)	

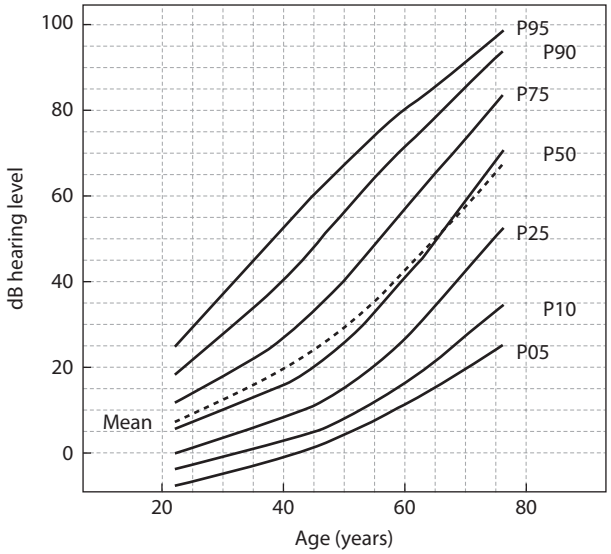

Figure 56.1 Hearing threshold and population percentiles for better ear at 8 kHz. Redrawn from Davis[14] with permission from Whurr Publishers, London.

TABLE 56.2 Prevalence of hearing impairment with age

Age group (years)	Prevalence (%)
18–30	2
31–40	5
41–50	10
51–60	17
61–71	30
71–80	53

Average threshold >30 dB HL; all causes; both ear average. Reproduced with permission from Davis A. *Hearing in adults.* London: Whurr Publishers; 1995.[14]

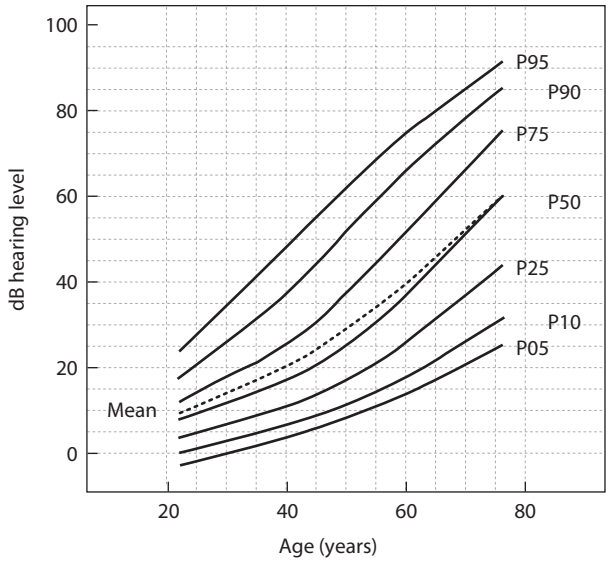

Figure 56.2 Hearing threshold and population percentiles for 4, 6 and 8 kHz average (better ear). Redrawn from Davis[13] with permission from Whurr Publishers, London.

It is probable that all these processes affect the cochlea in remarkably similar fashion but with a unique temporal course both in terms of onset and progression.[13] Almost invariably, databases displaying age-related, average hearing thresholds for either screened or unscreened populations show a marked increase in the rate of progression of the hearing loss once into the sixth decade. This is demonstrated in Table 56.2 and Figures 56.1 and 56.2.

It is, therefore, reasonable (although somewhat arbitrary) to attribute high-tone hearing loss in an individual over the age of 50 to age-related changes (in the absence of any alternative explanation). Under the age of 50 an alternative diagnosis should be considered. In the absence of any other clear diagnosis (e.g. noise, family history, ototoxic medication, systemic illness), it is reasonable to describe the loss as 'a non-syndromic, genetic, degenerative hearing loss'. With genetic mapping continuing apace, mutations and/or genetic explanations are becoming increasingly documented.[12, 13]

In addition, the problems and consequences of age-related hearing loss are compounded in the elderly as a result of additional degenerative processes in the central nervous system. This can result in a relative loss in neuronal plasticity, a loss of cognitive abilities and other sensory modalities, in particular, sight. The diagnosis of age-related hearing loss is, therefore, made on clinical grounds on the basis of a recognizable constellation of features.

Relatively recent research[15–17] tells us that age-related hearing loss impacts on psychological well-being as well as physical ability. Decreasing hearing acuity correlates with an increased incidence of falls,[18] depression[19] and dementia[20] in the elderly.[21] The feelings of imprisonment and anxiety that result from social isolation lead to reduced higher cognitive functioning which can in turn increase the economic and societal burden of age-related hearing loss.[22] It is therefore ever more important as the life expectancy of our population increases to make the diagnosis and offer treatment early.

PATHOPHYSIOLOGY

External and middle ear

Involvement of the middle ear in age-related hearing loss was suggested by Toynbee.[23] Several age-related changes occur in both the outer and middle ear (Table 56.3),[24] however these do not significantly contribute to resultant hearing loss.[25]

Inner ear

Schuknecht et al. hypothetically divided the age-related changes in the cochlea associated with hearing loss into six distinct types based on their histopathological studies.[26–28] Although this classification is deduced from a relatively small sample (n = 21), other authors[24, 29–31] have correlated clinical results with pathological findings leading to the consensus that this represents useful distinctions in the pathological substrate of age-related hearing loss.

Table 56.4 summarizes the different types and their pathological defining features known to date. The neural type of histopathology was believed to be the most common,[24] though a longitudinal study[31] has indicated that metabolic, and mixed sensory-metabolic phenotypes increase with increasing age.

TABLE 56.3 Summary of age-related changes in the outer and middle ear

Outer ear	Middle ear
Increased cerumen production	Stiffening, thinning, loss of vascularity of tympanic membrane
Reduced epithelial migration	Arthritic changes and ossification in ossicles and ossicular joints
Increased hair growth	Degeneration of middle ear muscles
Potential collapse of ear canal	Calcification of cartilaginous support of Eustachian tube
Enlargement of pinna	

TABLE 56.4 Histological subtypes of age-related hearing loss and the known defining features to date

Type	Defining features
Sensory	Loss of hair cells and sustentacular cells[32] at the basal end of the organ of Corti (Figures 56.3 and 56.4)
Neural	Degeneration of cochlear nerve neurons Cochlear ganglion cell loss
Vascular or metabolic	Atrophy of the cochlear stria vascularis Loss of strial tissue in the cochlea[33] primarily in the apical and middle turns of the cochlea[24]
Mechanical or cochlear conductive	Stiffened cochlear basilar membrane An increase in the number of fibrillar layers of the basilar membrane[6]
Intermediate	Submicroscopic changes of the cochlear duct[28] Possible changes in intracellular organelles involved in cell metabolism, decrease in synapse numbers and changes in endolymph composition[24, 25]
Mixed	A combination of the other five subtypes

The various histological types have been correlated with audiogram patterns in post-mortem studies:[26] sensory and neural histopathological types are associated with the common high-frequency loss pattern, with associated poor auditory discrimination abilities. In contrast, the strial type has been associated with a 'flat' audiogram and good discrimination abilities also seen in age-related hearing loss. It is not possible, however, to determine the site of pathology from audiometric data alone.[24] Given that the Schuknecht classifications are essentially hypothetical, it is not yet known whether these different histopathology patterns reflect the existence of a number of different underlying mechanisms for age-related hearing loss. Whilst cochlear hair cell loss has been the main focus of research into the pathophysiology of ARHL, the auditory neuroscience community have become interested in a precursive state wherein degeneration of cochlear synapses precedes hair cell loss and threshold elevation.[34] Whilst there is presently more evidence for this in animal models than humans, it does raise the possibility of novel potential therapies.[35]

Central nervous system

Age-related degenerative change in the central nervous system was suggested as a contributory factor in age-related hearing loss by Hinchcliffe.[36] Such change in the auditory system is relatively subtle[25] and highly variable;[24] a significant consequence is reduced plasticity, which in part accounts for the marked acclimatization period required for the elderly to obtain maximum benefit from hearing rehabilitation by amplification.[37, 38]

Central auditory processing abilities decline with age, and decrements in tests of temporal fine structure and word recognition and discrimination have been reported.[39, 40] Over recent years, there has been a strong association demonstrated between age-related hearing loss and cognitive impairment including dementia and depression.[21, 41] Although a causal relationship has not been proven, it is suggested that behavioural mechanisms such as the social isolation resulting from the chronic hearing loss results in reduced activation of the central auditory pathways leading to decreased cognitive performance.[19]

Animal models of age-related hearing loss, specifically inbred mice, have shed some light on mechanisms and pathological changes with age[33] and, in particular, upon metabolic mechanisms of age-related hearing loss. These include recent research into the possible roles of mitochondrial DNA mutations and reactive oxygen species.[42] It is hoped that such studies will lead to the development of targeted therapies applicable to humans although this prospect still remains distant.

GENETICS

The genetics of congenital, childhood and early-adult onset forms of deafness have been intensively studied and many of the responsible genes have been identified. However, the genetics of age-related deafness in humans are much more poorly defined and no associated genes or loci have been identified. The available data do, however, implicate genetic

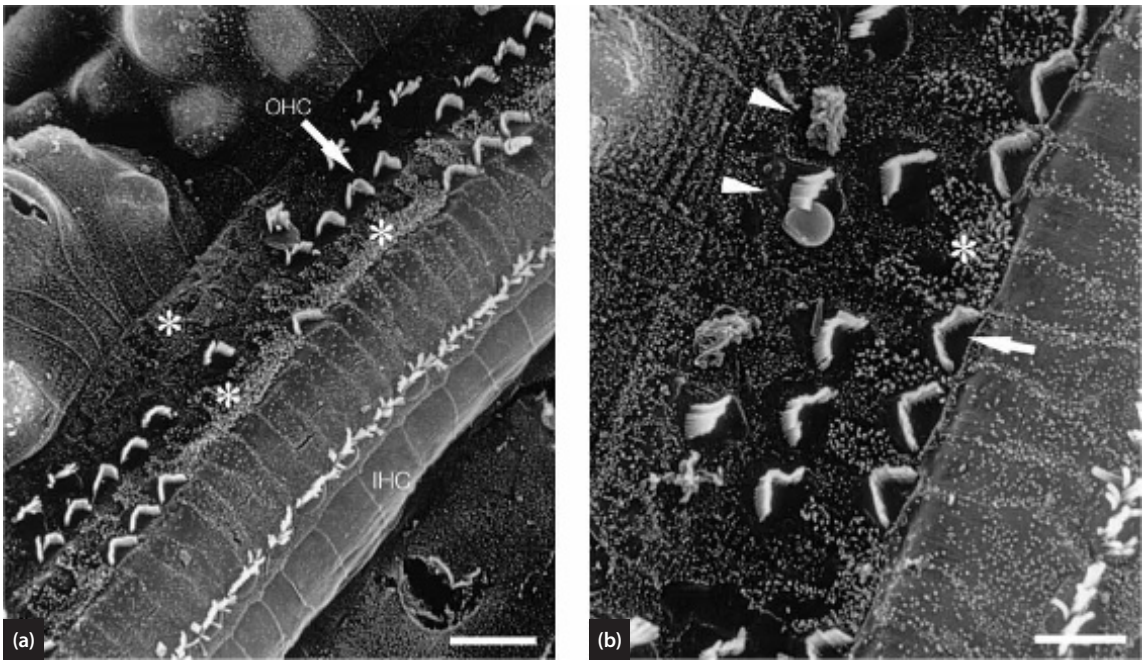

Figure 56.3 Scanning electron micrographs showing typical examples of the aged mammalian organ of Corti from a guinea pig. (a) The outer hair cell (OHC) rows show substantial patches where hair cells are probably missing (*) and in the process of degenerating, although the inner hair cells (IHC) are relatively undamaged. Scale bar: 20 µm. **(b)** Detail of the OHC region showing different levels of damage to the hair bundles of OHCs (arrowheads) including complete loss (*). The underlying hair cell is probably missing. Scale bar: 10 µm. Courtesy of Dr D.N. Furness, Mackay Institute of Communication and Neuroscience, Keele University.

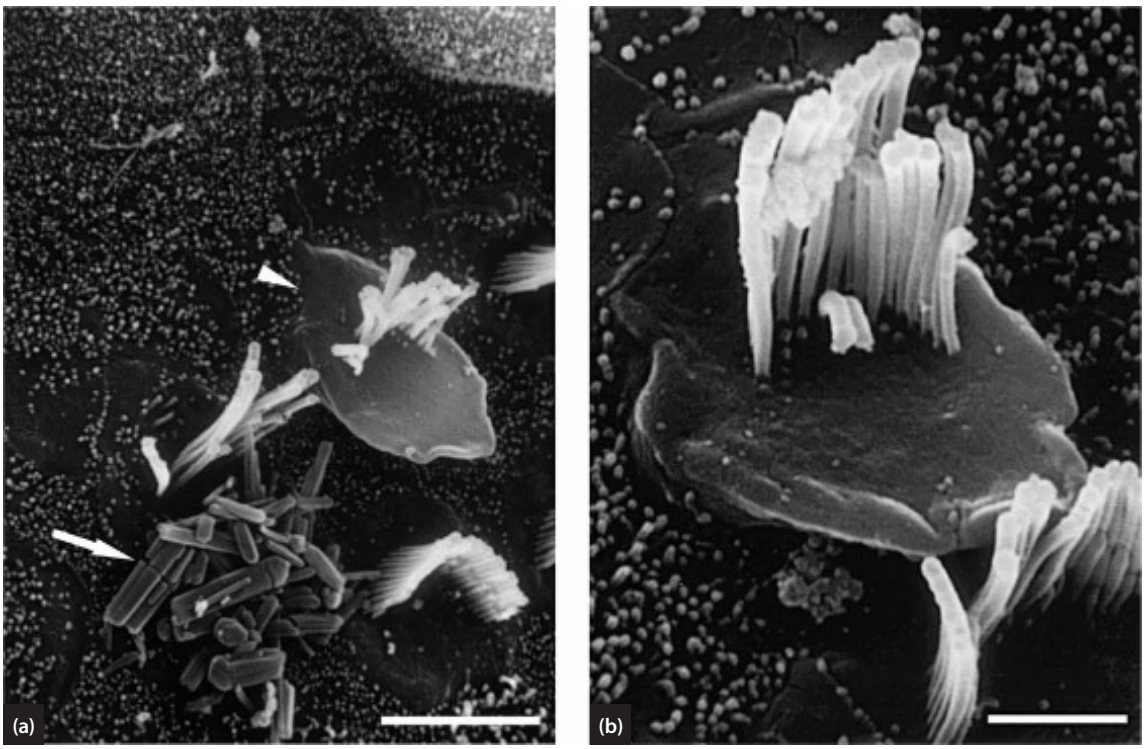

Figure 56.4 Scanning electron micrographs showing details of outer hair cell damage in an aged guinea pig. (a) Degenerating outer hair cells display different types of damage including, here, extrusion of the apical surface (arrowhead) and debris, probably from adegenerating cell (arrow). Scale bar: 10 µm. **(b)** Detail of the extrusion of an outer hair cell apex. The hair bundle itself is relatively intact. Scale bar: 2 µm. Courtesy of Dr D.N. Furness, MacKay Institute of Communication and Neuroscience, Keele University.

factors in causing age-related hearing loss. Standard methods for determining the genetic component of a condition involve twin studies, examining concordance rates in monozygotic versus dizygotic twins, and family-based case-control studies. Two studies assessing the contribution of genetic factors to age-related audiology thresholds and hearing loss are available. A Swedish twin study examined audiometric hearing thresholds in 557 male twin pairs aged 36–80 years, identified from the Swedish Twin Registry. Similarity in audiogram thresholds was consistently greater for monozygotic versus dizygotic twins in all age ranges, but particularly so in the youngest group. These findings were interpreted as showing that genetic and environmental factors are important sources of variation in hearing at all ages, with genetic factors being particularly important for younger men.[43]

A family-based case-control study examined members of the US Framingham Heart Study and Framingham Offspring Study cohorts. It compared aggregation of audiometric hearing threshold in spouse pairs versus sibling or parent–child pairs. It also examined the aggregation of hearing level in pairs where one member had age-related deafness, with either a sensory or a strial audiogram pattern. Significant aggregation of hearing thresholds was found in parent–child and sibling pairs, but not in spouse pairs. Parent–child and sibling aggregations in hearing threshold were also found when pairs including a member with a sensory or strial deafness phenotype were analyzed separately. Heritability (the proportion of population variance attributable to genetic variation) was estimated for the sensory age-related deafness phenotype at 35–55% and for the strial phenotype at 25–42%. All of the aggregations were stronger in women than in men.[44] A genome-wide linkage screen, carried out on the Framingham study population, failed to map any age-related hearing loss gene conclusively, perhaps because the test population lacked the power to do so.[45]

Genetic studies of mice have made an important contribution to the field of deafness and conclusively indicate that genetic factors can be important in age-related hearing loss.[12, 46] Many different inbred mouse strains show accelerated age-related hearing loss and in at least ten of these the gene involved is *ahl*, which maps to mouse chromosome 10.[47, 48] This gene is inherited in a recessive pattern. This same gene is also implicated in susceptibility to noise-induced hearing loss and to aminoglycoside-induced hearing loss.[49, 50] A mitochondrial genome variant that interacts with and modifies this locus has been identified.[51] A more recent study indicates that the *ahl* gene is the mouse orthologue of cadherin 23, a human deafness gene associated with non-syndromic hearing loss and Usher syndrome.[52] At least two other mouse age-related hearing loss loci, designated ahl2 and ahl3, exist,[53] with alh2 mapped to mouse chromosome 5.[54] Finally, it has been suggested that mitochondrial genome mutations or variations, either inherited or acquired with age, may contribute to age-related hearing loss in humans.[42, 55] The available evidence indicates that genetic factors are important in age-related hearing loss and in the determination of age-related hearing thresholds. The strength of the genetic effect in and the mode(s) of inheritance of the age-related deafness clinical phenotype are not yet clear, and much work is needed to identify the genes involved.

RISK FACTORS

Risk factors implicated in primary age related hearing loss (i.e. where underlying causes have been excluded) are not clear. Epidemiological studies have suggested two main categories of modifiable factors that may contribute to the development of age-related hearing loss: environmental factors (noise exposure,[56–58] cigarette smoking and alcohol use[59]) and health comorbidities (hypertension,[60] blood hyperviscosity[61] and cardiovascular and cerebrovascular disease[42]). Studies have failed to illustrate consistent associations of these factors with the development of age-related hearing loss in contrast to those considered non-modifiable factors such as increasing age, male gender and possible genetic predisposition. It is likely that these and other factors have complex interactions with each other and age-related hearing loss, but more work is needed to determine the associations between these factors.

DIAGNOSIS AND MANAGEMENT

HISTORY

Typically, the patient will describe a slow and insidious hearing problem. Often, the first symptom is difficulty in hearing conversation, particularly in the presence of background or competing sound. Normally, the description involves a lack of clarity rather than a loss of volume. The symptoms have often been present for many years and are frequently more of a problem to the rest of the family. Sometimes, tinnitus may be the presenting feature. These symptoms are, of course, no different from any other sensorineural hearing loss. As the hearing loss progresses, so the nature of the complaint may change. Patients may complain of a more obvious hearing problem and frequently having to ask others to repeat themselves. The television is often louder than is comfortable for other members of the household. These problems can all lead to significant domestic distress.

As the hearing loss worsens, a complaint of deafness becomes more apparent and recruitment may be described.[62] Recruitment is the abnormal growth in the perception of loudness by an individual with a hearing loss[63] and is exemplified by the line: ‘Speak up! No, don’t shout, I’m not deaf!’

Tinnitus is a frequent accompanying symptom (30–50%) and not uncommonly may be the most troublesome.[64] There is a strong and well-demonstrated correlation between worsening hearing thresholds and the presence of tinnitus.[65] The prevalence of troublesome tinnitus rises from 5% in the under-thirties to 16% in the over-sixties.[66]

Even if not particularly severe, the hearing loss may lead to social isolation, and depression may ensue.[19] This should be specifically asked for, especially in the elderly who often have less opportunity for social contact.[67] A positive family history of hearing loss in old age may often be encountered.

The frequency of falls increases with worsening hearing thresholds in old age.[16, 18] This can compound problems with social isolation and reduced overall mobility, and should be addressed with involvement of relevant allied

healthcare professionals and specialists as required. Given this relationship, recurrent falls in an individual may prompt earlier screening and enquiry into hearing loss.[22]

When making the diagnosis, it is important to be aware of other significant causes of sensorineural hearing loss.[68] Significant head injury, meningitis, serious systemic illness, often involving previous aminoglycoside treatment, and a strong family history of early hearing loss (indicating a non-syndromic hereditary/genetic degenerative hearing loss) should all be enquired for.

EXAMINATION

The patient will be older, normally at least in their fifties, to display some of the early symptoms. Typically, otological examination will be normal. However, evidence of either active or quiescent otitis media does not preclude the diagnosis. Age-related hearing loss occurs in all individuals to varying degrees and so appropriate allowance for coexistent pathologies will need to be made.

Investigations

Unfortunately, there is no specific test for age-related hearing loss. The first and often only investigation required is a pure-tone audiogram. Various audiometric patterns have been described and classified but the relevance of these is still debatable. Some argue that they indicate damage to different parts of the cochlea or auditory nerve. Most commonly, though, the audiogram shows a hearing loss which tends to be worse at the higher frequencies. Often in the early stages of the condition, the only finding will be a mild high-frequency hearing loss. As the condition advances there tends to be progressive loss of the middle (1 and 2 kHz) and even low (250 and 500 Hz) frequencies.[9]

If sufficient asymmetry exists, a magnetic resonance scan may be required to exclude an acoustic neuroma. No definite evidence exists on this issue but a difference of more than 10 dB averaged over the frequencies 0.5, 1, 2 and 4 kHz or 20 dB or more at any single frequency would be reasonably pragmatic indications. Scanning in the presence of unilateral tinnitus has been suggested. The presence of any associated middle-ear pathology will require further investigation on its own merits, as the diagnosis of age-related hearing loss in this group of individuals is only possible once all other reasonable causes of hearing asymmetry are excluded.

DIAGNOSIS

In an individual over the age of 60, with normal examination findings and a symmetrical (often predominantly high-tone) hearing loss, a diagnosis of age-related hearing loss is fairly secure. Diagnostic difficulties may arise if the patient is younger than expected or the condition seems to be progressing more quickly than expected. Here, there is often an overlap with the increasingly recognized and described, heterogeneous group of genetically determined, progressive, degenerative hearing losses. More often in this group there will be a family history of early age-related hearing loss. Whether this actually matters in terms of management of these patients remains a moot point.

MANAGEMENT

The management and rehabilitation of age-associated hearing loss (AAHL) can be directed to three broad areas: psychological and practical (both non-specific) and sensory (specific).

Non-specific management

Unfortunately, there is no way to return hearing thresholds to their pre-elevation levels of acuity. It is beneficial to give advice regarding the optimization of an individual's acoustic environment. This involves the reduction of background noise (as far as possible), face-to-face conversation to maximize exposure to non-verbal communication cues and an explanation of the problem, to allow the legitimization of their hearing loss.

Involvement of allied health professionals and general practitioners can offer psychological counselling and support in cases of severe hearing loss, especially in the presence of other comorbidities. This will help the patient to acknowledge their problem, which is often one of the first steps on the road to rehabilitation.

Practical measures for individuals with a more severe hearing loss include wireless headphones for use with their television, volume-controllable telephones and louder doorbells, often with an alternative alerting system such as a flashing light or vibrating pager system. Hearing dogs can take on such a role as well as providing a valuable source of companionship in the elderly. Lip-reading classes can be extremely valuable. As the hearing loss becomes more severe, a hearing aid or cochlear implant can take on an increasingly beneficial role.

Specific management

Systematic review has demonstrated that hearing aids are of benefit, even in cases of mild or moderate hearing loss,[69] and the benefits include improved health-related quality of life as well as listening abilities.

Binaural hearing has been shown[70, 71] to produce an approximate additional 10 dB signal to noise ratio advantage. Not surprisingly, then, a recent National Institute for Health and Clinical Excellence (NICE) report has suggested that there is significant benefit to patients in being fitted with binaural hearing aids.[72] The evidence suggests that digital aids are a substantial improvement upon the now obsolete analogue devices,[73] and there is very good evidence of the importance of follow-up and rehabilitative support after fitting to ensure maximum benefit and hearing aid use. Furthermore, success with hearing aid use in older adults has been shown to be greater in those where use is supported by their family members and in those with a positive attitude towards the technology.[74] Tinnitus should also be managed as part of the overall care package. Modern neurophysiological methods, such as tinnitus retraining therapy, utilize a combination of cognitive, directive counselling and sound therapy, including

hearing aids and/or white-noise generators, and success rates are reported in the region of 60–70%.[75] Anecdotal[76] evidence suggests open-fit hearing aids are particularly effective in this situation, and the reduction in the occlusion effect encourages usage and compliance for all indications.

The presence of comorbidities that affect cognition (dementia, for example), can significantly impact on an individual's ability and readiness to adapt to the use of hearing aids.[22, 77] In these situations, cooperation is required from caregivers and family members to support ear and hearing aid hygiene and assist with insertion of hearing aids. Early recognition of the need and thus early administration of hearing aids is likely to improve the time which is required for the individual to recognize speech and grasp the benefits of hearing aid technology.[77] This may reduce development of the psychosocial comorbidities that can occur with hearing loss.[22] And finally, whether cause or effect, there is a lower prevalence of depression and dementia symptoms in hearing aid users when compared with a similar elderly group of non-aided persons[78] with researchers increasingly undertaking trials of hearing treatment and support to reduce cognitive decline.[79]

BEST CLINICAL PRACTICE

- ✓ Make a thorough assessment of the patient to establish the level of hearing loss and consequent disability.
- ✓ Early recognition of hearing loss in the elderly may help to prevent the development of several psychosocial comorbidities.
- ✓ Treatment should include binaural digital hearing aids and appropriate audiological rehabilitative support, which may comprise assistive devices and lip-reading classes as well as advice and guidance regarding hearing aid usage.

FUTURE RESEARCH

- ➤ It is naive to believe that one can stave off the effects of ageing forever. However, progress in unravelling the genetics of ageing, and age-related hearing loss in particular, means that with advances in gene therapy we may be able to delay its arrival.
- ➤ Introduction of genes that programme for hair cell longevity or at least avoid early hair cell death, may be possible.[80]
- ➤ An increased understanding of cochlear physiology and molecular biology means that drug therapy may be able to slow the progress of symptoms. An example might be drugs or chemicals that could stimulate a genetic cascade for hair cell regeneration.
- ➤ Finally, where the hearing loss is unavoidable, continuing advances in electronics will hopefully allow better performance from hearing aids. In particular, the perennial thorn of signal detection in background noise might be ameliorated, perhaps by 'smart' programming.

KEY POINTS

- Age-related hearing loss is almost invariably inevitable.
- It occurs from the sixth decade onwards.
- It is usually symmetrical.
- The effects extend far beyond simple hearing loss.

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CHAPTER 57

NOISE-INDUCED HEARING LOSS AND RELATED CONDITIONS

Andrew McCombe and David M. Baguley

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: noise-induced hearing loss, diagnosis and management including prevention. Unfortunately, this produced a high yield but of relatively poor quality or narrow focus, thus most of the references have been hand-sourced from our personal collections on this subject. Also used are the references from the course 'Medicolegal aspects of noise-induced hearing loss' now run at the University of Southampton, and other references found during the course of our ongoing clinical and medicolegal practices.

DEFINITION

The term noise-induced hearing loss (NIHL) refers to a reduction in auditory acuity as a consequence of excessive noise exposure. This situation may be temporary and is described as temporary threshold shift (TTS) (although a strict definition regarding duration is not available), or permanent and described as permanent threshold shift (PTS). PTS may occur following repeated noise exposures, or following a single episode; the term 'acoustic trauma' has been used to describe the situation where a single exposure to an intense sound leads to an immediate hearing loss.[1, 2] The use of these terms does not carry any implication about the nature of the noise exposure (occupational or leisure) or about the noise itself (intensity, frequency, duration).

This chapter will also cover the other common adverse consequences of excessive noise exposure, which include tinnitus, hyperacusis (see also Chapter 61, Tinnitus and hyperacusis) and the relatively new condition of 'acoustic shock'.

AETIOLOGY

By its very definition NIHL is caused by exposure to noise. The sources of such noise are common and various, recreational or occupational. Many examples can be given, but of particular concern in younger people is the use of personal music devices, and regular attendances at clubs and concerts. Gunfire exposure, motor-racing and power tools for DIY are all potential culprits for an older age group.[3]

However, worldwide, occupational noise exposure represents one of the most prevalent, potentially preventable, sources of health impairment. Recent reports suggest that, outside Europe and North America, up to 25% of adult males of working age have evidence of occupational NIHL. This seems to be a particular problem in those countries moving from agriculture to a stronger manufacturing base for their developing economies.[4]

Like all biological insults, the effects on any individual from exposure to excessive noise levels are extremely variable and relatively unpredictable, especially at moderate exposure levels.[5] However, there is no doubt that, with increasing exposure to excessive noise levels, noise damage becomes inevitable. It is generally agreed that, for the human ear, sound levels below 80 dB(A) are unlikely to cause hearing damage, no matter how long one is exposed to them. Sounds of 130 dB(A) or greater will cause hearing damage after even short time periods in almost all exposed individuals. Between these two extremes the 'safe' period of exposure decreases as the sound level increases. In this

regard, noise can be thought of as a toxin, which exhibits its toxic effects in proportion to the total 'dose'. To try to quantify this relationship, the concept of the 'noise imission level' (NIL) was developed by Burns and Robinson.[6]

It is given by the equation:

$$\text{NIL} = \text{Lepd} + 10\log_{10}T$$

where Lepd is the daily noise exposure in dB(A) and T is the time of exposure in years.

So, as an example, a 20-year career with exposure to 85 dB(A) would produce an NIL of 85 + 13 = 98.

They also described the 'equal energy principle'. In essence, this states that if exposure to 85 dB(A) is safe for an 8-hour working day, then a doubling of sound intensity to 88 dB(A) effectively doubles the 'dose', and so is safe for only half that time, i.e. 4 hours. This principle may well hold for continuous noise exposure but is less certain for the more common situation of intermittent exposure.

PATHOPHYSIOLOGY

Although the tympanic membrane and ossicles may be damaged or disrupted in very high-impulse noise, such as an explosion, it is generally the cochlea that is the predominant site for the pathological manifestations of noise damage.

Pathological change associated with NIHL is the source of considerable scientific enquiry and some controversy, and hypotheses regarding mechanisms abound.[7] To this end, there has been great sacrifice by a variety of animals, in particular the cat, guinea pig and chinchilla! The majority of studies consider cochlear function, particularly metabolic and structural changes.[8] Recovery from TTS is thought to imply a role for metabolic mechanisms, and the persistence of PTS, for structural change mechanisms; there is also some experimental evidence in this regard.[9]

Metabolic mechanisms

Acoustic overstimulation could potentially lead to the excessive release of neurotransmitters associated with the transduction function of the cochlea. The possibility that excessive glutamate release may contribute to NIHL has been proposed, based in part upon experimental evidence that the administration of glutamate receptor antagonists may reduce TTS.[10, 11]

There is substantial experimental evidence from animal studies for change in cochlear blood flow associated with acoustic stimulation.[8, 12] Specifically, there are indications that stimulation with sound of moderate intensity increases cochlear blood flow, and with sound of high intensity decreases cochlear blood flow (this being a potential mechanism for cochlear dysfunction associated with noise exposure).[8] The mechanisms of these phenomena are unclear but may reflect metabolic demand. It should also be noted that there is some evidence that NIHL and cochlear hypoxia precede changes in cochlear blood flow.[13]

Other metabolic cochlear mechanisms that are the focus of experimental investigation include outer hair cell (OHC) plasma membrane fluidity, the role of glucocorticoid receptors and oxidative stress.[14–17] Such mechanisms are not mutually exclusive, and there is a consensus that NIHL is a multifactorial and complex situation.

Structural mechanisms

Changes to the micromechanical structures within the cochlea have been reported as possible mechanisms of NIHL. The suggestion has been made that depolymerization of actin filaments in stereocilia may be a substrate of TTS. Additionally, changes to non-sensory elements of the cochlea, such as swelling of the stria vascularis, afferent nerve endings and supporting cells, have been noted.[18]

Apoptosis and necrosis

There is evidence that both apoptosis (programmed cell death) and necrosis play a role in NIHL[9, 19, 20] and OHC are particularly vulnerable in this regard.[21] The progression of OHC death well after the cessation of noise has implicated apoptotic mechanisms.[22] Apoptotic changes in chinchilla OHC (specifically nuclear condensation and cell body shrinkage) have been detected 5 minutes after exposure to impulse noise, whereas necrotic change (nuclear swelling) appeared 30 minutes following exposure.[20] A present focus for research is the role of caspases (a family of cysteine-dependent aspartate-specific proteases) in cochlear hair cell apoptosis.[23]

The evidence above regarding metabolic and structural change in the organ of Corti following noise exposure is indicative of necrotic mechanisms being involved. It has been demonstrated, however, that the relationship between NIHL and hair cell dysfunction is complex. Specifically, it appears that in the rat, high-frequency hair cells die rapidly after noise injury, but that low-frequency hair cells may survive but without auditory function. This finding may account for the common observation that the relationship between hearing thresholds and hair cell damage is not direct.[24]

Synaptopathy

The adverse effects of excessive noise are not limited to the cochlear hair cells. There is a growing body of evidence that the synaptic connections between the inner hair cells (IHCs) and spiral ganglion cells may be especially vulnerable to noise insults (and indeed to ageing), and that this may occur even when the hair cells themselves remain intact.[21, 25] This latter scenario has been given the name 'hidden hearing loss', as audiometric thresholds would be unchanged, but those affected demonstrate difficulties with hearing in background noise.

Predisposing factors

A potential genetic basis for susceptibility to NIHL has been considered but, while this is well established in

animals, in humans it remains elusive.[26] Experimental evidence gleaned from studies with mice has implicated the *Ahl* gene[27, 28] and there are several strains of knockout mice (both homo- and heterozygous) that are more susceptible to NIHL than their littermates that are wild-type.[26]

A clinical interaction between NIHL and age-related hearing loss has been reported and supported by further data.[29–31] The suggestion is that, as individuals with NIHL age, the effect of ageing upon thresholds affected by NIHL is slowed but for adjacent frequencies is accelerated. Mechanisms underlying this observation are presently unclear. The observation that populations in minimally industrialized areas of the world (specifically the Sudanese desert) experience not only no NIHL but also no age-related deterioration of hearing is of interest, but this needs corroborating, and with some urgency while such populations exist.[21, 32]

Other factors demonstrated to have an association with susceptibility to NIHL in humans include smoking and certain disease states such as diabetes and cardiovascular disease.[33–36] Hood et al. noted a greater extent of TTS in individuals with blue eye colour, and an association with PTS has also been demonstrated.[37–39]

A further suggestion has been that recreational drug use causes greater risk of NIHL and tinnitus although it should be recognized that intoxicated individuals may take more risks with intense sound.[40] The combination of exposure to ototoxic agents and noise has been shown to be synergistic in animal models and the potential existence of a common pathway for cochlear ototoxicity and NIHL has been suggested.[41–43] A similar situation has been proposed in humans with regard to industrial solvents, and this warrants investigation.[44, 45] Henderson et al. noted that the individual variability in human susceptibility to NIHL was so great that the situation is complex, and much further research, both animal and human, is needed to substantiate fully the effect of other factors on it.[43]

DIAGNOSIS

Unfortunately, there is no specific test available to make the diagnosis of NIHL. Furthermore, there are two different settings in which a clinician may be required to make such a diagnosis: in the clinical setting and in a medicolegal context. Although the degree of accuracy required is quite different, it is surprising how often the course through the former (which often comes first) can influence the course in the latter. It is therefore most important that as accurate a diagnostic process as possible is pursued in the clinical setting in order to avoid later inconsistencies and reversals in the medicolegal process. At the very least, an acknowledgement of the areas of uncertainty is required.[46]

Of some help, though, in the latter setting is the requirement to make the diagnosis 'on the balance of probabilities' – or simply more likely than not!

There are additional problems with which the clinician must grapple when diagnosing NIHL. There is the enormous biological variability and individual susceptibility to the effects of noise, as well as the insidious nature of the progress of NIHL. In practical terms, this means that, often, by the time an individual presents with symptoms, the noise exposure will have ceased and, in all likelihood, there will be a contribution from the ubiquitous age-related degenerative process.[47, 48]

Historically, the diagnosis of NIHL has been fairly straightforward. Typically, an individual would present with a hearing loss, confirmed by audiometry, and a career of exposure to, relatively undisputed, excessive noise. The diagnostic process would include separating the effects of ageing from the effects of noise. This process would be accomplished by reference to one or more of the many standardized reference tables detailing hearing thresholds with age for typical screened and unscreened populations (e.g. the NPL tables, among others).[49–52] Removal of an 'average' value for age-related hearing loss leaves an assumed NIHL.

The choice of appropriate control group here is obviously important. Comparison of the subject with a highly screened control group, and their better hearing thresholds, may suggest a significant hearing loss due to noise, while a less highly screened control group (with poorer thresholds) may suggest near-normal hearing for an individual of that age.

Much has changed in recent years: heavy manufacturing industry has almost completely disappeared from the UK, and machinery performance and design have improved, as have hearing protection programmes. This has all led to a workforce that enjoys far less in the way of very high levels of excessive noise exposure. Consequently, there have been far fewer claims based on just a hearing loss; more often now claims will also focus on the often-associated symptoms of tinnitus and hyperacusis.

Furthermore, new industries and processes have arisen such as call centres and covert surveillance. These have brought novel and unique problems and patterns of exposure, culminating in a new condition: 'acoustic shock'.[53–55]

Finally, there have been the problems, alluded to earlier, of recreational noise exposure in a younger population, and an increasing recognition of early degenerative hearing processes and other adventitious hearing losses.[56] This latter point has led to a renewal of the debate regarding the most appropriate control group for comparison.[57] The screening of the control group effectively removes all other otological pathology, such as ear disease, head injuries, positive family history of hearing loss, alternative noise exposure and so on. The net result is a group with better hearing thresholds than a so-called 'typical population' group where far less screening has taken place. This distinction is exemplified by databases A and B for the corresponding groups in ISO 1999.[46, 51]

For practical purposes it is probably best to start from a diagnostic assumption that, in a possible case of NIHL, the individual will have a hearing loss composed of three parts: an age-related component, a noise-induced component and, finally, a third, idiopathic degenerative component. The clinician's task is to separate and calculate the relative contribution (if any) from the three sources.

In the end the diagnosis is based on a combination of the clinical picture that emerges from the patient or claimant and the audiometric findings and, in a large part, is influenced by the experience of the examining clinician.

History

The patient or claimant is far more likely to be male than female, usually in middle age, but sometimes older. They may be younger, especially if the complaint is more about tinnitus (with or without hyperacusis) than deafness. Women more frequently present with acoustic shock.

Inevitably, there will be a history of hearing difficulties. Typically, in the early stages, especially as the OHC are first affected by noise damage, a history of hearing difficulties in the presence of background noise is encountered. Normally, the description involves a lack of clarity rather than a loss of volume. Difficulty with the television being louder than is comfortable for the rest of the family is frequently reported. Telephone conversations may become more difficult. The symptoms will often have been slowly progressing for many years.

Tinnitus is a common accompanying symptom of NIHL and often occurs early in the course of the condition. In fact, post-exposure tinnitus is a useful symptom when making the diagnosis, especially if reported unsolicited. The main effects of tinnitus tend to be on sleep, mood and concentration. Impact in these areas should be detailed and any medical attendance for it noted. This will help in grading its severity.[58]

Hyperacusis is found in 40% of tinnitus sufferers and is becoming an increasingly volunteered accompanying symptom in NIHL. Its presence should be recorded. The instrument to determine severity that is in most common use worldwide is the Hyperacusis Questionnaire, though some issues with the factor structure have been identified.[59, 60]

As the hearing loss progresses, so the nature of the complaint may change. Patients may complain of a more obvious hearing problem and frequently having to ask others to repeat themselves. With further progression, a clear complaint of hearing loss occurs.

NIHL is found far more often in men and produces particular difficulties in social functioning. There is often a history of social withdrawal although this will rarely be volunteered. There is often increasing reliance on the spouse for social and family interaction and this can lead to marital stress. There may be embarrassment, loss of confidence, anxiety and frank depression.[61]

It is important to be aware of other significant causes of sensorineural hearing loss when making the diagnosis. Significant head injury, meningitis, serious systemic illness, often involving previous aminoglycoside treatment, and a strong family history of early hearing loss (indicating a non-syndromic hereditary/genetic degenerative hearing loss) should all be enquired for.

It is axiomatic that, for a diagnosis of NIHL to be made, there must be a history of noise exposure. In the clinical setting it is important to establish that there has been sufficient noise exposure to cause NIHL. In the medicolegal setting it is essential to be thorough about this. It is important to detail all the potential sources of noise exposure and assess typical noise levels and duration of exposure.[62] If one is not familiar with the suspect machinery or device, get the claimant to describe and explain it. A useful yardstick of background noise levels is the ability to hold some type of conversation in its environment (Table 57.1).

For gunfire noise exposure, the type of weapons used and number of rounds fired are important questions; heavy artillery is particularly damaging. Provision and type of hearing protection should be known, although this by no means guarantees protection.[63] Post-exposure tinnitus is a useful surrogate for the presence of a TTS.[64]

If the total noise exposure has come from a variety of sources, it is important to document the contribution from each carefully and thoroughly (including recreational exposure).

The problem of acoustic shock is very different and is thought to be more of an acute stress reaction. It is found typically in call-centre workers who are under some pressure to process high volumes of calls in a defined time period. The sound comes through their headsets and may be the result of a technical malfunction, or a malicious act by the individual on the other end of the phone line. The sound is unexpected and is perceived as both loud and unpleasant by the affected individual, although when measured it may be less than classically damaging sound levels of 85 dB(A) or above. Objective hearing loss is rarely a feature but multiple symptoms and high levels of psychological distress are often described. Common symptoms are summarized in Table 57.2. Theories exist that the problem represents a combination of an excessive 'startle' response, and/or a form of post-traumatic stress disorder.[54] In addition, there is a view that myoclonic activity of the tensor tympani muscle is involved.[50] The degree of psychological distress is often enough to

TABLE 57.1 Typical background noise levels based on communication ability

	Distance from speaker to listener		
Voice level	**4ft**	**2ft**	**At ear**
Loud voice	93 dB(A)		
Shout	99 dB(A)	105 dB(A)	
Impossible to hear			Over 110 dB(A)

TABLE 57.2 Common otological symptoms of acoustic shock (derived from Westcott[55])

Symptom	Occurrence (%)
Hyperacusis	84
Otalgia	81
Tinnitus	50
Imbalance	48
Hearing loss	18

force the individual to leave the job where the exposure occurred.

Examination

Typically, otological examination will be normal. However, evidence of either active or quiescent otitis media does not preclude the diagnosis. Age-related hearing loss happens in all individuals in varying degrees and so appropriate allowance for this and any other coexistent pathologies will need to be made.

Investigations

The cornerstone of investigation is a pure-tone audiogram, with both air and bone conduction to identify any conductive hearing loss. The usual clinical frequencies should be tested as well as 3 kHz and 6 kHz. The classical audiometric pattern is of a high-tone hearing loss with a notched appearance centred on 4 kHz or 6 kHz, with some recovery at 8 kHz. However, the classic notch is often absent or not obvious, particularly in the presence of significant age-associated hearing loss or other causes of hearing loss. Furthermore, the presence of a significant notch at 4 kHz on its own is not evidence of NIHL. There are numerous case reports and population surveys of 4 kHz notches in individuals with no history of noise exposure.[65–67]

Significant audiometric loss at frequencies below 2 kHz is extremely uncommon in NIHL. If present, it should raise suspicion of some other pathological process affecting the cochlea.

Some authors have suggested an analytical approach to the shape of the audiogram as an aid to predicting the likelihood of NIHL.[48, 68] This analysis merely helps to increase the confidence in making a diagnosis of NIHL. Lutman et al. have more recently produced a follow-up paper to their original guidelines which attempts to provide quantification of the noise-induced component of any high-tone hearing loss.[69]

Since 2007, and the judgement in a group action by textile workers in Nottinghamshire,[70] there has been a much greater reliance on the Coles, Lutman and Buffin (CLB) guidelines;[48] in fact, many solicitors will not proceed with a claimant's case if their audiogram does not meet the relevant criteria. This is helpful and does provide a degree of certainty and clarity, but a lack of conformity does not exclude the diagnosis. Nor does it help in cases where non-hearing loss symptoms dominate.

Tympanometry is helpful to confirm normal middle ear functioning. A conductive hearing loss is not due to noise exposure and can even provide some protection to the cochlea by virtue of the sound attenuation.

In those individuals in whom a significant non-organic component (feigned thresholds) is suspected, cortically evoked response audiometry, or otoacoustic emissions (OAE), may be required to provide a more objective measure of hearing thresholds.

In cases with significant asymmetry, a magnetic resonance imaging (MRI) scan may be required to exclude an acoustic neuroma. Significant asymmetry is unusual in NIHL but can be found in certain military personnel due to the 'shadow effect' from the head with shoulder-borne weapons. More than 10 dB at the same frequency is uncommon and will indicate the need for MRI scanning.[71]

Tinnitus pitch and intensity matching are often performed. Although they may help to describe the tinnitus, there is little evidence that they have a role in the assessment of tinnitus severity.[72]

Loudness discomfort levels are a useful measure of the presence of hyperacusis. They can also be used to monitor the effects of treatment.

There is some evidence of changes in OAEs and decreased, contralateral, OAE suppression with early noise damage, although these findings are still a long way from regular and reliable clinical application.[73–75] They may yet help in the diagnosis of noise-induced tinnitus without measurable hearing loss.[76]

At the present time there is no practical means of determining the extent of synaptopathy in an individual exposed to noise and research in this regard is underway internationally.[21]

Diagnosis and report writing

Diagnosis is simple in an individual with a clear and prolonged history of unprotected exposure to excessive noise, no evidence of any other otological pathology and an audiogram showing good preservation of mid and low frequencies but a significant high-tone hearing loss with classical notching at 4–6 kHz.

However, in practice, such a case is relatively rare. Most commonly, one is faced with an older patient who has developed symptoms as a result of the combined effects of ageing and NIHL. There will be a history of excessive noise but in many cases this will not be overwhelmingly impressive or, alternatively, hearing protection may have been provided. The audiogram will show a sensorineural hearing loss, often with loss of the middle frequencies too. In this situation it is necessary to tease out the effects of ageing, balance the remaining hearing loss against the described noise exposure and try to make a judgement based on one's experience of NIHL as to whether all of this remaining loss can be attributed to the noise. If not, a third idiopathic, degenerative process has to be invoked to explain the discrepancy.[48, 55, 69]

Help for this task comes from both the 'Black Book' and the NPL tables. The NPL tables are particularly useful as they describe average noise imission levels (NILs) for various hearing losses. Where there is a significant discrepancy between the required NIL for a hearing loss and the noise exposure supposedly responsible, the presence of an additional degenerative process becomes more likely.[77] The 'Black Book' provides disability values for various hearing losses and for typical age-related changes.[62]

A medical report requires all of these points to be addressed. A value should be attached to the noise-induced portion, and any other components, of the total hearing loss. In addition, the writer should make some effort to

calculate the relative contribution to the NIHL from each noise source, if there is more than one.

Tinnitus, if present, should be graded for severity and, again, the various contributions to its aetiology should be apportioned. Guidance for severity grading has been published.[60] By and large, the courts tend to accept the premise that the cause of any tinnitus (and hyperacusis) is the same as the cause of any coexisting hearing loss, and in the same relative proportions if there are multiple contributions, such as age and noise, among others. Tinnitus following noise exposure without apparent hearing loss is a little more controversial.[78] Obviously, this does not apply if the onset of tinnitus followed closely from a specific incident, such as an episode of acute acoustic trauma, a head injury or following a known ototoxic medication. In these cases the specific incident in question is more likely, on the balance of probabilities, to have been the cause.

The report should also include a section on prognosis in respect to both hearing loss and tinnitus. In particular, comment should be made regarding the need (either current or predicted) for any hearing aids or rehabilitative treatment, and, if possible, some indication of their costs.

With the relatively recent changes in the civil justice system leading to the production of the Civil Procedure Rules in 1999, it is important that an expert does not comment outside his field of expertise and, where there is a range of opinion on a point or subject, it is acknowledged and commented upon.[79]

MANAGEMENT, INCLUDING MEDICOLEGAL

Prevention

From a clinical perspective, once a diagnosis is made, further noise exposure should be reduced as far as possible. This may be by avoiding the excessive noise altogether or, if this is not possible, by the use of ear protection in the form of earplugs or earmuffs. Changes to working practices might also be suggested. In the occupational setting, legislation exists to enforce this.

Employers have a statutory duty under the Health and Safety Act 1974 to minimize risks to employees, including risks from excessive noise exposure.[80] The 1989 Noise at Work Regulations described two action levels for daily, personal noise exposure: a first action level at 85 dB(A) and a second at 90 dB(A). In addition, there was a peak action level of 140 dB.[81, 82] These were replaced in 2006 by the European Control of Noise at Work Regulations 2005, where each action level is 5 dB lower, respectively.[83, 84]

In summary, at the first action level, an employer should conduct a noise survey, embark on a programme of employee education and provide appropriate hearing protection. The use of this hearing protection is at the discretion of the employee until the second or peak action level is reached, when it becomes compulsory. The employer is required to identify those areas where hearing protection use is required. Regular hearing tests should be offered to employees where and when a potential risk is recognized.

The main thrust of the regulations, though, is to reduce noise exposure 'as far as reasonably practicable' by reduction of noise at source (or time of exposure), with hearing protection very much the last solution. This reduction may be by means of engineering (quieter machines) or acoustic (sound-isolating) solutions.

PERSONAL HEARING PROTECTION

There is evidence that the use of hearing protection reduces the risk of NIHL from noise in both recreational and occupational contexts.[83, 84] As regards hearing protection, the choice is between earplugs, earmuffs and active noise reduction. The choice will often depend on the performance of the protector and the environment in which it will be used. Earplugs may be personally moulded or 'off the shelf', and are made from silicone rubber, acrylics or closed cell foam. They are relatively cheap and particularly useful when other protective devices (e.g. helmets or goggles) must also be worn. The best earplug can perform as well as the best earmuff in terms of sound attenuation but they are harder to fit correctly.[85] It is well established that the real-world performance of ear protectors is significantly poorer than the laboratory scores, largely as a result of inadequate or incorrect fitting. Therefore, earmuffs are generally a more reliable form of ear protector. In a real-world setting, earplugs can be assumed to give approximately 10–15 dB of sound attenuation and earmuffs at least 15 dB.[86]

Active noise reduction is an electronic method of sound attenuation. It uses electronics to provide sound, inside a set of earmuffs that is 180 degrees out of phase with the ambient sound. This effectively cancels out the background noise. This is a very effective form of sound attenuation, particularly for lower frequencies (around 1000 Hz), but the electronics required are expensive. Its most frequent use is in military and aircraft settings where additional communication devices are required and it can be incorporated into the headset.[87]

Unfortunately, given the known variation in susceptibility to noise damage, adherence to all the regulations does not guarantee protection for all employees.

Non-specific management

Unfortunately, there is no way to replace the hearing that has been lost. In those individuals with a mild high-tone hearing loss, hearing aids may provide benefit, but this can be meagre.[88] The best that can be done in this situation is to give advice regarding the optimization of their acoustic environment. This involves the reduction of background noise (as far as possible), face-to-face conversation to maximize exposure to non-verbal communication cues and an explanation of the problem, to allow the legitimization of their hearing loss.

In more severe hearing loss, directed rehabilitation programmes including psychological counselling, can help the patient to understand and acknowledge their problem. This acceptance is one of the first and, most crucial, steps on the road to successful rehabilitation. Inclusion of, and support for, the individual's partner should also be provided as part of such a programme.[89]

Practical measures for individuals with a more severe hearing loss include infrared headphones for use with television, volume-controllable telephones and louder doorbells, often with an alternative alerting system such as a flashing light or vibrating pager system. Lip-reading classes can be extremely valuable.

Specific management

As the hearing loss becomes more severe, a hearing aid takes on an increasingly beneficial role. There is solid evidence of a significant benefit to the patient in being fitted with binaural digital hearing aids.[88] There is also good evidence of the importance of follow-up and rehabilitative support after fitting to ensure maximum benefit and hearing aid use.[90]

Tinnitus should be managed as part of the overall care package. Modern neurophysiological methods (such as tinnitus retraining therapy) utilize a combination of cognitive, directive counselling and sound therapy (including hearing aids and/or white-noise generators) and report useful success rates in the region of 60–70% in terms of improvement in the perception of tinnitus and its severity.[91] Hyperacusis responds well to similar treatment methods.

Acoustic shock really requires psychological treatment as much as anything else. Many sufferers are unable to continue that occupation. Tinnitus is a frequent symptom and standard tinnitus treatment strategies do seem helpful for this and a number of the other auditory symptoms.

Pursuing a claim

In the clinical setting, once a diagnosis of NIHL is made, the patient may well ask advice about pursuing a claim for damages. There are two options.

If the individual has worked for 10 years or more in one of the prescribed occupations, they may be entitled to statutory DSS compensation, available since 1974.[92] The hearing loss is calculated on the basis of the average hearing levels at 1 kHz, 2 kHz and 3 kHz.

$$[(4 \times \text{better ear} + 1 \times \text{worst ear}), \text{ divided by } 5]$$

The entry point is 50 dB HL, which equates to a 20% disability. The disability payments are relatively modest. For illustration, in 2016 a 20% disability attracted a payment of £33.60 per week and complete deafness (100% disability) £168. There are many who think this entry point is too high; it equates to an approximate 38% disability in the 'Black Book'.[62] A similar scheme has operated for the military pension scheme since 1987.

The second and more common option is to pursue a civil claim, where the burden of proof is on the claimant. For such a case to succeed, the claimant must demonstrate 'on the balance of probabilities' (i.e. more likely than not) that:

- there has been exposure to excessive noise levels
- the hearing loss has been a consequence of that exposure
- there was a foreseeable risk of injury from the exposure
- the case was brought in time (3 years from the time of awareness).

The claimant must retain a solicitor to coordinate the case. Such a solicitor can normally be found through the employee's union or work federation, or through the Citizens Advice Bureau.

FUTURE RESEARCH

- While the dangers of hearing loss associated with noise exposure have been known for many years, there remains much to discover about pathological mechanisms of NIHL, genetic susceptibility and the influence of other factors. Animal studies will be of assistance in building the knowledge base, as will human population studies.
- Sound conditioning protects against the adverse effects of future sound exposure.[93] Understanding the physiological and biochemical explanation for this may allow drug therapy to protect against or possibly reverse the effects of excessive noise exposure. Current areas of interest include the intratympanic administration of corticosteroids, and the use of antioxidant medication.[26]
- Explanation and understanding of these phenomena may also be helped by further research based on our knowledge that certain individuals naturally have 'tough' ears when it comes to noise exposure.
- Advances in our understanding of hair cell regeneration may allow treatment to encourage this to take place in the noise-damaged cochlea.

KEY POINTS

- In noise-induced hearing loss (NIHL) cases there are usually three components to the hearing loss: age, noise and an idiopathic component.
- The diagnosis is clinical and requires sufficient noise exposure and the presence of a hearing loss greater than expected from age alone.
- Tinnitus and hyperacusis are frequent accompanying symptoms and nowadays often present without any evidence of a hearing loss or only a modest hearing loss.
- Treatment is essentially preventative and involves personal hearing protection (earplugs or earmuffs) or reduction of noise levels at source.
- This is a diagnosis that frequently enters the legal arena.

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CHAPTER 58

AUTOSOMAL DOMINANT NON-SYNDROMIC SENSORINEURAL HEARING LOSS

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SEARCH STRATEGY

The data in this chapter may be updated by a search on NCBI PubMed, OMIM and the Hereditary Hearing Loss website at http://hereditaryhearingloss.org[1] using the keywords: autosomal dominant non-syndromic sensorineural hearing loss, next generation sequencing, hearing loss gene panel and DFNA.

INTRODUCTION

Hearing loss which is the result of damage to the hair cells within the inner ear, the vestibulocochlear nerve or central processing centres of the brain is called sensorineural hearing loss (SNHL). When SNHL occurs without any additional manifestations in at least one other body system, it is called 'non-syndromic' SNHL. This accounts for approximately 70% of all genetic SNHL cases, the other 30% being part of a syndrome in which clinical features form a recognizable association. According to mode of inheritance, non-syndromic SNHL can be autosomal dominant (AD) (15% of non-syndromic SNHL cases), recessive (80%), X-linked or mitochondrial.[2] Deafness is a highly heterogeneous disorder with genes encoding a plethora of different proteins involved in numerous pathways.

CLINICAL FEATURES OF AD NON-SYNDROMIC SNHL

Clinical evaluation of a patient with hearing loss includes involvement of a multidisciplinary team with audiologist, otolaryngologist, clinical geneticist and other specialists where appropriate. When environmental and syndromic causes of hearing loss have been excluded as far as possible, the hearing loss can be considered to be non-syndromic, until proven otherwise. If family history is available, a non-syndromic AD form of SNHL is recognized by the observation that several generations are affected; in a singleton case, probably due to *de novo* mutation, or reduced penetrance, the inheritance pattern is often not apparent.[2] To date, loci for more than 60 genes have been mapped (which means that the detailed chromosomal position has been localized), but only just over half of these genes have been identified.[1] Unlike the situation in which *GJB2* accounts for a significant proportion of cases recessive hearing loss, there is no single major gene accounting for a large proportion of dominantly inherited cases. Therefore genetic heterogeneity, relative clinical homogeneity (see 'History of AD non-syndromic SNHL gene discovery') and the fact that AD non-syndromic SNHL accounts for a minority of all genetic hearing losses means that genetic testing to achieve a molecular diagnosis has proved challenging and expensive until recently.

Clinically, AD SNHL is usually postlingual and progressive in contrast to non-syndromic autosomal recessive SNHL which is usually prelingual and more or less stable.[2, 3] There are some notable exceptions: mutations in some genes may cause prelingual or early childhood-onset hearing impairment such as those in *TECTA* (DFNA8/12) (**Figure 58.1**) and the recently described *CD164,* which may give rise to prelingual moderate to severe hearing loss with a distinctive mid-frequency 'U-shaped' pattern; *SIX1* (DFNA23), which may also cause prelingual high-frequency hearing loss associated with unilateral or bilateral ear pits; and *CRYM*, which may cause a downsloping, progressive hearing loss. Genes which cause onset of hearing loss in the first decade

include *WFS1* (DFNA6/14/38) (Figure 58.2), which can cause low-frequency progressive hearing loss (<2 kHz), *MYO6* (DFNA22), *HOMER2*, *OSBPL2* (DFNA67) (Figure 58.3), which causes a steeply sloping ('ski-slope') mild to profound progressive hearing loss, and *TMC1* (DFNA36), which can cause a high-frequency rapidly progressive hearing loss. However, even within a single family, age of onset of hearing loss, progression and even audiometric configuration can vary between individuals, making distinction between genetic causes difficult.

So, although some non-syndromic AD SNHL loci are associated with particular audiometric patterns or clinical presentations, such as mutations in *COCH*, also giving rise to prominent vestibular symptoms, a sufficiently distinctive, unique audiogram or clinical picture to confidently enable clinical diagnosis is unusual. This has spurred the development of 'AudioGene', an online automated tool which automatically analyzes audiometric data to predict the likely underlying genetic causes of hearing loss. It has been shown to have some success in predicting the gene/locus responsible for deafness based on audiogram,[4] particularly for *KCNQ4* mutations which cause a pattern of mainly high-frequency hearing loss and which has been found to be a relatively common form of dominantly inherited hearing loss.[5,6] Audioprofiles for many other loci have now been compiled and are available for use to try to predict the gene or locus involved based purely on audiometric pattern and progression. The currently known AD genes for SNHL are outlined in Table 58.1, together with age of onset and audiometric description.

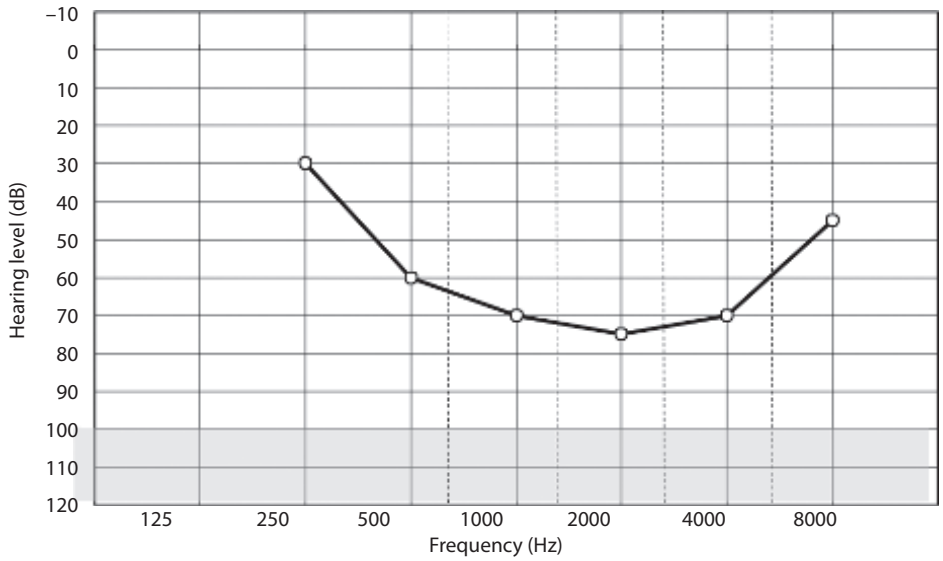

Figure 58.1 'U-shaped' or 'cookie-bite' audiogram typical of hearing loss caused by *TECTA* mutations.

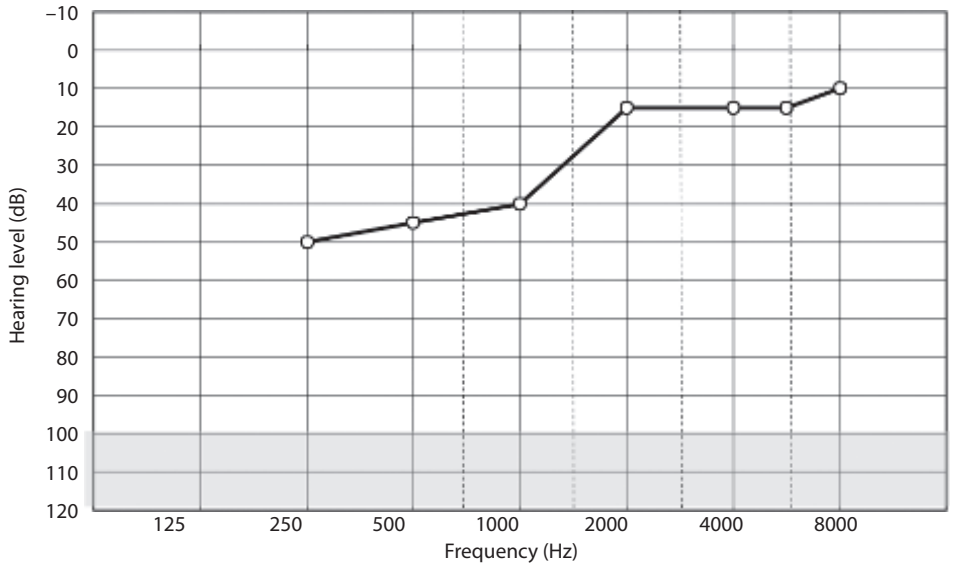

Figure 58.2 Low-frequency hearing loss seen with *WFS1* mutations.

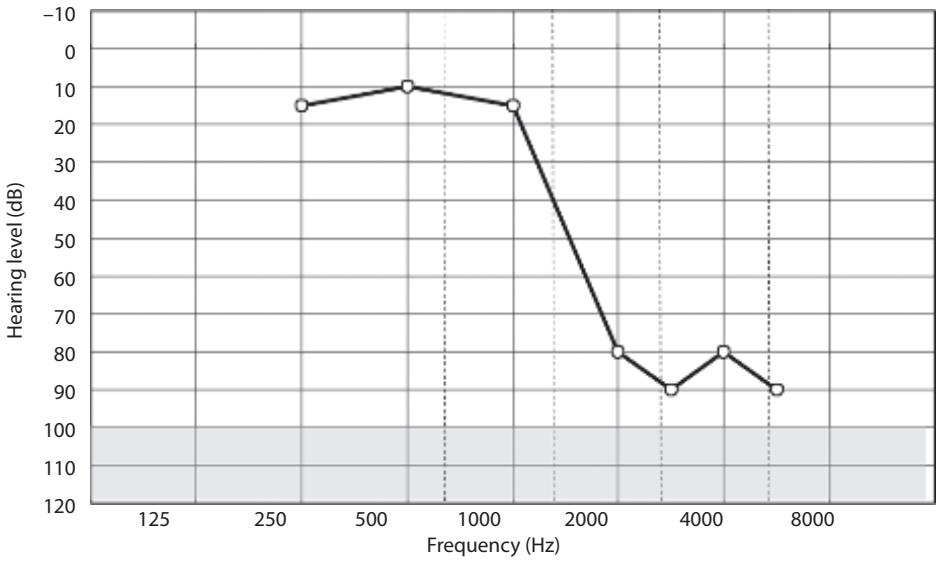

Figure 58.3 Steeply sloping, 'ski-slope' high-frequency hearing loss seen with OSBPL2 mutations.

HISTORY OF AD NON-SYNDROMIC SNHL GENE DISCOVERY

Non-syndromic AD SNHL can be identified by a multigenerational family history and is genetically heterogeneous with no single gene accounting for a high proportion of cases; there are currently 37 genes and 67 loci with yet unidentified genes listed on the Hereditary Hearing Loss website (see **Table 58.1**)[1] This extreme genetic heterogeneity makes genetic diagnosis of AD SNHL very difficult.

Box 58.1 defines the most important terms related to research in this area.

In 1992 the first AD SNHL locus (DFNA1) was mapped to chromosome 5q31 using linkage analysis in large multigenerational Costa Rican kindred. Five years later, in 1997, using laborious positional cloning as the human DNA sequence was not yet available, a splice mutation leading to a 4bp insertion in the mRNA and frameshift causing a truncating variant in *DIAPH1* gene was identified as the cause of AD SNHL in this family.[7, 8] Recently it has been shown that this leads to a constitutive activation of the encoded protein DIA1 by loss of autoinhibition.[9] In the same year, it was shown that an in-frame 9-bp deletion in *MYO7A* and a truncating mutation in *GJB2* were responsible for deafness in two families previously linked to DFNA11 and DFNA3A loci, respectively. Both genes were cloned after linkage analysis pointed to the two genes which were already known to cause autosomal recessive deafness.[10–12] Linkage analysis followed by positional cloning and sequencing of candidate genes further led to identification of *GJB3*, *DFNA5*, *COCH*, *POU4F3*, *TECTA*, *KCNQ4*, *TECTA*, *COL11A2* (see **Table 58.1** for full list).[13–19] Gene identification processes preceding the release of the human genome draft sequence in 2001[20] heavily relied on linkage analysis of large multigenerational families, bacterial artificial chromosome (BAC)-mediated cloning as well as singling out of candidate genes based on previous knowledge of gene function, mouse models or expression studies. In cases where no family members other than the proband were available, making linkage analysis impossible, a candidate gene approach was pursued (see **Box 58.1**). Examples of gene identification using the candidate gene approach are *GJB6*, *CRYM* and *MYH14* genes, which were selected as candidate genes based on expression in the cochlea and vestibule, and data from existing mouse models coupled with the knowledge that genes from the same family have been previously shown to cause deafness. However, due to extreme heterogeneity of SNHL, sequencing of candidate genes in large groups of patients had a low yield, identifying deafness-causing variants in only 1/198 deaf families for *GJB6*, in 2/192 families for *CRYM* and in 4/300 families for *MYH14*.[21–23] While the release of the human genome draft sequence in 2001 made targeted sequencing of candidate genes more straightforward, this approach is heavily biased as it relies on *a priori* knowledge of gene function and is therefore unlikely to reveal a novel deafness-causing gene or a novel pathway.

Since completion of the human genome (accomplished by Sanger sequencing), a demand for faster and cheaper methods led to the development of high-throughput sequencing called next generation sequencing (NGS) or massive parallel sequencing (MPS). On NGS platforms, millions of DNA fragments are sequenced simultaneously, enabling sequencing of the entire genome in a day.[24] This led to the development of the whole exome and genome sequencing techniques which have been successfully implemented in gene identification studies (see **Box 58.1**).[25] Exome sequencing is a robust, unbiased approach in which all protein-coding parts of the genome are amplified, sequenced and analyzed. Loci previously linked to AD deafness in families, containing hundreds of genes, could now be rapidly sequenced. Additionally, small families in whom linkage analysis was not feasible, could now be screened using whole exome sequencing (WES). The technique transformed genetic analysis and was soon applied in AD SNHL studies. Zheng et al. used a combination of linkage analysis and WES (with the analysis

TABLE 58.1 Autosomal dominant genes causing non-syndromic hearing loss (adapted from Hereditary Hearing Loss)[1]

Locus	Gene	Gene function	Onset (years)	Pattern of hearing loss	Reference(s)
DFNA1	*DIAPH*	Profilin ligand and target of Rho that regulates polymerization of actin, the major component of the cytoskeleton of hair cells of the inner ear	Postlingual (10)*	Low-frequency, rapidly progressive	8
DFNA2A	*KCNQ4*	Potassium channel; regulation of electrical signalling and the ionic composition of biological fluids	Postlingual (10–30)	Higher frequencies more affected, progressive	18
DFNA2B	*GJB3***	Gap junction protein, connexin 31; building blocks of GAP junctions; mediate diffusion of ions and metabolites between the cytoplasm of adjacent cells	Postlingual (20–40)	Higher frequencies more affected, progressive (one family described)	14
DFNA3A	*GJB2***	Gap junction protein, connexin 26; building blocks of GAP junctions; mediate diffusion of ions and metabolites between the cytoplasm of adjacent cells	Postlingual (6–20)	Higher frequencies more affected, or flat	12
DFNA3B	*GJB6**	Gap junction protein, connexin 30; building blocks of GAP junctions ; mediate diffusion of ions and metabolites between the cytoplasm of adjacent cells	Prelingual (age not mentioned)	High-frequency, progressive (one family described)	21
DFNA4	*MYH14***	Non-muscle myosin heavy chain IIC; ATP-dependent molecular motor which interacts with cytoskeletal actin	Postlingual (1st or 2nd decade)	Higher frequencies more affected, or flat	23
DFNA4B	*CEACAM16*	Carcinoembryonic antigen-related cell adhesion molecule 16 (CEACAM16) is an adhesion protein	Postlingual (early adolescence)	Higher frequencies more affected, or flat	26
DFNA5	*DFNA5*	*DFNA5* (*ICERE-1*); function unknown; it might be involved in apoptosis	Postlingual (5–50)*	Higher frequencies more affected, progressive	13
DFNA6/ 14/38	*WFS1*	Wolframin; transmembrane protein	Prelingual (5–15)	Low-frequency, gradually progressive	37, 38
DFNA8/12	*TECTA*	Alpha tectorin; structural component of tectorial membrane	Prelingual	Mid-frequency or high-frequency	17
DFNA9	*COCH*	Cochlin; extracellular matrix protein	Postlingual (16–52)	Higher frequencies more affected, gradually progressive	15
DFNA10	*EYA4*	Eye absent 4; transcriptional activator that interacts with members of other protein families to regulate early developmental event	Postlingual (20–60)	Flat, gradually progressive	39, 40
DFNA11	*MYO7A*	Myosin 7A; motor molecules that move along actin filaments	Postlingual* (before12)	Higher frequencies more affected, or flat, gradually progressive	10
DFNA13	*COL11A2*	Collagen, type XI, alpha-2; its association with type II collagen, which is known to be present in the tectorial membrane, led us to hypothesize that type XI collagen is essential for appropriate spacing of type II collagen within this structure	Postlingual (20–40)	Mid-frequency or flat, slowly progressive	19
DFNA15	*POU4F3*	Transcription facctor	Postlingual (18–30)	Higher frequencies more affected, progressive	16

(*Continued*)

TABLE 58.1 (*Continued*) Autosomal dominant genes causing non-syndromic hearing loss (adapted from Hereditary Hearing Loss)[1]

Locus	Gene	Gene function	Onset (years)	Pattern of hearing loss	Reference(s)
DFNA17	*MYH9*	Myosin heavy chain 9; non-muscle-myosin heavy-chain gene; localizes in the organ of Corti, the subcentral region of the spiral ligament, and the Reissner's membrane; contributes to cytoarchitecture	Postlingual (10)	Higher frequencies more affected, progressive	41
DFNA20/26	*ACTG1*	γ-actin gene; predominant actin isoform in the auditory hair cell; protein of the cytoskeleton	Postlingual* (7–30)	High-frequency, gently sloping, progressive	42, 43
DFNA22	*MYO6*	Myosin 6; unconventional motor molecule	Postlingual* (8–10)	Higher frequencies more affected, or flat, progressive	44
DFNA23	*SIX1***	Members of the SIX gene family encode proteins that are characterized by a divergent DNA-binding homeodomain and an upstream SIX domain, which may be involved both in determining DNA-binding specificity and in mediating protein–protein interactions	Prelingual (1–20)	High-frequency, sloping (one family)	45
DFNA25	*SLC17A8*	Vesicular glutamate transporter-3 (VGLUT3); VGLUT3 is essential for auditory coding at the IHC synapse	Postlingual (20 and older)	High-frequency, sloping, progressive	46
DFNA28	*GRHL2*	Grainyhead-like transcription factor	Postlingual (7 and older)	Flat, gently downsloping	47
DFNA36	*TMC1*	Transmembrane cochlear-expressed protein 1	Postlingual* (5–10)	High-frequency, rapidly progressive	48
DFNA39	*DSPP***	Dentin sialophosphoprotein	Postlingual (20–30)	High-frequency, progressive	49
DFNA41	*P2RX2*	Encodes the P2X2 receptor; in the inner ear, P2X2 receptors are thought to regulate sound transduction and auditory neurotransmission	Postlingual* (2nd decade)	Gently downsloping or flat, progressive	27
DFNA44	*CCDC50*	Encodes Ymer, an effector of epidermal growth factor (EGF)-mediated cell signalling that is ubiquitously expressed in different organs and has been suggested to inhibit downregulation of the EGF receptor	Postlingual (6–10)	Low- and mid-frequency, progressive (one family)	50
DFNA50	*MIRN96*	MicroRNAs (miRNAs) bind to complementary sites in their target mRNAs to mediate post-transcriptional repression, with the specificity of target recognition being crucially dependent on the miRNA seed region	Postlingual (12 onwards)	Flat, progressive	33
DFNA51	*TJP2 FAM189A2*	Tight junction protein; it is suggested that TJP2- and GSK-3β-mediate increase susceptibility to apoptosis of cells of the inner ear	Postlingual (4th decade)	High-frequency, progressive	31
DFNA56	*TNC*	Tenascin C; a member of the extracellular matrix (ECM); it is present in the basilar membrane (BM) and the osseous spiral lamina of the cochlea; it plays an important role in cochlear development	Postlingual (8–30	Low-frequency, ascending, progressive	28

(*Continued*)

TABLE 58.1 (*Continued*) Autosomal dominant genes causing non-syndromic hearing loss (adapted from Hereditary Hearing Loss)[1]

Locus	Gene	Gene function	Onset (years)	Pattern of hearing loss	Reference(s)
DFNA64	*SMAC/DIABLO*	Mitochondrial proapoptotic protein that is released from mitochondria during apoptosis and counters the inhibitory activities of inhibitor of apoptosis proteins	Postlingual (12–30)	Flat, progressive	51
DFNA65	*TBC1D24*	TBC1 domain family, member 24; GTPase-activating protein expressed in the cochlea;	Postlingual (3rd decade)	Gently downsloping, progressive	29, 52
DFNA66	*CD164*	Transmembrane sialomucin involved in cell migration and adhesion	Prelingual and postlingual (0–20)	Flat or mid-frequency, stable or progressive	53
DFNA67	*OSBPL2*	Oxysterol binding protein-like 2; possibly plays a role for the maintenance of hair cells' cytoskeleton	Postlingual* (10–30; possibly as early as 2)	Mild to profound, steeply sloping	30, 54
	HOMER2	Possibly has a role in cytoplasmic Ca^{2+} control	Postlingual* (*1st decade)	High-frequency, progressive	56
	CRYM	Mu-crystallin (CRYM; also known as 'NADP-regulated thyroid hormone-binding protein')	Prelingual (19 months)	Downsloping, progressive	22
DFNA70	*MCM2*	Nuclear protein important in cell cycle (onset of DNA replication and cell division)	Postlingual (earliest 13 years)	Mild to profound, slowly progressive, involving high frequencies or all frequencies	55
AUNA1	*DIAPH3*	Diaphanous-related formin 3; these proteins remodel the cytoskeleton by nucleating and elongating non-branched actin filaments, and they can also bind and stabilize microtubules	Postlingual (average 18.6)	Auditory neuropathy, moderate to profound, high-frequency, progressive (one family)	57
	KITLG	KIT receptor ligand	Prelingual	Unilateral or asymmetrical, Mild to profound	56
	DMXL2	Alpha subunit of rabconnectin protein complex that concentrates on synaptic vesicles	Postlingual (onset 2nd decade)	Mild to moderate, slowly progressive to severe to profound by 6th decade	22

*Onset can be in first decade; ** may also cause syndromic features in some families; reported in only one family.

BOX 58.1 Glossary of terms

Hereditary Hearing Loss website:[1] an important resource providing up-to-date information on mapped genes and loci associated with deafness as well as expression patterns of deafness genes
Linkage analysis: testing of DNA sequence variants that are near or within a gene of interest to track within a family the inheritance of a disease-causing mutation in a given gene; a prerequisite for linkage analysis is availability of a clinically well-characterized multigenerational family
Bacterial artificial chromosome (BAC): an engineered DNA molecule used to clone DNA sequences in bacterial cells (for example *Escherichia coli*)
Candidate gene approach: genetic analysis focused on the selection of genes that have previously been related to the disease in some way; it requires *a priori* knowledge of the gene's function, expression profile or pathway
Single nucleotide variant (SNV): a variation occurring in the genome when a single nucleotide in the genome is altered
Copy number variation (CNV): when the number of copies of a particular gene varies from one individual to the next
Whole exome sequencing (WES): a technique for sequencing all the protein-coding genes in the genome (known as the exome)
Whole genome sequencing (WGS): a technique that determines the complete genome sequence of an organism
Genetic heterogeneity: a term describing a single phenotype being caused by multiple genes and/or different variants in the same gene

focusing on the linked DFNA4 interval) to successfully identify a novel deafness gene *CEACAM16*.[26] Using similar approaches multiple novel genes followed: *P2RX2*, *TNC*, *TBC1D24*, *OSPBL2*.[27–30] However, in an Israeli family in whom AD deafness was linked to chromosome 9p13.3–q21.13, sequencing of all 121 genes in the linked region did not identify any potentially pathogenic variants because sequencing at that time was not able to detect quantitative variants such as duplications and heterozygous deletions. Using array comparative genomic

hybridization (a technique that can detect duplications and deletions in the genome), the cause of AD SNHL was found to be an inverted duplication spanning the *TJP* gene locus,[31] although new NGS technologies now offer sensitive tools for detection of genomic variants such as copy number variations (CNVs).[32]

Adding to the complexity of the molecular basis of SNHL is the discovery of a mutation in miR-96, a gene encoding micro RNA (miRNA) that binds to complementary sites in target mRNAs and mediates post-transcriptional repression.[33] It is therefore possible that other miRNAs may have a role in hearing and hearing loss. See **Table 58.1** for all non-syndromic AD SNHL genes.

Despite tremendous progress in sequencing techniques as well as exome sequencing becoming more and more cost-effective, the sequence produced by NGS is still imperfect. Certain regions are not well covered, particularly the 5′ regions of genes, or poorly assembled due to repetitive regions, and similarities in sequences of genes from the same family may be difficult to analyze. Therefore, although the process of sequencing the whole exome or genome is relatively fast, the downstream analysis requires a lot of time and expertise from bioinformaticians, genome analysts, molecular biologists and clinicians. While techniques will gradually improve and we will be able to produce an accurate sequence of the whole genome, the main challenge in the future will be interpretation of the variants, from single nucleotide variants (SNVs), insertions/deletion to CNVs. The whole exome sequence of one individual on average identifies between 70 000 and 90 000 SNVs; of them just over 21 000 SNVs are detected in coding regions.[34] The present and future challenge is how to reliably single out the disease-causing variant, which is especially difficult for novel genes with unclear functions. Current diagnostic yield with whole exome sequence technology is only ~25–30%; however, this is still higher than the diagnostic yield of other genomic assays such as karyotyping (<5%) and array comparative genomic hybridization (~15–20%). Currently, variants that cause Mendelian phenotypes have been identified in ~2937 human genes of the approximately 19 000 protein-coding genes predicted to exist in the human genome.[35] In the coming years, a huge number of additional variations in the genome will be produced by NGS and integration of this data will lead to better understanding of individual gene functions and identification of pathways leading to disease, which will result in improved diagnostic yield.

FUNCTIONS OF GENES INVOLVED IN NON-SYNDROMIC SNHL

Non-syndromic AD SNHL genes encode a variety of proteins essential for inner-ear function. Broadly, the non-syndromic AD deafness-coding genes with known function can be divided into four categories (adapted from Hilgert).[36]

1. Hair bundle morphogenesis (genes important for the development, structure and function of stereocilia in the hair cells):
   - proteins of the cytoskeleton: *ACTG1*
   - motor proteins: *MYO6*, *MYO7A*, *MYH9*.
2. Ion homeostasis (genes important in the recycling and transport of ions within the fluid-filled cochlea, often requiring energy):
   - connexins: *GJB2*, *GJB3*, *GJB6*
   - ion channels: *KCNQ4*, *SLC26A4*, *WFS1*.
3. Transcription factors (genes encoding proteins which are important for controlling expression of other genes, particularly during development): *EYA4*, *GRHL2*, *POU4F3*.
4. Extracellular matrix proteins (specialized structural molecules): *TECTA*, *COCH*, *COL11A2*.

CONCLUSIONS

Variants in 38 genes are currently known to cause non-syndromic AD SNHL; 21 loci are still awaiting gene identification together with numerous novel genes yet to be discovered. New sequencing technologies capable of sequencing the whole genome in a cost-effective manner are now, albeit still imperfect, in full flow and will lead to molecular diagnosis in many non-syndromic AD SNHL affected families. Due to high genetic heterogeneity, non-syndromic AD SNHL causing variants are individually rare or private, but collectively they play an important role in the pathogenesis of hearing loss.

Molecular genetic diagnosis is of critical importance for management of deafness, since it enables early and accurate clinical diagnosis, better prediction of the course of disease, early intervention essential for language and cognitive development, genetic counselling, as well as potential development of molecular treatments. As the whole genome sequence analysis is gradually making its way from research towards the diagnostic domain, clinicians must be aware of the genetic component of deafness and of the genetic tests and techniques available for molecular diagnosis.

BEST CLINICAL PRACTICE

- ✓ Always take a thorough history and ask about factors which may suggest a syndrome. History should include a 3 generation family history (or more if there is more significant information).
- ✓ Examine the patient to exclude obvious syndrome diagnoses (skin, pigmentation, facial appearance, general appearance).
- ✓ Request information (audiometry details) on other affected family members to look for similarity, or audiometric patterns in younger family members before progression.
- ✓ Investigate with visual acuity and dilated fundoscopy.
- ✓ Biochemical, immune and genetic testing where indicated by history/family history.

FUTURE RESEARCH

- Although the use of constantly evolving hearing loss panels has improved the molecular diagnosis of highly heterogeneous AD non-syndromic SNHL, the diagnostic yield is still limited as many SNHL genes are yet to be discovered.
- The identification of novel hearing loss causing genes has increased exponentially in the past few years; we are now faced with the challenge of accurate and consistent interpretation of novel variants and verification of these using functional studies.
- There is a need for clear guidelines and levels of evidence on inclusion of novel genes in hearing loss gene panels.
- Adequate guidelines and procedures should be set for genetic testing of children with hearing loss identified through newborn hearing screening to enable timely and sensitive clinical and molecular diagnosis.
- Affordable and timely molecular diagnosis will be important to ensure that novel genetic treatments can be offered to appropriate patients; novel therapies for dominant and recessive forms of hearing loss have proven successful in mice, and clinical trials in humans requires identification of suitable participants.[60–63]
- Finally, the rapidly changing landscape of SNHL genetic testing requires appropriate levels of genomic focused educational programs for genetic counsellors and clinicians who are the key to translation of the latest research findings into clinics.

KEY POINTS

- AD SNHL is characterized by marked genetic heterogeneity with most variants being private (e.g. disease-causing in a single family).
- It is usually, but not exclusively, postlingual and progressive.
- Linkage analysis coupled with whole genome/exome sequence analysis is a powerful tool enabling identification of novel pathogenic variants and discovery of novel genes and pathways in AD SNHL.
- Molecular diagnosis enables us to predict the progress of deafness and has important implications for early diagnosis, management of deafness and accurate genetic counselling for families.

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CHAPTER 59

OTOTOXICITY

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: ototoxicity, inner ear, hearing impairment, hearing loss, deafness, cochlea, aminoglycoside (and individual aminoglycoside), *cis*-platinum, salicylate, quinine, (loop) diuretics (or individual diuretics) and organic/industrial solvents (or individual solvents).

INTRODUCTION

The term ototoxicity is used to refer to the process by which a number of therapeutically useful drugs, certain environmental agents such as industrial solvents, and bacterial toxins cause damage to the peripheral end-organs of hearing and balance. This definition excludes agents which cause hearing impairment or balance dysfunction through primary action on the respective neural pathways and centres.

MODES OF ENTRY OF OTOTOXIC AGENTS TO THE INNER EAR

The complete enclosure of the inner ear structures within the temporal bone means that they are not exposed directly to potentially damaging environmental agents. Access to the perilymphatic compartment of the inner ear via the cochlear aqueduct from the cerebrospinal fluid (CSF) is possible and this may be a route of entry for bacterial toxins, such as those associated with meningitis. However, the cochlear aqueduct is not patent in many individuals and tends to close as an individual ages.[1] Access to perilymph is also possible from the middle ear cavity via the membrane covering the round window at the base of the cochlea and that filling the oval window over the vestibule. The permeability properties that determine what will and will not cross these membranes into the inner ear are not known. After entry into the perilymphatic compartment of the inner ear from the middle ear an agent would have access to the basal end of the cochlea and to the vestibular system. Subsequent drug distribution is somewhat complicated, influenced by a relatively slow diffusion rate away from the site of entry and localized clearance rates (e.g. along the cochlear aqueduct).[2–5] Nevertheless, if entry to perilymph is gained, because the basilar membrane is freely permeable, then there is direct access to the lateral membranes of the hair cells, to their synaptic regions and to the nerve fibres.

Potentially, bacterial toxins associated with middle ear infections as well as ototoxic drugs may enter the inner ear across the round window. There is evidence that some children who have had otitis media with effusion (OME) may develop extended high-frequency hearing loss, i.e. with a normal audiogram down to about 8 kHz but with significant threshold shifts at higher frequencies.[6, 7] This has been linked to what has become known as 'listening difficulties' that may underlie behavioural problems.[8] Temporal bones from patients who have had OME show loss of both inner and outer hair cells in the most basal regions of the cochlea[9, 10] and it is thought that this is caused by bacterial endotoxins released in the middle ear effusion crossing the round window membrane to access the basal coils of the cochlea. Ototoxic drugs may also reach the perilymph from the middle ear. In particular, the entry of aminoglycoside antibiotics applied to the middle ear cavity across the round and oval window membranes into the perilymphatic spaces of the inner ear is used as a clinical procedure to ablate hair cells in the vestibular system in cases of severe balance dysfunction

such as that resulting from unilateral Ménière's disease.[11] This approach is also a potential means for introducing therapeutics.[12]

Predominantly, however, ototoxic agents reach the inner ear through the blood supply but there are restrictions on the entry of agents to the fluids of the inner ear. Perilymph is not simply an ultrafiltrate of blood plasma, nor does it derive from CSF. The composition of perilymph is different both from CSF and from blood plasma and the composition of perilymph in scala vestibuli differs from that in scala tympani.[13] This indicates that perilymph is produced and circulated locally and that there is a so-called 'blood–perilymph barrier'. Glucose entry, for example, requires facilitated diffusion through glucose transporters.[13, 14] This may limit access of potentially damaging agents to the perilymphatic compartment. However, relatively little is known about the characteristics of this blood–perilymph barrier and how substances can cross it. Entry to endolymph in the internal compartment of the inner ear is even more restricted and endolymph composition is tightly controlled.[13] The principal boundaries between endolymph and perilymph, formed by selectively permeable membranes and tight junctions between adjacent cells, in the cochlea appear to be Reissner's membrane, at the level of the basal cells in the stria vascularis, and the network formed by the apical surfaces of the hair cells and adjacent supporting cells in the organ of Corti at the reticular lamina. In the vestibular system they are at the level of the tight junctions between hair and supporting cells in the sensory patches and between the epithelial cells that surround the endolymphatic, luminal spaces including the dark cells of the utricle and semicircular canals, the roofs of the utricle and saccule and the semicircular canals themselves. If an agent were to penetrate these boundaries, it would have access to the hair-bearing (apical) ends of the hair cells.

EFFECTS AND ACTIONS OF OTOTOXIC DRUGS

A diverse range of therapeutically useful drugs and some environmental agents have been reported to be ototoxic (Table 59.1). For some of these chemicals the evidence for ototoxicity is limited (see below); sometimes it derives from individual case reports, where other confounding factors may have contributed to the observed effect, and there are no confirmatory experimental studies in animals. The occurrence and extent of ototoxicity is to some extent dependent upon the dosing regime (or exposure conditions) but are compounded by the status of the patient receiving the drug and multiple drug regimes. Stress produced by infection may increase sensitivity as may malnourishment; the effects of aminoglycosides are more pronounced in nutritionally deprived animals.[15, 16] Drug interactions can also result in much greater damage than would be expected from single drug regimes. A number of ototoxic agents, including aminoglycosides, polypeptide antibiotics and anti-neoplastics, are also nephrotoxic so that possible damage to the kidney may result in reduced drug clearance and higher serum levels potentially increasing the risk to the inner ear. In addition, certain genetic factors may predispose to ototoxin-related damage (see below).[17] Individuals under similar conditions and with similar drug-dosing regimes differ in their sensitivity to ototoxic side effects. For these reasons it is not always possible to predict a likely effect following administration of a potentially ototoxic drug.

In Table 59.1 ototoxic drugs have been classified based on their therapeutic use, but perhaps a more useful classification derives from the sites and modes of action, which also provides a basis for illustrating the selective action of these different agents upon the inner ear. On this basis, ototoxins can be divided into three broad groups. The

TABLE 59.1 Compounds known to be or implicated in ototoxicity

Classification	Compounds
Aminoglycoside antibiotics	Amikacin, dibekacin, dihydrostreptomycin, framycetin, gentamicin, kanamycin, neomycin, netilmicin, ribostamycin, sisomicin, streptomycin, tobramycin
Macrolide antibiotics	Erythromycin, azithromycin, clarithromycin
Other antibiotics	Ampicillin, capreomycin, chloramphenicol, colistin (polymyxin E), minocycline, polymyxin B, rifampicin, vancomycin, viomycin
Antitumour agents	**Cisplatin (*cis*-platinum)** carboplatin Antinomycin, bleomycin, nitrogen mustards (e.g. mustine), misonidazole
Anti-inflammatory agents	**Salicylate** (aspirin) Fenoprofen, ibuprofen, indomethacin, naproxen, phenylbutazone,
Antimalarials	**Quinine**, **chloroquine**
Loop diuretics	Bumetanide, ethacrynic acid, frusemide (furosemide), piretanide
Iron chelators	Desferrioxamine
Beta-blockers	Practolol, propranolol
Contraceptives	Medroxyprogesterone
Industrial chemicals	**Trimethyltin**, **toluene**, **trichloroethylene**, **styrene**, **xylene**

first, exemplified by the 'loop' diuretics and erythromycin, have acute effects in the stria vascularis resulting in temporary hearing loss (temporary 'threshold shift' (TTS)). Agents in the second group, which includes salicylate and quinine, predominantly produce temporary impairment of hair cell function (TTS), often accompanied by tinnitus. These symptoms are completely relieved upon withdrawal of the drug. The third, and most significant, group of ototoxic agents cause death of the hair cells and permanent hearing loss (permanent threshold shifts (PTS)) and vestibular dysfunction. Aminoglycoside antibiotics and cisplatin (*cis*-platinum), as well as organic solvents, fall into this category. In mammals, the functional deficits resulting from the hair cell losses caused by these agents are permanent because, unlike the sensory epithelia in the inner ear in birds and other non-mammalian vertebrates,[18–21] the organ of Corti does not spontaneously regenerate hair cells to replace those lost, although the mammalian vestibular organs possess some capacity to regenerate hair cells.[22–27]

Agents affecting the ion-transporting epithelia

Those agents whose primary site of action is on the ion-transporting epithelia, the stria vascularis (SV) in the cochlea and the vestibular dark cells, adversely affect endolymph composition and, in the case of the SV, the endocochlear potential (EP). Such agents, including the loop diuretics, generally cause acute, completely reversible affects after a single drug administration,[28] although some cases of permanent deafness have been attributed to diuretic.[29] The SV has one the highest rates of oxidative metabolism in the body,[13] with oxygen delivered from the intraepithelial blood supply so agents that induce anoxia or ischaemia will affect strial activity. Aminoglycoside antibiotics and cisplatin[30, 31] may induce permanent strial pathologies although this does not necessarily correlate with effects on EP.

All **loop diuretics**, that is those diuretics whose principal site of action is in the ascending limb of the loop of Henle, including **ethacrynic (etacrynic) acid**, **furosemide (frusemide)**, **bumetanide** and **piretanide**, produce a transient hearing loss across most of the frequency range. This usually occurs following intravenous administration of large doses. The effects are rapid in onset, within minutes or hours, and persist for some hours but are usually completely resolved within a day if the drug is discontinued. Repeated diuretic administration does not appear to cause permanent damage to the inner ear. However, a single dose of diuretic when administered closely with a single dose of an ototoxin such as aminoglycoside or cisplatin which has the potential to cause hair cell loss only after chronic repeated treatment, results in rapid devastatingly extensive hearing loss and hair cell death (see below).

Histological studies of the temporal bones from patients who have died while on diuretic treatment[32, 33] have shown extensive oedema and swelling of the SV. Experimental studies in animals have confirmed the SV as the principle site of action and that diuretics produce a rapid, reversible decline in EP, falling from the usual +80 mV to negative values as low as around -40 mV, the K^+ diffusion potential.[34, 35] The rate of decline and the level of suppression are dependent upon the dose of drug administered.[28] The EP then recovers over a period of a few hours but takes several hours to return to normal levels after a single administration. In parallel with the decline in EP an extensive oedema occurs; the extracellular spaces become grossly enlarged (**Figure 59.1**) and strial thickness can almost double. This oedema is also reversible, resolving within about 2–4 hours, prior to complete recovery of EP.[35] The decline in EP correlates with threshold shifts in sound-evoked responses[36] and depression of otoacoustic emissions, a finding that provides evidence that EP is the power that drives the active mechanical responses of the organ of Corti in response to sound.[37] This illustrates the importance of EP maintenance to the cochlear

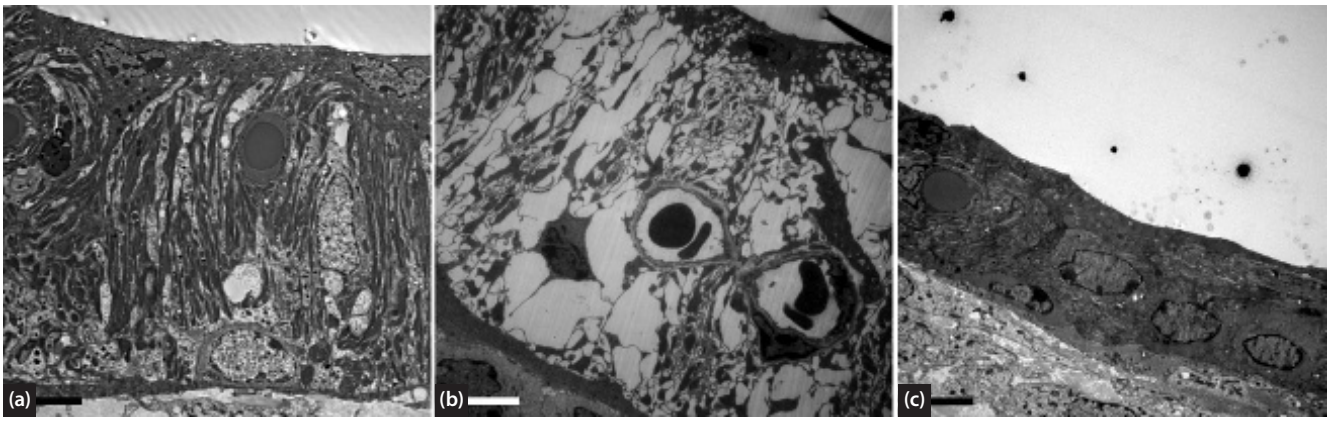

Figure 59.1 Effects of ototoxins on the stria vascularis (SV). Panels (a), (b) and (c) are all at the same magnification. (a) Cross section of the normal SV. **(b)** Effects of diuretic on the SV. There is significant oedema – enlarged extracellular spaces that are confined within the body of the tissue – and an increase in depth. The relative positioning of all the cellular elements of which the SV is composed is unaltered. **(c)** Atrophy of SV 12 weeks following chronic aminoglycoside treatment of the animal. The depth of the SV is significantly reduced. Scale bars on all panels: 5 µm.

amplification mechanism and why damage to the SV will cause hearing impairment.

The rapid onset of their effects suggests that diuretics gain direct access to their site of action through entry from the strial vasculature into the extracellular spaces of the SV and thus to the plasma membranes of all strial cell types including the basolateral membranes of the marginal cells. The development of oedema suggests that diuretics inhibit the ion-transporting processes: ions accumulating in the extracellular spaces would be confined by the tight junction sealing between basal cells, those between marginal cells and those between capillary endothelial cells, resulting in osmotic uptake of fluid. In the kidney, diuretics act on a Na/K/Cl cotransporter. The same cotransporter, NKCC1, localizes to the basolateral membrane both of vestibular dark cells and of marginal cell of the SV[38] and has been shown to be a target of the diuretics in the SV and vestibular dark cells.[39, 40] It is currently thought, therefore, that the diuretics reversibly inhibit the action of the electroneutral NKCC1 cotransporter, in the basolateral membranes of strial marginal cells and vestibular dark cells leading to inhibition of ion transport. In the cochlea, the generation of EP is thereby inhibited and along its entire length such that the consequent hearing impairment resulting from reduction of cochlear amplification is across almost the entire frequency range. (There is no equivalent of EP in the vestibular system so the effects are less pronounced.)

Na^+/K^+-ATPase is also present at high concentration on the basolateral membrane of marginal cells.[41, 42] Inhibition of this might have a similar effect as inhibition of the cotransporter. **Potassium cyanide**, along with its other actions in the body, causes TTS with a symptomatology similar to that of loop diuretics, thought to result from inhibition of marginal cell Na^+/K^+-ATPase.[43] **Macrolide antibiotics** such as **erythromycin** also produce effects similar to those of diuretics: generally transient threshold shifts[44] of the order of about 50 dB maximum across all frequencies[45] following high-dose intravenous administration; rapid, dose-dependent decline in EP in experimental animals;[46] an action on the basolateral side of the marginal cells affecting ion transport by these cells shown in isolated tissues maintained *in vitro*;[47] and, consistent with inhibition of ion transport in the SV, sections of temporal bone from patients who have died during a course of erythromycin therapy have shown extensive oedema of the SV.[45] However, the precise site of action of the macrolides in the SV has not yet been identified.

Agents causing reversible effects on hair cells

Salicylates and **quinine** cause TTSs across most of the detectable frequency range, and tinnitus. Dizziness is reported as a symptom of the use of either of these drugs, but there have been no experimental studies of their possible effects on the vestibular system. The ototoxic effects of these agents are generally reversible when treatment ceases; salicylates are rarely associated with permanent hearing loss.[48] Although it has been reported that excessive doses of quinine or chloroquine may result in permanent deafness,[49] quinine-induced ototoxicity is also usually completely reversible both in healthy volunteers and in patients with malaria.[50]

Salicylates produce threshold shifts across all frequencies simultaneously, indicating effects along the entire cochlear spiral. The shifts are usually no more than 40–60 dB and almost equal across the frequency range or somewhat greater at higher frequencies. These symptoms are completely reversible within 1–3 days following withdrawal of the drug and usually develop only at the high dosage levels used in treating rheumatoid arthritis, 2–5 g/day.[48] Salicylate enters perilymph rapidly after systemic administration, peak levels in perilymph being reached 1–2 hours after injection. The concentration in perilymph is linearly related to the serum concentration,[51, 52] and deterioration of auditory and neural thresholds is linearly related to perilymph salicylate concentration. Thus, the degree of threshold shift is quantitatively related to salicylate plasma concentration. These findings indicate that salicylate penetrates the blood–perilymph barrier readily.

Experimental studies in animals have shown that salicylate causes threshold shifts only at low stimulus intensities; responses to stimuli above about 60 dB appear to be unaffected. The tuning of responses of individual nerves to their characteristic frequency also is lost.[53, 54] In addition, otoacoustic emissions, are reversibly suppressed in humans[55, 56] and animals.[53, 54] These findings suggest effects of salicylate on OHCs and inhibition of the activity that produces signal amplification in the cochlea. EP is unaffected following salicylate administration[54, 57] and effects of salicylates on cochlear vasculature and thereby activity of the SV in generating EP are not considered to be a significant factor in their ototoxicity. Rather, OHCs appear to be the primary target of salicylate following its entry into the perilymph and access to a site of action on the basolateral membrane. Salicylates inhibit electrically driven motile responses of isolated OHCs.[58, 59] It is these responses that *in vivo* are thought to underlie the cochlear amplification mechanism.[60, 61] Investigation of basilar membrane mechanical responses to sound stimulation during salicylate perfusion *in vivo*[62] have confirmed direct effects on OHCs that adversely influence their active responses and thus, auditory sensitivity. The fast motile responses of OHC are driven by the 'motor' protein prestin, which is unique to OHC and is packed into its basolateral plasma membrane.[63] There is evidence that reversible interactions with anions produce conformational changes in prestin that result in the reversible electrically driven changes in OHC length.[64] Salicylate, an anion, appears able to interact with prestin and block this electromotility.[64]

Likewise, **quinine**, at therapeutic doses of 200–300 mg per day, can cause threshold shifts at all frequencies, effects which are usually entirely reversible, disappearing upon withdrawal of the drug.[50] As with salicylate, quinine enters perilymph rapidly,[65] reaching perilymph

concentrations directly related to serum concentrations and direct perfusion of quinine into the perilymphatic space revealed threshold shifts in a number of sound-evoked responses the magnitude of which are related to perilymphatic concentration of the drug between 10 µM and 100 µM.[66] However, unlike salicylate, quinine affects cochlear responses across all stimulus intensities, not just the lower ones, indicating a site(s) of action different from salicylate and not confined to the cochlear amplifier. It has been reported that at the lowest concentrations at which effects can be detected, around 0.05 mM, quinine does not affect OHC responses, such as OAEs, but produces a reversible elevation in threshold for the compound action potential (CAP), which derives from stimulation of inner hair cells (IHCs), without affecting neural tuning.[67, 68] Tuning derives from the activity of OHCs that produces amplification. This suggests that the initial site of action of quinine may be on the IHC, synaptic transmission at the base of IHCs, or/and upon the spiral ganglion neurons themselves, with OHCs affected only at higher concentrations. An effect of quinine at the hair cell synapse could also explain vertigo as the ready entry of the drug into perilymph would enable it to gain access to the basolateral membranes of vestibular hair cells. It has been found that quinine and its derivatives such as chloroquinine block nicotinic acetylcholine receptors (nAChR) composed of α9α10 subunits,[69] which are the predominant acetylcholine receptor subunit composition of hair cells in both chicks and mammals.[70, 71] Acetylcholine is the predominant efferent neurotransmitter in the cochlea. Efferent fibres synapse with the afferent neurones of IHC just below the hair cell body and modulate the responses of those afferents to stimulation, and they synapse directly with OHC whose activity is regulated by the efferent system. Thus, the effects of quinine may result from its action at these efferent synapses.

The ototoxic effects of salicylate and quinine thus derive from an ability to cross the blood–perilymph barrier freely, illustrated by the rapid onset of responses, so they may become distributed throughout perilymph along the entire cochlea, indicated by effects across the entire frequency range, and consequently gaining access to the basolateral membranes of hair cells and to the neurons and their synapses with the hair cells. Since the particular activities of OHC in producing signal amplification are associated with specializations along the basolateral wall, these will become vulnerable, as with salicylate. The characteristics of the symptomatology of the hearing impairment produced by salicylate and quinine thus provide an immediate insight into the likely routes of entry and potential sites of action of the ototoxins.

Agents that cause permanent hearing loss and balance disorders

The third group of agents are those whose administration causes permanent hearing impairment and/or balance dysfunction as a result of death of the hair cells. The ototoxicity of most of these agents usually develops only after repeated systemic administration; a single systemic application does not generally affect hearing or balance.

AMINOGLYCOSIDE ANTIBIOTICS

The aminoglycoside antibiotics constitute the clinically most important group of ototoxic agents. They are toxic to hair cells in all inner ear sensory patches in all vertebrate classes as well as neuromasts of the lateral line systems of fish and aquatic amphibia. Indeed, the nematocyst cells in marine and aquatic invertebrates, which are mechanotransducing cells thought to be evolutionarily related to vertebrate hair cells, are also affected by aminoglycoside.[72] Although all aminoglycosides are potentially both cochleotoxic and vestibulotoxic, the different aminoglycosides exhibit differences in their toxic potential and organ preference. Assessment of the degree and time course of functional impairment following cochlear perfusion with different aminoglycosides[73] and analysis of the extent of damage to cultured explants of the murine organ of Corti directly exposed to different aminoglycosides[74] have established similar rank orders of cochleotoxic potency for different aminoglycosides. These have indicated that neomycin is the most toxic, gentamicin, kanamycin and tobramycin less so, and amikacin and netilmicin least toxic, but such differential toxicity may not apply in a clinical setting. Streptomycin and gentamicin are considered more vestibulotoxic than cochleotoxic to humans, whereas amikacin and neomycin are primarily cochleotoxic in the human inner ear. The reasons for such preferences are not known, but it is not related to any site-specific uptake mechanism or drug levels in the tissues.[75] There are also species differences in susceptibility to the different aminoglycosides of which dihydrostreptomycin provides the most striking example.[76, 77] In early clinical use dihydrostreptomycin proved to be markedly toxic to the human cochlea. However, in the macaque monkey treated with large doses of dihydrostreptomycin for a prolonged period, there was only a very modest shift in auditory threshold at the highest frequency tested, and less than 10% of the hair cells were absent at the basal end of the cochlea.[77] In contrast, the patas monkey was affected in a manner similar to humans and appeared to be the only laboratory animal whose cochlea was sensitive to the toxic action of dihydrostreptomycin.

The effects of aminoglycosides usually become manifest only after days or weeks of parenteral treatment. Single systemic administrations are not normally damaging to the inner ear, but topical application of a single dose of the drug to the middle ear cavity can almost immediately initiate the progressive damage observed after chronic systemic treatment.[24, 78] The severity of the effects increases progressively with time, continuing after drug administration has been stopped; insidiously, in some cases, hearing impairment may not even begin until after treatment has ceased. The initial effect in the cochlea is a hearing loss confined to the high frequencies,[79] indicating hair cell damage in the most basal region of the cochlea. The hearing loss then continues progressively to include

successively lower frequencies, indicating a spread of the damage to hair cells apicalwards along the organ of Corti spiral and involving frequencies in the human speech range and thus ultimately to cause a permanent communication disability. A bilateral loss of 20 dB at two or more adjacent test frequencies is accepted as a hearing impairment.[80] However, most clinical audiometry usually covers the frequency range only from about 8 kHz downwards, whereas in the average person the high-frequency limit is about 16–18 kHz, so that the initial ototoxic effects of the drug will be missed unless high-frequency audiometry is used. Vestibular damage from systemic aminoglycoside administration results in severe unsteadiness that becomes worse in the dark. Perception of unreal movement, usually elicited by head motion, can also occur. Objective clinical assessment is, however, difficult and limited.[80]

Location and nature of lesions

Aminoglycoside-induced hair cell death occurs in a distinct pattern. In the organ of Corti, in line with the pattern of hearing loss, hair cells in the basal (high-frequency) coil are affected first, damage spreading progressively apicalwards with time and with increasing dosage. Outer hair cells are more sensitive than inner hair cells (**Figure 59.2**). IHCs do not usually appear to die until all the OHCs in their immediate vicinity and may persist for months after there has been complete loss of all OHCs.[81] The delay before IHCs are affected may suggest that their loss is a secondary event that occurs as a consequence of OHC loss and unrelated to the initial ototoxic events.[81]

There is also significant progressive loss of spiral ganglion neurons, the afferent nerves that innervate hair cells. This appears to progress following death of IHCs[76, 82] and has been ascribed to a loss of the neurotrophic factors NT-3 and BDNF derived from the IHCs that are necessary for neuronal survival[83, 84] together with loss of continuing stimulation normally provided by IHC activity. Perfusion of neurotrophic factors into the cochlea following aminoglycoside administration has been shown to ameliorate loss of the auditory neurons.[85] This has been suggested as a means to preserve cochlear innervation to enhance the efficacy of cochlear implants.[86, 87] However, recent work on the effects of noise and ageing has indicated that loss of a subpopulation of afferent terminals from IHCs may precede any overt hair cell loss.[88] This may be the basis of some more subtle forms of hearing impairment, such as difficulties in detecting speech in noise, when auditory thresholds as recorded by routine testing procedures are unaffected. The loss of the terminals is thought to occur by excess release of the neurotransmitter glutamate from the IHCs at synapses with afferent terminals causing excitotoxic damage to the nerve. However, it is not yet known if this occurs with aminoglycoside-induced injury.

In the vestibular system aminoglycoside-induced hair cell loss is seen initially in the central regions of the epithelia, i.e. at the crests of the saddle-shaped cristae and across the 'striola' along the middle of utricular and saccular maculae. HC loss then spreads progressively towards the peripheries.[89] There is also differential susceptibility among the vestibular organs; in an individual subject, cristae show greater HC loss than the utricle which in turn

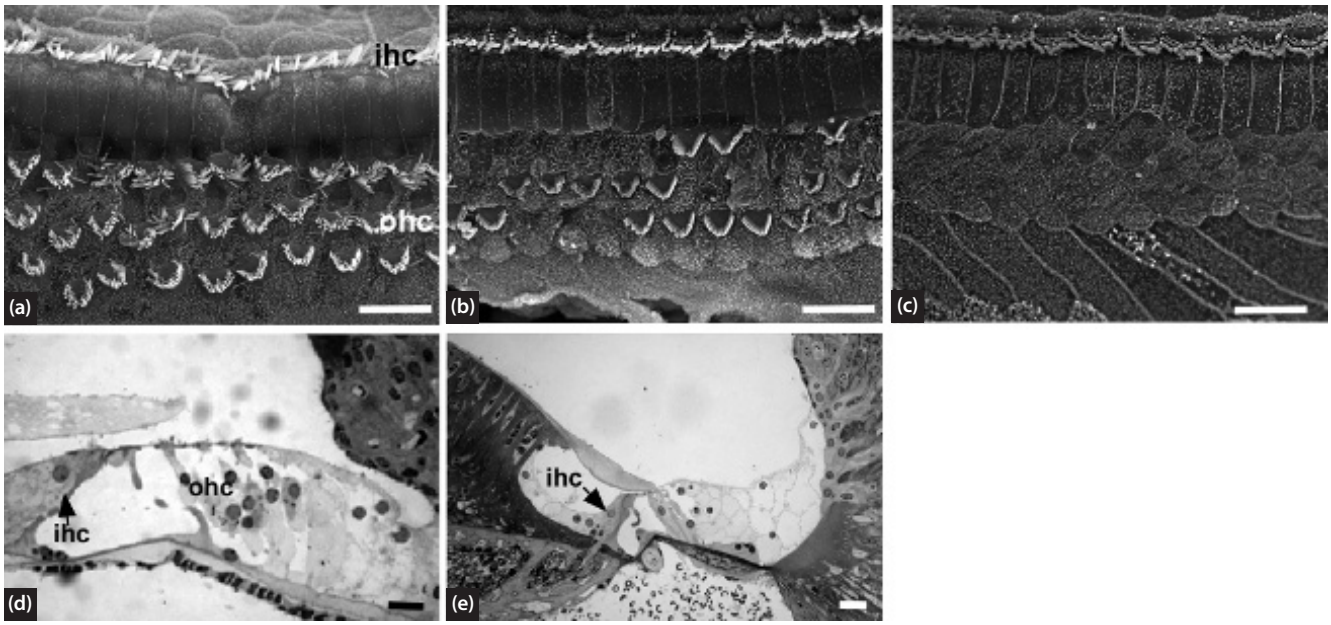

Figure 59.2 Effects of aminoglycoside in the organ of Corti. **(a,b,c)** Scanning electron microscopy of the apical surface of mouse organ of Corti in the apical coil: **(a)**, middle coil **(b)** and basal coil **(c)** after aminoglycoside treatment of animals. In the apical coil all inner hair cells (ihc) and almost all outer hair cells (ohc) are present. In the middle coil there is significant loss of ohc. In the basal coil, 6 weeks after the end of the treatment, all ohc are lost but almost all ihc are still present. **(d,e)** Sections of the organ of Corti of a mouse following chronic aminoglycoside treatment: **(d)** apical coil – all ohc as well as ihc are present; **(e)** basal coil – there are no ohc but ihc are present. Scale bars in all images: 10 µm.

shows more extensive damage than the saccule.[82] This differential susceptibility conforms to a differential uptake of aminoglycoside between the two hair cell types; immunohistochemistry has shown preferential uptake of gentamicin into the type 1 hair cells.[90] The type 1 hair cells predominate on those regions where damage is initiated and are thought to be more susceptible to aminoglycoside-induced damage than the type 2 vestibular hair cells.

The death of each hair cell is accompanied by expansion of the supporting cells around them to close the lesion and effect tissue repair (**Figure 59.2**).[27, 91–94] Supporting cells are not usually affected by aminoglycosides (or other ototoxins). Following the initial lesion closure by expansion of the supporting cells, reorganization of the sensory epithelium may continue for some time after hair cell loss and ultimately the crest of cells that normally constitutes the organ of Corti can become replaced by an apparently simple cuboidal-like epithelium across the basilar membrane.[95] In the organ of Corti lost hair cells are not replaced, but there is some evidence for regeneration of hair cells in the mammalian utricle,[23–26] including that of humans.[27] The extent to which this occurs is limited and only a proportion of the lost hair cells may be replaced by new ones.[24, 27] In birds and other non-mammalian vertebrates regeneration of hair cells is extensive and can lead to complete recovery of damaged sensory epithelia.[18, 21, 96] The replacement hair cells derive from the supporting cell population through initiation of cell division among the supporting cells and/or through direct non-mitotic transdifferentiation, or 'phenotypic conversion' of supporting cells into hair cells.[21, 22, 26, 97] Enhancing the phenotypic conversion mechanism is the basis of some attempts to develop therapies to induce hair cell regeneration in the mammalian inner ear.

Pharmacokinetics and mechanisms of toxicity

There is a linear relationship between serum concentration of aminoglycoside and the perilymph concentration,[2, 98] but aminoglycosides enter perilymph relatively slowly, the peak concentration after extravascular injection to guinea pigs occurring much later in perilymph (about 4 hours) than in serum (about 15–30 minutes). However, clearance from perilymph is delayed and the drug persists in the inner ear for some time. The half-life of aminoglycoside in the inner ear has been estimated as more than 30 days.[99] The peak level reached in perilymph after multiple dosing has been reported to be approximately 50–250 μM,[2, 99–101] but following systemic administration appears in greater amounts in the scala tympani of the apical turn than in the basal coil.[2] Aminoglycosides also enter endolymph, but only after a prolonged period following entry into perilymph. While this has been interpreted to suggest that aminoglycosides enter endolymph from perilymph,[99] some other evidence has suggested that they are taken up quite rapidly into marginal cells of the SV directly from the strial vasculature.[102] Once inside marginal cells there is the potential to enter endolymph directly. Whether there is a similar route into endolymph in the vestibular system, perhaps via dark cells, has not been tested. Nevertheless, persistence in perilymph and delayed entry to endolymph may account for the delayed effects of aminoglycosides. The delayed responses and the progressive effects may result from slowly increasing endolymphatic concentrations of the drug to critical levels that can cause damage. Several pieces of evidence from a range of experimental models suggest that aminoglycosides affect hair cells through access from their endolymphatic (apical) surface.

The susceptibility of all hair cell types in all vertebrate classes emphasizes that hair cells are specific targets of the aminoglycosides, and studies using radioactively or fluorescently labelled aminoglycosides administered to animals have shown that the drug is indeed taken up specifically into hair cells in the mammalian cochlea.[103, 104] The common feature of all hair cells is the transduction apparatus at their apical poles and it is apparent from a range of experimental studies in a variety of animal models that one of the major routes of entry for aminoglycosides into hair cells is through the mechanotransduction channels at the tips of the stereocilia.[105–107] In fact, aminoglycosides are one of the few known blockers of the hair cell transduction channel. Mutations in genes that encode proteins known to be involved in regulating opening of the transduction channels, such as myosin 7a, prevent entry of aminoglycosides into the hair cells and the hair cells are protected from lethal injury.[108] This demonstrates that entry of aminoglycoside into the hair cell is necessary to cause the cell death. Blocking entry would prevent aminoglycoside-induced hair cell death and one current line of research is to determine modifications of the aminoglycoside molecule that retain antimicrobial activity but are unable to enter the transduction channel.[109] Entry via the transduction channels could provide one explanation for the base-to-apex gradient in hair cell death along the cochlea: the probability of the open state of the transduction channels in OHCs in the basal coil is 50%, but the open state probabilities decrease towards the cochlear apex.[110] However, other/additional factors may also underlie the differential sensitivity to aminoglycosides of hair cells along the cochlear spiral.

Although entry into the cell is necessary for aminoglycosides to trigger hair cell death, it is not sufficient. Following systemic administration, gentamicin can remain inside hair cells for as long as 11 months without injury ensuing.[111] This implies that the cell death occurs only after some critical concentration of the drug has been reached inside the cell. Aminoglycosides cause death of hair cells by inducing apoptosis,[81, 91, 92, 112, 113] a programmed cell death pathway in which particular enzymes called caspases play the crucial roles. Gentamicin-induced hair cell death can be prevented by pan-caspase inhibitors.[112, 114, 115] A number of different cellular stress-activated biochemical pathways that lead to apoptosis have been identified as being triggered following aminoglycoside treatment[116–119] and offer potential therapeutic targets of intervention for preventing aminoglycoside-induced hair cell death.[120, 121]

One significant initiator of programmed cell death leading to apoptosis is generation of reactive free radicals.[122, 123]

Every cell in the body produces reactive oxygen species (ROS) as part of normal metabolism through enzymatic reactions and the oxidative respiratory mechanisms in mitochondria. Naturally produced ROS are normally removed as substrates or act as messengers in other biochemical reactions or they are neutralized by inherent cellular scavengers such as glutathione or specific enzymatic neutralizing systems such as superoxide dismutases. However, adverse conditions lead to overproduction and/or insufficient scavenging of ROS. The resultant oxidative stress upsets homeostatic redox balance, leading to damage to cellular components, proteins and lipids in particular, through oxidation/reduction reactions and can trigger cell death pathways.

There is evidence that hair cells may be vulnerable to oxidative stress. In strips of organ of Corti isolated from the cochlea and maintained in short-term culture, even without exposure to aminoglycosides, OHCs from the basal coil die much more quickly than those in apical coils. The survival of basal coil OHCs can, however, be enhanced by addition to the maintenance medium of free radical scavengers, including n-acetyl cysteine, salicylate and glutathione.[124] This indicates that in the cochlea, basal coil hair cells are more susceptible to oxidative damage than those at the apex. Effects of aminoglycosides that lead to the release of free radicals to levels in excess of cellular mechanisms to detoxify them has been considered one potential route through which aminoglycoside-induced hair cell death is triggered and a number of mechanisms of how this might occur have been proposed.[75, 120, 121] Following the discovery that mutations in mitochondrial genes that encode for mitochondrial rRNAs are associated with enhanced susceptibility to aminoglycoside-induced hearing loss (see below), a number of studies now suggest that aminoglycosides may damage mitochondria leading to production of ROS to lethal levels and release of pro-apoptotic factors from the mitochondria.[120, 121] Mitochondria are derived during evolution from bacteria and they contain their own distinct set of genes, separate from the genes encoded by the cell's nuclear DNA. These genes encode some of the mitochondrial proteins and the ribosomal- (r-)RNAs necessary for their translation. Bacterial r-RNAs are the target for aminoglycosides as antibiotics. Damage to mitochondria releases not only ROS but also a number of factors normally resident within mitochondria that regulate the cascade of reactions leading to apoptosis.

Suppressing the generation or enhancing the scavenging of ROS have therefore been proposed as potential therapeutic interventions for protecting hair cells from the lethal damage caused by aminoglycosides.[120, 125] However, the direct evidence that aminoglycosides trigger generation of ROS in hair cells *in situ* in the mature organ of Corti is limited. Nevertheless, in an experimental study the aminoglycoside apramycin, which has potent antibacterial activity and is used in veterinary medicine, was found to cause less hearing impairment and hair cell loss *in vivo* than other aminoglycosides and in explant cultures of the organ of Corti from neonatal mice generation of ROS was reduced in comparison with gentamicin.[126] The studies with apramycin are part of a further current line of investigation: to design aminoglycoside molecules with antimicrobial activity but which do not activate cell death pathways inside hair cells.

Effects of aminoglycosides on the stria vascularis

Although hair cells are the primary site of aminoglycoside action, the drugs are taken up quite rapidly into marginal cells in the SV.[127] A decrease in the volume of the SV (strial atrophy) has been observed in human temporal bones obtained within 2 weeks of aminoglycoside treatment.[128] In experimental studies in animals immediately following the end of a course of aminoglycoside treatment alterations to the stria can be seen at the same time as the earliest effects in the organ of Corti are apparent.[129] The subsequent decrease in the thickness of the stria is due to effects almost exclusively on marginal cells.[30] Some cells are lost by a process which shows morphological attributes of apoptosis, but the majority of marginal cells remain but with much reduced volume. Such alteration might be expected to affect EP and the ionic profile of endolymph, but EP appears to be maintained at close to normal levels for up to 4 weeks after the end of aminoglycoside treatment but is reduced by more than half 12 weeks after treatment when there is significant decrease in strial thickness (see **Figure 59.1**).[130] Interestingly, the changes to the stria and coincident relatively small decreases in EP that occur with aminoglycosides are similar to those seen with ageing in a gerbil model.[131] Here there is significant thinning of the stria but EP is little affected until the stria is less than one-third its normal volume when there is a catastrophic loss of EP. These results might suggest that there is significant redundancy in the stria; EP and organ of Corti activity can be maintained even when there has been considerable strial injury. Thus, it maybe that the stria can sustain injury for some time without a noticeable effect on auditory function, but in this 'compromised' state it might be less able to resist further insults. Consequently, a sudden loss of auditory function might ensue in conditions which would otherwise not be expected to cause hearing loss.

Confounding factors and genetics

The degree of vestibular or auditory impairment with aminoglycosides may depend upon the drug itself, the unit or total dose, the route and period of administration and the patient's age or pathological state; for example, the risk is substantially increased by impaired renal function.[132] The situation is further complicated in that the aminoglycosides, to varying degrees, are nephrotoxic. Genetic factors also play a role.[17] A predisposition to aminoglycoside ototoxicity is conferred by mutations in the gene that encodes 12s ribosomal RNA of mitochondria. The 'A1555G' missense mutation (an adenosine to guanosine substitution at base position 1555),[133, 134] a thymidine to cytosine mutation at 1095,[135] cytosine to thymidine missense at 1494,[136] and a cytosine insertion at position 961, all appear to confer particular sensitivity to aminoglycoside. In some

cases profound hearing loss may occur after only a single parenteral injection rather than the usual situation where hearing loss occurs only after several repeated administrations. The presence of these mutations in the mitochondrial chromosome has been identified through maternal inheritance patterns. The prevalence of A1555G mutation has been estimated as 0.19% in children in the UK[17] but is greater in Chinese, Arab-Israeli, Japanese and North American families[137, 138] and may be as high as 1% in these populations. A carrier rate of 17% of those developing aminoglycoside-induced hearing loss been estimated. However, the mutations appear to affect only the cochlea's sensitivity to aminoglycoside; there is no enhanced effect on the vestibular system, and no other organ of the system is affected. The reasons why only cochlear hair cells are affected or how the mutation enhances susceptibility are currently not known.

Aminoglycosides may also present a problem for those with tuberculosis and for cystic fibrosis patients. These antibiotics were first developed for use against tuberculosis and are still part of combination drug therapy against it. However, it has been estimated that as many as 80% of patients receiving aminoglycosides chronically to treat tuberculosis develop ototoxic side effects. There is also a significant incidence of hearing loss in cystic fibrosis patients who receive continuous treatment with aminoglycosides to combat pneumonia.[139–141] A further consideration is that aminoglycoside antibiotics can cross the placenta. Thus there is a potential to cause deafness in the foetus. Studies of development in animals have suggested a 'critical period' in development, when sensitivity to the ototoxic agent is greatest at around the time of the onset of auditory function during development. The existence and timing of a critical period in humans has not been identified but, based on anatomical findings comparing development of the human inner ear with that of experimental animals, it has been estimated that a critical period for the human cochlea maybe present in about weeks 18–20 of gestation. An ototoxic action of aminoglycosides during intrauterine life of human embryos has been reported.[141]

Interactions

Noise and aminoglycosides. Both epidemiological studies of the incidence of hearing loss in man and experimental studies in animals have indicated that noise exposure in conjunction with aminoglycoside may cause more extensive damage than with either agent alone.[143] Indeed, exposures under conditions in which neither noise nor the aminoglycoside alone would be expected to cause damage can result in marked auditory impairment and hair cell loss when the two agents are presented together. Animals reared in a sound-attenuated room do not take up gentamicin as extensively as animals raised in the environment of a normal animal facility.[144] This could result from increased uptake through the transduction channel; in the presence of sound stimulation, more transduction channels will be in the open state more frequently thereby enabling increased entry of the aminoglycoside than would be the case in a quiet environment. With increased sound exposure this effect will be enhanced. Thus, with exposure to noise, aminoglycoside uptake to a 'critical' level necessary to cause hair cell death would be reached more quickly. High sound pressure levels also lead to the generation of a variety of free radical species,[145, 146] which would exacerbate the effects of aminoglycoside-induced cellular stress.

Loop diuretics and aminoglycosides. Clinical experience and animal studies have also shown that coadministration of a single dose of loop diuretic with a single systemic administration of aminoglycoside, neither of which alone would cause hair cell loss, produces significant cochlear damage.[147] All aminoglycoside antibiotics have been found to interact with loop diuretics.[147] Administration of an intravenous dose of ethacrynic acid, frusemide or bumetanide shortly before a single, non-ototoxic dose of kanamycin rapidly produces depression of cochlear function which is permanent and associated with extensive hair cell destruction.[148, 149] A similar protocol applied to mice, subcutaneous injection of kanamycin followed after about 40–60 minutes with a single intraperitoneal injection of bumetanide causes almost complete loss of almost all OHCs within 48 hours of injections.[81] The SV is also affected, becoming progressively thinner through loss of marginal cells. The effects of the interaction are generally confined to the cochlea; no significant loss of hair cells is apparent in the vestibular system which appears to remain unaffected even at prolonged periods of time after all OHC have been lost from the organ of Corti.[81, 150]

The loop diuretics markedly increase the penetration of aminoglycosides into endolymph[151] and enhance uptake of gentamicin into cochlear hair cells.[81, 127] The potentiation of cochleotoxicity following systemic adminstration of both agents therefore likely arises because the diuretic enhances uptake of the aminoglycoside from the systemic circulation into endolymph. It is perhaps noteworthy that the interaction is only manifest when the time between administration of the two agents is relatively short, the diuretic administered no more than 1 hour before or 2 hours after the aminoglycoside[147] and that the vestibular system is not affected following the combined administration of single doses of these drugs. The timescale covers the time over which the EP is significantly reduced. The reduction in EP to negative values from the normally high positive potential may encourage entry of the cationic aminoglycoside into endolymph. Since there is no equivalent of EP in the vestibular system and diuretic does not cause a reduction of the positive diffusion potential of the vestibular endolymph, such enhancement of aminoglycoside uptake into vestibular hair cells would not occur.

CISPLATIN

Sites of action and nature of effects

Cisplatin (*cis*-dichlorodiammine platinum II [*cis*-DDP] or *cis*-platinum) is used to treat various tumours of soft tissue. Like the aminoglycosides, it is nephrotoxic as well as ototoxic.[120, 152–154] It has been estimated that the current clinical protocols for its use result in at least 60% of patients

suffering some degree of hearing impairment. Hearing loss often progresses after completion of drug therapy, which may in part be related to prolonged retention of platinum in the body; significantly higher levels of platinum than normal were detected in ex-patients at least 6 years, and in some reports longer, after the completion of *cis*-DPP therapy.[154, 155] Cisplatin induces a progressive loss of hair cells, the extent of which correlates with the dose of drug administered.[156] This occurs following repeated injections of relatively low drug doses (1 mg/kg daily) administered by intramuscular, intraperitoneal or subcutaneous routes, and after a single intravenous high dose (10–12 mg/kg).[31, 157, 158] The pattern of hair cell damage in the cochlea also resembles that of the aminoglycosides; hair cells in the basal coil of the cochlea are preferentially affected with damage spreading progressively apicalwards.[157, 158] As with aminoglycosides, the IHCs appear to be relatively resistant to damage following cisplatin administration.[159, 160] These histopathological findings correlate with assessment of auditory function in both animals and patients which shows an initial high-frequency hearing loss measured by auditory brainstem response (ABR), and suppression of otoacoustic emissions indicating an effect on OHCs.[161, 162] However, auditory neural threshold is increased to a greater extent than OAE, suggesting cisplatin may have direct effects upon the spiral ganglion cells themselves.[163] Since IHCs appear to be intact, these discrepancies suggest an effect at the level of the auditory nerve. Detachment of the myelin sheaths from type 1 spiral ganglion cells (those that innervate IHCs) has been observed and appears to progressively increase in extent in parallel with loss of OHCs. This suggests that the injuries at the two sites are separate phenomena.

Effects in the SV are also apparent. Cisplatin causes a decline in EP within 1 day of single intravenous high dose and it may become completely lost, though with lower repeated doses the effects take longer and appear less severe.[31, 164] Ultimately, strial atrophy develops several days or weeks after the end of the chronic treatment, which appears to be due primarily to apoptotic death of the marginal cells.[165, 166] That this was apparent in all turns of the cochlea when hair cell death was confined to the basal turns, as well as the fact that differing dosing regimes may influence which tissue is most affected,[167] suggests that effects in the stria and in the organ of Corti are independent of each other.

Cisplatin, therefore, appears to have effects at multiple sites in the cochlea: outer hair cells, spiral ganglion neurons, and the SV and perhaps also fibrocytes of the spiral ligament.[168] Furthermore, although not reported as extensively, cisplatin also causes vestibular dysfunction and loss of hair cells from vestibular sensory organs in patients.[169, 170] Experimental studies in a number of different animal models have confirmed HC loss from the vestibular organs in a manner similar to that resulting from aminoglycosides.[171, 172]

Mechanisms of action

Platinum can be detected in hair cells, spiral ganglion neurons and at particularly high levels in SV following repeated systemic administration of cisplatin.[173] Transport proteins megalin (LRP2), the organic cation transporter OCT2 (also known as SLC22A2) and the copper uptake transporter Ctr1 (SLC31A1) are thought to play roles in cellular entry of cisplatin. Ctr1 has been localized to hair cells, the SV and spiral ganglion cells in mice.[120, 153] Variations in the gene encoding megalin and that of Ctr1[174] have been associated with the severity of cisplatin ototoxicity, but the small size of the populations assessed requires caution in interpreting these results.[17] The uptake of the drug to strial marginal cells would assist potential entry into endolymph and this may be a crucial factor for access to hair cells.[153, 154, 159] A rapid deterioration in the auditory nerve response threshold is produced when cisplatin is present in the scala media at concentrations of about 5 mM, but no effect is apparent with perilymphatic perfusion at drug concentrations of less than 3 mM.[175] This suggests that one possible site of the drug action is at the apical end of the hair cells. Cisplatin has been shown to be able to block transduction currents in isolated hair cells from chicken,[176] and functional mechanotransduction channels have been shown to be required for uptake of fluorescently labelled cisplatin into hair cells in neuromasts of zebra-fish lateral line (a model system for screening for ototoxic drugs).[177] Thus, it is possible that, like aminoglycosides, cisplatin gains entry to endolymph from the SV, and an affinity for the hair cell transduction channel may underlie its specific action upon hair cells, but there is no conclusive evidence for this.

Once inside a cell cisplatin leads to cross-linking of nuclear DNA, which in proliferating cells, such as those of tumours, inhibits DNA synthesis, induces cell cycle arrest, suppresses transcription and ultimately leads to apoptosis. The majority of cells in the inner ear into which cisplatin enters are, however, non-proliferative. Nevertheless, damage to DNA is likely to occur which will activate DNA repair mechanisms. Polymorphisms in genes for two DNA repair enzymes, ERCC2 and XPC, have been associated as risk factors for cisplatin-induced hearing loss,[120, 152, 153] but the mechanisms underlying such risk are not clear. Cisplatin also binds to several other molecules, perhaps most significantly to sulphhydryl-containing molecules such as metallothineins and glutathione that scavenge free radicals and thereby it negatively affects redox balance. The binding to glutathione upsets the turnover and cisplatin ototoxicity correlates with a decrease in cochlear glutathione and significant decrease in the activity of glutathione peroxidise and glutathione reductase in cochlear tissues.[178] In addition, variants in the glutathione-5-transferase gene show a significant association with cisplatin ototoxicity.[17] Hearing loss in children receiving cisplatin has also been associated with genetic variants in two genes that encode enzymes in the methionine pathway that is involved in maintaining glutathione levels, thiopurine-5-methyltransferase (TPMT) and catechol-O-methyltransferase (COMT).[17, 179] Interference with antioxidant systems in the cochlea would lead to accumulation of free radicals and the consequent death of the hair cells though cisplatin may additionally cause generation of excess ROS,[120] possibly though effects in mitochondria.[153] However, there is evidence that agents

such as d-methionine and 4-methylbenzoic acid, which enable maintenance of glutathione levels or preserve the activity of associated enzyme systems, may be effective in preventing the ototoxic effects of cisplatin *in vivo* and clinical trials have been initiated.[152, 167, 180]

Interactions

Noise and cisplatin. There is some evidence, primarily from experimental studies in animals, that noise exposures above about 70 dB concurrent with cisplatin administration can induce hearing impairments and hair cell loss much greater than those expected from either the noise exposure conditions or cisplatin dosing regime alone.[181] In addition, cisplatin treatment appears to increase susceptibility to noise-induced hearing impairment and hair cell loss at prolonged periods after the end of cisplatin treatment.[182] Increased susceptibility to hearing loss in patients who have received cisplatin even some years prior to noise exposure has also been reported.[183] This may be a reflection of the long persistence of platinum in the body and might suggest prolonged suppression of antioxidant mechanisms. It argues for cautioning patients who have received cisplatin and perhaps long-term audiological follow-up.

Diuretics and cisplatin. Like aminoglycosides, a single dose of a loop diuretic administered shortly before or shortly after a single administration of cisplatin leads to extensive and quite rapid hearing loss and death of outer hair cells.[159, 184, 185] The underlying reason for this is likely to be similar to that with aminoglycoside–diuretic combination, the decline in EP enhancing uptake of the cisplatin into endolymph.

ORGANIC SOLVENTS

Exposure to high concentrations of organic solvents induce acute, reversible narcosis and neurotoxicity, but the possibility of ototoxic damage was initially recognized from the unusually high number of workers in the chemical industry who showed a hearing loss, and from case reports of hearing deficits in solvent abusers.[186] The effects of solvents may be exacerbated by concurrent exposure to high noise levels, or the converse, i.e. noise-induced hearing loss becoming more pronounced with concomitant exposure to certain solvents presenting a significant occupational hazard.[187, 188] Vestibular dysfunction may also follow from exposure to organic solvents but this may result from specific effects on vestibulo-oculomotor pathways in the vestibulocerebellum rather than from effects in the inner ear.[188] This would be classified as neurotoxicity rather than ototoxicity for the definitions used in this chapter.

A number of different aromatic solvents have been implicated in ototoxicity,[186] and in a comparative study conducted in rats of 21 different solvents 8 were identified as ototoxic: toluene, p-xylene, ethylbenzene, n-propylbenzene, styrene, ά-methylstyrene, *trans*-β-methylstyrene and allylbenzene.[189] Trichlroethylene has also been reported to be ototoxic.[190, 191] The features of the ototoxicity caused by all these agent are similar and are exemplified by the effects of toluene following exposure by inhalation in rats.[192] ABR and behavioural audiometry revealed auditory deficits after repeated exposures to high doses for periods of 2–16 weeks. Similar results were subsequently obtained after subcutaneous administration. Concomitant with the permanent hearing loss that results, OHCs are lost.[192, 193] Suppression of otoacoutic emissions by toluene confirms the OHCs as a site of injury *in vivo*.[194] However, unlike the ototoxins discussed above, the characteristic features of damage caused by toluene are:

- It is the mid-frequency ranges of hearing that are affected rather than the high frequencies,[190, 194] which coincides with HC loss in the middle and apical turns of the organ of Corti.[193–195]
- There is a distinct spread of damage from the third (outermost) row of OHCs inwards to involve subsequently the second and maybe the first row of OHCs. Additionally, the supporting cells, especially the third (outermost) row of Deiters cells, are affected.[193]

These features are characteristic effects of all the solvents implicated in ototoxicity.[189–191, 196, 197] The cell bodies of the afferent neurones may also be a target of trichloroethylene.[191] However, there are species differences in ototoxic susceptibility to solvents. While rats have proved to be sensitive, organic solvents do not cause damage in the inner ears of guinea pigs[198, 199] or chinchillas.[200] This obviously raises questions about the use of particular species of animals as models for the likely conditions in humans. However, it has been argued that the way solvents are distributed and metabolized in rats is similar to the human and thus that these animals are an appropriate model.[196]

Since organic solvents are minimally water-soluble their distribution in the inner ear is unlikely to be determined by entry into the fluid spaces. It is their distribution in the tissue that is significant. The pattern of damage across the organ of Corti, from outside to in, has suggested that the solvents reach the inner ear from the vasculature of the SV or the spiral prominence region just below it and then pass through the tissues to the organ of Corti.[196, 201] The cuboidal cells of the outer sulcus and the epithelial cells that connect the epithelia of the lateral wall to the organ of Corti along the basilar membrane may be a major transport route.[201] Upon reaching the organ of Corti, the supporting cells of the organ of Corti, the Hensen's cells that form the outer ridge of the sensory epithelium and the Deiters' cells that surround the hair cells, may then become injured. Deiters' cells, in particular those in the outermost row, have been reported to be the most vulnerable cells in the organ of Corti following styrene administration.[197, 202] The supporting cells are involved in the reuptake of K^+ from around the hair cells, and damage to these cells may therefore result in excessive K^+ levels around the OHC that would lead to their death. The effects of the solvents may be upon the membranes of the supporting cells and of the hair cells themselves. Loss of membrane integrity and cell swelling, perhaps as a consequence of membrane damage,

have been described as early events in the progression of damage in the organ of Corti. Whether the cell death is principally apoptotic[202] or necrotic[196] is contentious, but it has been reported that the death of Deiters' cells, unlike that of hair cells, is not prevented by antioxidants, suggesting that different mechanisms of cell death operate in the two cell types.[197]

Why damage is initiated in the middle frequency region of the cochlea is not clear. It may be of significance that the SV in the middle and apical cochlear turns is affected by trimethyltin,[203] perhaps indicating some characteristic of the vascular pathways and blood flow that may influence solvent distribution.

OTHER OTOTOXIC AGENTS

Good evidence for the ototoxicity of many of the other drugs listed in **Table 59.1** is relatively sparse. Vancomycin has been reported to cause transient hearing loss and/or tinnitus but many of these clinical reports derive from cases in which it has been used in combination with other potentially ototoxic drugs. The few experimental studies which have been performed suggest no loss of hair cells or permanent hearing impairment from systemic administration of polypeptide antibiotics even at very high doses.[204] Viomycin has been reported to be predominantly vestibulotoxic following chronic treatment regimes,[205, 206] and animal studies have confirmed that, after repeated systemic injections of relatively high doses, viomycin causes hair cell death in the vestibular sensory organs in a pattern similar to that seen with aminoglycosides.[207] Chloramphenicol has been shown to cause irreversible hearing loss following infusion into the middle ear cavity in animals,[208] presumably gaining access to the perilymph following uptake across the round window membrane, but clinical reports of hearing loss following use of chloramphenicol are rare. Polymyxin B when perfused through the perilymphatic spaces caused an almost immediate decline in cochlear microphonic (CM) potential followed shortly after by a decline in EP, suggesting separate effects on both the organ of Corti and the SV.[209] However, the rarity of clinical reports in which an ototoxic effect can be attributed directly to polymyxin B suggests the use of this antibiotic does not present a significant risk to the inner ear. Desferrioxamine (deferoxamine mesylate (DFO)) binds iron and is used in patients with β-thalassaemia to remove excess iron from the serum. In cultured explants of inner ear sensory epithelia DFO attenuates aminoglycoside-induced hair cell loss.[112] However, repeated high-dose systemic administration of DFO to patients has been reported to cause high-frequency hearing loss in about 20–40% of those receiving long-term therapy.[210–212] On the other hand, other clinical studies failed to identify a direct ototoxic effect of DFO[213, 214] and experimental studies with a mammalian model (chinchilla) could find no effects on cochlear physiology following long-term systemic treatment.[215] The reasons for these apparent discrepancies have not been resolved. Differences between experimental models may derive from the differences in susceptibility between species, known to be the case for aminoglycosides (above), and differing treatment regimes and/or patient groups may account for differences in clinical reports.[211, 216]

The reports of ototoxicity following the use of other agents listed in **Table 59.1** are often anecdotal and there are no rigorous, well-controlled clinical studies or experimental studies in animal models to confirm and define the ototoxic effects.

FUTURE RESEARCH

- Identification of the cellular stress mechanisms that lead to hair-cell death.
- Therapeutic interventions to inhibit stress-activated pathways or cell-death pathways.

KEY POINTS

- Ototoxic agents may affect hair cells directly; or ion-transporting epithelia and cochlear homeostasis; or both.
- Agents that affect stria vascularis (e.g. loop diuretics) cause temporary hearing impairment across all frequencies through inhibition of endocochlear potential.
- Agents such as salicylate and quinine that gain rapid access to perilymph, cause reversible hearing loss across all frequencies.
- Aminoglycoside antibiotics and *cis*-platinum cause permanent hearing loss that spreads progressively from high to low frequencies following chronic treatment regimes.
- Aminoglycosides and *cis*-platinum also cause vestibular dysfunction.
- Aminoglycosides and *cis*-platinum cause hair-cell death resulting in permanent hearing loss (and balance dysfunction).
- Hair-cell death follows entry of drug into endolymph and then into hair cells across the luminal surface of the cell probably via the transduction channels.
- One factor underlying hair-cell death may be production of excess free-radicals to toxic levels following aminoglycoside or *cis*-platinum challenges.
- Aminoglycosides and *cis*-platinum may cause atrophy of the stria vascularis. *Cis*-platinum may also have direct damaging effects on spiral ganglion neurones.
- Organic solvents (e.g. toluene, xylene, styrene) also cause hair-cell death and permanent hearing loss.
- Pattern of hair cell and hearing loss with organic solvents different from aminoglycosides and *cis*-platinum: lower middle cochlear turn and mid-range frequencies first affected, damage spreading progressively to lower and higher frequencies (apically and basally respectively along the cochlea).
- Various interactions – aminoglycosides with loop diuretics or with noise; *cis*-platinum with loop diuretic or noise; organic solvents with noise – produced greater damage and functional impairment than either agent alone.

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CHAPTER 60

IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS

Tony Narula and Catherine Rennie

SEARCH STRATEGY

The data in this chapter are based on searches in Medline, Embase and CENTRAL for randomized controlled trials in idiopathic sudden sensorineural hearing loss (ISSNHL). The Cochrane ENT Disorders Group's specialist register of controlled trials was also searched for additional references to randomized controlled trials in ISSNHL. Keywords used were sensorineural hearing loss (SNHL), sudden sensorineural hearing loss (SSNHL), idiopathic sudden hearing loss (ISHL), idiopathic sudden sensorineural hearing loss (ISSNHL), randomized controlled trials, controlled clinical trial and random allocation.

INTRODUCTION

Sudden sensorineural hearing loss (SSNHL) is an otological emergency for which a definitive aetiology and treatment remains controversial, but prompt recognition and management have been shown to improve hearing outcomes and quality of life. The estimated annual incidence is 5–30 per 100 000 persons[1–4] and 99% of cases are unilateral.[5]

The definition is a hearing loss of 30 dB or more, over at least three contiguous audiometric frequencies, that develops over 72 hours or less.[1,2,6] There is a long list of possible causes, but the vast majority of cases are idiopathic. The aetiology is identified in less than 5–10% of cases. Factors including autoimmunity, vascular insult and viral infection have been postulated in the pathogenesis. The low incidence and high spontaneous recovery rate of between 32% and 65%[2,7,8] have made the validation of empirical treatments difficult. In the literature there are large numbers of case series regarding treatments but a relative lack of large randomized controlled trials assessing interventions, as a result of which there has been a wide variation in management of SSNHL to date. The recent development of evidence based clinical practice guidelines for SSNHL[6] should begin to address the heterogeneity in clinical practice. Steroid treatment (either systemic or via transtympanic injection) or hyperbaric oxygen treatments are advocated, but many other treatment regimes have been explored.

SSNHL often affects healthy individuals and is a frightening symptom that prompts the individual to seek urgent medical attention. There is a wide age distribution with an average of 50–60 years and no sex preference.[9] Early recognition and prompt management of SSNHL may improve hearing recovery and the quality of life of the individual.

DEFINITION

SSNHL was described in the literature by De Kleyn in 1944.[10] The following definition is currently accepted in the literature and in clinical practice:

- Sudden hearing loss is defined as the rapid onset, occurring over a 72-hour period, of a subjective sensation of hearing impairment on one or both ears.
- The audiometric criteria of a 30 dB sensorineural loss in at least three consecutive frequencies can be difficult to show clinically as premorbid audiometry is rarely available. Therefore the hearing loss is defined in relation to the contralateral side.
- Idiopathic sudden sensorineural hearing loss is defined as SSNHL with no identifiable cause in spite of thorough investigation.

Clinicians must decide the degree of certainty they are comfortable with when making a decision that the hearing loss is 'new'. There are four levels of 'certainty' about the 'newness' of the hearing loss in the affected ear:

1. Very certain: patient had previous audiometric evaluation.
2. Certain: patient had no prior otologic history and feels his or her premorbid hearing was normal bilaterally.
3. Fairly certain: patient had a long-standing hearing problem and reports that the current episode of SSNHL is subjectively poorer.
4. Uncertain: the clinician feels there was some pre-existing hearing loss, but the hearing loss was never documented.[11]

It is important to differentiate between SSNHL and other causes of SNHL so that early diagnosis and management can be instigated. The possible identifiable causes of SNHL can be divided into the following categories: infectious, traumatic, neoplastic, autoimmune, toxic, circulatory, neurologic and metabolic (**Box 60.1**). The most pressing of these are acoustic neuroma, stroke and malignancy.[12] Despite the long list of possible causes the vast majority of cases are idiopathic.

CAUSES OF IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS

Several factors have been postulated as central to the aetiology of idiopathic sudden sensorineural hearing loss (ISSNHL). Possible causes include labyrinthine viral infection, vascular insult, intracochlear membrane rupture and autoimmune inner-ear disease.

Viral

Viruses, particularly the herpes family, can cause SNHL in acute infection and it is possible that reactivation of the latent virus could cause SSNHL.[13–15] However, the serological evidence for a viral aetiology in SSNHL is conflicting. Wilson et al. found patients with SSNHL to have a statistically significant increase in seroconversion for cytomegalovirus (CMV), influenza B, mumps, rubella or varicella zoster, and 63% of 122 patients had evidence of seroconversion.[16] In contrast, Xenellis et al. showed seroconversion in only 27% of 262 patients with SSNHL for Epstein–Barr virus (EBV), herpes simplex virus (HSV) I and II or CMV.[17] In a smaller study of 48 patients Gross et al. reported positive serology for EBV in 6% and enterovirus in 2%.[18] Mentel et al. studied 55 patients with SSNHL for serconversion to enterovirus, HSV and varicella zoster virus (VZV). They found seroconversion rates of 40% to enterovirus but no evidence of HSV or VZV seroconversion.[19] More recently a large Taiwanese population-based study investigated the frequency and risk for SSNHL following a recent herpes zoster attack in the general population. The results showed that SSNHL is a rare event in the 2 months following an attack of herpes zoster, and the risk of developing SSNHL is not increased among people who have had a recent herpes zoster infection compared with a matching population.[20]

BOX 60.1 Possible causes of sensorineural hearing loss

Infectious	Traumatic	Neoplastic	Autoimmune
Meningococcal meningitis Encephalitis Herpes virus (simplex, zoster, varicella, cytomegalovirus) Mumps Measles Human immunodeficiency virus Lyme disease Rubella Syphilis Toxoplasmosis	Barotrauma Perilymph fistula Intense noise exposure Inner ear decompression sickness Temporal bone fracture Ear surgery (stapedectomy)	Cerebellopontine angle tumours, e.g. acoustic neuroma meningioma Leukaemia Myeloma	Wegener's granulomatosis Rheumatoid arthritis Sjögren's syndrome Polyarteritis nodosa Relapsing polychondritis Lupus erythematosus Ulcerative colitis Cogan's syndrome Antiphospholipid syndrome Sarcoid Autoimmune inner-ear disease (AIED)
Toxic	**Circulatory**	**Neurologic**	**Metabolic**
Aminoglycoside antibiotics Loop diuretics NSAIDs Salicylates Platinum-based chemotherapeutic agents General anaesthesia	Vascular disease/alteration of microcirculation Vascular disease associated with mitochondriopathy Vertebrobasilar insufficiency Red blood cell deformability Sickle-cell disease Cardiopulmonary bypass	Multiple sclerosis Focal pontine ischemia Migraine	Hyperlipidaemia Thyrotoxicosis Diabetes

Examination of temporal bones reveals histopathological evidence which is consistent with viral infection in patients with SSNHL.[21,22] There was shown to be greater loss of neurons in the apical spiral ganglion compared to the basal region without corresponding loss of hair cells and dendrites. This suggests a viral cause since other conditions such as hypoxia, acoustic trauma, presbyacusis and hereditary conditions would result in changes at the basal region. Animal studies experimentally inducing a vascular cause of hearing loss have resulted in cochlear fibrosis and inner ear ossification, which has not been seen in the temporal bone studies of SSNHL patients.[23] Animal experiments have demonstrated viral penetration of the inner ear,[24] and the isolation of virus and viral antigens in perilymph of affected patients provides further evidence for the viral aetiology.

Many similarities have been drawn between SSNHL and Bell's palsy, both neurological conditions with a sudden onset and their symptoms that can be improved with steroid treatment. However, in Bell's palsy a viral aetiology has been demonstrated following the identification of virus in the endoneural fluid of the facial nerve in effected patients.[25] Although a viral aetiology has been hypothesized in SSNHL, the epidemiological, serological and histopathological evidence is inconclusive.

Vascular

The cochlea is supplied by an end artery, and hence is susceptible to damage by vascular occlusion, making a vascular cause for ISSNHL a popular theory. Many treatments to date have been recommended because they are thought to improve cochlear blood flow. Changes in blood viscosity could lead to cochlear ischaemia and hearing loss. However, patients with ISSNHL are no more likely than the general population to have a hyperviscosity disorder.

Ballesteros et al. evaluated 99 patients with SSNHL for thrombophilic genetic polymorphisms and coagulation studies associated with vascular disorders but did not find a significant difference between patients and controls.[26] However, Capaccio et al. investigated 100 patients with SSNHL for five prothrombotic genetic polymorphisms and found a statistically significant association between the incidence of these polymorphisms in the patient group when compared to the control population.[27] In another study by Capaccio ten patients with SSNHL and previously documented cardiovascular disease were found to have a significantly higher number of thrombophilic allelic mutations when compared to the previous 100 SSNHL patients with no history of cardiovascular disease. Einer et al. reviewed a number of haemostatic parameters in 32 SSNHL patients compared to controls.[28] They concluded that, although isolated aberrations in the haemostatic pathway were observed, these were not of decisive importance for the pathogenesis of sudden deafness.

Isolated case series have reported that patients with sickle-cell anaemia and Waldenstrom macroglobulinaemia have a higher risk of SSNHL, but this is usually reversible with treatment.[29,30] Strokes involving the anterior inferior cerebellar artery are associated with auditory and vestibular symptoms, but also cerebellar symptoms. The risk of stroke is also said to be higher in the SSNHL population.[31] In addition, SSNHL following cardiopulmonary bypass has also been reported.[32] Many of these are small studies, however, and there is a lack of experimental, histological and clinical evidence to support this theory.

Intracochlear membrane rupture

Rupture of the intracochlear membrane was proposed as a cause of sudden hearing loss but the evidence is only coincidental and studies looking at temporal bones of patients with SSNHL found no evidence of Reissner or basilar membrane rupture.[21]

Autoimmune

Historically the inner ear has been regarded as an immunoprivileged site, separated by the blood labyrinthine barrier. However, we now know that immunoglobulins (predominantly IgG) are found in the perilymph at a fraction of their serum concentrations.[33] The endolymphatic sac is thought to be the likely site for immune processing due to the presence of lymphocytes in the perisaccular tissues.[34]

SNHL has been reported in many systemic autoimmune disorders such as Wegener's granulomatosis,[35] rheumatoid arthritis,[36] polyarteritis nodosum,[37] Sjögren's syndrome,[38] Cogan's syndrome,[39] systemic lupus erythematosus,[40] ulcerative colitis[41] and relapsing polychondritis.[42] This provides some evidence that autoimmunity can damage the inner ear although it does not address organ-specific disease and an audiological investigation of patients suffering well-characterized systemic lupus erythematosus (SLE) found no significantly worse hearing than age, sex and socioeconomically matched controls.[43]

In 1979 McCabe described autoimmune inner-ear disease (AIED) a rapidly progressive bilateral SNHL that responded to steroid therapy. The cause is thought to be antibodies or immune cells that damage the inner ear and there are several theories as to how these may arise.[44]

Yoo et al. reported that rodents injected with type II collagen developed new-onset SNHL and pathologic cochlear changes that appear to be immune-mediated.[45,46] However, a more recent study found the incidence of anti type II collagen antibodies to be very low and disputed it as a cause of AIED.[47]

Harris and Sharp used bovine inner-ear extract as antigen in Western blot assays and detected antibody to a 68 kDa antigen in 35% of patients with progressive SNHL.[48] This is now known to represent the ubiquitous rather than inner ear-specific highly inducible heat shock protein 70 (hsp70).[49] Although hsp70 antibodies are elevated in autoimmune SNHL, they are not thought to be the underlying cause of hearing loss.[50] The frequency of antibodies against hsp70 is not different in patients and controls and therefore it is not useful in the diagnosis of AIED.[51] The presence of antibodies to hsp70 found

in AIED patients has been correlated to responsiveness to steroid treatment.[52] The sensitivity and specificity of anti-hsp70 for the diagnosis of AIED was 42% and 90% respectively, and their positive predictive value 91%.[53] Further research is required to understand the aetiology of AIED fully and to develop diagnostic tests.[54]

Damage to the inner ear results in the release of cytokines, which trigger immune reactions. TNF-alpha, IL-1A, NFkB and IkBa have all been found in the cochlea.[55]

Activation of cochlear nuclear factor kappa B (NFKB) has been proposed as a mechanism of SSNHL as it would account for clinical and histological observations, but there is no direct evidence.[23]

The inner ear may share common antigens with potentially harmful substances and T-cells and antibodies may damage the inner ear when trying to fight these antigens. COCH5B2 has been proposed as a target antigen.[56]

The basic problem with any autoimmune theory for ISSNHL is that one would expect an immune condition to affect both ears and ISSNHL is usually unilateral.

Ménière's disease

The first presentation of Ménière's disease may be as SSNHL and therefore it is important to consider in the differential diagnosis. The classic triad of Ménière's is episodic vertigo, tinnitus and deafness. The aetiology is unknown and theories include autoimmune activation and labyrinthine ischaemia. Patients develop endolymphatic hydrops, which results in the classical symptoms. The audiogram classically shows a low-frequency hearing loss.

While there have been a number of proposed aetiological theories, it is possible that they are not mutually exclusive; for example, a viral insult can cause direct neural injury, direct vascular structure injury or direct injury to erythrocytes, leading to secondary microvascular insufficiency. Viruses can also lead to inflammation resulting in vascular insufficiency. Autoimmune disease can lead to vasculitis through antiendothelial cell antibodies.

CLINICAL ASSESSMENT

History

The aim in evaluating any patient with SSNHL is to identify any treatable causes.

It is important to cover the following key points in the history:

- The onset of the hearing loss. Patients with SSNHL often first notice their hearing loss on awakening in the morning and a better prognosis is associated with a short history.
- Sudden onset of blockage or fullness warrants prompt investigation. SSNHL often presents as a full or blocked ear. As this is a common and non-specific symptom it can be underestimated by both patients and clinicians, thus leading to a delay in evaluation and treatment.
- The premorbid hearing level. SSNHL can be either a new loss or an incremental deterioration in an ear with a pre-existing loss. Conditions such as Ménière's disease can cause sudden fluctuations in hearing.
- A poorer prognosis is associated with increasingly profound hearing loss.
- Is the loss unilateral or bilateral? Unilateral loss is commoner but autoimmune disease and ototoxicity are more likely to be bilateral.
- Associated symptoms such as tinnitus, vertigo, dizziness and aural fullness should be asked about and may point to a diagnosis of endolympatic hydrops. Vertigo is present in 30–40% of cases of SSNHL[57, 58] and is a poor prognostic indicator.
- SSNHL is frequently associated with tinnitus, which can cause significant anxiety and depression for patients. It is therefore important to recognize the psychological response to the sudden loss of hearing.
- Any history of trauma, straining, diving, flying and intense noise exposure should be noted. Patients should be questioned about previous or concurrent viral infections.
- A past medical history of other diseases associated with sudden hearing loss should be explored as SSNHL can rarely be the first presentation of a systemic disease.
- Any history of previous ear surgery should be noted.
- A full drug history should be elicited to rule out ototoxicity.

Examination

A complete examination of the head and neck should be carried out on all patients with SSNHL. Otoscopy should be performed to exclude middle ear effusions, infections, cholesteatoma and wax impaction. Tuning fork tests should be performed to distinguish a conductive hearing loss (CHL) from a SNHL.[59, 60] A fistula test may help identify a perilymph fistula. A thorough neurological examination of cranial nerves and cerebellar signs is essential.

Investigations

Audiometry must be performed and may give an indication of prognosis, as a downward sloping audiogram is associated with a poorer outcome.

An MRI scan with gadolinium enhancement should be performed to exclude an acoustic neuroma but is also useful in evaluating multiple sclerosis and cerebrovascular accidents. Around 10–20% of patients with acoustic neuromas will report a sudden decrease in their hearing at some point in their history.[61] However, the incidence of vestibular schwannoma in patients who present with SNHL is considerably lower but still noteworthy. Several studies have demonstrated a relatively high prevalence of cerebellopontine angle tumours in SNHL patients ranging from 2.7% to 10.2% of patients who are evaluated with MRI.[12, 62–66] When an MRI is contraindicated (i.e. pacemakers, other metallic implants, claustrophobia), a fine-cut CT of the temporal bones with contrast may be used.

Other investigations to rule out identifiable causes should be focused by the history. Bloods including FBC, ESR, urea and electrolytes, lipid profile, glucose, thyroid function tests, clotting screen, VDRL, serology for Lyme disease and autoantibodies (antinuclear antibodies, anti-cardiolipin antibodies, lupus anticoagulant, antineutrophil cytoplasmic antibodies) may be requested if clinically indicated. The American Academy of Otolaryngology – Head and Neck Surgery guideline makes a strong recommendation against routine laboratory testing.[6]

PROGNOSIS

Four factors have been shown to affect recovery from ISSNHL:[67]

- time since onset – the earlier the presentation the better the prognosis
- age – there is a worse prognosis in the over 60s
- vertigo – a poor prognostic indicator
- audiogram – patients with profound hearing loss and a downward-sloping audiogram have a poorer prognosis.

It is important to reassure patients that around 50% of cases have spontaneous recovery with no treatment. Due to the lack of evidence for any single treatment the risks and benefits of each treatment should be discussed with the patient to enable them to reach an informed decision about their care. Patients should be followed up to monitor for delayed symptoms, and audiograms should be repeated. Evidence shows that improvement rate in the first 2 weeks may predict long-term outcome.[68, 69]

Long-term follow-up is recommended as some patients will have an underlying cause identified that is not evident at initial presentation.[62] Also patients with limited or no hearing recovery or persistent tinnitus will require ongoing support from the audiological and psychological services.[70]

Unilateral SNHL has a significant impact on patients' quality of life.[71] So too does SSNHL and perhaps more so, especially if dizziness and significant tinnitus are suddenly present.[72–74]

TREATMENT

The high spontaneous recovery rate for ISSNHL and its low incidence make validation of empirical treatment difficult. Many treatment regimens have been proposed (Table 60.1).

TABLE 60.1 Proposed treatment regimes for ISSNHL

Treatment	Examples
Anti-inflammatory/ immunosuppression	Steroids[2, 75] Prostacyclin[76]
Antiviral agents	Acyclovir[77, 78] Valcyclovir[79]
Vasodilators 5% carbon dioxide with 95% oxygen (Carbogen)[75,80]	Papaverine[80] Pentoxifylline[81–83]
Volume expanders/haemodilutors	Hydroxyethyl starch[82, 84] Dextran[80, 82, 85]
Calcium antagonists	Nifedipine[86]
Other agents and procedures	Iron[87] Vitamins[86, 88] Procaine[85] Hyperbaric oxygen[89, 90] Gingko biloba[81] Zinc[91] Co-enzyme Q10[92]

Steroids

SYSTEMIC STEROIDS

Steroid therapy is widely used as the standard treatment for SSNHL, although systematic reviews and meta-analyses have revealed no evidence of benefit of steroids over placebo.[7, 93–95] The evidence for steroids comes from Wilson et al. who found that steroids had a significant effect on the recovery of hearing in patients with hearing loss of 40–90 dB.[2] Moskowitz et al. confirmed Wilson's findings in 1984.[96] However, the methodology of these studies has been criticized.[93] Cinamon et al. compared treatment with prednisolone, placebo, carbogen and room air inhalations and found no significant differences between the four groups.[75] Nosrati-Zarenoe et al. performed a prospective randomized, triple-blind, placebo-controlled trial comparing oral steroids to placebo in 103 patients. Prednisolone or placebo was given at 60 mg/day for 3 days then 10 mg less each day until day 8. The results showed no significant difference in hearing improvement.[97]

A more recent meta-analysis of various medical treatments, including corticosteroids, showed a slight but not statistically significant improvement with medical therapy compared to placebo.[98]

Risk vs benefit of oral corticosteroid therapy

In view of the limited evidence to support steroid therapy in the treatment of ISSNHL, clinicians must weigh up the risks and benefits of the treatment for an individual patient. Although the evidence for corticosteroids is limited, it is one of the few treatments with demonstrated efficacy.[2, 77, 96, 99–104] In view of the significant devastating impact of a severe to profound SSNHL on an often otherwise healthy patient, the treatment should be considered.

Spontaneous improvement in hearing is most likely to occur during the first 2 weeks;[8] late recovery has been reported but is rare. Early corticosteroid treatment within the first 2 weeks is associated with the greatest hearing recovery, with minimal benefit after 4–6 weeks.[57, 103, 105–107]

Dose

The best treatment outcomes are associated with a single dose of oral prednisolone of 1 mg/kg/day, up to a maximum of 60 mg daily, for 10–14 days.[6] This is based on

the maximum adrenal output of hydrocortisone (cortisol), which is 200–300 mg/day during stress. Prednisolone is 4 times, methylprednisolone is 5 times, and dexamethasone is 25 times more powerful than hydrocortisone. A dose of 60 mg prednisolone is equivalent to 48 mg methylprednisolone and 10 mg dexamethasone.

Complications of systemic steroid treatment

Systemic corticosteroids have a wide range of potential side effects as they affect many organ systems. They can suppress the hypothalamic–pituitary–adrenal function causing Cushing's syndrome.[108] Possible side effects of corticosteroid use are given in **Box 60.2**.

In view of the associated side effects and limited evidence for efficacy, systemic corticosteroids may not be an appropriate treatment for patients with increased risk of complications. For example, these will include those with insulin-dependent or poorly controlled diabetes, labile hypertension, tuberculosis, peptic ulcer disease and prior psychiatric reactions to corticosteroids.[109] The severe side effects are typically associated with long-term high-dose usage and adverse events are rare with the short 10- to 14-day course of steroids recommended for SSNHL.

Super high-dose steroid therapy has shown greater hearing recovery than standard dose treatment but further research is required.[110] Caution should be taken when prescribing very high-dose steroids to reduce the risk of serious complications.

INTRATYMPANIC CORTICOSTEROIDS

Intratympanic (IT) steroid therapy is gaining popularity as a treatment for SSNHL, particularly in refractory cases or those in which systemic steroids may be hazardous, but again evidence is lacking.[100, 111–113] There have been many small studies, often with very small numbers, but many are retrospective, without controls, and the steroid dosage, delivery method and frequency of injection have varied considerably, making it difficult to assess and compare outcomes. The main advantage of IT treatment is the reduction in systemic corticosteroid side effects. IT steroids very rarely cause changes in serum glucose levels in patients with diabetes.[114] They may also be given to patients with cataracts, myasthenia gravis and glaucoma.[115]

BOX 60.2 Possible side effects of corticosteroid use

Possible side effects with short-term use	Severe but rare side effects
Gastritis	Pancreatitis
Increased blood sugar	Bleeding
Increased hunger	Cataracts
Behaviour changes, insomnia, irritability	Myopathy
Weight gain, salt and water retention	Avascular necrosis of humeral and femoral heads
High blood pressure	Diabetes
	Osteoporosis
	Opportunistic infections[108]

IT injection is associated with higher inner ear steroid levels[116, 117] so many authors have explored its use in the treatment of SSNHL. An early prospective study using IT steroids in patients with profound ISSNHL found only 3 of 25 patients had hearing improvement.[118] However, another study combining a high-dose prednisolone taper with IT steroids resulted in partial or complete hearing recovery in 14 out of 16 patients.[119] Three separate randomized controlled trials comparing IT + oral steroids with oral steroids alone found that the addition of IT steroids did not show a significant benefit when compared to corticosteroids alone, although there was a trend towards greater improvement with the combination therapy.[120–122] Filipo et al. investigated IT steroids as the sole initial treatment in SSNHL and showed improvement in 31 out of 34 patients.[123] The same author went on to compare IT steroid with IT saline in a randomized controlled trial and found a significant improvement in hearing in the steroid group compared to the control.[124] Dispenza et al. compared IT with oral steroids and found no significant difference between the two groups.[125] Lim et al. compared the efficacy of three different steroid treatments: IT, IT + oral steroids, and oral steroids alone. Their results showed similar hearing recovery rates in all three groups.[126] The efficacy of simultaneous versus subsequent IT steroid with oral steroids has also been studied. The results showed that the administration of simultaneous IT steroid with oral steroid did not confer additional hearing gain or earlier recovery rate over those that had subsequent treatment with IT steroid.[127] A systematic review concluded that IT steroids can be a valuable solution for patients with ISSNHL who either cannot tolerate systemic steroid therapy or are refractory to it.[114, 128, 129]

Choice of steroid and dose

The most frequently administered IT steroids are dexamethasone and solumedrol (methyl prednisolone sodium succinate). The research shows a wide variation in the concentration given. Most studies quote doses of 10–24 mg/mL dexamethasone and 30–40 mg/mL solumedrol. Higher concentrations may have better outcomes.

Use of facilitator

Improved transport across the round window membrane has been demonstrated in laboratory studies with the addition of facilitator agents such as histamine and hyaluronic acid.[130, 131]

Frequency and injection technique

Studies vary widely in the frequency of IT steroid injection, from self-administration several times a day by the patient across a grommet, to clinician administered on consecutive days, to weekly. A variety of methods of administration have been reported, via a spinal needle on a syringe, through a grommet or myringotomy, via a MicroWick or microcatheter,[132] hydrogel applications, and nanoparticles. Transtympanic needle or grommets are the most frequently used.[133] IT steroids have been used as

the primary treatment, in combination with other therapies and as salvage treatment.

Complications of IT steroids

Even though IT steroids are widely used in clinical practice they are associated with an inconsistent clinical response.[134] This is due to the wide variability in diffusion across the round window membrane leading to unpredictable intracochlear bioavailability. This variability is further exacerbated by any inflammation or scar tissue in the round window niche.[135, 136] Adverse effects with IT steroids are infrequent but include pain, transient dizziness, infection, persistent tympanic membrane perforation, possible vasovagal episode during injection, and the need for repeat visits. The main risk appears to be a persistent tympanic membrane perforation at the injection site.

The largest randomized controlled trial comparing oral versus IT steroid therapy for ISSNHL was conducted at 16 centres and recruited 250 patients.[137] All patients were recruited within 14 days of onset of their SSNHL and followed up for 6 months. The first group, of 121 patients, received 60 mg/day of oral prednisone for 14 days with a 5-day taper; the other 129 patients received four doses over 14 days of 40 mg/mL of methylprednisolone injected into the middle ear. The results showed that, for initial therapy of SSNHL, promptly administered and equivalently dosed oral and IT steroid appeared to be equally effective, with hearing improvement seen in more than 75% of treated patients. Since the results for the two groups were equivalent, decisions on the choice of treatment for an individual should be based upon the risk of potential side effects and cost. Side effects were reported by 88% of the oral group, such as elevated blood sugar, increased thirst, and sleep or appetite changes, and 90% of the IT group, such as transient pain at the injection site and brief caloric vertigo. These were the anticipated manageable side effects, most of which were resolved within 1–2 weeks.

HYPERBARIC OXYGEN

Impairment of vascular supply and the resulting cochlear ischaemia is one of the proposed aetiologies for SSNHL. Hyperbaric oxygen therapy (HBOT) delivers 100% oxygen to a patient at a pressure greater than 1 atmosphere. This results in an increase in tissue oxygenation as well as potentiating the response to infection and ischaemia.[138]

HBOT has been used in the treatment of SSNHL since the 1960s.[90] Since then, numerous studies have investigated the use of HBOT in SSNHL, although very few have been prospective randomized controlled trials. The most recent Cochrane review included seven identified randomized controlled trials, published between 1985 and 2004.[139–145] The criterion used for determining significant benefit was a 50% improvement in hearing. Although the chance of a 50% improvement was not significantly increased following HBOT, the chance of a 25% increase was and the number needed to treat (NNT) to achieve one extra good outcome was five. For people with early presentation of ISSNHL, the application of HBOT significantly improved hearing loss, but the clinical significance of the level of improvement is not debatable. The data also suggested that improvement may be related to the severity of the hearing loss on presentation. However, further evidence is required from future randomized controlled trials.

A more recent prospective randomized control of HBOT for SSNHL[146] compared HBOT + oral steroid with oral steroid alone. Success was defined as hearing regained completely (>50 dB improvement) or moderately (10–50 dB improvement). The results showed no significant difference between the two groups and therefore did not support the addition of HBOT to oral steroids. HBOT has also been used in combination with IT steroids.[147] When HBOT + IT steroid was compared to HBOT + i.v. steroid, the overall success rate was higher in the IT steroid group but the result was not statistically significant.

Complications of HBOT

Complications are rare but include damage to ears, sinuses and lungs from pressure changes; temporary worsening of short-sightedness; claustrophobia; and oxygen poisoning. No significant adverse events were reported in the studies reviewed. In a large study (782 patients) looking at HBOT for a variety of indications, the most frequent complication was difficultly equalizing pressure in the middle ear, which occurred in 17% of patients.[148] Rates of Eustachian tube dysfunction of up to 45% have been reported in other studies of HBOT for a variety of indications.[149] Although the reported rates of Eustachian tube dysfunction are lower in patients undergoing HBOT for SSNHL, this may be a result of concurrent steroid treatment.[150] Another common complication of HBOT is claustrophobia while undergoing treatment.[148, 150]

Disadvantages of HBOT

HBOT is an expensive and time-consuming intervention that is not readily available. Therapy typically involves multiple sessions of 1–2 hours over days to weeks. Typical treatments have consisted of between five and ten sessions.

The evidence supports possible benefit of HBOT as an adjuvant treatment in cases of acute SSNHL when used within 3 months of the onset of the hearing loss, with potentially more benefit noted in cases of severe to profound loss.[6]

OTHER THERAPIES

Michel and Matthias compared intravenous prostacylin therapy with saline and found no significant difference between the groups.[76]

Acyclovir has been used for the treatment of SSNHL both alone and in conjunction with steroids but neither shows any significant improvement in hearing. Valcyclovir, although better bioavailability has also been used in conjunction with steroids but again offers no improvement above controls.[77–79]

Agents thought to increase cochlear blood flow, papaverine, pentoxifylline, hydroxyethyl starch, dextran, nifedipine and ginkgo biloba show no difference between active treatment and controls.[80–86]

Kronenberg et al. compared intravenous procaine, dextran and placebo and found no significant differences in outcomes.[85]

SALVAGE TREATMENT

For patients who are refractory to systemic steroid therapy, salvage therapy has become popular. Both IT steroid and HBOT have been investigated as salvage treatments.

There is now a large body of research investigating the use of IT steroid therapy in this setting, including numerous case series, a number of randomized controlled trials and a meta-analysis.[100, 112, 113, 116–118, 132, 151–155] The methodology in many of these studies has been criticized, however the majority do show improved hearing outcomes after IT steroid therapy with reported improvement rates ranging from 8% to 100%.[100, 122, 128, 129, 156–160]

The meta-analysis identified 184 studies of which five met the inclusion criteria and were analyzed.[112, 155, 161–163] There was a statistically significant greater improvement in hearing on pure-tone audiometry in patients who received salvage IT steroids than in those who did not.[154]

Side effects of IT steroids for salvage therapy were reported by four of the five studies. Minor side effects included transient dizziness, ear pain, and tinnitus. Of the 203 patients in these studies, three developed tympanic membrane perforation. Of the three, one healed spontaneously, one was treated successfully with a paper patch, and one required a myringoplasty (in this patient a round window catheter was used). No infective complications occurred.

The main limitation of this meta-analysis is the small number of trials involved. Although all the studies included were randomized controlled trials, only one was blinded and placebo-controlled. The subgroup analysis found that dexamethasone rather than methylprednisolone, administered via injections rather than a round window catheter, tended to demonstrate better outcomes. However, in view of the limitations of the analysis, further work is required to demonstrate this conclusively. While this meta-analysis showed a statistically significant improvement in hearing, the degree of clinical significance is questionable, as the improvement in audiological thresholds may not confer an improvement in usable hearing to the patient.

HBOT has also been successfully used in the treatment of refractory SSNHL.[152, 164–166] Recent studies have compared HBOT with IT steroids and with combined treatment of IT steroids + HBOT. Yang et al. found that IT steroid, HBOT and combination therapy all offered some benefit in hearing improvement but the largest gain in word recognition score (WRS) and recovery in hearing, especially in the lower frequencies, was seen with combination therapy.[153] However, the numbers in these studies was small.

OUTCOMES ASSESSMENT

In order to assess and compare outcomes there need to be standardized outcome measures. Unfortunately, for a long time there were no widely accepted standards, however 2006 guidelines from AAOHNS proposed recommendations for outcomes assessment.[167]

All patients diagnosed with ISSNHL need follow-up audiological assessment; this may reveal other aetiologies, as ISSNHL could be the first presentation of another condition. Also it will identify which patients have ongoing hearing loss and those who may benefit from hearing rehabilitation. Audiological assessment is important in determining the benefit of any given treatment and to identify those who may be suitable for salvage therapy.

Yeo et al. evaluated the long-term results for a 3 month retrospective series of 156 patients diagnosed with ISSNHL.[168] Of 121 patients who recovered over the 3 months of follow-up, 45.5% showed a delayed recovery after the end of 10-day course of therapy. Of these 55 patients, 78.2% recovered within 1 month, 5.5% recovered within 1–2 months, 12.7% recovered in 2–3 months, and 3.6% recovered later than 3 months after discharge. Only one patient showed any recovery beyond 6 months. In view of these results 6 months has been given as a reasonable follow-up period.

In patients with permanent hearing loss early discussion regarding rehabilitation options can reduce patient anxiety. Ideally, these discussions should take place when a hearing loss is first identified, as temporary aiding during treatment may be beneficial.

In order to assess the benefit of treatments for ISSNHL the audiological assessment should compare the pure-tone audiometry (PTA), speech recognition threshold (SRT) and/or WRS at each appointment following diagnosis. The evidence from this comes from a meta-analysis that reviewed 20 studies investigating a variety of treatments for ISSNHL. Although the treatments were diverse, the majority of studies used PTA, and/or WRS to monitor the effectiveness of treatment leading to recovery of hearing.[7]

Definition of recovery and improvement

In one of the early studies on SSNHL Wilson et al.[2] defined recovery as follows:

- **Complete:** if the follow-up PTA (dB HL) or SRT (dB HL) improved to within 10 dB of pre-sudden hearing loss hearing levels.
- **Partial:** if the follow-up PTA (dB HL) or SRT (dB HL) improved to within 50% of pre-sudden hearing loss hearing levels.
- **No recovery:** if the follow-up PTA (dB HL) or SRT (dB HL) was less than 50% of recovery of pre-sudden hearing loss hearing levels.

American Academy recommendations for outcomes assessment

The American Academy of Otolaryngology–Head and Neck Surgery (AAOHNS) makes the following recommendations for outcomes assessment:[6]

1. Unless a previous asymmetry of hearing was known or suspected, the unaffected ear should be used as the standard against which recovery should be compared;

2. a complete recovery requires return to within 10 dB HL of the unaffected ear and recovery of WRSs to within 5% to 10% of the unaffected ear;
3. partial recovery should be defined in two ways based on whether or not the degree of initial hearing loss after the event of SSNHL rendered the ear non-serviceable (based on the AAO-HNSF definition); and
4. anything less than a 10 dB HL improvement should be classified as no recovery.

Associated symptoms of tinnitus, sensation of fullness, vertigo, or nausea following treatment should also be recorded.

The problems with these strategies are that:

- although improvement in pure-tone threshold may be statistically significant, it may not be clinically significant
- there is often no pre-existing audiology.

Smyth and Patterson developed the 'Belfast Rule of Thumb' based on analysis of the relationship between the patient's perceived subjective benefit and post-operative audiometric changes. Although designed to look at hearing outcomes following surgery, it can equally be applied to determine the benefit to patients following treatment for ISSNHL. In order for the hearing gain to be appreciated by the patient, the hearing in the affected ear must be brought to 30 dB or better or to within 15 dB of the contralateral ear.[169]

CONCLUSION

The aetiology and treatment of SSNHL remains controversial. Current research supports several possible aetiologies and, although a variety of treatment options have been investigated, there is no clearly optimum management. Early steroid treatment, either systemic or intratympanic, is advocated, and HBOT may be useful within the first 3 months. There is, however, still a need for high-quality evidence and further research to determine the optimal management.

BEST CLINICAL PRACTICE

✓ Patients presenting with SSNHL should be investigated thoroughly.
✓ When it has been determined that a patient has probable or certain ISSNHL, the diagnostic uncertainty and management options should be discussed with the patient.
✓ The physician should use their expertise in evaluating the risks and benefits of any specific treatment in the light of the patient's individual medical status.

FUTURE RESEARCH

➤ The variability in diffusion across the round window membrane has led to a number of studies looking at:
  ➤ the dose-dependent sensitivity of different hair cell types
  ➤ pharmaceutical and surgical approaches to alter the permeability of the round window membrane
  ➤ delayed drug release formulations to provide precise delivery of therapeutic agents into the inner ear.[170]
➤ The recent development of delayed-release gels placed on the round window membrane has the potential for continuous drug release[171] although they are still affected by the variable permeability of the membrane.[172] Microperforations in the round window membrane have been shown to be an effective means of increasing diffusion across the round window membrane.[173]
➤ The American Academy guidelines have highlighted the following areas in which further research is required:
  1. Investigation of the effectiveness of corticosteroid treatment vs a placebo.
  2. Further investigation of the benefit of HBOT. Current evidence looks promising; however, this is an expensive therapy and is not universally available. Standardised treatment protocols are needed.
  3. Develop standardised outcome criteria to aid the comparison of clinical studies.
  4. Further study the use of IT steroids as salvage therapy, particularly the optimal drugs, dosage, concentrations, and administration schedules for IT therapy.
  5. Develop criteria to determine at what level of hearing recovery IT steroids would be offered as salvage.
  6. Determine the percentage of patients who gain serviceable hearing as a result of treatment.
  7. Investigate the use of "combined therapy" (i.e. oral and IT steroids) in patients with ISSNHL.
  8. Develop long-term follow-up protocols for patients with ISSNHL.
  9. Evaluate therapies using standardised definitions and treatment protocols across studies.

KEY POINTS

- SSNHL is defined as a hearing loss of 30 dB or more, over at least three contiguous audiometric frequencies, that develops over 72 hours or less.
- The aetiology and treatment of SSNHL remain controversial, but prompt recognition and management have been shown to improve hearing outcomes and quality of life.
- Many alternative treatment strategies have been proposed.
- Steroid treatment (either systemic or via transtympanic injection) or hyperbaric oxygen treatments are advocated.

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CHAPTER 61

TINNITUS AND HYPERACUSIS

Don McFerran and John Phillips

SEARCH STRATEGY

Data in this chapter may be updated by searches of Medline, EMBASE, the Cochrane Library and Clinical Evidence *BMJ* using the keywords tinnitus and hyperacusis, focusing on pathophysiology, diagnosis and treatment. The data are supplemented by hand searches of specialized books and proceedings from relevant meetings where tinnitus was the main subject. The evidence in this chapter covers all evidence levels.

INTRODUCTION

It is unusual to read any authoritative text or publication about tinnitus without the obligatory introductory paragraph that educates the reader of the etymology of the word 'tinnitus', usually quoting its classical derivation and citing Dennis McFadden's description of the term.[1] It is true that the word tinnitus originates from the Latin word *tinnire* (to ring) and McFadden's description of tinnitus as 'the conscious expression of a sound that originates in an involuntary manner in the head of its owner, or may appear to him to do so' is appropriate. However, there is a lot more to these standard definitions than are worthy of further explanation. In the 1950s, Heller and Bergman studied the descriptions of 180 subjects (80 with reportedly normal hearing and 100 with hearing impairment) who were interviewed regarding sounds that they perceived when introduced into a soundproof booth. Despite many subjects describing a 'ring', this was only one of 39 descriptions reported.[2] In reality, the sound perceived by the patient does not have to be ringing, does not have to be a continuous sound, and in some cases can even represent complex sounds such as musical tunes. As an interesting footnote to one of the most commonly cited tinnitus publications, McFadden was the chairman of a working group set up in the US by the Committee on Hearing, Bioacoustics, and Biomechanics (CHABA) and in his preface to the group's report wrote: 'A number of my friends have noted that tinnitus is an unlikely topic for me to be reviewing and critiquing, and I am the first to agree. I do not consider myself to be an expert on tinnitus: I have never done research on the topic, nor have I ever seen a tinnitus patient.'

Tinnitus has been one of the bugbears of humanity for as long as medical records have been kept: ancient Babylonian clay tablets from more than 600 years BC contain multiple references to tinnitus together with instructions on how to treat the condition using incantations and charms.[3] **Hyperacusis** has a much shorter written history: one of the earliest mentions of the word was in 1881 in a book entitled *Imperfect hearing and the hygiene of the ear*, written by Laurence Turnbull, an American physician.[4] Although often considered as independent entities, there is no denying that an association exists between both of these symptoms, although this does not rule out a link with a common disorder, rather than one being the cause of the other.

Tinnitus and hyperacusis are both fascinating symptoms which, contrary to popular belief, are becoming much better understood with respect to their underlying causes and associations, and their ability to be successfully treated. As we observe advances in our understanding as the result of animal studies, the use of sophisticated imaging techniques, and developments in pharmacology

and psychology, more and more patients are benefiting. In this chapter we will provide an evidence-based overview of tinnitus and hyperacusis, from both a clinical and a research perspective. The psychological aspects of tinnitus will be discussed in Chapter 70, Understanding tinnitus: A psychological perspective, so only a brief summary of this management modality will be provided.

TINNITUS

DEFINITIONS AND CLASSIFICATION

The definition produced by McFadden and described above is still useful, though it would include the hallucinations of mental illness and exclude tinnitus that is perceived outside the body. Other attempts at a definition have included the sensation of hearing a sound in the absence of an external stimulus or a sound sensation in the absence of an external or internal acoustical source or electric stimulation.[5] While perhaps an improvement on the McFadden definition, these would still include auditory hallucinations of mental illness as a form of tinnitus and the latter definition would exclude some types of pulsatile tinnitus where there is an intracorporeal sound source. A completely unambiguous definition has yet to be published.

Many classifications systems have been historically used to define tinnitus, based either on the proposed underlying cause or on the associated symptoms.[6] For consistency we have divided tinnitus into pulsatile and non-pulsatile. Pulsatile tinnitus is considered to be either synchronous or non-synchronous, depending on whether the sound is in synchrony with the patient's arterial pulse. Throughout this chapter non-pulsatile, synchronous pulsatile and non-synchronous pulsatile tinnitus will be considered separately.

Tinnitus can also be divided into subjective or objective forms: in the former, only the patient is aware of the sound sensation: in the latter, the sound can be perceived by others, either unaided, using a stethoscope or a microphone and amplifier. The majority of people with tinnitus report subjective non-pulsatile tinnitus with no specific associated pathological process other than age-associated hearing loss: this is often referred to as subjective idiopathic tinnitus. As described above, the sound perceived in this type of tinnitus can take virtually any form. Mostly, the sounds reported are simple sounds: whistling, humming, ringing or tones. More complex sounds are sometimes described including voices or music. When such complex sounds are present, they are generally indistinct and do not carry specific meaning, unlike the auditory hallucinations of mental illness.

NON-PULSATILE TINNITUS

Epidemiology

The largest investigation into the epidemiology of tinnitus was carried out as part of a UK, Medical Research Council, Institute of Hearing, study of hearing (n = 48 313).[7] This study discovered that the prevalence of persistent spontaneous tinnitus in the adult population was 10.1%, defining persistent spontaneous tinnitus as tinnitus that arose spontaneously, not as a response to sound stimulus, and lasted for periods of 5 minutes or more at a time. Of those surveyed, 5% described their tinnitus as moderately or severely annoying and 0.5% reported that it had a severe effect on their ability to lead a normal life. Studies in other countries have produced broadly similar figures: prevalence figures in Italy have been reported as 14.5% of the population,[8] in the US as 14.9%[9] and in Sweden as 15.8%.[10] Until recently most tinnitus epidemiology studies were limited to Western populations but a few studies have emerged from other countries in the last few years. An overall figure of 5.2% was reported from Egypt, rising to 17.7% in patients over 60 years of age.[11] In Japan, 18.6% of people aged over 65 described tinnitus[12] and in a similarly aged population sample in Nigeria the figure was 14.1%.[13]

Very few incidence or longitudinal studies have been carried out. One of the few published longitudinal studies was undertaken in a community in Beaver Dam, Wisconsin, US. As part of this study, participants aged between 48 and 92 years who did not have tinnitus at baseline were studied over a 10-year period. At the 5-year time-point, the cumulative incidence of new cases of tinnitus was 5.7%;[14] at 10 years the figure was 12.7%.[15] The prevalence of tinnitus in the population at baseline was 8.2% and it is noteworthy that these people tended to show improvement rather than worsening of their tinnitus during the study.

The prevalence of tinnitus seems similar in men and women though there are some differences in the way that the sexes perceive the symptom: women are more likely than men to perceive their tinnitus as a complex sound.[16,17] Presence of a hearing loss increases the likelihood of an individual experiencing tinnitus and, in particular, a high-frequency hearing deficit is a good predictor of tinnitus. Previous noise exposure is also a good predictor: Davis found a prevalence of tinnitus of 7.5% in adults who gave a history of little or no noise exposure but 20.7% in those with high exposure.[18]

Tinnitus is perceived in both ears or in the middle of the head by approximately half of sufferers. A few people perceive it as an external sensation. The remainder have unilateral tinnitus, with left-sided tinnitus slightly more common than right-sided. The reason for this left-sided preponderance is unknown and cannot be explained by asymmetrical hearing loss.[19] The location of tinnitus is not necessarily a fixed entity: it is not unusual for someone to report that they initially thought the sound percept was an external sound due to a faulty electrical item in their home. It was only when the sound sensation was audible in a different location with no electrical appliances present that they realized they had tinnitus and the perception then became internal. Similarly, a number of people who present with unilateral tinnitus subsequently report that the symptom has become bilateral.

Several studies have demonstrated that the prevalence of tinnitus increases with age.[20, 21] This is likely to represent the known association of tinnitus with hearing loss although, interestingly, the tinnitus prevalence does not rise as steeply as that of hearing loss and some studies have shown tinnitus prevalence reaching a plateau around the age of 70 and, in some cases, even diminishing thereafter.[7] There is some evidence that older people are more annoyed by their tinnitus than younger people.[7] It is popularly assumed that tinnitus is a condition of adulthood. Tinnitus does, however, present in children, with prevalence figures not dissimilar to those in adults. This is discussed in more detail later in this chapter. Although tinnitus experience is common in childhood, relatively few seem to find the experience troublesome. Furthermore, it is unusual to see an adult with tinnitus who reports that they have had the problem since childhood, suggesting that children must, by and large, habituate to the symptom.

Various risk factors for the development of tinnitus have been suggested. These include socioeconomic class, smoking, alcohol consumption and other health issues such as previous head injuries, cardiovascular disease and hypertension.[7] Specific otological conditions including Ménière's disease, otosclerosis and vestibular schwannoma are associated with an increased risk of tinnitus: such cases are sometimes referred to as cases of 'syndromic tinnitus'. Numerous drugs have been cited as possible triggers for the development of tinnitus. In most cases the risk is low and the association has not been examined with any great degree of scientific rigor – it is probable that in many cases the link is either idiosyncratic or coincidental. A few drugs do have a more definite link with tinnitus and these include salicylates, quinine, aminoglycoside antibiotics, and some antineoplastic agents, particularly the platinum-based drugs. It has been suggested in a recent study that tinnitus development may have a small genetic predisposition.[22] There have been suggestions that certain personality types such as type D personality are associated with the development of tinnitus.[23] Most studies, however, have suggested that tinnitus patients have a normal gamut of personality types.[24]

Although many patients report that they feel that tinnitus is affected by dietary factors, there has been very little research in this area. A recent publication described a cross-sectional study of 171 722 adults aged 40–69 years who had agreed to participate in the UK Biobank scheme.[25] The authors subdivided tinnitus into persistent, transient and bothersome subtypes and investigated the association of the subtypes with reported consumption of common food groups. An increased report of persistent tinnitus was associated with fruit, vegetable and bread consumption and dairy avoidance. Reduced reporting of persistent tinnitus was associated with consumption of fish and caffeinated coffee and avoidance of eggs. Transient tinnitus reports increased with dairy avoidance and decreased with caffeinated coffee and brown bread consumption. Bothersome tinnitus reports decreased with consumption of wholemeal, wholegrain bread. Although the authors of this study controlled for as many other factors as possible, they highlighted several potential shortcomings in their study and stressed that these results only show evidence of an association between certain foods and tinnitus; they do not imply a causal link.

Two other studies have investigated the relationship between caffeine and tinnitus. The first of these studied the effect of caffeine abstinence on tinnitus and concluded that caffeine has no effect on tinnitus severity.[26] The second study followed 65 085 women aged 30–44 years at baseline over an 18-year period.[27] During the course of the study 5289 participants developed tinnitus; higher caffeine consumption was associated with lower risk of developing tinnitus.

In addition to risk factors, tinnitus has several comorbidities. Depression and anxiety are not infrequently seen with tinnitus and in many instances it is impossible to determine whether these neuroses have precipitated the emergence of tinnitus or vice versa.[28] Temporomandibular joint dysfunction has also been reported as a comorbidity.[29] The tinnitus community is split as to whether this is a causal association or simple coincidence. Disorders of sound tolerance are commonly seen in association with tinnitus: 40% of people with tinnitus report some degree of hyperacusis[30] and, when this association is reversed, 86% of people reporting hyperacusis also report tinnitus.[31] Disorders of sound tolerance are discussed in more detail later in this chapter.

Pathophysiology

The most prevalent presentation of tinnitus in the general population is that of a subjective non-pulsatile sound. Although, in this form, the link between high-frequency hearing loss and tinnitus might be taken as evidence for a cochlear origin for tinnitus, most modern research underscores the importance of central auditory pathways in both the development and maintenance of distressing tinnitus.[32–34] Traditionally, it was considered that tinnitus can exist in the presence of a perfectly functioning auditory periphery but recently the definition of normal hearing has been disputed as many cochlear hair cells may be damaged before an apparent hearing loss is demonstrated using conventional pure-tone audiometry; furthermore, there is evidence that patients with tinnitus may demonstrate hearing loss at frequencies much higher than conventionally tested using standard methods.[35]

Conversely, tinnitus can exist even if the auditory periphery has been completely destroyed or after the neural connections between ear and brain have been severed, as can be seen following some forms of vestibular schwannoma surgery.[36] In addition, damage to the auditory system does not automatically induce tinnitus: although noise-induced hearing loss increases the likelihood of someone reporting tinnitus, the majority of people with cochlear damage secondary to noise exposure do not have significant tinnitus. These observations have been drawn together in a concept that makes a distinction between the location, within either the peripheral or central auditory system, at which an initial tinnitus signal is generated and the subsequent central auditory mechanism by which this signal is misconstrued as a sound with the potential to become

a clinical problem. The point at which the initial signal generation occurs has been dubbed the **ignition site** and the ensuing central mechanisms have been entitled **promotion**.[37] Pathological events which create an ignition site do not inevitably generate tinnitus – the central promotion must also be present. This theory has clinical relevance in that, if tinnitus distress is maintained by central auditory pathways, it may be futile trying to correct peripheral auditory pathology.

While the exact mechanism behind tinnitus ignition is not fully understood, it is now considered that any pathology that can potentially damage the auditory pathways has the potential to result in tinnitus. The following text outlines some of the pathophysiological mechanisms that have been suggested as giving rise to tinnitus, but this list is far from exhaustive and many other hypotheses have been proposed. Likewise, these theories are not mutually exclusive.

PERIPHERAL MECHANISMS

Discordant damage of cochlear hair cells

Outer hair cells have been shown to be more susceptible than inner hair cells to damage by certain agents including noise and aminoglycoside antibiotics. It has been suggested that, in areas where outer hair cells have been damaged but inner hair cells remain, the tectorial membrane is no longer supported by the outer hair cells and can sag onto the inner hair cells, causing them to depolarize.[38]

Calcium channel dysfunction

Calcium is fundamental to several functions of cochlear hair cells and some drugs that are known to cause tinnitus, including salicylates and quinine, affect intracellular calcium levels. Noise also affects the concentration of intracellular calcium. It has therefore been suggested that calcium flux may be implicated in tinnitus generation.[38]

Glutamate receptors

Glutamate is the main excitatory neurotransmitter in the auditory system and several subgroups of glutamate receptor exist. AMPA receptors are the main receptors found on the auditory nerve fibres under the inner hair cells and are responsible for the fast transmission of information from the cochlea to the brain.[39] However, glutamate in large quantities is toxic to nerve fibres. This effect, which can be observed following significant noise exposure, is mediated by AMPA.[40] Another subgroup of glutamate receptors, NMDA receptors are also present in auditory nerve fibres though their function is still a matter of some speculation. It has been observed that pharmacological blockade of NMDA receptors can be protective against both salicylate-induced[41] and noise-induced tinnitus in animal models.[42] Although the evidence that glutamate receptors are directly implicated in the causation of tinnitus is at best circumstantial, they do offer a potential site for therapeutic intervention and this continues to be an active research area.

CENTRAL MECHANISMS

Increased spontaneous firing

There is always a certain degree of electrical activity in the auditory system even when there is no sound input to the ear. Damage to the ear results in reduced activity in the auditory nerve which in turn downregulates inhibitory processes in higher auditory centres, thereby potentially generating increased spontaneous activity in the auditory cortex that could be perceived as tinnitus.[43]

Increased central neural synchrony

Spontaneous neural activity in the auditory cortex is normally random and, when this activity becomes synchronized, this is the signal that a sound is present. If the peripheral auditory system is damaged, spontaneous cortical activity tends to become more synchronized and there is speculation that this can give rise to tinnitus.[44]

Reorganization of the cortical auditory map

The auditory system is tonotopically organized from cochlea to cortex: structures within the auditory system that deal with adjacent sound frequencies are situated beside each other. When the peripheral auditory system is damaged, one change seen in the auditory cortex is that neurons that received inputs from parts of the cochlea that have been damaged tune in to the nearest adjacent frequency input that is still active. This results in over-representation of frequencies adjacent to areas of damage and increased neural activity at those frequencies.[45] It has been suggested that this produces tinnitus.

TINNITUS MODELS

Rather than becoming fixated on the neurobiology of tinnitus, many clinicians prefer to view the functional basis for the symptom. Many psychological and neurophysiological models for tinnitus exist, some of which form the basis for contemporary tinnitus therapies. In 1984 Hallam et al. suggested that tinnitus was caused by 'some neurophysiological disturbance in the auditory system at any point between periphery and cortex'.[46] They went on to suggest that normally the central auditory system should habituate to this activity. However, in certain situations such as high autonomic arousal this process does not happen and the tinnitus activity can become intrusive. Treatment modalities that arose from this concept included the use of relaxation therapy to reduce autonomic activity and cognitive behavioural therapy to help change the emotional significance of the tinnitus.[47] Psychological models of tinnitus and psychological management strategies are discussed in greater detail in Chapter 70, Understanding tinnitus: A psychological perspective. In 1990 Jastreboff published what has become known as the 'neurophysiological model' of tinnitus, drawing together all the available knowledge at the time and suggesting that, in addition to events within the classical auditory system, tinnitus involved altered activity within the limbic system, reticular system and autonomic nervous system.[38] This model was then

used to produce a clinical application that became known as 'tinnitus retraining therapy' (TRT).[48, 49]

TINNITUS MODULATION

Over the last two decades it has become apparent that tinnitus can be influenced by stimuli from outside the auditory system: many patients with tinnitus can modulate their symptom by touching their face,[50, 51] clenching their teeth[52] or changing their gaze.[53] Although this was initially dismissed as a rare curio, it has become apparent that this phenomenon is quite common, highlighting the importance of links between the auditory system and other somatosensory pathways. Furthermore, this interesting phenomenon is currently being employed to form the basis of a novel form of tinnitus therapy.[54]

Investigation

BASIC AUDIOMETRY

Specific forms of tinnitus, such as tinnitus in the presence of Ménière's disease, may require specialist investigations. However, it is well accepted that all patients with tinnitus, in addition to having a thorough history and examination performed, require, as a bare minimum, a pure-tune audiogram. Many people with tinnitus complain that their ear or ears feel blocked and tympanometry is therefore often valuable.

TINNITUS-SPECIFIC AUDIOLOGICAL MEASUREMENTS

A number of specific tinnitus tests are available, but their reliability is variable, even when assessed using contemporary research methods.[55] Tests include the assessment of loudness discomfort levels, tinnitus pitch matching, tinnitus loudness matching and minimal masking levels.

IMAGING

Patients with unilateral tinnitus, an asymmetrical sensorineural hearing loss or associated neurological symptoms or signs require imaging to exclude the presence of a retrocochlear pathology such as a vestibular schwannoma. The modality of choice is MRI and there are now sufficient MRI options that even the claustrophobic, obese and those unable to lie flat should be able to undergo MRI scanning. The presence of non-compatible medical devices such as pacemakers or the presence of metal foreign bodies may still preclude MRI, in which case CT may be utilized.

TINNITUS QUESTIONNAIRES

Tinnitus questionnaires are an essential tool for research[56] and also have a role in the assessment of patients during routine clinical practice: their use has been recommended in the UK by the Department of Health's good practice guide.[57] There are a plethora of questionnaires available and there is no clear winner. Examples include the Tinnitus Handicap Questionnaire,[58] the Tinnitus Handicap Inventory (THI),[59] The Mini Tinnitus Questionnaire[60] and the Tinnitus Functional Index.[61] A survey of audiology departments in 2012 showed that the THI was the most popular tinnitus questionnaire used in the UK.[62] However, this study was conducted prior to the release of the Tinnitus Functional Index, which is claimed to have several advantages over its older competitors.

OTHER QUESTIONNAIRES

Because of the comorbidity of psychological conditions such as anxiety and depression with tinnitus, it is often helpful to use a mental health questionnaire such as the Hospital Anxiety Depression Scale (HADS).[63] Similarly, sleep disturbance is commonly reported in patients with tinnitus and it may be advantageous to use a sleep assessment tool such as the Insomnia Severity Index.[64]

VISUAL ANALOGUE SCALES

Visual analogue scores are considered useful, particularly in the research setting, when assessing specific components or consequences of tinnitus. Scores are usually formulated by putting a mark on a straight line, the ends of which represent the extremes of the parameter being assessed.

Mainstream treatments

To date a whole host of medicinal, device and psychological treatments for tinnitus have been proposed. The evidence base to support these treatments is poor at best, mainly due to a paucity of well-designed randomized controlled trials (RCTs). The scientific community has often been criticized for relying too heavily on the gold standard double-blinded RCT, but for conditions such as tinnitus, where many treatments may work via a placebo effect,[65] and there being a general natural improvement in symptoms with time, it is difficult to consider any other method of scientific evaluation as fit for purpose.

EXPLANATION AND REASSURANCE

An explanation of the condition and reassurance is a key initial step in the management of any patient with tinnitus. Often, the process of education and information giving is not the only treatment provided but, when provided in a formal setting, a number of RCTs are supportive of this modality.[66–68] A common report of patients seen in specialist tinnitus clinics is that clinicians who they have previously consulted have offered a very pessimistic view of tinnitus outcome. Reports such as 'the doctor told me that I would have it forever and nothing can be done' are all too common. This negative counselling is damaging for patients with tinnitus and should always be avoided.[69]

HEARING AIDS

As there is an association between tinnitus and hearing loss, it would make sense that providing hearing amplification would in part ameliorate a patient's symptoms. The literature lends some support for this[70, 71] but a recent

robust appraisal of the literature concluded that there was limited support from well-designed trials.[72] Hearing amplification may amplify external sounds and mask tinnitus, but indirect effects, such as improving communication, may reduce stress and anxiety that may be exacerbating the patient's symptoms.

Hearing aids first featured as a method of tinnitus management in the 1940s.[73] Currently, when supplemented with education and advice, hearing amplification is considered to be the primary intervention for a patient with tinnitus and aid-able hearing.[62] A large best practice consensus document has recently been published that recommends the provision of hearing aids in tinnitus patients even if they would normally be regarded as marginal hearing aid candidates.[74] A Delphi review of the use of hearing aids in the management of tinnitus, however, showed that, although there is some consensus among professionals, there is also still considerable disagreement.[75] Despite this lack of consistent good quality evidence, many clinicians encourage patients who have a hearing loss in addition to their tinnitus to try appropriate hearing aids even if they feel that amplification is not yet required for the hearing loss.

SOUND THERAPIES

Sound therapy can be used as part of TRT or as a standalone treatment. It is possible to use sound to completely or partly suppress, or mask, tinnitus in 95% of tinnitus patients in a clinic setting using specialist equipment, with 92% experiencing complete masking.[76] Translating this into practical treatment is less successful. Also, it has been suggested that complete masking is counterproductive as it may prevent habituation to the tinnitus signal. Proponents of TRT suggest that sound therapy is important but not used as masking. Instead, it is advocated that sound should be used at very low levels at a point where the added sound is just below the perceived level of the tinnitus.[77] Sound therapy at this so-called mixing or blending point is supposed to facilitate the habituation process, although there is conflicting evidence to the efficacy of this approach.[78, 79] There are three methods of providing wearable sound therapy: patients may wear hearing aids that produce masking by amplifying ambient sound (as discussed above), small ear level devices that generate wide-band sound (known as tinnitus maskers, sound generators, white noise generators or wide-band sound generators) or combination devices that blend the functions of the first two types of device. Whether such devices deliver masking or sound therapy at a mixing point simply reflects the output level that is set on the device. An alternative to donning a wearable device is to use an appliance that produces sound in the patient's immediate environment. This is referred to as environmental sound enrichment and can be delivered by devices such as electric fans, wind chimes, water features, prerecorded compact discs and electronic environmental sound generators. Sound from the latter two devices can be fed to a loudspeaker fitted into or under a pillow, allowing the patient to hear the sound while preparing for sleep without impinging on his/her partner. There are numerous programmes for computers and apps for smartphones that can be used to produce environmental sound enrichment.[80]

NOVEL SOUND THERAPIES

Several devices deliver forms of sound therapy that claim to specifically target tinnitus rather than simply offering masking or distraction.[81] Some purport to do this using sound on its own whereas others deliver sound stimulation while simultaneously stimulating other sensory systems.

Neuromonics®

Neuromonics® is a device that uses music modified to compensate for any hearing loss that the patient may have. The music has a large dynamic range with peaks and troughs with the intention that tinnitus is audible in the troughs. The sound therapy is accompanied by education and counselling and it is claimed that gradual exposure to the tinnitus during the troughs aids habituation. Several studies have been undertaken, mostly by the team that developed the device [82] and scientific rigour has been questioned.[83] An RCT compared Neuromonics® against ear-level sound generators and concluded that they had a similar effect on tinnitus.[84]

Serenade®

Work undertaken on a patient with profound hearing loss and tinnitus who had undergone cochlear implantation showed that certain stimulation paradigms were effective in ameliorating the tinnitus.[85] Extrapolating from this work, an acoustic stimulation regime was developed using temporally patterned sound altered to account both for any hearing loss and the pitch of the patient's tinnitus. This sound therapy is delivered via a device called Serenade® and the sounds have been dubbed S Tones.[86] There is now some evidence that S Tones may have a modest benefit compared to wide-band sound.[87]

Noise cancellation

Noise cancellation has been investigated as a possible tinnitus therapy. One device, Phase-Out, matches a therapeutic tone to the patient's tinnitus tone and then phase shifts the therapeutic tone by 6 degrees every 30 seconds. The suggestion made by the developer is that the therapeutic sound cancels the tinnitus for one-third of the total time.[88] Although some supportive research was published,[89] more scientifically robust research showed no benefit.[90]

Acoustic CR neuromodulation

One of the theories regarding the pathophysiology of tinnitus is that it is due to increased neural synchrony in the central auditory system (see above). It was suggested that a specific form of sound stimulation could be used to disrupt this pathological synchrony: four tones are delivered via headphones, two above and two below the dominant frequency of the patient's tinnitus. The technology is known

as Acoustic CR (Co-ordinated Reset) Neuromodulation and initial research looked promising.[91, 92] An RCT was planned.[93] This research was undertaken but the results were not published owing to deviations from the trial protocol. Following a freedom-of-information request by a UK tinnitus charity, a limited disclosure of the results was published online.[94] This stated that the end-of-study report did not report a significant difference in the primary outcome measure (global Tinnitus Handicap Questionnaire scores) between the treatment group and the placebo group.

Sound therapy with vagal nerve stimulation

Another theory regarding the pathophysiology of tinnitus is that of cortical map reorganization (see 'Central mechanisms' above) in which damage to the ear causes plastic changes within the central auditory system. Animal studies have suggested that direct electrical stimulation of the nucleus basalis in the forebrain in conjunction with stimulation of the sensory organ could reverse such changes. Clearly, this is too invasive to become a mainstream treatment but animal experiments have shown that stimulation of the vagus nerve paired with sound stimulation could potentially achieve the same effect.[95] Small-scale studies to stimulate the vagus nerve both by electrodes implanted against the nerve in the left side of the neck[96] and by the transcutaneous route[97] have been undertaken. As yet, however, there is insufficient evidence to reach meaningful conclusions and further work is required.

Mute button

Another therapy that utilizes crossover between the auditory system and other somatosensory pathways is Mute Button. This pairs acoustic stimulation with electrical stimulation of trigeminal nerve fibres in the anterior tongue. To date this treatment modality is only available in the Republic of Ireland and scientific evidence is limited to conference proceedings.

ULTRASOUND

Ultrasound has also been used to treat tinnitus: high-frequency sound is applied by a bone-conduction transducer. The rationale of this approach is that the ultrasound should stimulate the cochlea without interfering with the patient's hearing for sounds occurring in the normal auditory spectrum. An initial study reported optimistic results but this was not repeated.[98]

COMBINATION TREATMENT MODALITIES

Following publication of his neurophysiological model in 1990,[38] Jastreboff went on to generate a clinical management strategy that combined directive counselling and sound therapy to counteract the pathological positive feedback process and promote habituation to the tinnitus.[48] This process was subsequently titled tinnitus retraining therapy (TRT)[49] and the technique has been extensively discussed in a book which outlines a rigorous protocol.[99] However, the neurophysiological model, from which it is derived, can be interpreted differently and many tinnitus practitioners apply the clinical extrapolates of the model in a less rigorous fashion. A Cochrane systematic review has considered the evidence for the administration of TRT.[100] The initial findings were that, based on a single, low-quality RCT, TRT is much more effective as a treatment for patients with tinnitus than tinnitus masking.[101]

COGNITIVE BEHAVIOURAL THERAPY

The use of psychological techniques such as cognitive behavioural therapy (CBT) in the UK is hugely hampered by a lack of psychologists with appropriate tinnitus training. A Swedish group has investigated delivering CBT via the internet and initial results suggest that this may be a useful approach.[102] A Cochrane systematic review has considered the evidence for the administration of CBT and it was concluded that CBT resulted in no significant difference in tinnitus loudness, but CBT did result in a significant improvement in both depression scores and in quality of life scores.[103] A recent systematic review concluded that both CBT and TRT were effective treatments for tinnitus and neither was demonstrably superior.[104]

OTHER PSYCHOLOGICAL TREATMENTS

More modern psychological treatment modalities have recently been explored for efficacy in the management of tinnitus: these include mindfulness meditation[105] and acceptance and commitment therapy (ACT).[106] Initial reports appear optimistic. Psychological treatments are discussed in more detail in Chapter 70, Understanding tinnitus: A psychological perspective.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

Many forms of complementary medicine are promoted as being beneficial for tinnitus patients. A list of some of the more commonly used modalities is shown in **Box 61.1**. Many of these therapies involve much contact between the

BOX 61.1 Some of the complementary medicine therapies and exercise regimes that have been used in the management of tinnitus

Acupuncture	Hypnotherapy
Alexander technique	Massage
Aromatherapy	Meditation
Black cohosh	Osteopathy
Chiropractic	Reflexology
Craniosacral therapy	Reiki
Herbal medicine	St John's wort
Ginkgo biloba	Shiatsu
Homeopathy	Tai Chi
Ear candles	Yoga

therapist and patient and promote a sense of relaxation. It might therefore be expected that these therapies could help tinnitus patients, at least in a non-specific way.

Relaxation techniques have been studied as a specific therapy to treat tinnitus and three RCTs have been performed to assess their effectiveness.[107–109] These studies supported the efficacy of relaxation therapy for tinnitus intrusiveness but there was mixed evidence for its efficacy for depressive symptoms, and there was no evidence for an effect on anxiety.

In 2000 Park et al. systematically reviewed the efficacy of acupuncture as a treatment for tinnitus.[110] This review identified only six randomized trials: two unblinded trials and four blinded trials. The two unblinded trials demonstrated a positive effect of acupuncture treatment for tinnitus, whereas the four patient-blinded, sham-controlled studies demonstrated no significant difference between treatment with acupuncture and placebo.

There have been some claims that chiropractic manipulation benefits tinnitus patients, but there have been no scientific studies to substantiate any positive effect in comparison to placebo.

A note of caution must be sounded regarding the use of ear candles in the management of tinnitus. Not only has no benefit been demonstrated but in a few instances damage to the ear has resulted as a consequence of their use.[111]

Several exercise regimes such as Tai Chi and yoga have been promoted as helping patients with tinnitus. In these cases, no claim is made that the exercises treat the tinnitus directly but rather that the techniques promote relaxation and combat stress.

Ginkgo biloba has attracted more interest for the treatment of tinnitus than any other complementary therapy. The efficacy of ginkgo has had mixed support. A number of large double-blinded, placebo-controlled trials have been undertaken reaching different conclusions. In 2001 Drew and Davies failed to demonstrate a significant effect in treating tinnitus using ginkgo doses of 150 mg.[112] A double-blinded, placebo-controlled trial and meta-analysis of randomized trials recently concluded that ginkgo did not benefit patients with tinnitus.[113] Despite these reports it must be noted that the success of other studies has been based on much higher doses of up to a daily total of 480 mg of ginkgo extract.[114] Further supporting the role of ginkgo is a controlled study demonstrating a statistically significant reduction in tinnitus using an animal model.[115] Systematic appraisal of the role of ginkgo has been performed by way of a Cochrane review, which found no reliable evidence supporting its use as many of the studies performed have been flawed in one way or another.[116]

ELECTROMAGNETIC STIMULATION

Direct electrical stimulation of the ear has been shown to suppress tinnitus but delivering this stimulation is invasive and risks damage to the inner ear.[117] Partly because of this tantalizing glimpse of a tinnitus suppressant, other ways of delivering electrical and magnetic energy to the cochlea or central auditory system have been investigated. High-powered rare earth magnets have been placed in the ear canal but an RCT failed to show any benefit despite initial positive reports.[118] Electromagnetism has also been investigated: initial trials gave mixed results,[119] but the use of refined methods of delivery have promoted further interest in this area. Electromagnetism has been used in conjunction with functional imaging such as PET scanning or fMRI: pathologically active areas of brain are identified and electromagnetic therapy is then directed to this area.[120, 121] Repetitive transcranial magnetic stimulation (rTMS) can be delivered at a variety of different frequencies and in some circumstances employing complex wave administration.[122] A recent Cochrane systematic review has considered the evidence for the administration of rTMS and concluded that there is very limited support for the use of low-frequency rTMS for the treatment of patients with tinnitus.[123] When considering the impact of tinnitus on patients' quality of life, there was support from a single study with a low risk of bias based on a single outcome measure at a single point in time.

SYSTEMIC DRUG TREATMENTS

Although drug therapy should be relatively easy to investigate, much of the published information is of poor quality. The use of inert placebos, inadequate outcome measures and high drop-out rates are common in drug trials. Moreover, most trials have failed to make a distinction between helping concomitant psychological illness and direct effect on tinnitus. Tinnitus drug trials are often carried out on small groups of patients and consequently lack the power to detect small effects.

Psychoactive drugs have been used in the management of tinnitus, partly because tinnitus patients score highly for symptoms of psychological distress[28] and partly because many of the receptors that psychoactive drugs act upon are also found within central auditory pathways. While there is a role for such drugs in the treatment of any psychological or psychiatric disease that accompanies tinnitus, the situation with respect to the tinnitus itself is less clear. There are four reasonably well-constructed RCTs which investigated the use of tricyclic antidepressant drugs.[124–127] These all reported slight improvement in tinnitus but these conclusions may be attributable to methodological flaws, so no major conclusions can be drawn. A well-constructed trial of a selective serotonin reuptake inhibitor, paroxetine, showed no advantage over placebo for the majority of criteria investigated.[128] Benzodiazepines have been widely used in the management of tinnitus and some work has suggested that this group of drugs may have a direct effect on tinnitus.[129] Unfortunately, this research can be criticized for using an inert placebo and, in any case, the propensity for benzodiazepines to induce dependence restricts their usage.

Antiepileptic[130, 131] and antispasmodic[132] drugs have both been investigated for potential activity against tinnitus but the results have been disappointing. Likewise the use of vasodilators[133] and diuretics[134] has proved unhelpful. Betahistine is frequently administered to patients with idiopathic tinnitus: there is no scientific rationale for this action. In 2006 a group in China reported an improvement

in tinnitus loudness when subjects received betahistine as compared with subjects that received a control drug.[135] However, only a small number of subjects were studied and there have been no further studies published since to corroborate the original study authors' findings.

Local anaesthetic agents have offered one glimmer of hope for a possible pharmacological solution to tinnitus. Following a serendipitous discovery when procaine caused temporary abatement of tinnitus in a patient undergoing nasal surgery,[136] several trials have confirmed that intravenous injections of some ester and amide local anaesthetic agents cause short-term reduction of tinnitus. A double-blind, placebo-controlled, crossover trial investigated 16 patients who had post-operative tinnitus following translabyrinthine resection of a vestibular schwannoma.[137] Bolus intravenous injection of lidocaine produced significant short-term tinnitus suppression despite the fact that the auditory nerve had been divided during the surgical procedure. Although the trial can be criticized for using an inert placebo, the observations suggest that, at least within this group, the antitinnitus effect of the local anaesthetic agent was central rather than peripheral. Previous attempts to find a less hazardous and orally active agent that has the same beneficial effects as these local anaesthetics have failed.[138]

Two small-scale trials have shown that the hormone melatonin helps patients who have sleep disorders associated with tinnitus.[139, 140] As many patients with tinnitus do have sleep disorders,[141] this merits further investigation.

Tinnitus, like idiopathic sudden sensorineural hearing loss, has been thought to arise from a lack of oxygen secondary to vascular insufficiency. For this reason interest has been shown in the application of hyperbaric oxygen therapy to increase the supply of oxygen to the ear and brain to reduce the severity of hearing loss and tinnitus. A critical assessment of the role of hyperbaric oxygen therapy has been performed by way of a Cochrane review and no clear value could be demonstrated.[142]

As glutamate is the main excitatory neurotransmitter in the auditory system, there has been considerable interest in studying a variety of antagonist drugs, including memantine,[143] flutirpine[144] and neremexane[145] but no demonstrable benefits have been shown.

There have been sporadic reports of the successful use of drugs to treat specific subtypes of tinnitus. For example, it has been suggested that the antiepileptic drug carbamazepine can be effective in treating a variant of tinnitus that presents with an intermittent staccato quality, described as sounding like a typewriter or popping corn.[146] However, this report is from a small uncontrolled case series and better scientific evidence in the form of an RCT would be required before such therapy could be recommended.

REGIONAL DRUG TREATMENTS

Botulinum toxin has been shown to be beneficial through non-paralytic effects for conditions such as neuropathic pain and migraine. With respect to migraine, botulinum toxin is thought not only to block acetylcholine but also to inhibit the release of other neurotransmitters and neuropeptides involved in the autonomic pathway. Botulinum toxin A has been trialled in a small study of 26 tinnitus patients with the drug injected into soft tissues around the ear.[147] Benefit was demonstrated in the treatment arm as compared to the control arm but, due to the small number of patients recruited, no statistical significance was demonstrated.

INTRATYMPANIC DRUG TREATMENTS

The idea that drugs could have a therapeutic effect following instillation into the middle ear cavity has a long pedigree: work in the 19th century investigated the application of volatile vapours into the middle ear using Eustachian tube catheters.[148] Direct injection through the tympanic membrane was first utilized as a potential treatment for otosclerosis.[149] After initial enthusiasm this route of drug administration underwent a period when it was rarely used, but following the successful experience of using transtympanic administration of aminoglycosides in the treatment of Ménière's disease, the use of intratympanic therapies is once again being investigated for patients with subjective idiopathic tinnitus. It has been theorized that transtympanic administration allows direct labyrinthine drug absorption which may offer improved labyrinthine metabolism and hence reduction of tinnitus in those patients who have tinnitus in association with cochlear pathology. This mode of administration may appear to fly in the face of most modern theories of tinnitus pathophysiology, which suggest that the long-term problems of tinnitus occur in the central rather than peripheral auditory system. Events within the ear such as sudden sensorineural hearing loss, acute noise trauma or acute otitis media can trigger tinnitus and it has been suggested that there is a small therapeutic time window between the pathological event in the ear in these cases and the development of permanent changes in the central auditory system that produce troublesome tinnitus. It is therefore hypothesized that, in patients with sudden onset of tinnitus, there might be a short period when intratympanic treatments could be efficacious. Furthermore, it has been observed that some treatments that improve hearing, such as stapedectomy in otosclerosis, generally help any associated tinnitus. Extrapolating from this, intratympanic therapies that could potentially improve hearing could therefore also potentially be beneficial with any associated tinnitus.

Various agents, including steroids,[150] local anaesthetic agents,[151] anticholinergic drugs,[152] glutamate antagonists[153] and antioxidant compounds[153] have been delivered into the middle ear, either by single transtympanic injections, through perforations and grommets, or via an implanted micropump.[154] Most of the trials in this area are small observational studies. The solitary placebo-controlled trial in this field demonstrated no advantage of intratympanic dexamethasone over placebo.[155]

Although there has been no demonstrable benefit from using systemic glutamate antagonists in the management of tinnitus, interest in this class of drugs continues.

Some glutamate antagonists are too toxic to consider for regular systemic usage and consequently there has been interest in the intratympanic administration of these drugs. Recently there have been some encouraging results from preliminary studies investigating the use of esketamine, the S(+) enantiomer of ketamine, for acute 'inner-ear' tinnitus.[156] This compound acts as a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) subgroup of glutamate receptors. At the time of writing, larger-scale multinational trials are being conducted to decide whether the acute administration of this drug will prove to be a viable treatment in the future. Similarly, clinical trials are shortly expected to start for a sustained-release formulation of another NMDA antagonist, gacyclidine.

DIETARY SUPPLEMENTS

A large number of vitamins, minerals and other dietary supplements have been given to tinnitus patients in an effort to alleviate the condition. Some of the agents used are listed in **Table 61.1** although this is far from an exhaustive list.

There is some evidence that some of these compounds listed in **Table 61.1**, particularly the B vitamins, can help to defend the cochlea against noise trauma.[157] Indeed, some of the compounds on the list are being investigated for effectiveness in protecting people who are exposed to noise from developing tinnitus (see 'Prevention' below). However, there is no convincing evidence that they have any effect against established idiopathic tinnitus. The human cochlea has the body's greatest concentration of zinc. Some studies have demonstrated a significant decrease in zinc levels in some patients suffering from tinnitus and rectifying this deficiency has been shown to decrease tinnitus significantly.[158] Paaske et al., however, demonstrated little correlation between hypozincaemia and tinnitus[159] and no significant improvement in tinnitus with zinc supplementation. A randomized double-blind, placebo-controlled trial of the use of zinc in a population of tinnitus patients aged 60 or over showed no benefit with regards to their tinnitus.[160]

TABLE 61.1 Some of the dietary supplements that have been used in the management of tinnitus

Name of supplement	Class of supplement
Arginine	Amino acid
Beta carotene	Vitamin precursor
Calcium	Mineral
Club moss	Herbal
Coffee (unroasted)	Herbal
Cornus	Fruit
Folic acid	Vitamin
Foxglove	Herbal
Garlic	Herbal
Hydergine	Herbal
Ipriflavone	Bioflavonoid
Ligustrum	Herbal
Magnesium	Mineral
Manganese	Mineral
Melatonin	Hormone
Mullein	Herbal
N-acetylcysteine (NAC)	Antioxidant
Omega-3	Fish oil
Peruvian bark	Herbal
Plumbago	Herbal
Potassium	Mineral
Pulsatilla	Herbal
Salicyclic acid	Herbal
Selenium	Mineral
Sulphite of quinine	Herbal
Vegetable charcoal	Herbal
Vinpocetine and vincamine	Herbal
Vitamin A	Vitamin
Vitamin B1 (Thiamine)	Vitamin
Vitamin B3 (Niacin)	Vitamin
Vitmain B6 (Pyridoxine)	Vitamin
Vitamin B12	Vitamin
Vitamin C	Vitamin
Vitamin E	Vitamin
Wobezym	Enzyme formula
Zinc	Mineral

LASERS

Lasers have been used successfully in the management of some forms of chronic pain but the exact mechanism for this benefit remains contentious. Low-power lasers have been used in the treatment of tinnitus, applied either transmeatally or to the mastoid process. Although some workers have reported good results from such treatment,[161, 162] two well-constructed trials found no benefit above that derived from placebo.[163, 164]

SURGERY

Surgery has a definite role in the management of tinnitus associated with certain conditions such as otosclerosis when stapedectomy is reported as improving or eradicating tinnitus in 80–88.3% of cases.[165, 166] When tinnitus is associated with profound hearing loss, tinnitus suppression has been demonstrated as a secondary benefit of cochlear implantation. Improvement of tinnitus occurs in up to 86% of implanted patients and, interestingly, in up to 67% the benefit applies to the contralateral ear as well as the implanted ear.[167] There is no good evidence to support cochlear implantation for the sole purpose of tinnitus suppression and it would be ethically difficult to propose cochlear implantation for someone with significant residual hearing. The use of cochlear implantation with regard to the management of tinnitus in conjunction with single-sided deafness is discussed in 'Single sided deafness' below.

Destructive surgical procedures including VIIIth nerve neurectomy or selective cochlear neurectomy have been tried but there is no trial using good scientific methodologies such as validated outcome measures. Surgical treatments of Ménière's disease are generally aimed at control of vertigo and few trials have explored the effect on tinnitus. A Cochrane review of surgical treatments for Ménière's disease identified two studies that had commented on tinnitus outcome, both employing endolymphatic sac decompression. In both studies endolymphatic sac decompression showed no advantage over the control treatment with regard to tinnitus.[168]

PREVENTION

Cochlear damage caused by exposure to agents including noise, ototoxic agents and cytotoxic drugs is recognized as a trigger for tinnitus. Clearly, the best way to avoid damage from these agents is to avoid exposure to them: this is not always possible or practical. At a cellular level, the inner ear damage is generally mediated by a process of apoptosis[169] and this cascade has the potential to be therapeutically blocked. Driven in part by a need to protect military personnel from noise during combat,[170] several studies are researching the use of antioxidants including D-methionine (D-met),[171] ebselen[172] or a combination of beta carotene, vitamin C, vitamin E and magnesium (ACE Mg).[173] Stem-cell and gene therapies are also being investigated.[169]

PULSATILE TINNITUS

Pulsatile tinnitus is a form of tinnitus whereby the perception of sound is not that of a continuous form. The perceived sound takes on the form of a pulsation, clicking or fluttering. Pulsatile tinnitus is worthy of consideration as a specific subtype of tinnitus because the management of pulsatile tinnitus is different from that of the typical tonal tinnitus that patients report. Pulsatile tinnitus is classified as either synchronous or non-synchronous, depending on whether the tinnitus takes on the characteristics of a pulsation in synchrony with the patient's heart.

Synchronous pulsatile tinnitus

PATHOPHYSIOLOGY

Synchronous pulsatile tinnitus may present as the direct result of abnormal vascular anatomy in the vicinity of the peripheral auditory system. Systemic aberrations of the circulation, such as a hyperdynamic circulation, have also been implicated in the development of synchronous pulsatile tinnitus. Processes that result in altered arousal, altered selective attention, hearing loss, or altered cochlear blood flow or trauma may result in increased central auditory gain.[48] It has been proposed that, once this process has ceased, the increased gain will cause the subject to become more aware of their own physiological vascular pulsations. Table 61.2 summarizes the different pathological causes of synchronous pulsatile tinnitus.

TABLE 61.2 Pathological causes of pulsatile tinnitus

Type of pathology		Specific pathology
Vascular	Arterial	Atherosclerotic carotid artery disease[174] Arteriovenous fistula[175] Arteriovenous malformation[176] Intracranial aneurysm[175] Fibromuscular dysplasia of the carotid artery[177] Dissection of the carotid artery[178] Vascular anomalies of the ear[179] Vascular compression of the VIIIth nerve[180]
	Venous	Jugular bulb abnormalities[181] Dural venous sinus stenosis[182] Abnormal condylar or mastoid emissary veins[183] Idiopathic tinnitus, venous hum, essential tinnitus[184, 185]
Microvascular		Glomus tumour[186] Paget's disease[187] Cholesterol granuloma of middle ear[188] Meningioma of middle ear[189] Cavernous haemangioma[190] Histiocytosis X[191]
Circulatory		Increased cardiac output (anaemia, thyrotoxicosis, pregnancy)[192] Aortic murmurs[188]
Perceptual		Conductive hearing loss[193] Cochlear trauma[193]
Other		Benign intracranial hypertension[194–197] Superior semicircular canal dehiscence syndrome[198]

Whereas, traditionally, pulsatile tinnitus has been considered to be always a consequence of a primary vascular abnormality, over the last decade there has been a greater consideration of other primary causes. Intracranial hypertension is particularly gaining increased attention as a cause of pulsatile tinnitus.[196, 197] Idiopathic intracranial hypertension, or pseudotumor cerebri, is one cause of intracranial hypertension; this condition tends to occur more often in young, overweight women. Superior semicircular canal dehiscence syndrome is more usually featured in the medical literature as a cause of dizziness, however the emergence of this condition as a presentation of pulsatile tinnitus is beginning to gain acceptance.[198]

INVESTIGATION

Simple blood tests are considered helpful to exclude anaemia and thyrotoxicosis. In the absence of an obvious cause, synchronous pulsatile tinnitus requires imaging. Over the years there has been much debate regarding the ideal imaging modality. If otoscopy reveals a retrotympanic mass, a contrast-enhanced computed tomography (CT) of the temporal bone, brain and scalp is indicated.[199] If atherosclerotic carotid artery disease is suspected, duplex carotid ultrasonography can be helpful. Otherwise, the

advantages and disadvantages of magnetic resonance angiography (MRA) over contrast-enhanced CT has not been satisfactorily resolved. The gold standard mode of imaging the vascular system of the temporal bone, brain and scalp is via formal angiographic imaging, but this is not without risk, so this is often reserved for severe, recalcitrant cases where less invasive techniques have not revealed an obvious pathology. If idiopathic intracranial hypertension is suspected, an ophthalmological assessment, lumbar puncture, measurement of intracranial pressure and diagnostic reduction of intracranial pressure by draining off some cerebrospinal fluid may be required.

TREATMENT

Supportive

When no obvious cause is identified, providing reassurance that there is no untoward pathology present is often an important aspect of treatment. These patients may benefit from CBT or TRT to address the coexisting emotional effects of their tinnitus. Anecdotally, sound therapies can be used as for subjective idiopathic tinnitus though there is no evidence base to support this management.

Surgery

Surgery can play an important role in the management of pulsatile tinnitus,[195] depending on the causative pathology. Treatments may include decompressive and destructive procedures. Modern imaging techniques, and in particular MRI, have shown that vascular loops are commonly in close proximity to the cochlear nerves of patients with tinnitus. It has been suggested that laterally placed loops generate pulsatile tinnitus whereas vessels adjacent to the medial half of the nerve generate non-pulsatile tinnitus.[200] However, the prevalence of such loops in people who do not have tinnitus is unknown. Microvascular decompression of vascular loops in tinnitus patients has been used with very variable results, ranging from 40% improvement[201] to 77%.[202] The highly invasive nature of this surgery precludes its use in all but the most exceptional cases.

Non-synchronous pulsatile tinnitus

Tinnitus may manifest itself as a train of rhythmical clicks or a buzzing or fluttering noise or sensation that is not synchronous with the pulse. These sounds are often related to myoclonic activity resulting in repetitive contractions of the middle ear muscles, but other muscles within the head and neck region can be affected. Currently there is no evidence to suggest that the middle ear is part of a systematic myoclonic disorder. Within the middle ear, contraction of the tensor tympani and/or stapedius muscle are often proposed to be the cause of either a clicking or buzzing noise respectively; however, whether the associated tinnitus is the direct result of muscle contraction noise, vibration of the tympanic membrane or movement of the ossicular chain remains unknown.[203] The palatal muscles can also develop myoclonic contraction and this can produce sound that is audible to others. The clicking sound of palatal myoclonus is usually irregular with a frequency of one to two clicks per second. Involuntary palatal movements may be seen, either simply by inspecting the palate transorally or by visualizing the upper surface transnasally using a fibreoptic endoscope. Palatal myoclonus exists in two forms: symptomatic palatal myoclonus, which may be associated with lesions of the brainstem; and essential palatal myoclonus, which is usually idiopathic. It is generally essential palatal myoclonus that is associated with pulsatile tinnitus.

INVESTIGATION

The role of specialist testing for the assessment of middle ear or palatal myoclonus is unclear. While middle ear myoclonus can be diagnosed based on history and impedance changes on long-time-based tympanometry, an accurate differentiation between myoclonus of the tensor tympani and the stapedius muscle is not possible.[203] It is, however, important to differentiate a middle ear myoclonus from a palatal myoclonus. Palatal myoclonus usually produces an objective rhythmic sound that is associated with an involuntary movement of the soft palate and/or suprahyoid muscles. As palatal myoclonus has been associated with lesions in the central nervous system, MRI is recommended to exclude a pathology with the triangle of Guillain–Mollaret.[204]

TREATMENT

In cases of middle ear myoclonus, despite evidence to support the division of the middle ear tendons, a period of conservative treatment is recommended in the first instance. Pharmacological solutions that have been explored have included the use of benzodiazepines,[205] orphenadrine,[206, 207] carbamazepine,[208] piracetam[206] and botulinum toxin.[209]

Other reported supportive treatments include relaxation therapy,[210] psychotherapy,[211] tinnitus masking[212] and biofeedback,[212] although outcomes have been variable. In persistent cases, the surgical division of the middle ear tendons has been reported to be a definitive procedure: it is recommended that in these cases both tendons are divided as it is not possible to reliably identify the muscle which is responsible for the symptoms.

ALLIED CONDITIONS

Musical hallucination

As discussed earlier in this chapter, the sound perception of tinnitus can take virtually any form. A small number of patients report that they can hear music when none is present, usually describing short excerpts of music that they were familiar with in their youth. Although many feel that the music sensation is within their own head, some perceive it as an external sound. This may lead them to falsely accuse neighbours of playing the music, either unthinkingly or maliciously. The condition is more common in women, the elderly and those with significant

hearing impairment.[213] The association with hearing loss has led to the hypothesis that musical hallucination is caused by deafferentiation, in which reduced input to the central auditory system causes increased gain within the associative auditory cortex.[214] This results in the brain misinterpreting background neuronal activity as music. The difference between this and the 'earworm' or tune stuck in the head that we all get from time to time is that people with musical hallucination are convinced that the sound is real. It is important to ensure that the patient is not describing the auditory hallucinations of mental illness; if there is any doubt, a psychiatric opinion should be sought. Musical hallucination can rarely be associated with epilepsy so a neurological opinion is prudent. There is no substantial evidence base for the management of musical hallucination but addressing any associated hearing loss is anecdotally helpful.

Acoustic shock

Over the last quarter of a century a cluster of symptoms has been observed among call-centre operatives who are exposed to sudden unexpected sounds through their headsets or telephone handsets. This has become known as acoustic shock syndrome, acoustic shock injury or simply acoustic shock.[215–217] The symptoms of acoustic shock can be divided into immediate and delayed. Pain is the most common immediate symptom, with 81% of those affected describing otalgia, 11% describing neck or jaw pain and 7% describing facial pain. Tinnitus occurs in approximately half of these patients, and balance disorders are also common. Hearing loss is reported less frequently and, when it does occur, it is usually temporary. Delayed symptoms include hypervigilance, anxiety, sleep disorders, hyperacusis and a feeling of aural fullness. Examination is normally unremarkable and audiometry usually shows normal symmetrical hearing or an age appropriate sensorineural hearing loss. If there is any additional audiometric loss it is often of an atypical pattern and does not have the typical characteristics of noise induced hearing loss.

The sounds that cause acoustic shock have been analyzed and do not need to be excessively loud to trigger the symptoms. One study identified sounds with intensity in the range 56–100 dB whereas another reported sounds in the range 82–120 dB.[215, 218] One common feature of the causative sounds was that they had short rise times. It is not clear whether exposure to similar sounds when not wearing headsets can generate acoustic shock. Certainly there are anecdotal reports of other abrupt sounds generating similar symptom complexes. Sounds that are generated close to the ear seem more likely to cause these symptoms than distant sounds. The pathophysiology of acoustic shock remains obscure. Cochlear and central auditory system mechanisms have been suggested but the most popular current hypothesis is that acoustic shock represents tonic contraction of the middle ear muscles – tonic tensor tympani syndrome.[216, 219, 220] The management of acoustic shock is also uncertain. Many people with acoustic shock feel that they are being disbelieved or accused of malingering: supplying a diagnosis and offering general reassurance can be helpful in this respect. If the patient has persistent tinnitus and hyperacusis, these symptoms can be treated using the standard audiological or psychological techniques that are discussed elsewhere in this chapter. The question of whether someone who has experienced a significant acoustic shock can remain in call-centre employment is complex and as yet there is no consensus regarding the best course of action.

Low-frequency noise complaint

Low-frequency noise complaint is an unusual condition in which people report distress caused by the perception of intrusive low-frequency sound.[221, 222] This can result in major disruption of normal activities and is often associated with sleep disturbance. People with low-frequency noise complaint report sounds such as humming, rumbling or machinery noise. They generally feel that the sound is a real external sound, contrasting with standard tinnitus in which the person feels that the sound is within their own ears or head. Consequently, it is common for environmental health officers to be called in to investigate, but low-frequency sound levels are usually at or below hearing threshold. The UK and US press have been interested in this condition, christening the phenomenon 'The Hum' and referring to sufferers as 'Hummers'. There is no strong evidence base regarding either the pathophysiology or the management of this condition. In some cases there may be a real external sound source: dealing with this is the duty of environmental health teams. If there is no external source, which is the usual situation, techniques used for spontaneous idiopathic tinnitus can be utilized, including psychological treatments such as CBT[223] or audiological treatments using counselling and sound therapy.[224] Many people with low-frequency noise complaint are reluctant to embrace such therapeutic approaches because they remain convinced that their symptoms are generated by an external sound and do not represent a form of tinnitus.

Exploding head syndrome

Exploding head syndrome is a parasomnia phenomenon characterized by the perception of a sudden loud noise in the head or ears that occurs during a transition of sleep stages. Because there is an auditory hallucination some patients may be referred to tinnitus clinics though referral to sleep clinics or neurologists also occurs. Exploding head syndrome is generally hypnagogic, occurring at the interface from wakefulness to sleep, but can be hypnopompic, presenting at the onset of wakefulness. The range of sounds reported is large and includes sounds such as explosions, banging, roaring, voices yelling, a bell ringing or the thunder crack accompanying lightning. The auditory hallucination is accompanied by visual sensations in approximately 10% of cases, with sufferers describing experiences such as a brief vivid flash of light.[225] Other sensory experiences may be reported including a feeling of heat or an electrical sensation.[226, 227] The phenomenon is generally painless and has no serious medical sequelae

though understandably it may generate feelings of shock and fear. Tachycardia and palpitations have been reported after an episode. Historically exploding head syndrome has been said to be a rare,[228] to be more common in women than men[229] and to be more common in those over 50.[225] However, a study of 211 undergraduate students suggested that the condition may be more common than previously thought, may occur in younger people and may have no gender imbalance.[230] The natural history of the condition seems unpredictable from evidence derived from the available case reports, with some people reporting a single episode whereas others experience multiple events per night; the problem can be persistent over many years or can spontaneously remit.

Clinically, it is important to exclude other conditions such as nocturnal epilepsy or subarachnoid haemorrhage. If the patient describes significant pain, an alternative diagnosis should be sought. Once the diagnosis has been established, education and reassurance are reported to help. Various pharmacological agents have been assessed including tricyclic antidepressants,[226] anticonvulsants[231] and calcium-channel blockers.[232] However, drug studies have been small-scale and uncontrolled and further research is clearly required.

SPECIAL POPULATIONS

Tinnitus in children and adolescents

Tinnitus is not as rare in children as was once thought. In children with normal hearing, the prevalence of tinnitus can vary from 12% to 36%.[233] Tinnitus in children, like adults, is more common if there is hearing loss.[234–238] Tinnitus has been demonstrated to commonly occur in children with otitis media.[239, 240] Tinnitus in children, as compared to adults, presents itself in a different manner and, while many of the basic principles of tinnitus management still stand, a different approach is required when dealing with children. In 2015, the British Society of Audiology (BSA) published practice guidance on the management of tinnitus in children. Developed through the Paediatric Audiology Interest Group (PAIG) of the BSA by national specialists in paediatric tinnitus, the project was supported by the British Tinnitus Association and the guidance is available from the BSA website.[241]

Military personnel

The association between tinnitus and noise exposure is well known and military personnel experience both chronic noise exposure and sudden extreme noise exposure. Military personnel in the UK are legally protected during training, but in a combat situation the use of hearing protection may not be viable and noise exposure may be particular high. Indeed, noise levels can become so high that, even when wearing hearing protection, military personnel may be exposed to levels of sound that exceed safe limits.[170] In addition, service personnel may be exposed to ototoxic chemicals during their military service.[242] It is therefore perhaps not surprising that tinnitus is now reportedly the number one disability among US veterans.[243] Post-traumatic stress is high among service personnel and seems particularly high among those with concomitant tinnitus: a study of military veterans showed that 34% of those who attended a tinnitus clinic also fulfilled the diagnostic criteria for post-traumatic stress disorder.[244] Traumatic brain injury is also more common among military veterans and this may affect the central auditory system.[245] Management of tinnitus in this population is therefore often complex and may require a multidisciplinary approach.

Single-sided deafness

Acquired unilateral profound hearing loss is a relatively common clinical problem. A study in 2006 estimated that the incidence may be up to 8000 new adult cases per annum in the UK.[246] In a study of 21 patients with single-sided deafness, two-thirds reported tinnitus and in 29% the tinnitus was severe.[247] Various therapeutic interventions have been explored in these patients, including the use of contralateral routing of signal (CROS) hearing aids, bone-anchored hearing aids, bone-conduction hearing implants and cochlear implants. There is little evidence to support the effect of the first three of these options but there are several studies that have investigated cochlear implantation and a systematic review has suggested that tinnitus is generally lessened, at least during the period when the implant is activated.[248]

DISORDERS OF SOUND TOLERANCE

DEFINITIONS AND CLASSIFICATION

Hyperacusis is a word that is used to denote a specific disorder of loudness perception but is also frequently used as a blanket term to describe all forms of decreased sound tolerance. Originally, disorders of sound tolerance were divided into hyperacusis, defined as a dislike of loud sounds, and phonophobia, defined as a fear of particular sounds and loudness recruitment, which is a specific experience that is associated with cochlear hearing loss and specifically with dysfunction of the outer hair cells of the organ of Corti.[249]

Jastreboff and Jastreboff[250, 251] recognized that many of their patients reported dislike of particular sounds but their emotional response did not constitute fear. They therefore employed the services of a Cambridge University classicist, Guy Lee, who devised a new word, misophonia, which they defined as a strong dislike of specific sounds. This new classification has not garnered universal support and a recent publication from an international working group has proposed an alternative set of definitions for decreased sound tolerance comprising loudness hyperacusis, annoyance hyperacusis, fear hyperacusis and pain hyperacusis.[252] With this definition, loudness hyperacusis and pain hyperacusis approximate to the previous definition of hyperacusis, annoyance hyperacusis to misophonia

and fear hyperacusis to phonophobia. To further complicate the terminology of disorders of sound tolerance, the neurological community describes phonophobia as part of the symptom complex experienced during migraine attacks. Such patients generally report a general dislike of sounds which would probably equate better to the audiological definition of hyperacusis, rather than phonophobia. Clearly, this field is ready for rationalization and reorganization.

In the following section hyperacusis is discussed as a specific symptom, and misophonia and phonophobia will be considered later.

HYPERACUSIS

Definitions

Definitive descriptions depict hyperacusis as an 'unusual tolerance to ordinary environmental sounds'[253] and as 'consistently exaggerated or inappropriate responses to sounds that are neither threatening nor uncomfortably loud to a typical person'.[254] In simple terms, hyperacusis is dislike of sounds above a certain intensity.

Epidemiology

There is a paucity of data to define the prevalence of hyperacusis. The available population surveys have suggested a prevalence of between 8% and 15%.[255, 256] The relation between tinnitus and hyperacusis has long been recognized and it has been suggested that hyperacusis may be a precursor state for tinnitus. Approximately 40% of patients who present with tinnitus also complain of hyperacusis.[30, 257] Of those whose primary complaint is hyperacusis, up to 86% report tinnitus.[31]

Pathophysiology

Hyperacusis and tinnitus often present together, and often in combination with hearing loss. This had led to speculation regarding a common underlying aetiology.[258, 259] Nelson and Chen have suggested that increased perception of sound intensity in the auditory cortex (hyperacusis) together with the perception of phantom sounds (tinnitus) results from a common trigger (hearing loss). A number of conditions have specifically been associated with hyperacusis.[258, 259] Some of these conditions, such as Bell's palsy and Ramsay Hunt syndrome, are associated with facial nerve dysfunction. However, since it is likely that in these cases the mechanism is due to an increased perception of sound intensity, secondary to an inefficient or absent stapedial reflex, some have considered that the resulting 'sound sensitivity' cannot truly be defined as hyperacusis.[260] Williams syndrome is a disorder characterized by deficits in conceptual reasoning, problem solving, motor control, arithmetical ability and special cognition[261] and hyperacusis has been reported to feature in 90% of individuals with this syndrome.[254] As Williams syndrome is associated with an underlying dysfunction of 5-hydroxytryptamine (5-HT), some have considered that the effects of 5-HT in other conditions, including migraine, depression and post-traumatic stress disorder, may lead to the increased auditory gain that may be responsible for hyperacusis.[262] Many other mechanisms have been suggested to underpin the neurophysiology of sound perception, with Jastreboff and Hazell proposing the central auditory system as playing the key role in setting auditory gain and perpetuating the perception of increased loudness.[48]

Investigation

Hyperacusis questionnaires are available but their sensitivity to treatment responses limit their usefulness as an assessment tool.[263, 264] Some clinicians recommend the measurement of loudness discomfort levels (LDLs) to confirm the diagnosis and quantify the problem whereas others suggest that the test is unreliable, risks alienating the patient and making the problem worse and has limited value with regard to planning. Certainly, if LDL testing is proposed in a patient with hyperacusis, they should be thoroughly counselled beforehand and offered an opportunity to decline the investigation. Stapedial reflex testing should be avoided in patients with hyperacusis because the procedure involves a loud test tone that many hyperacusis patients find unpleasant or painful.

Treatment

The usual response to an increased perception of loudness is for the patient to use a variety of types of ear protection in the form of ear plugs or ear defenders. This will often have the opposite to the desired effect by further increasing central auditory gain and exacerbating the patient's distress: there is evidence that sound deprivation worsens sound tolerance whereas enhancement of the acoustic background improves tolerance.[265] Although TRT was introduced primarily for the treatment of tinnitus, with minor modifications, TRT has been advocated for hyperacusis, with several studies demonstrating improvements in loudness tolerance.[266, 267] Psychological treatments have been used in the management of hyperacusis and there is evidence to suggest that CBT is efficacious.[268] Although there are anecdotal reports that other psychological modalities such as mindfulness meditation and ACT are being used in the treatment of hyperacusis, there is as yet no supportive literature.

MISOPHONIA

Definitions

As discussed under 'Definitions and classification' above, the term misophonia was created in 2001 to define a group of patients who dislike particular sounds irrespective of the level of the sound.[250, 251] The neologism literally means strong dislike or hatred of sound. Within the

classification system, phonophobia was retained as a subsection of misophonia when fear is the dominant evoked emotion.

In the late 1990s North American audiologist Marsha Johnson[269] recognized a group of patients who demonstrated negative emotions to a range of specific sounds generated by other humans, often repetitive sounds and often produced by oral or pharyngeal action. Causative sounds included those of lip smacking, throat clearing, chewing or breathing. Typical emotions included anger, disgust or anxiety and patients often demonstrated avoidance behaviour. This was termed selective sound sensitivity syndrome. Other terms including soft sound sensitivity syndrome or 4S have also been used.

The word misophonia has not been universally accepted by otologists and audiologists but patient support groups and mental health professionals have adopted it much more readily and it has gradually become synonymous with selective sound sensitivity syndrome. There have been multiple reports of patients with misophonia associated with psychiatric conditions including obsessive–compulsive disorder,[270–272] eating disorders[272, 273] and Tourette syndrome,[274] which has led some clinicians to suggest that misophonia should be reclassified as a specific psychiatric condition.[272] The authors who developed the new word, misophonia, have opposed this proposed reclassification, stating that mental health issues are rare in their series of patients with misophonia. They go on to suggest that the other authors must be reporting patients with psychiatric conditions who have coincidental comorbid misophonia.[275] It seems likely that further debate in this field will ensue.

Epidemiology

Demographic details of misophonia are slowly emerging. Case reports and small series of patients have been reported from Europe,[272, 273, 276] North America,[277] South America[271] and Australia.[274] To date there is no gender difference but, because the number of subjects is small, this observation may be premature. The onset of the problem is generally peripubertal with the largest study (n = 157) demonstrating a mean age of onset of 12 years.[278] There is a dearth of information regarding the prevalence and incidence. Jastreboff and Jastreboff used figures regarding the prevalence of tinnitus and the comorbidity of tinnitus and misophonia to extrapolate a population prevalence figure of 3.2%.[275] However, a study performed in a group of psychology undergraduate students has suggested that the prevalence might be much higher: 23.4% of participants reported that they were sometimes sensitive to specific sounds and 19.9% felt that this has had an impact on their lives.[279]

Clinical features

Sounds that trigger misophonia are generally sounds produced by other humans and in many cases the sound is produced by a specific person, often another family member.[270–272] The most common causative sounds are orally generated including eating, breathing, whistling, gum chewing and lip smacking. Other repetitive sounds, such as fingernail clipping or clicking the top of a pen, may trigger the symptom.[272] Environmental sounds such as wind, rain or waves do not generally trigger misophonia. Sounds produced by the person with misophonia generally do not elicit a misophonia response even if the sound is very similar to their normal triggers. Anger, disgust or irritation are the most frequently described emotions,[278] followed by anxiety or panic. Most people with misophonia will display avoidance behaviour, trying to stay away from the trigger sound or sounds. A few will confront the person producing the sound but actual aggression seems uncommon.[274, 277] A few patients are reported to have developed tics as a response to their trigger sound and a few have developed coping strategies such as mimicking the causative sound.

Investigation

There is a general lack of data regarding the audiological status of patients with misophonia. One study investigated 20 patients with misophonia and 14 controls, using a form of evoked-response audiometry.[280] The results of this study suggested that patients with misophonia could have an underlying central auditory processing problem. A recent study compared six patients with misophonia and five controls when exposed to a range of sounds which included sounds such as birdsong, that are generally regarded as pleasant, and other sounds, such as fingernails on a blackboard, that are usually perceived as unpleasant.[270] Skin conductance measurements were obtained: both groups found similar stimuli to be unpleasant but the reaction demonstrated by the people with misophonia was greater than the reaction in the control group.

Various questionnaire tools for assessing misophonia have or are being developed. These include the Amsterdam Misophonia Scale,[272] the Misophonia Questionnaire,[279] the Misophonia Assessment Questionnaire,[281] the Misophonia Coping Response Survey[281] and the Misophonia Trigger Survey.[281] These tools have yet to enter widespread usage.

Pathophysiology

Various suggestions regarding the pathophysiology of misophonia have been made. These include abnormal activation of the limbic and autonomic nervous systems,[282] psychological conditioning to repetitive events,[272] a generalized hyper-reactivity condition, a defect in serotonin and dopamine utilization in the limbic system and basal ganglia, or a variant of synaesthesia.[270, 283] There is no robust scientific evidence behind any of these hypotheses and the mechanism must still be regarded as unclear. Moller has pointed out that, as the problem is linked to specific sounds, it is likely that the anatomical location of the problem is downstream from initial sound processing areas and may be situated in the inferior part of the temporal lobe where the nature of sounds or 'what' information is processed.[284]

Treatment

The management of misophonia is still a matter of conjecture.[285] Multidisciplinary team management has been suggested[286, 287] and, as both otological and mental health assessment may be required, this approach seems logical. Structural brain pathology has not been reported with misophonia so there is a low requirement to undertake brain imaging. Anecdotally, reassurance and education directed to both the patient and family may be helpful. The presence of an associated specific psychological problem may dictate a specific mental health pathway. CBT has been reported as effective in a single case.[269] Sound therapy can be used to desensitize patients: Jastreboff and Jastreboff suggest a treatment strategy based on TRT using a combination of counselling and sound therapy.[275] Allowing the affected person to wear headphones when in the presence of their misophonia trigger has also been suggested.[286] There is no pharmacological treatment yet identified, though drugs may have a role in the management of associated conditions such as anxiety.

BEST CLINICAL PRACTICE

- ✓ All patients with tinnitus should undergo a basic audiological assessment. Further investigation should be undertaken in the following groups: those with pulsatile tinnitus; unilateral tinnitus; tinnitus in association with asymmetric hearing loss; tinnitus in association with significant vertigo; tinnitus in association with neurological symptoms and/or signs.
- ✓ Comorbidities are common, particularly anxiety, depression and disorders of sound tolerance (hyperacusis). Insomnia is also common in tinnitus patients. These factors should be considered during the history-taking process.
- ✓ Although there is currently no drug treatment for subjective idiopathic tinnitus, drugs may have a role in the management of comorbid conditions such as anxiety and depression.
- ✓ Patients are often given negative counselling, being told that nothing can be done for tinnitus. While a cure for tinnitus remains elusive, there are many helpful management strategies, particularly sound based therapies, counselling and psychological therapies. Surveys have shown that many patients with tinnitus are investigated in secondary care but are never offered any therapeutic intervention. Negativity should be avoided, and patients should be referred onward to audiology, hearing therapy or mental health services as appropriate.
- ✓ When tinnitus is associated with hearing loss it is usually helpful to try and correct this loss, surgically if appropriate, or via the use of hearing aids.

FUTURE RESEARCH

Despite major advances in our understanding of tinnitus, many major questions remain unanswered. In particular, we do not fully understand the fundamental mechanisms behind the development of tinnitus in many groups of patients. There is no reliable method to consistently measure tinnitus, and a universally effective drug treatment does not currently exist. However, as we gain more understanding about this intriguing condition, basic research has introduced many different routes to allow the investigation of the pathophysiology, diagnosis and treatment of many of the different presentations of this condition. Furthermore, tinnitus and its allied conditions have become a focus of attention within many different disciplines outside the traditional domains of ENT and audiology. A number of major research organizations are currently investing significant amounts of money to research this condition. The goal for many is to identify a 'cure', but during this journey tinnitus research has benefited our understanding of how the auditory system and the brain perceive and process sound in ways that we might never have considered.

KEY POINTS

- Tinnitus is common: prevalence in the UK population is estimated at approximately 1 in 10. For about 1 in 200, tinnitus has a severe effect on the activities of daily living.
- Epidemiological studies suggest that most people with tinnitus go through a process of habituation and the impact of the symptom gradually lessens with time.
- Tinnitus is more common in people with a hearing loss but the degree of hearing impairment correlates poorly with tinnitus severity. About 1 in 10 people presenting with tinnitus have a normal audiogram. Tinnitus can exist after division of the auditory nerve.
- Modern models suggest that tinnitus is due to increased awareness of spontaneous electrical activity in the auditory system. Although changes in the auditory periphery can trigger tinnitus, the processes that cause the symptom to perpetuate and become distressing occur in the central auditory pathways and in associated brain regions, particularly the limbic system.
- Tinnitus is rarely a harbinger of serious pathology, but careful clinical assessment is recommended.
- A blocked sensation in the ears is common among tinnitus patients though generally there is no evidence of Eustachian tube dysfunction.
- Interventions that improve hearing are often helpful and various audiological and psychological management strategies for tinnitus have been developed.
- Disorders of sound tolerance are common but terminology is confused, pathophysiology is unclear and many questions remain regarding management.

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CHAPTER 62

EVALUATION OF BALANCE

Adolfo M. Bronstein

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: vestibular, eye movements, balance, clinical tests, dizziness and vertigo.

SYMPTOMS IN BALANCE DISORDERS

Patients with disorders of balance are common, not only in otolaryngology clinics but also in neurology, general practice, internal medicine and geriatrics. It can be estimated that dizziness, vertigo and unsteadiness accounts for one-fifth of referrals to ENT and neurology clinics. This is not surprising since approximately one-quarter of people experience dizziness at some time in their life and in 80% of cases this is severe enough to see a doctor.[1] The rise in ageing population worldwide is likely to increase these percentages since dizziness occurs in almost 50% of people over the age of 75 years.[2]

There have been many developments in the field of balance and vestibular testing but, as in other branches of medicine, nothing replaces a good clinical history. The techniques used and ranges of normality adopted by different vestibular laboratories can be very disparate and so 'positive', 'objective' vestibular findings must be taken strictly within the appropriate clinical context. Reciprocally, some clinical histories are so typical that the absence of corroborative findings on a single visit to the clinic should not make the clinician rule out a diagnosis: for example, a patient with brief vertigo on turning over in bed, so typical of benign paroxysmal positional vertigo (BPPV), but negative positional testing on his first visit.

The symptoms that patients with balance or vestibular disorders may report are vertigo, dizziness, nausea, motion intolerance, unsteadiness and oscillopsia. Associated anxiety and depression are also extremely common. It is of vital importance, in all balance symptoms, to identify triggers provoking the symptoms, such as position, movements or visual or acoustic triggers. It is equally important to determine if the symptom is acute, episodic or chronic, and whether it occurs alone or in association with other symptoms (e.g. audiological, visual or neurological).

Vertigo and dizziness

Vertigo, when defined as an illusion of either oneself or the environment rotating, is a reliable symptom. It indicates involvement of the angular motion sensing system, i.e. the semicircular canals and their central projections. However, such involvement can occur from the labyrinth up to the vestibular cortex so that the site of the lesion will have to be presumed by additional symptoms (**Table 62.1**). Of particular value are hearing loss or tinnitus, usually indicating labyrinthine or VIII nerve involvement, and brainstem symptoms such as frank diplopia, facial numbness/weakness and dysarthria. Acute vertigo is terrifying and disabling and its duration can be a good guide to diagnosis. In BPPV it is usually less than a minute; in migraine-associated vertigo (= vestibular migraine) it can be from minutes to many hours; in Ménière's disease a few hours; and in acute vestibular neuritis and consolidated brainstem stroke a few days.

Illusions that one is moving linearly, such as falling vertically downwards or linear vertigo, can arise from disorders of the otolith system but it is extremely difficult to confirm selective otolith lesions and thus the clinical value of linear vertigo as a symptom is less well established.[3, 4] There is no evidence to classify postural symptoms, such

TABLE 62.1 Additional symptoms helpful in the topographical diagnosis of balance disorders

Site of lesion	Symptom	Comment
Peripheral (labyrinth or VIII nerve)	Tinnitus	
	Hearing loss	
Special cases		
Labyrinthine	Ear fullness	Ménière's disease
CP angle	V, VI, VII cranial nerves	Extracanalicular growth
VII + VIII neuritis	Ext auditory canal vesicles + VII	Ramsay Hunt syndrome
Brainstem	Diplopia (III, IV, VI or skew deviation)	
	Facial numbness (V)	
	Difficulty swallowing, choking (IX, X)	
	Slurred speech (XII, cerebellum)	
	Uni-bilateral numbness, weakness, ataxia (long tracts, cerebellum)	
	Unilateral deafness (+ ataxia)	AICA infarct
Cerebral hemisphere	Unilateral weakness, numbness	
	Hemianopia (parieto-occipital lobe)	MCA/PCA
	Blindness (both occipital lobes)	Both PCAs
	Loss of consciousness	
	Syncope, cardiac arhythmia	Common
	Epilepsy	Rare (in vertigo)

AICA, anterior inferior cerebellar artery; MCA, middle cerebral artery; PCA, posterior cerebral artery.

as lateropulsion or retropulsion, as specifically otolith-related. Despite traditional emphasis on defining symptoms precisely, patients may find it difficult to describe clearly and experienced clinicians know that dedicated efforts to distinguish vertigo from dizziness in individual patients does not always pay off. Dizziness and giddiness are common terms employed by vestibular patients to describe their problems. There is no good definition for these terms. One should encourage the patient to describe what they mean by dizziness and/or to compare it to situations that they may have experienced. Body language is also important as many patients wave a hand round and round when describing their dizziness, implying actual rotational vertigo. When the dizziness is non-rotational, it is less certain that the problem lies in the vestibular system. Descriptions such as rocking or swimming sensations, light-headedness, walking on cotton wool, feeling detached, can also be vestibular. However, one often needs independent evidence to reach this conclusion. Such evidence may be difficult to find on vestibular testing, such as a significant caloric canal paresis, or a preceding history of rotational vertigo. There are numerous non-primarily vestibular causes of dizziness and light-headedness, including anaemias, drug toxicity and psychological dizziness to name just a few (Table 62.2).

TABLE 62.2 Some non-vestibular causes of dizziness

Type	Possible causes
Endocrine	Hypoglycaemia Adrenal failure Pheochromocytoma
Cardiovascular	Vasovagal syncope Orthostatic hypotension Embolic disease Cardiac dysrhythmias
Haematological	Hyperviscosity syndromes Anaemias
Psychological	Anxiety Phobias Panic attacks

Some patients indicate clearly that they have no 'head' sensations. They are unsteady, off balance or clumsy on their feet, 'not dizzy in the head'. They feel fine if seated or lying down. In such cases it is useful to ask if relatives or friends have made any comments about the patient's balance. If there is an objective, visible balance problem, this is more likely to be a neurological gait disorder, with patients just perceiving their own objective dysequilibrium. If these patients trip over or are pushed over in a crowd, they can stumble or fall. The lesion may lie anywhere in the somatosensory motor chain (peripheral nerves, spinal cord, cerebellum or cerebrum) and the clinician should enquire about symptoms represented at these various levels in the neuraxis, such as weakness, numbness, incoordination, tremor, sphincters, memory and other cortical functions. Enquiries as to the presence of falls as a result of poor postural balance should be actively made, particularly in the elderly patient. If present, prevention of further falls becomes an urgent matter. Fall-related complications in the elderly are a major killer and public health problem.[2]

Motion intolerance

Anyone who has ever been motion sick will understand that patients with vestibular disorders dislike movement. In the acute phase of Ménière's disease or vestibular neuritis the picture is dramatic. The patient is bedridden and terrified of even going to the toilet; any movement brings more vertigo, nausea and vomiting. Symptoms gradually settle over time. A patient with vestibular neuritis may have strong rotational vertigo and nausea for 3 days, followed by dizziness for 3 weeks and by light-headedness for 3 months. In these latter stages, however, patients tend to avoid head movements or looking at moving visual scenes. Unfortunately, in some patients, light-headedness, dizziness and motion intolerance can last for many months or years, for reasons that are not completely understood.

A complex interrelation between lack of effective vestibular compensation, idiosyncratic perceptual style, migraine and anxiety may be at play.[5]

Oscillopsia

The intolerance to visual motion mentioned in the previous paragraph is sometimes called visual vertigo, visually induced dizziness, space and motion discomfort, visuovestibular mismatch or simply 'the supermarket syndrome'.[6] This should not be confused with oscillopsia, which is the movement or oscillation of the visual surroundings.[7] Oscillopsia is described by patients as jumpy, jerky, bobbing, wobbly or sometimes just blurred vision. In the balance disorder patients, always consider the possibility that a patient's complaint of blurred vision or difficulty in focusing might be oscillopsia.

The critical question to ask a patient with oscillopsia is 'when': when does it happen?[7, 8] Is the oscillopsia present during movement, or only triggered or present in certain head positions, or unrelated to movements (Table 62.3)? Oscillopsia during head movements (e.g. while walking, driving, shaking the head) is due to a defective vestibulo-ocular reflex (VOR), typically bilateral vestibular lesions as encountered after meningitis, gentamicin ototoxicity or idiopathic. Oscillopsia present in certain head positions (e.g. lying but not seated or vice versa) is likely to reflect a positional nystagmus, usually of a central CNS origin. Oscillopsia unrelated to head movement can be continuous, in which case the patient is likely to have an acquired CNS nystagmus (e.g. acquired pendular nystagmus, downbeat nystagmus (DBN), torsional nystagmus) or just be paroxysmal, i.e. in attacks. Paroxysmal oscillopsia can be spontaneous, as in paroxysmal nystagmus and ocular oscillations of central origin, vestibular paroxysmia or, more commonly, voluntary nystagmus. Some patients with idiopathic bilateral loss of vestibular function present with paroxysmal oscillopsia.[9] Triggered paroxysmal oscillopsia is rare; the most common being the Tullio phenomenon,[10, 11] as in the superior canal dehiscence syndrome,[12] where patients report jumpy vision and lateropulsion in response to loud sounds or Valsalva manoeuvres.

TABLE 62.3 Causes of oscillopsia

When?	Syndrome	Examples
During head movements	Absent VOR	Ototoxicity, idiopathic, post-meningitic
Triggered by head movements	Positional nystagmus	Positional DBN
Unrelated to head movements		
Continuous	CNS nystagmus	DBN, pendular nystagmus
Paroxysmal	Paroxysmal eye oscillation	Voluntary nystagmus Progressive vestibular failure, vestibular paroxysmia

DBN, downbeat nystagmus.
Modified from Bronstein.[7]

Vertigo presentations

The first thing to ascertain is whether the patient's problem is a single vertigo episode (acute vertigo), recurrent (or episodic) vertigo or chronic dizziness. Once this is established the key to diagnosis lies in identifying triggering factors and associated symptoms. Tables 62.4, 62.5 and 62.6 summarize this topic.

SINGLE ACUTE EPISODE OF VERTIGO

An acute single spontaneous episode of rotational or 'true' vertigo can be encountered in acute vestibular neuritis (or neuronitis), which has no hearing symptoms, a vascular or inflammatory disorder of the labyrinth (labyrinthitis), usually with hearing loss, and a brainstem stroke, usually with other CNS symptoms. In all

TABLE 62.4 Vertigo presentations: single vertigo episode

Hearing	Possible cause
Hearing spared	Vestibular neuritis (or neuronitis or viral labyrinthitis or neurolabyrinthitis)
	Head injury
Hearing involved	Head injury
	Labyrinthine fistula
	Viral infection (mumps, Ramsay Hunt)
	Vascular disorder (labyrinthine stroke)

Modified from Bronstein and Lempert.[8]

TABLE 62.5 Vertigo presentations: episodic or recurrent vertigo: accompanying features

Accompanying feature	Possible cause
Positional	BPPV (on lying or turning in bed) Orthostatic hypotension (on standing)
Paroxysmal	Vestibular paroxysms
Migraine	Vestibular and basilar migraine
Hearing disorder	Ménière's syndrome or hydrops
Ataxia	Episodic ataxias
Brainstem symptoms	Transient ischaemic attacks (TIA)
Autonomic-anxiety-avoidance	Panic attacks
Faintness	Heart disease, vasovagal syncope
No accompanying features	Benign recurrent vertigo (BRV)*

* Benign recurrent vertigo,[13] recurrent peripheral vestibular disorder or vestibular Ménière's disease are names given to describe patients with recurrent peripheral vertigo which does not fall into any other category such as Ménière's disease or migraine.
Modified from Bronstein and Lempert.[8]

TABLE 62.6 Vertigo presentations: symptom triggers in patients with episodic vertigo

Trigger	Possible cause
Lying down, turning over in bed	BPPV
Standing up	Orthostatic hypotension
Neck movements	Any vestibular disorder
Pressure changes	Fistulas
Loud sounds	Tullio phenomenon
Alcohol, exercise	Episodic ataxias

Modified from Bronstein and Lempert.[8]

these conditions the vertigo is usually severe and prolonged, inevitably leading to autonomic symptoms, such as nausea, vomiting, pallor, sweating and malaise. It must be borne in mind that any vertigo is more tolerable when the head is kept still. Only provocation, not exacerbation, of vertigo by movements or positions of the head should be labelled as positional vertigo. The clinician should actively ask for additional hearing or CNS symptoms, such as slurred speech, facial or limb numbness or weakness, diplopia and swallowing problems. Intense vertigo can be so overwhelming that some patients may not volunteer other symptoms (Table 62.4). In recent years the distinction between peripheral and central acute vertigo has become a hot topic because of new available therapies for stroke, mainly thrombolysis. Given that the window of treatment opportunity is only a few hours, various 'red flags' have been described (see Box 62.1).

The presence of recent or concurrent general illnesses should be sought. In vestibular neuritis, patients can report a recent upper respiratory tract infection. Mumps can affect both the cochlear and vestibular labyrinth. Patients with herpes zoster oticus or Ramsay Hunt syndrome can have a peripheral facial palsy and show herpetic vesicles in the outer ear canal. The presence of risk factors such as smoking, hypertension, obesity or diabetes can suggest a vascular aetiology.

RECURRENT OR EPISODIC VERTIGO

The presence of triggers becomes critically important for diagnosis in the patient with recurrent vertigo or dizziness. Certain triggering by head movements, such as looking up, lying down or turning over in bed, are highly suggestive of BPPV. Incorrectly, clinicians often jump to the conclusion that dizziness related to neck movements (inevitably associated with head movements!) indicates cervical or vertebrobasilar vertigo before excluding a much more likely vestibular disorder.[15] Triggering by loud sounds or Valsalva manoeuvres suggests the Tullio phenomenon, often due to superior canal dehiscence or labyrinthine fistula. In some patients with migraine-associated vertigo, food or sleep deprivation or certain foods (chocolate, cheese, red wine) may be triggers. Orthostatic hypotension induces light-headedness, dizziness and even true rotational vertigo,[16] on standing up suddenly or after being standing up for a long time, particularly in the heat or motionless. Exercise, alcohol or stress can trigger an attack in patients with episodic ataxias or channelopathies, which usually includes vertigo (see Tables 62.5 and 62.6).[17]

BOX 62.1 'Red flags' for acute brain imaging in acute vertigo

Modified from Seemungal and Bronstein[14]

- Acute unilateral deafness
- Acute (occipital) headache
- Any central symptoms or signs
- A negative (normal) head-impulse test

Associated symptoms, such as aural fullness, tinnitus and hearing loss, may suggest Ménière's syndrome. Associated brainstem symptoms can indicate vertebrobasilar transient ischaemic attacks (TIA) whereas palpitations, breathlessness or loss of consciousness would suggest a cardiac arrhythmia. Patients with panic attacks can also report dizziness, palpitations, fear of dying and breathlessness but the social triggers and the ensuing avoidance behaviour are highly suggestive of this diagnosis – the three 'As', autonomic, anxiety and avoidance. Patients with presyncopal dizziness can report sensations of feeling hot or cold, clammy and sweaty, greying out of vision and bilateral tinnitus. The presence of frank ataxia may indicate paroxysmal ataxia (e.g. episodic ataxia type 1 or 2, spinocerebellar degeneration type 6 or other channelopathies). The presence of migrainous symptoms, such as visual aura, throbbing headaches, nausea, photophonophobia, must be enquired;[18] migrainous vertigo can precede, overlap, follow or occur independently of a migraine headache.

CHRONIC DIZZINESS

The majority of patients with a single acute vertigo attack recover fully and the majority of patients with recurrent vertigo are free of symptoms between attacks, but not all. Since vertigo and dizziness are so prevalent in the community, this small proportion of patients with long-term dizziness makes up enough absolute numbers to fill up specialized clinics.

There is no simple explanation as to why some patients do not fully recover from a single attack or episodic vertigo. The actual vestibular loss is unlikely to be the reason since patients with vestibular schwannomas rarely suffer from any troublesome dizziness. Hence, a slow rate of progression as opposed to an acute onset may play a part. Failure of the compensatory mechanisms is also often invoked and this may be due to a variety of factors. This evidence cannot be fully reviewed here but aggravating or limiting factors include:

- fluctuating vestibular lesion, as in hydrops, which poses a challenge to the central compensatory processes
- an idiosynchratic trend in some subjects to rely excessively on visual cues, or 'visual dependence', which perpetuates intolerance to visual motion (visual vertigo or supermarket syndrome)

BOX 62.2 Factors interfering with vestibular compensation

Fluctuating vestibular disorder
Additional disorder:
- CNS
- Peripheral nerve
- Cervical spine
- Visual

Lack of mobility
Drugs
Visual dependence ('visual vertigo')
Psychosocial

CNS, central nervous system.

- psychological factors, including pre-existing or reactive anxiety, depression or phobias
- excessive bedrest and lack of physical activity, sometimes prescribed by doctors unaware of the importance of motion exposure as a promoter of vestibular compensation
- excessive use of psychotropic and antivertiginous medication
- concomitant visual or neurological disorders (**Box 62.2**).

In the elderly, there are usually many of these factors operating simultaneously.

Finally, the otologist should bear in mind the possibility that the sense of unsteadiness reported by the patient may be due to a general medical disorder or to neurological or psychogenic gait disorders (**Box 62.3**). The latter, particularly in the form of an overcautious gait, can be triggered in the elderly by a fall or an episode of vertigo, so full investigation is warranted. Pain during locomotion (e.g. hip arthritis) will also aggravate any gait disorder.

BOX 62.3 Chronic dizziness – mental checklist

Is it oscillopsia rather than dizziness?...See Table 62.3
Is it a gait disorder?.....See Tables 62.10 and 62.11
Is it a general medical disorder?.....See Table 62.2

EXAMINATION OF THE PATIENT WITH A BALANCE DISORDER

One of the disappointing aspects of balance disorders is that both the ENT and neurological examination are often entirely negative, except perhaps in the acute phase. This should not bias clinicians into thinking that it is not worth thoroughly examining the patient; much money, time and suffering can be spared by carrying out a Hallpike manoeuvre instead of organizing a head scan in a patient with BPPV!

A standard neuro-otological assessment should include auroscopy, eye movement, positional manoeuvres and posture and gait examination. Auroscopy is covered in Chapter 73, Clinical examination of the ears and hearing.

Eye movements

CLINICAL EXAMINATION OF EYE MOVEMENTS

The vestibular system provides a powerful input to the oculomotor system so eye movements must be examined in detail. In a patient suspected to have a peripheral vestibular disorder (labyrinth and VIII nerve) one can consider that the examination has two broad aims.

1. One is to search for direct ocular signs indicative of a peripheral vestibular disorder, typically nystagmus, BPPV or a positive head thrust test (see under 'Head-impulse test' below).
2. The other is to exclude CNS lesions by making sure that non-vestibularly mediated eye movements are normal.

The oculomotor examination should include:

- search for spontaneous and gaze-evoked nystagmus
- convergence
- smooth pursuit
- saccades
- vestibulo-ocular reflexes
- positional manoeuvres.

General updated reviews of eye movement assessment are available.[19, 20]

If the patient reports diplopia, or if at any point during the examination the two eyes appear disconjugate, a formal examination of the individual cranial nerves III, IV and VI is mandatory. This usually requires a separate eye cover test in the six cardinal positions of gaze to identify the weak individual muscle or group of muscles (right – horizontal, up and down; left – horizontal, up and down). Before embarking on a complex examination with which the ENT surgeon may not feel completely at ease, it is useful to confirm with the patient whether he was aware of the presence of an old squint, weak/lazy eye or congenital nystagmus. If there is an infantile squint, the ocular examination is more difficult to interpret.

SPONTANEOUS NYSTAGMUS

The search for spontaneous nystagmus begins in the primary, straight-ahead position of the eyes. In the presence of nystagmus, ascertain the waveform – essentially sawtooth or jerk nystagmus (in which case you should identify the direction of beat) or pendular nystagmus, which has no fast-phase or beating direction (**Figure 62.1**). Since spontaneous nystagmus often enhances by convergence, it is convenient to examine convergence at the same time, by slowly moving an object in and out along the visual axis. Absence of convergence occurs in midbrain lesions but one must remember that reduced/absent convergence is extremely common in normal people above the age of 60 years of age.

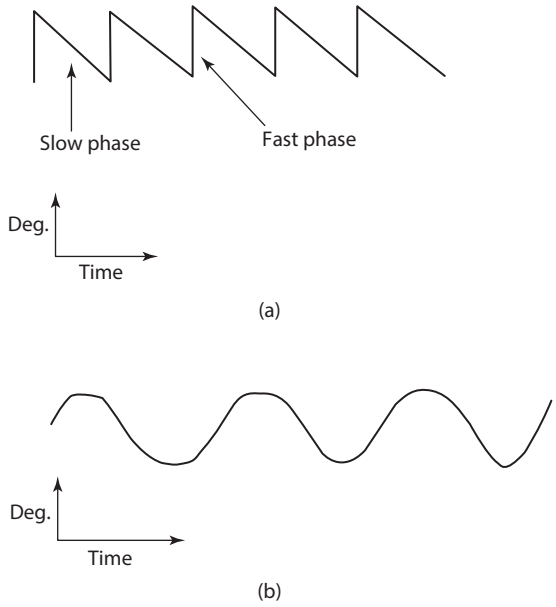


Figure 62.1 (a) Nystagmus waveforms, jerk or saw-tooth; and **(b)** pendular nystagmus. The former can be peripheral or central but the latter is only of central origin but usually non-acute.

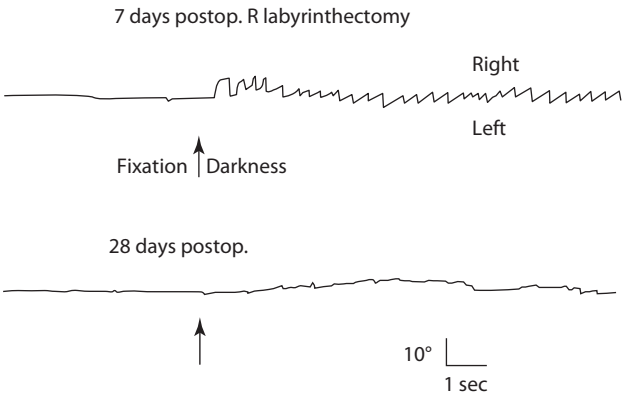


Figure 62.2 Acute and compensated peripheral vestibular nystagmus. Note that at 1 week after labyrinthectomy the nystagmus in the light was negligible but increased notably in the dark. At 1 month follow-up vestibular compensation had effectively reduced the nystagmus in the dark. Also note the rectilinear slow phase velocity of the nystagmus, in agreement with its peripheral origin.

While in primary gaze, one should undertake a cover test, particularly in patients with difficult-to-interpret eye signs. The cover test is usually part of the examination to assess diplopia and ocular alignment, but what we suggest here is a simplified version of the test, looking for the presence of latent nystagmus. Latent nystagmus is a common congenital oculomotor disorder.[3, 4] Typically, these patients have no nystagmus during binocular viewing but, on covering one eye, the uncovered eye beats horizontally away from the covered eye (both eyes beat but one can only see the uncovered one). It can be observed on covering one or the two (one at a time) eyes. The value of discovering latent nystagmus, which is essentially asymptomatic, lies in the fact that this condition is often associated with congenital squints, nystagmus, square wave jerks, abnormal pursuit or optokinetic nystagmus. Thus, finding latent nystagmus in a patient with an abnormal, 'central-looking' oculomotor examination strongly suggests that the findings are congenital rather than relevant to a recent complain of vertigo or loss of balance.

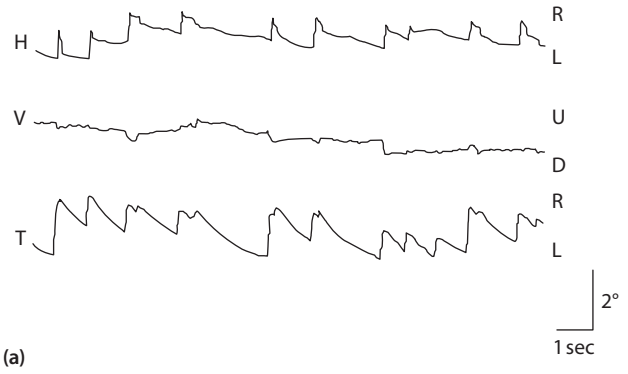
When examining nystagmus as well as other eye movements, patients have to be clearly instructed to look at a predetermined object and the eyes should be well illuminated. The presence of spontaneous nystagmus in primary gaze immediately raises the question of whether it is caused by a central or peripheral lesion. If the patient is in the middle of an acute vertigo attack, with severe unsteadiness and nausea, it can be peripheral or central, but if the patient comes as a routine ambulatory patient and does not look acutely ill, the nystagmus is more likely to be of central origin. In practice, a nystagmus of peripheral vestibular origin, observable by the naked eye in primary gaze, can only come from an acute, massive vestibular imbalance, as in vestibular neuritis, Ménière's attack, recent labyrinthine surgery or trauma (Figure 62.2). The nystagmus is essentially horizontal, with a minor torsional (rotatory) component. The fast phase beats contralesionally but can beat ipsilesionally in the acute irritative phase of a Ménière's attack.

Can a nystagmus like this result from a central lesion? Yes, in particular lesions in the VIII nerve root entry zone, vestibular nuclei or cerebellum but, almost invariably, there are additional brainstem symptoms and signs. Any other nystagmus is almost certainly of central origin. These differ from a peripheral vestibular nystagmus in waveform (e.g. pendular, a quasi-sinusoidal oscillation of the eye without distinction between slow and fast phases – Figure 62.1),[21] or beat plane (e.g. vertical up or downbeat or torsional nystagmus – Figure 62.3).[22] A large, horizontal nystagmus in a patient with no significant vestibular or neurological symptoms should always raise the possibility of congenital nystagmus.[23]

GAZE-EVOKED NYSTAGMUS

Soon after the acute stage of a peripheral vestibular lesion, the nystagmus is not visible in primary gaze but only on deviation of gaze to the opposite side of the lesion, i.e. in the direction of the fast phase. A useful classification for the severity of the nystagmus, based on this observation, has stood the test of time. First-degree nystagmus is a nystagmus only visible on gaze deviation in the direction of the fast phase, second-degree when present in primary gaze, and third-degree when it is also visible when the eyes are deviated in the opposite direction to that of the fast phase. A second- or third-degree nystagmus will enhance on gaze deviation in the direction of the fast phase (Alexander's law; Figure 62.4). However, the severity scale and Alexander's law apply mostly to peripheral vestibular nystagmus. For instance, DBN in primary gaze, which is always of central origin, often does not enhance on looking down but on looking sideways.

Nystagmus on gaze deviation can also indicate a central lesion. This is what is frequently called 'gaze paretic'



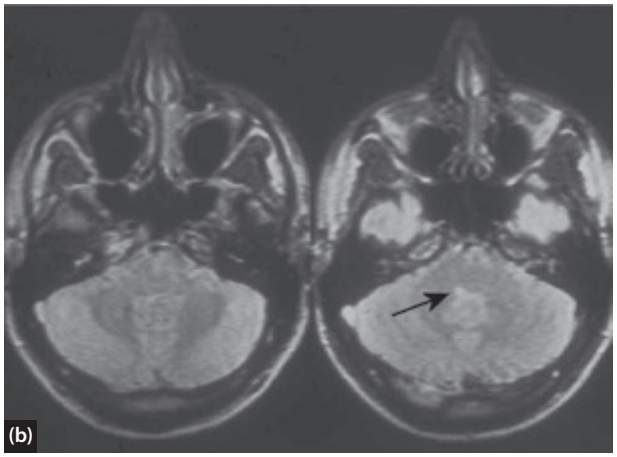


Figure 62.3 (a) Three-dimensional scleral search coiled oculography in a patient with a small demyelinating left-sided brainstem lesion, as shown on MRI **(b)** (arrow). The presence of a clinically observable torsional component in the spontaneous right beating nystagmus indicated that the lesion was central rather than peripheral. H, V and T are horizontal, vertical and torsional eye recordings. Left side of the brain is on the left side of the scan.

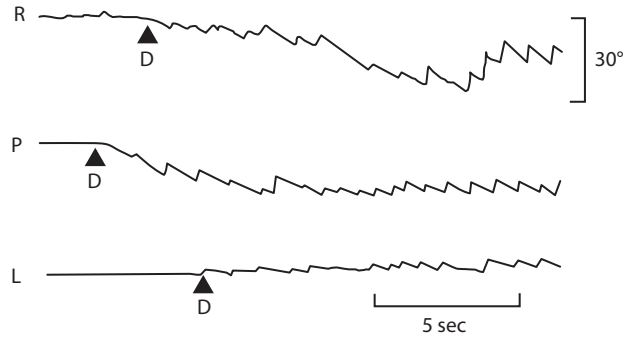


Figure 62.4 The effect of fixation and gaze deviation (L, left; P, primary; and R, right positions) on peripheral vestibular nystagmus. Horizontal EOG recordings begin in the light and continue in the dark (D). Note the increase of the nystagmus with gaze deviation in the direction of the fast phase (Alexander's law). Reproduced by kind permission of P. Rudge.

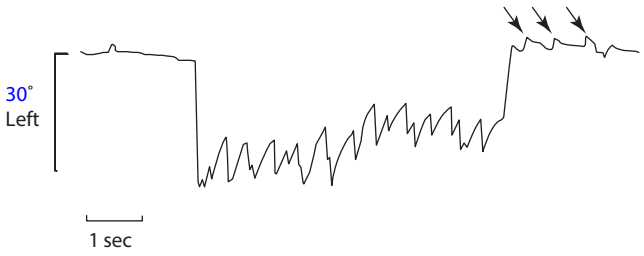


Figure 62.5 Left-beating gaze paretic and rebound nystagmus (arrows) in a cerebellar lesion. Note the exponentially decreasing slow phase velocity (slope) of the nystagmus. Reproduced by kind permission of P. Rudge.

nystagmus, not to be confused with the broader term 'gaze-evoked' nystagmus. A subacute peripheral vestibular lesion can have a gaze-evoked nystagmus, i.e. a second-degree nystagmus as discussed above. Instead, the term gaze paretic implies that the patient has difficulty in holding gaze in an eccentric position in the orbit. The eyes drift in centripetally with a slow phase which progressively decreases in velocity, until a new saccade refixates the eccentric target (Figure 62.5). This nystagmus, usually of larger amplitude than vestibular nystagmus, is due to damage to the gaze-holding mechanisms mediated by ipsilateral brainstem and cerebellar structures. An example of vestibular and gaze paretic nystagmus present in the same patient is Brun's nystagmus due to a large extracanalicular vestibular schwannoma. The vestibular nystagmus beats, as expected in any destructive vestibular lesion, in the opposite direction of the tumour. The coarser nystagmus, evoked by looking in the same direction of the tumour, is gaze paretic, due to cerebellar–brainstem compression (Figure 62.6). Gaze paretic nystagmus can be present in all directions of gaze in the same patient, typically in symmetrical processes such as cerebellar degenerations.

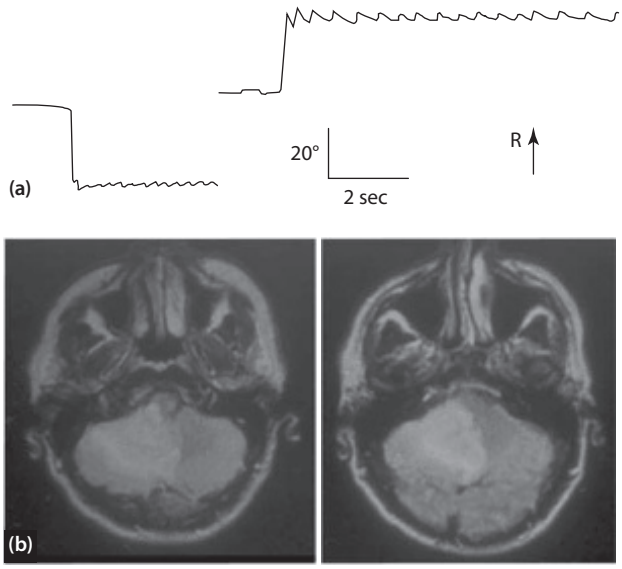


Figure 62.6 Brun's nystagmus due to a right-sided pontine glioma; **(a)** vestibular nystagmus on left gaze; **(b)** a larger gaze paretic nystagmus. Typically, large vestibular schwannomas compressing the brainstem produce this nystagmus combination.

SMOOTH PURSUIT EYE MOVEMENTS

When tracking an object with our eyes, we use a combination of fast (saccades) and slow-phase eye movements. Strictly speaking, only the latter should be considered smooth pursuit. When the target moves slowly (<10–15 degrees per second) the eye is capable of following it almost exclusively with smooth pursuit movements. The pursuit system is velocity limited so that, when targets move at velocities of 40–50 degrees per second or faster, the proportion of tracking carried out by saccades increases progressively. Clinically speaking, pursuit looks abnormal, or 'broken up', when the observer detects too much saccadic tracking; this gives a cogwheel, jerky appearance to the pursuit movements (**Figure 62.7**). The message for the clinician is: move the target slowly, otherwise everybody shows 'broken pursuit'.

Investigation of pursuit eye movements is a vital component of the neuro-otological examination. There may be occasional exceptions but, in principle, the presence of normal pursuit rules out a central vestibular disorder and, vice versa, a patient with balance symptoms and unequivocally broken pursuit movements almost certainly has a neurological rather than a labyrinthine disorder. In order for the clinician to reach these conclusions confidently, the examination has to be technically correct.

- Since pursuit movements are visually guided, rule number one is that the patient should be able to see the target correctly. Any object can be a target, not only the examiner's finger or pen. In patients who are too young, too old or with attentional problems, a substantial, solid target such as a key, a toy, a mobile phone or a credit card can increase performance. Make sure that in elderly subjects, with presbiopia and age-related convergence insufficiency, the object is presented at a comfortable viewing distance. Sometimes, the examination must be conducted with the patient wearing his/her own glasses.
- Rule number two is that the target has to be moved at a slow speed, taking 4–5 seconds to travel from right to left and vice versa (i.e. approximately 0.1 Hz). One cycle is usually not enough since many patients do not understand the task and tend to jump their eyes ahead of the target; the patient should be encouraged to 'glue your eyes to the target'. Pursuit should be investigated in the horizontal and vertical planes.

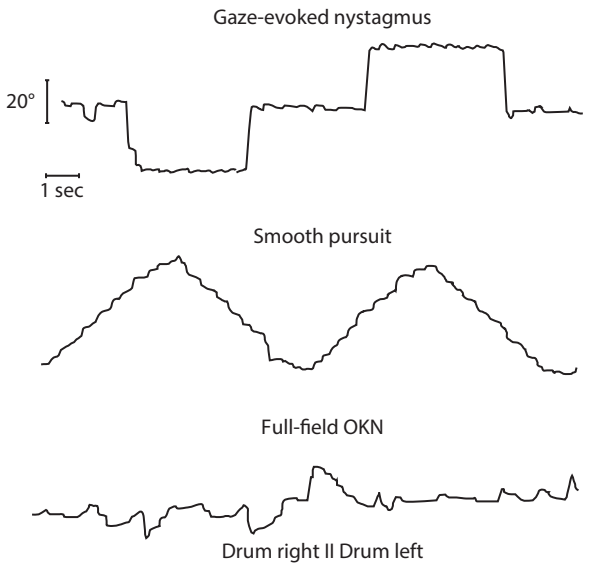


Figure 62.7 Cerebellar degeneration producing gaze-evoked nystagmus, broken ('cogwheel') pursuit and almost complete absence of optokinetic nystagmus.

It is easy to identify asymmetric pursuit, with excessive 'catch-up' saccades in one direction only. When pursuit is broken, say, to the right, the lesion is likely to be in the ipsilateral (right) cerebellum or parietal lobe. Brainstem lesions can have more complex effects (e.g. if they involve the vestibular nuclei which can generate nystagmus) but often are ispilateral too.[20, 24] Small asymmetries in the horizontal plane, if consistent, are significant. Asymmetries in the vertical plane are less useful since they occur in many normal subjects.

Global or pandirectional abnormalities of pursuit are somewhat more difficult to interpret. The reason lies in the fact that pursuit pathways are long, complex and multisynaptic, including visual pathways, parietal and frontal cortex, vestibular nuclei and cerebellar flocculus. This makes them vulnerable to trivial sources of mild diffuse CNS dysfunction, including ageing, psychotropic drugs and alcohol. The influence of age on pursuit is considerable, so one must be careful in diagnosing bilaterally abnormal pursuit in an elderly patient. During examination of pursuit or searching for spontaneous nystagmus, one may discover a limitation, or paresis, of gaze; this will be discussed under 'Saccadic eye movements' below.

SACCADIC EYE MOVEMENTS

Saccades are fast movements of the eyes (200–500 degrees per second) which allow us to shift gaze from one object of interest to another. Unlike smooth pursuit movements, that do require a visible moving target, saccades can be generated at will or command without a specifically defined target. These refixations occur incessantly so that gross saccadic defects are often detected while interrogating the patient. It should be said at the outset that just saying that a patient has abnormal saccades is not sufficient to make a topographic diagnosis; there are three independent properties of saccades to be clinically assessed: velocity (normal, slow or absent saccades, i.e. a gaze palsy), accuracy (normo-, hypo- or hypermetric) and binocular conjugacy (conjugate or dysconjugate, e.g. as in internuclear ophthalmoplegia).

With practice, all three aspects of saccadic function can be assessed in the clinic. Initially, however, it may be useful for the clinician in training to cross-validate subtle clinical findings with ocular movement recordings. One can gain some insight of saccadic velocity by simply asking the patient to look right, left, up and down. If one wishes to assess accuracy at the same time, however, a visible target should be provided, usually the examiner's

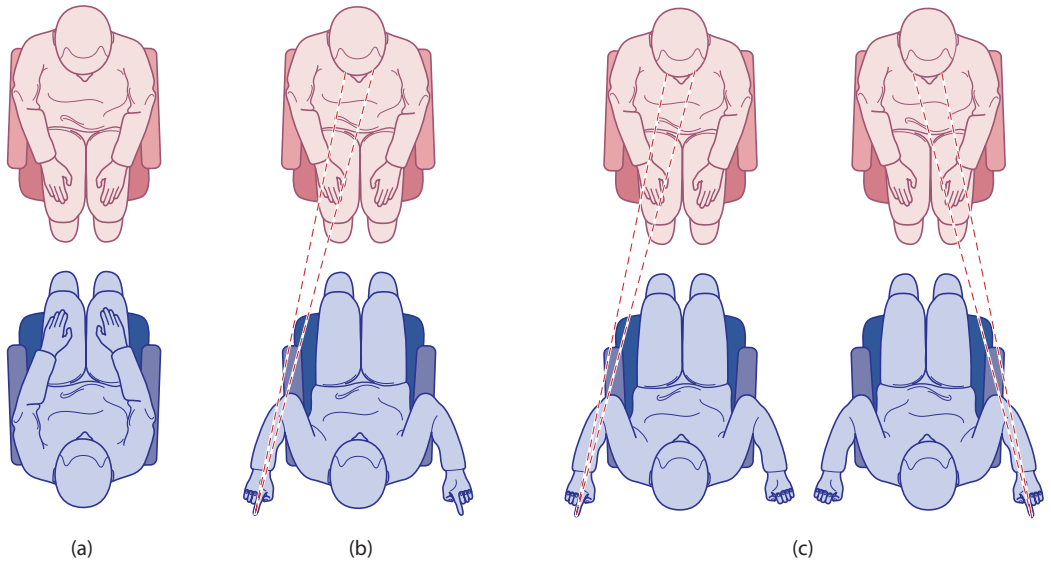


Figure 62.8 Different techniques for eliciting saccades during clinical examination: **(a)** on command; **(b)** self-paced; **(c)** visually elicited (to flicking fingers). During routine neuro-otological examination it does not matter which of these procedures, or combinations of procedures, is used. However, patients with cortical or basal ganglia disorder can show selective deficits with some but not other techniques. Redrawn with permission from Stell and Bronstein.[25]

finger placed 20–30 degrees to the right–left of primary gaze, for horizontal saccades, or up–down for vertical saccadic assessment. The patient can be instructed to look at the target when, for instance, the right or left finger flicks or when the hand opens up (Figure 62.8). It is customary, however, to reinforce the visual stimulus with a simultaneous verbal command such as 'right', 'left' (making sure to be directionally congruent with the patient's point of view) or 'pen', 'finger'. Subtypes of saccades (e.g. self-paced saccades, anti-saccades) can be elicited with more complex instructions and these can be selectively abnormal in frontobasal ganglia disorders, but these will not be reviewed here.[25, 26]

Saccadic velocity

A purely slowed-down saccade takes longer to travel from one target to another, but the movement is a unity, not fragmented. Saccadic slowing is the intermediate stage between normal velocity saccades and an absence of saccades (complete gaze palsy or paralysis). Neurodegenerative disorders involving the saccadic system reduce velocity from say 500 degrees per second to 100 degrees per second (taking up to 3–4 seconds longer than normal) before the patient becomes completely unable to transfer gaze at will or command (Figures 62.9 and 62.10).

Saccadic accuracy

Saccadic amplitude is normally slightly smaller than target amplitude; for example, for targets 30 degrees apart, the eye initial saccade is 27 degrees. In such cases the subject makes additional, smaller corrective saccades towards the target. Whereas one or two small corrective saccades can occur in normal subjects (usually bilateral in such cases), the presence of three or more corrective saccades is considered saccadic hypometria. Severely hypometric saccades look fragmented, often called 'multiple-step' saccades.

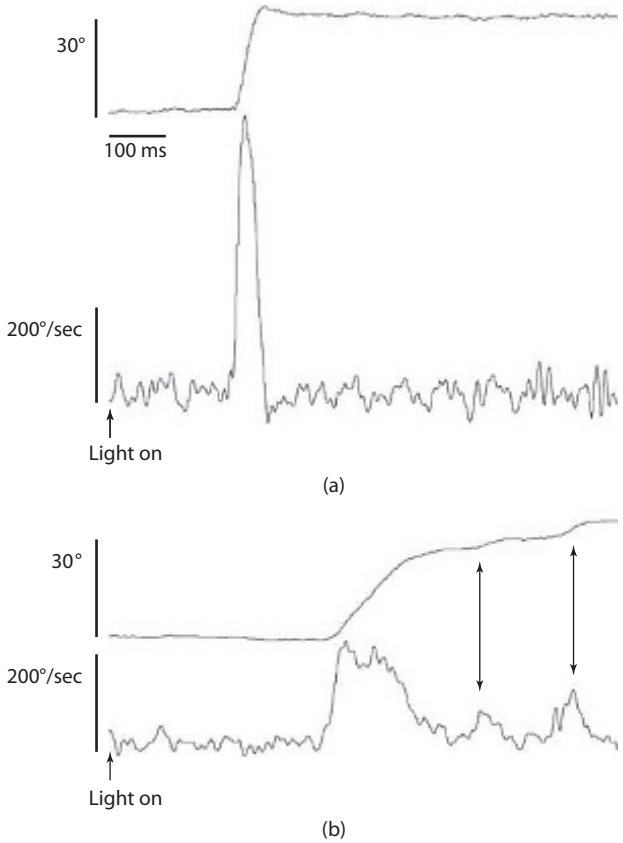


Figure 62.9 Examples of a normal saccade **(a)** and **(b)** a slow and hypometric saccade in a patient with a demyelinating brainstem lesion. Both the position (deg) and velocity (deg/second) traces are shown. The arrows point at two small corrective saccades.

In contrast, if the initial saccade is too large and travels past the target, the patient makes corrective saccades in the opposite direction of the initial saccade. This is saccadic hypermetria, a reliable cerebellar sign (anterior lobe)

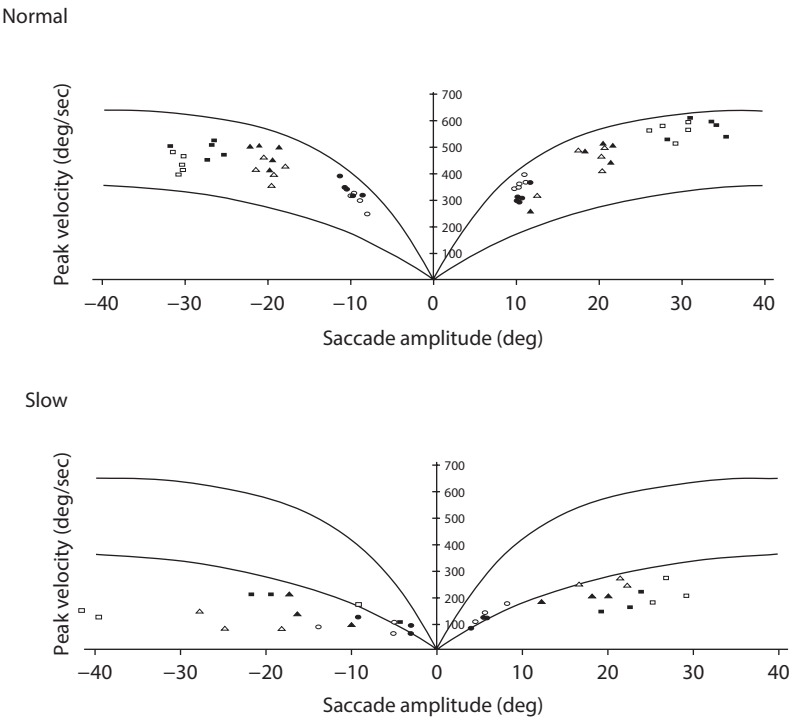


Figure 62.10 'Main sequence', obtained by plotting amplitude versus velocity of saccades in the normal and brainstem-lesioned subjects shown in Figure 62.9. The continuous 'butterfly' lines indicate the range of normality.

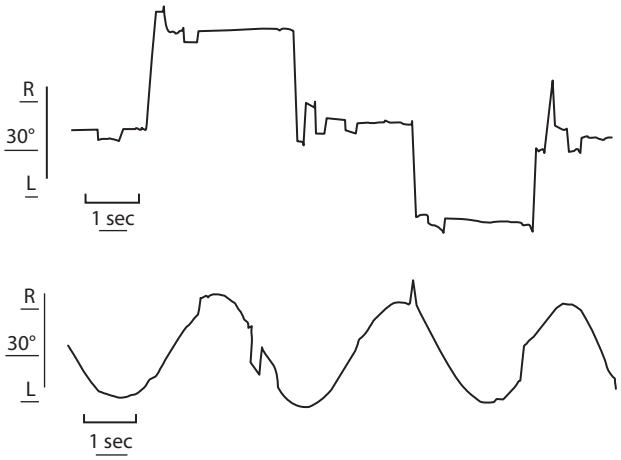


Figure 62.11 Eye movements in a patient with predominantly dorsal vermis cerebellar disease. Note the hypermetric saccades in spite of relatively normal smooth pursuit movements.

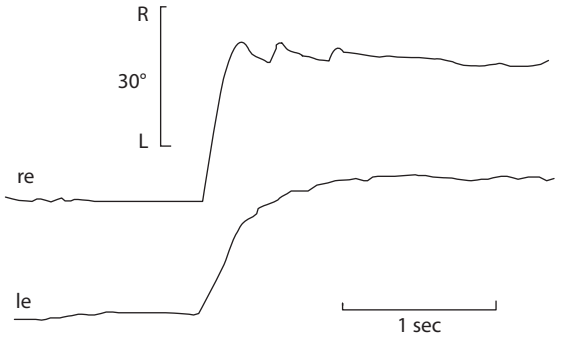


Figure 62.12 Separate eye EOG recording in a patient with a left internuclear ophthalmoplegia. Note the slower movement of the left eye to the right (adduction) and the right-beating nystagmus in the right (abducting) eye.

(Figure 62.11). The corrective saccade itself can be hypermetric so that the eye progressively homes in onto the target. The appearance and meaning is similar to abnormal past pointing during a 'finger–nose' test in an ataxic patient. By contrast, saccadic hypometria is much less specific and can be due to lesions in the cortex, basal ganglia, brainstem, cerebellum and oculomotor nucleus, nerve, muscle or metabolic (see Figure 62.9).

Saccadic conjugacy

When examining saccadic conjugacy (i.e. the two eyes should travel at the same speed), one should first make sure that there is no individual III, IV or VI nerve palsy (i.e. nuclear or infranuclear deficit). A common source of saccadic disconjugacy in the horizontal plane is, however, not nuclear but internuclear. This is the internuclear ophthalmoplegia (INO) in which the abducting eye saccades are fast and large whereas saccades in the adducting eye are slow and small. INOs are due to lesions of the medial longitudinal fasciculus (MLF) which connect abducens interneurons of the VI nucleus with medial rectus motoneurons in the contralateral III nucleus. Abducens interneurons cross the midline immediately to form the ascending MLF on the other side of the brainstem. Thus, a right INO means that right-eye adduction during gaze to the left is slow, hypometric or incomplete due to a right MLF lesion. Since innervation to the eyes is yoked, the attempt of the CNS to overcome the limitation in adduction makes saccades in the abducting eye to be larger (hypermetric). This sequence of overshoots in the abducting eye leads to the characteristic monocular, 'ataxic nystagmus' in INO (Figure 62.12).

Other essential 'supranuclear' clinical neuroanatomy concepts on saccades now follow.[24]

- The more important cortical areas for the generation of saccades are the frontal eye fields. At cortical level, saccadic control is contralateral, so that a left cortical lesion causes abnormal hypometric saccades towards the right.
- From these frontal (and also parietal) areas, pathways originate that reach the contralateral reticular formation of the brainstem, directly and indirectly.
- There are three important reticular saccadic areas.
  - A small central region in the pontomedullary junction (nucleus raphe interpositus (RIP)) which is the gateway for all saccadic movements; small lesions in this area can produce absence or slowness of saccades and quick phases of nystagmus in all directions.
  - The paramedian pontine reticular formation (PPRF) which generates the high frequency neuronal burst required to accelerate the eyes; this area is responsible for ipsilateral horizontal saccadic velocity so that a right side pontine lesion produces absence or slowness of saccades towards the right.
  - The midbrain reticular formation, in particular the rostral interstitial nucleus of the medial longitudinal fasciculus (RIMLF) responsible for the generation of vertical saccades. Lesions in this area can cause selective up, down or complete vertical saccadic gaze palsy or slowing, according to location and extension.
- Another area of importance for the accuracy (not velocity) of saccades is the anterior lobe of the cerebellum; lesions here can produce hyper- or sometimes hypometric saccades. Saccadic hypermetria strongly indicates cerebellar dysfunction but, in contrast, hypometria is not specific.

OPTOKINETIC NYSTAGMUS

The optokinetic nystagmus (OKN) system in man is not a truly separate oculomotor system but it will be briefly described here due to its historical and clinical value in neuro-otology. When a repetitive visual pattern moves in front of our eyes, such as a large curtain or traffic, our eyes follow one object with a smooth slow-phase movement. From time to time the eyes are reset in the orbit by a fast or quick component. This sequence of slow ipsidirectional and fast contradirectional eye movements constitute a visually or optokinetically elicited nystagmus. Its function is to complement the normal vestibular nystagmus during prolonged or slow head rotations. In animals, particularly those with poorly developed foveas, it is a peripheral retinal reflex. However, in man, particularly when OKN is elicited with a small handheld drum, the main contribution to the slow phase movement comes from the foveally driven smooth pursuit system. For these reasons, it is said that if smooth pursuit and saccades have been properly examined, what one can learn from observation of OKN is very little. Nevertheless, the alternating and repetitive nature of the nystagmus makes it sometimes easier to visualize some abnormalities; for example, a small asymmetry of pursuit may be easier to appreciate as an asymmetry of OKN.

OKN is usually investigated with a small hand-held striped drum (**Figure 62.13**). As in smooth pursuit assessment, the patient should be able to see the drum clearly; distance may have to be adjusted to age (presbiopia) and refractive defect of the patient. Subjects should be instructed to glance at the surface of the drum. If this fails to elicit nystagmus, one can try to ask the patient to follow or count the stripes as they pass by. The natural trend in the inexperienced examiner is to rotate the drum too fast, sometimes even letting the drum spin freely in front of a mesmerized patient. One or even half a stripe per second (for stripes of approximately 2–3 cm width) is what is required – if in doubt move it slower! If there is no drum available, OKN can be assessed with an open magazine or newspaper moved slowly in one direction and then the other. If what you want is to see nystagmus, the patient should be strictly instructed to look straight ahead; otherwise patients just follow a single word or image with smooth pursuit movements.

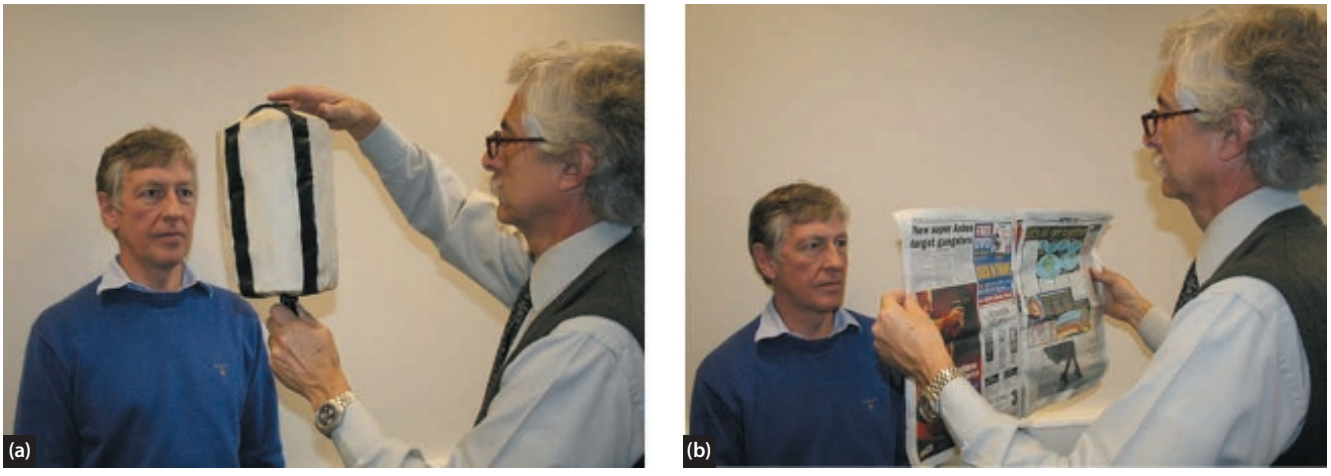


Figure 62.13 OKN elicited with **(a)** a small drum or **(b)** a newspaper. Rotation of the drum or movement of the large target object should be slow. The patient is usually instructed to look straight ahead, rather than follow the stripes or print.

The essential clinical neuroanatomy of OKN is that of pursuit, for the slow phase, and saccades, for the quick phase, but the clinician must be aware of the following practical points.

- The direction of OKN is defined by that of the fast phase. A directional preponderance of OKN to the right (elicited by drum rotation to the left) thus means that right-beating OKN is more active, better formed than left-beating OKN. Be aware that this usually means that slow-phase, smooth pursuit to the right is at fault.
- OKN assessment can be more useful than that of its pursuit-saccades constituents in cortical or subcortical lesions, due to the fact that a cerebral hemisphere is responsible for generating fast phases (saccades) contralaterally but slow phases ipsilaterally. Thus, a directional preponderance to the right of OKN observed in a right cortical lesion is due both to poor leftwards saccades and rightwards smooth pursuit. This functional coupling of slow and fast, oppositely directed eye movements is preserved in many brainstem areas so that, typically, a right brainstem lesion induces a left directional preponderance of OKN (e.g. by affecting the ipsilateral vestibular nuclei and ipsilateral PPRF saccade generators) (**Figure 62.14**). A right cerebellar lesion, with its massive loss of ipsilateral smooth-pursuit movements, usually generates a right directional preponderance of OKN.

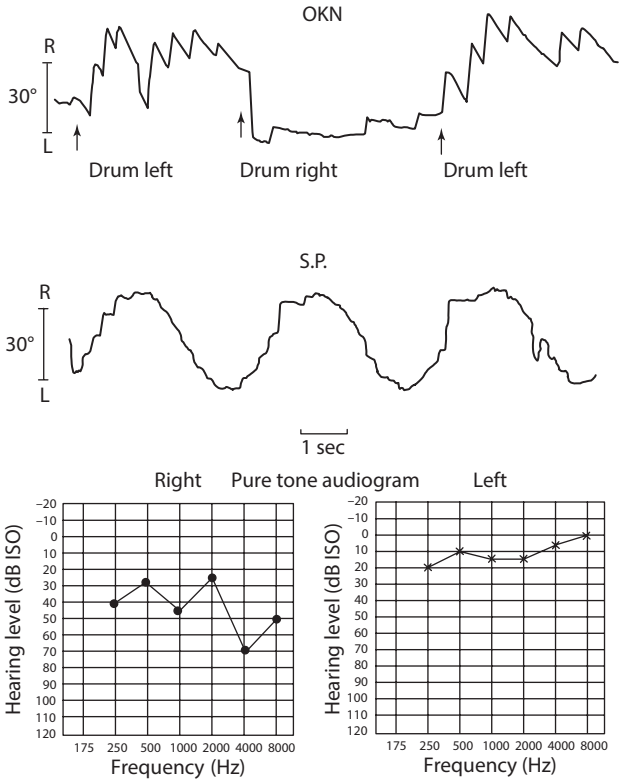


Figure 62.14 OKN asymmetry in a patient with an infiltrating brainstem tumour in the area of the right cerebellopontine angle.

- In disorders with selective or preferential saccadic problems (e.g. gaze palsies as in progressive supranuclear palsy) all one sees during OKN stimulation is the slow phase pursuit. Quick components of nystagmus are slow and scarce. This leads to the 'deviation of the eyes in the direction of the slow component of nystagmus' as described by Dix et al.[26] On reversing drum rotation direction, the eyes passively follow the drum, which is a useful sign in progressive supranuclear palsy.
- Peripheral (labyrinth and VIII nerve) lesions, unless acute and massive with clinically visible spontaneous nystagmus, leave OKN unaffected. A slight directional preponderance, concordant with the peripheral vestibular nystagmus, is all that can be observed in a peripheral disorder.

VESTIBULAR OCULAR REFLEXES

The vestibulo-ocular reflex serves a very specific function: to stabilize gaze in space during head movements. The VOR is what allows us to see clearly when we walk, run or turn our heads. It does so by generating slow-phase eye movements of equal velocity, but opposite in direction, to head movement. This is achieved by a three-neuron, short latency, reflex: a Scarpa ganglion neuron, a vestibular nucleus neuron and an oculomotor nuclear neuron (III, IV or VI).

For many years, clinicians relied almost exclusively on laboratory examination of the VOR, namely caloric or rotational tests. In the last 20–30 years, thanks to our increased understanding of the physiological basis of the vestibulo-ocular system and our improved skills in observing eye movements, we can now assess the VOR in the clinic room. Unilateral and bilateral loss of vestibular function can, in many cases, be identified clinically, but will be easier the more severe and the more acute the lesion is. In contrast, a unilateral, partial, long-standing, peripheral vestibular disorder cannot be detected clinically and a caloric test is required.

The clinical manoeuvres available rely on either:

- a slow doll's head manoeuvre, assessed by (i) direct observation of the eyes, (ii) measurements of visual acuity or (iii) ophthalmoscopy, or
- a fast version of the doll's head, the 'head-impulse' or 'head thrust' test (**Figure 62.15**).

THE DOLL'S HEAD (DOLL'S EYE) MANOEUVRE

This manoeuvre requires the patient sitting in front of the examiner, close enough to be able to observe the patient's eyes carefully. The patient is instructed to continuously fixate a feature of the examiner face (nose or bridge of nose), or an object across the room. The examiner then oscillates the patient's head from side to side, at a frequency of approximately 1 Hz. In the absence of VOR, the patient's eye movements will not be smooth but will be interrupted by 'catch-up' saccades towards the fixation target. This occurs because, at frequencies of 0.5–1 Hz, a head oscillation of ±30 degrees will generate peak head velocities of between 94 and 188 degrees per second, i.e. too high for the pursuit or cervico-ocular

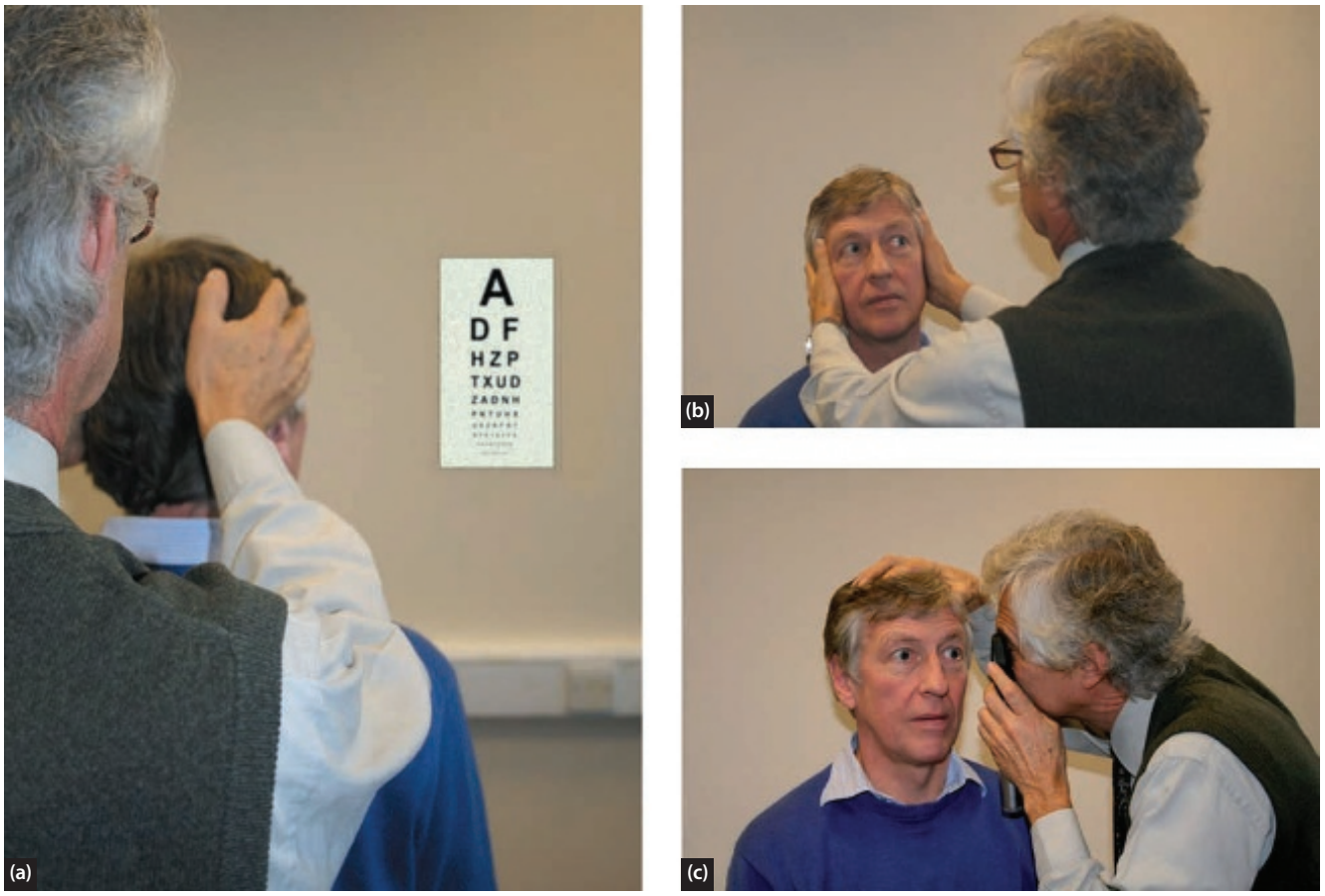


Figure 62.15 Techniques for assessing the VOR in the clinic. The general principle is that the examiner moves the patient's head, with two hands **(a)** and **(b)** or with one hand as in **(c)**. **(a)** Dynamic visual acuity. Two measurements of visual acuity are taken, one with the head stationary and one with the head oscillating at approximately 1 Hz. Reductions in visual acuity of two or more lines indicate bilateral abnormality of the VOR. **(b)** The examiner observes the patient's eye movements during either slow (doll's head) or fast, sudden head turns (head-impulse test). The presence of catch-up saccades towards a target (usually the examiner's nose) during a head turn indicates severe failure of the horizontal semicircular canal in the direction of the head turn. **(c)** The head is turned during ophthalmoscopy while the viewing eye maintains fixation on a distant object. If the optic disc remains absolutely steady, the VOR is functioning well. If the disc appears jerky during head (nose) turns in one direction, the ipsilateral horizontal semicircular canal is likely to be significantly impaired.

reflex to compensate.[27] As slow-phase eye movements are unable to keep up with the target, catch-up saccades are put in – and these can be easily observed if you are close enough. In patients with bilateral, complete or severe (>90%) loss of vestibular function (e.g. gentamicin ototoxicity, meningitis or idiopathic[9]), the manoeuvre is positive.

DYNAMIC VISUAL ACUITY

A similar movement of the head can be used to investigate the VOR while reading a visual acuity chart. A baseline, binocular visual acuity measurement is noted, for the sake of argument 6/6. Standing behind the patient, the examiner oscillates the patient's head at approximately 1 Hz while a new visual acuity measurement is taken. A normal subject's visual acuity does not change with respect to the baseline reading or it can deteriorate by one line, say, down to 6/9. A loss of two lines in visual acuity must be treated as suspicious and when three lines or more are lost, the results are frankly abnormal, i.e. indicative that the patient's VOR is grossly reduced. False positives may occur if the patient has a spontaneous nystagmus (e.g. a downbeating nystagmus) which is exacerbated by head movement and/or lateral gaze. However, this nystagmus should have been observed during conventional examination of the eye movements. False negatives occur if the patient himself oscillates the head, since they often 'cleverly' stop the head movement and get a snap of the visual acuity chart. In controlled conditions, a correlation between the degree of caloric response loss and dynamic visual acuity decrement was found.[28]

Although examination of the patient's eye during the doll's head manoeuvre can in some cases detect a unilateral vestibular lesion, this is detected more efficiently with the head-impulse test (see below). The reading or dynamic visual acuity test, as used clinically, cannot be applied to unilateral lesions.

OPHTHALMOSCOPY

A procedure first proposed by Zee[29] promotes the use of ophthalmoscopy for the assessment of vestibular disorders.

As the ophthalmoscope is a powerful magnifying glass, nystagmus of small amplitude can also be detected easily. However, as funduscopy is not routinely carried out by otolaryngologists, the reader is referred to the original reference and a recent brief review.[30, 31]

HEAD-IMPULSE TEST (OR HEAD THRUST TEST)

The value of VOR examination as described in the preceding sections is limited by the fact that they are all carried out with relatively low head velocities. The VOR is only really irreplaceable at high velocities and accelerations of the head. Pursuit, optokinetic or cervical mechanisms cannot fully take over from the VOR during brisk head movements. For this reason, Halmagyi and Curthoys have popularized the examination of the doll's head manoeuvre with discrete, sudden, brisk and unpredictable head turns, so that the VOR deficit is more apparent.[32, 33] In essence, the patient is seated with the examiner at close range so that the eyes can be observed carefully. The patient is instructed to fixate a target, preferably across the room (e.g. the video-camera lens if you wish to document the findings) or on the examiner's face. The head is turned in discrete steps of ±10–15 degrees, briskly, by the examiner thus producing head velocities of several hundred degrees per second. A fast right head (nose) turn will make a patient with right-sided vestibular loss introduce one or more catch-up saccades towards the target, i.e. towards the left. These catch-up saccades can be easily identified by a trained observer. The test is clearly useful for identifying acute unilateral peripheral vestibular deficits, for instance in patients with vestibular neuritis (neuronitis, labyrinthitis). In patients with chronic, compensated, incomplete unilateral lesions the test is often negative or inconclusive. A study comparing caloric testing versus the head-impulse test shows that the overall sensitivity of the head-impulse test is 34%.[34] This means that, when taking into account all patients with canal paresis, the sensitivity is low. However, specificity is high (100%) and all patients with a canal paresis ≥87% had a positive head-impulse test.[34] In the acute scenario the head-impulse test is extremely useful as it helps to confirm that an acute vestibular syndrome is of likely peripheral origin (abnormal result in vestibular neuritis). Although many small brainstem or cerebellar strokes show a normal head-impulse test, vascular lesions involving the labyrinthine artery (a branch of the anterior inferior cerebellar artery (AICA)) will also infarct the labyrinth hence producing vertigo, unilateral deafness and an abnormal head-impulse test when tuning the head towards the lesion. Combining the head-impulse test with other central oculomotor abnormalities indicative of a central lesion (skew eye deviation, bidirectional nystagmus) is, in experienced hands, more sensitive than diffusion-weighted image (DWI) MRI for the diagnosis of acute vertebra–basilar stroke (the HINTS for stroke protocol – head impulse, nystagmus characteristics, test for skew).[35, 36] Although HINTS is a nice protocol backed up by good research, clinicians should not forget many other hints or red flags suggestive of stroke (see **Box 62.2** above).

With practice it is possible to investigate clinically all six semicircular canals by moving the head obliquely in the planes of the vertical canals (LARP plane: left anterior–right posterior and RALP plane: right anterior–left posterior) (**Figure 62.16**).[37]

To feel fully confident with the head-impulse test one should be conversant with the oculomotor clinical examination and, like any other clinical manoeuvre, be shown how to do it – at least once. In some patients with spontaneous nystagmus or square-wave jerks the head-impulse test maybe inconclusive (i.e. it may be difficult to know whether you have seen the little saccade you are looking for, or just another square wave jerk). As with all other clinical procedures for VOR examination, the head-impulse test does not replace caloric testing. Quantitative versions of the test (video head-impulse test or VHIT) are now on the market and are useful (see vestibular testing below) but, despite pressure from the commercial manufacturers, they have not replaced the caloric test and perhaps they never will.

VESTIBULO-OCULAR REFLEX SUPPRESSION

When a subject rotates the head in the environment, his eyes adopt a pattern of alternating slow and fast phases, a physiological vestibular nystagmus (VOR). In a normally lit room this is aided by OKN. A property of the human brain, and other higher mammals, is the ability to suppress the VOR. This is executed by the vestibulo-ocular reflex suppression (VORS) system, closely related or identical to pursuit mechanisms and pathways. Abnormalities in VORS are thus indicative of central dysfunction, as discussed already for smooth pursuit.

Clinical examination of VORS is easy, both clinically and during oculography (**Figure 62.17**). The general principle is to oscillate the patient while he/she fixates a head-fixed target. Any obvious breakthrough nystagmus indicates poor suppression. In the clinic, this can be achieved by asking the patient to clasp the hands together in front of him and put the thumbs up as a target (**Figure 62.17b**); the patient can then oscillate side to side *en bloc*, by himself if standing up, or the examiner can oscillate the patient's swivel chair if sitting down. Alternatively, the patient can bite on a tongue depressor or ruler with his teeth, and fixate on the other end of the ruler or on an object attached to it while moving the head side to side (**Figure 62.17a**). As with pursuit, the oscillation should be slow, say 2–5 seconds from right to left, and vice versa (0.10–0.25 Hz) and one should have a good view of the patient's eyes.

Patients with peripheral vestibular lesions have normal VORS, or even 'super-normal' VORS as they are trained at suppressing their own spontaneous vestibular nystagmus. In central lesions, the abnormality of pursuit and VORS usually goes hand in hand, i.e. a patient with a right cerebellar lesion will show abnormal rightwards pursuit and abnormal VORS, with visible nystagmus breaking through, when oscillating the head towards the right.

Figure 62.16 Head movements required during the head-impulse test to investigate the horizontal canals (top, a–c) and the vertical canals (bottom, d–f). In the position shown in the figure the compensatory eye movement required during the head movement is horizontal (top) or vertical (bottom). Reproduced with permission from Bronstein and Lempert[8] and Bronstein et al.[37]

Figure 62.17 Clinical assessment of VOR suppression. The principle of the examination is that the patient fixates a head-fixed target during either **(b)** whole-body oscillation (his own thumbs) or **(a)** head oscillation (ruler or tongue depressor with an object on top, in the example shown the ear piece of an auriscope taped to the tongue depressor).

POSITIONAL MANOEUVRES

One of the most common causes of vertigo is BPPV, accounting for one-quarter of all patients with dizziness and vertigo. Positional manoeuvres are a vital component of the examination in the balance-disordered patient, particularly in light of the efficient treatments available for BPPV.

Positional manoeuvres must be conducted in all patients with vertigo or dizziness, particularly if provoked by head–neck movements or positions. Typical symptoms are vertigo on looking up, bending over, lying down and turning over in bed. If a patient is dizzy on standing up from the sitting position, the likelihood of the symptoms being primarily vestibular in origin is less. The latter challenges vascular orthostatic mechanisms but there is no reorientation of the head with respect to gravity.

The purpose of conducting a positional manoeuvre is to attempt to elicit vertigo, but vertigo is unpleasant. The patient should be made aware that despite modern technology this is the only way to make a diagnosis of a perfectly treatable condition such as BPPV. During the positional manoeuvre, and regardless of whether there is vertigo or not, the examiner should carefully observe the patient's eyes. In order to fulfil this purpose the following practical measures can be taken.

- Patients should be warned beforehand that, even if they feel vertiginous, they should look straight ahead at one point on the examiner's face (i.e. the nose or bridge of the nose). If the eyes are not in primary gaze or wandering around, the observation of the nystagmus is more difficult.
- At least one eye of the patient can be easily helped to stay wide open by one of the free hands of the examiner, as shown in Figure 62.18.
- Keep the patient in the head-down position for a few seconds. Some patients with BPPV show extremely long latencies, occasionally up to 20–30 seconds. If the suspicion of BPPV is strong, one should wait this long. In most cases, 10–15 seconds is sufficient, indeed most cases of BPPV have latencies of less than 5 seconds.

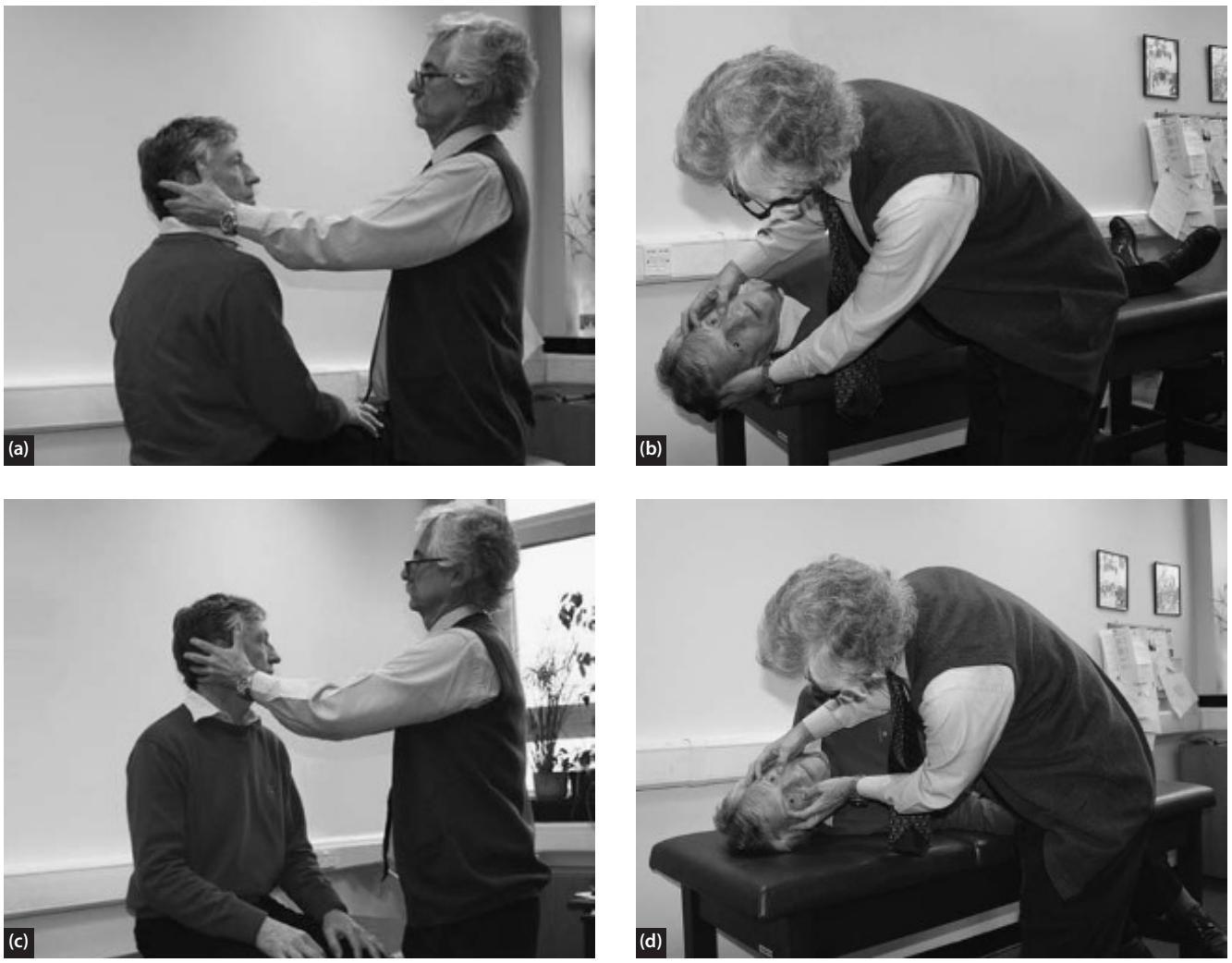


Figure 62.18 Positional manoeuvres. Examination technique for a right-sided, posterior canal BPPV. **(a,b)** The Hallpike manoeuvre, in which the head (face) is turned approximately 45° to the right. This is done so that the rotation, down to the head-hanging position, takes place in the plane of the right posterior canal. Note how the examiner's right hand can contribute to open the patient's eye widely. **(c,d)** 'Variant' Hallpike manoeuvre, starting from a sitting position. Note that the head reaches a similar final position, despite not actually being off the couch; this manoeuvre is useful if the couch is placed in between walls or cupboards.

There are no excuses for not doing a positional manoeuvre. However, two of the most commonly excuses heard are 'The couch in my room is placed awkwardly to do a Hallpike, I just cannot get the patient's head to hang off the couch' and 'We have not got Frenzel glasses in our clinic.' Wrong! A positional manoeuvre can be done with a couch in any position and Frenzel glasses are definitely not required for any positional nystagmus. **Figure 62.18a** and **b** show the conventional Hallpike manoeuvre with the head in the classical hanging position and a recommended alternative to the procedure when, for instance, the couch is placed between walls or cupboards (**Figure 62.18c** and **d**). Examination of these pictures shows that the final head position achieved is very similar. As to the use of Frenzel glasses, it must be remembered that all the classical descriptions of BPPV by Dix and Hallpike were carried out without Frenzel glasses. Presumably, the rationale for using Frenzel glasses is that, when the patient is able to fixate, the nystagmus can be potentially suppressed. However, the vast majority of patients either have or do not have BPPV. If they have BPPV, the nystagmus is extremely strong and so the patient is unable to suppress it with visual fixation. Furthermore, a critical component in the most common form of BPPV, posterior canal BPPV, is torsional (rotatory) nystagmus. The ability to suppress torsional nystagmus by visual fixation is less than nystagmus in other planes.[38] It is theoretically possible that Frenzel glasses could help in a patient with a mild form of BPPV. In practice, there seems to be no increase in diagnostic efficacy but controlled studies are lacking.

What can we expect to see during a Hallpike or variant Hallpike manoeuvre? The most common form of positional nystagmus is BPPV of the posterior canal. During a left-ear-down head hanging position one triggers a left posterior canal BPPV, with the main component of the nystagmus being torsional (or rotatory) beating clockwise from the observer point of view. This means that the upper pole of the patient's eye beats towards the patient's left shoulder. Technically speaking, it is left-beating torsional nystagmus, as expected from activation of the left posterior canal. A secondary upbeating component of nystagmus is often observed which is synchronous with the torsional beat. The nystagmus is often accompanied by intense vertigo and by the patient's attempt to close the eyes or to sit up – which the doctor will have hopefully instructed him/her in advance to resist. The characteristics of posterior canal BPPV are the presence of latency, as mentioned above, adaptation and fatigability. Adaptation refers to the decline and eventual disappearance of the nystagmus within a minute or so, usually less. Fatigability refers to the fact that on repeated positioning, the nystagmus and the vertigo are less with time. The patient can be reassured that usually the intensity of the symptoms will be less as we repeat the manoeuvre. Currently, one rarely repeats the manoeuvre to assess fatigability as it is advisable to proceed straight to repositioning treatment (see Chapter 64, Benign paroxysmal positional vertigo).

The positional manoeuvre should be conducted on both sides, particularly if no nystagmus is observed on the first side. On confirmation of the diagnosis, most specialists proceed to treatment with Epley or Semont manoeuvres. Partly because of fears that a new Hallpike after an Epley or Semont manoeuvre could undo the benefits of the treatment, many doctors do not do the Hallpike manoeuvre on the other side if BPPV has been diagnosed and treated on one side. If all symptoms resolve in the first session, that is end of story. If symptoms persist, the Hallpike manoeuvre will have to be carried out on a separate session on both sides. If the patient knows that a particular ear down provokes the vertigo, it is sensible to do the healthy side down first to increase patient confidence and so be able to examine both sides in the same session.

Several other types of nystagmus can be observed during the Hallpike manoeuvre, which are not posterior canal BPPV. In principle, a purely vertical nystagmus, be it up- or downbeating nystagmus, should be considered of central origin. Our review of 50 consecutive cases of positionally induced downbeating nystagmus we found that three-quarters of patients had independent evidence of neurological disease.[39] In the remaining quarter of patients the most likely diagnosis was anterior canal BPPV. Ideally, in anterior canal BPPV, one should see a torsional component added to the positional downbeating nystagmus. Of interest, the right/left specificity to trigger anterior canal BPPV seems less than for posterior canal BPPV.

A purely horizontal nystagmus can also be observed during a Hallpike manoeuvre. In a patient with a recent history of peripheral type positional vertigo, the diagnosis is almost certainly horizontal canal BPPV. As in posterior canal BPPV, it is usually due to canalolithiasis (free-floating particles in the lumen of the canal) and occasionally to cupulolithiasis (particles become adhesive to the cupula).[40] Horizontal canal BPPV produces intense nystagmus and vertigo and this happens when the head is turned both to the side of the lesion and to the opposite direction. The nystagmus usually beats in the direction of the face turn. The intensity of the nystagmus is stronger in the direction of the abnormal side, i.e. stronger right-beating nystagmus with the right ear down suggests right horizontal canal BPPV. Horizontal canal BPPV is a much more self-limiting condition than other canal BPPV and can disappear spontaneously in a few days.

When a patient gives a positive typical history of BPPV and no nystagmus can be elicited in the Hallpike or similar manoeuvres for posterior canal BPPV, other manoeuvres should be investigated. For horizontal canal BPPV the optimal plane of rotation should be in the plane of the canal. This can be achieved with the head end of the couch raised 20–30 degrees above the horizontal, followed by a full head turn about the longitudinal axis of the body in each direction. It can be estimated that the Hallpike (i.e. posterior canal) manoeuvre may not identify 20% of horizontal canal BPPVs. In other words, one in five patients with horizontal canal BPPV will require the specific horizontal canal manoeuvre for diagnosis.

For anterior canal BPPV, the left head-hanging Hallpike position should provoke a right anterior canal BPPV and vice versa. This is due to the coplanar orientation of the left posterior canal with the right anterior canal and

vice versa. However, a crucial factor in provoking anterior canal BPPV seems to be placing the head as low down as possible and this may be best achieved by taking the patient in one movement from the sitting upright position to the straight back, head hanging position.[39]

In summary, many positional manoeuvres exist and BPPV can come from any of the three semicircular canals. Bilateral cases, often post-traumatic, also exist. At least the Hallpike manoeuvre, or variant, for posterior canal BPPV must be carried out in all patients with head–neck movement or position triggered vertigo. If negative, the horizontal and straight back manoeuvre should be applied but the hit rate may be low. A typical nystagmus for posterior canal BPPV, with normal CNS examination, needs no imaging procedures. Successive failures to treatment should prompt imaging. Even in the absence of nystagmus, more than 80% of patients with a typical history improve with particle repositioning manoeuvres for posterior canal BPPV.[41] Observation of any other positional nystagmus, particularly if it lasts for longer than a month, should undergo detailed MRI investigation of the posterior fossa. Further details about examination and treatment of positional vertigo can be found in Chapter 64, Benign paroxysmal positional vertigo.

Laboratory assessment of eye movements

Not all patients with a suspected vestibular disorder, peripheral or central, require eye movement recordings (oculography); only a minority do. Not even patients requiring a caloric test may need eye movement recordings (see 'Caloric tests' below). In a research, academic or tertiary referral environment, vestibular and eye movement tests are conducted for a variety of reasons and not necessarily diagnosis. These are perfectly valid reasons such as research, training of medical and paramedical personnel and patient reassurance.

From the strictly clinical point of view, oculography is required firstly for formal vestibular testing, as this is usually conducted in the dark (Table 62.7). Otherwise, visual input may suppress spontaneous vestibular nystagmus and override abnormalities in rotational responses. Oculography is also required to elucidate the nystagmus waveform in some patients with spontaneous nystagmus, particularly when there is doubt if the nystagmus is acquired or congenital. Oculography is required when clinical examination of eye movements leaves doubts on the presence of a potentially significant abnormality such as INO or slow saccades.

The clinician must bear in mind, however, that routine oculographic examination, as carried out in most vestibular laboratories, will fail to answer these questions unless they are specifically formulated. This is no different to other special medical investigations.

Vestibular conditions that can be diagnosed clinically or with other laboratory investigations (audiograms, head scans) do not necessitate ocular recordings. Examples are BPPV, Ménière's disease and vestibular schwannomas. Formal vestibular testing in such cases is variably indicated according to the presence of complications, poor response to treatment, presurgical evaluation, evaluation of the 'healthy' labyrinth, or need for objective measurements on follow-up.

TABLE 62.7 Indications for oculography: eye movement recordings to investigate imbalance

Clinical problem	Recording/action
Assessment of eye movements in the dark	Is there vestibular nystagmus?
	Vestibular function (e.g. rotational test)
Nystagmus waveform	Vestibular versus gaze paretic?
	Acquired versus congenital?
Confirmation of subtle abnormalities of diagnostic value (e.g. abnormal pursuit, subclinical? INO?)	
Quantification	Research and follow-up

OCULOGRAPHY TECHNIQUES

There are many techniques available and they all offer advantages and disadvantages. The two techniques usually available in ENT or audiology departments are electro-oculography (EOG) and video-oculography (VOG). These two techniques are relatively easy to set up, inexpensive, non-invasive and have a range of signal linearity of approximately ±20–30 degrees, capable of coping with the large eye movements encountered during vestibular tests in the dark. The main disadvantages are poor spatial (EOG) and temporal (VOG) resolution, but in the clinical vestibular setting these two techniques are the ones to be recommended (note that EOG and electronystagmography (ENG), are synonymous). An increasingly popular use of VOG is as part of the video head-impulse test (VHIT).

Infrared oculography and the scleral search coil technique may be found in specialized departments with an interest in eye movement disorders. Infrared oculography has a small range of linearity which is not suitable for the large movements observed during vestibular testing. The search coil system has the single but major disadvantage of being a semi-invasive procedure as it requires wearing a copper wire coil embedded in a plastic contact lens.

EOG or ENG

In this technique, surface electrodes, usually disposable, are glued around the orbit. Pairs of electrodes record the difference in potential between the cornea and the retina and, since the corneal region is positive and the retina negative, the eye becomes a dipole. Two electrodes placed at each side of the orbit, right–left for horizontal movements or above–below the orbit for vertical movements, will detect movement of this dipole. The usual configuration of electrodes for conventional vestibular testing is two electrodes, one at each external canthus ('bitemporal recording'). This gives a better signal-to-noise ratio because the recording taken is of an ideal 'cyclopean' eye. If the patient has clearly disconjugate eye movements or if the question is whether this patient has got an INO, then simultaneous separate

eye horizontal recordings are needed. Vertical eye recordings are taken only occasionally in the vestibular scenario; there are not many instances when they are required, and they are often dogged by blink artefacts. If the question is whether the patient has a vertical nystagmus, ophthalmoscopy, Frenzel glasses or video techniques are often more reliable. Major disadvantages are that EOG cannot record torsional eye movements and that many other biological potentials can be picked up with periocular electrodes as artefacts, such as electroencephalography or electromyography. The presence of drifts in the recording and low voltage potential in some ocular diseases indicates that EOG, although popular, is far from ideal.

VOG

Small video cameras can be mounted on goggles to obtain good quality images of the eye. Infrared cameras work in darkness and these images can be used to directly observe the presence of nystagmus in the absence of visual fixation (videonystagmoscopy). If the images are further processed, on- or offline, so that traces or measurements are obtained, the technique is called VOG. The main limitation of this technique as compared to EOG/ENG is temporal resolution. This depends on the sampling video rate, usually 50 Hz, i.e. a video image taken every 20 ms; the velocity of a saccade, which only lasts 50–100 ms, may not be reliably measured. Other types of eye movements, all much slower than saccades, can be confidently recorded but eyelid artefacts and occasional difficulties with the eye-tracking software are also troublesome. Most commercial VOG systems are two-dimensional (2D) (horizontal and vertical) but the more sophisticated are 3D and this offers the unique advantage of being able to non-invasively record torsional eye movements.

Routine EOG or VOG

Oculography can be carried out very selectively, for instance to see if a patient has normal or abnormal rotational responses, but often a battery of investigations are grouped in a 'routine' ENG or VOG. There are many variations to this routine but it essentially involves a search for spontaneous and gaze-evoked nystagmus, visually guided eye movements (pursuit, optokinetic and, if requested, separate eye saccadic velocities) and a vestibular test, namely caloric or rotational stimulation. Mostly, the analysis of the eye movement trace is carried out automatically or semi-automatically by computer; automatic artefact rejection is often suboptimal. The analysis is often collated by a technician who then produces a report to the physician or surgeon. There are therefore a number of possible weak links in the chain which can potentially mislead the clinician. I have seen many untenable diagnoses of 'central vestibular disorder' on the basis of artefactual ENG or poor-quality interpretation.

Since it makes no difference whether an abnormality is detected by direct clinical observation or by oculography, the various possible findings and their interpretation have already been discussed above. Herewith we will concentrate on any added value or new aspects of the examination that can be provided only by oculography.

SPONTANEOUS AND GAZE-EVOKED NYSTAGMUS

A spontaneous nystagmus present in primary gaze or evoked by eccentric gaze can have many different meanings. Features helpful to the differential diagnosis are the effect of visual fixation and waveform characteristics, to be discussed below. The plane (horizontal, vertical, torsional) of the nystagmus is also a critical feature but it is best decided on clinical grounds, unless high-performance 3D oculography is used. With the head upright, horizontal or horizontotorsional nystagmus can be peripheral or central but any other direction, namely torsional (unless in the Hallpike position) or vertical, in principle indicates CNS disorder. The reader is referred to specialized references for neurological nystagmus.[21, 22, 42]

Visual suppression

Nystagmus of peripheral vestibular origin is suppressed, sometimes completely abolished, by visual fixation. Thus, peripheral vestibular nystagmus increases in size and slow phase velocity in the absence of visual fixation, that is, in the dark or with Frenzel glasses (**Figure 62.4**). In contrast, central lesions usually damage pathways involved in the suppression of nystagmus (VOR suppression) and so the nystagmus enhances little, not at all or even diminishes in the dark. Thus the effect of darkness on nystagmus is an extremely useful aid to the differential between labyrinthine and neurological nystagmus (**Table 62.8**). This can also be carried out by direct inspection of the eyes behind Frenzel glasses or with modern commercial video cameras which have a standard inbuilt infrared lens ('handycams'). The search for nystagmus must be done in the primary position of the eyes and on gaze deviation right and left by 20 or 30 degrees. There are no hard rules but a nystagmus which is less than 2–3 degrees per second on gaze deviation in the dark is not significant. Significant nystagmus is not only induced by vestibular or CNS lesions but also by neuropharmacological agents and alcohol.

Nystagmus waveform

There are two basic types of waveforms. Saw-tooth or jerk nystagmus, intercalating a fast and a slow phase (see the examples in **Figures 62.2**, **62.3**, **62.4** and **62.5**), and pendular nystagmus, a quasi-sinusoidal waveform with no distinct fast phases (**Figure 62.19**). Jerk nystagmus can be peripheral or central; pendular nystagmus is always central, but not always ominous as it may be congenital or secondary to severe visual loss.

Due to the ability of the normal CNS to suppress nystagmus, the rule of thumb is any large amplitude nystagmus recorded in the light, particularly if it does not enhance in the dark, is of central origin. The exception could be an acutely ill vestibular patient (vestibular neuritis, attack of Ménière's disease). It is not appropriate to review the many types of neurological nystagmus in a general chapter

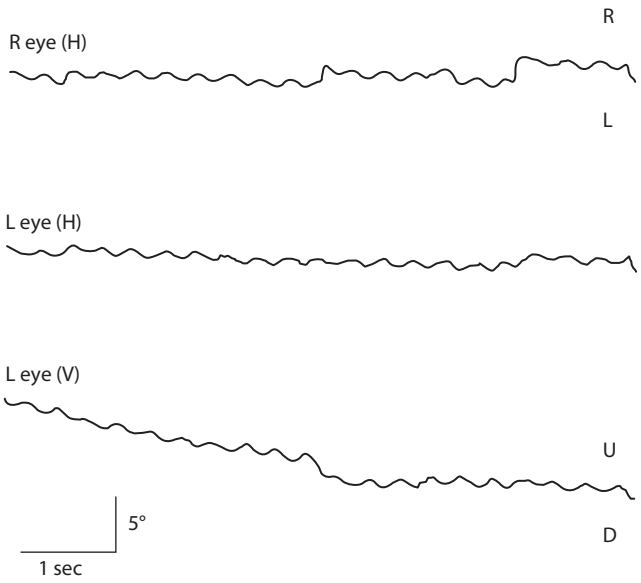


Figure 62.19 Pendular nystagmus in a patient with multiple sclerosis. The presence of simultaneous horizontal and vertical components, in this case in the left eye, produces complex movement trajectories (elliptical, 'banana'-shaped, circular). With kind permission from M. Gresty.

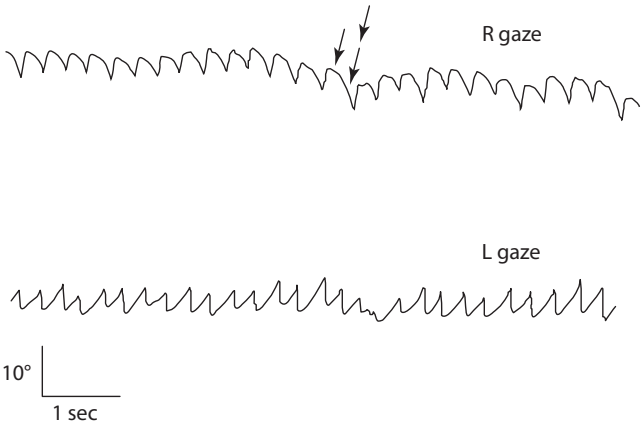


Figure 62.20 Exponentially increasing slow phase velocity in a patient with congenital nystagmus (CN).

TABLE 62.8 Differential diagnosis between central and peripheral nystagmus

Characteristic	Peripheral	Central
Plane	Hor or Hor > Tors	Any
Amplitude	Acute ++	++/+++
	Chronic +/–	++/+++
Fixation removal*	Appears/enhances	Variable (can diminish)
Waveform†	Rectilinear (jerky)	Exponential (jerky)
		Pendular

* By oculography, Frenzel glasses or fundoscopy in the dark.
† By oculography.
Hor, horizontal; Tors, torsional.

on the assessment of balance but it is worth mentioning some useful steps for the differential, peripheral versus central and acquired versus congenital nystagmus.

As mentioned under 'Clinical examination of eye movements' above, jerk nystagmus can be of peripheral or central origin. A jerk nystagmus of peripheral vestibular origin has a typically linear slow phase (Figure 62.4). Linear means that the velocity of the slow phase is constant and it is so because the magnitude of the velocity at rest is a direct measure of the vestibular tonus asymmetry. CNS lesions can also create a vestibular imbalance but they usually involve in addition central integrating mechanisms. This makes the slow phase of nystagmus to be non-linear, particularly during eccentric gaze, typically with an exponentially decreasing slow phase in velocity (Figure 62.5). A jerk nystagmus with a slow-phase velocity exponentially increasing (Figure 62.20), however, strongly suggests the diagnosis of congenital nystagmus, although some exceptions have been reported.[43] The diagnosis of pendular nystagmus is usually easy by simple clinical inspection and confirmed with recordings but establishing whether it is acquired or congenital is not possible on simple oculographic criteria. Patients with acquired pendular nystagmus usually have clinically severe vascular or demyelinating brainstem disease whereas patients with congenital pendular nystagmus have congenital or infantile visual loss and defects.

By way of summary (Table 62.8), a typical peripheral vestibular nystagmus is small in the light but increases amplitude in the dark and shows linear slow-phase velocity in the horizontal (or horizontotorsional) plane. It normally follows Alexander's law of increasing in magnitude when looking in the direction of the fast phase. Additional findings can be a caloric canal paresis (see under 'Caloric tests' below) or a positive head-impulse test contralateral to the beat direction of the fast phase, as in vestibular neuritis. Also, there should be no oculographic evidence of CNS lesion, namely visually guided eye movements should be normal.

VISUALLY GUIDED EYE MOVEMENTS

The clinical significance of abnormalities of pursuit, OKN, saccades and VOR suppression is the same whether documented clinically or by oculography. Recording very slow saccades or broken pursuits that have been definitely observed by the naked eye will not add anything to the diagnosis. Recording of mild abnormalities for confirmation of a questionable clinical abnormality is reasonable and, in addition, may provide a baseline for future comparisons on follow-up.

Saccades

Technical variations are unlimited but nowadays most oculography systems are computer-controlled. The target for saccades (or pursuit) can be projected, generated by rows of light emitting diodes (LED) or directly viewed on a computer screen. Unless specified, recordings are usually only conducted in the horizontal plane. For saccades, the target jumps to different locations and the latency (reaction time), velocity and accuracy of the saccade

is measured. Saccadic latency is a less important parameter for balance assessment. Since there is a fairly fixed relationship between the amplitude and the peak velocity of saccades (called the 'main sequence'), the results are often presented as an amplitude-velocity plot, with or without an exponential curve fitted (see **Figures 62.9** and **62.10**). The significance of slow and inaccurate saccades has been discussed above under 'Clinical examination of eye movements'.

Smooth pursuit

For smooth pursuit, the target slowly oscillates with a triangular or sinusoidal trajectory. Usually a range of frequencies and/or velocities are explored. Results are often expressed as 'gain', the ratio between peak velocity of the eye and peak target velocity. At low frequencies and velocities, say 0.10 Hz, peak target velocity 10 degrees per second, normal gain is close to unity. As frequency/velocity increases, gain values drop. In neurological patients, gain at a single frequency are lower than control, and the drop out occurs early. As discussed under 'Clinical examination of eye movements' above, abnormalities can be uni- or bilateral. The possibility that poor pursuit performance is just due to simple attentional factors is higher during laboratory than during clinical assessment, when the clinician can encourage and observe the patient directly. During all oculography procedures audiologists and technicians need to be trained to keep an eye on the patient's alertness, to recognize artefacts due to drowsiness and to urge patients to stay awake and cooperative.

Optokinetic nystagmus, particularly as elicited in the clinic with a small drum, is just a combination of pursuit and saccades. Large vestibular laboratories add a full-field encircling drum, covered in vertical black and white stripes, for OKN investigation, which is a more powerful stimulus. Whereas a peripheral vestibular asymmetry can occasionally bias small drum OKN, full-field OKN is never affected by a peripheral disorder (**Figure 62.21**).[44] As with all other visually driven eye movements, abnormalities are indicative of central disorder and can be uni- or bilateral (see under 'Clinical examination of eye movements' above). Although one often refers to asymmetries of OKN as directional preponderance (DP) of nystagmus, what matters is on which side the slow-phase velocity is subnormal. Thus, a left DP of OKN is due to the fact that the leftwards slow phase is subnormal; as a consistency check, the vast majority of patients should also have abnormal pursuit and VOR suppression during leftwards motion.

VESTIBULO-OCULAR REFLEX

In practice, there are three ways of assessing the VOR: clinically as discussed above, with caloric irrigation or with rotational stimuli. Electrical (galvanic) stimulation of the VOR has historical and experimental value. This will not be discussed here except to say that galvanic stimulation excites the VIII nerve afferents directly and this was occasionally used to distinguish if a caloric unresponsive ear was due to an VIII nerve lesion (absent galvanic response) or a labyrinthine lesion (present galvanic response).[45]

CALORIC TESTS

The principle of the caloric test is that changes in temperature in the external auditory canal influence the level of activity of the vestibular labyrinth. The caloric test is still the main test available to any clinician to assess individual-ear vestibular function whereas rotational tests stimulate both labyrinths simultaneously.

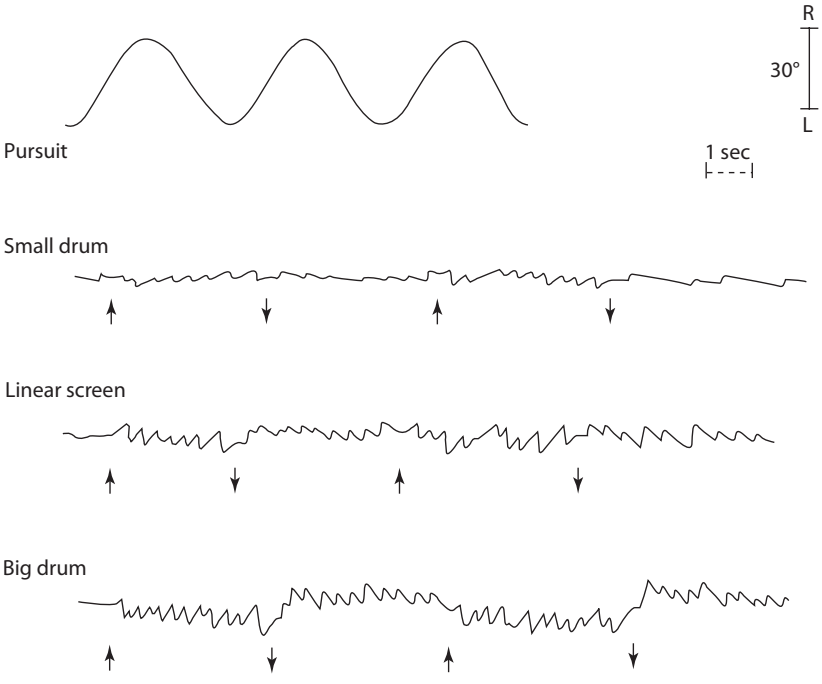


Figure 62.21 Pursuit and OKN in a patient with a right-sided acute peripheral vestibular lesion. Pursuit and big drum OKN are normal but minor directional preponderances (DPs) with the small drum can be observed in the acute phase (in this case to the left). Arrows represent drum or screen motion direction reversal. Reproduced with permission from Mossman et al.[44]

The disadvantages are that some patients cannot tolerate the caloric test (because of local discomfort or induced vertigo) and that disease or anatomical variability in the middle and external ear can preclude irrigation or interfere with the results.

To some extent, the mechanism of the caloric response is still debated. In order to obtain a satisfactory nystagmic response, the subject has to lie down with the head raised 30 degrees above horizontal. This places the horizontal semicircular canal in an approximately vertical position; the more lateral position of this canal leaves it more accessible to external temperature changes. The mechanism commonly invoked as responsible for the caloric nystagmic response is that the thermal change induces convection currents in the horizontal canal (when placed vertically) and thus cupular deflection. This hypothesis is strongly supported by the fact that, if the position of the subject during a caloric test is inverted (supine to prone), then the direction of the nystagmus reverses.[46] This is expected because the direction of the convection current will be reversed (note, convection currents occur in a gravitational field). However, the finding that a caloric response can be partly obtained in minimal gravity conditions, such as in the Space Lab mission, indicates that a direct thermal effect on the end organ is also present.[47]

Irrigation of the external auditory canal can be carried out with water or air. In the conventional procedure, two temperatures are used, one above and one below body temperature. Water irrigation at 30 °C and 44 °C (37 ± 7 °C) is the standard technique. In the original description by Fitzgerald and Hallpike,[48] the procedure follows the order left cold, right cold, left warm, right warm, for standardization purposes, with each irrigation lasting 40 seconds,[49] but this order is not essential. Temperature in the temporal bone has to be minimally stable before the next irrigation, so at least 5 minutes since the end of the previous irrigation has to be allowed for. Air irrigation offers the main advantage that it can be used in patients with eardrum perforations, but responses appear to be less consistent than with water. Technical modifications have improved this,[49] but insufficient patient data are available. If the surgeon needs to know whether there is any vestibular function at all in a perforated ear, then the answer is an air caloric test. For routine balance function assessment, water irrigation is preferred.

In the conventional testing position described above, cold irrigation induces horizontal nystagmus beating in the opposite direction of irrigation, and ipsilaterally during warm irrigation (cold-opposite-warm-same (COWS)). In this way, left cold and right warm irrigation induce right-beating nystagmus, and vice versa. Recording of the nystagmic response is usually carried out with EOG or VOG, often as part of a 'routine' computerized assessment. Measurements are taken of the velocity of the slow-phase component of the nystagmus and these are often displayed as a function of time. However, the original description by Fitzgerald and Hallpike is based on direct clinical measurement of the duration of the response and this technique is perfectly acceptable.

There are five main abnormalities of the caloric response.

1. Bilateral absence of caloric nystagmus, as in aminoglycoside ototoxicity or postmeningitis (see **Table 62.9**).
2. Unilateral canal paresis, a reduced/absent response from one ear, as in unilateral vestibular schwannoma or vestibular neuritis.[48, 50] Canal pareses can also be caused by a brainstem lesion in the VIII nerve root entry zone or vestibular nuclei but usually there will be other CNS symptoms or signs.[51]
3. DP, essentially an asymmetry in the VOR.[52] A right DP indicates that right-beating nystagmus is stronger, i.e. longer duration or faster slow-phase velocity according to the technique used, than left-beating nystagmus. A typical example is a patient with a, say, left vestibular neuritis. Initially the picture will be dominated by the complete left canal paresis and the spontaneous right-beating nystagmus. With time, all there may be left over is a right DP. Even if the caloric canal paresis does not recover at all, irrigation of the healthy right ear can show longer/stronger responses during warm irrigation (rightwards nystagmus) than cold irrigation (leftwards responses). Unfortunately, the finding of a DP in isolation is not specific and can be due to lesions ranging from the labyrinth to the cortex.[53, 54] One of the many possible visual representations used for canal paresis and DP is shown in **Figure 62.22**.
4. Abnormal VOR suppression. During caloric testing, VOR suppression is investigated in two possible ways.
   - With the conventional Fitzgerald and Hallpike technique the duration of the patient's nystagmus is directly timed in the presence of optic fixation. Once the nystagmic response has finished in the light the patient's eyes should be examined with either Frenzel glasses or an infrared viewer. In normal subjects or patients with peripheral vestibular disorders the caloric nystagmus then re-emerges. The duration of this nystagmus in the absence of optic fixation should be measured and the value compared to that obtained in the light.[56] Typically, a caloric nystagmic response in the light will last 80–160 seconds and this would be extended by 20–60 seconds without fixation. Values of less than 20 seconds may indicate loss of VOR suppression but this should be corroborated with clinical

TABLE 62.9 Causes of bilateral caloric hypofunction

Cause	Percentage (%)
Neurological (cerebellar degenerations, postmeningitis, neuropathies)	25
Ototoxic (usually gentamicin)	25
Miscellaneous (e.g. autoimmune, Ménière's, head trauma)	25
Idiopathic	25

Modified and simplified from Rinne et al.[9]

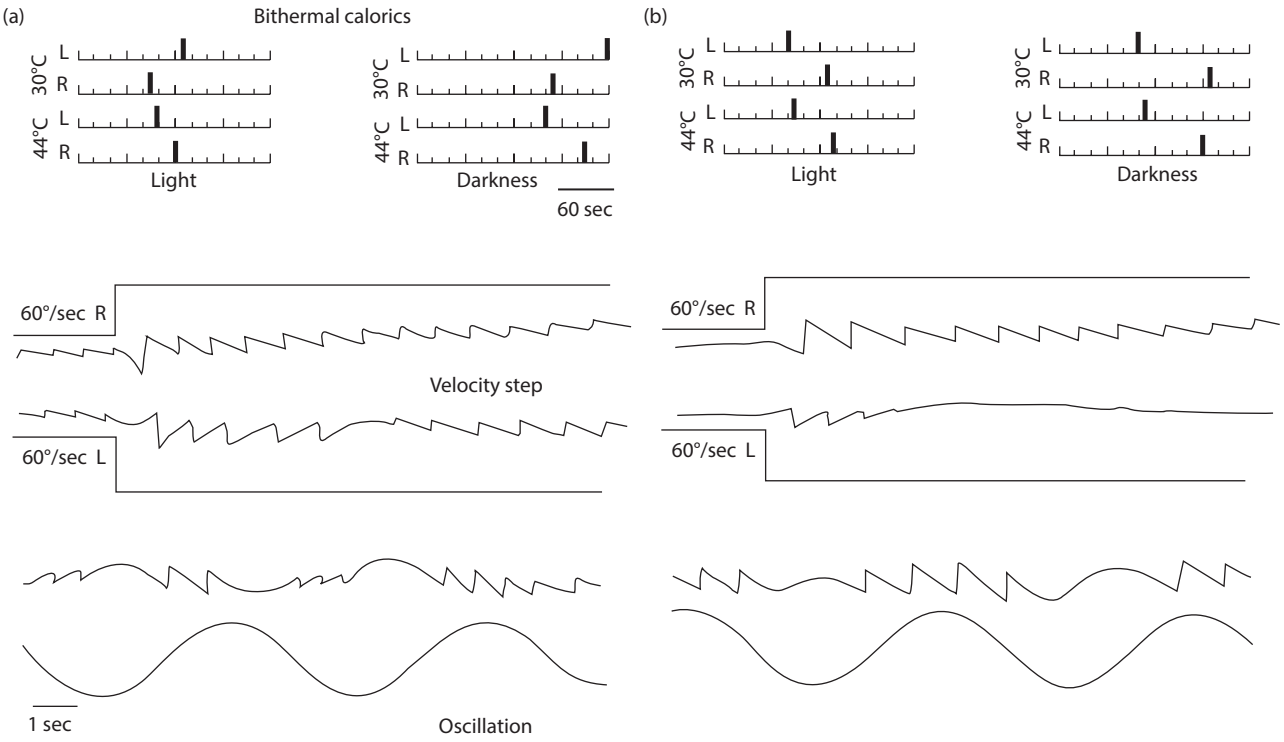


Figure 62.22 Caloric and rotational nystagmic patterns. (a) Right DP; **(b)** left canal paresis. Idealized recordings. Redrawn with permission from Bronstein et al.[55]

or rotational assessment of VOR suppression. It should be noted that subjects regularly exposed to intense vestibular stimulation may show little or no visible nystagmic response in the light but the response will be of normal magnitude without visual fixation. This can be observed in ballet dancers, acrobats, jet-fighter pilots and some patients with peripheral vestibular disorders with repetitive vertigo attacks.[57]

- VOR suppression is more often assessed by providing a fixation light for a period of 10–20 seconds in the middle of the caloric response. This requires ocular recordings and the results are expressed as the absolute or relative amount of reduction in slow phase velocity brought about by fixation. Results will depend, to some extent, at which point in time the fixation target is presented, but usually a reduction of approximately 50% is expected. With any technique, lack of VOR suppression indicates the presence of a central disorder of eye movement control, usually correlated with pursuit disorder, often of cerebellar/brainstem origin.[58]

5. Perverted nystagmus. This is the name given to the phenomenon whereby, instead of the expected caloric-induced horizontal nystagmus, one observes nystagmus in other planes, for example DBN (note, a minor torsional component added to the main horizontal nystagmus can be accepted as normal). If the caloric test is carried out pretty 'blindly', for instance with EOG in the dark, perverted nystagmus may be missed. However, perverted nystagmus rarely occurs in isolation, as it indicates posterior fossa disease, and other cerebellar or brainstem ocular signs should be seen.

ROTATIONAL TESTS

Most rotating chairs are motorized and computer-controlled so that velocity and rotational waveform can be delivered accurately. The patient's head should be comfortably immobilized, otherwise his own head movements interfere with the test and unwanted side effects, such as nausea, may develop. There are many velocity profiles used but here we will describe two of the more commonly used, velocity steps and sinusoidal oscillation (Figure 62.22). The more recently developed video head-impulse test will be described after the traditional rotational examination.

Velocity step or 'impulsive' rotational test

The stimulus consists of a sudden increase in chair velocity, say from 0 to 60 or 90 degrees per second. The time taken to reach this velocity, i.e. acceleration time, is of the order of 1–3 seconds.[48] Testing is conducted either in total darkness or with light-tight goggles. This elicits per-rotational nystagmus which slowly decays and eventually stops (if it does not stop the subject inadvertently may not be in total darkness). Full chair velocity is maintained for 60–90 seconds, or until any rotationally induced nystagmus disappears. At this point the chair is suddenly stopped and a similar nystagmic response, in the opposite direction, occurs (post-rotational nystagmus). The whole sequence

is then repeated in the opposite direction. Clockwise or rightwards rotation induces right-beating nystagmus (following the principle that the function of the VOR is to generate a slow-phase velocity in the opposite direction of head rotation); the stopping response is in this case a left-beating nystagmus.

As mentioned above, the nystagmus is of maximal intensity immediately after acceleration ('starting') or deceleration ('stopping') and then gradually (exponentially) decays. One can obtain time measurements of the response, such as duration of the nystagmus or time constant of decay of the slow phase velocity. In addition, the peak velocity of the slow phase component should be measured, which can be expressed as 'gain', the ratio between eye velocity and chair velocity. As with caloric testing, one assesses the overall level of activity and right–left response symmetry (DP) but normal values depend on stimulus parameters and laboratories.

I should like to mention that it is possible to obtain a semi-quantitative velocity-step assessment with an office swivel chair, to deliver rotation, and Frenzel glasses, to remove fixation. In this case, nystagmus duration is directly timed during the 'stopping response'. Stimulus velocity can be reasonably controlled by the examiner walking the chair round at a constant rate; for example, four steps per cycle (revolution) will deliver approximately 90 degrees per second and this should be maintained for 40–60 seconds and then suddenly stopped. Beware that you will be as dizzy as your patient, so plan your actions carefully!

Notice that, during rotation with the head in the normal upright position, or slightly tilted forwards to keep the lateral semicircular canals in the horizontal plane, the nystagmus will be almost exclusively horizontal. If the head were to be tilted backwards as much as possible, (e.g. the patient's face pointing up), the vertical semicircular canals (anterior and posterior) will now be placed in the plane of rotation. On stopping the chair the nystagmus observed is mostly torsional and so, timing its duration, assesses the function of the vertical canals *en bloc* (right and left, superior and inferior canals). Placing the head obliquely down to the left stimulates the left anterior–right posterior (LARP plane) semicircular canals; rotating with the head obliquely down to the right stimulates the right anterior–left posterior (RALP plane) canals. In order to fully assess vertical canal function accurately, however, one requires sophisticated 3D oculography and precision positioning of the head in a 3D rotating device.[59] The 3D VHIT can assess high acceleration function of all six canals with relatively simple and inexpensive technology (see below). However, it is not clear how much vertical canal testing adds to the day-to-day diagnosis and management of vestibular patients.

In summary, the 'impulsive' rotational test has been successful in practice since Barany's days. It has the advantage that it can be administered in a relatively short period of time, it is reproducible and is less affected by the patient's mental status than sinusoidal testing.

Sinusoidal rotation

In this test the velocity of the chair is sinusoidally modulated (**Figure 62.22**, bottom). Usually, a range of frequencies are used from approximately 0.05 Hz to 1 Hz, while the peak velocity of the stimulus is kept constant. This arrangement has the effect that acceleration increases progressively. A problem with this test is that a gentle oscillation in the dark is soporific and too predictable. Patients can be drowsy, giving responses difficult to interpret, or produce responses which are influenced by prediction and therefore look more normal than they really are. In order to avoid these complications, stimuli combining sinusoids of various frequencies in a random or pseudo-random fashion have been developed; these are effective but complicated software is required.

The results are usually expressed as gain (slow-phase eye velocity/chair velocity) and phase (the difference in degrees between maxima and minima of the chair and eye velocity waveforms), both plotted as a function of stimulus frequency. As in other vestibular tests, one examines the overall strength of the vestibular response, in this case as gain, and degree of asymmetry both as gain and phase. Unfortunately, variability is large from subject to subject and within the same subject due to concentration and mental set, both in health and disease.

The gain of the VOR in the light is, as mentioned earlier, close to unity. The test is normally conducted in the dark where normal gains at middle frequencies are between 0.4 and 0.8 but these values are only indicative; normal data should be collected under strict conditions, including mental tasks (e.g. mental arithmetic or imaginary targets). Indicative values of asymmetry should be larger than 20–30%, the lower gain and larger phase error occurring during the hemicycle with rotation towards the side of the vestibular lesion.

Although frequently used in research, in the clinic the sinusoidal test has problems with result variability and the time required for appropriate testing. An advantage is that it is an easy and reliable way of assessing VOR suppression by comparing gain values in the dark and those obtained during rotation with a chair-fixed target.

Interpretation of rotational results

Regardless of the technique, there are three main abnormalities of rotational responses.

1. Bilateral reduction or absence of response, as in bilateral vestibular failure, for instance due to ototoxicity, postmeningitis and idiopathic.[9]
2. Asymmetry, or DP, which if considerable (say >30%) is a valuable indicator of vestibular system disorder but, unfortunately, not a good localizing sign per se. However, an isolated DP is often the only 'objective' finding in a balance disorder patient. In the absence of any central vestibular or oculomotor disorder, it is supporting evidence in favour of a peripheral vestibular disorder but specificity and sensitivity data are lacking.

3. Loss of VOR suppression, investigated by providing a chair-fixed target during part of the rotation, indicative of central disorder (see 'Vestibulo-ocular reflex suppression' above).

VIDEO HEAD-IMPULSE TEST

In the last few years, computerized, video-based versions of the head-impulse test have appeared in the market. The physiological principle has been explained above but a head motion sensor and a VOG system records the head and eye velocity response. This makes detection of the corrective 'catch-up' saccades described above (see 'Vestibulo-ocular reflex' and 'Head-impulse test' above) easier, more objective and quantitative; the gain of the vestibulo-ocular response (peak eye velocity/peak head velocity) is also measured (Figure 62.23). At the same time, like with any automated analysis system, the possibility of recording and wrongly measuring undesirable artefacts such as blinks also increases. Therefore, the clinician should carefully compare his/her own findings during the clinical head-impulse test (HIT) with the results of the VHIT. As with other vestibular tests, the VHIT can detect uni- and bilateral loss of vestibular function (both by a low gain and by the presence of catch-up saccades). In contrast to conventional rotational tests, the side of the hypofunction can be reliably detected with VHIT but the level of agreement with the 'gold standard' caloric test is not great, particularly in chronic, compensated lesions. In many cases, particularly if there is clinical –VHIT discrepancy, a caloric test is warranted. Discrepancies will not always be due to technical problems though. The VHIT tests the VOR at high frequencies/accelerations of the head (a head impulse lasts 0.5 seconds = 2 Hz) whereas a caloric response lasting 2 minutes can be converted thus: 1/120 seconds = 0.008 Hz! Hence selective or preferential

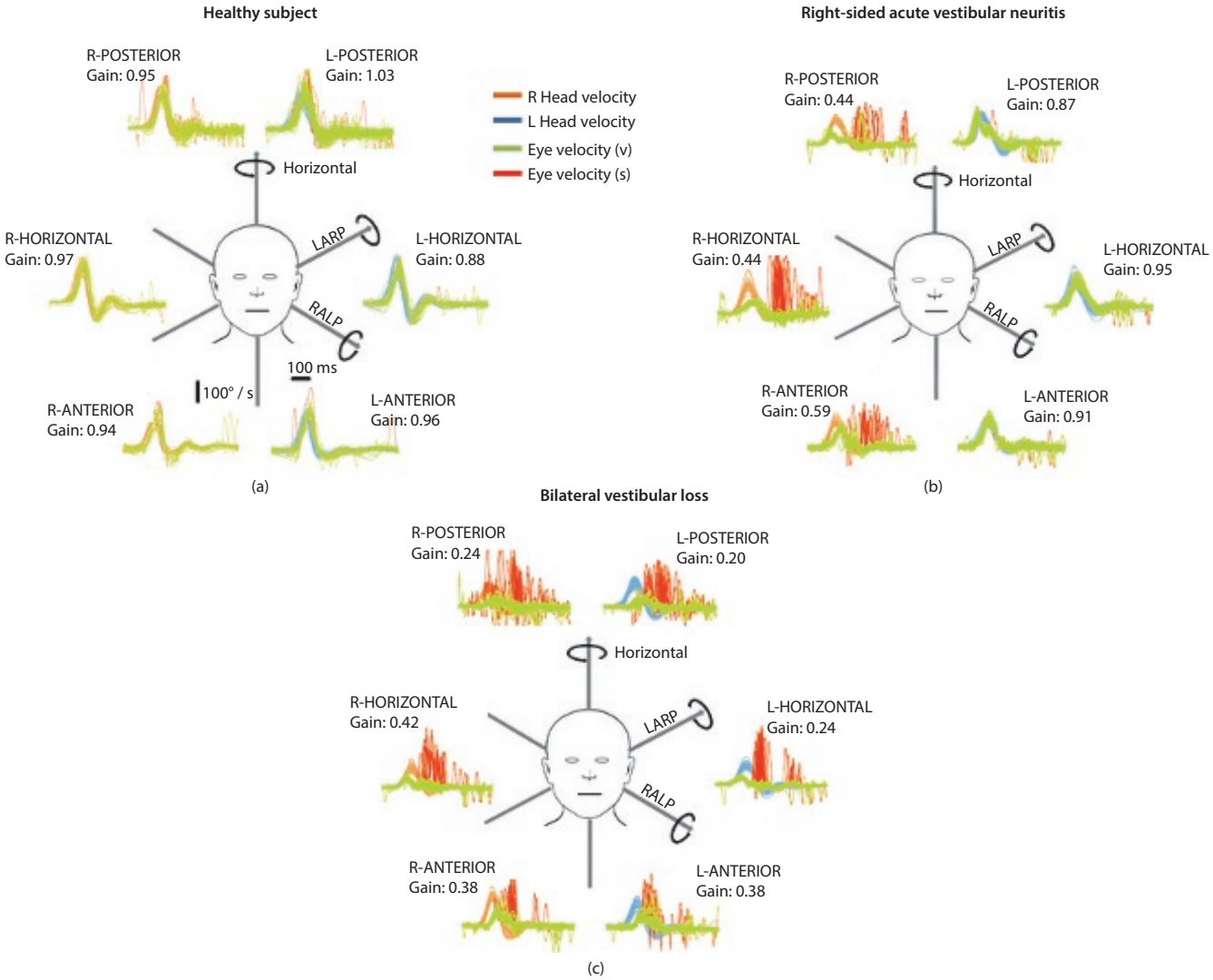


Figure 62.23 **(a)** A normal healthy subject, with gain values close to unity for all six canals and no 'catch-up' saccades. **(b)** A patient with neuritis of the right superior and inferior vestibular nerve showing reduced gain (close to 0.5) and many catch-up saccades (spiky traces). **(c)** Results in a patient with bilateral vestibular failure, showing low gains (0.2–0.4) in all six canals. Reproduced from Bronstein et al.,[37] with permission.

involvement of the high- or low-frequency VOR would produce selective abnormality in one but not the other test.

Several factors have contributed to the success of the VHIT, despite the fact that both the clinical HIT[60] and the VHIT are relatively new tool in diagnosis.[61] In contrast to rotating devices, VHIT systems are relatively cheap and take much less space than rotating chairs. Testing time is also shorter than a routine EOG/VOG rotational or caloric assessment and, usually, better tolerated by the patient even if all six canals are being assessed. Finally, the timing is also right. Acute vertigo has become 'fashionable' again given the need to separate acute vertigo due to vestibular neuritis from posterior fossa stroke, which requires thrombolytic treatment within 3–4 hours of vertigo onset. As mentioned already, in this scenario the clinical or video HIT can be critical in separating a unilateral peripheral vestibular deficit (likely vestibular neuritis – no thrombolysis needed) from brainstem–cerebellar ischemic stroke (thrombolysis often provided). Despite this success, most users and scientists using VHIT devices with no conflict of interest do not believe that this new development has replaced or will replace caloric testing in the near future.

Examination of postural balance

The investigation of postural balance is influenced by the clinician's own background. More research using posturography comes from ENT or audiology departments than from neurology ones,[30, 31] which could mean that ORL specialists see more dizzy patients than other specialists. It could also mean that neurologists tend to rely on their own clinical assessment of posture and gait, which is understandable since almost all neurological diseases impair gait and posture. Regardless of the clinician's background, the value of direct clinical observation of gait and posture in patients with unsteadiness cannot be overemphasized. I will first summarize the clinical examination of posture and gait and then address the contribution of posturography.

CLINICAL EXAMINATION OF BALANCE, POSTURE AND GAIT

Gait unsteadiness is associated with a wide range of disorders.[55] If it has never been associated with vertigo, dizziness, oscillopsia or hearing disorder, it is unlikely to be due to vestibular disease.[62] It is important to realize, however, that patients with mild gait disorders often describe their problem as dizziness and therefore do turn up in ENT and neuro-otology clinics.

It is usually possible to establish a topographical diagnosis (site of lesion) in a gait disorder on the basis of clinical observation of gait and a neurological examination (Tables 62.10 and 62.11).[63–65]

It is beyond the scope of this chapter to describe the many diseases with gait disorder. However, the aspects required when examining a patient with gait unsteadiness listed in Table 62.11 will be reviewed.

TABLE 62.10 Topographical classification of gait abnormalities

Level of abnormality	Topographical classification
Lower levels	Peripheral lesions: mono/polyneuropathies, root lesions and myopathies Vestibular and visual lesions
Medium levels	Spinal and brainstem lesions
Higher levels	Cerebellar syndromes
	Subcortical disorders (basal ganglia and internal capsule): Parkinson's disease, orthostatic tremor, choreas and corticospinal tract lesions
Highest levels	Frontal lesions of the cerebral cortex, white matter in the semioval centre and periventricular area (vascular, degenerative diseases, demyelinating, tumours and hydrocephalus) Cautious gait and psychogenic gait disorders

Modified from Dominguez and Bronstein,[63] Nutt et al.,[64] Marsden and Thompson.[65]

TABLE 62.11 Examination of posture and gait

Aspect	Examination
Posture	Head and neck Trunk Stance and Romberg test Postural reflexes
Walking	Step initiation Stepping pattern Associated trunk and arm movements Eyes closed walking
Neurological and relevant skeletal examination	

Modified from Dominguez and Bronstein.[63]

Posture

Observation of head and trunk posture can provide immediate useful information. There are abnormal tilts or rotations in dystonia, flexed posture in Parkinson's disease, hyperextension in progressive supranuclear palsy (PSP) and titubation in cerebellar disease. In lesions of the vestibular nuclei, as in the lateral medullary (Wallenberg) syndrome, there can be an ipsilesional ear-down head tilt, together with a skew eye deviation (ipsilesional lower eye) and ipsilesional body pulsion.

Observation of stance will reveal a broadening of the base of support in diffuse vascular disease, frontal lesions, cerebellar lesions, sensory ataxia, acute or bilateral vestibular lesions and patients with a cautious gait. Lateropulsion can be seen in acute unilateral peripheral vestibular lesions and in lateralized brainstem–cerebellar lesions. Midline brainstem–cerebellar lesions can show retropulsion. Minor degrees of unsteadiness can be brought about by asking the patient to put the feet together or in the heel-to-toe position. A 'bouncy' stance, with head-trunk oscillations about 2–3 Hz, may be observed in ataxic or ataxic–spastic disorders, typically in

multiple sclerosis. A shaky 'tremulous' stance, with higher-frequency oscillations, can be seen in some patients with Parkinson's disease and orthostatic tremor.

The Romberg test, originally described for patients with tabes dorsalis, is positive in patients with dorsal column or severe afferent polyneuropathy. A positive Romberg means that the patient shows a tendency to actually fall, unlike normal subjects and almost all patients with balance problems who show a small to moderate increase in body sway on eye closure. Only in the acute phase of a peripheral vestibular disorder will the Romberg test be positive, usually with an ipsilesional fall. In a patient with either cerebellar degeneration or polyneuropathy, a high level of unsteadiness on eye closure may indicate the presence of additional bilateral vestibular failure.[9] This syndrome has been named CANVAS (cerebellar atrophy, neuropathy, vestibular arreflexia syndrome).[66] Patients with anterior lobe cerebellar degeneration may show the characteristic trunk oscillation or titubation only on eye closure; when mild, this may just be visible as a tremor of the ankle extensors ('dancing tendons'). On a practical note, anyone who can stand on either foot unaided, with eyes closed, is unlikely to have any objective and organic postural balance problem.

Postural reflexes are an important part of the balance examination, particularly when the patient's dizziness cannot be explained in vestibular terms. They are examined by gently pushing and pulling the upper trunk. This can be carried out by standing behind the patient so he/she cannot anticipate the precise timing and direction of the push (forwards or backwards) to the shoulders. In akinetic syndromes, these responses may be completely absent – such as in Parkinson's disease, PSP and small vessel white matter disease with or without parkinsonism – patients falling rigidly like a log. A few shuffling steps backwards (retropulsion) or forwards can be seen in the early stages. In cerebellar syndromes, particularly anterior lobe disease, the trunk pushes may unmask a trunk titubation, observable as a 'trunk rebound' in response to the push. In the elderly, with fear of falling or a cautious gait, trunk pushes trigger a startle, panic-like response. Vestibular patients may be unsteady but the overall pattern of the response is preserved.

Walking

Step initiation can be impaired in frontal lesions, including the gait ignition failure syndrome[64, 65] and as part of the akinesia in the Parkinsonian syndromes. Initiation of gait is hesitant, the feet appearing to be stuck to the ground ('magnetic feet'; 'slipping clutch' phenomenon).

The steady-state stepping pattern may be less disturbed in patients with difficulty in step initiation, once they are off. In akinetic-rigid, Parkinsonian syndromes steps are often shallow, short and slow but with preserved rhythm. In contrast, cerebellar patients show irregular rhythm, variable length, oscillations and a wide base, giving a lurching, 'drunken' appearance to their walking. Patients with severe loss of sensory information from the lower limbs (sensory ataxia) lift the feet high and place them on the ground under intense visual control; in dorsal column lesions the heels strike the ground first (tabetic gait), in cases with ankle extensor weakness (foot drop) the toes make contact first (steppage). In spasticity, the knee-extensor and ankle-flexor hypertonus leads to the characteristic slow gait with circumduction movements of the leg during the swing phase.

The normal associated movements of the arms while walking are lost in Parkinson's disease. Unilateral loss of arm swing can be a useful early sign in Parkinson's disease and hemiparesis. The arms of patients with a cautious gait reach out as if expecting to fall and step with apparently unnecessary care, giving the appearance of 'walking on ice'. Although a cautious gait can be part of a psychogenic gait disorder, it can be triggered by a vestibular, vascular or falling episode. Sometimes this is the only finding in elderly patients.

Walking with eyes closed in a straight line can reveal a previously unsuspected degree of unsteadiness or a cautious gait in patients with bilateral loss of vestibular function. In somatosensory ataxia this task is often impossible. In unilateral vestibular lesions, particularly in the acute stage, patients veer in the same direction as the lesion. A paradoxical improvement while walking fast has been reported in acute vestibular lesions.[67] In the Unterberger test, instead of walking along, the patient is asked to walk on the spot with the eyes closed. In unilateral vestibular lesions the patient turns towards the hypoactive side. It is helpful to ask the patient to keep the arms and index fingers pointing forwards towards the examiner's index fingers; this allows a more precise assessment of the degree and consistency of turning (**Figure 62.24**).

Figure 62.24 The 'stepping on the spot' or Unterberger test. Lining up of the examiner and patient's fingers is useful to document mild abnormalities when the patient steps with the eyes closed. Repetition of the test, for consistency, is essential.

Summary of the relevant neurological examination

We present a summary of the neurological examination relevant to balance and gait disorders, in the hope that it may guide the non-neurologist who suspects a neurological cause for unsteadiness or gait disorder. Weakness of the legs can be documented by asking the patient to push against the examiner's hands with different muscle groups or by asking the patient to stand/walk on tiptoes or heels, crouch and rise. Identification of weakness of the ankle extensors is paramount as these muscles are responsible for toe clearance during the swing phase of the gait cycle. Lower-limb weakness is a major contributor to the gait disorder in muscle, root and peripheral nerve disease, motorneurone and corticospinal tract disease; the tendon jerks will be exaggerated in pyramidal tract disease and depressed or absent in all the others; extensor cutaneous plantar responses (Babinski sign) can be found in pyramidal lesions.

Normal somatosensory function is needed for voluntary placing of the feet while walking, as well as for the proprioceptive reflexes controlling upright posture. At least pinprick, tuning fork and joint position sense must be examined in the lower limbs. If large fibres carrying proprioceptive input are involved, the ankle and sometimes patella jerks will be absent and the Romberg test will be positive.

Gait disorders due to neurological involvement at medium or high levels (see **Table 62.10**) will have associated clinical neurological features. In spinal cord compression or lesions there is often sphincter dysfunction and sensory disturbances in the limbs. At brainstem level, cranial nerve involvement including central vestibular and ocular–motor disorders; at cerebellar level, trunk titubation, intentional tremor, abnormal eye movements including nystagmus; at basal ganglia level, Parkinsonian features (including tremor, cogwheel rigidity, hypomimia, bradikinesia, loss of postural reflexes) dystonic limb or neck posturing and choreoathetosis.

It is important to keep in mind the unabated weight of the clinical neurological examination in the assessment of balance and gait disorders. Observation of gait, postural reflexes and the Romberg test followed, if appropriate, by a quick examination of lower limb power, coordination, reflexes and tuning fork are likely to help more than posturography. Normal CT and MRI scans are extremely valuable but do not exclude neurological disease (e.g. Parkinson's disease) and posturography findings usually lack topographical and aetiological specificity. Functional (psychogenic) disorders can only be diagnosed on the basis of an inconsistent or theatrical gait pattern, in a patient with essentially normal findings. Finally, particularly in the elderly, examination of the skeletal and cardiovascular examination or referral may hold the key to the cause of balance or dizzy symptoms. Cardiovascular syncope is a major cause for unexplained dizzy spells and falls in the elderly, regardless of whether the patient reports loss of consciousness or not.[68, 69]

Posturography

Strictly speaking, posturography is any means of recording postural activity, not only sway or force platforms which are indeed the most convenient way. In fact, 'sway' platforms do not actually measure body sway but foot torque (Nm), conveniently expressed as movement of the centre of foot pressure (cm). For standard clinical purposes, platform signals alone are acceptable but research questions often require additional recordings such as photoelectrical or electromagnetic recordings of head sway, accelerometry of head or trunk motion and EMG signals from the lower limbs. If the patient just stands quietly on the platform, with eyes open or closed, the procedure is called static posturography. When additional balance perturbations or stimuli are added (e.g. moving platform, visual stimuli, muscle vibration), it is called dynamic posturography.

Three general questions can be asked in this area.

1. Has posturography advanced the knowledge of how the postural systems work?
2. Has posturography taught us how posture is impaired in certain patient groups?
3. Does posturography help in the management of an individual patient complaining of a balance problem?

The answer to the first two questions is certainly yes, but opinions are divided as to the third.

Posturography has been useful in defining the contribution of the different sensory-motor components in postural control. The first attempts to generate a comprehensive system approach to postural control were led by Nashner and coworkers.[70–73] They suggested that postural balance is maintained on the basis of a limited repertoire of centrally generated muscle synergies. During slight perturbations to balance, the body behaves essentially as an inverted pendulum, pivoting around the ankle joints. Muscular responses are organized in a distal-to-proximal manner, with activation of distal muscles such as tibialis anterior and soleus occurring earlier than proximal ones; this is the 'ankle strategy'. Larger perturbations to balance, or lesser possibility of response such as when standing on a narrow beam, leads to movements around the hip joints and earlier activation of proximal muscles, such as abdominal, paraspinalis, quadriceps and hamstrings; this was called the 'hip strategy'.

The posturography system designed by Nashner consists of a support platform and a visual surround which can be moved angularly about an approximate inter-ankle axis. This setting allows for the ankle and visual information available to the subject to be, at least partly, neutralized by means of coupling the visual surround or the support surface to the AP sway movements of the subject. This set-up formed the basis of the commercial product 'Equitest', a computerized dynamic posturography (CDP) system, in particular, a testing protocol known as the sensory organization test. If patients with vestibular deficits are allowed to stand freely on this system, they show little

or no difficulty if the platform is stationary, with normal visual information (e.g. stable surrounds) or with eyes closed. When either or both the platform and visual surround are sway coupled, patients have poor balance performance.[74, 75] When presented in a historical context, the findings in vestibular patients seem trivial. Clinicians have known for decades that vestibular patients are usually normal in static conditions and that the way to unveil their unsteadiness is to examine them with eyes closed under conditions of reduced proprioceptive accuracy (e.g. on a mattress – reviewed in Martin).[76]

POSTUROGRAPHY IN PERIPHERAL VESTIBULAR DISORDERS

Clinical observation of patients with severe acute, unilateral vestibular disorders (e.g. vestibular neuritis) shows that they tend to fall towards the side of the lesion on eye closure – i.e. in the direction of the slow phase of nystagmus.[77] This can be documented by posturography but with little practical clinical benefit for the individual patient. In the compensated state, static posturography with eyes open or closed is usually normal. CDP shows increased sway, in conditions in which the support surface, the visual surroundings or both simultaneously are unstable (sway referenced). In some early series, 100% of patients have been reported abnormal when both visual surround and support surface are sway referenced,[75] in others this figure drops to around 50%.[78] In a small but carefully controlled series, ten patients with severe unilateral caloric reduction were abnormal when tested in the acute stage only under unstable support/visual surroundings.[79] Within 2 weeks, all patients regained total normality in all test conditions. The reasons for these discrepancies are not clear but the inability to confirm the earlier optimistic reports is one of the reasons underlying the current disaffection with the technique.

What clinicians want to know is what the added value of posturography is, in comparison with traditional testing of the vestibular system. A comparison between posturography and the caloric test showed that the caloric test correlates better with a history of vertigo and that CDP can show abnormalities in patients with normal caloric function.[80] This finding can be interpreted essentially in two ways: either posturography is capable of detecting abnormalities that caloric tests cannot (which it can – think of a spinal cord lesion or Parkinson's disease as a cause of unsteadiness) or posturography can give false positive results. There is no simple solution to this problem and, as outlined above, the clinician's beliefs, training background and interests will influence his decision.

A similar problem arises when comparing CDP with inexpensive alternatives. To a large extent, the sophistication of the commercially available CDP systems comes from the fact that the support surface and the visual surround can be moved. Clinical observation of a subject's balance while standing on rubber foam (which makes lower limb proprioceptive input inaccurate) and with either optically reversing goggles or a Chinese lamp (dome) on their head (which makes visual input unreliable) makes a reasonable, inexpensive approximation to CDP. This is sometimes called the 'clinical test of sensory integration and balance' or simply the 'foam and dome' test (**Figure 62.25**). A study compared CDP with its clinical counterpart and found an excellent correlation between the two sets of results.[81] This is good news to clinicians, particularly in rehabilitation, who may want to assess postural control thoroughly but are not prepared to make a large investment. Another comparison between results in moving-platform posturography and clinical analysis of posture with subjects standing on foam also reported significant correlation, with sensitivity and specificity of 90% and above.[82] Surprisingly, static posturography has been reported to have a good predictive value to help in identifying elderly subjects at risk of falls.[83]

Bilateral vestibular lesions are easily diagnosed clinically and with conventional laboratory tests – an audiogram is a much more helpful test by comparison. Posturography in these patients has limited value in diagnosis but studies have been of interest in defining the contribution of the vestibular system to postural control. Static posturography is normal in most patients with bilateral vestibular failure.[84, 85] It has been known for more than 70 years[76, 86, 87] that a sudden tilt, particularly if the patient is on a mattress and blindfolded, throws these patients off balance. This observation has been confirmed with dynamic posturography, including the fact that rotation of the base of support is more effective than translation in unmasking the postural deficit.[88, 89] Although patients tend to use more hip strategy,[89] latencies and muscle synergies are not essentially different from normal. EMG amplitudes in lower limb musculature are reduced by more than 50% during platform tilts and this may explain why they actually fall.[90–92] If the postural responses to movements of the support surface are indeed centrally patterned, these findings indicate that vestibular input is essential for adequate gain setting of early muscular components operating at 80–120 ms.[92] The alternative explanation that independent vestibulospinal or vestibuloreticulospinal pathways mediates the observed effects is equally possible and compatible with known latencies following direct vestibular activation.[93, 94] Answering this question is difficult with whole-body postural responses, as investigated by posturography. However, isolated motion stimuli to the head showed delayed neck responses[95] in bilateral vestibular patients, indicating that short latency vestibulocollic responses (about 25 ms) have a specific role in righting the head during sudden perturbations.[93]

POSTUROGRAPHY IN NEUROLOGICAL DISORDERS

As already emphasized, it would be naive to think that a posturography assessment could screen for a neurological deficit. Even if results were abnormal, the topographical and etiological specificity of the finding would be very low.

Patients with peripheral neuropathy have increased sway and this correlates with the loss of vibration sense in the lower limbs.[96–99]

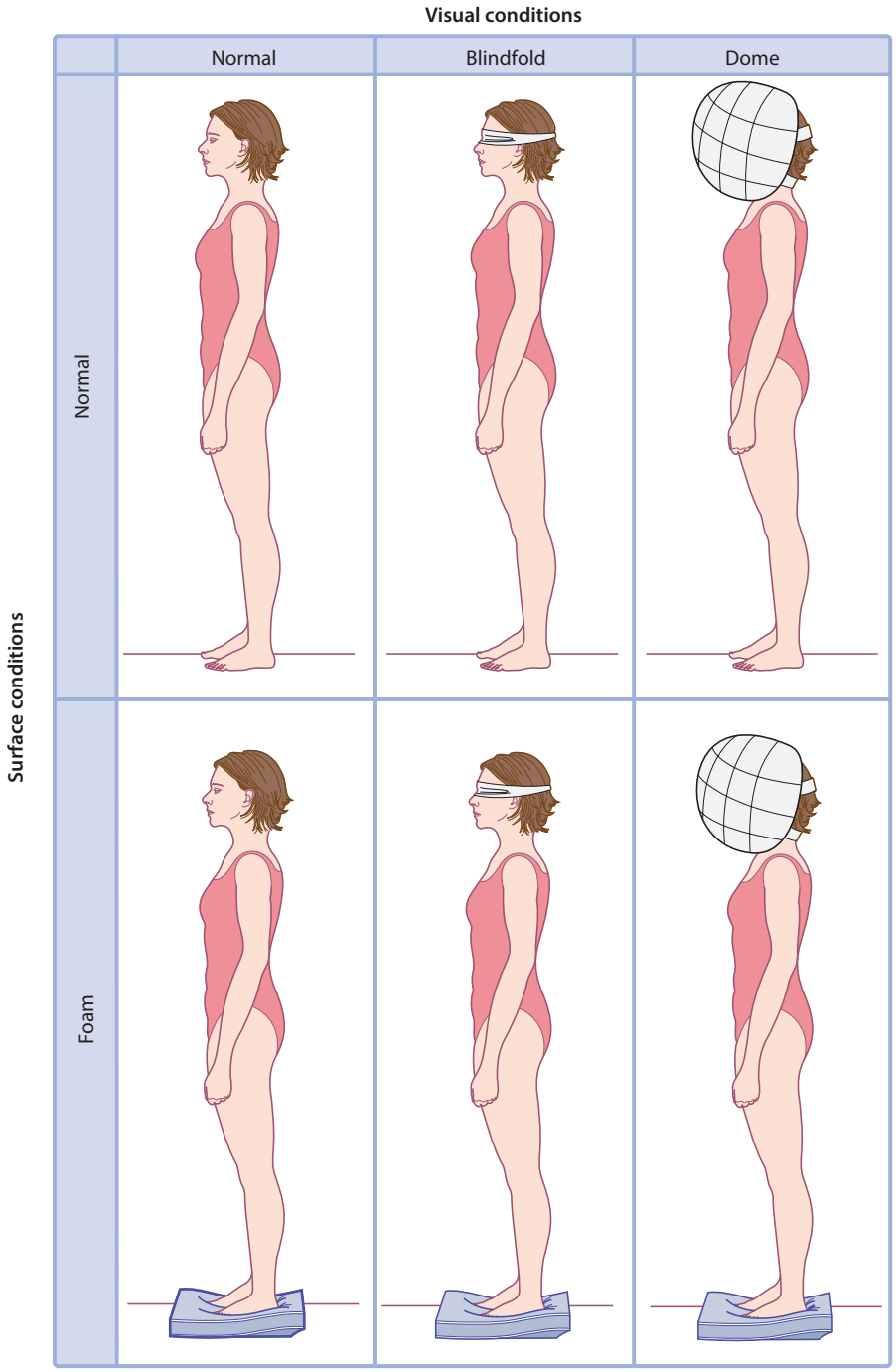


Figure 62.25 The 'foam and dome' test. The six testing conditions (visual 3 × support 2) correspond approximately to those of computerized dynamic posturography (CDP) as in the Equitest. Redrawn with permission from Pavlou et al. in Bronstein et al.[55]

The balance disorder in cerebellar disease is due to loss of muscle coordination,[100] central modulation of vestibular and somatosensory mechanisms,[101] neural adaptation to vestibular loss[102] and recalibration and learning processes.[103] On the basis of comparisons between lateral versus anteroposterior sway, eyes closed versus eyes open (EC/EO or Romberg quotient) and the frequencies of sway involved, four cerebellar sway patterns can be identified.[104] Perhaps the single most useful finding is the presence of a body tremor at approximately 3 Hz in patients with anterior lobe degeneration, either alcohol-induced or degenerative. In clinical practice, however, this tremor can be detected clinically and the value of posturography in its diagnosis has been questioned.[105]

The commonest basal ganglia disorder is Parkinson's disease and approximately one-third of patients report falls.[106] Falls, however, are not common in the early phases of conventional, idiopathic Parkinson's disease, in contrast to other 'parkinsonisms' such as PSP (Steele–Richardson–Olszewski syndrome).[107] Despite the

significant contribution made by posturography to the understanding of the postural disorder in Parkinson's disease,[108–112] there is very little room for the technique in the management of patients. Of possible diagnostic interest is the fact that in some patients the tremor is recorded by the platform,[108] in which case frequency analysis will show a peak of tremor activity at frequencies between 4 and 6 Hz, well beyond those of body sway (<1–2 Hz). Other conditions with unsteadiness and high-frequency peaks in posturography recordings include some cerebellar ataxias, with a 3 Hz tremor discussed before,[104, 113] and orthostatic tremor.[114, 115] Orthostatic tremor is a relatively rare disorder, usually misdiagnosed as a psychogenic balance problem, but platform recordings can easily identify the pathognomonic high-frequency tremor, typically at 16 Hz (**Figure 62.26**). During platform fore–aft motion postural reflexes are elicited and the stepping responses in parkinsonian patients are usually abnormal (hypometric and multiple stepped)[116] but, again, for the clinician the simple trunk pulls described above are equally useful.

PSYCHOPHYSIOLOGICAL UNSTEADINESS

Some patients report dizziness in surroundings with intense visual motion or repetitive visual patterns, such as driving, supermarkets, crowds, disco lights or ironing striped shirts. We use the term 'visual vertigo' or visually induced dizziness to describe these patients, when there is clinical and/or laboratory evidence of a vestibular lesion without clinically obvious psychiatric disorder.[117] Such patients are 'visually dependent', in that they rely excessively on visual cues for spatial orientation and postural control. Visual motion or optokinetic stimuli makes them selectively unsteady,[5] particularly if the vestibular disorder is central or if there is additional strabismus.[117] Posturographic and perceptual measures of visual dependence are correlated, albeit weakly, and this is important because identification of visual dependence helps in the selection of appropriate vestibular rehabilitation. This may also be identified with CDP, or its clinical version, the 'foam and dome' test, during testing conditions with sway-referenced visual surroundings. However, simple questionnaires[118] are equally useful to identify visually susceptible patients who are likely to benefit from additional optokinetic stimulation during vestibular rehabilitation.

PSYCHOLOGICAL UNSTEADINESS

The relationship between psychological disorders and balance is extremely complex. Anxiety can create dizziness and vice versa and there is no easy solution to this common 'chicken and egg' clinical dilemma.

Both vestibular[119] and anxiety patients[118] show increased sway in response to visual motion. Patients with panic and agoraphobia also show excessive sensitivity to platform or visual surround motion.[120] It has also been reported that posturography can identify inconsistent and incoherent responses in patients with non-organic dizziness.[121–123] An increase in sway frequencies of up to 8 Hz has also been reported in some patients with psychogenic unsteadiness.[124]

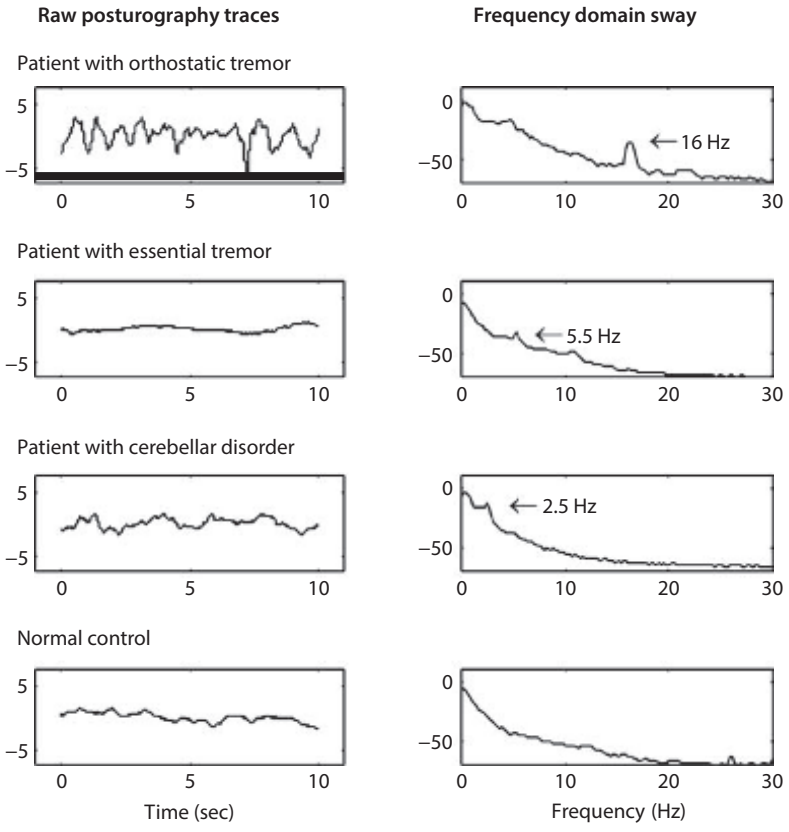


Figure 62.26 Fast Fourier analysis of posturography platform signals in patients with tremolous or 'shaky' stance. Reproduced with permission from Yarrow et al.,[115] with permission from Elsevier.

However, clinicians should rely on a constellation of negative findings (neurological, vestibular and imaging) and positive malingering or conversive (functional) features, as well as an appropriate psychological profile before making such a diagnosis.[125]

SUMMARY OF POSTUROGRAPHY

In summary, there is debate as to the clinical usefulness of posturography for the day-to-day management of patients.[126–129] A report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology remains a good and objective introduction to the topic for non-subspecialized clinicians.[130] The specialist panel concluded in 1993 that dynamic posturography had a promising role in the assessment of balance disorders patients. The ensuing discussion 25 years later testifies that such potential has not been fully developed. I am only able to make only one definite diagnosis with posturography, orthostatic tremor, but this is a rare condition. Similarly good specificity is also seen with the 3 Hz body postural tremor in certain cerebellar lesions, but the tremor is also observed clinically.[105]

The rationale behind clinical posturography is that it tests postural control as a whole, with the various sensory inputs interacting in physiological ways and mimicking potential real-life challenges to upright balance. This is its strength and its weakness at the same time, the latter because of its lack of topographic specificity. The findings of a meta-analysis of posturography indicates that its overall sensitivity and specificity is of the order of 50%.[131] As expected, the diagnostic power was enhanced if patients with CNS lesions were included in the studies surveyed, but this is of little consolation since there are much better ways of diagnosing CNS disease than posturography. It is often said that posturography can be useful for rehabilitation, and indeed posturography has been instrumental in proving the value of vestibular rehabilitation.[132, 133] However, the daily problem in neuro-otology is the patient who is not objectively unsteady, but still reports off-balance sensations and dizziness. Whether posturography has anything to add to simple questionnaire assessment of symptoms remains an open question.

OTOLITH AND PERCEPTUAL ASSESSMENT

Otolith and perceptual assessment tests will be discussed briefly because they are currently evolving and are rarely available as a routine test in clinical departments. We will briefly describe linear acceleration tests of otolith function but vestibulo-evoked myogenic potential (VEMPs, ocular and cervical) are thought to be of otolithic origin and so they will be mentioned in this section as well. Perceptual tests of vestibular function, with an emphasis on the procedure known as the subjective visual vertical (SVV), will follow.

Otolith testing

LINEAR ACCELERATION TESTS

The otoliths are selectively stimulated by linear acceleration, including gravity.[134] Due to their morphology and curved trajectory of the polarization vectors of the hair cells, both the utricular and saccular maculae are sensitive to multiple axes of linear acceleration. The predominantly horizontal orientation of the utricules, however, makes them mostly sensitive to accelerations in this plane (i.e. right–left, fore–aft) or tilt away from this plane. The predominantly (para) sagittal orientation of the sacculi makes them more sensitive to sagittal plane tilt (pitch tilt) and acceleration (e.g. fore–aft, rostrocaudal). One should remember that linear acceleration is also generated during rotatory motion (centrifugal and tangential acceleration) and this has been recently exploited in the field of otolith testing. Here, I will present the general principles of otolith testing and the reader interested in any individual technique should pursue the original references.

Otolith testing is technically challenging. The generation of pure linear acceleration of sufficient magnitude (>0.2 g) under controlled conditions requires motorized sleds running on precision tracks (**Figure 62.27c**). Although a linear acceleration version of the head-impulse test, the clinical head heave test can provide information on the utricular–ocular reflex,[135] but this has not been validated against quantitative techniques.

Centrifugal and tangential accelerations can be generated with rotating devices but these have to be powerful and sturdy to carry the weight of a human subject placed eccentrically from the rotational axis. Perhaps the simpler way to obtain tangential acceleration of the head and stimulate otolith–ocular reflexes is to make the subject lean forwards onto an eccentric chin- or headrest, while seated on a conventional rotating chair (head-eccentric rotation).[136, 137] Following this principle, one can also rotate a person around an earth-vertical axis passing through one of the labyrinths, thus creating a centred labyrinth and an eccentric labyrinth. Only the latter is subjected to tangential and centrifugal acceleration and this test is the only test capable of providing information on each individual utricle (eccentric centrifugation).[138, 139]

Another way of obtaining controlled stimulation of the otolith is to rotate the subject about an axis which is tilted (off-vertical axis rotation (OVAR)) or orthogonal ('barbeque-spit rotation') with respect to the gravitational vector; in these tests the stimulus is provided by the continuous reorientation of the head with respect to gravity.[140, 141] It is important to note that, whenever the linear acceleration is generated by rotation, the otolith response is assessed either by subtracting the component due to angular motion (e.g. subtracting head-eccentric response from head-centred response, in the head-eccentric test) or by waiting until the angular VOR has ceased (e.g. in OVAR or BBQ rotation). Finally, a simple way of stimulating the otoliths is head tilt with respect to gravity. This can be refined with

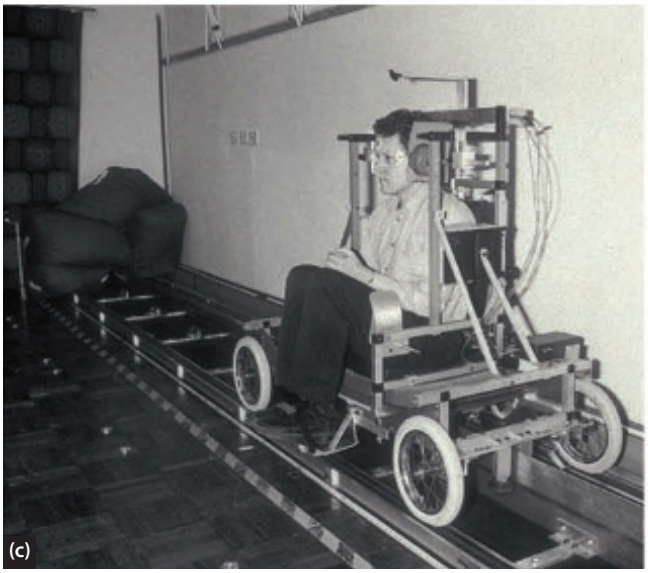


Figure 62.27 Otolith testing devices I. (a,b) Ocular counter-rolling measured by 3D VOG during body tilt. **(c)** Oculography (in this case conventional horizontal EOG) during lateral linear acceleration.

precision gimbals systems (**Figures 62.27a** and **b**).[142] A summary of the stimulation techniques for otolith assessment is presented in **Figures 62.27**, **62.28** and **62.29**.

What can be measured to assess otolith function? The more common measure is the slow-phase eye movement response, called linear or translational VOR or, more generally, otolith–ocular reflexes.[143] Recording of eye movements during otolith testing also poses technical problems. The forces involved usually generate more movement artefact than during conventional rotational or caloric procedures. In addition, the relatively small size of the otolith–ocular response, coupled with the fact that an important component of the otolith response is ocular torsion (not recorded by EOG or conventional VOG), often requires 3D oculography (VOG or search-coil technique).[138] Another response, which can be measured during linear acceleration, particularly in centrifugal tests,[144] is the SVV which largely follows ocular torsional position (see 'Subjective visual vertical' below).[145]

Difficulties in testing the otoliths are not only technical. The orientation of the hair cells is such that a single utricle (or sacculus) is capable of sensing linear accelerations in all directions. Thus, deficits due to unilateral otolith lesions are usually only acute and transient. For instance, the horizontal otolith–ocular reflex in response to interaural linear acceleration remains abnormally asymmetric for

Figure 62.28 Otolith testing devices II. These techniques can be used with relatively minor modifications of a conventional rotating chair. Comparison of **(a)** head-centred and **(b)** head-eccentric horizontal eye movements, during horizontal rotation. [136, 137] Otolith stimulation is provided by the tangential acceleration present during head-eccentric oscillation. **(c)** Off-vertical axis rotation (OVAR). Otolith stimulation is due to head reorientation with respect to gravity during rotation.

only approximately 4 weeks after a unilateral vestibular nerve section.[143] Torsional and visual vertical deficits may be unmasked during eccentric centrifugation.[138, 144]

In summary, there are many tests of otolith function and most have been validated in patients with acute vestibular lesions (spontaneous or surgical). Such lesions are not selective and destroy not only the otoliths but large parts of the vestibular labyrinth. In such circumstances there is little clinical doubt that a patient has sustained unilateral vestibular damage and so documenting otolith involvement in such cases is just a research exercise. The challenge of devising a test of otolith function in a patient who lacks independent evidence of vestibular lesion still remains. Currently, there is no validated test to confirm that a patient has a selective otolith lesion. Claims that the SVV is a selective test of otolith function[3, 146] have not been scientifically

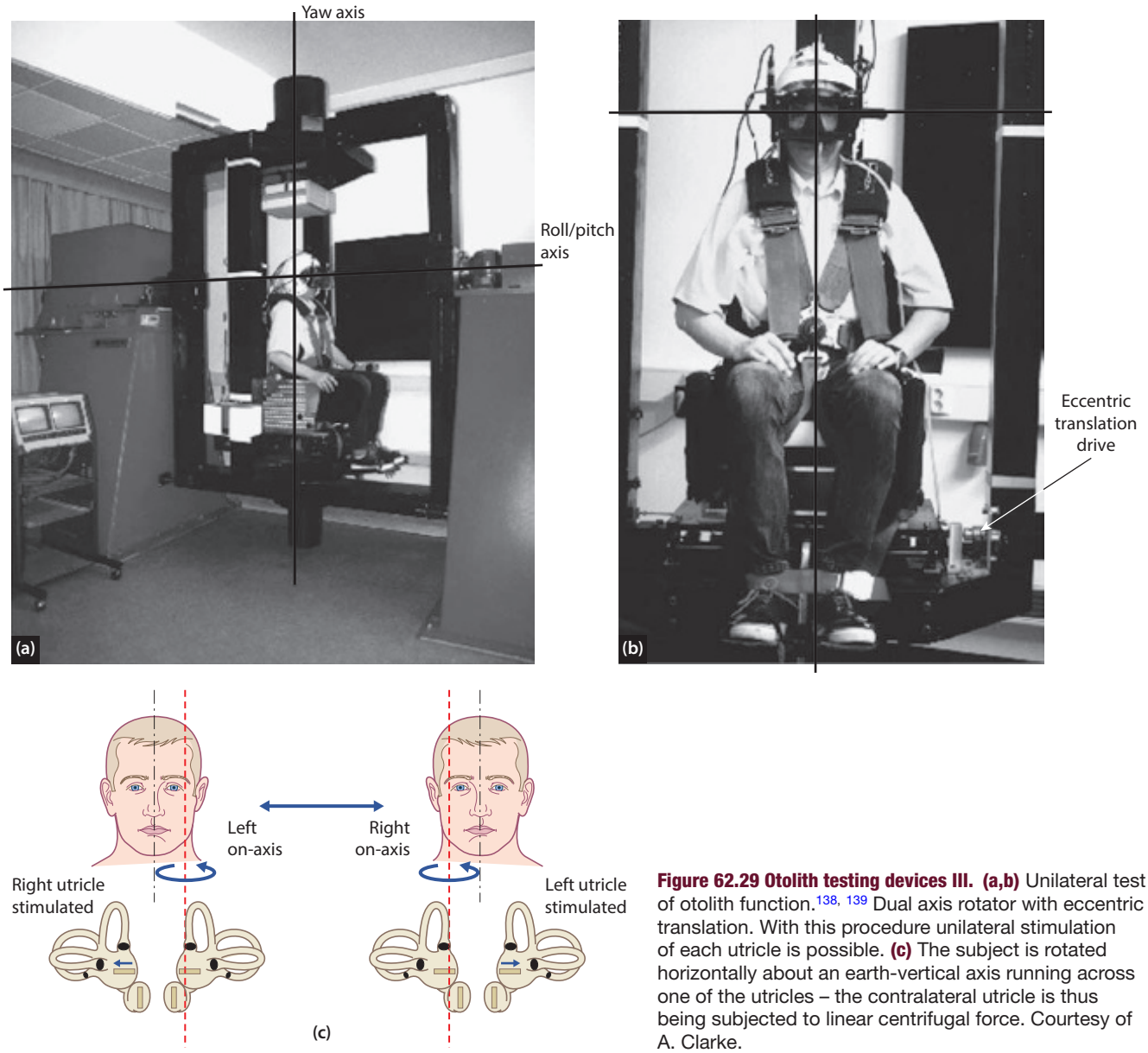


Figure 62.29 Otolith testing devices III. (a,b) Unilateral test of otolith function.[138, 139] Dual axis rotator with eccentric translation. With this procedure unilateral stimulation of each utricle is possible. **(c)** The subject is rotated horizontally about an earth-vertical axis running across one of the utricles – the contralateral utricle is thus being subjected to linear centrifugal force. Courtesy of A. Clarke.

validated. Furthermore, this view has been seriously challenged on the basis of clear experimental evidence showing that vertical semicircular canal input also induces tilt of the visual vertical.[147]

VESTIBULAR-EVOKED MYOGENIC POTENTIALS

Loud sounds can activate the vestibular labyrinth. If these sounds are brief in duration (clicks), the total amount of energy delivered to the ear is small and the procedure harmless. Using averaging techniques similar to those in brainstem auditory evoked potentials, an electromyographic (EMG) potential can be identified from neck muscles.[148, 149] The response is a sound-evoked vestibulocollic (or vestibulospinal) reflex and this is often called the cervical vestibular-evoked myogenic potential (cVEMP). The technique can be easily set up in any clinical neurophysiology or audiology department with access to calibrated sound generators, averaging equipment and surface recording electrodes and several devices are available commercially.

A useful feature of this procedure is that it can investigate each ear separately. The main response is an ipsilateral positive deflection at 13 ms (P13) and a negative deflection at approximately 23 ms (N23). Conductive deafness, by obstructing the clicks reaching the labyrinth, interfere or abolish the reponse, so auralscopy and a pure-tone audiogram are necessary if the response is absent. However, as expected from a genuine vestibular response, vestibular-sparing, sensorineural deafness does not interfere per se with the cEVMP. All available evidence indicates that the main inner ear structure activated by sound is the sacculus, so cEVMP can be considered an otolith test.[150]

Clinical applications of this test are developing. The main practical diagnostic use is for the diagnosis of the superior semicircular canal dehiscence syndrome, or more generally

the Tullio phenomenon.[149] These patients have lower threshold, higher amplitude potentials from the symptomatic ear only, even when the radiological abnormality is bilateral. (It is worth noting that, although useful, this test is not essential for diagnosis as, in most of these patients, one can usually see torsional nystagmus by naked eye or video-techniques in response to loud sounds or Valsalva manoeuvres.) The mechanism as to why a presumed saccular potential has abnormally high sensitivity in a superior semicircular canal syndrome is not exactly understood.

Clinical evidence suggests that the afferent fibres of this reflex travel in the inferior vestibular nerve. Patients with acute vestibular neuritis and absent caloric and cEVMP do not develop secondary BPPV.[151] This suggests that the absent cEVMP indicates loss of inferior vestibular nerve afferents which carry the macular fibres from the posterior semicircular canal; a deafferented posterior canal cannot produce symptoms of BPPV. Halmagyi et al. reported two patients with acute vertigo, normal lateral semicircular canal function but selective loss of posterior semicircular canal function as shown by absent cEVMP[53] suggestive of selective inferior nerve vestibular neuritis.

More recently, short-latency ocular EMG potentials recorded with periorbital surface electrodes in response to air-conducted sound and bone vibration have been elicited, which have been called ocular VEMPs (oVEMPs).[152] They are thought to represent a crossed excitatory utriculo-ocular response, hence a functional test of the superior vestibular nerve (as opposed to cVEMPs – inferior nerve). Ocular VEMPs can also be enhanced and show low thresholds in patients with superior canal dehiscence[153] but overall their clinical applicability has not yet gained wide support.[154]

Ideally, one would like to think that absent VEMPs would imply a selective, probably otolithic abnormality in a given patient with a vestibular-sounding history of dizziness but normal clinical and laboratory examination. Unfortunately, this does not seem to be the case and the meaning of an isolated VEMP abnormality is unclear, particularly in patients older than 40 years of age.[155] In patients with acoustic neuromas, however, an abnormal VEMP can occasionally be the only vestibular finding.[156]

PERCEPTUAL AND SUBJECTIVE VERTICAL TESTING

Perceptual tests of vestibular function were in use well before oculography came along with the advancement of electronics in the 1950s. Perceptual tests have underwent a revival in the last 20 years once the vestibular community realized that vestibulo-ocular test results often do not correlate well with patients' symptoms. The VOR is a simple reflex but a patient is a complex human being. It was therefore felt that assessment of how a patient perceives vestibular sensation may be more clinically relevant than oculography. Although the principle is sound, perceptual tests do not replace, but rather complement, eye movement tests, as oculography provides a more objective measure of vestibular function. In patients with long-standing blindness or eye movement disorders such as congenital nystagmus or chronic external ophthalmoplegia, perceptual tests are the only vestibular tests possible.

The simplest perceptual test is to ask the patient to compare subjectively the quality and intensity of the vestibular sensation for right and left stimuli. The stimuli can be the ones used in routine vestibular tests. Extremely useful information can be gained from simply asking a patient with a large congenital nystagmus or a complete ophthalmoplegia if they experience vertigo from caloric irrigation on both ears. The information can be improved by timing the duration of the vertigo or asking the patient to consider the subjectively better ear as 100%, and then estimate how much the other ear's vertigo is reduced. No formal normative data are available for this test but I personally give weight when a patient says that one ear is down 50% or more. (Note that most patients wrongly believe that the 'sick' ear is the one producing more, not less, vertigo!) In the appropriate clinical context this information can help in the diagnosis of a dizzy patient, specifically when they suffer from pre-existing visual or oculomotor disorders.

Even in patients undergoing conventional eye movement tests of vestibular function, enquiring about the quality of the sensation experienced during the caloric or rotational test can be extremely useful. One must not forget that a fundamental problem in the clinic is finding out if a patient's complaint of dizziness is of vestibular origin or not. In this scenario, a patient's equating the calorically elicited sensation to that of his own dizzy spells brings in considerable support for a diagnosis of vestibular disorder and, vice versa, when a patient says that his own dizziness does not resemble at all the caloric-induced vertigo.

Before the advent of EOG, the main quantitative vestibular perceptual test was cupulometry.[157] This test consists of measuring the duration of the postrotational sensation to a range of velocities, so that the sensitivity and time constant of decay of the sensation could be measured. The procedure could also be conducted with direct observation of the nystagmus with Frenzel glasses. In either case, the procedure took far too long to complete, was tiring for the subject and is no longer in use.

We have developed specific quantitative perceptual testing protocols, measuring either perceived displacement or velocity, to investigate vestibular function in patients with congenital nystagmus,[158] external ophthalmoplegia[159] or in selective semicircular canal lesions.[160] A useful aspect of these perceptual tests is that they can be conducted with the head placed in different positions, thus providing potentially useful information on vertical canal function.

SUBJECTIVE VISUAL VERTICAL

Intuitively, the perception of verticality must relate to the otoliths since these are linear acceleration/gravity sensors. However, one can easily conclude that one is lying sideways by the unambiguous asymmetry in pressure/contact cues between the two sides of the body, and/or by seeing that all buildings or trees appear to be tilted to our eyes. These examples illustrate that the perception of verticality is mediated not only by vestibular but also by proprioceptive and visual inputs.

In the clinical setting, the test of verticality more commonly used is the subjective visual vertical (SVV). The technique is easy, low cost, simple and reliable; examples include a system simply based on a bucket[161] and a laptop-based system with free download.[162] Essentially, a subject sits in front of an adjustable straight luminous line (**Figure 62.30**). The line may be viewed either in the dark or against a verticality cue-free background (e.g. all white or covered in dots). The subject's task is to set the line to what he/she thinks is real (gravitational) vertical. Normal subjects are quite accurate, all settings being within 1–2 degrees of real vertical.[163] The line can be either remotely controlled by the subject or an assistant adjusts the line according to the subject's instructions.

Initial excitement with this test was justified as vestibular lesions produce definite abnormalities of the SVV. Acute unilateral peripheral vestibular lesions produce tilt of the subject's SVV settings ipsilaterally.[141] Initially, in the acute stage, the tilt is of the order of 8–10 degrees but gradually disappears within a few months as compensation develops.[145]

Vestibular brainstem lesions cause larger and longer-lasting SVV tilts.[164, 165] Lesions involving the vestibular nuclei create ipsilateral SVV tilt (usually with an ocular-tilt reaction or skew eye deviation with the lower eye ipsilesional). Lesions in the upper brainstem induce contralateral SVV tilts and skew deviations with the upper eye ipsilesional, indicating a central vestibular pathway decussation at pontine level. Initially, these findings were thought to represent a global disruption of verticality perception due to an otholitic asymmetry. However, brainstem lesion patients with large tilts of the SVV usually show normal perception of verticality to other modalities, such as the haptic or tactile vertical or the perception of whole-body verticality (subjective postural vertical).[166, 167] Furthermore, 3D oculography has demonstrated an almost one-to-one correlation between torsional eye position measurements and SVV tilts.[145] Therefore, all evidence indicates that, for most, the tilt of the SVV is secondary to torsional VOR bias (i.e. ocular tilt), not a primary perceptual defect.

So long as the ocular torsional tilt (and usually associated skew) were due to an otolith–ocular pathway asymmetry, the SVV would still be useful as a simple test of otolith function. However, experimental studies have shown that sustained ocular torsion, skew deviation and SVV tilts can all be induced by pure stimulation of the vertical semicircular canals.[6, 147, 168] To summarize, SVV tilts of labyrinthine or brainstem origin can be taken to indicate an imbalance in the torsional ocular system. Claims of any specificity to otolith function (peripheral or central) are not tenable but a combined otolith–vertical canal effect is more likely.

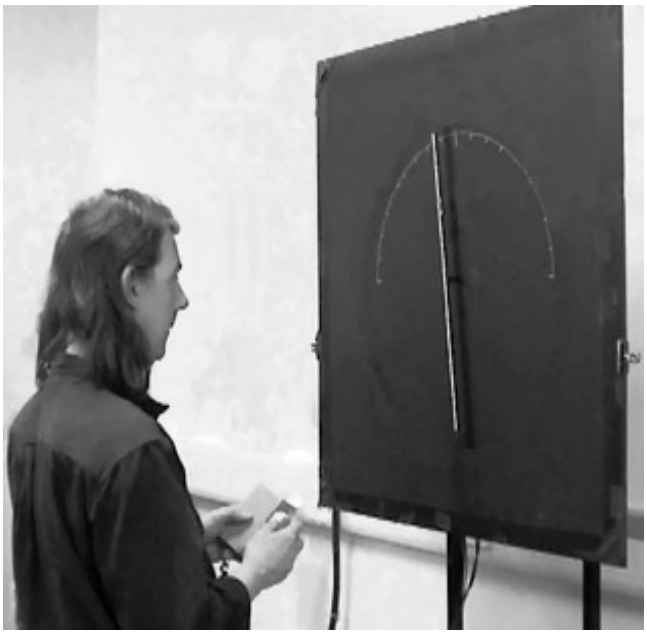


Figure 62.30 Measurement of the subjective visual vertical (SVV).

Hemisphere lesions can also induce tilts of the SVV but the magnitude is smaller; when the tilt is large, this is due to involvement of mesodiencephalic subcortical areas.[164, 165] The polarity is also variable. Interpretation of a cortical tilt is further confounded by the fact that proprioceptive input can also influence the SVV.[169] It is safer at this stage to consider any SVV tilt of cortical origin as due to disruption of central multisensory integration rather than to involvement of central vestibular pathways.[170] An extreme example of cortically induced tilt of all modalities of verticality perception (visual and postural) is seen in some stroke patients who develop the 'pusher syndrome'.[171] These patients 'push' themselves in the direction of their hemiparesis in order to align their body with the perceived tilted gravitational vector complicating the rehabilitation process. The subjective postural vertical can be measured with whole-body tilt devices of the type shown in **Figure 62.27a** and **b**[166] but this is only carried out for research purposes.

FUTURE RESEARCH

- Despite the fact that vertigo, dizziness and imbalance can comprise up to a fifth of all ENT and neurology patients, the problem is not taken seriously. This situation will get worse as population age increases, and further research in the area of dizziness in the elderly is required.
- Very few clinicians make the effort to cross the border between ENT and neurology, and more interdisciplinary centres are required.
- Few attempts are being made at classifying vestibular disorders on the basis of scientific evidence but the Bárány Society is currently attempting this.
- Further research is needed into laboratory diagnostic tools; studies comparing diagnostic efficiency are lacking. Pressures from equipment manufacturers on clinicians with little time for serious thoughts on the subject complicate matters further.
- More vertigo specialists in emergency departments are also needed to differentiate benign causes of vertigo from posterior circulation stroke, which often requires thrombolytic treatment acutely.
- Neuro-otologists should educate their peers, showing that understanding dizziness is not difficult and does not necessarily involve complex laboratory testing but good clinical skills.

KEY POINTS

- History taking remains the main approach for diagnosis of a patient with balance disorder.
- Rotational vertigo indicates semicircular canal system involvement, but the lesion can lie anywhere between the labyrinth and the cortex.
- Dizziness, giddiness and off-balance feelings can also indicate vestibular disease but care needs to be exercised as they may reflect a general medical condition, oscillopsia, gait disorder or psychological problems.
- Establish if there are additional aural or neurological symptoms and whether the vertigo/dizziness is acute, episodic or chronic.
- In patients with episodic vertigo always consider migraine.
- ENT and neurological examination is important but peripheral vestibular patients may only have signs in the acute phase of a disorder.
- Think 'stroke' in patients with acute vertigo. If the nystagmus is horizontal and unidirectional, there are no central symptoms/signs or deafness and the head-impulse test is positive, it is likely to be vestibular neuritis.
- So, you are interested in neuro-otology? If you are an ENT person, persuade a neurologist to work with you. If you are a neurologist persuade an ENT person. Both ENT and neurologists have to persuade an enthusiastic audiologist and/or physiotherapist to join the team.
- Cervical vertigo, if it exists, and vertebrobasilar insufficiency are grossly overdiagnosed. Always consider that dizziness on head–neck movements may be due to a vestibular disorder and do a Hallpike manoeuvre.
- Careful eye movement examination has two main aims: (i) detect any nystagmus, (ii) rule out CNS disease, since central vestibular disorders show additional abnormalities of pursuit, VOR suppression or saccades.
- Only a minority of patients require formal oculography for diagnosis.
- Caloric testing is cheap, efficient and examines one ear at a time. You do not need oculography to carry out caloric tests. The video head-impulse test (VHIT) is useful to detect canal paresis but it does not replace the caloric examination.
- Clinical assessment of posture and gait is a vital part of the examination. It is cheaper and better than posturography.
- There is no simple and clinically reliable way of testing the otolith system.
- Vestibular-evoked myogenic potentials (VEMPs) test otolith function but paradoxically they are most useful to detect superior canal dehiscence, a semicircular canal abnormality.

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CHAPTER 63

MÉNIÈRE'S DISEASE

Vincent W.F.M. Van Rompaey

SEARCH STRATEGY

Data in this chapter may be updated by a search on Medline and the Cochrane Database of Systematic Reviews using the keywords Ménière's disease and endolymphatic hydrops.

INTRODUCTION

Ménière's disease is an idiopathic inner ear disorder characterized by recurrent spontaneous vertigo accompanied by fluctuating or progressive sensorineural hearing loss, tinnitus and aural fullness in the affected ear.[1] Of all audiovestibular symptoms, the vertigo episodes are experienced as the most incapacitating.[2]

The histopathological correlate is highly linked to endolymphatic hydrops, a finding which is not pathognomonic to Ménière's disease, but more likely a marker for overall disordered inner-ear homeostasis. Ménière's disease is, by definition, the idiopathic type of endolymphatic hydrops. A clear differentiation is made with the secondary type presenting a similar clustering of symptoms (which is called Ménière's syndrome) caused by, for example, syphilis, trauma, autoimmune disorders. Because Ménière's disease is an idiopathic condition lacking a gold standard for diagnosis, the search for an evidence base is difficult. Diagnostic criteria have been published but are based on expert opinion.

Ménière's disease affects the quality of life significantly and generally is treated with counselling on dietary restrictions, drug therapy and surgical interventions to prevent recurrence of vertigo. Hearing loss is treated by means of hearing aids, bone-conduction implants in cases of unilateral deafness and cochlear implantation in cases of bilateral profound hearing loss.

This review gives an overview of the current state of knowledge about Ménière's disease with a specific focus on management of vertigo, hearing loss and tinnitus.

EPIDEMIOLOGY

Incidence and prevalence

The exact incidence and prevalence of Ménière's disease are unknown and in fact difficult to demonstrate in any population because of inherent difficulties to diagnose this condition after exclusion of all other possible causes. First-line physicians tend to overdiagnose Ménière's disease in patients with chronic vertigo (with or without recurrent vertigo or any additional symptoms). In a secondary or tertiary referral balance clinic it is difficult to establish the exact catchment area. In a study on a Finnish population by Kotimäki et al.,[3] a prevalence of 43.2 per 100 000 persons and an incidence of 4.3 definite Ménière's disease per 100 000 persons per year was reported (1992–1996).

Age

The age of onset is more commonly reported in the second to sixth decade of life. Only 1–7% of Ménière's disease cases are seen in the paediatric population.[3] Surprisingly, 9% of all patients experience the start of Ménière's disease at the age of 65 or more, with a higher incidence of drop attacks.[4]

Sex

There is no difference in the female-to-male ratio.[3]

Sporadic and familial

While Ménière's disease is sporadic in the majority of cases, an estimated 5–15% of cases are familial.[5] Several candidate genes have been proposed for Ménière's disease, including *AQP2*, *KCNE1*, *KCNE3*, *HCFC1*, *COCH*, *ADD*, *HSPA1A*, *PTPTN22* and *IL1*. Many of them are linked to inner ear ion and water transportation. *AQP2* is one of the aquaporin water channel genes,[6] *KCNE1* and *KCNE3* are potassium channel genes[7] and *ADD1* is linked to a sodium–potassium pump activity regulator.[3] *COCH* is linked to cochlin protein production, which is part of the extracellular matrix of the inner ear.[8] *COCH* gene is also known as *DFNA9* and leads to progressive non-syndromic deafness and bilateral vestibular areflexia.[9] *HCFC1* is associated with the host cell factor C1 which has been involved in cell cycle control and transcriptional regulation during herpes simplex virus infection.[10] *HSPA1A* is related to single nucleotide polymorphisms of the heat-shock protein 70 gene,[11] *PTPN22* encodes a lymphoid protein phosphatase[12] and the interleukin-1 gene (*IL1*).[13] A higher prevalence of autoimmune diseases and longer spells of vertigo have been reported in patients affected by a familial form of Ménière's disease.[14, 15] The familial form is more prone to present bilaterally during a lifetime.[16]

PATHOPHYSIOLOGY

Endolymphatic hydrops

The cause of Ménière's disease is unknown. Hallpike and Cairns suggested the relationship with endolymphatic hydrops in 1938.[17] This finding was independently reported by Yamakawa in 1938.[18] However, this theory remains controversial although endolymphatic hydrops was observed in all temporal bones studied in deceased patients with Ménière's disease.[19] Foster and Breeze provide a critical review on temporal bone histopathology.[20] Clinical data supporting the theory of endolymphatic hydrops is based on electrocochleography and delayed magnetic resonance imaging after intratympanic or intravenous administration of gadolinium-based contrast agents. A large summating potential has been observed in 50–70% of patients with Ménière's disease, which can be reduced with administration of hyperosmotic substances.[8] Based on animal studies and clinical studies using cone-beam computed tomography, anatomical variations in the temporal bone could be identified that may predispose for blockage of the endolymphatic canal or foreign protein deposition in the perilymph, both of which have been observed to cause endolymphatic hydrops.[13, 21] Endolymphatic hydrops, however, is not pathognomonic to Ménière's disease. Endolymphatic hydrops was observed in a significant number of temporal bones from patients with hearing loss, without the classical symptoms of Ménière's disease.[22] Delayed MRI after intratympanic injection of gadolinium-based contrast agent in unilateral Ménière's disease reveals bilateral endolymphatic hydrops quite frequently.[23] Additionally, the use of diuretics does not unequivocally lead to an improvement of symptoms and/or hydrops. Membrane ruptures have been suggested to cause the acute episodes of vertigo. However, Merchant et al. observed clear histologic examples of membrane ruptures in patients without a history of vertigo, which contradicts this theory.[22] Based on a large human temporal bone study, Merchant et al. suggested that the endolymphatic hydrops observed in Ménière's disease might be a marker for disordered inner ear homeostasis in which a yet unknown factor produces both the clinical symptoms of Ménière's syndrome and endolymphatic hydrops.[22] Potential etiological or precipitating conditions include genetic variations, infection, vascular risk factors, diet, allergy, autonomic, endocrine and autoimmune factors.

Autoimmune factor

In approximately 1 in 3 patients with Ménière's disease there seems to be an autoimmune factor. Several theories were suggested, including cross-reactions between similar antigens, innocent bystander damage due to cytokine release, acquired intolerance to inner ear antigens (covert from the immunological system and exposed by trauma or infection), genetic factors (extended major histocompatibility complex haplotype).[24–26]

Viral factor

A viral etiology has been suggested as well, most often involving the herpes simplex virus. Viral structures have been observed by means of transmission electron microscopy in the vestibular ganglion cells of one Ménière's disease patient, which supports this theory albeit one case.[27] Vertigo control in 91% of Ménière's disease patients by means of acyclovir treatment also supports the potential viral etiology.[27]

Allergic factor

An association with allergy has been observed by Derebery. Vertigo control (Class A and B) was achieved in 47.9% (n = 137) accepting allergy treatment.[28] Potential mechanisms include the endolymphatic sac targeted by the allergic reaction, deposition of circulating immune complexes in the fenestrated blood vessels of the endolymphatic sac and stria vascularis and viral antigen-allergic interaction with T-cell homing to the endolymphatic sac.[29]

Vascular factor

It has been observed that endolymphatic hydrops impairs blood flow autoregulation.[30] The combination of endolymphatic hydrops and venous obstruction has shown to induce vertigo attacks similar to Ménière's disease in an animal model.[31]

DIAGNOSIS

Diagnostic criteria for Ménière's disease

The most recent guidelines for the diagnosis in patients with Ménière's disease were issued in 2015 by the Classification Committee of the Bárány Society, The Japan Society for Equilibrium Research, the European Academy of Otology and Neurotology (EAONO), the Equilibrium

TABLE 63.1 Diagnostic criteria for Ménière's disease (other causes excluded)

Diagnosis	Criteria
Definite Ménière's disease	≥ Two definitive spontaneous episodes of vertigo lasting 20 minutes to 12 hours + Audiometrically documented low- to medium-frequency sensorineural hearing loss in the affected ear on at least one occasion before, during or after one of the episodes of vertigo + Fluctuating aural symptoms (hearing, tinnitus or fullness) in the affected ear
Probable Ménière's disease	≥ Two episodes of vertigo or dizziness, each lasting 20 minutes to 24 hours + Fluctuating aural symptoms (hearing, tinnitus or fullness) in the reported ear

Committee of the American Academy of Otolaryngology–Head and Neck Surgery (AAO–HNS) and the Korean Balance Society.[32] According to these guidelines, the diagnosis of Ménière's disease in a vertigo patient is based on clinical symptoms and exclusion of identifiable other etiologies, rendering Ménière's disease idiopathic. They provide 2 degrees of certitude: definite and probable Ménière's disease. The definition of each of these categories can be found in Table 63.1. In the most recent 2015 guidelines, diagnostic criteria were suggested without providing minimal outcome criteria for use in daily practice in the absence of a gold standard test. Therefore, minimal outcome reporting is still based on the 1995 criteria issued by the AAO–HNS.[1]

A typical attack of Ménière's disease can be defined by the direction of the spontaneous nystagmus.[33] In the irritative phase the nystagmus will beat towards the affected ear in a horizontal or horizontal–torsional direction, a finding which usually lasts less than 1 hour. In the paretic phase, the nystagmus will beat away from the affected ear and last hours to days. In the recovery phase the nystagmus again beats towards the affected side because peripheral vestibular function recovers.

Particularly in the later stages of Ménière's disease, drop attacks (also known as Tumarkin crises) can develop. These may be related to acute otolythic dysfunction. The patient suddenly drops to the ground (without losing consciousness) without associated vertigo.

For the record, 'low-frequency sensorineural hearing loss' is defined as: increases in pure-tone thresholds for bone-conducted sound that are higher (i.e. worse) in the affected ear than the contralateral ear by at least 30 dBHL at each of two contiguous frequencies below 2 kHz. In cases of bilateral low-frequency sensorineural hearing loss, the absolute thresholds for bone-conducted sound must be 35 dBHL or higher at each of two contiguous frequencies below 2000 Hz. If multiple audiograms are available, demonstration of recovery of low-frequency sensorineural hearing loss at some point in time further supports the diagnosis of Ménière's disease. Bilateral synchronous sensorineural hearing loss (symmetric or asymmetric) can occur in some patients.

Figure 63.1 demonstrates the hallmark low-frequency sensorineural hearing loss and its recovery after low-sodium diet.

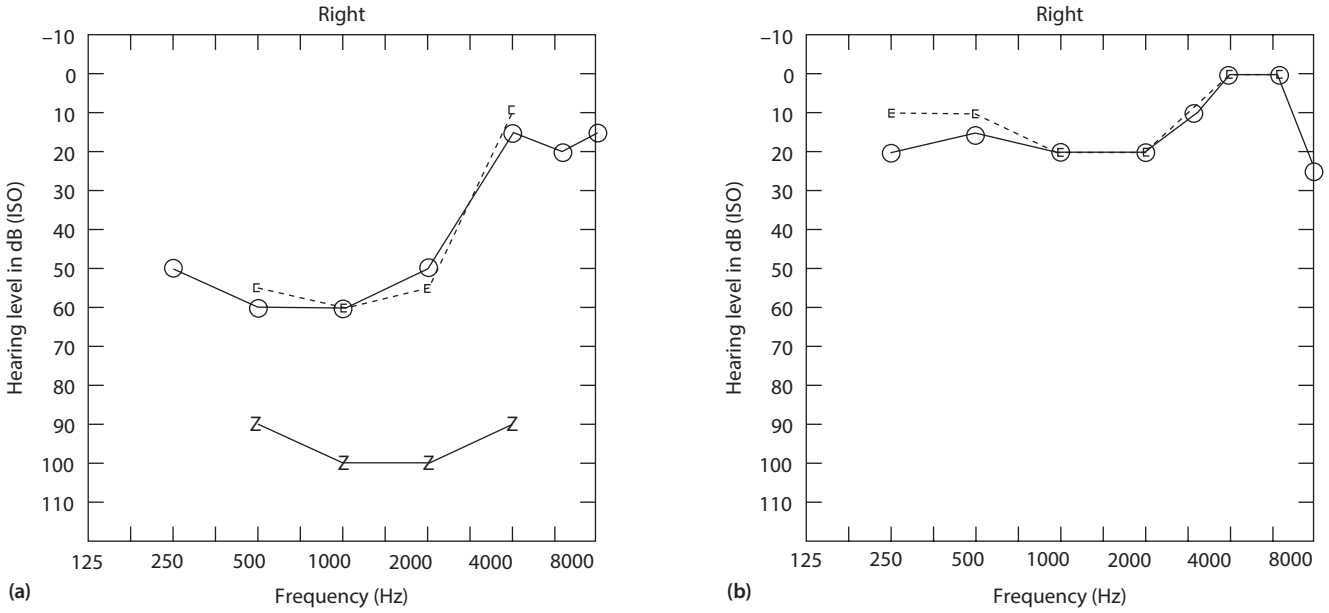

Figure 63.1 Audiogram in Ménière's disease. This patient, a 14-year-old female, began to have attacks of acute spontaneous vertigo with right-sided aural fullness and then tinnitus. **(a)** Audiogram on presentation shows a 60 dB low-frequency hearing loss with normal acoustic reflexes (Z), indicating a fully recruiting cochlear hearing loss. **(b)** Audiogram after 4 months of treatment with a rigorous low-sodium diet shows normal pure-tone thresholds.

The 2015 guidelines define Ménière's disease as an idiopathic syndrome of endolymphatic hydrops and therefore other causes have to be excluded. The following conditions are explicitly mentioned: transient ischemic attack, vestibular migraine, vestibular paroxysmia, recurrent unilateral vestibulopathy, vestibular schwannoma and endolymphatic sac tumour. The 1995 guidelines also mention trauma or surgery, infection (syphilis) and inflammatory disorders (Cogan's syndrome) as potential causes of endolymphatic hydrops and refer to the work of Schuknecht and Gulya for further causes.[34] The latter article additionally reveals the 'embryopathic symptomatic endolymphatic hydrops', related to inner ear malformations, and the 'acquired symptomatic endolymphatic hydrops' (also known as 'delayed hydrops'), related to trauma and inflammation caused by viruses, bacteria or spirochaetes. The case of a patient with bacterial meningitis and subsequent labyrinthitis was given to demonstrate the presence of 'delayed hydrops'. This report was published in the early 1980s and is limited by the contemporary state of the art where, for example, only polytomography was available as imaging tool. According to the 2015 guidelines the term 'delayed hydrops' should be avoided in favour of 'delayed Ménière's disease' in cases of sensorineural hearing loss antedating the vertigo spells.

To exclude these Ménière-like diseases any diagnostic technique available to the clinician should be used: for example, full clinical examination of the head and neck region (including vestibular examination), liminal and speech audiometry, tympanometry, multidetector computed tomography (CT scan) of the temporal bone (with or without intravenous injection of iodine-containing contrast), MRI of the posterior fossa (with intravenous injection of gadolinium), blood analysis (haematology, thyroid, biochemical and genetic testing). The posterior fossa MRI with intravenous administration of gadolinium is the most sensitive examination to exclude cerebellopontine angle and inner ear pathology (in the absence of any contraindications to MRI).

Since the diagnosis of Ménière's disease is based on a syndrome of idiopathic endolymphatic hydrops, it is good practice to challenge the diagnosis during follow-up of the patient. Simultaneously, these patients can report vertigo unrelated to their Ménière's disease, which needs careful examination and separate treatment. In the differential diagnosis of Ménière's disease, vestibular migraine, vestibular paroxysmia and chronic subjective dizziness have to be considered. These conditions can also coexist with Ménière's disease and need to be treated separately.[35] Unfortunately, since all of these conditions are idiopathic, their diagnosis relies on expert opinion-based criteria.[36] Diagnostic criteria for vestibular migraine,[37] vestibular paroxysmia[38] and chronic subjective dizziness[39] can be found respectively in **Tables 63.2**, **63.3** and **63.4** to enable direct comparison.

Diagnostic tools to detect endolymphatic hydrops

Evidence supplementary to the diagnostic criteria (which are in fact based only on history and audiometry) can be provided with electrocochleography (ECoG) or cochlear hydrops analysis masking procedure (CHAMP). More recently the use of delayed MRI after intratympanic injection of gadolinium has enabled the clinician to demonstrate endolymphatic hydrops *in vivo*.

ELECTROCOCHLEOGRAPHY

Electrocochleography records sound-evoked electrical activity near the cochlea by means of transtympanic or extratympanic measurement. This technique is not routinely available and was therefore not included as a minimal outcome criterion of the 1995 Committee guidelines. ECoG is assumed to measure endolymphatic hydrops by evaluating the amplitude ratio of the action potential (AP) and the summating potential (SP). The SP amplitude is increased by displacement of the basilar membrane towards the scala tympani. **Figure 63.2** demonstrates ECoG findings in the same patient as in **Figure 63.1**. Diagnostic SP/AP-ratio thresholds were suggested by Wuyts et al. by performing a meta-analysis of published results.[40] These thresholds differ between extratympanic and transtympanic electrodes and are presented in **Table 63.5**.

Diagnostic SP amplitude thresholds were also suggested when using tone-burst stimuli. These suggestions are not based on a meta-analysis because of insufficient data, but reflect the proposal of the Prosper Ménière Society's

TABLE 63.2 Diagnostic criteria for vestibular migraine

Diagnosis	Criteria
Vestibular migraine	A. At least five episodes with vestibular symptoms of moderate to severe intensity, lasting 5 minutes to 72 hours B. Current or previous history of migraine with or without aura according to the International Classification of Headache Disorders (ICHD) C. One or more migraine features symptoms with at least 50% of the vestibular episodes: (1) headache with at least two of the following characteristics: one-sided location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity (2) photophobia and phonophobia (3) visual aura D. Not better accounted for by another vestibular or ICHD diagnosis
Probable vestibular migraine	A. At least five episodes with vestibular symptoms of moderate or severe intensity, lasting 5 minutes to 72 hours B. Only one of the criteria B and C for vestibular migraine is fulfilled (migraine history *or* migraine features during the episode) C. Not better accounted for by another vestibular or ICHD diagnosis

TABLE 63.3 Diagnostic criteria for vestibular paroxysmia

Diagnosis	Criteria
Definite vestibular paroxysmia	Patients suffered from a minimum of five vertigo attacks and fulfilled one criterion of each category (A)–(E): A. *Vertigo attacks:* Vertigo attacks (rotatory as well as to and fro vertigo) with short duration (seconds to minutes), which ceased spontaneously B. *Vertigo triggers:* Attacks occurred while in rest, were induced by a specific head and/or body position, or by a specific change of head and/or body position C. *Accompanying symptoms:* Attacks were accompanied by at least one of the following additional symptoms: unsteadiness of stance and/or gait, lateralized tinnitus, decreased hearing function or subjective sensory irritations, such as a feeling of pressure within or around one ear D. *Additional criteria:* The diagnostic procedures in addition to the anamnestic aspects revealed a neurovascular compression of the eighth cranial nerve on MRI scans including CISS sequences, a hyperventilation-induced nystagmus, a detectable progress of vestibular deficit over the course of disease, or patients responded positively to treatment E. *Exclusion:* Any other possible pathology or disease explaining the symptoms had to be excluded
Probable vestibular paroxysmia	Patients suffered from a minimum of five vertigo attacks and fulfilled criterion (A) and additionally at least three criteria out of the categories (B)–(E)

TABLE 63.4 Diagnostic criteria for chronic subjective dizziness

Diagnosis	Criteria
Chronic subjective dizziness	1. *Subjective unsteadiness or dizziness*: Persistent (≥3 months) sensations of unsteadiness or non-vertiginous dizziness that are present on most days. These symptoms may be described as: • rocking, swaying, or wobbling that is usually not apparent to others • a feeling that the floor is moving or wavy • light-headed, foggy or cloudy in the head • heavy-headed or full in the head • spinning 'inside the head' without a perception of movement of the visual surround • a feeling of dissociation from the environment
	2. *Hypersensitivity to motion*: Chronic (≥3 months) hypersensitivity to one's own motion, which is not direction-specific, and to the movement of objects in the environment
	3. *Visual dizziness (also known as visual vertigo)*: Exacerbation of symptoms in settings with complex visual stimuli, such as displays in grocery stores or shopping malls, or when performing precision visual tasks (e.g. reading or working on a computer).

International Standard.[41,42] SP amplitude is typically measured at 10 msec after stimulus start. Unfortunately, no studies were available on extratympanic ECoG through tone-burst stimuli.[40]

COCHLEAR HYDROPS ANALYSIS MASKING PROCEDURE (CHAMP)

The hypothesis of CHAMP is that endolymphatic hydrops causes changes in the response properties of the basilar membrane, i.e. travelling wave velocity is faster by basilar membrane stiffening in endolymphatic hydrops. These changes lead to impaired high-pass noise masking of auditory brainstem response (ABR) to clicks in stacked ABR. Unfortunately, different groups have reported conflicting results.[43–46] These results are potentially due to the different standards and diagnostic thresholds used. Therefore, the CHAMP cannot be used (yet) to prove or disprove the diagnosis of endolymphatic hydrops in Ménière's disease patients.

DELAYED MRI AFTER INTRATYMPANIC OR INTRAVENOUS INJECTION OF GADLINIUM

Since 'certain' Ménière's disease involves the histopathologic confirmation of endolymphatic hydrops, this level of certitude is only reached post-mortem and clinically irrelevant to the patient. Electrophysiological testing (such as ECoG or CHAMP) is based on measuring sound-evoked electrical responses and therefore quite circumstantial evidence for endolymphatic hydrops. The intratympanic injection of gadolinium-based contrast agent (hereafter called gadolinium) provides a potential *in vivo* biomarker to evaluate the perilymphatic and endolymphatic spaces separately. Gadolinium loads into the perilymphatic space without entering the endolymph in healthy inner ears.[47]

Normative values have been established in healthy volunteers.[48,49] Based on the study on normal individuals by Nakashima et al.,[49] the upper limit for enlargement of the endolymphatic space of the vestibule should be set at 33%. This new technique for visualizing endolymphatic hydrops demonstrated, surprisingly, that Ménière's disease is essentially a bilateral condition. Bilateral endolymphatic was observed in 79% of patients with unilateral definite Ménière's disease. Pyykkö et al. also argued that Ménière's disease rather is a continuum from monosymptomatic patients with endolymphatic hydrops to the full-blown patient profile of definite Ménière's disease.[23] This technique certainly is promising and might be helpful as a biomarker to confirm endolymphatic hydrops in cases

where clinical suspicion is present. Gadolinium can be administered intravenously 4 hours before MRI or intratympanically 24 hours before MRI. We remind the clinician that the intratympanic use of gadolinium is strictly off-label.

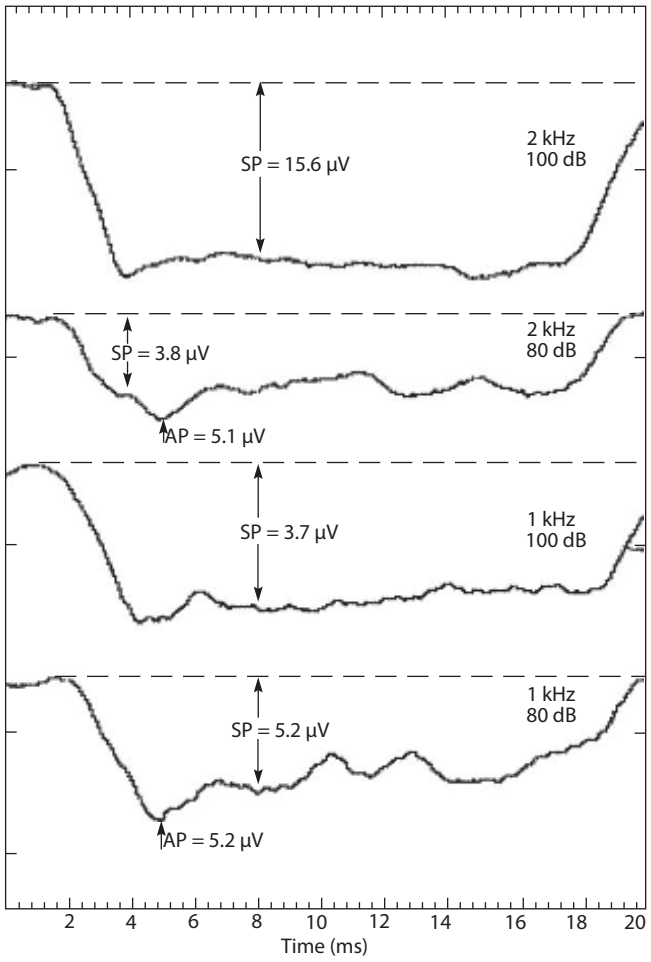

Figure 63.2 Electrocochleogram (ECoG) in Ménière's disease. Transtympanic ECoG of the patient whose audiogram is shown in Figure 63.1, showing large negative summating potentials (SP) in response to 16 ms, 1 kHz and 2 kHz tone-bursts at 80 and 100 dB nHL. The mean absolute negative SP levels in patients with definite Ménière's disease, who have subjective thresholds below 40 dB nHL, are as follows: 2 kHz, 100 dB 46 mV; 2 kHz, 80 dB 44 mV; 1 kHz, 100 dB 44 mV. These results show that tone burst ECoG responses are more likely to be abnormal in patients with Ménière's disease than are click-evoked responses.[75] Figure courtesy of W. Gibson, Sydney, Australia.

TABLE 63.5 Electrocochleography SP/AP ratio and SP thresholds

	Stimulus	Thresholds	
		Extratympanic	Transtympanic
SP/AP ratio	Click	>0.42	>0.35
SP	Tone-bursts	–	<–2 µV (<–3 µV at 1 kHz)

OUTCOME REPORTING

Vertigo

DEFINITION

The definitive spell of Ménière's disease is described as spontaneous rotational vertigo (i.e. the sensation of motion when no motion is occurring relative to Earth's gravity) lasting at least 20 minutes. The severity of vertigo is reported as prostrating or incapacitating by the patient. This spell might be followed by a period of disequilibrium, a sensation present for up to several days. The definitive spell is usually accompanied by nausea and/or vomiting. Consciousness is not lost during or after the spell. While examining the patient during the definitive spell, horizontal nystagmus (with or without torsional component) is always present.

FREQUENCY OF VERTIGO

The frequency of vertigo should be evaluated over a period of 6 months. The average number of definite spells per month lasting at least 20 minutes is used in the reporting index as shown in Table 63.6. Any treatment can only be evaluated 2 years after treatment started. At that follow-up visit, the frequency of vertigo over the last 6 months has to be reported. Class F is the category of Ménière's disease patients who require 'secondary treatment' due to disability from vertigo (e.g. vestibular nerve section).

SEVERITY OF VERTIGO

The AAO–HNS Committee released an update in the AAO–HNS Bulletin of April 2014. Its main consideration was that in the 1995 guidelines outcome reporting was based totally on frequency of vertigo, while information on the severity of vertigo spells would be more appropriate. Table 63.7 includes five categories ranging from 'no vertigo' to 'extreme attack'.

FUNCTIONAL LEVEL

It has been reported that Ménière's disease symptoms are highly intrusive in comparison to other conditions.

TABLE 63.6 Summary of reporting guidelines

Numerical value	Class
0	A (complete control of spells)
1–40	B
41–80	C
81–120	D
>120	E
Secondary treatment initiated due to disability from vertigo	F

Numerical value = $(X/Y) \times 100$, rounded to the nearest whole number, where X is the average number of definitive spells per month for the 6 months 18–24 months after therapy and Y is the average number of definitive spells per month for the 6 months before therapy.

TABLE 63.7 Severity of vertigo

Scale	Category	Definition
0	No vertigo	No vertigo
1	Mild attack	Brief episode of vertigo lasting less than 20 minutes and/or vague sense of disequilibrium lasting less than 2 hours
2	Moderate attack	Vertigo lasting 20–60 minutes and/or disequilibrium lasting greater than 2 hours with reduction in daily activities from 0% to 50%
3	Severe attack	Vertigo lasting more than 1 hour with or without accompanying nausea and vomiting, with or without lingering disequilibrium lasting greater than 2 hours with reduction in daily activities of 50–100%
4	Extreme attack	Vertigo lasting more than 1 hour with nausea and vomiting and persistent lingering severe disequilibrium requiring bedrest the entire day

Only fibromyalgia, human immunodeficiency virus (HIV) infection, anxiety disorders and chronic fatigue syndrome/myalgic encephalomyelitis are more intrusive, as reported by Arroll et al.[50] Functional level, commonly related to work or active recreational pursuits, is mainly related to the intrusiveness of the vertigo spells. The six categories are shown in **Box 63.1**.

DIZZINESS HANDICAP INVENTORY

The Dizziness Handicap Inventory (DHI) has gained widespread acceptance as a useful instrument to evaluate the handicap resulting from vertigo and achieves a responsiveness superior to other patient-reported outcome measures.[51] It has been used frequently as an outcome measure in clinical trials to document the effect of medical, surgical and rehabilitative interventions.[52]

MÉNIÈRE'S DISEASE OUTCOME QUESTIONNAIRE

In 2004, Kato et al. published an 18-item multiple-choice questionnaire for evaluating quality of life in patients with Ménière's disease before and after endolymphatic sac surgery: the Ménière's Disease Outcome Questionnaire (MDOQ). This questionnaire includes three domains: physical, emotional and social well-being. It was designed as a retrospective survey enabling patients to evaluate their symptoms after surgery and not requiring baseline analysis. This feature makes the MDOQ easy to use but it also reflects its main limitation: the retrospective and post-hoc evaluation.[53]

ELECTRONYSTAGMOGRAPHY

Electronystagmography cannot confirm the diagnosis itself, but reflects the residual horizontal semicircular canal response to caloric stimulation. In patients with Ménière's disease, these results can vary quite significantly. In case of treatments that aim for destruction of labyrinthine function (such as intratympanic injection of gentamicin or a vestibular nerve section), electronystagmography can measure residual function and evaluate the treatment's effectiveness to destroy vestibular function. However, the absence of caloric response does not invariably predict long-term vertigo control.[54]

Hearing loss

Hearing loss is essential in the diagnosis of certain, definite and probable Ménière's disease. If no hearing loss was documented, the patient can only be allocated

BOX 63.1 Functional level scale

Regarding my current state of overall function, not just during attacks (check the ONE that best applies):	
1. My dizziness has no effect on my activities at all.	
2. When I am dizzy I have to stop what I am doing for a while, but it soon passes and I can resume activities. I continue to work, drive, and engage in any activity I choose without restriction. I have not changed any plans or activities to accommodate my dizziness.	
3. When I am dizzy, I have to stop what I am doing for a while, but it does pass and I can resume activities. I continue to work, drive, and engage in most activities I choose, but I have had to change some plans and make some allowance for my dizziness.	
4. I am able to work, drive, travel, take care of a family, or engage in most essential activities, but I must exert a great deal of effort to do so. I must constantly make adjustments in my activities and budget my energies. I am barely making it.	
5. I am unable to work, drive, or take care of a family. I am unable to do most of the active things that I used to. Even essential activities must be limited. I am disabled.	
6. I have been disabled for 1 year or longer and/or I receive compensation (money) because of my dizziness or balance problem.	

TABLE 63.8 Staging of definite and certain Ménière's disease

Stage	Pure-tone average of 0.5–1–2–3 kHz (dB)
1	≤25
2	26–40
3	41–70
4	>70

to the possible Ménière's disease group (in the presence of other qualifying symptoms). The 1995 Committee guidelines combine the use of pure-tone audiometry and word recognition scores in order to evaluate hearing loss. However, they only use the pure-tone average of 0.5, 1, 2 and 3 kHz for staging of certain and definite Ménière's disease. The proposed staging system can be found in Table 63.8. This pure-tone average should be calculated on the worst audiogram during the 6 months before the start of treatment. The staging system cannot be used in probable and possible Ménière's disease according to the 1995 Committee guidelines. Once the patient is allocated, the stage cannot be changed. No suggestion was made to incorporate word recognition in staging, but a positive change of 15% in speech discrimination was considered clinically significant.

Tinnitus and aural fullness

According to the 1995 Committee guidelines, the evaluation of tinnitus and aural fullness is at the discretion of the clinician.

TINNITUS FUNCTIONAL INDEX

For evaluation of tinnitus severity, several self-reporting questionnaires have been developed and are currently in use. However, many questionnaires were not designed to maximize responsiveness (i.e. to measure positive or negative change after treatment). For this reason an expert panel based in the US and New Zealand developed the Tinnitus Functional Index (TFI).[55] In this study, a 13-point reduction was considered a clinically meaningful reduction of TFI scores.

VISUAL ANALOGUE SCALE

The visual analogue scale has been in use for reporting complaints that are difficult to quantify. Using the visual analogue scale, the patient has to indicate a value between 0 (no symptoms) and 10 (maximal intensity). The visual analogue scale can also be used for evaluation of average and maximal tinnitus loudness.[56]

MANAGEMENT

Based on the levels of recommendation produced by the Oxford Centre for Evidence-based Medicine we will discuss all different aspects in the management of Ménière's disease patients.

Diagnosis

The diagnosis of Ménière's disease can be suspected by acquiring a systematic otovestibular history (including family history and personal drug, trauma, surgery and disease history) while excluding all other potential causes of the Ménière's syndrome due to secondary endolymphatic hydrops, as required by the 2015 guidelines (recommendation grade D). Liminal and speech audiometry is essential to support the diagnosis of definite Ménière's disease. The clinician should be aware that there is considerable overlap in diagnostic criteria for vestibular migraine, vestibular paroxysmia and chronic subjective dizziness. It is uncommon but possible that more than one condition can be diagnosed and requires separate treatment.

There are no studies on how to exclude other potential causes of endolymphatic hydrops, which is left at the discretion of the clinician. A blood sample can be taken to evaluate thyroid and immunological status if thyroid disease or autoimmune diseases are suspected. Genetic analysis is not routine practice in every balance clinic. *COCH*-mutations can be screened in unaffected family members to provide information on individual prognosis. An MRI scan of the cerebellopontine angle can be performed after intravenous administration of gadolinium-based contrast agent to exclude inner ear malformations, neurovascular conflicts with the vestibulocochlear nerve, cerebellopontine angle and intralabyrinthine lesions (most often the vestibular schwannoma) or white matter lesions of inflammatory or vasculoischaemic origin. ECoG can demonstrate the electrophysiological substrate of endolymphatic hydrops. Delayed MRI after intravenous or intratympanic injection of gadolinium-based contrast agent can visualize endolymphatic hydrops and can provide an *in vivo* surrogate for the histopathologic confirmation of certain Ménière's disease.

Hygienic measures

DIETARY RESTRICTIONS

Dietary restrictions on sodium and caffeine are traditionally advised by clinicians to prevent the development of endolymphatic hydrops.[57] However, this hypothesis was only recently confirmed by means of a retrospective study.[58] Luxford et al. demonstrated that implementation of a low-sodium and caffeine-free diet had a statistically significant effect on functional level in Ménière's disease patients. Those patients who were compliant longer than 6 months had larger improvement in vertigo frequency and functional level. The latter group of patients also had a higher rate of class A/B vertigo outcome.

Recommendation Counselling may include a low-salt and caffeine-free diet.

Medication

DIURETICS

Diuretics, including hydrochlorothiazide, acetazolamide or a combination of hydrochlorothiazide and triamterene, are still the first-line medical therapy for Ménière's disease patients in many clinics. Their therapeutic mechanism is to reduce endolymphatic volume and pressure.[57] Osmotic diuretics, such as oral urea powder twice a week, are rarely used as a 'salvage oral therapy' to reduce endolymphatic hydrops. Thirwall and Kundu published a 2006 Cochrane analysis on the use of diuretics in patients with Ménière's disease. This analysis was assessed as up-to-date in 2009. Unfortunately, there was insufficient good evidence of the effect of diuretics on vertigo, hearing loss, tinnitus or aural fullness in clearly defined Ménière's disease.[59] Diuretics, however, can cause electrolyte disturbances and potentially interact with patient-specific drugs and conditions.

BETAHISTINE DIHYDROCHLORIDE

Betahistine dihydrochloride (hereafter called betahistine) is an oral preparation of a histamine precursor marketed in Europe as a specific treatment for patients with Ménière's disease. Betahistine is an analogue of histamine with weak agonist properties at histamine H1 receptors and more potent antagonistic effects at histamine H3 receptors.[60, 61] James and Burton published a 2001 Cochrane analysis on the use of betahistine in patients with Ménière's disease.[62] This analysis was assessed as up-to-date in 2010. Unfortunately, according to this analysis there was insufficient evidence to identify whether betahistine has any effect on vertigo control in patients with Ménière's disease. Six trials involving 162 patients were included. No trial met the highest quality standard set by the review because of inadequate diagnostic criteria or methods, and none assessed the effect of betahistine on vertigo adequately. Most trials reported some form of vertigo control. However, these results may have been caused by bias in the study design. Another, more recent, meta-analysis (performed by an employee of pharmaceutical company Abbott, commercializing Betaserc) demonstrated an overall beneficial effect of betahistine.[63] This study was not restricted to Ménière's disease and also includes 'vestibular vertigo', which might induce bias. Additionally, this meta-analysis introduces internal unpublished (Duphar) reports on placebo-controlled clinical studies with betahistine, which is a controversial issue (bypassing the challenge of peer review). High-dosage betahistine dihydrochloride (up to 480 mg or 30 tablets each day) has been reported in a case series to be effective in patients with Ménière's disease who do not respond sufficiently to lower dosages.[64]

Recommendation First-line medical treatment to prevent recurrence of vertigo may include betahistine dihydrochloride 16 mg thrice daily and/or diuretics. Betahistine has a limited side effect profile while diuretics can cause electrolyte disturbances, potentially interact with patient-specific drugs and conditions.

Transtympanic and intratympanic therapies

TRANSTYMPANIC LOW-PRESSURE THERAPY (MENIETT)

This therapy was established after reports of subjective improvement of acute vertigo attacks when pressure changes were induced in a pressure chamber.[65, 66] Based on these reports, the Meniett device was conceived, producing a repetitive 0.6-second pulse of low pressure (ranging from 0 to 20 cm H_2O) transmitted through a ventilation tube.[67] The treatment consists of three to four cycles of a 5-minute treatment sequence. A recent Cochrane review had to conclude that there is no evidence to demonstrate the effectiveness of positive low-pressure therapy.[68]

INTRATYMPANIC INJECTION OF CORTICOSTEROIDS

The suggested therapeutic mechanism of corticosteroids is inner ear homeostasis via transmembrane water transporters, the aquaporins.[69] Based on a 2011 Cochrane analysis by Phillips and Westerberg, one randomized placebo-controlled trial was identified comparing intratympanic injection of dexamethasone to saline solution.[70] This trial demonstrated a statistically significant improvement of vertigo frequency and severity measured 24 months after treatment start. Substantial vertigo control (Class A and B) was achieved in 11 patients (100%) of treatment group versus 4 patients (57%) in the control group.[71, 72] Therefore the authors of the Cochrane analysis concluded that limited evidence is available to support the effectiveness of intratympanic steroids in patients with Ménière's disease. An important aspect is that patients were only included if failing a combination of dietary restrictions and medical therapy with vasodilator and diuretics for 6 months.

INTRATYMPANIC INJECTION OF GENTAMICIN

Aminoglycosides are infamous for their vestibulotoxicity after intravenous use. There are several pathways that might cause this effect including excitotoxicity through N–methyl–D–aspartate (NMDA) receptor binding[72] and production of reactive oxygen species[74] which can be influenced by the antioxidant N-acetylcysteine.[74] Schuknecht first reported on intratympanic therapy with aminoglycosides as early as 1956.[75, 76] Based on a 2011 Cochrane analysis by Pullens et al., two randomized placebo-controlled trials were identified demonstrating the beneficial effect of intratympanic injection of gentamicin on vertigo control in Ménière's disease patients.[77] A meta-analysis was deemed impossible due to clinical heterogeneity. Huon et al.[78] did perform a meta-analysis which was published in 2012 confirming the beneficial effect of intratympanic gentamicin on vertigo control: 87.5% Class A and B. Sensorineural hearing loss was reported in 0–38.7% of cases. After the publication of these two articles another randomized controlled trial was published in 2012

comparing intratympanic gentamicin with dexamethasone.[79] Because different injection schedules were used, this trial could not be blinded. In the intratympanic gentamicin group substantial vertigo control (Class A and B) was achieved in 30 patients (93.5%) at 2-year follow-up. In the intratympanic dexamethasone group, substantial vertigo control was achieved in 17 patients (61%).[79]

Noteworthy is that intratympanic injection of gentamicin has demonstrated its effectiveness in patients with Ménière's disease experiencing drop attacks (Tumarkin crisis).[80]

Recommendation Salvage treatment in case of medical treatment failure may include repetitive intratympanic injections of dexamethasone (recommendation grade A), which enable substantial and long-term vertigo control in 80% of refractory cases without significant hearing loss. In refractory cases after intratympanic injection of dexamethasone, intratympanic injection of gentamicin (as-needed) can be offered (recommendation grade A). This treatment is based on the vestibulotoxic effect of gentamicin and aims to destroy vestibular hair cell function (therefore also called partial chemolabyrinthectomy). The typical Ménière's disease vertigo attacks are not detected and do not provoke nystagmus. Consequently, the patient does not experience vertigo any more but may develop some imbalance or visual vestibular mismatch.

Intratympanic injection of gentamicin may also be indicated in 'end-stage' patients who develop drop attacks/Tumarkin crises.

Sensorineural hearing loss is a potential complication of this treatment and should be considered in the evaluation of the individual patient.

Surgery

ENDOLYMPHATIC SAC SURGERY

Based on a 2010 Cochrane analysis by Pullens et al. (updated in 2013) only one surgical modality was studied in randomized controlled trials, i.e. endolymphatic sac surgery. Neither of the two studies reported any beneficial effect over grommet insertion or mastoidectomy,[80] therefore the authors concluded that there is insufficient evidence to support endolymphatic sac surgery in Ménière's disease. A more recent systematic review and meta-analysis of available clinical studies (although lacking a control population) supported the use of endolymphatic sac surgery in Ménière's disease patients refractory to medical treatment.[81] Different surgical approaches to the endolymphatic sac were compared including endolymphatic sac decompression and mastoid shunting. Sood et al. calculated a respective average of 79.3% and 76.4% vertigo control (Class A and B) at 12 months (short-term) and 81.6% and 75.7% at 24 months (long-term). Average hearing preservation rates (within 10 dB of pre-operative thresholds) were respectively 72.8% and 71.4% at 12 months and 71.6% and 69.3% at 24 months. These numbers, however, might reflect natural Ménière's disease progression since control groups are lacking.[82]

TENOTOMY OF THE TENSOR TYMPANI AND STPEDIAL MUSCLE TENDONS

Conflicting results have been reported on tenotomy of the tensor tympani and stapedial muscles' tendons.[52, 83–85] The suggested mechanism of action in Ménière's disease patients is that the tympanic membrane is pushed laterally by increased cochlear pressure against the ossicular chain. By sectioning the tensor tympani muscle this effect is (partially) alleviated.[86] Positive results were only reported in one centre that published several case series.[83–85] Randomization of patients undergoing intratympanic injection of gentamicin into one group who had simultaneous tenotomy and another group without tenotomy could not reveal any statistically significant differences.[52]

SELECTIVE VESTIBULAR NERVE SECTION

Surgical section of the vestibular nerve while preserving the facial and cochlear nerve can be used as an alternative to intratympanic injection of gentamicin to produce vestibular areflexia. Several case series were reported, but only three case-control studies were published reporting a similar outcome as intratympanic injection of gentamicin.[87–89] Hillman et al.[88] reported 90% substantial vertigo control (Class A and B) in the selective vestibular nerve section group, while 66% was observed in the intratympanic injection of gentamicin group, which favours the selective vestibular nerve section group on a statistically significant level. These results might have been provoked by the relatively low dosage of gentamicin (26.7 mg/mL) the authors used and the short irrigation time of 10 minutes in the supine position. Hearing preservation rates were 72% in the selective vestibular nerve section group and 52% in the intratympanic injection of gentamicin group. Statistically significant differences were reported favouring selective vestibular nerve section. However, pre-operative hearing was also better in the selective vestibular nerve section at a statistically significant level. Colletti et al.[89] reported substantial vertigo control (Class A and B) in 95.8% of selective vestibular nerve section cases and 75% of intratympanic injection of gentamicin cases. Schmerber et al.[90] observed recurrence of disabling vertigo in 7% of selective vestibular nerve section cases and 11.4% of intratympanic injection of gentamicin cases, while respective numbers of 74% and 85.7% hearing preservation were reported. The hearing preservation rate in intratympanic injection of gentamicin cases might have been biased by the specific inclusion of cases with pure-tone averages over 40 dB (only Class C and D hearing cases). All the studies mentioned above have significant limitations including their retrospective nature, selection bias, etc. A proper systematic review (and meta-analysis of raw data if possible) of selective vestibular nerve section is currently lacking. Randomized controlled trials using sham procedures are impossible due to ethical reasons in this type of surgical procedure and preclude the establishment of level 1 evidence. The conception of a delayed-start study design would enable randomization and increase the level of evidence.[91]

Recommendation Selective vestibular nerve section aims to abolish vestibular afferent signalling totally and is usually considered as an alternative to intratympanic injection of gentamicin in case of intact hearing or as salvage treatment after intratympanic injection of gentamicin.

There is insufficient evidence to support transtympanic low-pressure therapy (Meniett), endolymphatic sac surgery or tenotomy of the tensor tympani and stapedius muscles' tendons.

KEY POINTS

Diagnosis

- The diagnosis of Ménière's disease can be suspected by acquiring a systematic otovestibular history (including family history and personal drug, trauma, surgery and disease history).
- Potential causes of secondary endolymphatic hydrops need to be excluded.
- Liminal and speech audiometry is essential to support the diagnosis of definite Ménière's disease.
- There is considerable overlap in diagnostic criteria for vestibular migraine, vestibular paroxysmia and chronic subjective dizziness.
- An MRI scan of the cerebellopontine angle after intravenous administration of gadolinium-based contrast agent is the most sensitive imaging method to exclude inner ear malformations, neurovascular conflicts with the vestibulocochlear nerve, cerebellopontine angle and intralabyrinthine lesions (most often the vestibular schwannoma) or white matter lesions of inflammatory or vasculo-ischaemic origin.
- ECoG can demonstrate the electrophysiological substrate of endolymphatic hydrops.
- Delayed MRI after intravenous or intratympanic injection of gadolinium-based contrast agent can visualize endolymphatic hydrops and can provide an *in vivo* surrogate for the histopathologic confirmation of certain Ménière's disease.

Treatment

- Counselling includes a low-salt and caffeine-free diet.
- First-line medical treatment to prevent recurrence of vertigo may include betahistine dihydrochloride 16 mg thrice daily associated with diuretics.
- Salvage treatment in cases of medical treatment failure may include repetitive intratympanic injections of dexamethasone, which enable substantial and long-term vertigo control in 80% of refractory cases without significant hearing loss.
- In refractory or end-stage cases (Tumarkin crises), intratympanic injection of gentamicin (as needed) can be offered.
- Sensorineural hearing loss is a potential complication of this treatment and should be considered in the evaluation of the individual patient.
- Selective vestibular nerve section aims to abolish vestibular afferent signalling totally and is usually considered as an alternative to intratympanic injection of gentamicin in case of intact hearing or as salvage treatment after intratympanic injection of gentamicin.

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CHAPTER 64

BENIGN PAROXYSMAL POSITIONAL VERTIGO

Yougan Saman and Doris-Eva Bamiou

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: benign paroxysmal positional vertigo, posterior canal, horizontal canal and anterior canal.

INTRODUCTION

Benign paroxysmal positional vertigo (BPPV) is the commonest presenting cause of vertigo with an estimated lifetime prevalence of 2.4%.[1] In studies of both young adults and the elderly a prevalence of 9% has been described.[2, 3] It has a characteristic history and can easily be diagnosed on examination. Treatment can be performed in the clinic with a good outcome, making it the most rewarding vestibular condition to manage. BPPV may, however, be associated with a reduced quality of life, falls and depression, in which case the term 'benign' may be misleading, particularly when unrecognized and therefore untreated.[2]

The first clinical description of positional vertigo is attributed to Barany in 1921 and in 1952 Dix and Hallpike were the first to clearly describe the provoking maneuvers.[4, 5] Dix and Hallpike coined the term 'benign paroxysmal positional vertigo' in view of the associated benign (non-cancerous) origin and momentary (paroxysmal) bursts of intense vertigo upon head movements (positional).[5] Lanska and Remler provide a concise historical account of the work that has led to our understanding of this condition.[6]

PATHOPHYSIOLOGY

Otoconia are calcium carbonate crystals embedded in the macula of the utricle and saccule. They have a greater density than the surrounding endolymph thus making the macula sensitive to changes in linear acceleration and, importantly, gravity. The semicircular canals, on the other hand, are sensitive to changes in angular acceleration. In BPPV otoconia from the utricle are thought to collect in the semicircular canals, making them abnormally gravity-sensitive. The net result is that changes in head position with respect to gravity result in an abnormal displacement of the cupula and stimulation of the corresponding vestibular afferents. This results in the characteristically abnormal eye movements and vertigo.

There are two theories of how this might occur. **Cupulolithiasis** proposes that degenerative otoconia stick to the cupula making it gravity-sensitive. Post-mortem findings of such deposits in patients who had suffered from BPPV add weight to this theory.[7]

The more recent theory of **canalolithiasis** gained momentum after surgical observations of free-floating debris in the posterior semicircular canal during an occlusion procedure.[8–10] This theory suggests that degenerative

otoconial debris float freely in the endolymph of the semicircular canal. When exposed to gravity, the otoconia fall to the lowest part of the canal, causing a change in endolymph pressure with subsequent displacement of the cupula. The change in pressure is due to a hydrodynamic 'plunger effect' where the otoconial debris act like a piston creating endolymph flow which deforms the cupula. This theory explains the 'latency' (delay in onset) of the nystagmus that is related to the time taken for the otoconial debris to fall and the initial adherence to the membranous canal. In addition, it may also better explain the 'fatiguability' as with repeated movements the otoconial debris may be dispersed or may become trapped in some part of the canal.[8]

While the majority of BPPV cases seem to be more compatible with the theory of canalolithiasis, some cases with atypical features may be explained on the basis of cupulolithiasis. Canalolithiasis may be converted to cupulolithiasis when otoconial debris floating in the canal attach to the cupula.

SYMPTOMS AND NATURAL COURSE OF THE DISEASE

BPPV most commonly arises from the posterior semicircular canal (p-SCC). Much less frequently the horizontal semicircular canal (h-SCC) is involved while the anterior canal (a-SCC) is very rarely affected.[3, 11–15] Honrubia et al.[14] report the prevalence of p-BPPV, h-BPPV and a-BPPV in their clinic as being 93%, 5% and 2% respectively, although other authors report a higher prevalence of about 8–10% for h-BPPV.[3, 16] Using electronystagmography (ENG) to make the diagnosis, Jackson et al. report posterior canal BPPV in 66.9%, horizontal canal in 11.9% and 21.2% with anterior canal.[17] BPPV may also arise from pathology of more than one canal on one or both sides.[3, 15, 18, 19]

The propensity for the accumulation of particles in the posterior canal is postulated to be related to anatomical factors such as the size of the common crus of the posterior and superior semicircular canals, its position below the utricle when supine and its dependent position when both erect and supine. Particles can become trapped in the posterior canal; any debris that may have entered the superior canal is more likely to fall back into the utricle.[20]

In the upright position, the horizontal canal's opening into the utricle is undermost, thus facilitating particle migration out of the canal, while the posterior canal's opening is uppermost. Therefore, the horizontal canal can be easily cleared by natural head movements but the posterior canal is a trap for any particles that have entered it. Similarly, particles may leave the horizontal canal just by the action of the person rolling over in bed whereas particles in the posterior canal will only be shifted backwards and forwards. This may explain the infrequent presentation of h-BPPV.

During manoeuvres, p-BPPV can be converted to either a-BPPV or h-BPPV to p-BPPV and a-BPPV to p-BPPV.[13, 21, 22] Similarly, bilateral apogeotropic h-BPPV may spontaneously convert to bilateral geotropic and is attributed to debris located in the anterior part of the canal sticking to the cupula dislodging and shifting to the posterior part of the canal.[16] Plugging of the horizontal canal presenting with persistent spontaneous nystagmus, vertigo and oscillopsia has also been described.[23]

The hallmark of p-BPPV is vertigo lasting seconds with or without nausea and imbalance on lying down, sitting up from the lying position, or rolling in bed and when extending or flexing the neck. These symptoms can present in clusters with several attacks per day. In between attacks or shortly after successful treatment, patients are either symptom-free or experience a sensation of imbalance. This sensation of imbalance can be described as 'walking on pillows' and may be attributed to the underlying damage of the otolith organs.[24] However, some patients may report atypical symptoms, and it is worthwhile conducting the positional tests in all patients presenting with episodic vertigo.[25] In the majority of cases the BPPV symptoms will subside within a few weeks, but in up to 30% the symptoms may persist for months.[16, 24] Choi et al. report BPPV as recurrent in 12.5% of cases and persistent in 10%.[26]

AETIOLOGY

Hallpike described ear disease in 66 out of 100 BPPV patients, although in only 28 ears was it on the side with the BPPV.[5] No cause has been found in 34–86% of patients.[12, 26–28] These cases have been termed 'primary' or idiopathic BPPV. However, there may also be an association with other pathologies:

- BPPV occurred in 9.8–15.3% of cases following vestibular neuritis.[29–31]
- Otosclerosis may be associated with BPPV in up to 51% of patients and may also occur following stapedectomy.[12, 28, 32, 33]
- Studies have suggested that Ménière's disease may be found in up to 2% of cases but it has been reported to occur in up to 30% of cases.[12, 27, 28] It has been postulated that hydropically induced damage to the maculae or partial obstruction may be responsible.[34]
- Head trauma is one of the most common causes of BPPV in 14.5–18%[12, 28] and can involve more than one canal.[19, 35] The force of the injury may cause the release of otoconia into the endloymph. BPPV can also result following traumatic spinal cord injury in up to 14.5% of cases.[36]
- Patients with positional vertigo may have migrainous vertigo. Migrainous symptoms during the positional episodes, atypical features of positional nystagmus and frequent recurrence of symptoms may differentiate between BPPV and the central positional syndrome due to migraine.[37]
- Otosclerosis and osteopenia are found with greater frequency in females with BPPV, particularly older postmenopausal women.[38–40]

- BPPV also is associated with progressive cochlear or vestibular failure, vertebrobasilar ischaemia and other vestibular disorders.[12, 28]

The common feature of these conditions is that they may lead to dislodgement of otoconia from the utricle, which may invade one or several semicircular canals after days, weeks or months.

In idiopathic BPPV, which becomes more prevalent with advancing age, release of otoconia is probably related to degeneration of the otolith organs. Risk factors that may initiate an acute episode of BPPV include prolonged bedrest, bending forward with the head down, and general anaesthesia, because the supine, head-down and head-reclined position (e.g. during intubation) lower the opening of the posterior canal, thus promoting the penetration of particles.[1]

DIAGNOSIS OF BPPV

Diagnosis of BPPV is made on the basis of typical signs (nystagmus) and symptoms (vertigo and nausea) provoked by specific positional tests. Understanding the characteristic eye movements during these tests will help in making the diagnosis.[41] Our understanding of vestibular eye movements is based on fundamental principles described by Ewald:

- The direction of eye movement is in the plane of the canal or canals that are stimulated.
- In the horizontal canal, endolymph flow towards the ampulla (ampullopetal) results in an excitatory and stronger response than flow away from the ampulla (ampullofugal), which is inhibitory. The opposite holds true for the vertical canals.

For example, the posterior canal and anterior canal pairs are stimulated when performing the Dix–Hallpike test. The patient is seated along the couch, feet up, and the head is turned 45 degrees towards the side being tested, aligning the vertical canals with the sagittal plane. The head is brought down briskly over the end of the couch to lie 30 degrees below the horizontal while maintaining a position 45 degrees to the side being tested. Patients should be counselled prior to the test about dizziness but that they are to try and maintain their eyes open for examination.

The **L**eft **A**nterior and **R**ight **P**osterior canals (**LARP**) are stimulated during the right Dix–Hallpike and the **R**ight **A**nterior and **L**eft **P**osterior (**RALP**) in the left Dix–Hallpike. During the right Dix–Hallpike there is ampullofugal (excitatory) flow in the right posterior canal and ampullopetal (inhibitory) flow in the left anterior. Normally this balances out and there is no nystagmus. However, if there were particles in the posterior canal, the ampullofugal forces would be greater, resulting in a net excitatory effect and eye movement consistent with the plane of the canal. The slow-phase eye movements when excitatory would be towards the right ear or downwards and inwards via the ipsilateral superior oblique muscle and the contralateral inferior rectus muscle. The fast phase would be upwards and outwards or upbeating geotropic-torsional nystagmus. This is best seen by closely watching the scleral vessels. The nystagmus typically reverses when sitting up. A cupulolithiasis type BPPV can also rarely occur and is characterized by nystagmus that occurs without latency and does not fatigue.

The side-lying test is an alternative and has been shown to produce similar results to the Dix–Hallpike.[42] In contrast to the Dix–Hallpike, the head is turned 45 degrees away from the side being tested such that the vertical canals are in the frontal plane. The patient is quickly moved to a supine-lying position with the neck hyperextended 20 degrees. The typical torsional nystagmus is seen beating towards the lowermost ear.

Similarly, the anterior canal during a right Dix–Hallpike or side-lying tests will be inhibited, i.e. flow will be ampullopetal. If particles are present, they will cause an inhibitory effect which will predominate causing the opposite nystagmus to the posterior canal – beating downwards and intorsional in the ipsilateral eye. The straight head-hanging manoeuvre has also been shown to be useful to diagnose a-BPPV where the head is extended backwards to a head-hanging position of the end off the bed from seated to supine.[43]

Horizontal canal BPPV is assessed using the roll test. The head is flexed 30 degrees, bringing the horizontal canal into the axial plane, and is then briskly rolled to one side. The same is repeated to the opposite side. In the majority of cases the nystagmus will be horizontal and geotropic and towards the ear being tested. When turned to the opposite side, the nystagmus will reverse and beat towards the undermost ear again. When a canal is stimulated with an ampullopetal force, the nystagmic response is greater (Ewald's second law), therefore the ear containing the loose particles would generally present with the brisker nystagmus hence helping to make the diagnosis. An apogeotropic nystagmus is also described and is thought to be related to cupulolithiasis.[16] In this situation, when the head is turned to the affected side, the force is ampullofugal hence the nystagmus will beat away (apogeotropic) from the affected ear.

Frenzel glasses can be used to better observe the nystagmus or it can be recorded with electro- or video-oculography. As BPPV can sometimes coexist with other vestibular disorders and the history can sometimes be atypical, many would perform a Dix–Hallpike routinely as part of a vestibular assessment.

Differential diagnosis

Causes of vertigo that need to be distinguished from BPPV include otological and neurological among others.[44] Otolological disorders include Ménière's disease, vestibular neuritis, labyrinthitis, superior canal dehiscence syndrome and post-traumatic vertigo. Neurological disorders include vestibular migraine, vertebrobasilar insufficiency, demyelinating lesions and

CNS lesions. It is important to discriminate BPPV from positional vertigo arising from central pathology. Such pathology may exist in the pontomedullary brainstem or vestibulocerebellum, with lesions often found dorsolateral to the fourth ventricle or in the dorsal vermis.[24, 45] A central lesion should generally be suspected when features different from BPPV are present or when brainstem or cerebellar signs are found. Single characteristics of BPPV such as latency, duration and time course of nystagmus, and fatigability with repeated positioning can also occur in central positional vertigo. However, it is unlikely that a central lesion mimics the entire nystagmus pattern of BPPV. The most reliable criterion to distinguish BPPV from central positioning vertigo is the direction of nystagmus: when the affected canal is optimally stimulated in BPPV by specific head positioning in the canal plane, the nystagmus always beats in the plane which is expected from activation of that particular canal.[45, 46] Thus, in the Dix–Hallpike position, p-BPPV always provokes a combined torsional and vertical component, which is expected from the connections between the p-SCC and specific eye muscles. Likewise, h-BPPV evokes horizontal nystagmus of maximal intensity after specific positioning for the horizontal canal.

In contrast, central positional nystagmus is not attributable to the stimulated canal plane. Purely vertical or torsional nystagmus, verified by examination under Frenzel glasses, should always raise the suspicion of a central lesion as it cannot be explained by stimulation of a single semicircular canal. Central positional nystagmus often persists as long as the precipitating head position is maintained whereas BPPV produces transient nystagmus and vertigo, except for the horizontal cupulolithiasis variant. Moreover, central positional vertigo and nystagmus usually does not fatigue with repetitive positioning. Another feature distinguishing central positional vertigo from BPPV is its monophasic course that makes the diagnosis highly unlikely in a patient with a long-standing history of recurrences and remissions. Rarely, central pathology may mimic typical BPPV except for response to therapeutic positional manoeuvres.[16] In summary, imaging of the posterior fossa is required when:

- nystagmus is atypical for any of the BPPV syndromes
- brainstem or cerebellar signs are present
- positional vertigo does not resolve with repeated therapeutic manoeuvres.

In a patient with central positional vertigo and normal imaging, migrainous vertigo or drug effects (e.g. amiodarone) should be considered.[47, 48] When central positional nystagmus without vertigo occurs as an isolated finding, imaging is often negative and a specific diagnosis cannot be made.

Other causes of dizziness include anxiety disorders and postural hypotension.

TREATMENT OF P-BPPV

Repositioning manoeuvres

EPLEY'S REPOSITIONING MANOEUVRE

The canalith repositioning manoeuvre (CRM) (**Figure 64.1**) has been recommended following evidence-based reviews by the American Academy of Neurology and American Academy of Otolaryngology – Head and Neck Surgery Foundation.[44, 49] A recent Cochrane meta-analysis has found that the CRM on its own is effective in close to 80% of cases.[50]

Epley developed the canalith repositioning procedure (CRP) in 1992 based on the theory of 'canalolithiasis' in order to move the particles from the posterior canal into the utricle via the common crus.[51] It is well tolerated and non-invasive. Patients should be counselled about the procedure and the possibility of vertigo prior to commencement. The affected p-SCC is identified by the Dix–Hallpike manoeuvre and the latency and duration of nystagmus is noted in order to determine the timing of the procedure. The patient is seated longitudinally on the couch facing away from the examiner and brought down with the head turned by 45 degrees to the affected side and extended over the edge of the table, just as in the Dix–Hallpike manoeuvre, and can of course follow on from the Dix–Hallpike. The head is then turned 90 degrees to the opposite side, rotating the body 90 degrees so that the patient is lying on the side, while the head is maintained firmly in place is the next step. The head is then rotated a further 90 degrees so that the patient is looking obliquely downwards. The patient is then asked to swing their legs over the side of the couch in anticipation of the next step which involves the patient being brought to the sitting position with the head turned 45 degrees to the unaffected side. The CRP finishes with the patient in the sitting position and the head turned forward 20 degrees. Epley advocated repeating the manoeuvre until there is no nystagmus or no progress made in the last two cycles. He reported total resolution of symptoms in 90%, and resolution of BPPV but persistence of other symptoms in 10% of patients after the initial CRP treatment. There are several modifications of this manoeuvre involving longer maintenance at each position and gradual position changing with 30-second intervals.[52, 53] A recent Cochrane review suggested limited evidence to support postural restrictions post-treatment, but to remain upright and limit head movement for 24–48 hours appears to offer increased treatment benefit.[50]

A modified Epley's manoeuvre has also been used for self-treatment and its efficacy compared to the efficacy of the Brandt–Daroff exercises. The authors reported a 64% success rate after 1 week in the group of patients that were given the Epley's manoeuvre compared to 23% in those given the Brandt–Daroff exercises. Treatment failures in the Epley's group were attributed either to early discontinuation or to inaccurate performance of the manoeuvre.[54]

Figure 64.1 Epley's repositioning manoeuvre. Left posterior canal BPPV. The patient is sat on the table with the head turned 45° to left side (affected side) **(a)**, and **(b)** brought down rapidly with the head still turned 45° to the affected side and extended over the edge of the table. Note that the neck is well supported. **(c)** The head is then turned 90° to the opposite side (right). **(d)** This is followed by rotating the head and body 90° facing downwards (135° from the supine position). **(e)** The legs are then displaced over the side of the table in anticipation of a return to a seated position, and **(f)** the patient is brought to a sitting position with the head turned forward.

SEMONT'S LIBERATORY MANOEUVRE

Semont, Freyss and Vitte devised what is known as the Semont's liberatory manoeuvre (**Figure 64.2**) that involves laying the patient on the affected side from a seated position, with the face turned upwards 45 degrees away from the affected canal.[55] The patient is quickly swung through the sitting position without pausing to the opposite side with the face now facing downwards by 45 degrees. The head position relative to the shoulder remains unchanged during the manoeuvre and the position should be maintained for 5 minutes. The patient then slowly resumes the sitting position. The authors reported resolution of symptoms in 92% of patients treated once or several times with this manoeuvre.[58] While studies have shown an improvement when this procedure is performed, a superior benefit to CRP has not been conclusively demonstrated according to one review[44] and is possibly not as good as CRP according to another.[49] Some authors, however, maintain that the ease of use makes it a useful option.[56]

BRANDT–DAROFF POSITIONAL EXERCISES

In 1980, Brandt and Daroff proposed a mechanical self-treatment that is based on Schuknecht's hypothesis of cupulolithiasis.[57] This consists of a rapid sequence of lateral head/body tilts. Starting from the sitting position, the patient rapidly moves to the challenging position, i.e. lying on the affected side (nose 45 degrees up)

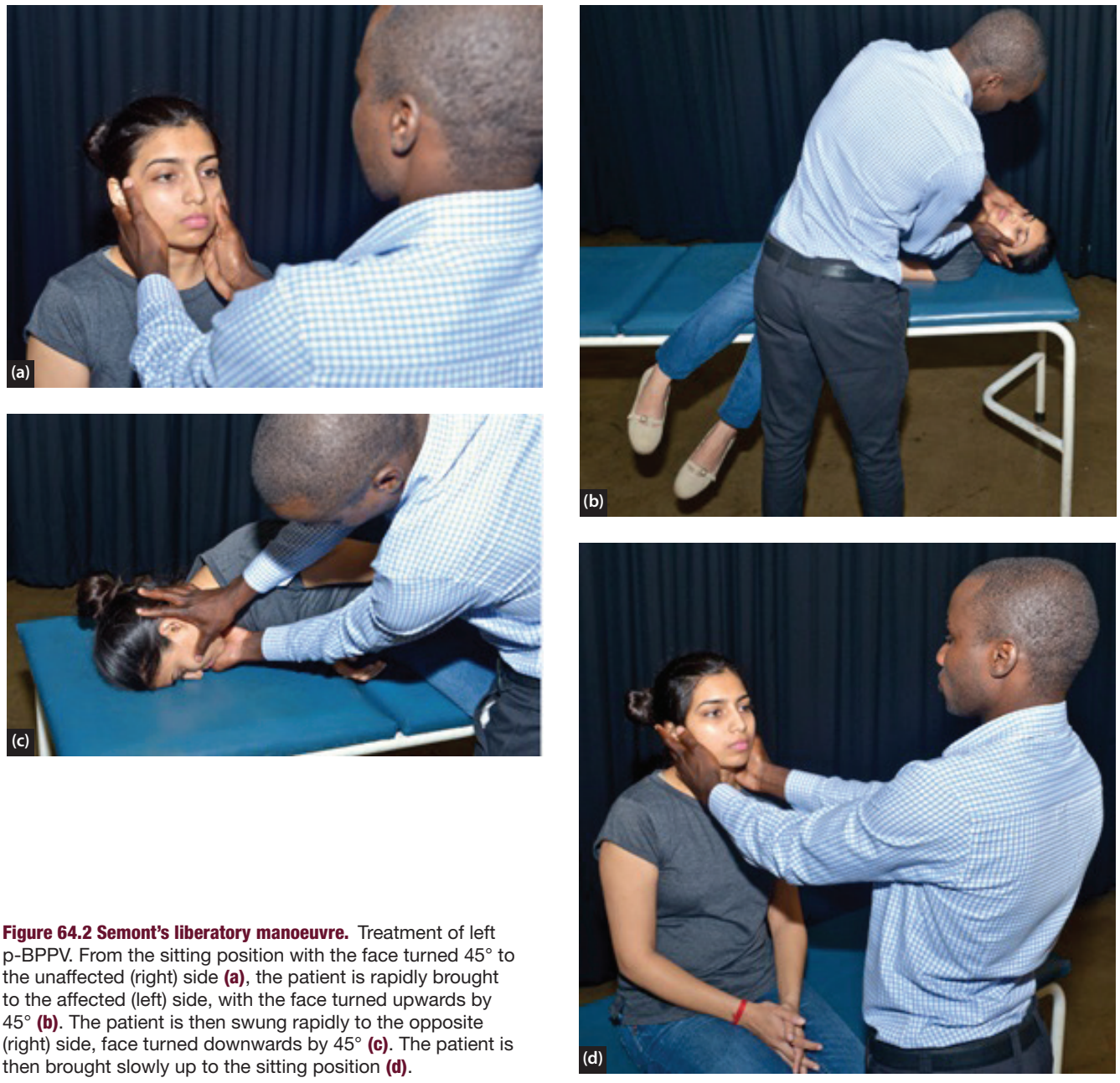

Figure 64.2 Semont's liberatory manoeuvre. Treatment of left p-BPPV. From the sitting position with the face turned 45° to the unaffected (right) side **(a)**, the patient is rapidly brought to the affected (left) side, with the face turned upwards by 45° **(b)**. The patient is then swung rapidly to the opposite (right) side, face turned downwards by 45° **(c)**. The patient is then brought slowly up to the sitting position **(d)**.

and remains in this position for at least 30 seconds or until the vertigo subsides. The patient then sits up for 30 seconds and thereafter assumes the opposite head lateral and nose-up position for 30 seconds before sitting up. This is repeated for 15 minutes three times daily. The authors reported that 66 out of 67 patients experienced complete relief from BPPV within 3–14 days, the exception being one patient who had a a perilymphatic fistula. Clinical experience has shown that response rates are usually lower and a controlled trial showed resolution of BPPV in only 23% after 1 week.[54] Thus, Brandt–Daroff involves dozens of self-induced vertigo attacks before BPPV may eventually disappear. For this reason, they are no longer a first-line treatment of BPPV. A review has shown that Brandt–Daroff exercises are not as effective as CRP.[49]

FACTORS THAT MAY INFLUENCE THE OUTCOME OF REPOSITIONING MANOEUVRES

Reports on whether the application of mastoid oscillation improves the efficacy of the particle-repositioning manoeuvre are contradictory, and in any case, the success rate of the CRP alone is quite high.[58, 59] Some clinicians give post-treatment instructions that include sleeping with two high pillows, wearing a collar and postural restriction for 48 hours after the repositioning manoeuvre. A≈recent Cochrane review has found a lack of evidence to suggest a benefit from mastoid oscillation although a significant but limited benefit may be obtained from postural restriction.[50]

The effect of the duration of symptoms before treatment on CRP success rate is controversial, as some authors report it to be a negative prognostic indicator while others report no correlation.[52, 60, 61] Patients with BPPV due to head trauma tend to improve less with treatment than idiopathic BPPV patients while patients with previous 'vestibular neuronitis' seem to have a better prognosis than patients with BPPV due to other aetiologies.[52, 62]

Studies have assessed the treatment of patients with positional vertigo but no detectable nystagmus on positional testing, i.e. 'subjective' BPPV. In these studies the side to treat was chosen on the basis of the symptoms reported on positional testing.[63–65] Tirelli et al.[63] found that treatment of 43 patients with positional vertigo without positional nystagmus by a modified Epley resulted in a 60% complete recovery rate and a 6% persistence of symptoms compared with a 90% complete recovery rate in 90 patients with typical BPPV. Haynes et al. reported symptomatic improvement with 86% in subjective BPPV after performance of an average of 1.1 Semont's manoeuvres and in 91% of patients with objective BPPV after 1.6 manoeuvres on average.[64] Neither of the studies included a control group with a sham manoeuvre. Weider[65] also reported on 48% of their cohort of 44 patients with symptoms of BPPV with no nystagmus on positional testing. Twelve patients had complete relief following an Epley manoeuvre but patients with long-standing symptoms were less likely to report a good result. It has been suggested that a subgroup of these patients may have otoconial debris in the short arm of the posterior canal.[66] However, other reasons could relate to the fatiguable nature of the nystagmus in BPPV, a mild form that may be suppressed by visual fixation or poor detection without the use of Frenzel glasses.[64]

The CRM has been recommended following evidence-based reviews by the American Academy of Neurology and American Academy of Otolaryngology – Head and Neck Surgery Foundation,[44, 49] and has been found to be effective on its own in nearly 80% of cases. The use of additional interventions such as post-treatment postural restrictions may further increase the treatment benefit but there is limited evidence to support this and only a small increase in treatment efficacy.[50] Hunt et al. did not find added benefit in using mastoid oscillation or additional steps with the Epley manoeuvre. There is no evidence to support the use of medication.[44, 49]

COMPLICATIONS AND ADVERSE REACTIONS

Several patients report gait instability following CRP, possibly due to the new position of the canaliths in the utricle.[67] Complications of CRP include conversion of p-BPPV to a-BPPV or h-BPPV in about 6% of treated patients.[13] In addition, the nystagmus may convert to a rapid form that persists and is unaffected by positional testing, possibly due to canalith jam, and these cases may be treated by the combination of the application of vibration with repositioning manoeuvres.[68]

Both Epley's and Semont's manoeuvres involve some neck strain and may be uncomfortable or impossible to perform in patients with severe cervical problems. The best solution in this situation is to do an Epley's manoeuvre on a couch where the upper half of the body can be lowered by 20–30 degrees, which obviates the need for head reclination. Brandt–Daroff exercises can be an alternative but are sometimes not pursued for long enough by immobile, elderly patients with neck pain.

Recurrence of BPPV increases with length of follow-up and eventually occurs in most patients. It is more likely in patients with secondary causes and should be treated with repeated positional manoeuvres.[26, 69]

Surgical treatment of BPPV

In a series of 5364 BBPV patients over a 20-year period, 53 patients failed to respond to repositioning manoeuvres and underwent p-SCC occlusion surgery.[70] While all were cured of their vertigo, nine patients suffered some degree of permanent hearing loss, ten developed objective balance dysfunction on caloric testing while five complained of subjective imbalance. Two patients later developed h-BPPV in the same ear and eight developed p-BPPV in the opposite ear, with two patients needing bilateral posterior canal occlusion. A number of case series describing the results of posterior canal occlusion can be found in the literature with similar results for control of the BPPV and many reporting the attendant risk of hearing loss and subjective dizziness.[71–77]

Gacek has advocated singular neurectomy via a transcanal approach for patients with chronic disabling vertigo for longer than a year and has reported on his and the results of others over three decades.[78–81] Surgery was performed on 242 patients, with 10 undergoing bilateral procedures. Complete relief (negative Dix–Hallpike) was achieved in 96.8% of cases with nine patients (3.7%) suffering sensorineural hearing loss.[81]

TREATMENT OF H-BPPV

Repositioning manoeuvres

'FORCED PROLONGED POSITION' ON THE HEALTHY SIDE

Vannucchi et al. advised patients with h-BPPV to lie down on the healthy side for 12 hours in order to facilitate gravitation of the debris into the vestibule by maintaining the affected h-SCC uppermost.[21] They reported total recovery within 3 days in 74.3% of cases out of 35 treated patients. They described occasional conversion of h-BPPV to homolateral p-BPPV, which was successfully treated with a Semont's manoeuvre. By contrast, the rate of recovery within 3 days in the group of patients who received no treatment (15 patients) and in those treated by head shaking (24 patients) was 26% and 16% respectively. Obesity and cervical spondylosis were factors that did not permit maintenance of the position for the time required.

270-DEGREE 'BARBECUE' MANOEUVRE

Lempert and Tiel-Wilck report the successful treatment of h-BPPV in two patients by an adaptation of Epley's manoeuvre.[82] This consists of turning the patient's head initially and then the body from the supine position in three 90-degree-step rotations (total 270 degrees) towards the unaffected ear. The body will eventually assume the prone position with the affected ear facing down, following which the patient will sit up. The rotation is performed within half a second and the head positions are maintained for 30–60 seconds.

Nuti et al. reported that, while both the 'barbecue' manoeuvre and the forced prolonged position are effective treatments for h-BPPV, the forced prolonged position may be successful in slightly more cases than the barbecue manoeuvre, which, however, achieves immediate results.[83]

360-DEGREE YAW ROTATION

Baloh et al. initially suggested a 180-degree rotation to the unaffected side with little success and then successfully treated two patients with h-BPPV with a 360-degree yaw rotation performed in 90-degree steps at 30-second intervals.[84] Casani et al. report an 89% success rate in 55 cases with geotropic h-BPPV treated by a combination of the 360-degree yaw rotation and forced prolonged position after one to three attempts.[16]

LIBERATORY MANOEUVRES

De la Meilleure et al. used this manoeuvre in six patients with h-BPPV. From the supine position, the head is lifted by 30 degrees, turned to the affected side and maintained in that position for 5 minutes.[15] The head is then turned quickly 180 degrees to the other side while maintaining 30-degree flexion and held there for 5 minutes. After the manoeuvre, the patient is asked to avoid head shaking and not to lie down for the next 48 hours. A 100% success rate has been reported, but patients may require treatment for bilateral h-SCC or for coexisting p-BPPV. Contraindications for this manoeuvre are cervical spondylosis, vertebrobasilar insufficiency or neck pain during the manoeuvre. The recommendation to perform an abrupt head rotation casts doubt on the safety of this procedure as vertebral artery dissection has been occasionally observed after chiropractic manipulations of a similar type.

Appiani et al. used the liberatory manoeuvre proposed by Asprella et al. for geotropic h-BPPV with a 78% cure rate after the first and 100% cure rate after the second attempt.[85] This manoeuvre begins with the patient seated on the side of the couch. A side-lying position is then quickly assumed on the unaffected side and maintained for 1 minute after the cessation of the nystagmus. The head is then quickly turned 45 degrees downwards and the position maintained for 2 minutes followed by a slow return to the sitting position. A similar manoeuvre, termed a 'modified Semont's', was used by Casani et al. for nine patients with apogeotropic h-BPPV with 55% success rate after two attempts.[16] The only difference between the Appiani manoeuvre and what Casani proposed is a rapid return to the seated position at the end.

A prospective randomized controlled trial for geotropic h-BPPV was conducted in 179 consecutive patients comparing the barbecue rotation, the Gufoni manoeuvre and a sham manoeuvre.[86] The Gufoni manoeuvre for geotropic nystagmus begins with the patient seated in an upright position and rapidly tilted to the unaffected side followed by a swift 45 degree downward turn of the head (nose down). A few minutes later the patient resumes a seated position. For apogeoptrpoic nystagmus the patient lies on the affected side followed by an upward turn of the head.

Outcomes included the resolution of vertigo and positional nystagmus assessed within 1 hour of two applications of each manoeuvre and the percentage resolution at 1-month follow-up. Both on the assessment day and at 1-month follow-up the barbecue rotation and Gufoni manoeuvre showed better responses than the sham manoeuvre, with no significant difference between the two procedures.

In another prospective randomized controlled trial of 157 consecutive patients with apogeotropic h-BPPV the Gufoni, head shaking and a sham manoeuvre were assessed.[87] Outcome measures included the resolution of vertigo and positional nystagmus assessed after a maximum of two applications on the same day, the following day and at 1-month follow-up. The therapeutic manoeuvres were better than the sham on the same day and at 1-month follow-up with no significant difference between the two. The Gufoni manoeuvre did, however, have a higher conversion rate to other types of nystagmus.

A prospective randomized controlled study of 63 patients with geotropic h-BPPV compared the Lempert (270 degree barbecue manoeuvre) manoeuvre with no treatment.[88]

Outcomes include patients' self-reported resolution of vertigo after the resolution of nystagmus and the time course in remission of positional vertigo. No significant difference was found in the time course of remission of positional vertigo between treated and untreated groups.

A prospective cohort was compared with retrospective data assessing prolonged forced position, head shaking and no treatment in patients with geotropic horizontal BPPV.[21] Forced prolonged position on the healthy side was significantly better than head shaking or no treatment at 3-day follow-up.

COMPLICATIONS AND ADVERSE REACTIONS

H-SCC canalolithiasis may convert to cupulolithiasis after a rotation manoeuvre, which, exceptionally, may in turn convert to horizontal canal-plugging by head shaking. The horizontal canal-plugging will be characterized by continuous unidirectional nystagmus that is not affected by positional testing. However, vigorous head shaking or gentle head percussion may unplug the canal.[23]

TREATMENT OF A-BPPV

A 96.7% efficacy has been reported for the modified Epley manoeuvre performed on 30 successive cases with a-BPPV.[89] The modified Epley starts using the Dix–Hallpike with the head turned 45 degrees away from the affected ear and brought to 30 degrees below the horizontal. It is kept in this position for 30 seconds then elevated while maintaining a supine position with the head at 45 degrees for 1 minute. A seated position is then assumed with the chin bent forwards at 30 degrees.

An alternative manoeuvre has been described involving moving from a seated to a head-hanging position with the head 30 degrees below the horizontal. After 30 seconds the head is brought to a chin-to-chest position for 30 seconds and then to a seated position for another 30 seconds. During the manoeuvre otoliths move towards the common crus and utricle. The authors described 84.6% success after a single manoeuvre, with complete resolution in all cases with repeated manoeuvres.[90]

BEST CLINICAL PRACTICE

- ✓ For posterior semicircular canal BPPV the canalith repositioning manoeuvre is safe and effective on its own in close to 80% of cases.
- ✓ Surgical options can be contemplated with long-standing BPPV where there has been no response to repeated appropriate repositioning manoeuvres.
- ✓ Imaging of the posterior fossa is required when:
  - ✓ nystagmus is atypical for any of the BPPV syndromes
  - ✓ brainstem or cerebellar signs are present
  - ✓ positional vertigo does not resolve with repeated therapeutic manoeuvres.

KEY POINTS

- BPPV is the commonest cause of peripheral vertigo.
- If unrecognized or poorly treated BPPV can lead to significant morbidity.
- BPPV results from particles floating in the semicircular canals (canalolithiasis) or attached to the cupula (cupulolithiasis).
- The posterior semicircular canal is most often affected.
- The vertigo typically lasts seconds and is positional.
- The majority of cases are idiopathic.
- The diagnosis is made using positional tests that produce nystagmus and vertigo.
- Repositioning manoeuvres displace the particles back into the vestibule and are successful in the majority of cases.

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CHAPTER 65

SUPERIOR SEMICIRCULAR CANAL DEHISCENCE

Harry R.F. Powell and Shakeel R. Saeed

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords superior semicircular canal dehiscence and superior semicircular canal dehiscence syndrome.

HISTORY

The association of vertigo or oscillopsia induced by pressure change or loud sounds, with dehiscence of the superior semicircular canal (SSC) was first described in 1998.[1] Using the scleral coil technique Lloyd Minor's team noted that eye movements evoked by sound or pressure stimuli aligned with the SSC.[2] Dehiscence of otic capsule bone overlying the SSC was identified on computerized tomography (CT). Superior semicircular canal dehiscence (SSCD) syndrome has subsequently become a recognized clinical condition that encompasses a wide variety of vestibular and auditory symptoms.

In 1949 Cawthorne[3] postulated that a 'third window' mechanism accounted for the positive Hennebert sign of labyrinthine fistula. Dehiscence of bone over the SSC and consequent connection with the middle cranial fossa provides a third mobile window into the inner ear in SSCD syndrome (SSCDS). Typical third window symptoms of SSCD occur either as a result of movement at the dehiscence from raised intracranial pressure, or at the oval or round windows from loud sounds or straining (e.g. a Valsalva manoeuvre against closed nostrils forcing air up the Eustachian tube and into the middle ear). Resultant alterations in inner ear fluid dynamics due to the third window cause increased firing of vestibular afferents and transient momentary vertigo.

As familiarity with SSCDS has increased there has been a massive increase in publications in the world literature, particularly in the last 5 years, as clinicians and scientists attempt to unravel the aetiopathogenesis and optimal diagnostic and management strategies for this relatively new condition.

PATHOPHYSIOLOGY

A constellation of symptoms can occur with SSCDS and the severity and spectrum of symptoms varies enormously. The mechanisms for all of them are not yet fully understood. However, the third window symptoms that underpin how the condition was discovered occur in two main ways. Marked inward movement of the stapes (raised middle ear pressure or loud sounds) leads to increased ampullofugal flow of endolymph away from the ampulla of the SSC (on the affected side), which is excitatory and causes tonic upward eye movement and ipsilateral intorsion (rotation of the upper pole of the eye towards the midline). Conversely, inward movement at the dehiscence causes ampullopetal flow towards the ampulla, which is inhibitory and causes tonic downward eye movement and ipsilateral extorsion.[2] The physiological basis for the variability of symptoms and signs between patients is not yet understood.[4] Suggested reasons are differences in the elasticity of the dura over the SSCD, differences in compliance of the round window

membrane, relative patency of the cochlear aqueduct and variance in the size of the dehiscence.[5]

EPIDEMIOLOGY AND AETIOLOGY

A 0.5–0.6% prevalence of SSCD has been observed in histological studies of cadaveric temporal bones.[6, 7] By comparison, reported prevalence from studies reviewing high-resolution temporal bone CT scans was 4–8%.[7–9] This discrepancy is explained by the effect of partial volume averaging in CT, which reduces with higher resolution finer slice collimation. Dehiscence alone is not sufficient to cause the syndrome, and many patients have dehiscence but are asymptomatic.

SSCDS could be congenital, acquired or a combination where a genetic predisposition followed by a secondary event triggers SSCDS. Predominant middle-aged onset and a statistically significant increase in prevalence with increasing age[10] make a pure congenital cause less likely. However, SSCDS has been reported in children[11] and affected siblings,[12] implicating genetic factors. Due to protrusion of the membranous labyrinth into the middle cranial fossa in fetuses, adhesion with the overlying dura has been postulated to prevent entire bone coverage of the SSC in some individuals.[13]

Ossification of the petrous bone over the labyrinth occurs from birth to the age of 3.[6] If the bone is insufficient, the resulting morphological abnormality may predispose certain individuals to SSCDS. Shearing force from a closed head injury, trauma to the temporal bone, slow erosion of thin bone, increased dural elasticity with time or sudden increase in intracranial pressure are all suggested secondary triggers.[14] A cadaveric study concluded that, when only an endosteal layer is present over the SSC, this is susceptible to a second event which could cause dehiscence and hence the SSCDS.[15] A progressive negative balance of labyrinthine osseous metabolism occurring with a congenital thin layer of bone over the SSC has also been suggested.[16] Absence of a single convincing theory suggests a combined or multifactorial aetiopathogenesis is responsible for SSCDS.

CLINICAL MANIFESTATIONS

Patients may present with a variety of signs and symptoms, either exclusive vestibular symptoms, less commonly exclusive auditory symptoms[12] or a combination. One study showed that, when the dehiscence is greater than or equal to 2.5 mm on CT, patients tend to experience combined auditory and vestibular symptoms.[17] Auditory symptoms include hearing difficulty/loss, autophony, pulsatile tinnitus and a description of hearing their eye movements or their footfall. The latter are from abnormal amplification of certain sounds in the body due to increased sensitivity to bone-conducted sound. The hearing loss is an apparent conductive loss with greater air–bone gap (ABG) in the low frequencies due to supranormal bone-conduction thresholds and suspected dissipation through the dehiscence of acoustic energy transmitted by air-conduction mechanisms.[18, 19] There is consensus from some studies that the dehiscence size correlates with the size of the ABG.[20, 21] The autophony of SSCDS usually involves hearing their own voice but not their breathing when compared with patients who have patulous Eustachian tube.[22] The Weber tuning fork test typically lateralizes to the affected side and patients may be able to hear a tuning fork placed on the lateral malleolus of the ankle.[23]

The Tullio phenomenon of vestibular symptoms occurring in response to loud sounds was first noted in patients with otosyphilis and described in 1929. Transient vertigo, imbalance and oscillopsia can all occur with loud sounds or intracranial or middle ear pressure changes in SSCDS and the physiological third window effect is responsible. Generalized imbalance may be a result of fluctuation in the vestibular system that the brain struggles to compensate for. Although a non-specific symptom, generalized imbalance has been shown to improve in patients undergoing surgical treatment for SSCDS.[19, 24]

INVESTIGATIONS

Cross-sectional imaging

High-resolution CT is the gold standard for identification of SSCD. The imaging data are reformatted in the coronal plane as standard (**Figure 65.1a**) but can also be reformatted in the plane of the SSC (Pöschl view) (**Figure 65.1b**) and/or the orthogonal plane (Stenvers view).[25, 26] Due to partial volume, averaging CT results in false-positives and overestimation of dehiscence size as shown in a study comparing CT and surgical findings.[27] To improve specificity and positive predictive value 0.5 mm collimated scans with Pöschl plane reformatting are advised.[28] More recently the senior author and colleagues have been utilizing cone beam CT to give higher-definition imaging and improve sensitivity and specificity.

Using magnetic resonance imaging as an adjunct or instead of CT has been suggested in an attempt to reduce ionizing radiation exposure. Fast imaging employing steady-state acquisition (FIESTA) MRI has been shown conclusively to exclude SSCD, with negative predictive values as high as 100%,[29] but MRI cannot consistently diagnose thin or dehiscent SSCs.[30]

Vestibular evoked myogenic potentials

Vestibular evoked myogenic potentials (VEMPs) are recorded in response to high-intensity narrow-band clicks or tone bursts. In ocular VEMP (oVEMP) testing surface electrodes beneath the eye pick up excitatory responses of the extraocular muscles. Sensitivity and specificity of oVEMPs are reported as greater than 90%[31] and their use has been suggested as a screening tool for SSCDS prior to high-resolution CT and consequent radiation exposure. Cervical VEMPs are short-latency relaxation potentials recorded by surface electrodes placed on the skin over the ipsilateral sternocleidomastoid muscle when it is

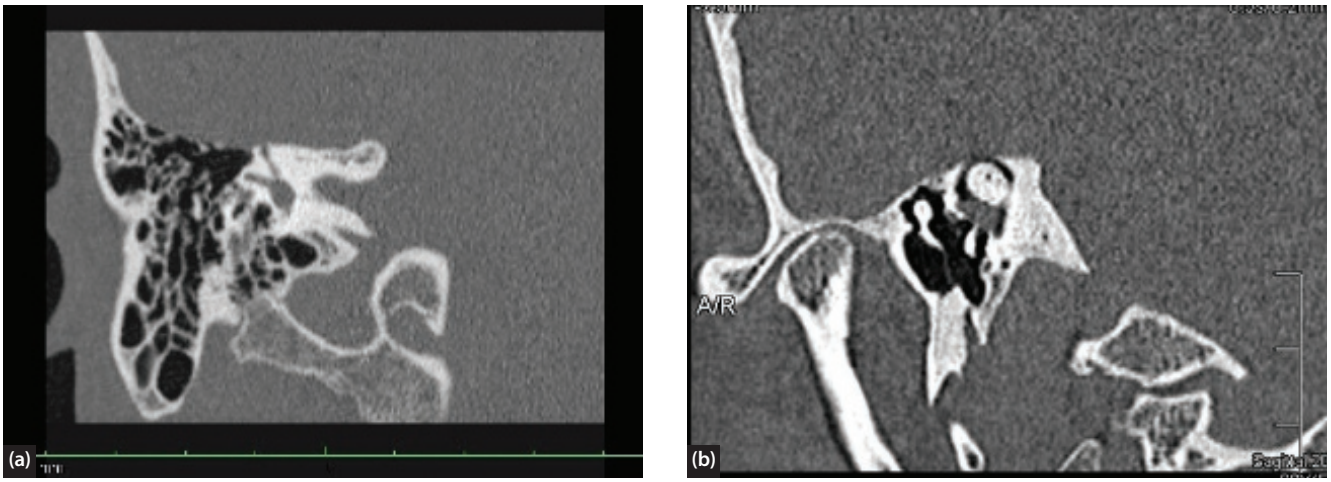

Figure 65.1 CT images of dehiscent right superior semicircular canal. **(a)** Coronal, **(b)** oblique coronal reformat in plane of SSC ('Pöschl view').

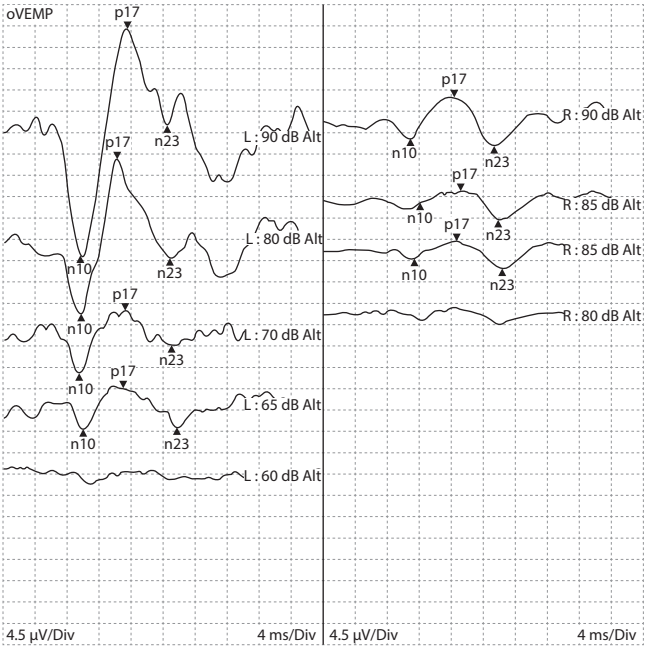

Figure 65.2 Cervical VEMP traces from a patient with left SSCDs. The lowest measurable response (initial inhibition followed by excitation) is at 85 dB on the normal right side. Responses on the left side are present down to 65 dB, which is lower than normal and suggestive of a third window.

tonically contracted (Figure 65.2). Cervical VEMP sensitivity and specificity for diagnosing SSCDS ranges from 80% to 100%.[31] VEMP responses are likely to be from the saccule (cervical) and utricle (ocular).[32–34] It is postulated that the saccule is more sensitive to sound stimuli than normal when there is a third window from SSCD.

Patients with SSCDS have VEMP responses present at lower than normal thresholds for the affected ear in both air conduction and bone conduction.[33] Some studies have also shown larger VEMP amplitudes.[23, 35]

Accurate diagnosis of SSCDS is reliant upon concordant clinical, radiological and electrophysiological findings.

MANAGEMENT

Patients with mild symptoms that are not intrusive or bothersome should be treated conservatively and given advice on avoidance of triggers or stimuli.[19, 36] Ventilation tube insertion has been beneficial for some patients with predominant pressure-related symptoms.[36] This reduces the influence of pressure change in the middle ear cleft but does not deal with the pathology directly.

Surgical management has evolved since 1998. Techniques that address the SSC itself include plugging, capping and resurfacing.[37] Initially, access was through a middle fossa craniotomy.[1] In 2009 the first transmastoid approach to the SSC was described.[38] Round window reinforcement has more recently been proposed in a multicentre series with six surgeons using a permeatal or endaural approach.[24]

If symptoms are disabling or detrimentally affecting a patient's day-to-day life and when those symptoms are predominantly attributable to a diagnosis of SSCDS, surgical management should be offered. The procedure, its risks and alternatives should be explained to enable patient-centred decision-making. In a single-centre series spanning 3.5 years 25/37 patients were offered surgical intervention.[19] The choice of technique or approach is obviously determined by the experience of the surgeon and team.

Middle fossa craniotomy has the advantage of direct visualization of the dehiscence. The disadvantages are the inherent risks of craniotomy and temporal lobe retraction and the necessity for longer inpatient hospital stay. Plugging, capping, resurfacing or combined plugging and resurfacing can all be achieved. The aim of capping and resurfacing is to cover but not occlude the SSC with the intention of inflicting less post-operative dysequilibrium or imbalance. These techniques are also thought to carry lower risk to the cochlea and consequent sensorineural hearing loss than plugging.[39] Bone, cartilage grafts, hydroxyapatite cement or fascia have all been used. A combination of temporalis fascia, bone pâté and/or bone wax have been used for plugging.[37]

An endoscopic middle cranial fossa (MCF) approach has been described.[40] It did enable shorter operative and recovery times but still carries the risks of craniotomy.

The transmastoid (TM) approach has become more common as otologists have become familiar with SSCDS. Kirtane et al.[38] adapted Lorne Parnes' technique for occlusion of the posterior semicircular canal described for benign paroxysmal positional vertigo (BPPV)[41] and applied it to the SSC as TM plugging. The disadvantage or main criticism from sceptics was a lack of direct visualization of the dehiscence. TM resurfacing[19, 39] has subsequently been reported using silicone elastomer sheeting (silastic) or a combination of bone pâté and fibrin sealant (Tisseel) to cover the dehiscence. TM resurfacing requires skeletonization of the labyrinth and exposure of the MCF dura lateral to the SSC. The dura can then be lifted off the MCF floor and the extent of the dehiscent SSC identified with the reflective surface of a round knife (**Figure 65.3**). The TM approach may be less feasible when there is significant 'overhang' of the dura lateral to the SSC or if there is extensive tegmen dehiscence requiring simultaneous reconstruction.[36] Another anatomical variant that poses a particular challenge to TM resurfacing is if the orientation of the dehiscence is such that the exposed canal, particularly the posterior limb, faces obliquely/medially.[19]

Round window (RW) techniques may in future obviate the need for craniotomy or mastoidectomy. Kartush hypothesized that patients previously thought to have perilymph fistula and successfully treated with round and/or oval window patching may actually have had SSCDS.[24] RW occlusion was reported using bone wax and fascia[42] but results were not replicable, heralding adaptation to RW reinforcement techniques utilizing temporalis fascia, tragal cartilage and perichondrium, fat, loose connective tissue, gelatin sponge and/or silastic.[24] Advantages include shorter anaesthetic/operative time and recovery, lower morbidity and none of the risks of intracranial surgery. The temporary nature of reinforcement does permit recurrence of symptoms if and when mobility of the RW recurs and thus the third window effect is re-established.[40] Proponents suggest RW reinforcement as an alternative option for patients with SSCDS in a better- or only-hearing ear, if a patient is not medically fit for general anaesthetic or longer general anaesthetic procedure and if/when the diagnosis is uncertain, to elucidate symptom improvement prior to more definitive surgery.[24]

OUTCOMES AND COMPLICATIONS

A 2015 systematic review and meta-analysis of 150 procedures from 20 studies reported an overall success rate of 94% for four methods of canal repair (plugging, capping, resurfacing or combined plugging and resurfacing), with no statistically significant differences observed between them.[43] The 10/150 procedures where there was no improvement in symptoms were considered failures; the successes include some patients with partial resolution of symptoms. The data analysis recognized a 100% success rate for combined resurfacing and plugging in 19 patients. The review found no significant difference in outcome when comparing the middle fossa approach with the TM approach.[43] Limitations to the meta-analysis include lower numbers of TM procedures and resurfacings compared with numbers of middle fossa approaches and pluggings. This may prove to be a consequence of time and experience as the TM technique shows promise, carries fewer risks and is gaining favour.[19, 44]

For 19 patients undergoing RW reinforcement techniques there was a statistically significant improvement in 8/9 symptoms of SSCDS (the exception being hearing loss).[24] RW reinforcement has distinct advantages but the potential temporary nature of the technique and the lack of intervention with the SSC itself necessitate ongoing/further evaluation in SSCDS. The Superior Semicircular Canal Dehiscence Patient Survey used in the RW study has already been used by other investigators evaluating benefit of interventions for SSCDS[19] but further study is required to assess its validity.

Combined major and minor complication rates have been reported as 12% (13/105) for MCF procedures and 16% (7/45) for TM SSCDS procedures.[43] The observed difference was not statistically significant. There were nine

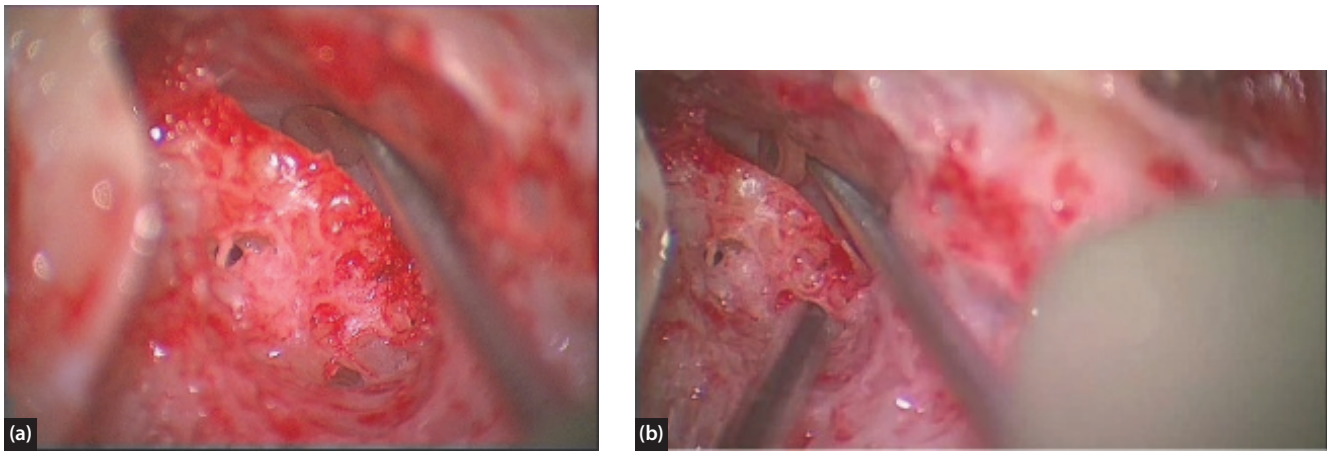

Figure 65.3 Intra-operative images from a left-sided resurfacing procedure. The position of the dehiscent lumen **(a)** and the dehiscent anterior limb **(b)** of the SSC are visualized in the reflective surface of the round knife.

major complications, six permanent total sensorineural hearing losses (four plugging; two resurfacing or capping) and three facial nerve injuries (respective approaches/techniques not reported). The 11 minor complications included transient sensorineural hearing loss, BPPV and transient post-operative dysequilibrium.

Exceptionally delicate surgical plugging technique to minimize the risk of rupture of the membranous labyrinth and consequent permanent sensorineural hearing loss cannot be emphasized enough. The risk of facial nerve injury is suspected to be higher in the MCF approach; however, significant experience of any chosen or preferred surgical technique is essential before attempting surgery for SSCDS.

CONCLUSION

As the experience of clinicians and surgeons treating SSCDS increases, so does the body of world literature to support or refute diagnostic and management strategies. Conservative management is advocated unless symptoms are bothersome. Current surgical interventions show high success and low complication rates. A focus on accurate diagnosis, patient-centred decision-making and a drive to improve the quality of patient care should enable ongoing publication of high-quality evidence. This should underpin future decision-making in all areas of SSCDS management as our experience and understanding of this relatively new condition evolves.

BEST CLINICAL PRACTICE

- ✓ The diagnosis of SSCDS requires a positive triad of history with typical clinical features, high-resolution CT and recording of VEMPs at lower than normal thresholds on the affected side(s).
- ✓ Patients whose SSCDS symptoms are affecting their quality of life should be considered for intervention in light of the severity of their symptoms.
- ✓ With sufficient neuro-otological experience of the surgical techniques, candid discussion of the options enables patient-centred decision-making. It is important to note, however, that in our experience, patients with multiple vestibular pathologies or atypical vestibular symptoms are the ones for whom SSCD surgery has not been curative (although they do report improvement in their SSCD symptoms).

FUTURE RESEARCH

- ➤ To elucidate the aetiopathogenesis of this condition and potentially thus enable development of preventative treatments.
- ➤ Investigate the physiological explanations for those symptoms not yet understood and investigate the causes for variable symptom severity.
- ➤ Robust evaluation of the RW reinforcement techniques.
- ➤ Further meta-analysis of surgical techniques.

KEY POINTS

- There are a huge variety of symptoms associated with SSCDS.
- Some of these are attributable to the third window, some are related to increased sensitivity to bone conducted sounds but for the remainder the pathophysiology is not yet understood.
- Third-window symptoms include transient vertigo, imbalance and/or oscillopsia in response to loud sounds or intracranial or middle ear pressure changes.
- SSC dehiscence alone is not sufficient to cause the syndrome; many patients have dehiscence but are asymptomatic.
- Patients with SSCDS have VEMP responses present at lower than normal thresholds for the affected ear in both bone conduction and air conduction.
- Patients with symptoms that are not intrusive or significantly bothersome should be managed conservatively and advice given regarding avoidance of triggers or stimuli.
- Transmastoid surgery enables shorter hospital stay and does not carry the risks of intracranial surgery when compared to the middle fossa approach.
- The round-window reinforcement technique shows promise; potential advantages are shorter surgical duration and less surgical morbidity with a suspected lower risk of sensorineural hearing loss. For some patients, the technique has only provided temporary relief and it does not deal directly with the SSC.

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CHAPTER 66

VESTIBULAR NEURITIS

Charlotte Agrup

SEARCH STRATEGY

Data in this chapter may be updated by searches of Medline, EMBASE classic, EMBASE Ovid, CENTRAL (Cochrane Central Register of Controlled Trials), The Cochrane Ear, Nose and Throat Disorders Group Trials Register and additional sources for published and unpublished trials. Language was restricted to English.

INTRODUCTION

Sudden onset of sustained severe dizziness, nausea, sickness and postural imbalance is the characteristic presentation of vestibular neuritis. The patient will typically complain of vertigo (a subjective sensation of rotation/movement) and symptoms will worsen with change of position and head movements. The severely affected patient will not be able to walk unsupported but will prefer to lie down on their side, often lying on the affected ear. With milder cases the patient feels dizzy and imbalanced with some nausea but may not feel unwell enough to render seeking medical advice.

Even though vestibular neuritis is the preferred nomenclature, labyrinthitis is more commonly used among laymen and also medical professionals. However, if used strictly, labyrinthitis includes cochlear pathology (hearing loss/tinnitus) in addition to the vestibular symptoms. Other terms such as acute idiopathic peripheral vestibular dysfunction and vestibulopathy are occasionally also used.

In the adult population, around 40% of all dizziness is caused by a peripheral vestibular pathology (which includes the vestibular end organs of the inner ear and/or the vestibular nerve).[1] Of these peripheral pathologies, 3–23% have been reported to be due to vestibular neuritis.[1] There is only one publication on the prevalence of vestibular neuritis, which reports an occurrence rate of around 3.5 per 100 000.[2] This may well be an underestimate of the true incidence of the condition since no diagnosis is made in a substantial proportion of people who do not seek medical advice.[3] There is no difference in gender prevalence in vestibular neuritis and the typical age of presentation is around 40–50 years old. Although present in the paediatric population, it is much less common, with a suggested prevalence around 1.8% in children presenting with vertigo.[4]

The severe acute symptoms of vestibular neuritis normally last for between 3 and 7 days and are followed by gradual spontaneous resolution. The majority of cases will recover over a period of 6–12 weeks due to the effect of a number of different complex mechanisms collectively called central vestibular compensation.[5] A general rule appears to be that the more vestibular function that is lost during an acute episode of vestibular neuritis the more severe symptoms will be. However, different patients react very differently to symptoms.

PATHOAETIOLOGY

A selective inflammation of the vestibular nerve is the most favourable aetiology. Inflammation of a nerve may cause demyelination and associated loss of function, which can be irreversible. Temporal bone studies have shown evidence of chronic inflammatory changes of the vestibular nerve with diffuse perivascular lymphocytic infiltrates, consistent with post-infectious inflammatory changes.[6] These changes can be seen months to years after the initial acute episode. There is indirect evidence of inflammation of the vestibular nerve but not of inflammation of the

vestibular neurons and therefore vestibular neuritis is the preferred nomenclature, not vestibular neuronitis.

Vestibular neuritis may have a viral cause which is supported in some patients by the history of a preceding or coinciding cold/flu or epidemics of cases, at a workplace or among family members. However, this is not a prerequisite for the diagnosis. Reactivation of a latent virus has been suggested and the presence of herpes simplex virus type 1 (HSV-1) DNA in human vestibular ganglia and nuclei has been shown.[7, 8] Also colocalization of latent HSV-1 and CD8+ T-cells in vestibular ganglia further supports the hypothesis that HSV-1 reactivation is possible and may cause vestibular neuritis.[9, 10] Although HSV-1 is the most favourable viral agent, there is evidence that several other human viruses can cause isolated peripheral vestibular dysfunction, including rubella, cytomegalovirus, Epstein–Barr virus, adenovirus and certain strains of influenza types A and B.[11]

Using magnetic resonance imaging (MRI) an isolated enhancement of the vestibular nerve in connection with vestibular neuritis has been shown, supporting an inflammatory response.[12] Also, a decrease in vestibular nerve cross-sectional area and height in patients with unilateral vestibular neuritis has been shown using constructive interference in steady-state (CISS) parasagittal MRI.[13]

The evidence of viral infection being the aetiology remains indirect and circumstantial[14] and other aetiologies of acute vestibular loss are certainly possible, such as surgical unilateral vestibular deafferentation (i.e. vestibular neurectomy). Head trauma may cause acute vestibular loss and immunological causes have also been suggested.[15, 16] In the patient with vascular disease, particularly the elderly, a vascular aetiology seems likely but is very rarely proved.

CLINICAL PRESENTATION AND DIAGNOSIS

Vestibular neuritis presents with symptoms and clinical signs related to sudden, isolated unilateral vestibular loss. Symptoms typically consist of sudden onset of persistent vertigo (commonly a subjective sensation of rotation) with associated distressing autonomic symptoms such as nausea, vomiting, sweating and pallor. Severe symptoms would normally last for a few days before gradually starting to spontaneously resolve. There should be no associated cochlear symptoms (hearing loss and tinnitus), neurological symptoms or signs of brainstem lesion.

The vestibular nerve has two branches, the superior and inferior nerve. The superior nerve is more commonly affected with vestibular neuritis, which may be explained by its course through a longer and more narrow bony canal making it susceptible to swelling (associated with inflammation) causing entrapment.[17] Accordingly, only approximately 18% of vestibular neuritis affects the inferior nerve.[18, 19] The presentation of symptoms, clinical findings and results of vestibular testing will depend on which branch of the vestibular nerve (i.e. part of the vestibular system) is affected. Superior vestibular neuritis presents with a vestibular lesion that affects the anterior and horizontal semicircular canals and utricular function but spares the posterior semicircular canal function and most of the saccular function. In contrast, inferior vestibular neuritis affects the posterior semicircular canal function and the saccular function. Although vestibular neuritis is mostly unilateral, bilateral sequential involvement has been reported.[20]

Visual vertigo, dizziness provoked by visual environments with repetitive or moving visual patterns, is common with a peripheral vestibular dysfunction.[21] For this reason, this group of patients dislikes visually busy environments (such as traffic, crowds and supermarket aisles) which will induce dizziness/imbalance and a sensation of disorientation. Benign paroxysmal positional vertigo (BPPV) is a common sequel to vestibular neuritis and will develop in the affected ear in 10–15% of cases.[20] However, in a study of patients with inferior vestibular neuritis, none showed BPPV as a sequel. Anxiety disorders and panic episodes are very common in association with vertigo/imbalance. It is likely that, in some patients, vestibular dysfunction may play an important role in the aetiology of these disorders[22] and often anxiety and panic episodes may be the main presenting symptoms associated with the vestibular neuritis.

Diagnostic criteria for vestibular neuritis have been suggested by Coats (**Box 66.1**)[23] but there are no generally agreed specific criteria. History, clinical examination and vestibular tests are the basis for diagnosing vestibular neuritis and a clear, detailed history provides a big step towards a certain correct diagnosis.

The most characteristic clinical finding with sudden unilateral loss of vestibular function is the spontaneous peripheral vestibular nystagmus (**Box 66.2**). An acute loss of peripheral vestibular function results in a slow vestibular-induced drift of the eyes in the same direction as the lesion. This drift is interrupted by rapid saccadic eye movements in the opposite direction, towards the healthy ear. This combination of slow and fast eye movements constitutes the spontaneous peripheral vestibular nystagmus. The nystagmus is horizontal with a torsional component, its direction is defined by the fast phase and it is described as first-, second- and third-degree nystagmus. In acute severe cases, the nystagmus is initially present with optic fixation but, in milder cases and during recovery, there will be no visible nystagmus with optic fixation and it is not until the optic fixation have been removed that the nystagmus will be present. Of note is that, when only the

BOX 66.1 Modified diagnostic criteria for vestibular neuritis suggested by Coats[23]

Acute onset of non-recurrent vertigo often accompanied by nausea and vomiting
Absence of cochlear symptoms (hearing loss/tinnitus) or signs of central nervous involvement
Commonly unilateral partial or complete peripheral vestibular lesion
Complete subsidence of symptoms within 6 months

BOX 66.2 Characteristics of the spontaneous peripheral vestibular nystagmus

- Unidirectional
- Horizontal
- Conjugate
- Temporary
- Enhanced by removal of optic fixation
- Obeys Alexander's law

BOX 66.3 Characteristic clinical examination findings with acute vestibular neuritis

- Horizontal–torsional spontaneous nystagmus, beating away from the side of the lesion, more vigorous without optic fixation
- Headthrust test positive on the same side as the lesion
- Gait test and Unterberger test show deviation to the side of the lesion
- Romberg test shows marked increase of sway

inferior vestibular nerve is affected, spontaneous nystagmus is rare. It is also important to note that other types and directions of nystagmus (i.e. purely torsional, vertical or dysconjugate nystagmus) indicate a central pathology and should prompt further investigations.

Clinical examination

A detailed medical examination including neuro-otological examination, general neurological examination and examination of the cardiovascular system is essential and confirms diagnosis. The neuro-otological examination should include examination of the external ear and otoscopy, in addition to assessment of vestibulo-ocular and vestibulospinal function.

Examination of eye movements is a must and should include the cover test (looking for strabismus), the full range of eye movements and gaze testing (looking for nystagmus with central gaze, 30-degree left gaze and 30-degree right gaze, preferably with and without optic fixation). With the left and right gaze testing it is important that the angle does not exceed 30 degrees since a larger angle can induce physiological end-point nystagmus (beating in the same direction as the gaze). In the majority of patients the spontaneous nystagmus will subside within 48 hours and the nystagmus with optic fixation disappears within 1–2 weeks. However, with removal of the optic fixation (e.g. by using Frenzel glasses or videonystagmography (VNG) goggles) the spontaneous nystagmus may be observed for as long as 5–10 years.

The **headthrust test** is a simple bedside test of the horizontal vestibulo-ocular reflex and is positive for the side that causes the corrective saccades, indicating a vestibular dysfunction on the same side. A **Hallpike test** to exclude positional vertigo should always be performed, in the non-acute stage, since it is not unusual for BPPV to follow after the acute vestibular neuritis. Clinical tests assessing vestibulospinal function are non-specific and often insensitive. However, tests of stance and gait provide an indication of the extent of the patient's disability and interaction of vestibulospinal activities with other systems. A tendency to sway on the **Romberg test** may suggest peripheral vestibular pathology and a marked increase in sway has been demonstrated in elderly patients with a unilateral vestibular hypofunction.[24] Also with the **gait test** (5 m walk with the eyes open and then with eyes closed) a deviation towards the side of the peripheral vestibular lesion is commonly seen. The **Unterberger test** has been shown to have poor sensitivity and specificity.[25] However, with a peripheral vestibular dysfunction the patient may also deviate to the side of the lesion during this test.

Characteristic test findings are summarized in **Box 66.3**.

Diagnostic vestibular testing

The use of diagnostic vestibular testing confirms diagnosis. These testing facilities are only available at specialist centres and consist of the caloric test, videonystagmography/electronystagmography (VNG/ENG), cervical and ocular vestibular-evoked myogenic potential (c- and oVEMP), subjective visual vertical and horizontal and video head impulse test (VHIT). A detailed explanation of these different tests is beyond the scope of this chapter and they will therefore be discussed only briefly where they have particular relevance to vestibular neuritis.

The **caloric test** is the gold standard for diagnosing unilateral peripheral dysfunction, with a reduced or absent response on the affected side. In the study by Sekitani et al. 50% of patients with vestibular neuritis, investigated with the caloric test, were shown to have a partial canal paresis.[2] Of note is that, when only the inferior nerve is affected, the caloric test, which depends largely on the horizontal canal function, is normal. The **VNG/ENG recordings** of eye movements allow a more detailed evaluation compared to the clinical examination, in addition to providing a record of the eye movements. A number of the standard battery of eye movement recordings help to identify a unilateral vestibular dysfunction, for example the gaze testing with identification of the typical peripheral nystagmus, but also central neurological pathologies can be identified (typically cerebellar lesions).[26] The **rotatory chair** (used in combination with VNG or ENG) is the gold standard for diagnosis of bilateral vestibular loss. The standard test battery can also identify a peripheral vestibular asymmetry.[26]

The oVEMP and cVEMP can determine which branch is affected in an episode of vestibular neuritis (the superior or inferior vestibular nerve). Studies have shown that, when the superior nerve is affected, oVEMP is abnormal and cVEMP is normal (reduced or absent n10 amplitude at the eye contralateral to the lesion and large asymmetry ratio with oVEMPs as opposed to normal amplitude and asymmetry ratio with cVEMPs). Contrarily, when the inferior vestibular nerve is affected, the oVEMP is normal and the cVEMP is abnormal (increased asymmetry ratio and reduced or absent amplitude response).[27, 28]

Subjective visual vertical and horizontal are quick to perform and both show a deviation to the side of the lesion with vestibular neuritis.[29] The VHIT is a relatively new development and it has been suggested that video recording of the head impulse test improves the sensitivity of this test.[30] An abnormal VHIT has been shown to be associated with a vestibular loss of more than 62.5% identified with the caloric test. On the other hand, with a caloric deficit of less than 40%, the VHIT is normal.[31]

RECOVERY AND RESOLUTION

As mentioned above, the majority of patients with vestibular neuritis recover fully without intervention within 6–12 weeks. This process may be partly related to restoration of peripheral vestibular function[32] and partly to development of vestibular compensatory mechanisms which involve brainstem, cerebellar, cortical and spinal functions.[5, 33] The recovery does not follow a linear pattern but symptoms will often fluctuate. However, a ground rule is that reoccurring symptoms will not be as severe as symptoms appearing during the initial vestibular insult.

Vertigo is experienced when there is an asymmetric resting activity between the two vestibular nuclei (localized in the brainstem). Neural recordings in animals recovering from a unilateral peripheral vestibular lesion show that central compensation depends on an increased spontaneous neural activity in the ipsilesional vestibular nucleus and a decreased spontaneous neural activity in the contralesional nucleus, thereby rebalancing activity of the left and right vestibular nuclei.[34, 35] Some of resolution of symptoms can be related to recovery of peripheral vestibular function and 50–70% of patients have been shown to have a complete recovery of peripheral vestibular function assessed by using the caloric test.[36, 37] In line with this, around 20% of patients have been shown to remain symptomatic following surgical unilateral vestibular deafferentation, limiting peripheral vestibular recovery.[38] However, there is a lack of correlation between recovery of clinical symptoms and caloric recovery: where there has been no restoration of peripheral function some patients feel well recovered but up to 20% of patients experience continued symptoms despite normalization of caloric testing.[39] Hence, there are other factors than recovery of peripheral vestibular function that are significant for patient recovery.[40]

Patients who are able to compensate fully for the vestibular loss will mostly remain asymptomatic and unaware they are balancing using mainly one ear rather than two; they will feel subjectively 'back to normal'. In some patients, especially the elderly and those with additional central nervous system disorders, the compensation is often not as effective. This will lead to chronic peripheral vestibular dysfunction (with a persistent sensation of imbalance) or recurrent episodes of decompensation (with recurrent episodes of imbalance). Complaints about sensations of floating, rocking, lightheadedness, disorientation and/or depersonalization are frequent with decompensation.

The recurrence rate of vestibular neuritis is very low and may involve the other side. In a study by Huppert et al. only 1.9% of patients developed a second vestibular neuritis within 39 months after the first episode.[20] The patient would typically have only one episode of sudden-onset vertigo and any recurrent episodes that occur could be explained by episodes of temporary decompensation. However, with recurrent symptoms, other aetiologies must be considered, such as migrainous vertigo, BPPV and Ménière's disease.

MANAGEMENT AND TREATMENT

Symptomatic treatment with antiemetic medication during the acute stage is often required, and antihistamines, anticholinergic agents and antidopaminergic agents are the most commonly used drugs. Fluid replacement may be necessary in particularly severe cases. Most antiemetics are vestibular sedatives and will suppress the stimulus of sensory mismatch which is required for habituation and compensation. It is therefore important that they are only used during the acute stage since prolonged use has been shown to prevent development of vestibular compensation. Accordingly, regular vestibular sedatives are not indicated in patients with chronic dizziness and should preferably not be given for longer than 3 days, following which they should be used only as an emergency medication on an as-required basis.

Vestibular neuritis may cause adverse effects on quality of life, affecting activities such as driving, employment and loss of confidence in everyday living. An important part of management is to advise the patient clearly of the benign nature of the condition and to reassure patients their symptoms will settle. Also inform patients of the fluctuant nature of the recovery process and the common prevalence of decompensation. Advice on safety is important and may be required with regards to driving, workplace and increased risk of falls.

There is at present no clear consensus with regards to specific treatments for vestibular neuritis. Benefit of treatment with oral corticosteroids, in the acute stage of vestibular neuritis, has been suggested.[41] There are some published studies comparing the effectiveness of oral corticosteroids (methylprednisolone) with placebo,[42] but the studies are small and of low methodological quality. This Cochrane review[42] showed an overall significant effect of corticosteroids compared with placebo medication on complete caloric recovery at 1 month. On the other hand, there was no significant effect on complete caloric recovery at 12 months or on the extent of caloric recovery at either 1 month or 12 months. In addition, there was no significant difference between corticosteroids and placebo medication in the symptomatic recovery (using the Dizziness Handicap Inventory score) at 1, 3, 6 and 12 months. Accordingly, there is currently insufficient evidence to support treatment of patients with acute

vestibular neuritis with corticosteroids, particularly considering the risk of adverse side effects.

Despite the suggested possible viral aetiology of vestibular neuritis, no benefit of antiviral treatment in the acute stage has been shown.[41]

Vestibular rehabilitation is a safe and effective treatment for unilateral vestibular dysfunction and is required in some patients to enable recovery and development of effective compensation.[43] The central nervous system needs the stimulus of sensory mismatch for habituation and compensation and controlled studies have indicated that vestibular exercises can accelerate balance recovery and development of compensatory mechanisms.[33] Whether more frequent exercise leads to faster recovery is not known.

The vestibular rehabilitation should be started when the acute stage of nausea and vomiting has passed. It is thought that vestibular compensation develops more quickly and more effectively if the person is active as soon as possible.[44] Vestibular rehabilitation could partly consist of the Cawthorne–Cooksey exercises as well as gait retraining.[44] Although there is insufficient evidence to discriminate effectiveness between different forms of vestibular rehabilitation, more customized vestibular exercises are most probably of benefit with additional visual exercises to manage the visual vertigo.

Cognitive behavioural therapy may be required in the group of patients in which anxiety and panic disorders are the main presenting symptoms associated with the vestibular neuritis.

BEST CLINICAL PRACTICE

- A detailed medical history and examination including neuro-otological examination, general neurological examination and examination of the cardiovascular system is essential and confirms diagnosis.
- With recurrent episodes of vertigo other aetiologies must be considered such as vestibular migraine, benign paroxysmal positional vertigo and Ménière's disease.
- Sudden onset severe vertigo presenting with associated hearing loss, headache and/or neurological symptoms indicate other pathology than vestibular neuritis and require prompt further investigations.
- An important part of management is explanation and reassurance about the benign nature of the condition.
- The majority of patients with vestibular neuritis recover fully spontaneously within 6-12 weeks due to central vestibular compensation. However, in the elderly patient the compensation is often not as effective.
- Vestibular rehabilitation is a safe and effective treatment in patients who do not recover fully.
- Most symptomatic treatments (antiemetic medications) are vestibular sedatives and should only be used during the acute phase, preferably no longer than 3 days.

FUTURE RESEARCH

- ➤ Further research to clarify the pathogenesis of vestibular neuritis is essential for the development of effective specific treatment modalities.
- ➤ Development of specific diagnostic criteria for vestibular neuritis is imperative for research into evidence based specific treatments.
- ➤ Better understanding of development of vestibular compensatory mechanisms will enable improved guidelines for individualized and more effective rehabilitation of vestibular neuritis.

KEY POINTS

- Vestibular neuritis typically presents with one acute episode of sudden-onset vertigo and, if recurrent episodes occur, other aetiologies must be considered.
- The typical peripheral nystagmus is horizontal and increases when the optic fixation is removed.
- The presence of auditory or neurological symptoms indicates a different diagnosis.
- Symptomatic treatment during the acute stage may be required but should preferably not be given for longer than 3 days and is not indicated in patients with chronic dizziness.
- If the patient has atypical symptoms, consider referral to a balance specialist.

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CHAPTER 67

VESTIBULAR MIGRAINE

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: vestibular migraine, migraine and migrainous vertigo.

CLASSIFICATION AND DEFINITIONS

Migraine is common. Almost everyone will either have experienced the condition personally or have friends, family or other acquaintances who are sufferers. The disorder has long been recognized from antiquity as a 'sick headache' or similar description. However, the understanding of the spectrum of migraine manifestations, pathophysiology and management options has increased rapidly over the last 20 years. The story of the concept of 'vestibular migraine' is a part of this fast expansion of understanding.

Migraine is defined by the International Headache Society International Classification of Headache Disorders (ICHD), most recently ICHD-3 beta (**Box 76.1**).[1] Of note, there is no objective diagnostic test and the diagnosis rests with the patient's subjective description of the symptoms, as well as the clinician's assessment that no other disorder better accounts for the clinical presentation. This can be supported to some extent by behavioural observation, especially in those unable to provide a history, such as young children.

The definition is intended to be workable for clinicians, and also to be of use to those executing clinical trials and other research into headache disorders. In addition to the features tabulated in **Box 76.1** there are many other characteristics of migraine that may be encountered in clinical practice. These include other sensory aversions such as osmophobia, motion sickness, sensitivity to alcohol in the form of hangover headaches, and family history. The latter, however, is of limited diagnostic utility given the frequency with which migraine occurs in the general population.

Migraine is primarily and most commonly an episodic disorder. In some cases symptoms it can become chronic. Even in those individuals whose phenotype has evolved to a chronic form, symptoms are usually fluctuating. Even in chronic migraine, careful history taking will elicit an initial period of episodic symptoms.

In about 30% of patients there is experience of aura (**Box 67.2**), comprising fully reversible focal neurological symptoms. These are characteristically followed by a migraine headache, although some individuals experience aura without headache.

Vertigo is mentioned three times in relation to migraine in this classification system. Firstly, it relates to benign paroxysmal vertigo of childhood, a condition of vertigo without headache that occurs in younger children and is thought to be a migraine precursor. Secondly, vertigo can be part of the aura of basilar-type migraine. The key feature of vertigo in basilar-type migraine is that the vertigo is thought to form part of a posterior circulation aura. To identify this with confidence it should conform to the timing definitions for an aura as laid out in **Box 67.3**. In addition, there should be other identifiable posterior circulation symptoms such as dysarthria, tinnitus, reduced hearing, diplopia, visual symptoms simultaneously in both temporal and nasal fields of both eyes, ataxia, decreased level of consciousness or simultaneously bilateral paraesthesias.

However, in neuro-otology and dizziness clinics, the majority of patients who describe dizziness and

BOX 67.1 Migraine headache as defined by ICHD-3 beta (2013)

A. At least five attacks
B. Headache 4–72 hours' duration
C. At least two of:
   - unilateral
   - pulsating
   - moderate/severe
   - aggravation by routine physical activity
D. During headache at least one of:
   - nausea and/or vomiting or
   - photo- and phonophobia
E. Not attributed to another disorder

BOX 67.2 Definition of aura

Fully reversible symptoms:
- sensory, visual, speech disturbance
- at least two of:
  - homonymous visual symptoms and/or unilateral sensory symptoms
  - at least one aura symptom develops gradually over ≥5 minutes and/or different aura symptoms occur in succession over ≥5 minutes
  - each symptom lasts between ≥5 minutes and ≤60 minutes
- migraine headache begins during the aura or follows aura within 60 minutes

BOX 67.3 Migraine with brainstem aura (formerly basilar-type migraine)

A. At least two attacks fulfilling criteria B–D
B. Aura consisting of visual, sensory and/or speech/language symptoms, each fully reversible, but no motor or retinal symptoms
C. At least two of the following brainstem symptoms:
   - dysarthria
   - vertigo
   - tinnitus
   - hypacusis
   - diplopia
   - ataxia
   - decreased level of consciousness
D. At least two of the following four characteristics:
   - at least one aura symptom spreads gradually over 5 minutes, and/or two or more symptoms occur in succession
   - each individual aura symptom lasts 5-60 minutes
   - at least one aura symptom is unilateral
   - the aura is accompanied, or followed within 60 minutes, by headache
E. Not attributed to another disorder

BOX 67.4 Vestibular migraine

A. At least five episodes with vestibular symptoms of moderate or severe intensity lasting 5 minutes to 72 hours
B. History of migraine according to IHS classification
C. Migraine feature with >50% of attacks:
   - headache with two of unilateral, throb, moderate–severe, aggravation by movement
   - photo- and phonophobia
   - visual aura
D. Not better accounted for by another disorder

vertigo in association with migraine headaches and other migrainous phenomena, do not meet strict criteria for aura.[2] This led to the proposal by Neuhauser in 2001 to define an entity they called **migrainous vertigo**. This definition was updated in 2012 in a joint statement by the International Headache Society and the Barany Society and termed **vestibular migraine** (VM) (**Box 76.4**, also in the Appendix section of ICHD-3 beta),[1] which is the third type of migrainous disorder mentioned in the classification system. The validity of the diagnosis has been supported by long-term follow-up studies in which its stability has been demonstrated over a period of up to 9 years.[4]

To be confident of the diagnosis of VM, note that criterion B in **Box 67.4** must be fulfilled, i.e. the patient must have a history of typical migraine, although this does not necessarily need to be highly active at the time of presentation. There is also a definition of **probable vestibular migraine**, in which criteria A and E are fulfilled but only one of B or C. **Definite vestibular migraine** was found to be a highly stable and valid diagnosis over 10 years or so in a longitudinal study, with probable VM unsurprisingly much less so.[5] Note also that migraine may be a risk factor for incomplete compensation from an acute vestibular episode, the pathophysiological basis for which is as yet incompletely understood.[6]

Other terms are encountered in the literature such as migraine-related dizziness, migrainous vestibulopathy and vertiginous migraine, but these have not found widespread international acceptance or standardized definitions.

EPIDEMIOLOGY

There has been only one large population-based epidemiological study of VM in the community.[7] In this study, which took place in Germany, the lifetime prevalence was estimated at 0.98%, two-thirds of participants with VM had consulted a doctor but only 20% of these were diagnosed correctly. Age-adjusted health-related quality of life scores (SF-8 Health Survey) were consistently lower in participants with VM compared to dizziness-free controls. As for migraine, there is female preponderance. It may be more common in women in mid-life, with 1 year prevalence of 5%.[8] This would make it one of the most common causes of episodic vertigo, more common than disease (population lifetime prevalence estimated at 0.12%[9] to 0.5%,[10] although less common than benign paroxysmal positional vertigo.

There are epidemiological associations between migraine and a number of vestibular disorders, including Ménière's disease,[11] benign paroxysmal positional vertigo,[12] episodic ataxia type II[13] and motion sickness.[14]

BOX 67.5 Six-fold relationship between migraine and vestibular symptoms

1. Benign paroxysmal vertigo of childhood (migraine precursor)
2. Migraine with brainstem aura (formerly basilar-type)
3. Vestibular migraine
4. Epidemiological and clinical associate of other vestibular disorders (e.g. Ménière's disease, benign paroxysmal positional vertigo, episodic ataxia type II, motion sickness)
5. Risk factor for slow compensation from acute vestibular event
6. Secondary vestibular migraine (underlying episodic vestibular disorder triggers migraine episodes)

BOX 67.6 Pitfalls in diagnosis

Many patients deny a history of migraine when first asked about headaches so, if VM is suspected, it is worth enquiring specifically about the experience of headache, including any that the patient describes as a 'normal' headache.

While it is increasingly recognized that vestibular symptoms can result from migrainous processes, it is also known that vestibular stimulation can act as a trigger for migraine headaches.[16] This means that some patients with vestibular symptoms and migraine have an underlying vestibular disorder that is triggering migraine headaches. To reduce headache frequency in these patients, the underlying vestibular disorder must be addressed.

While primary migraine is one of the commonest headache disorders, it should be recognized that there are many other causes of both primary and secondary headache. These should be delineated and managed appropriately.

Various mechanisms have been proposed for these associations including inner ear vasospasm,[15] overlapping pathophysiologies[11] and a secondary triggering effect of vestibular disorders on episodes of headache.[16] This latter mechanism distinguishes primary VM, in which vestibular symptoms are attributable to migrainous processes, from secondary VM, in which symptoms of migraine are triggered by a vestibular disorder that causes episodic vertigo (**Box 67.5**).

Migraine is also known to be associated with poor recovery from acute vestibular disorders, although the mechanism of this effect is not entirely clear.[17]

In summary, the current state of knowledge suggests that there are therefore six ways in which vestibular symptoms and migraine can coexist (see **Box 67.5**).

PATHOLOGY AND GENETICS

Theories about the pathology of VM derive from theories of pathogenesis of migraine. Migraine is considered a disorder of sensory modulation, involving both neural and vascular tissue.[18] Many theories of migraine pathogenesis centre on the 'trigeminovascular reflex', with aminergic brainstem nuclei activating trigeminal afferents responsible for the pain of migraine headache that is a central characteristic of the disorder.

Migraine is well recognized as a familial disorder and there are documented pedigrees of families with VM.[19] Rare forms of migraine where there are associated neuro-otological findings have a simple Mendelian inheritance with specified identified mutations (familial hemiplegic migraine Types 1–4 with mutations in *CACNA1A*, *ATP1A* and *SCN1A* and the episodic ataxias Types 1–7 with mutations in *KCNA1* and *CACNA1A*). These data suggest that migraine and its neurological manifestations are mostly likely ionopathies. However, a single genetic mutation for common forms of migraine, including VM, remains elusive, despite extensive work in this area. Genome-wide association studies have identified several candidate variations for common migraine, but the pathological significance of these is yet to be confirmed.[20–22]

Cortical spreading waves of depression of Leao are thought to be analogous to the aura symptoms of migraine.[23] Such a phenomenon affecting brainstem structures such as the vestibular nuclei has been proposed to account for some types of episodes of migraine-associated vertigo.[24] However, this theory does not account for all the clinically observed features of VM, including the time course of attacks that commonly last for several hours or days.

Another possible source for the vestibular symptoms of VM is ion channels within the inner ear. These are critical for neuronal excitation as calcium enters the neurons and potassium exits it into the endolymph. Serotonin, known to have an important role in the modulation of migraine headache, influences neurovascular homeostasis within the mouse inner ear.[25]

Yet another suggested theory is the possibility of vasospasm of the vestibular branches of internal auditory artery causing the ischaemia of the labyrinth and then resulting in cochleovestibular dysfunction experienced in migraine-associated vertigo.[26]

CLINICAL ASSESSMENT

Potential pitfalls in diagnosis to be aware of are given in **Box 67.6**.

History

The key feature of the history is the presence of episodic vestibular symptoms. In some patients with chronic symptoms the symptoms can be present constantly but are subject to fluctuation. Episodes can be of variable duration. Much discussion has taken place over whether very short-lived episodes (less than 5 minutes) can be classified as VM. There is no doubt that such episodes are frequently reported by individuals who otherwise have clear-cut VM, but on current criteria the diagnosis may not be made in those with exclusively short-lived episodes.

Figure 67.1 Everyday situations of work and leisure. (Images courtesy of artur34/arrbrey/Nathan Greenwood FreeDigitalPhotos.net.)

Headache need not necessarily be a prominent feature of the presentation, but it is useful for distinguishing VM from other causes of episodic vertigo.

Photo- and phonophobia are key diagnostic symptoms that should be specifically and carefully enquired about, since they are easily missed.[27] Sensitivity to self and visual motion are frequently associated, and can persist between acute episodes (the 'interictal period'). This can result in avoidance of everyday situations at work and at leisure, such as supermarkets, transportation systems and leisure activities (**Figure 67.1**).

Family history is often sought and can help in some settings but the statistical yield of such enquiry is low due to the high prevalence of migraine in the general population. A history of motion sickness may be of use since migraine and motion sickness are strongly linked.[14]

Other aspects of the history should be directed to symptoms that may be suggestive of an alternative diagnosis, such as the unilateral auditory symptoms of Ménière's disease. Similarly, consider in the history both other causes of primary headache (e.g. tension-type) and less common but potentially serious secondary causes of headache such as intracranial space-occupying lesion, meningitis, subarachnoid haemorrhage, temporal arteritis, primary angle-closure glaucoma, idiopathic intracranial hypertension and carbon monoxide poisoning.

Examination

The physical examination of patients with VM in the interictal period is usually normal. However, some patients report significant visual motion intolerance that can be detected during eye movement examination. One study of patients with VM in the acute setting found a range of eye movement abnormalities including positional nystagmus,, spontaneous nystagmus, mixed and central type patterns.[28] The presence of interictal eye movement abnormalities should alert the examiner to consider the possibility of either a different disorder altogether (e.g. episodic ataxia type 2) or an underlying neurological disorder causing migraine via secondary effects. **Figure 67.2** shows the MRI scan of a patient who presented with frequent headaches and episodic vertigo but was found to have a meningioma in the cerebellopontine angle that was thought to be contributory.

Neuro-otological investigations

Pure-tone audiometry is usually normal in VM, but it can also be helpful in differentiating VM from Ménière's disease in which low-frequency unilateral hearing loss may be detected. A directional preponderance may be

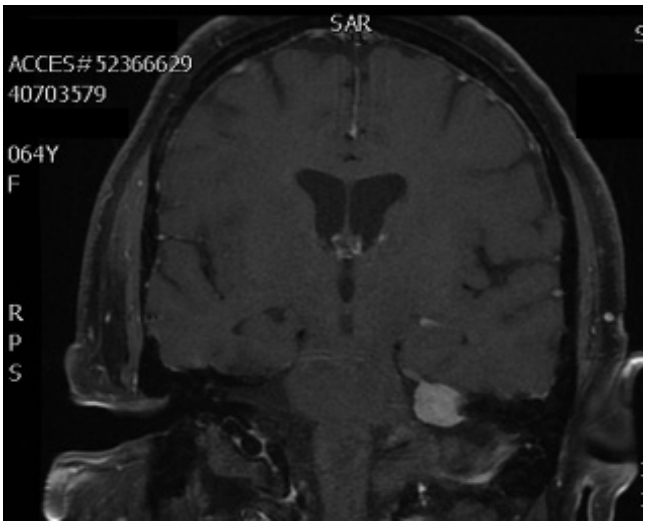

Figure 67.2 MRI scan of a patient who presented with frequent headaches and episodic vertigo but was found to have a meningioma in the cerebellopontine angle.

seen on rotation testing in around half of cases, abnormal posturography is present in around one-third and a canal paresis on caloric testing in around a quarter.[29] Vestibular-evoked myogenic potential (VEMP) abnormalities are likewise non-specific and variable.[30]

Other investigations

MRI scanning can be helpful in selected cases to look for secondary neurological disorders. In cases where the history is typical and examination findings normal, MRI scanning may not be required.

MANAGEMENT

The most important aspect of management after the correct diagnosis is a clear explanation to the patient about the nature of the condition. This is essential since the condition is frequently present over long periods and patients need to become expert in self-management of the disorder. Because migraine is usually thought of as primarily a headache disorder, careful discussion about how migraine may be responsible for vestibular symptoms is often required. The evidence base for management of VM is generally weak, and recommendations are generally made on the basis of what is known about management of other kinds of migraine.

Lifestyle

In some cases, trigger factors for migraine are clearly identifiable. These may be dietary, although there is no convincing evidence that large-scale exclusion diets are beneficial. Keeping regular sleep, exercise and meal times is advisable. In some cases patients can take action to avoid triggers, but this is not always possible (e.g. external stressors).

Drugs

ACUTE RELIEF

Migraine headache should be managed along standard lines with analgesics or migraine-specific relief medicines such as the 5HT1B/D agonists ('triptans'), taking care to avoid analgesic-overuse headache. Further up-to-date guidelines can be consulted.[31, 32] Acute symptoms of vertigo can be managed with vestibular sedatives such as prochlorperazine, cyclizine or cinnarizine. These drugs are not suitable for long-term administration. Nausea can also be relieved by vestibular suppressants; domperidone can also be used for this purpose.

PREVENTIVES

When symptoms of headache and vertigo together are sufficiently intrusive to justify the risk of adverse effects, migraine prophylactic agents can be considered. This judgement is made on an individual basis by each patient. These include propranolol, topiramate and many others. Medication can be selected according to comorbidities and individual preferences with regards to adverse effect profiles.[31, 32]

Physiotherapy

Vestibular rehabilitation can be used to manage symptoms of VM, especially head and visual motion intolerance, and associated underlying fixed vestibular deficits. Progress can be slower than in other conditions. Vestibular rehabilitation can also be associated with an increase in headache frequency, which may justify a decrease in the threshold for starting prophylactic agents.

Psychological

VM can be associated with secondary psychological effects that can be considered on neurochemical, neuroanatomical and neuropsychosocial levels. Patients with VM have higher rates of psychological symptoms than many other vestibular disorders.[33] The interaction of migraine, anxiety and vestibular symptoms is sufficiently common for the concept of migraine anxiety-related dizziness (MARD) to have been proposed.[34] Secondary psychological disorders such as anxiety and depression should be recognized and treated appropriately by medical and/or psychological means as indicated.

Other treatments

There is some evidence that acupuncture is of benefit when combined with other treatments.[35] Riboflavin, coenzyme Q10 and magnesium are all nutritional supplements with low-level evidence of efficacy in migraine.

Some of the pitfalls in effective management are given in **Box 67.7**.

BOX 67.7 Pitfalls in management

It is important to ensure patients have had adequate trials of medications before labelling them ineffective. Starting doses of drugs may not be adequate for therapeutic purposes. Patients should be supported to increase doses where appropriate.

Patients with VM can have a high rate of dropout from physiotherapy programmes due to increases in associated symptoms. The threshold for starting migraine prophylactics may need to be lowered in these patients.

Patients with unidentified and untreated secondary psychological disorders have a poorer prognosis. Consider such factors in individuals who are failing to make expected progress.

FUTURE RESEARCH

- Further work on the pathophysiology of VM is required to delineate ways in which it might be similar to or differ from other migraine subtypes.
- Genetic studies are likely to advance knowledge about pathophysiology through novel technologies such as exome sequencing.
- The evidence base for clinical trials is currently very weak, although some clinical trials have been registered and are proceeding at the time of writing.
- Due to the nature of the condition, including its episodic and unpredictable prognosis, multicentre trials are likely to be required to show adequate power.

KEY POINTS

- Vestibular migraine is a subtype of migraine in which vestibular symptoms predominate.
- Diagnosis is made predominantly on the history.
- Objective vestibular tests are usually normal although peripheral or central abnormalities can be seen in some cases.
- Management options include lifestyle modifications, medication, and physiotherapy, depending on symptom severity and frequency.

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CHAPTER 68

VESTIBULAR REHABILITATION

Marousa Pavlou

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: vestibular rehabilitation, balance re-training, adaptation and novel techniques.

INTRODUCTION

Customized vestibular rehabilitation (VR) incorporating appropriate movements and sensory exposure is currently the standard of care for patients with peripheral vestibular disorders. Approximately 50–80% of individuals completing a customized programme achieve significant subjective symptom, dynamic visual acuity, gait and postural stability improvements.[1–5] A direct relationship has also been demonstrated between VR treatment outcome and improvements in psychological state[5, 6] and quality of life,[7–9] while specialized adjuncts to VR, such as exposure to visual motion stimuli, have been shown to significantly improve symptoms of visually induced dizziness,[5, 6, 10] which refers to symptoms of dizziness, disorientation and/or unsteadiness provoked or exacerbated in situations involving visual–vestibular conflict (e.g. walking down supermarket aisles) or intense visual motion (e.g. watching wide-screen movies).

However, despite a strong body of evidence supporting the use of VR for the management of peripheral vestibular disorders, referrals to VR remain low. A qualitative study evaluating clinicians' (neurologists, primary care, otolaryngologists) perspectives regarding the factors which influenced their management of people with vestibular disorders found that they were often unaware of the concept of VR and wanted to learn more to improve the healthcare delivery of their patients.[11] The main aim of this chapter is to provide an overview of VR including: (i) the physiologic basis, (ii) customized VR techniques including novel and supplementary techniques, (iii) factors that may affect outcome, and (iv) its efficacy for peripheral and central vestibular disorders.

NEUROPHYSIOLOGICAL BASIS FOR VESTIBULAR REHABILITATION

Habituation, adaptation, substitution and/or sensory reweighting comprise the neurophysiological basis for vestibular compensation and the improvements noted following a VR programme, with recent findings showing structural changes in grey matter volume in certain brain areas after people with vestibular neuritis have recovered functionally.[12]

Habituation is a decrease in the magnitude of the response to repetitive sensory stimuli.[13] Initial VR programmes such as the Cawthorne–Cooksey[14, 15] exercises are a type of habituation and involve repeating the provoking movement at regular intervals until symptoms are no longer experienced. However, although components of this exercises programme may still be used today, the evidence advocates customized VR programmes which focus on an individual's deficits and incorporate exercises based on multiple neurophysiological components.[2, 4, 16–18]

The vestibulo-ocular reflex (VOR) is responsible for our ability to maintain fixation on a target during head movement. The VOR functions to stabilize images on the retina during head movement by producing compensatory eye movements, simultaneously and at the same rate, in the direction opposite to head movement. Therefore the

'gain' of the VOR (eye velocity/head velocity) should be equal to 1.0. In people with a peripheral vestibular disorder, the VOR gain can be reduced, resulting in retinal image slip with visual blurring during head rotations.[19] Retinal image slip provides an error signal which generates VOR response changes that decrease (i.e. improve) the gaze error.[20–22] Adaptation exercises[23] (see 'Vestibular rehabilitation interventions' below) incorporating gaze fixation and head movements are prescribed to simulate retinal slip to promote VOR improvement with a reduction in blurring of the visual image during head movement. Recently it has been reported that, in addition to retinal slip, saccadic substitution and specifically compensatory saccades (the substitution of a saccade in the direction of the deficient VOR)[24] also contribute to improvements in VOR gain with a decrease in gaze instability.[25] The use of compensatory saccades appears to be related to the severity of vestibular hypofunction.[25]

Sensory reweighting is the central nervous system's ability to adapt its relative reliance on a specific sensory modality for orientation depending on environmental conditions, task demands and/or pathology.[6] Therefore, if a sensory input is reduced, absent or unreliable, other sensory inputs are centrally upregulated or weighted-up. For instance, in the dark or in the presence of unstable visual surroundings, when visuopostural responses are unavailable or unreliable respectively, the efficiency of vestibulo-proprioceptive responses increases whereas visuopostural responses are downregulated.[26] Similarly, a patient with uni- or bilateral vestibular failure will develop increased postural responses to visual motion stimulation.[27] It is thought that, by performing exercises in environments with altered sensory information, VR is able to affect a person's use of sensory information or sensory reweighting.[28]

Optokinetic stimulation can induce adaptation of specific vestibular parameters including VOR reflex gain in primates, healthy individuals and chronic peripheral vestibular patients.[16, 20, 29] Regarding patients' symptoms, post-rotational vestibular sensation duration also reduces in healthy subjects with exposure to repetitive, vestibular or optokinetic stimulation.[30] Short-term repeated exposure to visuovestibular exercises has been found to induce adaptive changes, decreasing (improving) the magnitude of visual dependency in healthy controls.[31] It is believed that improvements noted in visually induced dizziness following a programme of VR incorporating exposure to optokinetic stimulation is due to a decreased over-reliance on visual input for perceptual and postural responses. The underlying mechanism is likely to relate to motion-induced changes in neuronal excitability in visual motion cortical areas (V5/MT).[32, 33] PET and fMRI studies involving small or large-field optokinetic stimulation without additional vestibular stimulation note activation in cortical areas related to visual motion processing and eye movement control, and deactivation of parietoinsular vestibular cortices indicating a reciprocally inhibitory visual–vestibular interaction.[34–36] Similarly, when multisensory vestibular cortex areas are stimulated, bilateral deactivation is noted in visual and somatosensory cortex areas.[34, 37] It is suggested these interactions have a functional significance and indicate a sensory reweighting process, with greater weight given to the more reliable input thus suppressing the possible mismatch between contrasting sensory information.[36] Recurring exposure to conflicting visual input is also believed to promote reduced visual reliance and foster a more effective use of vestibulo-proprioceptive cues through sensory reweighting.[38] Overall, however, the mechanisms mediating sensory reweighting in postural control remain poorly understood.[39]

VESTIBULAR REHABILITATION INTERVENTIONS

Clinical assessment

A thorough assessment is required prior to the onset of VR. Vestibular function tests to assess for accuracy and normalcy[40] can be evaluated bedside by examination of spontaneous, gaze-evoked and positional nystagmus, dynamic visual acuity and headthrust tests.[41, 42] The recently developed Vestibular/Ocular Motor Screening test, which includes five domains (smooth pursuit, horizontal and vertical saccades, near point of convergence distance, horizontal VOR and visual motion sensitivity), is reported as a brief, sensitive vestibular/ocular screen for people with sport-related concussions that can be performed by physiotherapists.[43, 44]

The patient history will provide information regarding symptom severity, frequency, duration and triggers as well as falls history. Several validated questionnaires can aid in quantifying this information including the Vertigo Symptom Scale,[45] Dizziness Handicap Inventory,[46] Situational Characteristic Questionnaire[27, 47] and Activities-specific Balance Confidence Scale.[48, 49] A physiotherapist will also perform objective and subjective tests to identify functional deficits in people with a vestibular disorder, including the completion of questionnaires regarding perceived handicap due to their symptoms, objective static and dynamic balance tests (i.e. the modified Clinical Test of Sensory Integration and Balance (CTSIB),[50, 51] dynamic computerized posturography) and gait measures (i.e. gait speed, Functional Gait Assessment[52]).[40] Muscle strength, range of movement and sensation will be assessed and the eye, head and body movements or positions and challenging environments (e.g. visually 'busy' or unstable surroundings, irregular or compliant surfaces) which provoke symptoms will be identified in order to design an appropriate exercise programme.

Treatment goals are devised to address each person's individual subjective (i.e. dizziness, giddiness, nausea) and objective symptoms (postural and gait instability, falls). These goals often include:

- improve functional balance, gait and ability to perform daily activities
- decrease falls risk
- decrease symptom severity
- improve VOR function
- improve sensory integration and reweighting ability
- patient education.

VR should be based on the eye, head and postural exercises that provoke a patient's symptoms. Adaptation exercises (Figure 68.1)[23] incorporating gaze fixation and head movements and postural exercises are prescribed to promote recovery of VOR and vestibulo-spinal reflex function. Gaze fixation exercises are practised with varying target distances (i.e. 2 m, 1 m, 0.5 m) since VOR gain varies with target distance (closer targets require higher gains).[53] Fixation exercises are given to patients with oscillopsia and/or decreased VOR gain, most often seen in peripheral vestibular disorders.

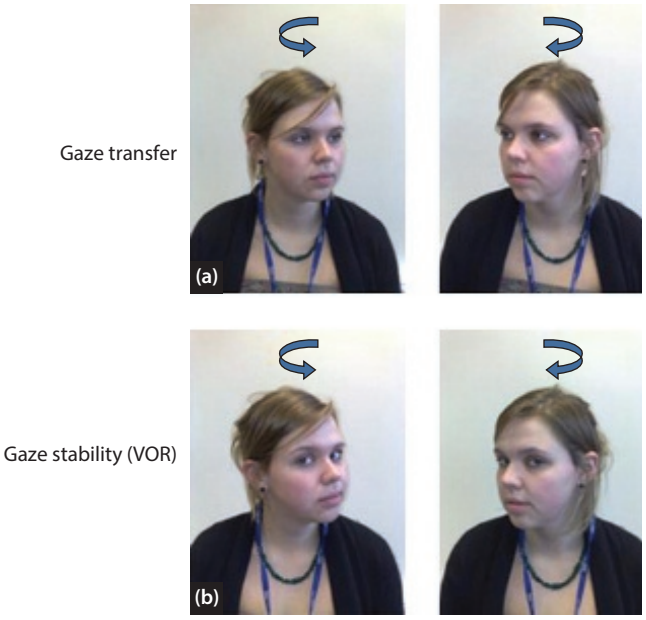

Figure 68.1 Gaze transfer and adaptation exercises[54] included within a vestibular rehabilitation programme. During 'gaze transfer' **(a)** the normal head and eye movement required for transferring gaze from one object to another is practised. The exercise can initially be practised without head movements with objects placed approximately 40 cm apart at eye level. During adaptation exercises **(b)** the vestibulo-ocular reflex (VOR) is being stimulated. This is responsible for maintaining a steady gaze on a fixated object with progressively faster head movements.

Saccades can support higher speed functional eye movements in people with bilateral vestibular hypofunction in whom the VOR gain is extremely reduced or absent.[40] Patients are asked to practise saccadic or gaze transfer exercises whereby they quickly shift their gaze between two horizontal or vertical targets. As the VR programme progresses, the complexity and difficulty of exercises should increase and therefore exercises will be practised in sitting, standing and walking on level ground or compliant surfaces (e.g. foam). Table 68.1 includes examples of commonly prescribed exercises, which can also be viewed online.[42]

Many people with a vestibular disorder will experience some level of balance and gait dysfunction. Exercises which focus on retraining postural alignment and movement strategies may need to be incorporated whereby patients learn to maintain an upright posture during progressively more difficult tasks including eyes closed and standing on compliant surfaces, with progressively reduced feedback about position.[55] The goal when retraining movement strategies is to develop those successful in moving the centre of gravity relative to a stationary base of support (ankle or hip strategy) and changing the base of support relative to the centre of gravity (stepping strategy). Retraining a coordinated ankle or hip strategy involves practising voluntary anterioposterior and lateral sway, without taking a step. Facilitating a hip strategy involves faster and larger displacements than an ankle strategy and may include activities such as tandem or single leg stance.

TABLE 68.1 Examples of commonly prescribed exercises in vestibular rehabilitation

Type of exercise	Examples
Head exercises (performed with eyes open and eyes closed)	Bend head backwards and forwards Turn head from side to side
Eye movement exercises	Head stationary follow movement of finger left and right/up and down Head movement to look back and forth between two vertical or horizontal targets
Visual fixation exercises	Perform head exercises while fixating stationary target Perform head exercises while fixating moving target
Positioning exercises (performed with eyes open and closed)	While seated, bend down to touch the floor While seated, turn to look over shoulder to left and then right Bend down with head turned first to one side and then the other Lying down, roll from one side to the other Sit up from lying supine and on each side
Postural exercises (performed with eyes open; eyes closed under supervision)	Practise static stance with feet as close together as possible Practise standing on one leg, and heel-to-toe Repeat head and fixation exercises while standing and then walking Practise walking in circles, pivot turns, up slopes, up stairs, around obstacles Stand and walk in environments with altered surface and/or visual conditions with and without head and fixation exercises Aerobic exercises, e.g. alternate touching the fingers to the toes, trunk bends and rotation

Retraining externally induced postural responses involves pushes or pulls of various amplitudes, speed and direction applied at the hips or shoulders, or the use of moving surfaces. Stepping can be practised by shifting the patient's weight to one side and then quickly bringing the centre of gravity back towards the unweighted leg, or in response to large anterioposterior or lateral perturbations. Multidirectional stepping, and stepping over a visual target or obstacle can also be practised.[55]

When the ability to select appropriate sensory input for postural stability is disrupted, exercises focus on asking patients to maintain balance in situations where the availability and accuracy of one or more sensory inputs is varied.[56] Sensory strategy retraining aims to help people with a vestibular disorder learn to effectively select appropriate sensory information for balance in various environments. Treatment focuses on maintaining balance during progressively more difficult static and dynamic balance and gait exercises while the availability and accuracy of sensory input are systematically varied. People who overrely on somatosensory cues for orientation (i.e. difficulty when walking on uneven surfaces, changing between different types of floor surface) practise tasks while sitting, standing or walking on surfaces with disrupted somatosensory cues such as compliant foam, moving platforms or tilt boards. For people with a visual dependency this involves exercises where visual input is incorrect, conflicting or absent, in order to learn to rely more on proprioceptive and available vestibular cues.[38] Guerraz et al.[27] suggested that rehabilitation programmes promoting desensitization and increased tolerance to visual stimuli through exposure to visual motion (i.e. optokinetic stimulation) would be specifically beneficial for patients with visual vertigo (VV). Advanced techniques in VR incorporate exposure to optokinetic stimuli[5] (**Figure 68.2**) or virtual reality[57] (**Figure 68.3**) environments. When the optokinetic stimulation has been incorporated into both the treatment session and the home programme, improvements have been noted in postural and gait stability, visually induced dizziness and psychological state, including depression and anxiety.[5] Easily accessible and economical computer games, YouTube videos or a DVD including visual stimulation recorded from the clinical equipment (i.e. optokinetic test in neuro-otology departments)[58] can also be used. Regardless of the type of optokinetic or virtual reality stimulus employed, exposure should be gradual and progressive.

People with a vestibular disorder may complain of poor concentration and memory impairment and a cognitive–vestibular function interaction has been highlighted in this population.[59] People with a vestibular disorder appear to have decreased attentional resources available when simultaneously performing a cognitive and posture or gait task (i.e. dual tasking) with priority given to maintaining the motor task to the detriment of performance on the cognitive task.[60, 61] Postural studies in standing, though, show varying results with regards to the effect of an additional cognitive task on postural sway, with some reporting that

Figure 68.3 Four aisles from a virtual reality supermarket,[57] showing a progression in visual complexity.

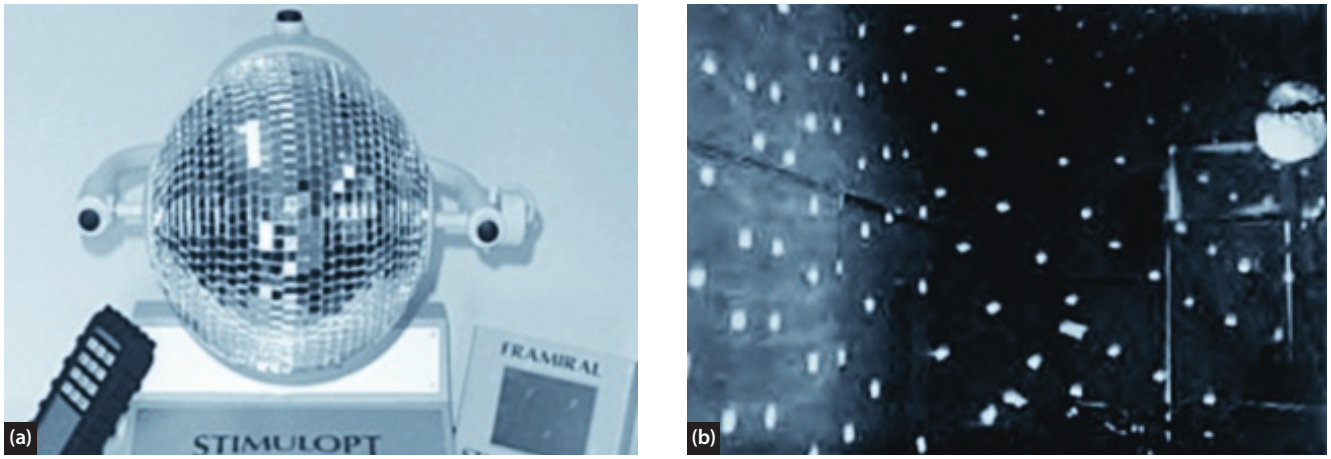

Figure 68.2 Apparatus used for full-field optokinetic stimulation-based intervention.[5] **(a)** A photo of the visual environment rotator apparatus (Stimulopt, Framiral, France). **(b)** Participants are asked to stare ahead while the apparatus rotates in different directions and at differing speeds. Participants practise exercises in sitting, standing and walking either towards and away from the stimulus or alongside it with or without vertical or horizontal head movements.

sway increases (i.e. worse),[62] decreases (i.e. improved)[63] or no change.[61] The disparate findings may be due to variations in task difficulty as well as the ability to isolate obvious sensory mismatches so they do not draw on attentional resources.[64] More recent studies investigating gait performance while performing a simultaneous cognitive task (dual-task) consistently show a significantly decreased gait speed[65, 66] and greater ataxia and deviation from a linear path[65] in this population when dual-tasking. Although no studies have specifically assessed the impact of incorporating dual task training within a VR programme, findings in older adults with increased falls risk show an increase in dual-task gait speed after training[67] and clinicians often include dual-task training into VR programmes when a functional deficit is noted in this area. Dual-task training involves practising progressive balance exercises (e.g. tandem standing or walking with or without upper limb activities) while simultaneously performing a secondary task such as counting backwards by 3s, recounting daily activities.[68] During training patients are asked either to constantly maintain attention on both tasks or to focus attention on one of them.[69]

Motor, sensory and cognitive strategy retraining should occur in parallel rather than sequentially. General characteristics of VR include specificity, repetition, progression, and patient education, for example explaining that initially symptoms may worsen, and improvement may be uneven. Patients should be aware that, even after symptoms have largely resolved, a temporary reoccurrence may occur during periods of stress, fatigue or illness. Patients should be advised to stop exercising and seek advice if they experience neck pain, loss of consciousness or vision, sensations of numbness, weakness or tingling in the face or limbs, or increased migraine frequency.

Novel and supplementary techniques

Various authors have discussed the potential benefit of virtual reality as a therapeutic protocol to improve postural and gait stability, VOR gain and subjective symptoms.[68–70] Two studies using a limited field-of-view head-mounted device noted improvements in VOR gain and symptoms in patients with a peripheral vestibular disorder.[69, 71] Two randomized controlled trials comparing customized VR versus virtual reality-based VR reported no significant pre–post treatment between-group differences in gait speed, functional gait performance, computerized dynamic posturography or subjective symptoms despite one study using a full-field immersive virtual environment consisting of a grocery store model[56] while in the other the low-cost Nintendo Wii Fit Plus® was employed (**Figure 68.4**).[72] The lack of difference in findings between the customized vestibular rehabilitation exercises versus virtual reality based rehabilitation in the two aforementioned studies[56, 72] may be due to the fact that both small- and large-field optokinetic stimulation shows similar reciprocally inhibitory visual–vestibular interactions, indicating that sensory reweighting occurs independently of visual field size and other factors including frequency,

Figure 68.4 A patient practising a balance exercise using the Nintendo Wii Fit Plus® system.[73]

velocity, texture, stimulus area and position within the visual field.[34–36, 73] Pavlou et al.[5] reported that this may explain why significant improvements were noted for both full and limited field-of-view optokinetic stimulation without significant between-group differences in their study. However, it should be noted that virtual reality systems may provide a more enjoyable rehabilitation method to re-train balance.[72]

Sessoms et al.,[74] however, reported that 12 sessions virtual reality exposure without additional VR provided greater benefit in gait speed and weight shift in people with traumatic brain injury (TBI) and vestibular dysfunction compared to virtual reality (6 sessions) plus VR (6 sessions). It is important to note that balance and vestibular exercises were practised during exposure to the virtual reality environment, thus providing multidimensional tasking. This provides a form of VR that is more demanding and may possibly be more appropriate than traditional techniques for people requiring more challenging tasks and who are required to operate at a higher level of performance in their profession (athletes, military servicemen).[75]

Current literature therefore suggests that virtual reality is beneficial and may offer a more enjoyable exercise method, particularly with regards to the Nintendo Wii® system.[73] Further work is needed, however, to identify the specific role of virtual reality within VR, particularly with regard to the patient groups for whom it is most suitable and to the optimal virtual reality format.

FACTORS AFFECTING OUTCOME

The relationship between psychological and dizziness symptoms is well documented as is the significant correlation between depression and anxiety in people with vestibular dysfunction.[82, 83] People who experience higher levels of somatic anxiety report greater handicap[84] and show a delay in recovery.[85] Every effort should be made to identify and act on these negative factors, referring the patient for counselling and/or adding psychopharmacological medication as appropriate. Studies combining VR with explicit cognitive behavioural therapy demonstrate improvements in patients' ability to cope, function, subjective symptoms and satisfaction with care.[86, 87] However, the clear additional effect of combining cognitive behaviour therapy with VR remains unknown.

People with peripheral or central vestibular disorders may experience visuomotor symptoms, such as oscillopsia or diplopia, which are capable of disrupting recovery and rehabilitation. Rehabilitation specialists should enquire directly about such symptoms. It has recently been reported that binocular vision abnormalities may affect the improvement of visually induced dizziness symptom improvement and these findings may have important implications for the management of subjects with refractory vestibular symptoms.[88] Clinicians need to be aware of the possible negative effect of this type of binocular abnormality on visually induced dizziness treatment outcome in order to manage their own and the patient's expectations from treatment.

Patients with vestibular migraine can adhere to and benefit from VR.[5, 89, 90] However, Bronstein and Pavlou[55] reported that, in their experience of treating patients with migraine-associated dizziness, an initial exercise programme including fewer exercises (i.e. three maximum) is better tolerated and adhered to. The exercises should be practised only once daily initially and gradually increased to twice daily. As symptoms and tolerance improve the number and total duration of daily exercises progressively increases. It is important for improvement to be noted with exercises such as those in **Table 68.1** before progressing to the inclusion of optokinetic stimuli.

Other factors that may impact on VR treatment outcome are listed in **Box 68.1**.

BOX 68.1 Factors that may delay vestibular compensation (adapted from Bronstein and Pavlou)[56]

- Fluctuating vestibular disorder (i.e. Ménière's disease)
- Migraine
- Additional disorder:
  - CNS
  - Peripheral nerve
  - Cervical spine
  - Visual (reduced visual acuity, modified optics (e.g. cataract operation), strabismus, diplopia)
- Age
- Lack of mobility (orthopaedic problem, forced bedrest, psychological/fear)
- Medication (antivertiginous drugs)
- Psychosocial
- Visually induced dizziness

EFFICACY OF VESTIBULAR REHABILITATION

VR, in the form of appropriate movements and sensory exposure, is currently the standard of care for patients with peripheral vestibular disorders regardless of age and symptom duration.[2, 4, 5, 91] Customized VR programmes provide greater benefit than generic ones (Cawthorne–Cooksey).[2, 4, 5, 91, 92] A recent Cochrane review and other systematic reviews have validated the safety and effectiveness of VR for the management of unilateral vestibular dysfunction.[93, 94]

People with bilateral vestibular hypofunction have an increased falls risk[95] and in one study a significant percentage of participants reported that they had to alter or change their professional activities and/or required the presence of another person due to the level of disability they experienced.[96] However, a number of studies have reported significant improvements in gaze, postural and gait stability, balance confidence, subjective symptoms and perceived handicap from dizziness in people with bilateral vestibular hypofunction,[1, 4, 97] with a systematic review stating that there is moderate strength evidence to support VR for improvements in gaze and postural stability but further work is need to identify its benefit for International Classification of Functioning, Disability and Health (ICF)–Participation outcome measures.[98]

In people with Ménierè's disease, management has been challenging due to recurring vertigo episodes. Long-term management may include dietary changes (low salt), medications (betahistine, steroids) and/or ablative therapy (e.g. intratympanic gentamicin administered to the affected ear).[99] Specifally for VR, significant improvements in postural stability, subjective symptoms and quality of life have been noted with customized VR physical exercises[2] or incorporating balance exercises with exposure to a virtual reality platform.[100] In the study by Garcia et al.,[100] participants in both the control and treatment groups had been given dietary recommendations and prescribed 48 mg/day of betahistine, however improvements were only noted in the treatment group.[100]

Some studies report similar responses for patients with peripheral, central and mixed pathology, but others claim poorer outcomes for the latter two groups. Differing results may be due to individual study variations regarding treatment duration (patients with central deficits are expected to require a longer duration for improvement), extent and location of central deficit (cerebellar dysfunction appears to reduce the effect of rehabilitation) and any additional cognitive or neuromuscular deficits.[101] Cerebellar and vascular disease, migraine and traumatic brain injuries (including concussion) are examples of central vestibular disorders associated with dizziness.

Current evidence suggests that VR can improve dizziness, gait and postural stability after mild traumatic brain injury (or concussion).[102, 103] In people with persistent neck pain, headaches and/or dizziness following a sports-related concussion, the time to return to sport is reduced following a programme of VR combined with cervical exercises.[104] McCulloch et al.[105] published clinical guidelines for rehabilitation providers regarding progressive return to activity after military mild traumatic brain injury and VR was recommended for those experiencing persistent dizziness and/or balance symptoms.

As stated above, people with vestibular migraine benefit significantly from a VR programme.[88, 106, 107] Patients with vestibular migraine or migraine history and a peripheral vestibular disorder can also tolerate and benefit from customized VR incorporating optokinetic exposure; surprisingly, migraineurs report significantly greater improvements for visually induced dizziness compared to non-migraineurs.[5] It has been suggested medication may help control visually induced dizziness symptoms in migraineurs, enabling them to better tolerate the exercises and thus leading to greater improvement.[89] However, Vitkovic et al.[107] reported that a 6-month VR programme without optokinetic exposure showed similar improvements in both participants with vestibular migraine and those with vestibular symptoms without migraine and, for the former, improvements were noted regardless of medication regime, although medication was not controlled for.

FUTURE RESEARCH

Further work is needed regarding:

- optimum interventions
- treatment duration
- long-term outcome
- the efficacy and potential benefit of novel techniques, i.e. virtual reality.

KEY POINTS

- VR is the mainstay of treatment for people with peripheral vestibular disorder.
- Evidence is emerging for its benefit in people with central vestibular disorders, particularly mild traumatic brain injury.
- VR should be informed by assessment and individually designed based on each person's impairments.

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CHAPTER 69

AUDITORY NEUROPATHY SPECTRUM DISORDER AND RETROCOCHLEAR DISORDERS IN ADULTS AND CHILDREN

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SEARCH STRATEGY

Data in this chapter may be updated by Medline and PubMed searches using the keywords 'auditory neuropathy', 'auditory neuropathy spectrum disorders', 'retrocochlear hearing loss' and 'auditory dyssynchrony'.

AUDITORY NEUROPATHY SPECTRUM DISORDER

Auditory neuropathy spectrum disorder (ANSD) is a specific form of hearing impairment when the patient can hear the sound of speech but has difficulties understanding the words. In infants, this problem understanding speech leads to difficulties developing speech. ANSD is caused by pathology in the inner hair cells of the cochlea or the auditory nerve and its synapses (i.e. 'neural' hearing loss). One of the major features of ANSD is that testing frequently shows pure-tone audiometric thresholds that are relatively well preserved but speech thresholds that are markedly impaired. It is in this context that the acoustic brainstem-evoked response (ABR) is performed and often found to be delayed or absent. Thus the concept of auditory dyssynchrony has arisen, i.e. the loudness of sound is relatively well perceived but the synchronization of acoustic signals is not adequate to evoke an ABR, or to elicit the stapedius reflex, or to suppress the contralateral otoacoustic emissions (OAEs). Because this synchronization requires the integrity of the VIIIth nerve, these causes of hearing loss were first described in the literature as 'auditory neuropathy' then 'auditory neuropathy/dyssynchrony', but since 2008 have been referred to as 'auditory neuropathy spectrum disorder' (ANSD).

The hearing difficulty in ANSD is typified by a characteristic pattern of abnormalities on audiological testing:

- normal to raised pure-tone auditory thresholds
- poor speech discrimination
- delayed, or absent, ABRs
- normal OAEs and cochlear microphonics.

There are many causes of ANSD and it is only with recent developments in assessing the function of cochlear receptor elements (inner and outer hair cells) that a finer definition of ANSD and a more accurate classification of aetiological factors have been possible.

Historical perspective

INCONSISTENT MEASURES OF HEARING

The term 'auditory neuropathy' arose as a way of grouping together those hearing disorders where observations of inconsistent measures of hearing are made, i.e. where hearing sensitivity is better than might be expected from the ABRs. The first publications presenting these paradoxical findings of absent ABR and behavioural audiometry[1–4] described children who responded behaviourally to moderate- or low-intensity sounds but had absent ABR.

PRESENCE OF OTOACOUSTIC EMISSIONS AND COCHLEAR MICROPHONICS

The first report of a further inconsistent test abnormality which helped to define both the concept and the diagnosis of neural synchrony disorder, came in 1991.[5] An 11-year-old boy was described with the characteristic findings of absent event-related potentials and acoustic reflexes with poor performance on temporally based psychoacoustic tests, but who had present click-evoked OAEs and cochlear microphonics. These latter two findings strongly pointed to normal preneural hearing. Further papers confirmed the presence of OAEs[6,7] in similar patients. One of these studies describes four infants in a special care baby unit who failed the ABR test but passed the click-evoked OAE screen. These infants were found in a series of 100 neonates admitted to the ITU. By following the infants, they observed that two out of the four showed normalization or reversal of the ABR abnormalities, but the other two retained their abnormal ABR. They concluded that, in instances where either no response or early waveforms only were obtained, ABR was insufficient as the sole evaluator of hearing sensitivity. They recommended concomitant use of behavioural audiometry with ABR and OAEs, and the importance of follow-up to guard against inappropriate diagnoses of cochlear hearing loss (see below).

SEQUENCE OF NAMES USED TO IDENTIFY THE DISORDER

'Auditory neuropathy' (AN) was first used as a clinical term by Starr and others in 1996[8] to describe patients whose hearing impairment was attributed to 'neuropathy of the auditory nerve'. Their hearing dysfunction was characterized by absent or disordered ABR in the presence of normal, even robust, preneural responses evidenced by the recording of normal OAEs or cochlear microphonics (CMs) in the same patients. The concept of 'auditory neuropathy/dyssynchrony' (first coined in 2001[9]) has challenged thinking about the physiology of hearing, and has provided a model for examining the role of neural synchrony of the VIIIth nerve and brainstem, and its impact on auditory perception. In 2008, after extensive review,[10] the term auditory neuropathy spectrum disorder was first adopted as a way of describing the heterogeneous and multifaceted nature of this disorder and the different ways ANSD affects patients, with symptoms ranging from very mild to very severe.

Further study has permitted the characterization of this group of disorders, and better assessment of these patients. These cases are now recognized as relatively common (5–12% of those previously considered to have severe to profound hearing loss in paediatric populations,[11,12] with an estimated 1 in 7000 of neonates, assessed by universal newborn hearing screening,[13] showed abnormal VIIIth nerve function) and probably represent a heterogeneous group where the common feature is disordered temporal processing (i.e. synchronization of sound). Progressive AN is reported in association with age-related degenerative changes, toxic effects of noise, mitochondrial, genetic and autoimmune disorders, etc.[14] The first large series[15] identified 49 cases from 543 patients who had either no ABR response or absent waves III and V. In seven patients, the audiometric data ranged from normal hearing to moderate impairment, i.e. 14% had better hearing sensitivity than might have been expected from their ABR, which was completely absent in these cases. Each of these seven patients also had abnormal acoustic reflex findings. Although the range of deficits as identified on medical, behavioural and electrophysiological testing was variable, there were many common features, including perinatal insults such as perinatal asphyxia, hyperbilirubinaemia or head injury. Tests of psycholinguistic abilities revealed significantly worse performance in auditory as compared to visual tasks, and speech discrimination testing revealed worse scores than would have been predicted from the patient's hearing thresholds in the majority.

Causes of auditory neuropathy

In classifying the causes of auditory neuropathy, **Table 69.1** identifies those aetiologies that are genetic or acquired congenitally, and **Table 69.2** identifies those that are acquired postnatally, including causes of retrocochlear hearing loss.[16] It should be remembered that some of the genetic causes only present with hearing impairment in adulthood, and so the tables do not differentiate 'paediatric' from 'adult' hearing disorders. The evidence for these aetiologies to be included in the tables is given by the references cited in the tables. The majority of the references are individual, or a series of, case reports with audiological, electrophysiological, imaging and in some papers histopathological evidence for a nerve VIII or brainstem cause of hearing impairment.

Starr[52] suggests an aetiological classification of AN that distinguishes between presynaptic and postsynaptic lesions. He suggests the following 'groupings' of AN:

- **Type I postsynaptic AN:** plus vestibular and peripheral neuropathies, e.g. Charcot–Marie–Tooth disease
- **Type I postsynaptic AN:** plus optic nerve disorders accompanying nuclear and mitochondrial mutations, e.g. Leber's optic atrophy, Wolfram syndrome (or 'DIDMOAD')
- **Type II presynaptic AN:** inner hair cell and neurotransmitter disorder, e.g. AN seen in otoferlin and *GJB6* mutations
- **AN unspecified:** affected sites unknown.

However, there is evidence to suggest that AN associated with specific gene mutations may change or progress to involve both pre- and postsynaptic locations. For example, patients with mutant *OPA1* gene show demyelination and axonal loss in advanced stages of disease and patients carrying the *DIAPH3* mutation show progressive deterioration of hearing thresholds from moderate to profound with gradual disappearance of OAEs.[53] Various types of genetic

TABLE 69.1 Genetic and congenital causes of auditory neuropathy

Genetic causes		
Non-syndromal	Non-syndromal recessive auditory neuropathy due to mutations in the otoferlin gene,[1, 17, 18] mutations in the pejvakin (*DFNB59*) gene[19] and in the connexin 26 gene[30] Non-syndromal autosomal dominant auditory neuropathy due to mutations in the *AUNA1* and *PCDH9* genes[20] Non-syndromal X-linked recessive auditory neuropathy due to the *AUNX1* gene[20]	
	Delayed maturation of auditory pathways[2]	
Syndromal	Degenerative conditions, with peripheral neuropathy	Hereditary sensory–motor neuropathy (HSMN), i.e. Charcot–Marie–Tooth[21]
		Friedreich's ataxia[22, 23]
		Roma (gypsy) families[24]
		Refsum disease[20]
	Degenerative conditions, without peripheral neuropathy	Usher syndrome[25]
		Mitochondrial myopathies: • MELAS[10] • chronic progressive external ophthalmoplegia[26, 27] • Mohr–Tranebjaerg syndrome 'deafness/dystonia peptide'[28]
Congenital causes		
Toxic/metabolic		Perinatal risk factors:[11, 29] • asphyxia • respiratory distress syndrome • low birthweight • cerebral palsy • hyperbilirubinaemia

TABLE 69.2 Acquired causes of auditory neuropathy and retrocochlear hearing loss

Acquired causes		
Infection	Viral	Herpes zoster/herpes simplex: • Ramsay Hunt[31, 32] • Bell's palsy[32]
		CMV[33]
		HIV/AIDS[34]
	Bacterial, fungal/ spirochaetal	Basal meningitis:[35, 36] • pneumococcal • meningococcal • haemophilus • tuberculosis • cryptococcosis • coccidiomycosis
		Syphilis
		Borrelia[37]
Immune-mediated	Post-infective	Guillain–Barré
	Vasculitic/ granulomatous	SLE, rheumatoid arthritis, sarcoid, Behçet's
Demyelination	Multiple sclerosis:[38, 39, 50–51] • VIIIth nerve • brainstem	

(Continued)

TABLE 69.2 ***(Continued)*** Acquired causes of auditory neuropathy and retrocochlear hearing loss

Acquired causes	
Neoplasia/ neoplasia-related	Vestibular schwannoma[40] Meningioma Cerebellopontine angle lesion
	Carcinomatosis[41]
	Radiotherapy
Metabolic/toxic	Uraemia[42]
	Paget's disease[43]
	Organic mercury[44]
	Cisplatin[45]
	Haemosiderosis[46]
Vascular	?Migraine[47]
	Posterior inferior cerebellar artery syndrome (PICA)
	Macrovascular:[48, 49] • posterior fossa aneurysms • AV malformations • vascular loops

mutations in AN result in different pathological changes in the auditory system as discussed by Manchaiah et al.[20] For example, the *AUNA1* gene is associated with changes in the distal auditory nerve, including dendrites and inner hair cells, the *OTOF* gene is associated with changes

mostly within the inner hair cells, the *AUNX1* gene results in demyelination and axonal loss of the auditory fibre, the pejvakin/*DFNB59* mutation is responsible for pathology in neural cell bodies in the auditory pathway from the spiral ganglion to the inferior colliculus causing degraded neural function, the *MPZ* mutation is associated with loss of auditory nerve fibres and ganglion cells and the *GJB2* mutation causes impairment of inner hair cells/synapses and/or auditory nerve terminals.[30]

Clinical presentation

Perhaps one of the more helpful ways of understanding the complaints of patients with AN is to consider the description given in an early account of patients with this disorder.[54] The case is of a young girl called 'Eve', who was identified at the age of 8 years because she had difficulty following her teacher's instructions at school and did not improve when placed in the front row of the class. She had measures of pure-tone hearing and ABR that were inconsistent with each other. Her evoked responses, both middle latency and cortical, were absent and tests of auditory processing were especially affected, but her hearing thresholds suggested better hearing than these would imply. Her comments prior to implantation were recorded as follows:

'seeking
so
desperately
to
underSTAND

The calls, the bangs, the thumps, the beats…

HEARING
FEELING

but never *TRULY* comprehending'

The common clinical features of patients with AN are that their hearing difficulties are worse with speech than with simple environmental sound, and using the telephone causes particular difficulty. Patients complain that they can identify the speech sounds and the language used, but they cannot understand the words. Their difficulties are always more marked in noisy environments when there are competing signals. The effect of an AN can be thought of as causing a 'time-smear' of sound. The severity of the hearing impairment may be variable (see **Figure 69.3**) and can range from transient, intermittent, to stable and deteriorating.

Pathophysiology

AN shows some features similar to other peripheral neuropathies. The latter have: (i) elevated thresholds for sensation; (ii) altered perception (paresthesia); (iii) rapid adaptation to stimuli; (iv) absent or hypoactive deep tendon reflexes. By comparison, patients with AN have varying degrees of elevation in pure-tone thresholds[55] (see (i) above); have altered perception of hearing (see (ii) above); exhibit absent acoustic middle ear reflexes (see (iii) above); have disordered or absent auditory nerve conduction (see (iv) above).

PHYSIOLOGY

In the physiology of audition, sound energy is transduced to electrical stimuli in the cochlea and transmitted via the auditory nerve. The inner hair cells in the organ of Corti (see **Figure 69.1**) are responsible for this transduction process as has been shown by Russell and Sellick[56] who first demonstrated the importance of the inner hair cells in this process. The afferent auditory nerve consists of 95% type I myelinated nerve fibres (with many type I nerve fibres innervating one inner hair cell), and 5% type II nerve fibres (each type II nerve fibre innervating many outer hair cells (OHCs)). The cell bodies of both these types of bipolar neurons lie in the spiral ganglion. The arrangement of type I neurons in relation to inner hair cells is conducive to synchronous neural impulses whereas the arrangement of type II neurons is not.[57] Thus these respective neural anatomical arrangements have implications in relation to the diagnosis of AN, where it is proposed that the afferent neural pathway is involved (**Figure 69.1**).

The auditory nerve is a myelinated cranial nerve, with the myelin in the distal portion of the nerve being derived from Schwann cells (which are responsible for myelination of peripheral nerves), while that more proximally is derived from the oligodendroglia (cells supplying myelin in the central nervous system). The change between the two different types of myelin occurs as the auditory nerve exits the internal auditory meatus at the porus acousticus. Neuropathies affecting the auditory nerve are considered to be due to either demyelination (see below) or axonal degeneration.

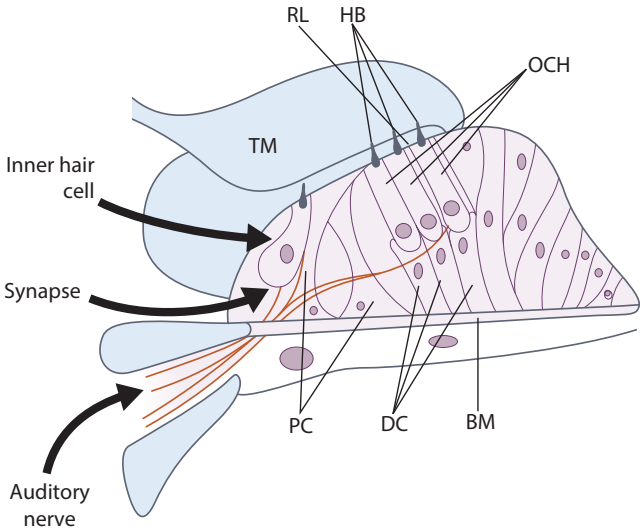


Figure 69.1 Diagram depicting proposed sites of lesion in auditory neuropathy. BM, basilar membrane; DC, Deiter's cells; HB, Habenula perforata; OHC – outer hair cell; PC, Pillar cells; RL, Reticular lamina; TM, tectorial membrane.

A combination of the two can also occur. The two functional consequences of these processes are a disruption of temporal synchrony of the auditory neural signals due to demyelination and a reduction of amplitude of neural signals because of axonal loss respectively. It is proposed that loss of neural synchrony (as can happen with demyelination) causes auditory nerve signals to be out of phase with the acoustic stimulus such that an averaged auditory brainstem response is not detected. Furthermore, dyssynchrony causes temporal tasks of audition to be disrupted (as tested by gap detection, localization and low-frequency pitch discrimination).[57, 58] Additionally, axonal loss results in reduced auditory neural input and therefore is also implicated in the absence of ABR recording, the loss of acoustic middle ear reflexes and disruption of temporal processes.

Demyelinating pathology results in the loss of the normal, rapid, 'saltatory' conduction of action potentials from one node of Ranvier to the next along the nerve fibre. This results initially in a conduction block where action potentials diminish to such an extent that the onward propagation of the neural impulse is halted. Over time the voltage-sensitive sodium channels (which are normally concentrated at the nodes of Ranvier) diffuse into the axon shorn of myelin, allowing for slow propagation of action potentials and hence slow neural impulses. Further, demyelination has been shown to cause increased sensitivity of nerve fibres to temperature increases, explaining cases of temperature-sensitive auditory neuropathy.[57] Finally, demyelination causes ephaptic transmission or 'cross-talk' between adjacent nerves that has the potential to interfere with synchronous auditory signals essential for understanding complex sounds such as speech.

Site(s) of lesion

It is now generally agreed that the term 'auditory neuropathy' encompasses heterogeneous conditions where the site of lesion may occur anywhere along the auditory pathways from the inner hair cells (IHCs) of the cochlea distally, through to the auditory brainstem pathways centrally (the afferent auditory pathway) (**Figure 69.1**). There is evidence accumulating to indicate at least three different sites of dysfunction:

- electromechanical transduction at the IHCs (including synaptic transmission)
- axons, cell bodies and myelin sheaths
- efferent influences through the olivocochlear feedback pathways.

ELECTROMECHANICAL TRANSDUCTION AT THE INNER HAIR CELLS

IHC disorders have been studied in animals[60] and have shown that anoxia and toxic agents (e.g. cisplatin) selectively impair IHC function, effectively removing the transduction process, including the release of neurotransmitters. Using the chinchilla animal model, scattered IHC loss (replicating the effects of sustained hypoxia) was induced, and OAEs, ABR thresholds and single unit tuning curves recorded at the inferior colliculus in the midbrain were measured. IHC damage correlated with ABR signal changes, but it was noted that individual inferior colliculus neurons had relatively normal thresholds across the frequencies, despite the loss of IHCs. This suggested that the number of active neural elements was reduced to the point that the remotely recorded compound action potential was reduced in amplitude. The single unit data was interpreted as implying that low threshold information was nonetheless reaching the central auditory system, and hence the dissociation of ABR and inferior colliculus neural thresholds. Extrapolating, it was suggested that patients with scattered IHC loss would have a reduced number of 'information channels', and therefore the speech information transferred to the brain would depend on the amount of redundancy in the system. However, studies of adult temporal bones have not shown isolated IHC loss.[61] [Level 1 evidence]

An excess of neurotransmitters, i.e. an infusion of synaptic agonists, has been shown to cause attenuation of auditory nerve activity.[57] A disorder affecting the synapse between the IHCs and the dendrites of the auditory nerve could account for many of the electrophysiological features of an auditory neuropathy. The disorder could be pre- or postsynaptic, affecting the release of neurotransmitters from the IHCs or their receptor sites on the dendritic cells. In neonates with an abnormal ABR release of neurotransmitters is deficient from ribbon synapses due to deficient ion vesicle turnover and acquired excitotoxic effects of noise damage on these synapses with subsequent neural degeneration.

The effect of stimulus rate on the ABR may be a useful tool in investigating synaptic dysfunction. In healthy controls, an increase in stimulus repetition rate results in an increase in the latency and decrease in the amplitude of wave I. Electrocochleography (ECoG) has also been used to identify presynaptic versus postsynaptic lesions in auditory neuropathy. Prolonged summating potential (SP) latencies indicated a presynaptic lesion whereas a normal latency SP often followed by a negative 'dendritic potential' (DP) was associated with a postsynaptic lesion. Electrically evoked auditory brainstem response (EABR) measured following cochlear implantation showed a normal EABR waveform in patients with prolonged SP on ECoG (presynaptic lesion) while EABR waveforms were either absent or of poor morphology in patients whose SP on ECoG had a normal latency with evidence of DP (postsynaptic lesion) (**Figure 69.2**).[62]

AXONS, CELL BODIES AND MYELIN SHEATHS

There are 30 000 auditory nerve fibres, most of which have diameters of approximately 3 µm. Type I nerve fibres, which innervate IHC, make up 95% of the afferent fibres, with 10–30 neurons innervating each IHC. Type II nerve fibres make up the remaining 5%, each one making contact with many outer hair cells (OHCs) (see above). These nerve fibres are myelinated bipolar neurons with their cell bodies in the spiral ganglion.

Distinguishing whether a neuropathy is principally demyelinating or axonal in type is primarily determined

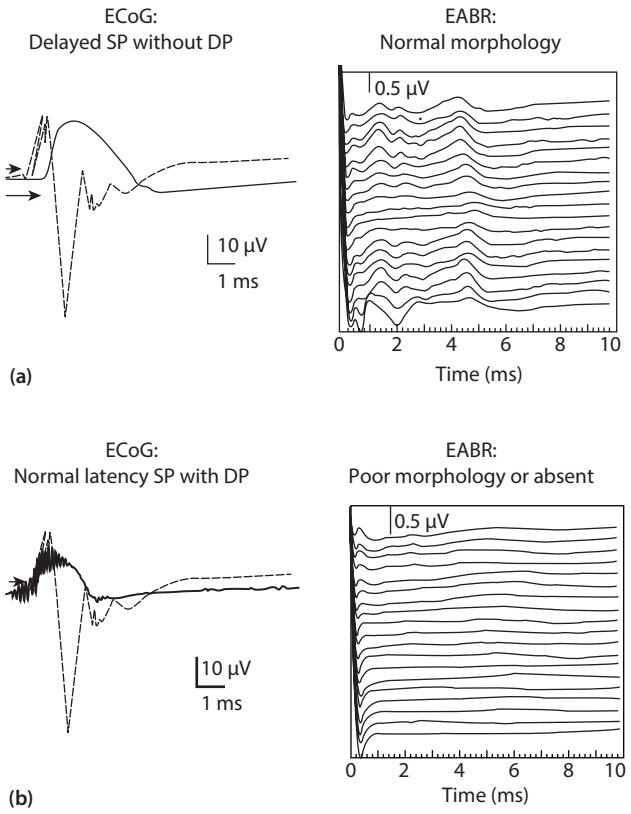


Figure 69.2 Precochlear implantation ECoG waveforms compared with postcochlear implantation EABR showing correlation between **(a)** delayed SP and normal EABR (presynaptic lesion) and **(b)** normal latency SP with DP and absent or poor morphology EABR (postsynaptic lesion). Redrawn with permission.[60]

histologically following biopsy, clearly not a procedure applicable to the auditory nerve. In the circumstances, electrodiagnostic studies (nerve conduction studies) can provide a functional categorization for the type of neuropathy. A patient with late-onset HSMN, beginning at age 40, and presenting with a hearing loss 10 years later, came to autopsy at the age of 77 years. Histopathological examination of both auditory and sural nerves showed a significant loss of nerve fibres more extensive in the sural nerve than in the auditory nerve. Photomicrographs of a section of the patient's auditory nerve and an age-matched control showed an extensive loss of large nerve fibres in the former. This woman's neuropathy was inherited in an autosomal dominant fashion, with genetic analysis of the affected members of the pedigree showing a duplication disorder on the *MPZ* gene of chromosome 1. The *MPZ* gene (myelin protein zero) was the first gene associated with auditory neuropathy in patients with Charcot–Marie–Tooth disease (CMT). The *MPZ* gene codes for a protein required for myelin formation and adhesion. Preserved cochlear hair cells were found on postmortem examination of a patient with CMT together with decreased spiral ganglion cells and degeneration of the residual axons. The proximal auditory nerve showed axonal loss and incomplete myelination at the entrance to the brainstem. [Level 1 evidence]

EFFERENT INFLUENCES THROUGH OLIVOCOCHLEAR FEEDBACK

Auditory efferent fibres travel from the olivocochlear bundle in the midbrain through the VIIIth nerve to the cochlea. Studies of the effects of the efferent pathway have demonstrated a reduction in the compound action potential (CAP) following electrical stimulation of the olivocochlear bundle in humans.[63–65] The contralateral pathway involves only crossed afferent fibres and is believed to mediate the suppression of OAEs in the presence of noise.[65] The ipsilateral pathway to the OHCs, however, involves crossing of both the efferent and afferent fibres. The suppression of OAEs in the presence of noise is known as the medial olivocochlear reflex, and has been studied in detail[65–67] showing the greatest suppressive effect in the 8–18 ms time period in the lower frequencies with low-intensity stimuli and with binaural noise (using a forward masking paradigm).

Two patients with AN, followed for some time, showed robust OAEs but, in both, contralateral noise failed to suppress their OAEs.[66] Three 'foil' subjects were chosen as controls: one with a similar audiogram to patient 1, one with a Bell's palsy and absent stapedius reflex thresholds (i.e. absent middle ear muscle reflexes), and one with bilateral temporal lobe disease. Testing of the 'foil' subjects showed that isolated normal hearing at 2 kHz, absent middle ear reflexes and conscious cortical awareness of sound did not contribute directly to the lack of efferent suppression.

Their suggestions to explain this included:

- deficiency of synchronous activation of type I afferent fibres (originating at the base of the IHCs), so they cannot activate efferent feedback
- restriction to only using type II afferent neurones (originating at or near the OHCs) to support normal zones of pure-tone sensitivity.

Discharge of primary neurons, synchronized by a primary deficit in the efferent system, has largely been discounted following studies on patients with unilateral auditory neuropathy,[67] where the function of the efferent system on the side with the profound hearing loss has been demonstrated to be functional (i.e. OAEs on this side can be partially suppressed by noise to the good ear). The efferent system requires input from the afferent system to be activated. The two patients above show the effects of disconnecting the afferent system from efferent stimulation and revealing this disconnection by leaving the patients with an absence of both static (middle-ear mediated) and dynamic (medial olivocochlear system mediated) efferent suppression.

Test battery

- Baseline audiometric tests
  - Pure-tone audiogram
  - Tympanogram
  - Stapedius reflex thresholds

- Electrophysiological tests
  - ABRs
  - ECoG
  - CMs
  - OAEs, both with and without contralateral suppression
  - Middle latency responses (MLRs)
  - P300
- Behavioural auditory tests
  - Speech recognition tests
  - Temporal pattern tests:
  - frequency pattern tests
  - temporal gap detection

Figure 69.3 shows a range of test results from a 7-year-old male patient with auditory neuropathy.

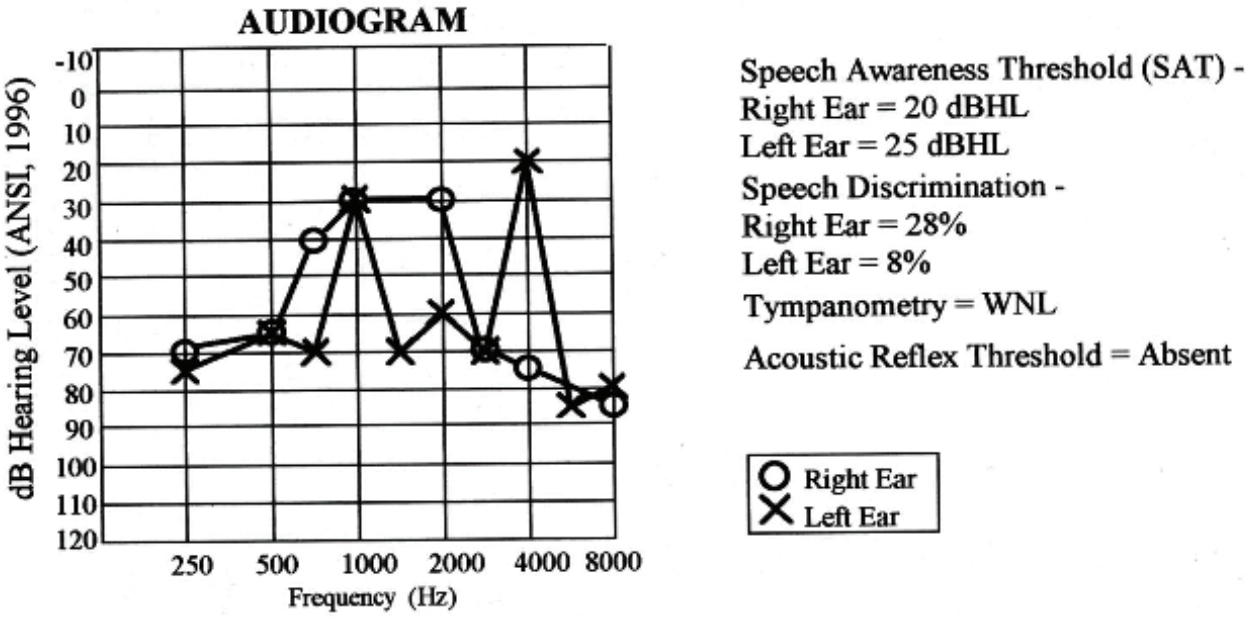


Figure 69.3 **(a)** Audiogram, **(b)** transient-evoked otoacoustic emissions and **(c)** auditory brainstem responses from a 7-year-old male patient with auditory neuropathy. Reproduced with permission.[55]

ACOUSTIC BRAINSTEM EVOKED RESPONSES

Acoustic brainstem evoked responses (ABRs) are detected by scalp electrodes and are a far-field reflection of electrical activity generated by the VIIIth nerve and brainstem auditory pathways in response to acoustic stimuli. Waves I and II are thought to come from generator sites in the distal and proximal sections of the VIIIth nerve, respectively, and III, IV and V from generator sites within the brainstem auditory pathways.[68] It has been proposed that the absent ABR of the patient with AN can be explained by the altered temporal synchrony of the auditory brainstem pathway, suggesting that, in these patients, auditory nerve and brainstem discharges are not precisely time-locked to the acoustic signal, so that short duration components (i.e. of 1 ms) are cancelled in the averaging process, rendering them indistinguishable from background electrical levels.

PURE-TONE AUDIOMETRY

Pure-tone audiometric thresholds show varying configurations of hearing thresholds (**Figure 69.4**) and variable degrees of hearing impairment (**Figure 69.5**).

Otoacoustic emissions (OAEs), first described in 1978,[64] are low-intensity sounds generated by the active movement of the OHCs of the cochlea. They are a marker of cochlear function and are left intact after section of the auditory nerve.[69] These acoustic echoes are evoked by stimulation with transients (clicks) at 80–86 dB sound pressure, and, typically, responses to 260 stimuli are captured over a time frame of the first 20 ms after stimulus application. These transient evoked otoacoustic emissions (TEOAEs) are present if the response amplitude, after subtraction of background noise, is 4 dB or more, and the waveform is reproducible in at least three octave bands. Measurement of distortion product otoacoustic emissions (DPOAEs) allows specific testing of a restricted region of OHCs, giving more frequency-specific information than TEOAEs. This is achieved by stimulation with two continuous tones of different frequencies (f1 and f2) that evoke DPOAEs that are largest at the 2f1–f2 frequency.

From the first papers describing TOAEs in these patients[8, 64] it was evident from the clearly recognizable waveforms that the hearing disorder was not due to significant dysfunction of the cochlear OHCs. On the occasions when these patients were monitored over a period of time, some started to lose their DPOAEs from small regions of the cochlea and this was attributed to a lack of trophic factors on the OHCs due to the auditory nerve disorder. Another study that describes the results of OAE testing in 17 children thought to have AN failed to show OAEs in either ear in more than half of their patients (8/17, with intersubject variation in behavioural hearing thresholds varying from 10 dB to 120 dB). However, in this latter report, how the authors felt confident to diagnose auditory neuropathy is questioned.

Contralateral suppression of OAEs can occur if noise (set at a level 5 dB louder than the click) presented to the contralateral ear fails to reduce the TEOAEs by 1 dB or more. This may occur if either the afferent pathway from the contralateral ear or the efferent pathway on the recorded side (via the olivocochlear bundle in the brainstem and carried with the inferior vestibular division of the VIIIth nerve) is dysfunctional.

Two studies have reported the lack of contralateral suppression of OAEs in patients with AN.[66, 70] The second of these describes the absence of contralateral suppression of OAEs in all eight of the patients tested from their series of ten. This is consistent with VIIIth nerve pathology occurring in either the contralateral afferent or the ipsilateral efferent pathway.

Cochlear microphonics (CMs) are an electrophysiological response generated in the cochlea to acoustic signals.[71] They represent the early components of the ABR and are small in size and susceptible to contamination by electroacoustic artefact. They can be better determined by reversing the click phase, at 5–25 ms, from condensation to rarefaction. They occur in the 0.7–1 ms window post-stimulus and show similar waveform characteristics to the stimulus itself[72] (the endocochlear potential of +80 mV is not measurable in humans). Transtympanic electrocochleograms indicate that the phase reversal to the click occurs at the level of the

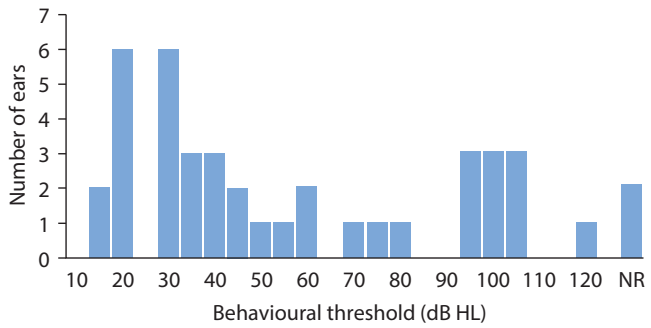


Figure 69.4 The distribution of behavioural thresholds (three-frequency average) for 38 years with auditory neuropathy. Reproduced with permission.[15]

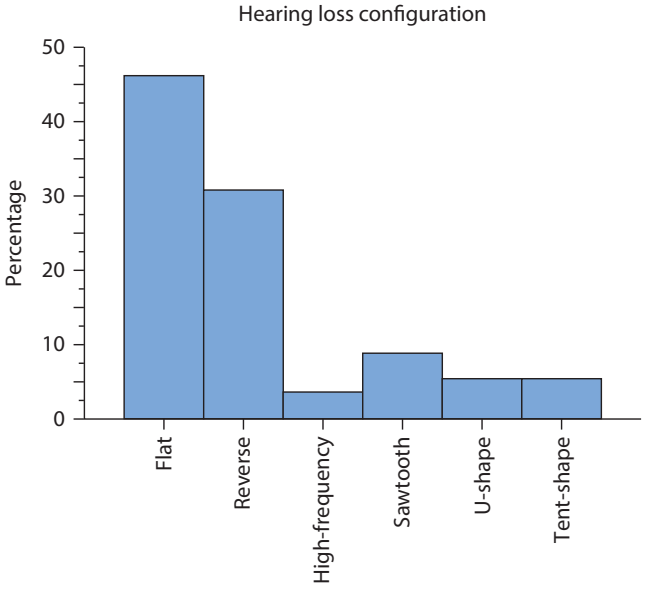


Figure 69.5 Hearing loss configuration (audiogram shape) distribution from a database of 59 patients with auditory neuropathy. Reproduced with permission.[95]

cochlea itself, and therefore the presence of CMs is indicative of a preneural response to sound.

Where investigation of the neural response is the primary aim, alternating polarity clicks are used in the recordings of the ABR because they cancel the cochlear potential and overwrite the CAP. This generates a 'microphonic-free' ABR leaving only the desired summating and action potentials, as evidence of a neural response. Thus, OAEs are preneural phenomena that reflect the integrity of the OHCs of the cochlea, whereas ABRs and the summating and CAP of the ECoG are tests of neural synchrony. The common stimulus to all these phenomena is the broad-spectrum 100 µs pulse.

The enhancement and detection of CMs was studied in five infants who had paradoxical results to hearing testing in a series of 60 deaf children.[73] By performing latency–intensity ABR studies using condensation and rarefaction clicks through insert earphones, intact preneural responses to sound with the characteristics described in **Table 69.3** were identified. It was suggested that, if diagnosticians do not have access to OAEs, patients with AN can be detected by comparison of ABR responses to condensation and rarefaction clicks at 100 µs (**Figure 69.6**).

Insert earphones are recommended[64] for recording ABRs to enable the separation of the stimulus artefact from cochlear potentials. The response of two opposite polarity clicks can be compared, with search for phase reversals and lack of shifts in latency with intensity changes. Adding the positive and negative polarity traces may uncover small residual neural events.

STEADY-STATE POTENTIALS

Sixty patients have been tested using steady-state potentials (SSEPs) to study the evoked potentials in the frequency domain rather than in the temporal domain, on the basis that the SSEP threshold might be more resistant to the effects of neural dyssynchrony. The study conclusion, however, was that SSEPs at a high rate had little or no predictive value for hearing thresholds in children with auditory neuropathy.

Tympanometry and stapedius reflex thresholds from 500 to 4000 Hz are also used in the test battery, as activation of the middle ear muscles (i.e. stapedius) by high-intensity sound is dependent on the integrity of the VIIIth nerve. The latter were absent in all ten patients in one study of auditory neuropathy,[8] irrespective of the pure tone threshold.

Speech recognition tests have been an essential item of the test battery for recognizing AN. Speech intelligibility is affected out of proportion to that expected if the pure-tone loss were entirely of cochlear origin. Speech intelligibility scores, tested at comfortable hearing level, are reduced disproportionately to the extent of the pure-tone impairment.[74] These scores are calculated from the average audiogram thresholds at 1, 2 and 4 kHz and, if the score falls below predicted values, the hearing impairment is likely to be retrocochlear in nature. Expected sentence recognition scores are calculated using the PTA to find the number of audible cues available to the patient and dividing by the total number of audible cues in the speech spectrum.

PSYCHOPHYSICAL

Further transmission of neural impulses via the auditory nerve to the brainstem is followed by auditory projections to higher centres where perceptual registration and cognitive elaboration takes place (see Chapter 48, Physiology of hearing). Psychophysical measures can also be used to assess patients with AN. They include the following tests which may be required to distinguish central auditory processing disorders from retrocochlear hearing disorders:

- monaural low redundancy speech tests, i.e. speech stimuli, presented to one ear
- dichotic/binaural interaction tests, i.e. stimuli presented to both ears, the task requiring the patient to attend to

TABLE 69.3 Comparison of the response characteristics of cochlear microphonics, compound action potentials and otoacoustic emissions (reproduced with permission)[73]

Response	Source	Measured by	Response to stimulus polarity inversion	Response to intensity decrease
Cochlear microphonic	Primarily from outer hair cells	Far-field or near-field electrical recordings using signal averaging and common-mode rejection	Inverts and follows the polarity of the stimulus; is not forward maskable and does not change in latency during simultaneous masking	No latency shift
Compound action potential (CAP)	Primary afferent neurons in primarily the basal turn of the cochlea	Far-field or near-field electrical recordings using signal averaging; comprises wave I of the ABR and the CAP of the ECoG	Does *not* invert, but shifts in latency by about one-half period of the stimulus; reductions in size and increase in latency occur during simultaneous masking in the same ear	Increase in latency at roughly 0.3 ms per 10 dB decrease in intensity
Otoacoustic emissions (OAEs)	Outer hair cells, with response size in humans probably mediated by the middle ear, transfer function	Sensitive microphones and amplifiers in response to clicks or tone pairs in the 2f1–f2 paradigm	Invert in polarity	No obvious change in latency with change in intensity

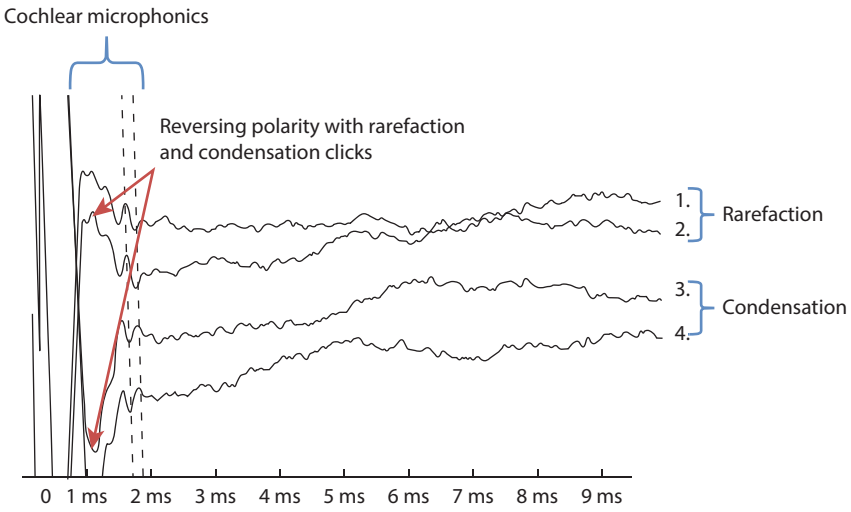


Figure 69.6 Acoustic brainstem evoked response to condensation (Con) versus rarefaction (Rar) polarity clicks. Note the complete biphasic inversion of elements even beyond 2 milliseconds. Reproduced with permission.[72]

one ear only, or both at the same time e.g. competing sentence tests
- temporal tests, i.e. sequencing tasks (e.g. the temporal gap detection test with a silent period embedded in a noise burst)
- modulation transfer function tests, i.e. fluctuations in levels of steady-state noise.

Further details are presented later in the chapter under 'Differential diagnosis'.

KEY POINTS

Criteria for diagnosis of auditory neuropathy

Evidence for preneural response to sound

- Normal otoacoustic emissions (OAEs)*
- Normal cochlear microphonic (CM)*

Evidence for abnormal neural synchrony

- Absent or severely abnormal acoustic brainstem auditory evoked responses**
- [Absent contralateral suppression of OAEs]
- [Absent middle ear reflexes]

plus

- Pure-tone thresholds ranging anywhere from normal to severely impaired

Diagnosis requires simultaneous presence of a pre-neural response to sound * *plus* abnormal neural synchrony **

PAEDIATRIC AUDITORY NEUROPATHY SPECTRUM DISORDER

Prevalence of disorder

A rigorous study[15] has been reported of 20 subjects fulfilling the criterion for AN, 12 of whom were identified from the Victorian Hearing Screening Programme for children considered at risk of hearing loss, and 8 of whom were identified by parental concern or failure to develop speech and language normally. An incidence of AN as 2.09% of those who failed ABR screening (n = 39), and 0.23% of those children at risk for hearing loss (n = 5199), i.e. 2/1000, was reported. A review of published literature which looked at prevalence of AN in the well-baby population and the false negative rate of OAE based on newborn hearing screening programmes showed that prevalence of AN in children in population hearing screening was between 0.006% (SD 0.006) and 0.03% (SD 0.02). The false negative rate, however, due to children with AN not detected through newborn hearing screening programmes using only OAEs is between 4% and 17%.[75]

Table 69.4 summarizes the results of the larger studies of paediatric populations assessed for AN.

From the studies in Table 69.4, it can be seen that the prevalence of AN in the population of children with permanent hearing loss is 5.1–15.38%, i.e. approximately 1 in 10. This compares with 1 in a 100 of those suspected of hearing loss (0.5–1.29%), or 2 in a 1000 of the 'at risk' population (0.23%).

Comorbidities such as developmental and learning delays, attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD), autism spectrum disorders, visual problems, blindness, cerebral palsy, motor disorders, apraxia, inner ear malformation, seizures and various syndromes are reported in up to 54% of children with AN. These can have an adverse influence on the child's speech and language development in addition to the underlying AN. In 2008 the Guidelines Development Conference on the Identification and Management of Infants with AN, meeting in Lake Como, Italy, considered the many aspects of AN, including comorbidities, and proposed the term 'auditory neuropathy spectrum disorder' in an attempt to encompass the heterogeneous nature of the condition.[10]

Causes of paediatric auditory neuropathy

PERINATAL RISK FACTORS

The first report of perinatal risk factors in babies who failed the ABR test but passed the click-evoked OAE

TABLE 69.4 Prevalence of disorder in neonates/children

Authors	Study population	Number with absent ABRs	Those fulfilling criteria for AN	% of study population with AN
Kraus et al. 1984[4]	543 with suspected hearing loss	49 with absent ABRs	7 with no worse than moderate hearing loss (14.3% of those with absent ABRs)	1.29% of those with suspected hearing loss
Davis and Hirsh 1979[1]	200 clinic population		1	0.5% of clinic population
Berlin et al. 1994[12]	60 children diagnosed as 'deaf'		5 with absent ABRs and present OAEs	12% of deaf children
Rance et al. 1999[15]	5199 with increased risk of hearing loss	37 with absent ABRs	12 subjects with absent ABRs and present CMs	0.23% of those at risk of hearing loss
Madden et al. 2002[11]	428 children with sensorineural hearing loss (SNHL)		22 with CMs/OAEs but absent ABRs	5.1% of children with permanent hearing loss
Foerst et al. 2006[76]	5190 children with hearing concerns and risk factors for hearing loss, of whom 3415 were tested with ABR and TEOAEs	379 with elevated or absent ABRs	32 with OAEs present but absent ABRs	0.94% of children at risk of hearing loss
Talaat et al. 2009[77]	112 children aged 6–32 months, with severe to profound hearing loss		15 with absent ABRs and OAEs present	13.4% of children with permanent hearing loss
Kirkim et al. 2008[78]	23 786 babies had universal newborn hearing screen; 2236 were referred for further tests	65 with absent or elevated ABRs	10 with absent or elevated ABRs and clear OAEs	15.38% of children with hearing loss, and 0.044% of babies undergoing universal newborn hearing screen

screen came in 1996. Four out of 100 fulfilled these criteria: one had periventricular leukomalacia, two were low birthweight and one was very low birthweight; three were diagnosed with having a respiratory distress syndrome; two received ampicillin and gentamicin; and three had hyperbilirubinaemia necessitating either exchange transfusion or phototherapy. Two out of these four normalized or reversed their ABR abnormality. Although these observations did not prove causality in any of the cases, the findings did imply that perinatal factors were likely to be involved, with some factors possibly causing temporary abnormalities only.

In an extensive report of neonates with AN[15] neonatal risk factors were documented and details of bilirubin levels recorded. Increased bilirubin (>350 µmol/L) was identified in 50% (Table 69.5).

Perinatal risk factors for AN were also analyzed in a retrospective study[11] of 22 patients with present OAEs and CMs but absent ABRs. These patients were identified from 428 children with permanent hearing loss in a paediatric otology clinic. Sixty-eight per cent of the children with AN had a complicated perinatal course, with hyperbilirubinaemia in 50%, prematurity in 45%, ototoxicity in 41%, neonatal ventilator dependency in 36% and/or cerebral palsy in 9%. In 36% a possible genetic link was identified, although this was apparently of a non-syndromic type as no other anomalies, particularly peripheral neuropathy, were identified. Following these children for an average of 32 months, 50% showed an improvement, not accounted for by normal development, within 1–15 months, and those with hyperbilirubinaemia

TABLE 69.5 Hearing loss risk factors in subjects with auditory neuropathy (reproduced with permission).[15] Figures in brackets represent the bilirubin level in micromoles/litre, except where otherwise indicated

Child	Risk factor	Other disabilities	Gestation
1	Jaundice (1010)		37
2	Jaundice (792)		36
3	Jaundice (467)		39
4	Jaundice (420)		40
5	Jaundice (380)		41
6	Jaundice (353)/hypoxia	Cerebral palsy	34
7	Hydrocephalus/hypoxia		33
8	LBW (900 g)/hypoxia		25
9	Parental concern	Cerebral palsy	40
10	Unilateral middle ear malformation	Unilateral facial palsy	39
11	Neonatal meningitis		39
12	Parental concern		41
13	Jaundice (540)		40
14	Jaundice (470)/hypoxia		32
15	Jaundice (420)		41
16	Jaundice (390)/hypoxia		31
17	None	Cerebral palsy	40
18	None		39
19	None		39
20	None		39

were more likely to improve than those without hyperbilirubinaemia ($p < 0.04$ at 2 kHz). Prematurity and perinatal anoxia were shown to predispose to bilirubin encephalopathy, with the risk for kernicterus and permanent sequelae being much higher at serum bilirubin levels thought to be safe for term babies.[6] 'Finer tools' such as ABR and other event-related potentials, have been recommended for use alongside biochemical measures to predict the risk of kernicterus and its sequelae. Children with hyperbilirubinaemia would thus appear to represent a unique subpopulation of patients with AN and require surveillance electrophysiologically as well as behaviourally.[79]

As children treated in neonatal intensive care units are found to have higher incidence of AN, the Joint Commission on Infant Hearing (JCIH, 2007) have recommended that infants treated in neonatal intensive care have their hearing tested using auditory brainstem response audiometry.[80]

KEY POINTS

Perinatal factors implicated in auditory neuropathy spectrum disorder

- Prematurity
- Perinatal anoxia/respiratory distress syndrome
- Low birthweight
- Hyperbilirubinaemia (>350 µmol/L)*
- Ototoxicity
- Cerebral palsy
- Neonatal ventilator dependency

* This level may be lower in preterm babies.

GENETIC

Non-syndromic recessive hearing loss is thought to account for approximately 40% of all cases of childhood hearing loss. Where that hearing loss has been demonstrated to have the characteristics of AN, genetic causes of the disorder have, until recently, only been associated with syndromic hearing loss, i.e. CMT[21] and Friedreich's ataxia.[22, 23] However, mutations in the otoferlin (*OTOF*) gene have been demonstrated to be associated with non-syndromic recessive auditory neuropathy (NSRAN).[17] The causative gene in four families was sought using a genome-wide linkage study and a critical region on chromosome 2p23 was identified that contained the *OTOF* locus. Out of eight alleles, four *OTOF* mutations were observed in the NSRAN families: a frameshift, a splice site and 2 missense mutations. These patients have been helped by cochlear implants but not by hearing aids. Thus, finding the genetic cause of this NSRAN has implications not only for aetiological diagnosis in newborn screening but also for prognosis and habilitation. Otoferlin is expressed in the IHCs in the region where afferent synaptic contacts are located.[17]

More recently, mutations in the pejvakin (*DFNB59*) gene, located on chromosome 2q31.1-q31.3 were identified in four families with AN. Pejvakin is a protein found in the cell bodies of neurons in the afferent auditory pathway and is thought to cause neural dysfunction.[19] Mutations to connexin 26 (*GJB2*) genes have also been implicated in auditory neuropathy. In a study reported in 2008, three children with hearing loss but preserved OAEs underwent transtympanic ECoG that showed normal CMs but abnormal neural responses.[30] [Level 1 evidence]

IMPACT ON NEONATAL HEARING SCREENING PROGRAMMES

Importantly, the association of a screening ABR fail and an OAE pass raises questions about whether OAE should be universally employed as the only initial screening tool for hearing loss infants in special care baby units.

Various protocols have been recommended for neonatal hearing screening.[6, 63, 73] One ABR intensity series protocol requires an estimate of threshold immediately if the infant fails an initial 60 dB nHL or 30 dB nHL test in either ear,[61] advising that records should be kept of threshold estimates and indicators of site of lesion (i.e. cochlear or neural). As ABR is also insufficient as the sole evaluator of hearing sensitivity, particularly if no response or early waveforms only are obtained, some[6, 63] recommend OAE testing at the same time as the ABR threshold series. Ideally, a system that can collect ABRs and OAEs simultaneously from the same sleeping infant is recommended. The importance of follow-up with the concomitant use of behavioural audiometry with ABR cannot be underestimated to guard against inappropriate diagnoses of cochlear hearing loss or reversible ABR abnormalities.[10, 63, 73]

KEY POINTS

Neonatal hearing screening programmes

- Checks of ABR and/or CMs should be considered in **high-risk newborns** who undergo OAE testing as their primary screening tool.
- Clinicians and audiologsts should include **auditory neuropathy spectrum disorder** in their differential diagnosis of SNHL in children.
- Patients with **hyperbilirubinaemia** should be seen as a distinct subset of those patients fulfilling the criteria for AN, particularly because they tend to show a distinct audiological improvement during the first year of life.

ADULT NEUROLOGICAL AUDITORY NEUROPATHY AND BRAINSTEM HEARING LOSS

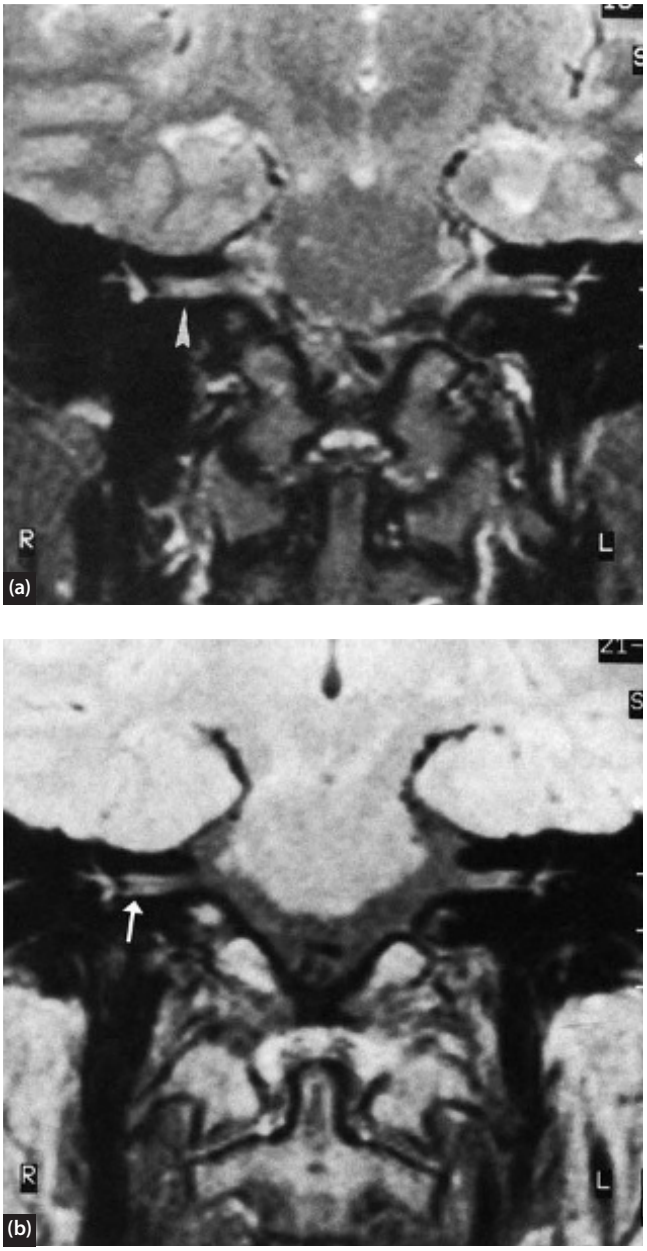
Neurological causes of AN and retrocochlear hearing loss include those with first-order cochlear neuronal degeneration (i.e. VIIIth nerve lesions) and those with pathology of the second-order cochlear neurons within the brainstem.

Multiple sclerosis

Multiple sclerosis (MS) is a disorder characterized by multiple areas of demyelination in the central nervous

system, and the clinical diagnosis rests upon the demonstration of two or more such lesions. Acoustic brainstem evoked response audiometry has been used for nearly 40 years in patients presenting with a single lesion suggestive of MS, to detect other sites of demyelination. In the first study in this area, wave V was the most consistently abnormal wave in patients with MS.[50] A correlation was demonstrated between this ABR abnormality and clinical evidence of a brainstem lesion due to MS in 79% of patients, but there was also an ABR abnormality in 51% of those patients without clinical signs of MS related to the brainstem. However, the presentation of MS with acute hearing loss is rare, and reported in only 1–3.5% of patients.[81, 82] Demyelinating lesions have been identified in the VIIIth nerve;[83, 84] in the nerve root entry zone/cochlear nucleus;[52, 85] and in the pons.[38] Conversely, an MRI study of 354 patients with sudden hearing loss, tinnitus and vertigo identified abnormalities in 12 (34.5%), only 2 of whom showed focal hyperintensities that were subsequently found to be the first evidence of MS.[86]

MRI and electrophysiological correlates have been reported as evidence for demyelination in the VIIIth nerve:[39] a small hyperintense lesion along the cochlear nerve which decreased in size and disappeared with steroid treatment (**Figure 69.7a, b**), and, in parallel, a return to normal of the ABR (**Figure 69.7c**). Wave I was initially undetectable, then delayed and finally normal, with invariably normal interpeak latencies throughout the time



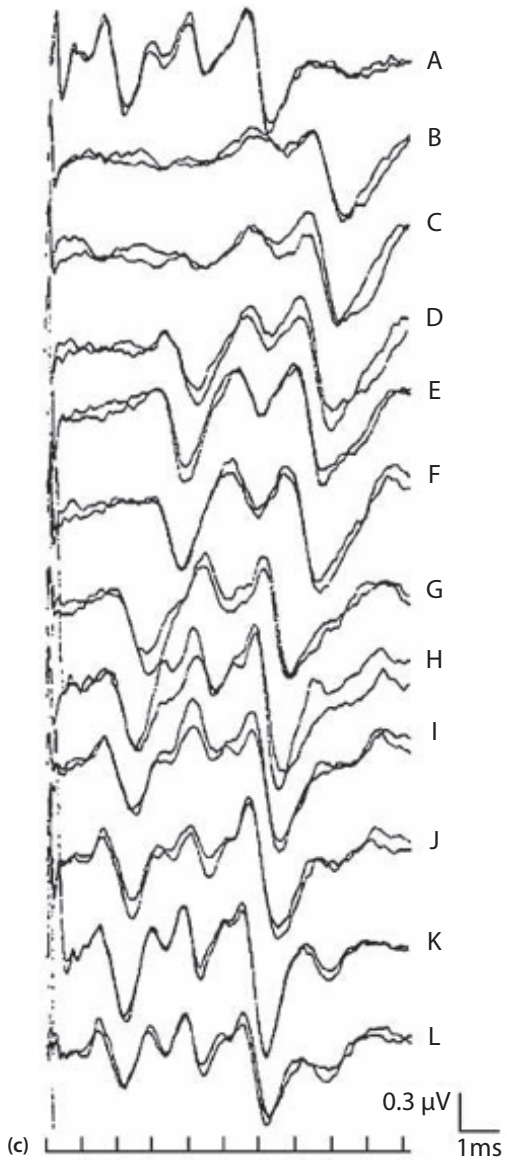


Figure 69.7 **(a)** Coronal T2-weighted MRI: mild enlargement of the right VIIIth nerve inside the internal auditory canal, and punctate area of hyperintense signal (arrow). **(b)** Coronal T2-weighted MRI: no lesion seen along the right VIIIth cranial nerve. **(c)** ABR recordings (rarefaction clicks, 65 dB SL intensity, 22.1 Hz frequency, Cz–A2 electrodes) before (A), and after (B–L), right sudden hearing loss. Reproduced with permission.[37]

frame of the recordings. The ABR abnormalities are likely to have been related to the sudden hearing loss because the ABR had been normal in previous testing, and then improved in parallel to the clinical recovery.

This was the most caudal site of a demyelinating lesion in MS reported to that date, and the authors felt that the lesion could still be accounted for as an abnormality of central myelin as the transition zone from glia to Schwann cells is quite distal in the VIIIth cranial nerve. Transtympanic ECoG[84] has also been used to demonstrate a disturbance of synchronization at the level of the first-order cochlear neurons in a patient known to have MS who developed sudden hearing loss. Investigation identified enhanced latency of the CP, a normal CM and SP, but absent ABRs, showing this hearing loss to have the characteristics of an AN. MRI has allowed the progression of demyelinating lesions of the ventral cochlear nucleus near the entry zone of the VIIIth nerve to be documented in MS patients with sudden hearing loss[52, 86] and also in MS patients with hearing loss who have pontine lesions.[39]

Extrinsic and intrinsic tumours of the cerebellopontine angle

There are a number of tumours of the cerebellopontine angle (CPA) which can present with retrocochlear hearing loss: cerebellar medulloblastoma, neurinoma, meningioma, cholesteatoma, ependymoma, jugular glomus tumour and metastasis. Imaging will generally identify these tumours and, in the case of metastases, CSF lumbar puncture for cytological examination, or serological search for antineuronal antibodies (anti-ro, anti-la, anti-RNP, anti-Jo-1, anti-SCL-70) will lead to the diagnosis. Cerebellar medulloblastomas are particularly common in childhood (25% of all intracranial neoplasia) where they tend to be midline, but in adulthood they tend to be located laterally and can present as CPA lesions. In a study comparing AN and neural deafness in acoustic neuromas, the following similarities in auditory tests were reported: presence of tone decay, normal distortion product OAEs and CMs and poor speech perception which was out of proportion to the pure-tone audiometry configuration. However, ABR abnormalities were different. In patients with acoustic neuromas only wave I of the ABR was seen with following waves absent, whereas in patients with AN ABR was absent or, when present, abnormal wave I was seen.[87]

Auditory neuropathy plus peripheral neuropathy

In a series of 70 cases of AN,[88] no aetiology was identifiable in 40% of affected individuals. The AN was typically bilateral and affected men and women equally. In general, ANs have been considered to be an infrequent associate of peripheral neuropathies but, where they do occur, other cranial neuropathies (i.e. optic, trigeminal and facial neuropathies) occur more frequently. However, a peripheral neuropathy was identified in 18/70 (26%) of the cases cited above following clinical assessment of deep tendon reflexes at the ankle, vibration sense at 128 Hz in the foot and investigations with nerve conduction studies plus sural/peroneal nerve biopsy. Hereditary sensory–motor neuropathy (HSMN) was found in 9 out of 70 of the patients, with 3 families providing all 9 of these cases. Several different genetic disorders may present with HSMN, and one Roma family from Slovenia[24] was shown to have a mutation on chromosome 8q24. In these patients, the peripheral neuropathy occurred first, and sural nerve biopsy demonstrated a mixed axonal and degenerative neuropathy, with hearing loss only developing later. These cases also had bilateral vestibular failure, presumably on the basis of VIIIth nerve involvement, and demonstrated a recessive mode of inheritance. [Level 1 evidence]

NERVE CONDUCTION STUDIES

This investigation allows the detection of a peripheral neuropathy and its characterization as a demyelinating or axonal type neuropathy. A demyelinated nerve fibre has a much reduced membrane resistance and increased capacitance to current draining through the axonal membrane and the action potential falls off much more rapidly than in a normal nerve fibre because of the reduced membrane resistance. The action potential cannot reach any excitable region of the axon with sufficient amplitude to regenerate itself. The result of this is a slowing of conduction velocity, and a widening of the whole nerve action potential as multiple axons become affected by the demyelinating process (**Figure 69.8**). Demyelinated axons also have an impaired capacity to transmit trains of impulses. Such high discharge rates would typically be seen in response to intense acoustic stimuli, contributing to the appreciation of loudness and mediating reflex activation of middle ear muscles and olivocochlear reflexes, explaining the absence of stapedius reflexes and loss of contralateral suppression of OAEs in patients with AN.

Two patients with AN who have a temperature-sensitive hearing loss have been reported. Demyelinated axons may also demonstrate 'cross-talk' (ephaptic transmission) between fibres, with one active fibre initiating impulses in an adjacent fibre, possibly accounting in the auditory system for distortion in the coding complex of speech. However, in an axonal neuropathy, there is no conduction delay and therefore relative preservation of velocity but reduced size of the nerve action potential due to the reduced number of functioning axons. This becomes more evident the greater the distance from the cell body, with the longest fibres most susceptible to pathology. This is likely to affect the low frequencies on the audiogram as the longest cochlear fibres extend to the apex of the cochlea.

The neuropathy associated with CMT type I is characteristically demyelinating, and that of CMT type 2 is axonal. The axonal neuropathy theoretically should not

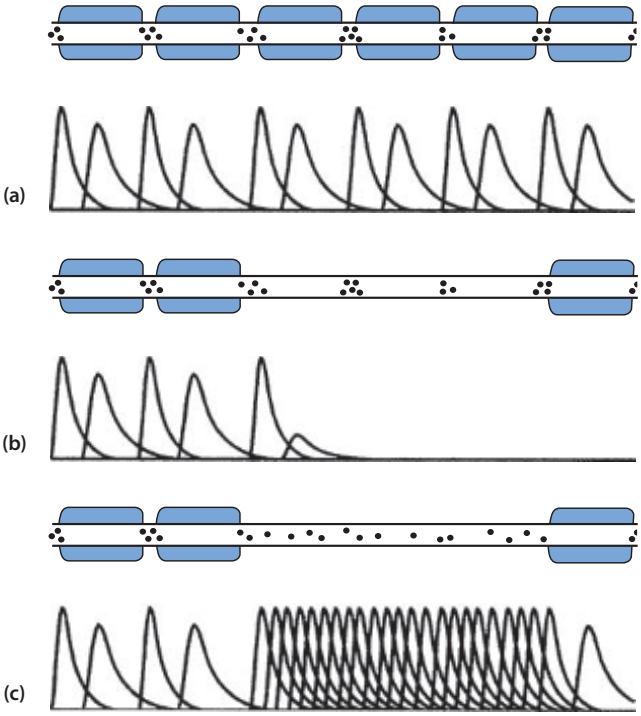


Figure 69.8 A diagrammatic representation of what happens when a nerve fibre becomes demyelinated. The blue regions are the myelin sheath. The dark dots are the voltage-sensitive sodium channels that are concentrated at the nodes of Ranvier. Three conditions are shown: **(a)** normal, **(b)** conduction block and **(c)** demyelination with slowing. The action potential is represented stroboscopically as it is conducted along the axon. The trace in (c) shows what happens when the sodium channels diffuse into the bare axon. The action potential can now regenerate itself, but this occurs over much shorter distances than when the axon was myelinated and the conduction velocity is therefore very slow. Redrawn with permission.[53]

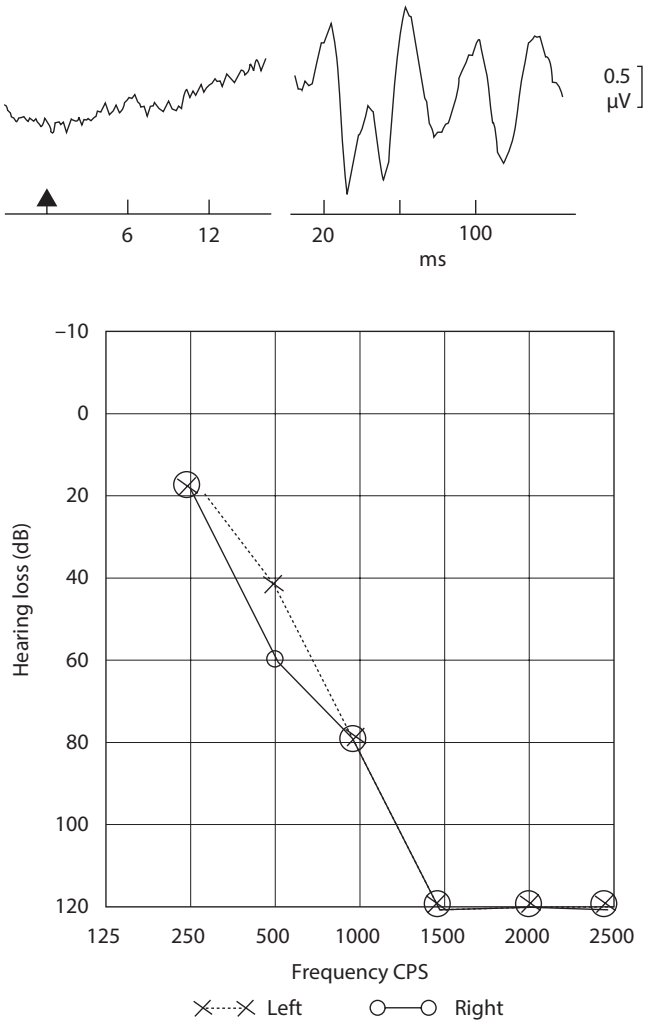


Figure 69.9 Pure-tone audiometry and acoustic evoked responses in a patient with congenital myotonia administered with high-dose quinine. Reproduced with permission of Dr Peter Rudge, The National Hospital for Neurology and Neurosurgery, London).

affect neural synchrony in the VIIIth nerve. However, as the axon and its myelin sheath are so closely related, one cannot exist without the other, and an axonal neuropathy is often accompanied by signs of secondary demyelination, which would then impact on neural synchrony, as above. Delmaghani et al. have described an autosomal recessive type of auditory neuropathy due to pejvakin, a protein within cell bodies of neurons of the afferent auditory pathway which causes neural dysfunction in the auditory nerve. *DFNB59* encodes pejvakin.[19]

DIFFERENTIAL DIAGNOSIS

Sharply sloping high-frequency hearing loss of cochlear origin

Quinine at a high dose is known to selectively destroy the OHCs of the cochlea. The pure-tone audiogram in Figure 69.9 shows a sharply sloping SNHL, induced by quinine in a patient with congenital myotonia. The acoustically evoked responses from the same ear are also shown, illustrating that in the time frame 0–12 ms, there are no reproducible waveforms (i.e. no ABR) whereas the MLRs are identifiable.

Distinction of auditory neuropathy from brainstem neuropathy

In a patient with normal preneural function but abnormal ABRs, only a full battery of tests as above can begin to distinguish a primary cochlear neuron lesion from a secondary cochlear neuron lesion. This would include other tests of neural synchrony such as stapedius reflex thresholds, in addition to ABRs, and, if the former are present, this might suggest a lesion higher in the brainstem than the pathways required to activate the facial nerve nucleus and cause contraction of the stapedius muscle bilaterally. Similarly, the type of ABR abnormality, specifically the pattern of abnormal or lost wave latencies, may give a relative clue as to site of lesion although, as in the case of MS, these patterns of abnormality have less localizing value than might be expected.

Central auditory processing disorders

With the advent of clinically available central auditory function tests, it has become possible to distinguish central auditory processing disorders (CAPDs) from other causes of deficits/delay in some children with language, reading and/or spelling difficulties. A 'bottom-up' approach to understanding these difficulties better now includes use of the behavioural central auditory tests.[89, 90]

- monaural low redundancy speech tests, i.e. speech stimuli, presented to one ear, that are:
  - degraded in frequency content
  - embedded in competing signals (multispeaker babble).
- dichotic/binaural interaction tests, i.e. stimuli presented to both ears, the task requiring the patient to attend to one ear only, or both at the same time:
  - dichotic digits
  - competing sentence tests.
- temporal tests, i.e. sequencing tasks:
  - frequency pattern test
  - temporal gap detection.

These are in addition to baseline audiometric tests and electrophysiological tests such as ABRs, MLRs, P300 and mismatch negativity. The characteristic abnormality of speech perception disproportionately poorer than the degree of hearing loss, plus abnormal ABRs in the presence of OAEs/CMs but absent stapedius reflex thresholds and absent contralateral suppression of OAEs, will distinguish patients with AN from those with CAPD.[91]

KEY POINTS

Differential diagnosis of auditory neural spectrum disorder

- Sharply sloping high-frequency hearing loss of cochlear origin.
- Distinction of auditory neuropathy from brainstem neuropathy.
- Central auditory processing disorders/language acquisition disorders.

AMPLIFICATION AND HABILITATION/ REHABILITATION STRATEGIES

Patients whose test results fulfil the criteria for AN represent a heterogeneous group. Not only is the site of lesion likely to vary, from the IHCs and synaptic connections within the cochlea to axonal degeneration and demyelination of the first- or second-order cochlear neurons, but also loudness sensitivity varies, as demonstrated by pure-tone audiometric thresholds. Degraded speech perception inconsistent with pure-tone sensitivity remains the common feature.

Early language intervention

For those children with auditory neural dyssynchrony, the onsets of plosive consonants and transitions, which make speech intelligible, would appear to be lost, preventing these children from categorizing or sequencing sounds. This makes early language intervention critical. A phoneme-based language therapy seems reasonable as it includes other tools for communication as well as audition. 'Cued speech' has been advanced as an adjunct to aural rehabilitation, as a way of 'eavesdropping' on family conversations, as it allows children to 'hear English phonemes and English grammar with their eyes'. It is a method whereby cues to vowel and consonant sounds that are difficult to perceive from lip-reading can be given by synchronous hand-shapes presented alongside either the mouth or pharynx of the speaker. These cues will give syntax and phonological structure to language and are more easily learned by parents. However, cued speech cannot aid in the phonological representation of language for children who are deaf or hard of hearing.

Total communication

Total communication uses spoken language and elements of sign language to link the different communication systems. Recognizing that each child with AN has a vast array of needs and that, for the individual, acquisition of language will also affect acquisition of culture, use of a system such as total communication to link aural–oral and manual communication systems would seem to have much to recommend it in a prelingual child.

Will hearing aids help?

Various studies have examined the benefits of hearing aids,[4, 15, 92] and shown variable results. In the earliest of these studies, three out of four patients fitted with hearing aids reportedly derived little benefit from amplification. In a later study, of 15/20 patients prescribed hearing aids, 8 were developmentally mature enough for speech perception threshold levels to be assessed, and 4 showed significantly increased aided threshold levels. Anecdotal reporting in the remaining 7 children suggests that 4 of these had benefited from hearing aids. The main concern regarding the use of hearing aids in patients with AN is that they can cause significant noise exposure and permanent threshold shift (up to as much as 20 dB HL) in children with SNHL.[93] It has been observed that TEOAEs may deteriorate in some children with AN after hearing aid use.[92, 93] Thus, the use of an algorithmic approach to hearing aid fitting and real-ear measures to verify parameters of the hearing aid needs to be calculated in much the same way as for the risk–benefit analysis for children with SNHL (**Table 69.6**).

Gap detection and modulation transfer function are abnormal in AN patients, and it has been hypothesized that these patients have 'a (time) smeared internal representation of a physical stimulus'.[55] A speech-processing type of hearing aid with a high-frequency emphasis to enhance high-frequency transient speech sounds (i.e. consonants) has been recommended. Also the use of directional microphones and personal FM systems to improve

TABLE 69.6 Breakdown of otoacoustic emission status by hearing aid status (reproduced with permission[54])

	OAE present		OAE absent		OAE once present now absent		All patients	
Hearing aid status		%		%		%		%
User	5	16	4	80	3	50	12	30
Past user	12	39	1	20	3	50	15	37
Never used	14	45	0	0	0	0	14	33
Total	31	100	5	100	6	100	42	100

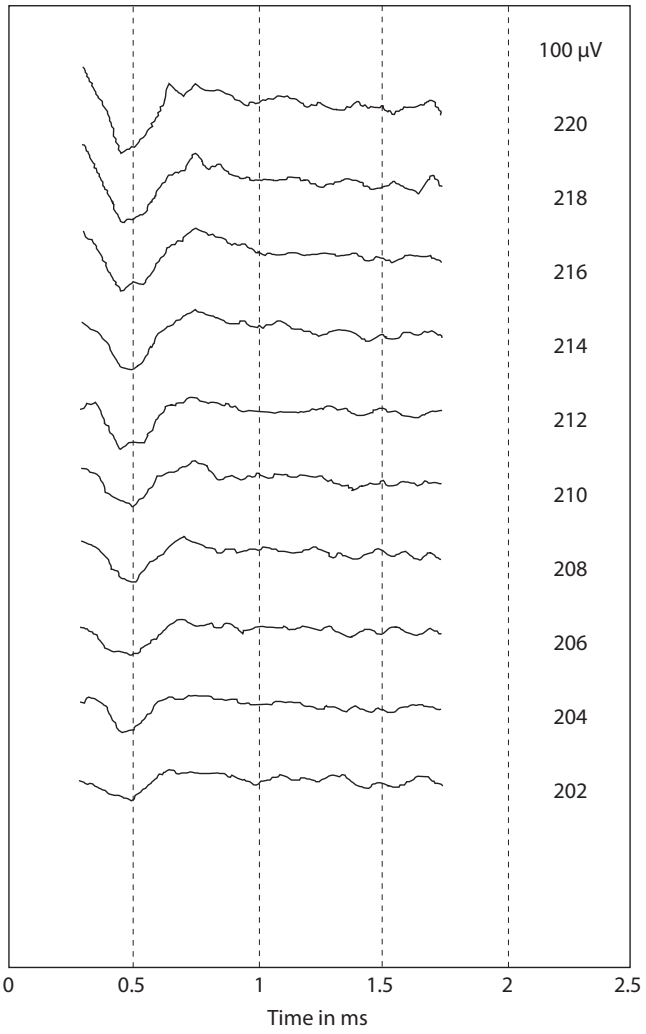
the signal-to-noise ratio in those patients with pronounced difficulties with speech in background noise has been proposed.[94]

Use of cochlear implants

The question arises as to whether cochlear amplification could be predicted to be of value and, if so, which patients would be likely to show a benefit. Theoretically, the patient with axonal degeneration/demyelination of the VIIIth nerve might not benefit from cochlear implantation (CI). However, electrical stimulation has been shown to produce synchronous ABRs in the presence of peripheral auditory nerve demyelination.[78] The potential benefits to these patients would be that CI provided consistent neural firing and the stimulus itself might promote neural survival and restore temporal activity. The disadvantages of CI would be not only the risk of surgery and anaesthesia, but also the chance that the electrode insertion might damage the cochlea itself and destroy residual hearing. Thus, proceeding to CI would need to be made with a thorough assessment and careful counselling of the child's family.

Studies published demonstrate the benefit of CI in children with AN. One child who wore aids from the age of 21 months for 2 years, and who was then fitted with a cochlear implant, was reported as receiving no benefit.[15] Six children with AN in whom CI was performed have also been reported.[95] Four of these children represented two sets of siblings, and all had undergone a trial period of powerful behind-the-ear-aid use. Five out of the six benefited significantly from implantation, as judged at the 1-year evaluation period using developmentally appropriate speech perception testing, with and without visual cues. Three of these children were considered to have adequate language and communication skills to attend mainstream school, having started their education in oral preschool for children with hearing loss. One child, however, showed no benefit from his CI. His understanding at 1 year post CI relied entirely on context, routines, gestures and lip-reading. There were no clear reasons why this particular child should have failed to benefit from CI.

Neural response telemetry (NRT) was used to assess neural synchrony and temporal coding post-CI (**Figure 69.10**). NRT uses a subtraction technique to remove the ECAP from the stimulus artefact using a forward masking paradigm.[95] The presence of the ECAP is interpreted as



NRT : Child C
Recording parameters:
Stimulating electrode 10
Recording electrode 12
Averages = 100

Probe:
Current level = variable
Pulse width = 25 µs/phase
Rate = 80 Hz

Masker:
Current level = fixed (220 units)
Pulse width = 25 µs/phase
Advance = 500 µs

Figure 69.10 Electrical compound action potential recording for 'Child C'. Reproduced with permission.[94]

indicating that electrical stimulation has restored some degree of synchrony and temporal encoding at the level of the cochlear nerve. These authors conclude that CI should be performed only after a trial of conventional amplification and that each decision to implant must be based on the individual circumstances. Children in the Sydney Cochlear Implant programme who had bilateral profound hearing loss were studied to examine the efficacy of CI. The study included 54 children and 15 of them were found to have cochlear nerve anomalies. Cochlear implant outcomes in terms of open-set speech discrimination were found to be poor in this group. Implant evoked electric auditory brainstem response (EABR) was uniformly poor in this cohort of children whereas children with normal cochlear nerves and AN had better open-set speech discrimination.[95]

In another study of 140 patients with a diagnosis of ANSD, over 40% were born pre-maturely and 38% had abnormal pre-operative MRI findings of the brain and inner ear. Thirty-seven per cent of these patients received cochlear implants, and 50% of those implanted demonstrated open-set speech perception abilities after implantation. None of those with cochlear nerve deficiency in the implanted ear achieved open-set speech perception abilities. Structural integrity of the cochlear nerve is therefore integral to achieving good outcomes following CI.[96]

BEST CLINICAL PRACTICE

- ✓ Suspect AN in patients whose pure-tone audiograms are normal or show a mild to moderate loss but who exhibit poor speech discrimination or delayed speech.
- ✓ Request electrophysiological tests of hearing including measurements of OAEs and ABR audiometry (preferably with measurement of CMs) to confirm diagnosis.

FUTURE RESEARCH

- ➤ Clear test protocols need to be developed for newborn hearing screening programmes to ensure that:
  - ➤ cases of AN are not missed (i.e. if only OAEs are performed)
  - ➤ those who have absent ABRs are not assumed to be profoundly deaf and amplified inappropriately (i.e. if OAEs are not performed).
- ➤ Test protocols for site-of-lesion diagnosis in patients with retrocochlear hearing disorders are needed, to distinguish:
  - ➤ first-order cochlear nerve lesions
  - ➤ second-order cochlear nerve lesions
  - ➤ central auditory processing disorders.
- ➤ Research is needed into the identification of predictors of stable AN vs progressive AN vs reversible AN vs maturational delay.
- ➤ Further work is needed in the following areas:
  - ➤ the relationship of pathophysiology to signs and symptoms
  - ➤ perceptual effects of AN
  - ➤ prospective case-controlled studies of hearing aid use versus CI
  - ➤ the identification of factors predicting the benefit from one type of hearing prosthesis over another
  - ➤ AN as a marker for neurodegenerative conditions.

KEY POINTS

- Auditory Neuropathy Spectrum Disorder (ANSD) is characterized by electrophysiological evidence of normal or near normal cochlear function (normal OAEs or cochlear microphonics) and abnormal auditory nerve signal transduction (abnormal ABR).
- Hearing may be normal or show mild to severe loss on pure tone audiometry.
- Speech discrimination is poor and language development may be delayed.
- Aetiologies are genetic or acquired.

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CHAPTER 70

UNDERSTANDING TINNITUS: A PSYCHOLOGICAL PERSPECTIVE

Laurence McKenna, Elizabeth Marks and David J. Scott

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: tinnitus, hyperacusis, psychology, cognitive and CBT.

INTRODUCTION

Affecting 10–15% of the population at any one time,[1] tinnitus is one of the most common persistent physical symptoms to affect humankind. Most individuals habituate to tinnitus with just 5% of the population reporting mild to moderate disturbance and 1–2% reporting severe and chronic disturbance attributed to tinnitus.[2, 3] The challenge for tinnitus researchers and practitioners is to understand why such variability exists and to develop effective interventions for those who suffer.

Medicine has traditionally focused upon the psychophysical characteristics of tinnitus. This 'linear' model fails to account for findings that acoustic characteristics of tinnitus are poorly related to its severity or treatment outcome,[4, 5] and that psychological treatments can lead to broad improvements in psychosocial measures, even when tinnitus loudness does not change.[6] More modern perspectives take into account the complex moderating and mediating factors in the experience of tinnitus; these are principally psychological and social in nature and interact with the underlying psycho-physiological changes.[7] To this end, a biopsychosocial model[8] provides a useful framework for understanding tinnitus.[9]

The biopsychosocial model of health and illness

The biopsychosocial model places health and illness within the context of the psychological and social influences affecting an individual, together with their biology. This approach offers a theoretical foundation for a multidisciplinary approach to tinnitus management. It explains how psychosocial factors influence the individual's behaviour in response to tinnitus (i.e. illness behaviour),[10] which in turn affects their health and well-being. This model implicitly indicates the influence of the doctor–patient relationships on treatment outcome. The clinician is thus responsible for minimizing unintentional iatrogenic harm and supporting patients' compliance with treatment recommendations. The focus of treatment is on a multidisciplinary approach that enables patients to manage tinnitus and its impact upon their life themselves, rather than being 'cured' of it.

Admittedly, few studies directly explore a biopsychosocial approach to tinnitus. However, there are convincing similarities between chronic pain and chronic tinnitus.[11, 12] In particular, both are linked to changes in the CNS after being triggered by peripheral changes, and both are associated with anxiety, depression, insomnia and reinforce each other within a vicious circle. A biopsychosocial approach to tinnitus would thus be a fruitful avenue for research.

PSYCHOSOCIAL FACTORS IN TINNITUS

Patients disturbed by tinnitus most commonly complain of emotional distress, insomnia and problems with sustained concentration and cognitive functioning. Over time, these difficulties have broader consequences, disrupting other aspects of daily life such as sleep.[13] There may also be

predisposing or precipitating psychosocial factors that make tinnitus-related distress a more probable outcome, such as personality traits, emotional state, psychiatric illness and cognitive style.

Personality factors

It is possible that stable personality characteristics can affect how an individual reacts to tinnitus and thus influence the degree of distress they experience. Studies have supported the idea that specific personality traits are associated with tinnitus severity, in particular, traits of perfectionism,[14] life satisfaction[15] and anxiety sensitivity[16, 17] have been found to relate to increased tinnitus severity. Optimism is negatively associated with tinnitus distress.[15] Erlandsson and Persson[18] found that 50% of a subgroup of more distressed tinnitus patients were diagnosed as suffering from a personality disorder.

Establishing a causal relationship between personality variables and tinnitus distress is challenging. These studies assume such traits were present through most of the person's life, and that anxious or depressed dispositions are not the product of tinnitus. Anxious traits identified in people soon after the onset of tinnitus have been found to predict greater tinnitus distress 6 months later.[19] These observations suggest that, when tinnitus arises in people who are already emotionally strained, it is more likely to lead to distress. Another study[20] examined the relationship between type D personality (a generally gloomy view of life and social inhibition), tinnitus distress and quality of life and found that the impact of type D personality on tinnitus severity was in part mediated by the presence of anxiety and depression. Additional evidence supports the idea that the relationship between personality variables and distress is not direct but is mediated by cognitive variables such as dysfunctional thoughts,[21] particularly catastrophization,[22] and tinnitus-specific illness perceptions.[23]

Cognitive variables related to tinnitus

The process of targeting illness perceptions begins right from the emergence of the illness and will be affected by the approach taken by healthcare professionals. In tinnitus, as in all illness, it is important for the whole care of a patient to be directed towards enhancing more helpful illness perceptions.

As well as general disposition, an individual's style of thinking about tinnitus is important in determining the nature of their experience of tinnitus. The psychological perspective suggests that distress arises because tinnitus is interpreted in a threatening way. The most common themes in the thinking of distressed tinnitus patients reflect despair, persecution, hopelessness, loss of enjoyment, a desire for peace and quiet, and beliefs that others do not understand.[24] Higher tinnitus distress is associated with more reported unhelpful thoughts about tinnitus.[24–26] Beliefs that tinnitus will lead to dreadful consequences (i.e. thoughts that overstate the impact of tinnitus, minimize the ability to cope and which involve rumination or excessive worry) appear to be particularly important. These kinds of catastrophic thoughts are associated with fear, which increases attention towards the tinnitus and reduces quality of life.[9] Catastrophic thinking has been observed to be associated with high subjective tinnitus loudness, poorer coping, depressive symptoms and with more frequent medical visits.[22] Catastrophization in the early stages of the tinnitus experience appears to have a pivotal role in determining the long-term distress, since patients quickly become caught in a vicious cycle of anxious and depressed thoughts about tinnitus, intensifying the intrusiveness, increasing distress and prompting frequent help-seeking behaviours, which in turn may maintain unhelpful illness beliefs.

The perception of an illness is known to influence coping behaviours and outcomes in chronic illness,[27–29] and, if interventions are to be helpful, they should address specific illness perceptions. Although research into illness perceptions in tinnitus is limited, one study reported on significant relationships between depression and anxiety and the perception of tinnitus in terms of the symptoms attributed to it and perceived consequences.[30] It has also been observed that an internal locus of control in tinnitus (i.e. the perception that you can control what happens to you rather than being affected solely by external factors) is associated with habituation, reduced psychological distress and reduced severity.[31–33]

With the perception of tinnitus determining its severity and related distress, psychological factors are clearly central to the tinnitus experience. This has direct implications for a clinician, as illness perceptions are influenced by historical, social and cultural context. Clinicians have a responsibility to remain aware of their contribution to this psychosocial context, as clinical contact will directly influence how a patient learns to perceive their tinnitus. Patients will benefit from a hopeful but realistic assessment of tinnitus, so it would be worth avoiding a purely biological focus on tinnitus, as this would suggest that there is 'nothing to be done'. Instead, offering a viewpoint that takes psychosocial factors into account will enable the patient to see potential areas of adaptability, leading to more helpful illness perceptions and thus possibly reducing distress.

Emotional consequences: Anxiety and depression in tinnitus

Patients with tinnitus report higher rates of psychiatric problems compared to the general population. In the late 1980s the use of formal psychiatric assessment tools demonstrated that 63% of a tinnitus sample could be classified as psychiatrically disturbed and that 78% had experienced one or more major depressive episodes in their lifetime, compared to 21% of a control group.[34] Since then other researchers have reported similar figures using both formal assessment[16, 26, 30, 35, 36–38] and self-report tools for measuring anxiety and depression.[39–42]

Psychological distress in tinnitus patients can clearly be a reaction to the tinnitus, but emotional disorders can also act as a trigger for tinnitus.[43] Goebel and Floetzinger[44]

found that, in 64% of tinnitus patients classified as suffering from a psychiatric disorder, the disorder preceded the onset of tinnitus. Clinical observations show that the more distressed the patient becomes the more problematic the tinnitus. Studies point to a link between problematic tinnitus and depression,[44, 45] with indications that the severity of tinnitus relates to the severity of the depression.[36] Stress is also thought to aggravate tinnitus, with evidence that a high workload and difficult shift-work patterns contribute to tinnitus distress.[46] An interaction between tinnitus distress and poor psychological state has been noted by others,[34] who found that depressed tinnitus patients reported more psychological and somatic complaints than those who were not depressed. Since the non-depressed group did not report more problems than the control group, the authors concluded that the problems reported by tinnitus patients were more closely related to the depression than to the tinnitus.

There is a risk of circularity of argument here, since anxiety symptoms often form part of tinnitus severity measures.[47] However, even when this is taken into account, tinnitus patients report greater than average cognitive anxiety (worry and negative self-talk) and somatic anxiety (rapid heart rate and shortness of breath), which continues after treatment.[30] There is also evidence that depressed and anxious patients report more tinnitus distress and severity,[14, 32, 48, 49] and that anxiety at onset predicts tinnitus distress 6 months later.[19] The interaction between tinnitus and psychological state is implicated by the relationship between post-traumatic stress disorder (PTSD) and tinnitus,[50] where it is likely that the symptoms of PTSD and tinnitus are mutually aggravating. The impression created by the literature is of a diathesis–stress interaction taking place in which the diathesis is the vulnerability to distress, and tinnitus level is the stress.[51]

Tinnitus and suicide

Of those individuals with tinnitus who do commit suicide, it seems that psychological and demographic factors play a more important role than tinnitus itself.[52–55] Jacobson and McCaslin[56] conclude 'it is not tinnitus per se that results in suicide but concomitant psychiatric conditions that amplify the effects of tinnitus on the individual patient'. Lewis et al.[53] found 40% of suicides occurred within a year of tinnitus onset and about 50% within 2 years. Psychological features known to increase the risk of suicide include hopelessness, helplessness, fear and anger. If patients are provided with messages about their tinnitus that evoke such psychological states, then their vulnerability to suicide is likely to increase.

Behavioural responses to tinnitus

Studies of the coping strategies used by tinnitus patients suggest that both avoidant coping strategies[34, 57, 58] and active coping styles[16] are associated with worse tinnitus. Hesser and Andersson[17] found that behavioural avoidance in an effort to reduce or stop tinnitus was a significant mediator in the relationship between anxiety sensitivity and tinnitus distress and tinnitus handicap. Kleinstäuber et al.[59] reported that tinnitus-related fear-avoidance behaviour is highly correlated with anxiety and depressive symptoms and plays an important role in predicting tinnitus handicap. Fear-avoidance behaviour serves to maintain catastrophic thinking. Thus, habituation may be enhanced by a middle-way that involves acceptance and engagement with *life* rather than employing strategies that involve either avoidance or attempts to *defeat* tinnitus.

Concentration/attention problems

Many tinnitus patients complain of difficulties in concentration or attention that they attribute to tinnitus. Research suggests a relationship between tinnitus and inefficiency in cognitive processing. Initial theories suggested that cognitive difficulties are a result of emotional distress,[26, 60] but such studies did not directly assess attention problems, and do not account for the fact that observed difficulties in cognitive functioning were not explained by differences in emotional state.[61–64] Other theories claim that attentional resources are depleted as the individual attends to the tinnitus, and related experiences.[65, 66] It has been argued that tinnitus acts as a competing stimulus that attracts attention away from other things.[67, 68]

Sleep

Sleep disturbance is one of the commonest tinnitus complaints with as many as 71% of tinnitus patients reporting problems sleeping.[69] It is particularly prevalent among children with tinnitus[70–71] and is the main reason why parents seek help for their child. An epidemiological study found poor sleep was reported by 14% of men and 28% of women in an older adult population with tinnitus.[72]

Sleep problems tend to be associated with more distressing tinnitus,[73-77] although direction of causality is unclear. Insomnia is not an inevitable consequence of tinnitus,[78] so tinnitus is probably not a specific sleep antagonist. A premorbid sleep disturbance may create an opportunity to focus upon tinnitus, thus emphasizing a lack of sleep.[79] It may be the anxiety associated with the tinnitus rather than the tinnitus per se that causes sleep problems, as seen in the cognitive behavioural model of tinnitus.[80, 81]

Family and relationships

The way a patient responds to tinnitus may act as a stressor within personal relationships. Emotional distress or avoidance of situations as a result of tinnitus can adversely affect relationships. It is important to consider how the social environment influences tinnitus. For example, the way in which people perceive the negative attitudes of others (e.g. people will treat me differently or get annoyed with me) is associated with severity and reduced quality of life.[82] Other people's responses to the patient can also have an impact by affecting their level of disability. As might be expected, punitive responses and poor marital cohesion tend to result in demoralization,

particularly in the context of depression.[83] Perhaps more surprisingly, solicitous responses by spouses can also have a detrimental effect, with enquiries about tinnitus increasing distress.[84] It is thought that both punitive and rewarding responses to tinnitus impede habituation.[83] Helpful responses to tinnitus should thus be supportive, acknowledging the distress, without encouraging further distress-related behaviour. This approach would seem to be relevant to all social contexts including the clinical one.

TREATMENTS FOR TINNITUS

Cognitive behavioural therapy

The main psychological therapy used in the management of tinnitus is cognitive behavioural therapy (CBT). CBT is an effective psychological treatment for a range of psychiatric disorders.[85, 86] It can bring benefits to individuals with long-term physical health conditions and somatoform disorders,[87, 89] insomnia[89] and tinnitus.[90]

CBT MODEL AND RATIONALE

CBT seeks to change *overly* negative thoughts and beliefs about tinnitus (and other issues causing distress), thus breaking unhelpful feedback cycles, reducing distress and improving habituation. Many of the negative thoughts that people hold about tinnitus are accurate: 'I have tinnitus,' 'I will never have silence.' However, they may also be troubled by thoughts that are inaccurate or unhelpful and which can increase tinnitus-related distress: 'Tinnitus will drive me mad' or 'This is affecting me so much I must be a weak person.' Thoughts tend to become more 'distorted' as stress levels increase and mood deteriorates. In CBT, the patient is helped to recognize the link between thoughts, mood and behaviour and to identify and challenged 'distorted' or unhelpful thoughts. The patient can then generate alternative, realistic and helpful thoughts.

Behaviour is also targeted because the actions taken by a person to reduce tinnitus tend to keep them focused upon tinnitus, reduces their quality of life and maintains their distress, by preventing the opportunity to test out and disprove negative (and often distorted) cognitions. Avoidance behaviours play a particularly important role in inhibiting habituation or even sensitizing a person to tinnitus or hyperacusis-related information. In therapy, unhelpful behaviours are identified and support for change is provided,[7] for example through exposure to noisy and quiet environments. Baguley and colleagues[1] outline a standard CBT package. CBT is time-limited (six to ten weekly sessions) and teaches skills that will enable the person to become their own 'therapist'. Homework assignments reinforce the skills learnt in therapy sessions. After therapy ends, a follow-up session can be offered to maintain progress. CBT for tinnitus can also be successfully delivered on a group basis.[91]

EVIDENCE BASE FOR COGNITIVE BEHAVIOURAL THERAPY

CBT is a well-validated treatment for tinnitus[90, 92] and a number of meta-analyses describe the beneficial effects of CBT on tinnitus-related distress. Andersson and Lyttkens[93] analyzed 24 studies (n = 700) of psychological therapy; this showed strong to moderate effect sizes on tinnitus annoyance post-treatment and at follow-up. CBT (Cohen's d = 1.1) was more effective than other psychological treatments (Cohen's d = 0.30) on ratings of annoyance in controlled studies. Smaller effect sizes were obtained for measures of negative affect and sleep problems. Effects upon tinnitus loudness were weaker and disappeared at follow-up. The largest meta-analysis to date[90] looked at 15 randomized controlled trials (n = 1091) and found CBT to have a significant positive impact on tinnitus-related distress (effect sizes ranging from 0.44 to 0.7) as well as a significant positive effect on mood. The benefits of CBT remained significant at follow-up.

Cochrane reviews of CBT for tinnitus[6, 94] have used tinnitus loudness as a primary outcome and tinnitus severity (a global measure of distress or quality of life) and depression as secondary outcomes. They found no effect of CBT upon tinnitus loudness but tinnitus-related distress improved with effect sizes ranging from 0.64 to 0.91. This review found a mild but significant impact on depression when compared with a waiting list control (effect size = 0.37). Since CBT is not designed to change tinnitus loudness, it is perhaps not the most appropriate primary outcome indicator, particularly as many CBT studies do not even measure it.

Self help and the internet

CBT equips patients with skills that ultimately should allow them to cope with difficulties on their own. As such, interest has grown in CBT-based self-help treatments that involve minimal therapist contact.[96] Bibliotherapy (self-help books or manuals) offers significant benefits, enhanced by minimal therapist support but attrition rates are higher[96, 97] and effect sizes smaller than in regular CBT.[6, 90, 93] Internet-based CBT delivers self-help via a computer programme, with therapist support provided over email. Outcomes are superior to self-help manuals in relieving tinnitus distress and depression,[98–100] with reports of benefits equal to those found in regular CBT,[100] although attrition rates can again be high.[101]

'Third wave' therapeutic approaches

'Third wave' approaches refer to CBT that has been developed and extended by increasing the emphasis upon accepting unwanted thoughts and feelings.[103] Suffering is regarded as a normal part of life, and attempts to resist or change suffering can potentially perpetuate distress. There are two overlapping strands: acceptance and commitment therapy (ACT) and mindfulness-based therapies such as mindfulness-based cognitive therapy (MBCT). ACT has been shown to reduce tinnitus distress,[103] with

effects equivalent to conventional CBT[104] and that surpass tinnitus retraining therapy.[105] ACT has been delivered effectively via the internet,[106] and a comparison of internet-delivered CBT and ACT found that acceptance mediated therapeutic change in both approaches. Mindfulness in the form of MBCT was originally developed as a treatment for recurrent depression[107] for which it is now a NICE recommended treatment.[108] More recently, MBCT has been developed for tinnitus and a randomized-controlled trial has found MBCT to be superior to applied relaxation in reducing tinnitus-related distress.[109] Further trials are under way.

HYPERACUSIS

Hyperacusis has been studied much less than tinnitus. Nonetheless, the evidence that does exist suggests that the two symptoms share many psychological characteristics and processes. As in tinnitus, patients with hyperacusis often report elevated levels of emotional and psychological distress, particularly anxiety.[110] Reports that 56% of patients with hyperacusis have at least one psychiatric disorder[111] is comparable to tinnitus patients. However, hyperacusis may exacerbate distress further, as tinnitus patients who report comorbid hyperacusis also report increased levels of psychiatric disorder compared to patients with only tinnitus.[44] The association between hyperacusis and emotional distress clearly points towards a need to improve our understanding of the psychological factors maintaining hyperacusis.

Behavioural responses in hyperacusis are characterized by avoidance and safety behaviours (avoiding noise and using ear protection).[110] Such behaviour is comparable to the fear-avoidance found in tinnitus and pain.[60] As in tinnitus, hyperacusis has important social implications. If patients react to noise with avoidance, their capacity to engage in normal daily activities and effective interpersonal functioning will be inhibited. However, here and in many other aspects of hyperacusis the research evidence is sparse, so the conclusions that can be drawn are limited.[110]

With such limited evidence, there is understandably little consensus about treatment strategies for hyperacusis. If we consider the presentation of hyperacusis in the clinic, two forms of intervention are indicated. The first is that of desensitization to sound.[111] This involves the use of white noise generators with sound levels gradually increased over time. There is, however, no evidence on the efficacy of this treatment. Weaknesses in extant studies of sound therapy for hyperacusis are present due to the reliance upon loudness discomfort levels (LDLs) as a subjective and unreliable measure and the paucity of peer reviewed studies.[110] To assess the value of LDLs as an outcome measure, well-controlled outcome studies are required.

The second main treatment approach involves talking therapies to reduce the distress that accompanies hyperacusis. Given the observation that anxiety is the predominant comorbid psychiatric presentation for patients with hyperacusis, CBT may be an effective treatment strategy.[112] A randomized-controlled trial of six sessions of CBT for hyperacusis, using psychoeducation, applied relaxation, exposure to sound and behavioural activation to reduce avoidance of noise, found improvement in LDLs and depression.[113] This is the first RCT into CBT for hyperacusis so further studies are needed before firm conclusions can be made.

SUMMARY

The experience of tinnitus involves the complex interaction of biological, psychological and social processes; this interplay is likely to be of relevance to hyperacusis as well. Psychological distress, particularly anxiety and depression, are common experiences among tinnitus and hyperacusis patients. Negative thoughts (particularly catastrophic thoughts), avoidant behaviour and emotional distress also act as provocations for tinnitus and hyperacusis-related problems. These processes are particularly important in determining the overall experience.

While a biological solution may still be the holy grail of tinnitus treatment, currently psychological treatments appear to offer the most effective remedy for patients. A psychological approach is unlikely to make tinnitus (or hyperacusis) disappear, but it can lead to a significant reduction in distress, and enable people to return to living a more 'normal' and meaningful life. The consultation with the clinician is a critical part of the experience of tinnitus (and probably hyperacusis) as it shapes the social context of tinnitus and can have a profound impact upon psychological processing. The clinical environment will shape the thoughts, behaviours and emotions of patients and their significant others, and therefore provides an important opportunity for therapeutic benefit, or a risk of iatrogenic harm. It is incumbent on the clinician to be aware of the multiple mechanisms at work in tinnitus and of the effective therapeutic strategies that can support them.

FUTURE RESEARCH

- More research is needed into a biopsychosocial approach to tinnitus.
- Mindfulness-based cognitive therapy has been shown to be superior to applied relaxation in reducing tinnitus-related distress. Further trials are needed.
- We need to improve our understanding of the psychological factors maintaining hyperacusis.
- Cognitive behavioural therapy for hyperacusis has shown improvement in loudness discomfort levels and depression. Further studies are needed before firm conclusions can be made.

KEY POINTS

- The experience of tinnitus is as much a psychological as a biological process.
- Cognitive factors, particularly catastrophic thinking, are leading determinants of tinnitus-related stress. The influence of personality type seems to be mediated by cognitive processes and emotional state.
- The clinical encounter can influence the patient's thinking for better but care is needed as an overly biological approach can contribute to negative thinking.
- Behavioural processes, particular avoidance and escape behaviours maintain and exacerbate distress.
- CBT and acceptance based psychological therapies can reduce tinnitus related distress.
- A number of psychological processes are common to both tinnitus and hyperacusis.

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CHAPTER 71

AUDITORY PROCESSING DISORDERS ACROSS THE AGE SPAN

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: auditory processing disorder, aging, children, cognition, language, diagnosis and management.

PREVALENCE AND DEFINITION

Approximately 5% of children and 1–10% of adults who present to audiology departments with complaints of significant listening difficulties in noise or in group conversations have normal pure-tone thresholds.[1, 2] In a proportion of these patients, their listening symptoms are attributed to functional deficits in sound processing within the extended central auditory nervous system.[3] This clinical presentation is categorized as auditory processing disorder (APD, category H93.25 in ICD-10).[4] This clinical presentation has attracted considerable debate that is summarized to some extent in several consensus statements from professional audiological organizations.[5–9] However, there is no international consensus on what constitutes APD as yet, nor is there explicit agreement on diagnostic criteria for this clinical entity.

AETIOLOGY ACROSS THE AGE SPAN

In children, as well as in adults, APD may be diagnosed in the background of neurological disease such as brain tumours, stroke, trauma, prematurity or low birthweight, epilepsy and brain infections or demyelinating conditions.[10] In some cases, APD may also be the first or even the only feature of neurological disease, both in children[11] and in adults[12] (see also **Figure 16.1** from Bamiou and Iliadou)[13], highlighting the need for clinicians to maintain a high clinical index of suspicion and to investigate for neurological causes. APD may also overlap with several developmental disorders such as language impairment (LI), dyslexia and attention-deficit and hyperactivity disorder (ADHD) and in such cases the clinician should carefully consider whether the clinical presentation is due to deficits in higher-order language or cognitive domains rather than to the deficits within the auditory modality.[14–17] Clinical comparisons of children with APD versus children with specific LI and/or dyslexia find broadly similar profiles in these children.[13, 15, 18] This has led to speculation that these language-based disorders may be different labels or parts of the spectrum of the same developmental disorder.[3, 15] Another subtype of APD is the 'spatial processing disorder' (SPD).[19] SPD is attributed to the presence of a prolonged history of chronic otitis media in childhood which gives rise to deficits in binaural auditory processing due to the prolonged or fluctuating auditory deprivation. SPD is thought to be present in 6% in a population with high incidence of chronic otitis media and in up to 15% in children referred for speech-in-noise difficulties.[19, 20] In adults, APD may be a feature of psychiatric presentations such as schizophrenia and some subtypes of dementia, or of central presbycusis, which is a multifactorial condition characterized by senescence-related and/or disease-related brain changes.[21–23]

THE DIAGNOSTIC APPROACH

The diagnostic process includes history taking, including patient/teacher/parent questionnaires, followed by targeted medical examination. Children and adults with APD have difficulties with speech in noise, auditory attention, localization of sound and other auditory difficulties.[24–26] The history should establish the patient's and/or carer's main concerns and related symptoms, and the symptom onset and progression. Children may experience difficulties in the classroom and psychosocial difficulties that may persist well into adulthood.[27, 28] Key symptoms and difficulties are summarized in **Box 71.1**. History should also include medical history (to ascertain risk factors/other impacting factors), as well as early developmental, educational and professional history of the individual, and family history for related disorders (hearing, auditory processing, other developmental, neurological disorders). This part of the evaluation will also include questionnaires, which are used to collect as much information as possible for the clinical presentation.[15, 25, 26, 29]

The initial information collected during the medical interview will guide the choice of appropriate audiological tests, which should include a thorough assessment of peripheral auditory function as well as tests of auditory processing, both speech and non-speech. The American Speech-Language-Hearing Association (ASHA) technical report proposes that, in addition to pure-tone audiometry and speech-in-quiet tests, a central auditory processing battery should include tests for auditory discrimination, temporal processing and patterning, dichotic speech, monaural low-redundancy speech, binaural interaction, and electroacoustic and electrophysiological measures (see **Table 71.1**).[5, 6] The rationale behind this proposal (which is still followed by most audiology clinics worldwide) is that one needs to check thoroughly cochlear and auditory nerve integrity and subsequently different domains of central auditory processing. However, with a few exceptions for tests developed in recent years, clinically available tests are affected by a range of higher-order factors.[30]

Assessments of other domains such as language and cognition are of paramount importance in order to provide a clearer understanding of the patient's communication profile and needs while other medical

BOX 71.1 Key symptoms and difficulties of auditory processing disorder

Difficulties understanding speech: In background noise, acoustically challenging/complex acoustic environments, when speech quality is degraded
Difficulties discriminating speech: Difficulties repeating or recalling similar-sounding words
Sound localization/streaming difficulties: Difficulties identifying the source of a sound; with separation of auditory foreground from auditory background
Auditory attention/memory difficulties: Difficulties recalling instructions; difficulties concentrating in noise
Hyperacusis: With or without a diagnosis of autism spectrum disorder
Need for multisensory cues: For example, seeking visual/facial cues to better understand
Disproportionate educational/cognitive/language difficulties:

- In the presence of normal audiometry and no other developmental disorders OR
- In the presence of normal audiometry and other diagnosed developmental disorders (specific LI attention deficit disorder; autism; dyslexia) and (i) DESPITE implementation of appropriate interventions or (ii) when other specialists or the educational environment seek further advice/assessment on management of the auditory aspect of this presentation

TABLE 71.1 An APD test battery[6]

AP domain	Test assesses	Test examples
Auditory discrimination	Ability to differentiate similar acoustic stimuli that differ in frequency, intensity and/or temporal parameters	Difference limens for frequency, intensity and duration; psychophysical tuning curves; phoneme discrimination
Auditory temporal processing	Ability to analyze acoustic events over time	Pattern tests; gap detection in noise; fusion discrimination, integration; forward and backward masking
Dichotic listening	Ability to separate (i.e. binaural separation) or integrate (i.e. binaural integration) disparate auditory stimuli presented to each ear simultaneously	Dichotic consonant–vowels, digits, words, sentences
Low-redundancy speech recognition (monaural)	Recognition of degraded speech stimuli presented to one ear at a time	Filtered, time-altered, intensity altered, speech-in-noise or speech-in-competition
Binaural interaction	Binaural processes dependent on intensity or time differences of acoustic stimuli	Masking level difference, localization, lateralization, fused-image tracking Listening in spatialized noise
Other tests		
Electroacoustic measures	Otoacoustic emissions, acoustic reflex thresholds and acoustic reflex decay	
Electrophysiological measures	Auditory brainstem response (consider middle latency response, cortical event-related potentials and other responses)	

investigations ought to be considered as required, and additional information gathered (e.g. school observation).[5, 6] It is also useful to establish how the individual and their family perceive and explain their communication-related difficulties, any previous related assessments conducted and any remedial action taken or strategies implemented.

The diagnostic decision-making will synthesize this information in order to interpret reported symptoms in the light of test/assessment results and other contextual factors. However, it must be noted that professionals in the audiology field use different diagnostic criteria for APD and a recent review by Wilson and Arnott revealed nine different diagnostic criteria with a diagnostic yield of 7.3% up to 96% for APD.[31]

CONFOUNDING FACTORS AFFECTING APD TEST PERFORMANCE ACROSS THE AGE SPAN

Throughout the age span different confounding factors might affect APD test performance and hence the aetiology and diagnosis of APD.

In children, the extent to which non-sensory factors, such as working memory and attention skills, might affect negatively the performance on APD tests is still under debate.[32, 33] This is because some non-auditory cortical areas, which are also involved in the neural processing of sound, such as inferior prefrontal cortex and the posterior temporoparietal areas, are still in development until the age of 10 years.[32] Thus, it is discussed whether the variability in the APD performance reflects the maturation aspects of cognitive skills rather than some specific auditory processing skill impairment. Additionally, some auditory processing tests include highly cognitively demanding tasks, especially those including verbal response, such as dichotic digit or frequency pattern test.[33] Thus, maturation aspects of cognitive skills (late or incomplete maturation) combined with highly cognitively demanding tasks might lead to confounding results and difficulties in interpretation. To minimize the cognitive influence, the use of intratest comparison measures, such as right ear advantage index and humming-label differential,[34] are taken into consideration. Additionally, the need for cross-modality testing is also discussed.[35, 36]

In middle-aged and elderly individuals, age-related hearing loss as well as age-related cognitive decline might also lead to difficulties in interpretation of APD performance.[37–41] Age-related cognitive decline is a well-known confounding factor for auditory processing performance, particularly because of the cognitive–sensory interaction that is observed with ageing.[42, 43] Research has also demonstrated that some tests are more susceptible to hearing loss effects, especially tests involving understanding speech. This is because the broadband nature of speech signals requires reasonable audibility over at least 4000 Hz for discrimination.[23, 44]

Given the increasing recognition of the influence of many confounding factors affecting auditory processing test performance, the appropriate selection of tests as well as their careful interpretation must be taken into consideration on APD diagnosis. Assessment of elderly subjects' cognitive skills, such as working memory, would be useful before interpreting their performance on auditory processing tests. In addition, both the degree and configuration of the hearing loss must also be taken into consideration, especially when considering results of auditory processing tests involving verbal stimuli. For children, further studies should focus on the development of clinical auditory processing tests with low cognitive demand to reduce the impact of non-sensory factors on APD performance.

MANAGEMENT STRATEGIES

The goal for APD rehabilitation is to improve the functional deficits of individuals with specific impairments that are impacting on their communication and overall well-being. In order to achieve maximum functional benefit, a multidisciplinary team approach should be employed.[45] Generally, a comprehensive management programme for APD should focus on the following three areas:[45, 46]

- to remediate the disorder by means of techniques that aim to harness the brain's ability for change (i.e. neuroplasticity) in order to enhance neuroauditory function (e.g. auditory training)
- to improve access to auditory information by changing the environment (e.g. signal enhancement strategies, including frequency modulation systems/remote microphone hearing aids and teacher/speaker based adaptations)
- to improve listening and learning skills by teaching children and adults various compensatory strategies to overcome their residual functional difficulties (e.g. metacognitive and metalinguistic training).

Auditory training

Auditory training (AT) aims to capitalize on the brain's ability for structural and functional reorganization in response to sensory input across the lifespan. This brain 'plasticity' may involve the activation of inactive neuronal connections and/or the formation of more efficient synaptic connections within the brain; such changes are often associated with behavioural changes.[47, 48] AT involves listening exercises that aim to improve auditory system function and to achieve successful auditory learning, i.e. a relatively permanent improvement of perception and behaviour.[49, 50] AT studies in normal adults indicate that learning is better when the listener works hard enough for attention to be taxed.[51] It is also important to train with a wide variety of materials and situations since studies indicate that learning may not generalize to untrained material.[52] AT can be categorized as formal or informal. Informal AT can be a school- or home-based programme

as well as therapy conducted by a speech and language therapist or audiologist in the clinic, and it involves predominantly language-based tasks that tap into multiple processes concurrently. Examples of informal AT are discriminating similar-sounding notes on a keyboard for training temporal patterning skills phoneme discrimination exercises for training auditory discrimination skills and listening to lyrics of songs for training speech-in-noise ability.[45, 48] Formal AT is typically conducted in a controlled setting, such as a clinic or a lab, by audiological professionals, or at home, by means of CDs/web-accessed services. Formal AT uses acoustically controlled training paradigms with the ability to specify and precisely alter the stimuli.[53] Formal AT employs a variety of auditory tasks including tonal and speech stimuli.

There are several commercially available computer-based AT programs in the English language, for both adults and children (see **Table 71.2** for some key examples). Post-training improvements are reported on a range of auditory and non-auditory measures for a broad range of paediatric populations with disorders that overlap APD, in APD populations as well as in adults.[49, 54–58] However, it remains unknown which program works best (compared to others) and what the optimum dosage and long-term benefits are.

Signal enhancement strategies

Signal enhancement strategies include environmental modifications, to reduce the synergistic deleterious effects of noise and reverberation of the acoustic environment on the target speech (or other acoustic) signal, and assistive listening devices such as remote microphone hearing aids (RMHAs). (For a list of environmental modifications that can be applied in school classrooms or elsewhere, please see BSA APD document, page 55[7] – discussion of these is beyond the scope of this chapter.) RMHAs are personal listening devices that bypass high-level classroom noise and transmit clearer speech to the child's ears. RMHA use may improve speech understanding by 53%.[59]

Studies of children with abnormal speech-in-noise performance due to abnormal auditory processing show improved speech reception even without FM (after 5 months FM use), improved observer-rated listening and behaviours as well as improvements in higher-order processing such as working memory after 12 weeks and spelling after 6 weeks.[27, 54, 60, 61] Importantly, some behavioural improvements in phonological processing have been shown to correlate with improved consistency of electrophysiological neural response to complex sounds (after 1 year of RMHA use), indicating that such interventions may have positive effects on brain plasticity.[62] There are a couple of studies in adults with auditory perceptual problems, in the presence of auditory neural pathology within a diagnosis of Friedreich's ataxia and another study in adults with multiple sclerosis.[63, 64] The study by Rance et al. on Friedreich's ataxia patients that included both children and adults reported a mean 18% improvement in communication and 20% improvement in speech-in-noise intelligibility with FM versus without FM in a hearing disability questionnaire that assessed listening in the patient's everyday situations after 6 weeks' use. Lewis et al. similarly reported good benefit in their adults with multiple sclerosis, indicating that this technology can be applicable for a wide range of APD presentations across the age spectrum.[64]

Compensatory strategies

Compensatory strategies are taught in order to help overcome dysfunction and maximize the use of auditory information.[45] These strategies may include, for example, 'active listening' where the individual is taught how to taking responsibility for their own listening, strategies that aim to enhance memory (e.g. auditory memory enhancement or auditory directives training) or attention (e.g. auditory vigilance strategies), and linguistic and metacognitive strategies.

TABLE 71.2 Computer-based AT programs for adults and children: key examples

AT for children	Description
FastForWord (Scientific Learning Corporation, USA)	This is an adaptive intervention program that employs acoustically modified non-speech and speech sounds (e.g. elongated tones, slower-rate speech sounds) and is designed to train temporal processing, speech perception and language comprehension skills.
Earobics (Houghton Mifflin Harcourt)	The activities aim to improve sound awareness, discrimination of sound in noise and quiet, sequencing sound, associating sound with letters, understanding of complex directions with and without background noise, and memory for sounds and words, and include items to strengthen reading, spelling and comprehension.
LisN & Learn (NAL, Australia)	This aims to improve listening in noise for children diagnosed with spatial processing disorder (SPD). It involves word identification from a target sentence that appears to emanate from 0° azimuth while background noise (looped children's stories) comes from either + or - 90° simultaneously.
Adult AT	
'Listening and Communication Enhancement' –LACE (Neuroton)	This is marketed as top-down intervention for speech-in-noise difficulties and includes degraded speech tasks, cognitive tasks and interactive communication strategies screens.
Brain Fitness Program for auditory processing (Posit Science)	This includes six adaptive exercises which aim to enhance the fidelity in auditory sensory input and language representations. It is specifically designed for older adults.

Curriculum modifications (such as preteaching new material, giving breaks to the student during the day) are also widely used. These are not formally validated in controlled studies, but there is good consensus that such strategies are of considerable benefit.[4]

AUDITORY TRAINING BENEFITS ON AUDITORY PROCESSING AND TOP-DOWN SKILLS: GENERALIZATION OF LEARNING

It is well established that AT improves auditory trained tasks. However, the extent to which auditory learning transfers to top-down skills such as language and reading skills remains unclear. This topic is important due to the co-occurrence of APD with other learning difficulties such as dyslexia, phonological disorder and ADHD. Some studies have demonstrated learning generalization following non-linguistic AT to measures of language, including reading, speech perception and phonological awareness.[65–67] Others reported on-task learning but no generalization to higher-level measures of language skills.[52, 68]

According to Mossbridge et al., generalization of learning can only occur if the neural circuits modified during training also influence the untrained task performance.[69] In general, during perceptual training such as AT training, several abilities are trained simultaneously (e.g. linguistic, cognitive and perceptual skills), thereby hindering investigation into how factors related to the training may affect the extent of generalization. Despite that, there is considerable evidence that the characteristics of the trained tasks might influence the transfer and specificity of learning.[51] The involvement of complex cognitive skills in AT for children, for instance, might act as a limiting process in the generalization of sensory learning due to the non-maturation of cognitive functions until adulthood.[32] Another important factor is the time course of training. Halliday et al.,[52] for instance, delivered AT for 6 hours and discussed if this length of time was sufficient to observe learning transfer, given that previous research reported successful transfer in training of more than 10 hours.[70, 71] Murphy et al. delivered non-linguistic AT for 9 hours and, as Halliday et al., found no generalization of learning.[68] Given the conflicting findings, further studies should investigate the extent to which different lengths of the same training affects learning followed training.

CONCLUSION

Despite the considerable research addressing APD aetiology and the development of several clinically available tests, APD diagnosis is not straightforward and it must be carried out taking into account all possible confounding factors affecting the test performance across the age span. A multidisciplinary approach aimed at the differential diagnosis between APD and other disorders with similar profiles is essential. Currently, several different management strategies are available to rehabilitate APD but well-designed studies are still needed to determine the extent of learning generalization and overall real-life benefits for the affected individual following the training as well as what is the best training method for the different populations with APD.

KEY POINTS

- Despite the lack of international consensus on diagnostic criteria and management of auditory processing disorder (APD), it is well-accepted that children and adults may experience significant listening difficulties in the presence of normal pure-tone audiograms, which might be categorized as APD.
- Different confounding factors such as memory, attention and hearing loss, may interfere on auditory processing test performance across the age span; as a consequence, an appropriate selection of tests as well as their careful interpretation must be taken into consideration on APD diagnosis.
- A multidisciplinary team approach should be employed for APD rehabilitation taking into account varied strategies such as auditory training, signal enhancement and compensatory strategies.

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CHAPTER 72

NEUROPSYCHIATRIC ASPECTS OF VESTIBULAR DISORDERS

Julius Bourke, Georgia Jackson and Gerald Libby

SEARCH STRATEGY

Data in this chapter may be updated based on searches of relevant textbooks, PubMed and other online search tools using the keywords: chronic dizziness, unexplained dizziness, functional dizziness, psychogenic dizziness, phobic positional vertigo, space and motion discomfort, chronic subjective dizziness, alone and in combination with psychopathology, anxiety, stress, depressive disorder and psychiatric.

INTRODUCTION

Psychogenic, somatoform or functional dizziness refers to dizziness in the absence of objective organic pathology or an alternative diagnosis that is able to explain its presence. It is a common problem: 20% of primary care patients seek help for dizziness during their lifetime,[1–4] it is chronic in 30% of these[3] and 10% with chronic dizziness are functionally impaired.[2] Typically, patients are initially referred to cardiology, neurology and specialist vestibular clinics but in 30% of cases investigations and diagnosis are unable to account for the symptoms.[5]

'Psychogenic dizziness' is, however, a 'catch-all' diagnosis that is steeped in misunderstanding. Recent concepts of phobic positional vertigo, space and motion discomfort and chronic subjective dizziness have done much to clarify a syndrome of unexplained chronic dizziness. This has aided a disabled and sadly often disregarded patient group in terms of understanding and ultimately treatment. The common thread running through these three descriptive concepts is the presentation of dizziness with a predominance of anxiety and disordered affect that must be appropriately managed for an optimal outcome.[6]

Here we focus on the importance of neuropsychiatric contributions to these disorders and their treatment from a primarily psychopharmacological but also psychotherapeutic perspective.

NOMENCLATURE

Agoraphobia

In the 19th century, Karl Westphal described a disorder defined by debilitating dizziness, spatial disorientation and anxiety when exposed to open spaces: agoraphobia. Agoraphobia subsequently became a syndrome defined more by a phobic response to situational exposure and heightened anxiety with or without panic attacks, rather than by dizziness per se.

It was not until the 1950s that the concept of psychogenic dizziness as a clinical entity re-emerged. Since then, various approaches to reaching this diagnosis have been described.[7–9] The core premise to all of these proposed diagnostic strategies was the presence of dizziness without true vertigo, typically occurring in anxious individuals, replicated by hyperventilation and combined with the presence of psychiatric symptoms preceding the onset of dizziness. There are assumptions here that are problematic: that anxious individuals do not suffer from vestibular disorders and that individuals with vestibular disorders do not suffer from anxiety. This is obviously not so.

Phobic positional vertigo

In the mid-1980s, Brandt and Dieterich defined phobic positional vertigo (PPV): postural dizziness with a

subjective sense of disturbed posture and unsteadiness, which could be precipitated by complex and motion-rich environmental and situational stimuli. Similar to the concept of psychogenic dizziness, Brandt and Dieterich noted a prominence of anxiety-related symptoms, obsessive–compulsive personality traits and biological or vegetative symptoms, more typical of disorders of affect.[10] Precipitants for the disorder were noted as vestibular disorders and stress. They reported that PPV was the second most common cause of dizziness presenting to their practice and the most common in younger adults.[10]

Longitudinal studies have demonstrated that, as a diagnostic entity, PPV is a stable construct,[11] still being clinically identifiable in patients followed up 5–15 years later. As such, PPV demonstrates a chronicity with a fluctuating course of improvement and exacerbation of symptoms but without full remission.[11] Long-term follow-up also determined that the high incidence of major depressive and anxiety disorders in this cohort of patients was chiefly responsible for the significant disability and poor prognosis of the disorder.[10] The involvement of these neuropsychiatric disorders in disability and poor prognosis is something well recognized today in a variety of different clinical conditions. In PPV, this was so much the case that it has been debated as to whether PPV was in fact a vestibular or a psychiatric disorder. However, in spite of the strong link between anxiety, panic and major depressive disorder, PPV was argued to be a distinct pathology closely linked to these syndromes, rather than occurring as a direct sequela of them.[10, 11]

PPV was, therefore, a stable, reliable and inclusive diagnosis. However, in spite of its diagnostic stability, treatment studies of PPV were disappointing (involving a mixture of reassurance, behavioural desensitization through increasing exposure and serotonergic antidepressants). Longer-term studies have demonstrated some improvement in symptoms but rarely resolution, with almost half of all patients relapsing in the subsequent 12 months, once or repeatedly.[11]

Space and motion discomfort

Space and motion discomfort (SMD)[12] unified the previously described situationally specific syndromes characterized by anxiety and phobic symptoms combined with dizziness, such as street neurosis,[13] space phobia[14] and motorist vestibular disorientation syndrome.[15] SMD refers to the physical symptoms that arise when the sensory information necessary for normal spatial orientation is inadequate or conflicting. In SMD, visual and proprioceptive input is thought to compensate for defective vestibular sensory input, with consequent visual or proprioceptive dependence and heightened sensitivity to these inputs.

SMD describes discomfort that includes dizziness, imbalance or anxiety in situations characterized by certain spatial or motion characteristics. The avoidance of these symptoms leads to the avoidance of the situations likely to precipitate them and, ultimately, to increasingly phobic and disabling behaviour.

SMD therefore refers to situationally specific vestibular symptoms occurring with anxiety and ultimately resulting in phobic avoidance. A questionnaire measure for SMD has been successful in identifying vestibular dysfunction across five groups (panic disorder, agoraphobia with panic disorder, other anxiety disorders, major depressive disorder and healthy controls), with the highest frequency of vestibular dysfunction and SMD being in patients with agoraphobia with panic disorder.[16] In support of this, most studies, although not all, have found a high incidence of abnormalities on vestibular function tests in panic disorder, especially those with agoraphobia.[17] SMD is therefore common in anxiety disorders and its presence predicts vestibular dysfunction. Jacob et al. have subsequently suggested that the absence of panic disorder or acrophobia (a fear of heights) reduces the probability of peripheral vestibular dysfunction and that, where this dysfunction is present, it is likely to complicate the phenomenology of anxiety disorders.[18]

Psychiatric dizziness

Furman and Jacob[17] proposed the more narrow definition of 'psychiatric dizziness', namely dizziness occurring 'exclusively in combination with other symptoms as part of a recognized psychiatric symptom cluster and this symptom cluster is not itself related to vestibular dysfunction'. That is to say that dizziness occurring with panic attacks was 'psychiatric' but that dizziness occurring between panic attacks was not. The caveat made by the proponents here was that this diagnosis did not exclude the possibility of 'functional' or 'psychogenic' overlay, whereby non-psychiatric dizziness is exacerbated by the presence of psychopathology through 'amplification of somatic sensations'. They noted that this was most common in those disorders where hypochondriacal concerns were prominent (anxiety and panic disorders, major depressive disorder and somatoform disorders) as well as those with particular personality traits, citing those found by Brandt in his PPV sample (predominantly obsessive–compulsive).[10] Based upon their definition of 'psychiatric dizziness', Furman and Jacob[17] suggested that PPV was a reflection of vestibulopathy with 'psychogenic overlay' and that its aetiology in this regard was related to a predominance of particular personality trait clusters.

Chronic subjective dizziness

In the early 2000s, Staab and Ruckenstein[19–21] noted that what was previously described as psychogenic dizziness lacked diagnostic specificity as it was also present in migraine, mild traumatic brain injury and dysautonomias. Staab et al. further refined these concepts, removing emphasis from the presence of psychiatric phenomena and presenting the new diagnostic formulation of chronic subjective dizziness (CSD). Staab et al. concede that anxiety is responsible for most of the morbidity of somatoform dizziness but explain that it was not included as a core symptom in order to avoid the assumption that the syndrome is psychiatric alone.[5]

CSD consists of three central components, namely chronic subjective dizziness (of 3 months or more),

hypersensitivity to motion stimuli (including one's own movement) and difficulty or exacerbation of symptoms with complex visual tasks (e.g. reading, writing, using a computer). Three subtypes were described:[19]

- **Neurotological:** This group had a current or past history of transient illnesses (e.g. neuronitis, adverse drug reaction) or intermittent phenomena (e.g. migraine, Ménière's) that triggered secondary anxiety disorders that were predominantly phobic.
- **Psychogenic:** These patients exhibited primary anxiety disorders that resulted in dizziness, with panic disorder being the most frequent cause.
- **Interactive:** This group included those patients with a neurotological complaint that exacerbated a pre-existing anxiety disorder (most often generalized anxiety disorder).

Notwithstanding these subdivisions and the absence of anxiety as a core defining symptom, as a group, patients diagnosed with CSD are nearly all diagnosed with either psychiatric or neurological disorders.[20] Staab's group reported 59.7% of CSD patients demonstrating either primary or secondary anxiety. Others have suggested that this is higher, with one group reporting a clinic sample in which almost 80% were diagnosed with anxiety.[22]

CSD has been met with more consistent psychopharmacological treatment responses than PPV,[21] although psychotherapy has been less successful[23] and without long-term improvement beyond 6 months.[24, 25]

Persistent postural-perceptual dizziness

A further diagnostic category has been divined in a consensus document recently published: persistent postural-perceptual dizziness (PPPD),[26] which is expected to be added to the international classification of vestibular disorders (ICVD).

The diagnostic criteria include dizziness, unsteadiness, or non-spinning vertigo that are present pervasively over three months or more and which are exacerbated by upright posture, active or passive movement, and exposure to moving or complex visual stimuli.[26] This novel nomenclature represents a synthesis of the terms that have gone before over the past three decades. Within this context, PPPD allows for chronic vestibular symptoms that can be precipitated by other conditions that disrupt balance or cause vertiginous symptoms including dizziness. This takes into account peripheral or central vestibular disorders as well as other general medical and neuropsychiatric comorbidity, whilst emphasizing that it is not a psychiatric but a functional disorder, similar to the ideas underpinning CSD. Although yet to be fully pathophysiologically defined, it is thought to arise from an abnormality in function, including multi-sensory information processing, integration of spatial orientation and threat assessment. This brings pathophysiological concepts of functional vestibular disorders in line with the current neurophysiological understanding of other functional syndromes in which this has been demonstrated.[27] A problem similar to that found in the other functional syndromes also penetrates PPPD, namely the heterogeneity of pathoaetiology, presentation, response to treatment and so prognosis. Subtypes of PPPD are therefore proposed to exist. There is an argument that necessarily arises here – namely is there a single PPPD or a number of subtypes?[26] This too is a debate that has raged in the world of functional syndromes and which has been widely reported (for example the debate between Professors White and Wessely regarding 'lumping' and 'splitting'[28]).

The opinion of the authors of this chapter is that the assumption that subtypes exist, differing physiologically but giving rise to the same or similar phenotypes, matches clinical experience better than does the assumption that all similar presentations are the same. As noted above, this allies the concept of PPPD with other functional syndromes.[27] Such subtypes are yet to be explored fully and until defined are likely to impact upon studies of treatment strategies and responses to them. Any future research involving management strategies will need to take this into account as otherwise, results will need to be interpreted with caution in a similar manner to the interpretation of those studies performed to date, involving a variety of different historical diagnostic terms and criteria.

The importance of anxiety in chronic dizziness

The presence of personality traits that predispose to a state of anxiety (**Table 72.1**) along with varying degrees of clinically significant anxiety and avoidance behaviour have been consistent in the diagnostic formulations of unexplained chronic dizziness. Although the nomenclature has changed and with it the emphasis on these factors, they remain of fundamental importance.

Anxiety and major depressive disorders are common in patients with CSD but do not occur in all cases. The prevalence is, nevertheless, high: 60% of patients with CSD have clinically detectable and significant levels of anxiety, while 45% of patients with CSD have a major depressive disorder. This constitutes 75% of the CSD sample[10, 29] and is higher than in other vestibular disorders,[30–32] although these differences are not sufficient to differentiate between CSD and 'organic' vestibular disorders alone.

More recent studies using the CSD criteria have suggested that high trait anxiety (see **Table 72.1**) or a pre-existing anxiety disorder may predispose an individual to CSD and high state anxiety during an episode of vestibular dysfunction may act as a precipitant, while concurrent psychopathology contributes to disability in those with CSD.[33–36] However, this is perhaps an oversimplification since predisposition to high trait anxiety and anxiety disorders (personal history, personality traits and family history of anxiety disorders) also seems relevant as it is in these predisposed individuals that CSD is typically more chronic.[34] This would not come as a surprise to a liaison psychiatrist, seasoned in the diagnosis of functional somatic syndromes affecting other body systems, because this pattern of vulnerability is the same, so much

TABLE 72.1 Definitions

Trait anxiety	Refers to the general level of anxiety and stress that an individual characteristically experiences as a trait related to their personality. Trait anxiety is relatively stable. Higher levels of trait anxiety would typically be found in a characteristically anxious individual.
State anxiety	Refers to the emotional response experienced in the context of particular situations or events and so is a measure of anxiety that fluctuates with context. Threatening situations, including those experienced on a day-to-day basis, will result in raised levels of state anxiety. State anxiety is not a stable phenomenon and measures will vary depending on context.
Agoraphobia	A situationally specific anxiety disorder. Anxiety typically arises in public and crowded spaces, although it may be a lack of obvious exit or escape that precipitates the anxiety. Subgroups exist, determined by whether panic disorder is present or absent, although panic attacks are frequently present and some suggest that agoraphobia itself is a complication of these. ICD considers agoraphobia in terms of being with or without panic disorder, while DSM works in terms of panic disorder with or without agoraphobia.
Panic disorder	An anxiety disorder, the hallmark of which is panic attacks. These episodes are severe and associated with physical symptoms and disability. In ICD, the disorder is graded as moderate (one attack per week over 4 weeks) or severe (four per week over a 4-week period). DSM does not grade the disorder in the same way, referring instead to recurrent attacks and at least a month of persistent rumination over their recurrence and a behaviour change that accompanies this.
Conversion disorder	The presence of unfeigned neurological symptoms affecting voluntary motor or sensory function in the absence of an accompanying neurological diagnosis to explain them. The onset of symptoms is typically associated with a significant psychosocial stressor. In ICD, conversion disorders are referred to as dissociative disorders.
Malingering	The intentional production or feigning of physical or psychological symptoms or disabilities motivated by external stresses or incentives.
Factitious disorder	The consistent and repeated feigning of symptoms in the absence of a confirmed physical or mental disorder, disease or disability. The motivation for this behaviour is almost always obscure and presumably internal, and the condition is best interpreted as a disorder of illness behaviour and the sick role. Specifically, the unconscious desire appears to be to fill the sick role – to be a patient. Individuals with this pattern of behaviour usually show signs of a number of other marked abnormalities of personality and relationships.

so that a debate as to whether they are in fact representative of a single functional somatic syndrome has ensued.[37]

Ultimately the importance of recognizing and treating anxiety is not down to nomenclature and diagnostic criteria alone: the effect of anxiety on the disability suffered from a comorbid diagnosis[38] and its impact on suicide risk[39] are significant.

DIFFERENTIAL DIAGNOSIS

Although chronic dizziness frequently occurs in combination with clinically significant anxiety, there are additional considerations in the case of the patient who presents with chronic vestibular symptoms, negative investigation results and/or a significantly poorer response to treatment than expected.

The differential diagnosis in this instance should include conversion disorder[40] and, more rarely, malingering[41] and factitious disorder.[42] These are identifiable through a careful clinical history and by tracking the clinical course of the presentation and its response to treatment. The differences between these clinical syndromes are summarized in **Table 72.2**.

It is important to ensure that these differential diagnoses are taken into consideration on a secondary basis, i.e. other diagnostic and treatment avenues must be considered first. Care must be taken here and the diagnosis of conversion disorder should be made by a psychiatrist. The diagnoses of factitious disorder and malingering are potentially harmful to a patient's subsequent medical care and should be made with caution and, in the instance of factitious disorder, must include the early involvement of a psychiatrist.

NEUROANATOMICAL MODEL

The association between anxiety and mood disorders and chronic dizziness can also be found in and potentially explained by the overlap in neural correlates. Animal studies suggest that vestibular deafferentation is associated with increased anxiety-related behaviour,[43–45] while highly anxious strains of mice perform more poorly on tests of balance,[46, 47] with performance improving on administration of benzodiazepines[46] or SSRIs.[47]

In human models, the parabrachial nucleus is important in balance and dizziness with dense reciprocal connections with vestibular nuclei.[48] The parabrachial nucleus is also of importance in the experience of anxiety and related symptoms, including panic.[49–52] It has reciprocal connections with the amygdala, infralimbic cortex, hypothalamus and, via midline structures, the insula.[53–55] Functional neuroimaging studies involving caloric stimulation have also implicated the insula and hippocampus.[56, 57] Insula has been implicated in numerous interoceptive phenomena,[58] including pain,[59] as well as emotional processing.[60] Reciprocal connectivity between insula and amygdala, which is also vital in emotional, anxiety and stress responses,[49, 51, 52] forms a network of both functional and structural connectivity that is strongly associated with both state and trait anxiety.[61]

TABLE 72.2 Clinical differentiation between CSD, conversion disorder, factitious disorder and malingering

	CSD	Conversion disorder[40]	Factitious disorder[42]	Malingering[41]
History	>3 months subjective imbalance or dizziness Hypersensitivity to motion, including one's own or the environment's Exacerbation with complex and motion-rich stimuli	Subjective report of dizziness Difficulties with standing or moving Presence of other neurological complaints such as sensory loss, typically not fitting an anatomical pattern Onset of symptoms may coincide with a readily identifiable stressor Involves 'primary gain' (an unconscious internal motivator)	Subjective reports of dizziness May be accompanied by other varied symptoms History often inconsistent when taken on more than one occasion Falsified names and dates of birth may be used Recurrent presentations at multiple and often geographically diverse hospitals may be discovered May be a history of medical training or employment in an allied field Primary motivation is to be 'the patient'	Subjective reports of dizziness May be accompanied by other varied symptoms History often inconsistent when taken on more than one occasion Involves secondary gain (an external motivator that may or may not be unconscious, e.g. avoiding having to work)
Neurological examination	Normal	Symptoms are inconsistent with clinical signs and do not match anatomical pattern Symptoms may vary with distraction	Symptoms are inconsistent with clinical signs and do not match anatomical pattern Symptoms may vary with distraction	Symptoms are inconsistent with clinical signs and do not match anatomical pattern Symptoms may vary with distraction
Neurological and vestibular investigations	Non-diagnostic (normal or minor abnormalities that do not explain the clinical picture)	Normal May be minor incidental abnormalities that do not explain the clinical picture	Normal May be minor incidental abnormalities that do not explain the clinical picture	Normal May be minor incidental abnormalities that do not explain the clinical picture
Management	SSRIs SNRIs CBT VBRT	CBT Abreaction[96] Longer-term psychotherapy Hypnosis SSRIs or other antidepressants may be useful in treating an underlying depressive or anxiety disorder	Views on management strategies vary The more complex and chronic factitious disorder is often difficult to provide an intervention for Approaches include confrontation, non-confrontation and, in certain circumstances, compulsory detention through mental health legislation Underlying psychopathology must also be adequately treated	Confrontation is rarely successful and more indirect approaches that allow the patient to save face are more advisable The success of management approaches is inversely related to the rewards that are motivating the malingering

CSD, chronic subjective dizziness; SSRIs, selective serotonin reuptake inhibitors; SNRIs – serotonin–noradrenaline (norepinephrine) reuptake inhibitors; CBT – cognitive behavioural therapy; VBRT – vestibular balance rehabilitation therapy.

Connectivity between amygdala and hippocampus is well established and is also of known importance in stress-related responses, which in turn may serve to strengthen this network.[62] The effect of anxiety, mediated by the optimization of autonomic responses through cortisol release, is to switch the amygdala 'on' while switching 'off' the hippocampus. This serves to promote the learning of fear-related information (amygdala) and ensuring that resources are not wasted on more complex aspects of memory and learning (hippocampus). The strength of the 'learning' that occurs during heightened anxiety helps to explain why fear- and anxiety-related memories and associated behaviours are typically the hardest to extinguish. In turn, this might explain why the adequate recognition and management of anxiety is of vital consideration in the morbidity, chronicity and disability of chronic dizziness.

Functional connectivity between the vestibular nuclei and hippocampus is also of importance. Animal models have suggested that this connectivity is a potential link between vestibular lesions and the cognitive deficits seen in patients affected by them,[63, 64] with long-term non-spatial memory deficits arising in rats after bilateral (but not unilateral) vestibulectomy.[65] A small case control series has provided support for this in humans, with hippocampal down-regulation in patients with bilateral vestibular lesions as compared to healthy controls, suggesting that functional hippocampal deficits occur as a consequence of a chronic lack of vestibular input.[66] It has been proposed that anxiety disorders arising in the context of vestibular disorders occur as an indirect consequence of these cognitive deficits.[43] However, research in this area is contradictory[67] and, given that the dorsal raphe nucleus innervates limbic structures, including amygdala, in addition to vestibular nuclei,[48, 68] it is possible that affective aberrations directly influence vestibular networks, while the contribution of the vestibular system to autonomic control[69, 70] may explain how vestibular dysfunction gives rise to anxiety.[71] This interaction between networks, affective tone modulating vestibular function versus vestibular function affecting autonomic tone, has the potential to explain why vestibular complaints are common in psychiatric disorders and why psychopathology is common in vestibulopathy.

NEUROCHEMICAL MODEL

Studies examining the management of disorders such as CSD have predominantly focused on the use of medications that increase monoaminergic (serotonin, noradrenaline and dopamine) neurotransmission (see below). The monaoamines are considered central in the pathophysiology of anxiety and panic disorders.[49, 51, 72–74] Serotonin receptors are present in the vestibular ganglion,[75] with direct serotonergic innervation from the dorsal raphe nucleus (DRN – the largest serotonergic nucleus)[76] and collaterals projecting to amygdala.[68] Serotonergic activity in the vestibular nuclei has an effect on the responsivity of motion-sensitive neural pathways,[77] although the vestibular nuclei also receive non-serotonergic innervation from DRN, including gamma-aminobutyric acid (GABA) and neuropeptides. The locus coeruleus (the principal site for noradrenaline synthesis in the brain) innervates the vestibular nuclei and the cerebellum, in addition to connectivity with limbic areas such as orbitofrontal and anterior cingulate cortices, hippocampus and hypothalamus.[78, 79] These connections may be implicated in SMD and postural sway in patients with anxiety disorders.[18] It has been proposed that these monoaminergic inputs to the vestibular system mediate the effects of anxiety and the responsivity of these systems to novel stimuli.[80]

COGNITIVE BEHAVIOURAL MODEL

The cognitive behavioural models for PPV and CSD are similar and rely on an understanding of behavioural conditioning.[10, 21]

Vestibular symptoms result in strong physiological responses, often with anxiety. Anxiety, especially panic, results in strong physiological responses and physical manifestations that can include vestibular symptoms. These responses result in similar subjective experiences (e.g. lightheadedness, the room spinning, change in heart and respiratory rate). The two of these working in tandem result in a powerful conditioning response and anxiety in particular is a powerful reinforcer of behaviour. Hypervigilence for feared symptoms, particularly in given situations where they might be expected, means that this conditioning is able to sensitize responses to subsequent motion stimuli that may resemble or herald the onset of actual vestibular symptoms, which in turn further reinforces a sensitized response. Both anxiety and vestibular symptoms are unpleasant and the two major behavioural responses to these experiences are exaggerated rescue responses (reaching for something to stabilize the perceived motion) and avoidance. Avoidance is a powerful behavioural reinforcer and in this instance its effects are reciprocal – it reinforces itself. The feared consequences of symptoms that result in such strongly conditioning physiological responses, whether vestibular or anxiety in origin, also lead to the development of cognitive distortions such as catastrophization, lending greater weight to the worst perceived outcome.

It is the potent reinforcing effects of avoidance and associated cognitive distortions that are thought to lead to greater chronicity in such disorders and, as a consequence, greater disability, similar to the pattern seen in agoraphobia.

Cognitive behavioural therapy is aimed at psychoeducation to improve understanding of the origin of symptoms, the reattribution of the misinterpretation of anxiety-related symptoms in order to reduce catastrophization, the development of coping skills through the use of relaxation techniques, which in turn enables gradual exposure to both internal (such as through the use of hyperventilation to recreate symptoms) or external (exposure to environments associated with vestibular symptoms) phenomena. The approaches applied in vestibular rehabilitation are similar to those central to CBT but focus more on the behavioural elements, aiming for a reduction in pathological avoidance as a route to habituation to aversive stimuli.

TREATMENT STRATEGIES

Psychopharmacology

To date, no large-scale randomized controlled trials have been performed in cohorts of patients diagnosed with chronic dizziness with and without psychiatric morbidity. There is some variation in the diagnoses used to recruit to these trials on account of the timing in the historical changes in nomenclature detailed above. Uncontrolled trials indicate that selective serotonin reuptake inhibitors (SSRIs)[81–84] and serotonin–noradrenaline (norepinephrine) reuptake inhibitors (SNRIs)[85] may be of benefit for chronic dizziness in the presence of anxiety and major depressive disorders and that this benefit is independent of improvement in psychopathology.[86] However, in being from uncontrolled studies, these results should be interpreted with caution. Staab and Ruckenstein[86] examined the response of the three subtypes of CSD to SSRIs. They report that the otogenic and psychogenic subtypes demonstrated 'more complete' responses than did the interactive. This is likely to be a reflection of the fact that this subtype is likely to exhibit greater chronicity and treatment resistance requiring higher doses, longer treatment course, pharmacological augmentation perhaps in addition to subsequent psychological interventions.

There is sufficient evidence for the use of SSRIs in this group of patients, although further work is necessary; in particular, larger randomized and controlled trials and long-term follow-up studies are still lacking. Studies to date would advise starting at a lower dose than would be ordinarily used in the treatment of anxiety and affective disorders, with a gradual titration to the lower end of this treatment range. The major caveat here is that presence of anxiety symptoms typically requires higher doses than mood disorders do, and a longer course of treatment. A dosage limitation in this regard would provide a false ceiling and an unfair disadvantage to many patients. Another important factor to note is the potential for a dizziness to appear independently of the underlying diagnosis and as a consequence of the SSRIs. This may be in the form of a side effect but may also occur as part of the withdrawal phenomena associated with members of this family with longer half-lives (e.g. paroxetine and fluoxetine).

Psychotherapy

Psychotherapy, specifically cognitive behavioural therapy, has been examined in a number of trials looking at PPV or CSD.[24, 25, 87] In an uncontrolled trial in 41 patients, Edelman et al.[87] suggest that CBT is effective in improving scores of dizziness, avoidance behaviour and disability with high effect sizes after only three sessions but without effect on anxiety or mood-related symptoms. The response after so few sessions is surprising and may explain the lack of efficacy against psychopathology (between six and eight sessions are standard here) but this was conducted in relatively small cohorts of patients and was uncontrolled. The important question that is obviously begged by this potentially positive data after such a brief intervention is whether this clinical response is sustained. No details were provided on follow-up in this initial study but the same group reported that the effects were sustained at 6 months in a subsequent report.[25] This is promising, given that earlier groups suggest that at 12 months after an initial intervention no benefits are sustained.[24]

Vestibular balance rehabilitation therapy

Vestibular balance rehabilitation therapy (VBRT)[88] aims to facilitate the process of compensation and involves a habituation programme that ultimately encourages the 'avoidance of avoidance'. VBRT therefore also engages the behavioural component of the CBT model and is in this way similar in principle to graded exercise therapy in chronic pain syndromes such as fibromyalgia and chronic fatigue syndrome. VBRT is effective against hypersensitivity to motion, improves confidence with balance and reduces avoidance behaviour.[89] Early forays into the combination of VBRT and CBT have yielded mixed results from small randomized trials, with positive results in terms of disability but without effect on the core symptoms of vertigo, anxiety or depression.[90, 91] This is perhaps not surprising with respect to symptoms of vertigo, as exposure to the activity that provokes symptoms is core to the process of compensation (part of the goal of VBRT); the patient needs to experience the symptoms in order for these subsequently to diminish.[91]

AN APPROACH

The assessment and management of patients with complaints such as chronic dizziness is complicated by assumptions that are potentially made with ease. The first is that the discovery of psychopathology may lead to the assumption that this alone explains the presentation, preventing appropriate investigation being sought.[92] On the flip side of the coin, the discovery of 'organic' pathology may result in a lack of appropriate assessment and treatment of psychopathology,[93] with the ensuing negative effects on chronicity and disability. It is also a problem that those initially referred to 'organic' clinics are often reluctant to accept input from a psychiatrist,[94] as a consequence of both stigma and a fear that their disabling problem is being accounted for by 'just being in their head'.

The best practice in this regard is the early involvement of a psychiatrist. Ideally, this should be one who specializes in this area and is familiar with the practice of vestibular medicine. Even more optimal is the psychiatrist who is embedded in the outpatient department with vestibular specialists and is seen as being part of not just the same team but the same process. The advantage of this in terms of the patient's appraisal is that being seen by the psychiatrist is not in any way remote from being seen by the vestibular specialist. The advantage to the clinicians is that investigation can continue from both medical disciplines concurrently, contributing to a complete and ideally seamless clinical picture and subsequent management. We have

reported on the success of such practices from an inpatient perspective with another group of disorders that are met with very similar conflicts.[95]

CONCLUSIONS

Chronic dizziness is commonly associated with psychiatric morbidity, most frequently in the form of anxiety. The presence of anxiety adds to both chronicity and disability, irrespective of whether it is primary or secondary in nature. The early involvement of an appropriately experienced psychiatrist in the comanagement of this patient group for the detection and early management of such comorbidities is vital and need not delay ongoing vestibular investigations, which can be pursued in parallel.

BEST CLINICAL PRACTICE

Psychopathology should be an early consideration in the assessment of patients and, when present, should be actively treated as part of the overall diagnosis and management strategy. Optimally, this should be performed in conjunction with a psychiatrist working in tandem with vestibular specialists, rather than in a remote clinical environment.

FUTURE RESEARCH

- ➤ Rigorously designed randomized and placebo-controlled trials should form the mainstay of future research at this juncture, unified by the use of current nomenclature to define diagnostic groups.
- ➤ Such trials might explore the efficacy of the SSRIs, the SNRIs, CBT and VBRT independently, as comparisons and in combination with one another as well as in isolation.
- ➤ Further to this, the new concept of 'Persistent postural-perceptual dizziness' will require careful exploration for diagnostic reliability and stability and the identification of subgroups that may otherwise hamper the interpretation of results of studies into both pharmacological and non-pharmacological interventions.

KEY POINTS

- Psychopathology commonly coexists with chronic vestibular disorders.
- Typically this is in the form of disorders of anxiety and affect.
- Concurrent psychopathology is a source of chronicity, disability and suicide risk.

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CHAPTER 73

CLINICAL EXAMINATION OF THE EARS AND HEARING

George G. Browning and Peter-John Wormald

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search focusing on reviews using the keywords: examination and ear/otology/otoscopy, otoscopy, wax, cerumen, syringing and ear, tests/clinical and hearing, tuning fork, Rinne, Weber and Bing tests.

PINNA

The external ear or pinna is constructed of a cartilage skeleton covered by skin and soft tissue. The cartilage forms an outer helix and an inner antihelix. These structures surround the conchal bowl which is shielded anteriorly by the tragus (Figure 73.1). In humans the physiological purpose of the pinna is to collect high-frequency sounds which are thereby amplified in the external auditory canal. These normal features of the pinna are assessed as part of the initial examination of the external ear.

It is necessary to identify external surgical scars used for access, which are most commonly endaural (Figure 73.2) or post-auricular (Figure 73.3). These scars can be thin and may be difficult to see but, if present, alert the otoscopist to the potential for surgical abnormalities, especially in the attic, such as open mastoid cavities. Other scars to harvest graft material such as tragal cartilage and temporalis fascia are also worth identifying.

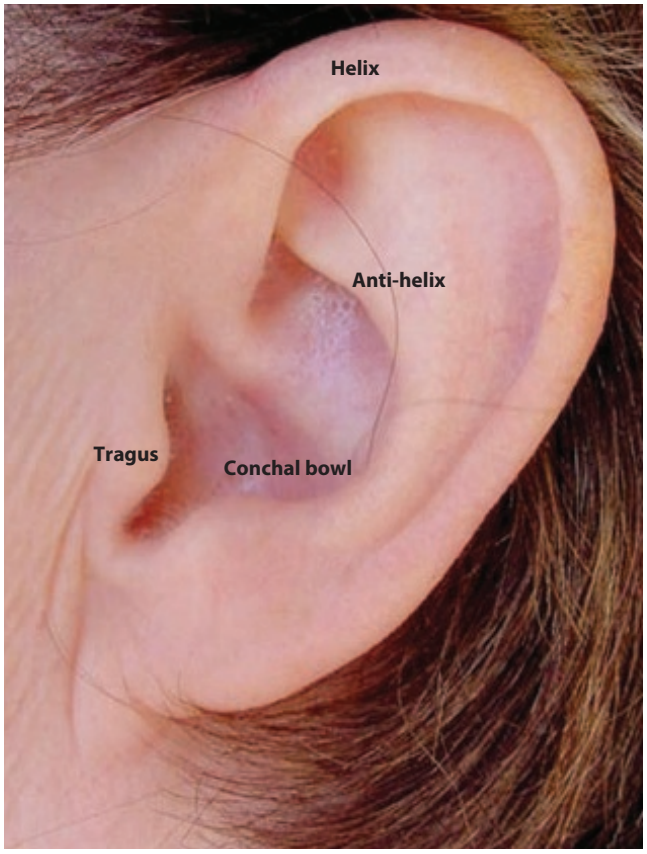


Figure 73.1 Anatomy of the ear (pinna).

EXAMINATION OF THE EXTERNAL AUDITORY CANAL

The external canal consists of a cartilaginous outer third and a bony inner two-thirds. It is angled and needs to be straightened before examination is attempted. This is done by gently pulling the pinna posterosuperiorly (Figure 73.4). This aligns the cartilaginous canal with the bony canal and should allow visualization of the

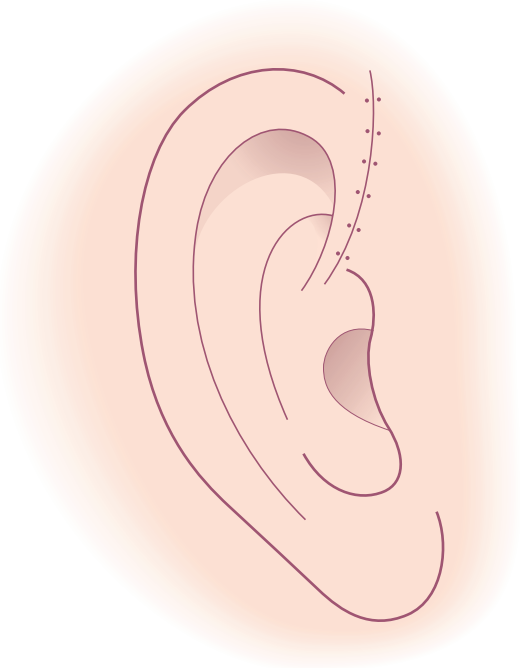


Figure 73.2 Endaural incision (right ear).

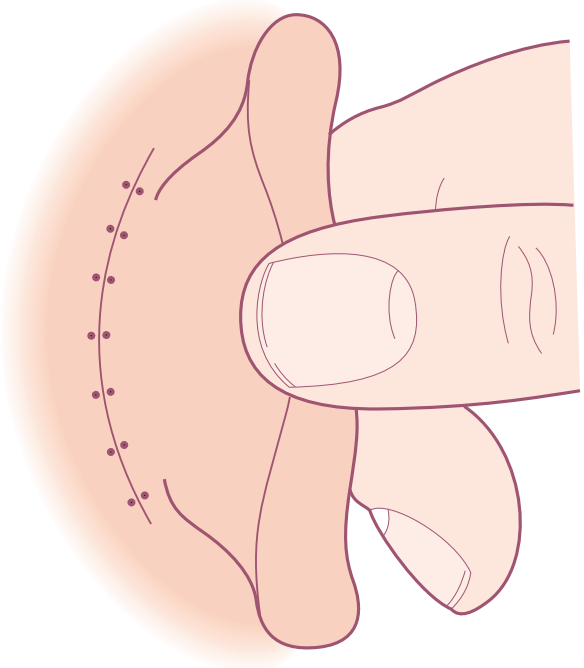


Figure 73.3 Post-auricular incision (right ear).

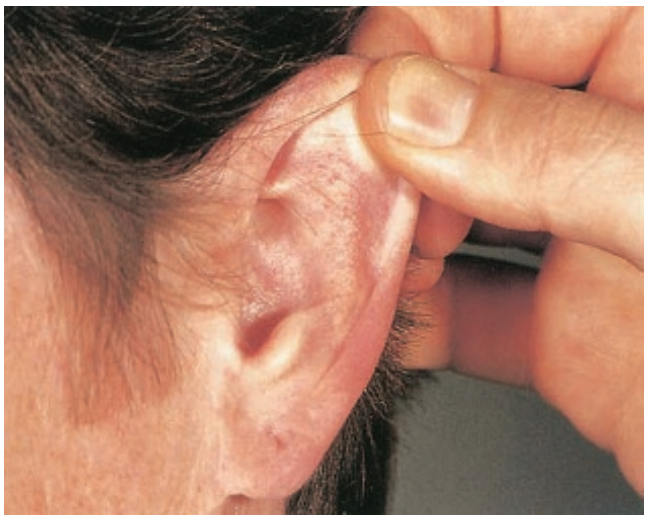


Figure 73.4 Positioning of ear for otoscopy.

entire canal and tympanic membrane. The temperomandibular joint creates an anterior bulge in the deep external canal that may obscure the anterior inferior tympanic membrane. A high proportion of adults and children will have visually occlusive wax plugs, where the tympanic membrane cannot be seen in its entirety. In clinical practice, visually obstructive wax is more common in those who wear a hearing aid. Patient indications for wax removal are the feeling that the ear is blocked, perhaps associated with impaired hearing. Clinical indications for removal are if the patient has otological symptoms that require the external auditory canal and tympanic membrane to be assessed, such as ear discharge, otalgia and hearing loss.

WAX PRODUCTION

Wax is produced by the hair-bearing skin of the external auditory canal. Wax is a combination of desquamated skin and cerumen formed by glands in the base of the hair follicles. Hairs are present in the outer third of the external canal. Most external canals are self-cleaning with the desquamated skin migrating up to the hair follicles where it is separated from the dermis and mixes with the cerumen to form wax. The wax migrates down the hair and migrates out of the ear canal (Figure 73.5). The most common finding is partial occlusion of the canal (Figure 73.6). In the majority of patients this will be an incidental, symptomless finding. In those with otological symptoms, wax

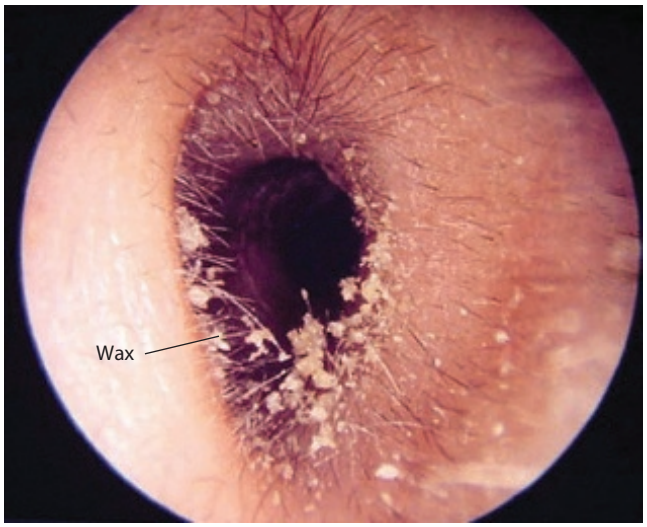


Figure 73.5 Wax on the tips of external canal hairs.

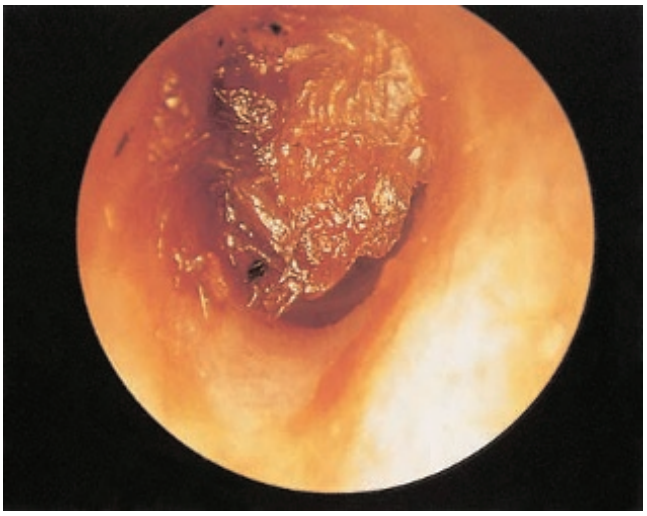


Figure 73.6 Wax totally obscuring view of right tympanic membrane. Associated hearing impairment is unlikely.

will need to be removed to enable the canal and tympanic membrane to be assessed. It is relatively uncommon for wax to cause a hearing impairment. It requires the wax to be impacted deep in the canal by the use of cotton buds or an ear mould for it to act like 'ear defenders' that are used to limit noise exposure.

Wax is amenable to removal by non-specialists by water syringing most commonly using a pressure-controlled irrigator. Specialists prefer to remove wax under direct vision with the aid of a headlight, microscope or endoscope, often via a speculum with ear wax hooks, Jobson Horne probes or suction irrigation.

WAX SOFTENING

In primary care settings various wax softening agents including olive oil, sodium bicarbonate and commercial agents such as Cerumol are frequently used to aid wax or ease of wax removal. Such substances are effective[1] but there is no evidence to support the use of one agent rather than another. Adverse effects are not common but can include skin irritation. In secondary care their previous use requires to be noted if there is inflammation of the skin of the ear canal.

EAR TOILET

In primary care ear toilet is mainly confined to clearance of wax. In secondary care, though removal of wax is the predominant reason, debris including pus, dried pus and blood will also require to be removed to aid assessment and management. Performing toilet under direct vision, especially if this is magnified with a microscope or endoscope, greatly aids the process of clearing out difficult areas including the attic and open mastoid cavities. Patients will tolerate extensive toilet better if they are in a relaxed position on a reclining chair or couch. They should be informed as to what to expect, especially the noise of suction or irrigation of water. The latter on occasions can cause a short episode of vertigo especially if the irrigation fluid is not at body temperature.

Syringing

Syringing to remove visually obstructing wax or wax considered potentially to be causing a mild hearing impairment is now most frequently performed by suitably trained, paramedical staff (**Figure 73.7**). As this is most often not performed under direct vision and the otoscopic diagnostic skills of the operator will be limited, there are usually firm contraindications to syringing. So ears with a discharge or previous ear surgery are not permitted. These contraindications do not apply to specialists in secondary care settings.

In the UK, various Health Boards have produced guidelines readily available online with titles such as *Ear irrigations: guidelines for Community Nursing*. That by Derby City Primary Care Trust can be recommended.[2]

Microscopic/endoscopic suction toilet

Ear toilet with magnification is popular among specialists as it allows the external canal and tympanic membrane to be magnified while wax, pus or debris is removed using a suction cannula or other instrument. The magnification afforded by the microscope or endoscope allows the ear to be cleaned with great precision and with minimal patient discomfort. Irrigation of troublesome areas with a small syringe filled with water often aids the process. Because such toilet is performed under direct vision, adverse effects including trauma to the ear canal or tympanic membrane/middle ear are uncommon. Haemorrhage, if it occurs, can be easily controlled.

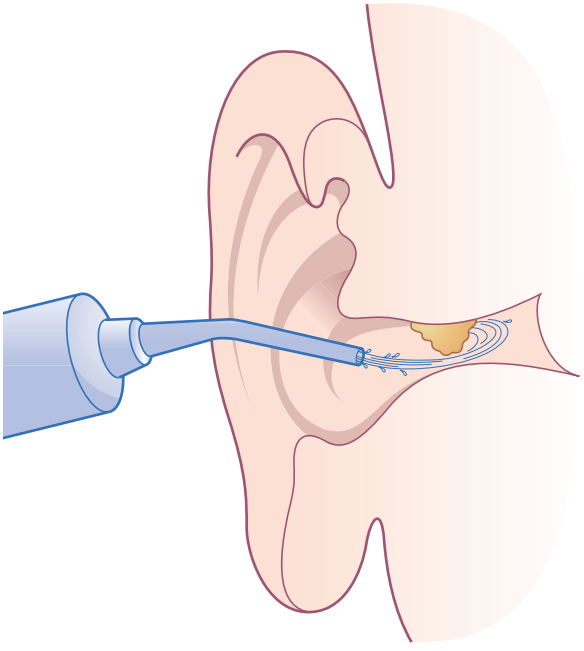


Figure 73.7 Wax syringing. The water bypasses the wax and is reflected by the tympanic membrane to expel the ear wax.

Mopping the ear canal

A mop can be used to remove discharge or debris from the ear canal for management purposes of otitis externa and active chronic otitis media, as well as allowing visualization of the underlying canal and tympanic membrane. Mopping can be performed without the aid of equipment such as suction which is the main alternative method. It can also be performed, after adequate instruction, by paramedical staff and patient carers.

A mop is made by winding a thinned-out piece of cotton wool around the end of an orange stick. Care should be taken to ensure that the stick extends only halfway into the cotton wool (Figure 73.8) and that the mop is about the same diameter as the stick. The protrusion of cotton wool beyond the end of the stick will ensure that, if the mop touches either the deep canal skin or the tympanic membrane, no damage will occur or pain be felt.

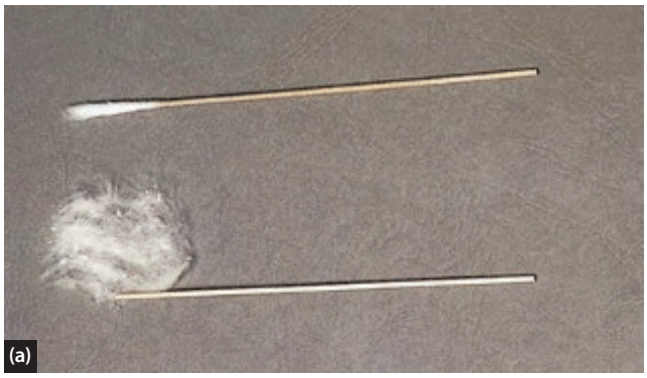
OTOSCOPY

With an otoscope

The first decision when performing otoscopy with an otoscope (auriscope) is to choose the most appropriate size of speculum (Figure 73.9). A narrow speculum limits the visible canal and/or tympanic membrane. The otoscope then has to be moved around and all the subsequent images mentally pieced together like pieces of a jigsaw until the overall picture is established (Figure 73.10). The larger the speculum, the less reconstruction will be needed by the examiner.

With an endoscope

Endoscopy with a short 4 mm diameter straight-view rigid scope has the advantage of not requiring a speculum. It is therefore perhaps more able to be angled to see the different areas including the attic and open mastoid cavities. If attached to a camera, both the patient and others can view the ear, allowing permanent photographic records to be kept electronically. Condensation of the lens is the main drawback. This can be mitigated to some extent by wiping the lens with an alcohol swab.



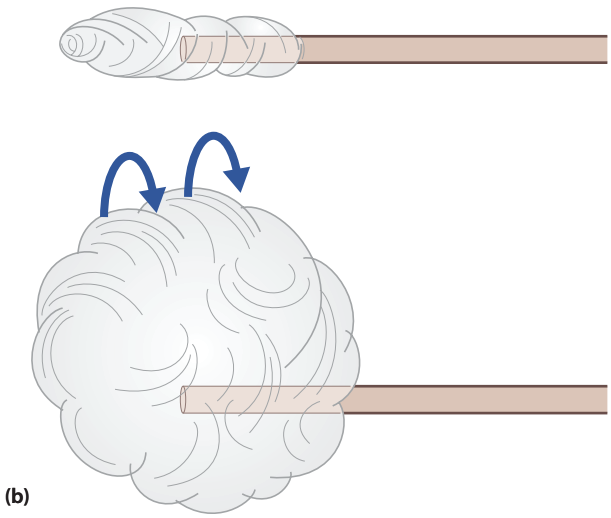


Figure 73.8 (a,b) Method of making a cotton bud.

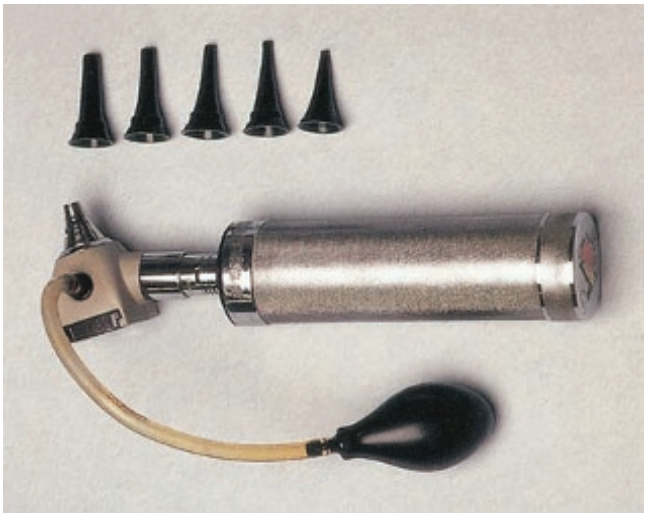


Figure 73.9 Closed pneumatic otoscope.

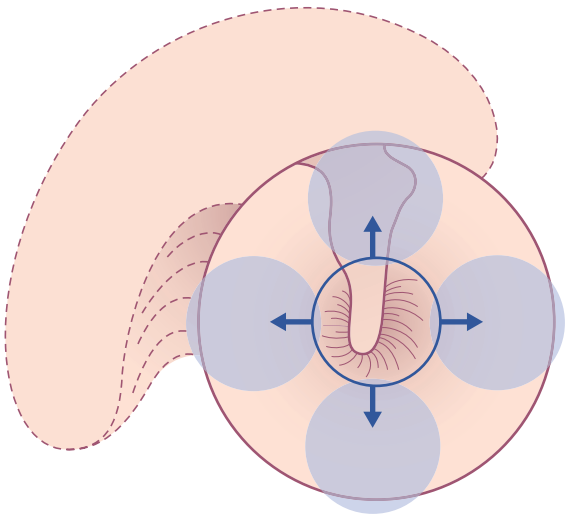


Figure 73.10 A wide view of the attic is obtained by multiple views via a speculum.

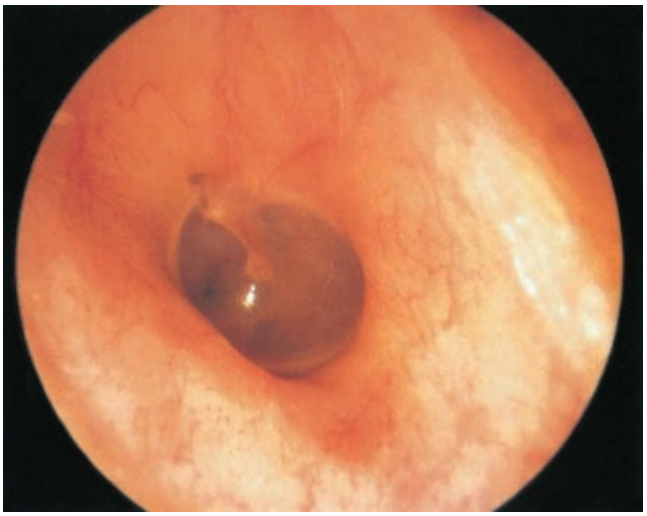


Figure 73.11 Normal skin in the left external auditory canal.

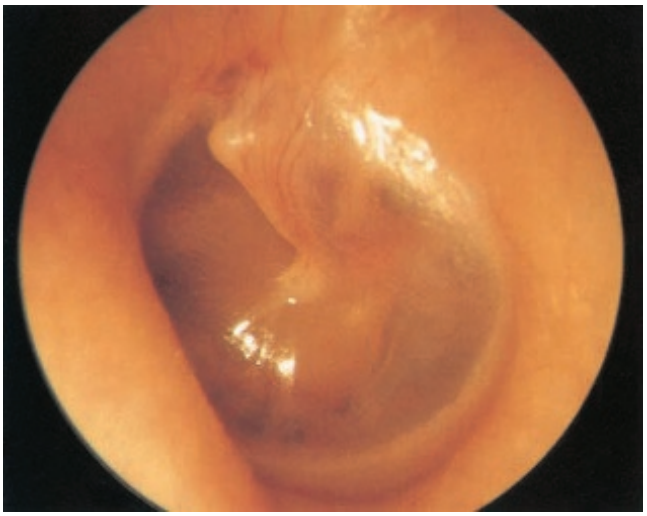


Figure 73.12 Normal left tympanic membrane. The anterior pars tensa is not entirely visible due to anterior canal bulge of the temporomandibular joint.

Normal external canal

The outer third of the normal external canal has hair-bearing skin which is relatively thick as it contains the ceruminous glands. At the junction of the cartilaginous and bony canal, the skin thins without glands and covers the underlying bony canal (Figure 73.11). This allows the bony prominence formed by the impression of the temperomandibular joint to be clearly seen anteriorly. This prominence allows photographs of tympanic membranes to be identified as either a left or a right ear as the prominence is always anterior (Figure 73.12). In some photographs taken through a Hopkins rod, the bony prominence may not be obvious.

Structured otoscopy

With the increased availability of texts on the pathology of the external canal and tympanic membrane,[3, 4] otoscopy is becoming easier for practitioners to learn. If a structured approach to otoscopy is taught, diagnostic skills improve and disease patterns are more easily recognized and appropriately dealt with.[5] The most recognizable feature in most ears is the handle of malleus and this should be the first structure sought (Figure 73.13). The umbo and lateral process should be identified and the adjacent tympanic membrane visualized (Figure 73.13). The tympanic membrane can be divided into the pars tensa and the pars flaccida (Figure 73.14). The examiner should then decide if the pars tensa is intact and, if this is the case, whether it is in its normal position. Clues as to its normal position should be sought in identifying the angle of the handle of the malleus. Foreshortening indicates retraction of the tympanic membrane medially as does lipping around the annulus creating a 'neoannulus' (Figure 73.15). Loss of the light reflex, while less important, may be caused by retraction, inflammation or scarring of the tympanic membrane (Figure 73.16). The tympanic membrane is normally a grey, slightly translucent colour. Hyaline degeneration of the fibrous layer sometimes associated with calcium deposition occurs as a consequence of previous episodes of middle-ear inflammation. This increases the whiteness of the tympanic membrane and can be a diffuse thickening

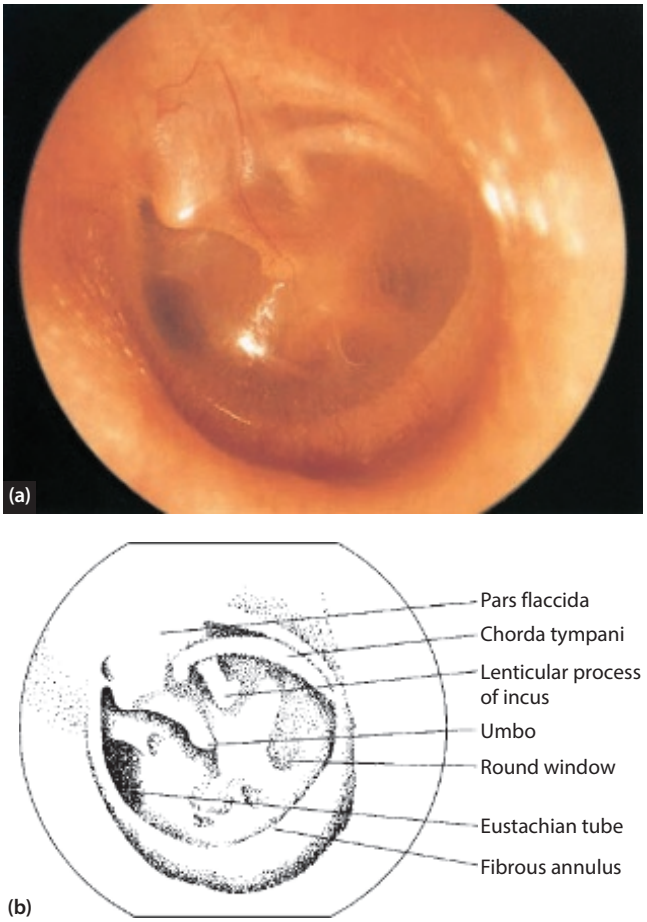


Figure 73.13 (a) Normal left tympanic membrane. **(b)** Important middle-ear anatomy structures often identified behind the tympanic membrane.

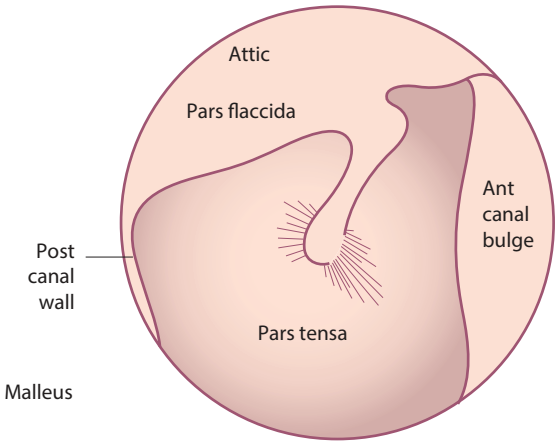


Figure 73.14 Diagram of the ear indicating the pars tensa and pars flaccida. Redrawn with permission from Browning, *Updated ENT.* 3rd ed. London: Hodder and Stoughton; 1994, p. 2.[6]

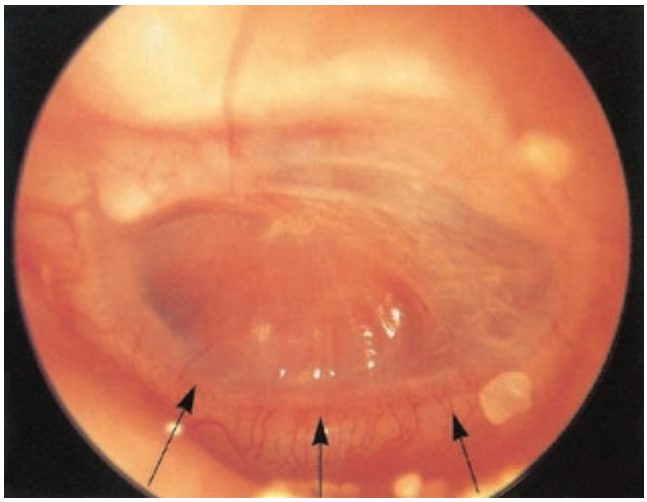


Figure 73.15 Severely retracted position of the malleus handle in otitis media with effusion (left ear). As retraction develops, a neoannular fold may form (arrows).

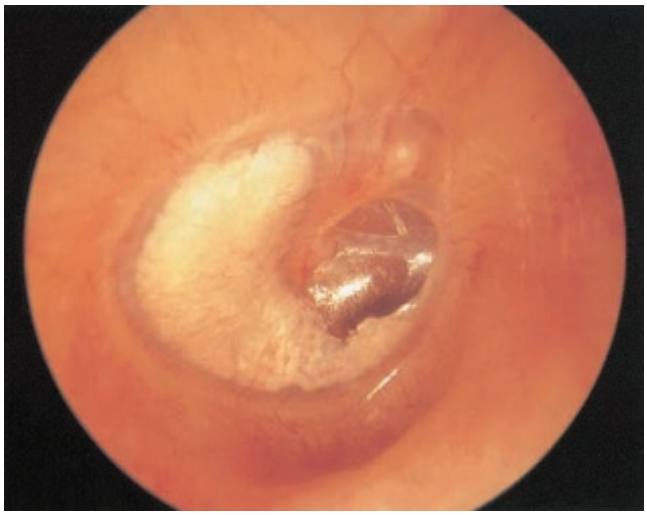


Figure 73.16 Tympanosclerotic plaques, extending from posterior to inferior. Remainder of the tympanic membrane scarred (right ear).

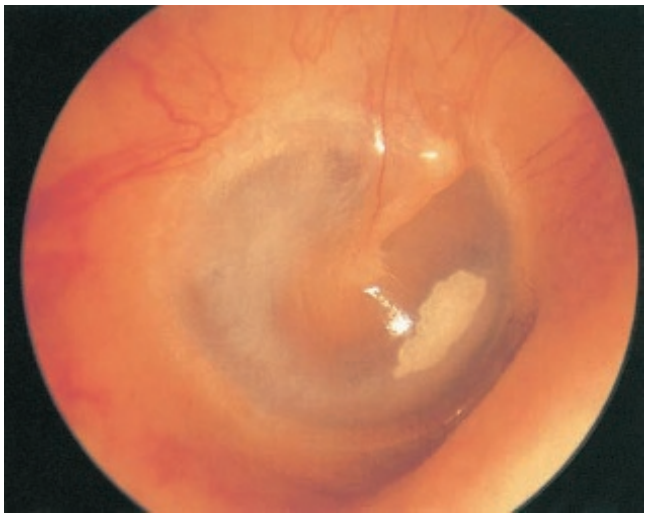


Figure 73.17 Chalk patch on the anterior pars tensa (right ear).

of the tympanic membrane or isolated tympanosclerotic plaques (Figure 73.17). Previous grommet insertion produces a rather characteristic crescent-shaped deposition of calcium in 32% (CI 30.6,32.8) of patients (Figure 73.18).[7] Tympanosclerosis may also fixate the middle ear ossicles with a resultant conductive impairment. If the tympanic membrane is perforated posteriorly, the ossicular chain may be visible. In Figure 73.19 the malleus handle, long process of the incus and stapes are all seen through a subtotal perforation in an ear with active, mucosal chronic otitis media.

Changes in the tympanic membrane and ossicles as a result of ageing

The tympanic membrane may lose its translucency and become less transparent with age. It had also been thought

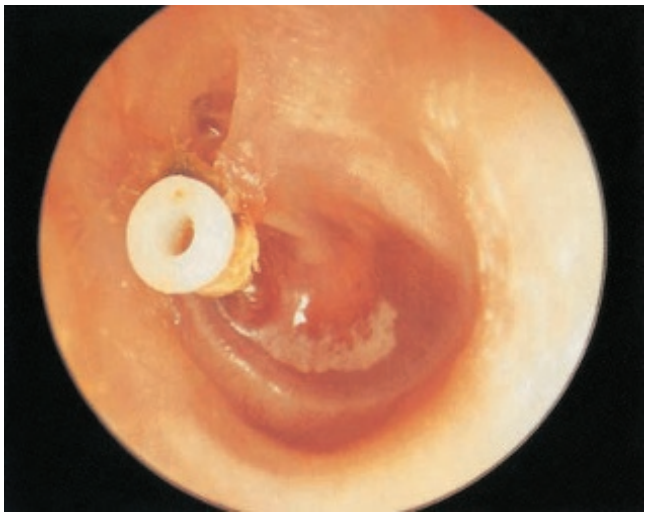


Figure 73.18 Extruded ventilating tube with otoscopic recurrence of middle ear fluid. Left ear retracted and yellow.

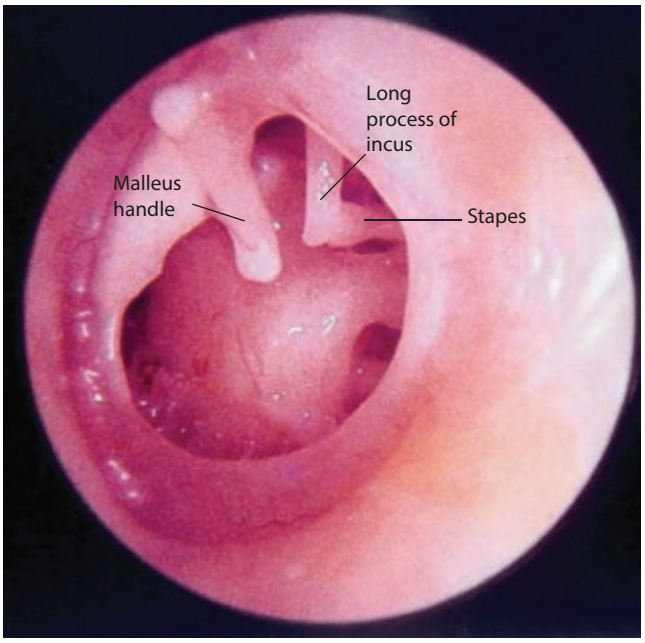


Figure 73.19 Perforated tympanic membrane with visible ossicular chain.

that the ossicular chain increased in stiffness with age. However, Holte[8] showed that there was no change in the middle ear resonance, admittance or tympanometry width with increasing age. The less translucent tympanic membranes seen with increasing age are likely to be as a consequence of episodes of middle ear inflation rather than directly related to ageing.

CLINICAL ASSESSMENT OF HEARING

It is useful before clinically assessing the hearing to have some idea of how impaired the patient is overall. If communication is difficult without hearing aids, this would suggest a bilateral severe or profound hearing impairment. If they find it difficult to hear conversation when out of sight of the speaker, they will have a bilateral mild to moderate impairment. The history from the patient and from any attending partner or friend as to what situations cause difficulty is also helpful. More often it is the attendant person who gives a truer record of the overall disability. One should be particularly wary if an individual is adamant that they have no hearing impairment.[9] Ascertaining whether the patient has a better hearing ear helps direct the clinical assessment, rather than being 'correct' in many instances.

Questionnaire assessment

Several questionnaires are available for ascertaining the degree, if any, of an individual's hearing impairment. These have been primarily designed as screening instruments[10] and are not sufficiently specific to determine the requirement for audiometry in secondary care. Individual questions from these questionnaires that ascertain the circumstances in which the patient finds hearing difficult can, of course, guide subsequent management.

Free-field speech testing

This is the main method of clinically assessing an individual's hearing[11] and is applicable to both adults and older children.[12] Its main value is in primary care when audiometric facilities are not available as a screening test for a hearing impairment. In secondary care its value is also as a screening test to determine whether an audiometric assessment is required. In addition, the test is such that it can assess the relative severity of a hearing impairment in each ear, which is sufficiently reliable to guide management. It can also be useful to demonstrate to the patient or parent of a child the presence/lack of a hearing loss.

GENERAL TECHNIQUE

The examiner explains to the patient that a combination of letters and numbers are going to be whispered or spoken and the patient's task is to try to repeat them. A number–letter combination is chosen as this has a reasonable mix of consonants that allows a relatively broad range of frequencies to be tested. For less experienced testers to have a list of these to read from allows a more consistent voice level to be produced. The examiner then positions themselves behind the patient so that the subject cannot lip-read and in a loud voice confirms that they understand the task by saying very recognizable numbers such as '99'. The next step depends on whether the patient is being screened to detect a hearing impairment or each ear is being screened separately for a hearing impairment.

SCREENING TECHNIQUE

When the tester is standing behind the subject at arm's length from their head and the subject cannot repeat more than 50% of the number–letter combinations spoken in a whispered voice, they will have a hearing impairment of at least 30 dB HL in both ears (Table 73.1).[13] The main variable to ensure control for is the level of the whispered voice. Some suggest that fully exhaling before whispering gives more consistent voice levels. It must also be remembered that testing has to be in a quiet environment.

If each ear requires to be tested, the non-test ear requires to be masked as sound attenuation across the skull from

TABLE 73.1 Sensitivity and specificity of a hearing impairment being detected by an individual's inability to hear a whispered voice at 60 cm (reproduced from Browning et al.[13] with permission)

PTA	Impairment (db HL)	Percentage	
		Sensitivity	Specificity
PTA over 0.5, 1 and 2 kHz	≤25	86	94
	≤30	95	90
	≤35	100	84
PTA over 0.5, 1 and 2, 4 kHz	≤25	91	96
	≤30	96	91
	≤35	98	86

one side to the other ear is in the region of 15 dB. Adequate masking is achieved most easily by the examiner closing the ear canal in the non-test ear by pressing the tragus over the canal with a finger. The tragus is then rubbed to produce a continuous masking noise that is in the region of 40 dBA. The examiner then positions themselves at full arm's length on the test-ear side of the patient which is approximately 60 cm from the test ear. The number–letter combinations are again whispered and the subject is asked to repeat them. If they cannot do this on more than 50% of occasions, the hearing level in that ear will be 30 dB HL or poorer.

While this test is not as accurate as pure-tone audiometry it will give the examiner a reasonable idea of the hearing, especially in the low frequencies (speech frequencies). The free-field speech test will in most cases (90–100 %) detect a hearing loss of greater than 30 dB with a false-positive rate of 13–30%.[13]

In primary care such voice testing can be sufficiently sensitive and specific to discriminate those requiring onward referral for audiometric testing.[12, 14]

DETERMINING THE DEGREE OF IMPAIRMENT IN EACH EAR

In secondary care the above 'by ear' screening method can be extended to determine the likely level of the impairment if the subject is not able to repeat what is said in a whispered voice. This requires the examiner to move their head in position from arm's length (60 cm) to 15 cm from the ear and repeat the test again in a whispered voice. If the subject can do this, that ear has a mild impairment (Table 73.2).[13] If they are unable to do it, the voice level is raised to a conversational level and the test repeated at arm's length. If the subject is able to do this, they will have a moderate hearing impairment and the conversational voice is then tested at 15 cm. If unable to repeat this, the subject has a severe impairment or poorer. If the test is to be taken any further, tragal rubbing will provide insufficient masking and a Barany box will be required.

The main variable between tests and testers is the reproducibility of the voice levels. Examiners should frequently compare their results with the audiogram to ensure that their conversational voice level and whisper levels are giving consistent results.

TABLE 73.2 Comparison of free-field voice thresholds and pure-tone average (PTA) over 0.5, 1, 2 and 4 kHz (after Swan and Browning)[14]

Voice level	Distance (cm)	Loudness (dBA)	PTA mean percentiles	
			5th	95th
Whisper	60	12	–	27
	15	34	20	47
Conversation	60	48	38	60
	15	56	48	67
Loud	60	76	67	87

Tuning fork tests

Tuning fork tests have a potential role in ears with a normal tympanic membrane to distinguish between a conductive and a sensorineural hearing impairment when accurate pure-tone audiometry, with both air and bone conduction, is not available. In these circumstances, if they suggest a conductive hearing impairment, then otosclerosis is the most likely diagnosis. Tuning fork tests have relatively little value if otoscopically the ear is abnormal with otitis media with effusion and acute or chronic otitis media where, by definition, there must be a conductive defect. What one requires to know in these ears is the magnitude of the conductive defect and pure-tone audiometry is the only method of doing this by measuring the air–bone gap.

The most commonly used forks are the 256 Hz and 512 Hz forks, as these give more reliable responses than the 1024 Hz fork.[14, 15] Tuning forks are activated by striking them lightly against the elbow. The sound generated should not be audible until the fork is brought close to the ear. Striking them against a solid object may produce harmonics that distort the pure-tone generated by the fork and result in an unreliable test. A correctly activated tuning fork held up to the ear generates about 70 dBA, while one activated by pushing the tines together and letting go can generate slightly higher levels (89–90 dBA).

In theory, masking should always be applied to the non-test ear, especially for bone conduction. However, such masking cannot be done by bone conduction as this would affect both ears. Consequently, it has to be done by air conduction and a Barany box is used because it generates sufficient noise. Other methods of masking (tragal rubbing and paper) produce an insufficient volume of noise to adequately mask the tuning fork.[13, 15]

RINNE TEST

The standard **loudness comparison method** of performing the Rinne test compares the relative loudness of air conduction against bone conduction. In ears with normal hearing or a pure sensorineural hearing impairment, the tuning fork will sound louder opposite the ear canal (air conduction) than when placed on the mastoid bone behind the ear (bone conduction). Therefore, with the tuning fork activated, the patient is asked to say which of the following sounds louder: the fork placed within 2 cm of the external auditory canal or placed firmly on the flat bone of the mastoid behind the pinna. To aid bone contact with the tuning fork base it is advisable to hold the patient's head with the other hand to prevent it from moving.

The alternative method of performing the Rinne test is the **threshold comparison method**. Here, the activated fork is held opposite the external canal until it is no longer heard. It is then placed on the mastoid bone. If the sound is heard again, then bone conduction is better than air conduction and there is a conductive impairment. This method of performing the Rinne is not as reliable as the relative loudness comparison method (Figure 73.20).[13, 16]

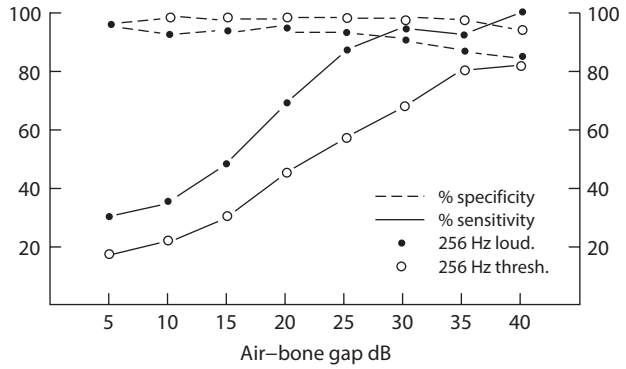


Figure 73.20 A comparison of the sensitivity and specificity of the 256 Hz fork using a loudness comparison method against the 512 Hz fork using a threshold method, in detecting air–bone gaps of various magnitudes. Redrawn with permission from Browning et al. Clinical role of informal tests of hearing. *J Laryngol Otol* 1989; **103**: 7–11.[13]

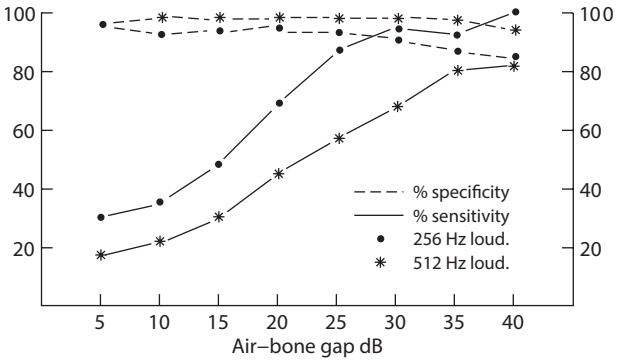


Figure 73.21 A comparison of the sensitivity and specificity of the 256 Hz against the same forks in detecting air–bone gaps of various magnitudes, but using the loudness comparison method. Redrawn with permission from Browning et al. Clinical role of informal tests of hearing. *J Laryngol Otol* 1989; **103**: 7–11.[13]

In practice, masking of the non-test ear only requires to be done when testing a poorer-hearing ear (determined by voice testing) and the bone conduction is louder than the air conduction. A false-positive Rinne could result in these circumstances by the bone conduction being heard by the better-hearing ear.

Although many clinicians use a 516 Hz tuning fork, the 256 Hz fork gives superior sensitivities and specificities (Figure 73.21). The 256 Hz Rinne tuning fork test will detect a conductive defect above 30 dB in 90% of patients (Table 73.3). Between 20 and 30 dB, the sensitivity will fall to 70% and between 10 and 20 dB it will be less than 50%.[13, 15–20] The specificity of the test is high above 30 dB conductive defect but falls as the air–bone gap narrows. The false-positive and false-negative rates again depend on the air–bone gap (Figure 73.20).[13] The false-positive rate in normal patients is 20%.[13, 15–20]

Table 73.4 shows the results with a 512 Hz fork in greater detail. Using the loudness comparison method, it shows there is a third type of response of no difference in loudness (ac = bc). This makes the test uninterpretable in up to 10% of patients with an air–bone gap of 11–40 dB at 512 Hz.

TABLE 73.3 Size of air–bone gap (dB) which would be correctly identified by Rinne test on various percentages of occasions

Fork	Study	Confidence limits		
		50%	75%	>90%
256 Hz	Crowley & Kaufmann (1966)[17]	25 dB		30 dB
	Gelfand (1977)[20]		40 dB	
	Browning et al. (1989)[13]	15 dB	20 dB	30 dB
512 Hz	Crowley & Kaufmann (1966)[17]	25 dB		30 dB
	Wilson & Woods (1975)[18]			40 dB
	Gelfand (1977)[20]		40 dB	
	Golabek & Stephens (1979)[19]	19 dB		
	Browning et al. (1989)[13]	20 dB	25 dB	40 dB

BING TEST

The Bing test is based on the principle that, if there is a conductive hearing loss, occlusion of the external auditory canal will not augment the sound of the tuning fork in the test ear. This is what would happen in those with normal hearing or a pure sensorineural hearing loss. The test is performed by placing the activated tuning fork on the mastoid bone and then occluding the external auditory canal with a finger. If the patient reports that this makes the bone-conduction sound louder, there is unlikely to be a conductive impairment. However, if it remains the same, then a conductive impairment is likely.

The sensitivity and specificity of this test are low as it frequently suggests a conductive hearing loss in patients with normal hearing.[18] The reliability of the Bing test correctly identifying an ear with a conductive deafness is only slightly better than chance (57–66%).[18] Today it is used less frequently than the Rinne to identify a conductive impairment in ears with a normal tympanic membrane as its sensitivity is less although its specificity is similar.[21]

WEBER TEST

The Weber tuning fork test is only applicable if a patient has unilateral or asymmetrical hearing. The test is based on a tuning fork placed centrally on the skull being heard

TABLE 73.4 Comparison of the Rinne test results with a 512 Hz tuning fork against the air–bone gap at 0.5 Hz using a loudness comparison (after Browning and Swan)[16]

Air–bone gap (dB)	Percentage ears		
	AC > BC	AC = BC	BC > AC
0–10	97	1	2
10–20	61	11	19
21–30	32	8	60
31–40	42	8	49
40+	10	0	90

AC – air conduction; BC – bone conduction.

louder in an ear with a conductive impairment or in an ear with better sensorineural thresholds. This distinction is only possible if the examiner has performed a clinical test of hearing previously and knows which ear is the better-hearing ear.

The test is performed by placing an activated tuning fork over the forehead, on the bridge of the nose or over the incisor teeth. The tuning fork can also be placed in the midline over the vertex of the skull. The patient is asked to identify in which ear the sound is heard or alternatively in which ear the sound is louder. If it is heard in the better-hearing ear, then the poorer ear has a sensorineural impairment. If it is heard in the poorer ear, then it has a conductive impairment.

Unfortunately, the Weber test has a low sensitivity and specificity and is marginally better than chance.[15, 19, 22] It is still in use but this test should not be relied upon, as the chance of accurately and reliably identifying conductive and sensorineural deafness is only 33%.[22]

OVERALL ROLE OF TUNING FORK TESTS

With the general availability of pure-tone audiometry, the distinction between a conductive and a sensorineural hearing impairment should generally be made on a comparison of the air- and bone-conduction thresholds, masked where appropriate. The air–bone gap will also give a measure of the magnitude of any conductive defect, which is essential when assessing the potential role of surgery to improve the hearing. Tuning fork tests should be held in reserve for otoscopically normal ears where satisfactory audiometry is not available to diagnose otosclerosis and should always be interpreted in the light of their generally low sensitivity and specificity.[23]

BEST CLINICAL PRACTICE

- ✓ Wax or pus that obstructs the view of the tympanic membrane is most easily removed by non-specialists by syringing.
- ✓ Wax softeners to aid syringing are of 'benefit' but there is no evidence to support a specific softener. [Grade A]
- ✓ Specialists will frequently use suction with microscopic vision to clear the canal.
- ✓ In otoscopy, the speculum should be as large as practicable.
- ✓ Free-field speech tests with a whispered voice at 60 cm from the ear can be used when audiometry is not available to detect those with a hearing impairment.
- ✓ Tuning fork tests are insufficiently reliable to make a distinction on their own between a conductive and a sensorineural hearing impairment. They are not recommended except when reliable audiometry is unavailable to test an ear that is otoscopically normal, mainly to diagnose otosclerosis. [Grade A]
- ✓ If the middle ear is otoscopically abnormal, there will be an element of a conductive hearing impairment to any hearing loss. In this situation tuning fork tests have minimal added value.

KEY POINTS

- Wax is a normal phenomenon.
- Wax only needs to be removed if it causes deafness or if the patient has symptoms related to the ear and the tympanic membrane cannot be visualized.
- The features of a normal tympanic membrane need to be recognized.
- Structured otoscopy provides a tool to evaluating normal from abnormal.
- Clinical assessment of hearing is useful in the primary care setting as a screening tool for hearing loss.
- The Rinne tuning fork test can distinguish between a conductive and sensineural hearing loss but the Weber tuning fork test has little clinical value.

ACKNOWLEDGEMENTS

Figures 73.2–73.4, 73.6–73.13, 73.15 and 73.16–73.18 are redrawn or reprinted from Wormald PJ and Browning GG, *Otoscopy: a structured approach*. London: Hodder Arnold; 1996.[3]

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CHAPTER 74

FURUNCULOSIS

Malcolm P. Hilton

SEARCH STRATEGY

Data in this chapter may be updated by a search using the keywords: furuncle; ear, external and infection; otitis externa; ear, external and *Staphylococcus aureus*; alone and in combination.

DEFINITION

Furunculosis is a localized form of otitis externa resulting from infection of a single hair follicle. Hair follicles are only present in the lateral (cartilaginous) segment of the external auditory canal. Furunculosis is therefore confined to the lateral canal.

Bacterial invasion of a single hair follicle results initially in a well-circumscribed deep skin infection. As the infection progresses, a pustule forms and this progresses to local abscess formation, often with considerable associated cellulitis and oedema. Bacteria attach initially to the cells of the stratum corneum and proliferate around the ostium of the hair follicle. There is deeper invasion of the hair follicle between the inner and outer root sheath.[1]

DIAGNOSIS

Histology is the reference standard for diagnosis (**Figure 74.1**) but is never obtained in routine clinical practice. Symptoms do not usually discriminate furunculosis from severe diffuse otitis externa. The affected ear is extremely painful, feels blocked and exudes a scanty serosanguinous discharge. The pinna and tragus are tender on palpation. Otoscopic examination may be difficult if the external auditory canal is severely oedematous but usually establishes the diagnosis. Characteristically, the oedema and inflammation are restricted to the lateral segment of the canal, with relative sparing of the medial canal and an unaffected tympanic membrane. If the infection is advanced, the abscess may be seen to be pointing into the canal or have discharged already. If the oedema and secondary cellulitis spread to the post-auricular crease, the condition may be mistaken for acute mastoiditis as the pinna is protruded and swollen. Even very gentle movement of the pinna by the examiner causes pain and tenderness in furunculosis but it is typically painless in mastoiditis. Differentiation can be difficult and there are no good studies to examine the sensitivity and specificity of these clinical findings.[2]

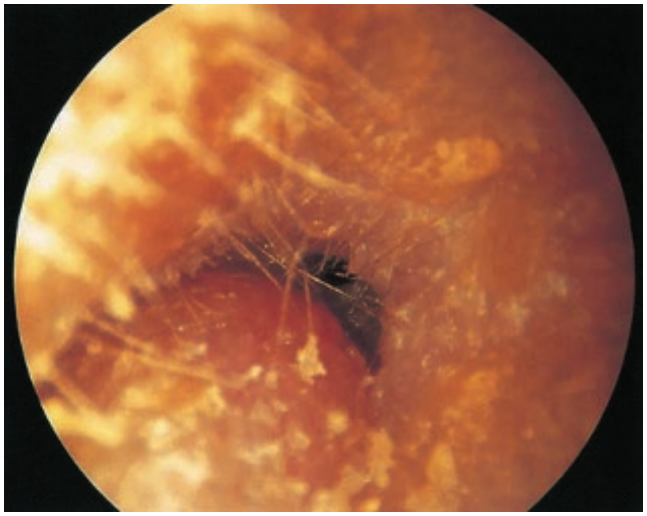

Figure 74.1 Furuncle of the right external auditory canal. Localized rather than generalized oedema of otitis externa. Reproduced with permission from Wormald and Browning, *Otoscopy: a structured approach.* London: Hodder Arnold; 1996.[3]

Samples for bacteriological culture may guide therapy but do not contribute to the diagnosis of the disease.

AETIOLOGY AND EPIDEMIOLOGY

Staphylococcus aureus (*S. aureus*) is the most common organism causing furunculosis. Uncontrolled case series suggest that pathogenic strains of *S. aureus* responsible for furunculosis (at all body sites; not restricted to otological furunculosis) are of different phage types from *S. aureus* causing other skin infections such as impetigo and scalded skin syndrome.[4] The *S. aureus* frequently express genes for Panton–Valentine leucocidin (PVL).[5] *In vitro* evidence demonstrates that leucocidal toxins commonly isolated from pathogenic strains of *S. aureus* trigger lysis of phagocytic cells and may have an important role in cutaneous infection.[6] Sporadic cases of furunculosis happen when pathogenic organisms are introduced into the canal in the context of other local risk factors (e.g. heat, humidity, trauma, maceration).

Recurrent furunculosis presents as repeated episodes of infection at multiple sites. Colonization of the external nares and, less commonly, the perineum with the pathogenic strain of *S. aureus* is also a contributing factor in many cases of generalized recurrent furunculosis.[7, 8] Several conditions appear to be associated with recurrent furunculosis including hypogammaglobulinaemia, diabetes mellitus and dysphagocytosis.

OUTCOMES

If untreated, the infection usually progresses to a localized abscess, which then discharges into the external ear canal. Providing there is adequate drainage, the infection will resolve spontaneously. The infection can also spread towards the deeper tissues, where it may cause a diffuse soft-tissue infection spreading to the pinna, post-auricular skin and parotid gland.

Repeated infection can cause permanent scarring and fibrosis of the external canal with subsequent meatal stenosis. Ultimately, this may also predispose to chronic diffuse otitis externa.

MANAGEMENT OPTIONS

Furunculosis of the external canal is exquisitely painful and appropriate analgesics should be offered to all patients. No evidence exists that compares the efficacy of different analgesics. A recent systematic review of treatment for otitis externa specifically excluded furunculosis from consideration.[9]

Treatment choices include:

- oral or systemic antistaphylococcal antibiotics (penicillinase-resistant penicillin, macrolide, cephalosporin, clindamycin or quinolone)
- topical treatment (antibiotics, astringents, hygroscopic dehydrating agents)
- incision and drainage.

No evidence can be presented on the resolution rate for any individual treatment strategy or to compare the efficacy of different treatment strategies. Oral antibiotic treatment is recommended in the early stages of the disease. Severe spreading soft-tissue infection should be treated with intravenous antibiotic therapy. Abscess formation is an indication for formal drainage. After the abscess has discharged, surgically or spontaneously, topical treatment is preferable. Topical antibiotics active against staphylococcus are usually prescribed. Insertion of a wick into the ear canal facilitates treatment in the presence of severe canal oedema and narrowing. Alternative topical agents are available. Glycerol and ichthammol solution has a specific antistaphylococcal action[10, 11] and is hygroscopic, thus causing dehydration of the canal tissue. Aluminium acetate solution is an astringent as well as a hygroscopic agent.

For patients suffering generalized recurrent furunculosis who are carriers of pathogenic strains of *S. aureus*, each episode of furunculosis is treated on clinical merit but additional therapy should be considered. Options include:

- eradication therapy with nasal mupirocin
- eradication therapy with oral flucloxacillin or azithromycin for 14 days
- bacterial interference therapy: deliberately implanting a non-pathogenic strain of *S. aureus* (strain 502A is the most popular) to recolonize the nares and skin.

All treatments appear to show more rapid and effective resolution of colonization and subsequent infections compared with controls although there is a high spontaneous resolution rate of 75% over 2 years for untreated patients.[12, 13] It has been reported that correction of specific biochemical abnormalities (e.g. hypoferraemia, low serum zinc) may lead to a marked reduction in the frequency of infections.

BEST CLINICAL PRACTICE

- ✓ Furunculosis may be difficult to distinguish from simple but severe otitis externa.
- ✓ Optimum treatment combines specific antistaphylococcus antibiotics, either systemic, topical or in combination, along with topical treatment to reduce the oedema and swelling of the external auditory meatus.
- ✓ Strong analgesia is indicated.
- ✓ Incision and drainage is indicated when an abscess has formed.
- ✓ Eradication of nasal carriage of *S. aureus* should be considered in patients with recurrent furunculosis.

FUTURE RESEARCH

Comparative studies are needed of topical antibiotic/steroid drops (e.g. gentamicin with hydrocortisone) versus glycerol/ichthammol and/or aluminium acetate solution.

KEY POINTS

- Furunculosis is localized otitis externa.
- It is caused by staphylococcal infection of a single hair follicle.
- Oral antibiotics are the treatment of choice before abscess formation.
- Formal incision and drainage are recommended if an abscess forms.
- Severe associated soft-tissue infection or cellulitis is an indication for systemic antibiotic therapy.

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CHAPTER 75

MYRINGITIS

Samuel A.C. MacKeith

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: granular myringitis, chronic myringitis, myringitis granulosa, acute myringitis, bullous myringitis and myringitis bullosa haemorrhagica.

INTRODUCTION

Myringitis is, simply, inflammation of the tympanic membrane. It commonly occurs as part of either acute bullous myringitis or granular myringitis (which is usually described as a chronic disorder). These two terms represent two distinct clinical entities and are therefore considered separately in this chapter.

ACUTE BULLOUS MYRINGITIS

DEFINITION

Bullous myringitis (BM) is an acute inflammatory condition affecting the tympanic membrane (TM) characterized by the presence of bullae or vesicles on the surface of the TM. The bullae may be single or multiple, may affect a segment or the whole of the TM and may even spread on to the adjacent ear canal.[1–4]

PATHOLOGY

The bullae are believed to develop between the middle fibrous and outer squamous layer of the TM due to extravasation of serous fluid or blood, although this has never been confirmed histologically.[4, 5]

AETIOLOGY

The exact aetiology remains unclear. The long-held belief that BM was pathognomonic for mycoplasma pneumonia has been largely dispelled.[3, 6] Most of the evidence suggests the underlying pathogens to be similar to those seen in acute otitis media (AOM), namely bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, beta-haemolytic streptococci, *Moraxella catarralis* and respiratory viruses such as rhinovirus, enterovirus, respiratory syncytial virus, influenza A and parainfluenza virus.[2–5] Interestingly, *Streptococcus neumoniae* is consistently noted as the predominant bacterial pathogen

in BM. In most large case series published, BM is diagnosed with concurrent AOM in almost all (97%) cases.[1] This, in conjunction with the comparable aetiological pathogens, supports the theory that BM may simply represent a severe variant of AOM.[3] In contradiction with this theory is the fact that BM is known to occur (albeit less commonly) in isolation or with external ear canal disease where the pathogenesis may be different. What seems apparent is that the aetiology of BM (as with AOM) is a complex interaction of viral and bacterial pathogens in a susceptible host producing a severe acute inflammatory reaction affecting the TM.

EPIDEMIOLOGY

Although the true incidence is unknown, BM has been reported as occurring in 5.7% of children under 2 years of age in a 1-year follow-up period and in the same cohort to occur in 1 in every 20 episodes of AOM.[1] It is more common during the winter and, though it may occur at any age, it is most prevalent in the age group 2–8 years. This differs from AOM, which is more common in children under 2 years of age.[7, 8]

PRESENTATION

Diagnosis of this condition is clinical. Typically, patients present with sudden-onset severe otalgia, usually unilateral and often in association with an upper respiratory tract infection.[1, 2, 4] In most patients the pain is thought to last only 1–2 days[9] although discomfort may persist for longer, even after rupture of the bulla. A cohort of 2028 children under 2 years of age compared the symptoms of 86 diagnoses of BM (of which 97% had concomitant AOM) with the symptoms of AOM alone. They found symptoms to be more severe in BM, with higher rates of earache (58% vs 29%), fever (62% vs 41%) and excessive crying (80% vs 65%), again suggesting BM to be a severe variant of AOM.

Otoscopy reveals bullae on the TM (**Figures 75.1** and **75.2**). Rupture of the bulla may be associated with scanty serosanguinous otorrhoea, which is usually short-lived due to the absence of a TM perforation. In view of the high incidence of associated middle-ear effusion, conductive hearing loss is very common. However, mixed or sensorineural hearing loss is also well documented.

Sensorineural hearing loss

The prevalence of a sensorineural component to the hearing loss has been reported to occur in 15–66% of cases.[7, 8, 11–14] According to these series, complete recovery of hearing is seen in 57–100% of cases, regardless of treatment. Comparison of these studies is difficult due to significant heterogeneity regarding audiological criteria, follow-up and treatment. A further criticism is that none had pre-existing audiological data, meaning that sensorineural hearing loss (SNHL) which did not improve may in fact be long-standing. In addition, all these reports are in adults. We therefore do not know the patterns of hearing loss in the paediatric population in which this disease is predominant.

The pathogenesis of SNHL in BM is unknown but stapedial reflexes and auditory brainstem responses have implicated the cochlea as the site of the lesion.[8, 15]

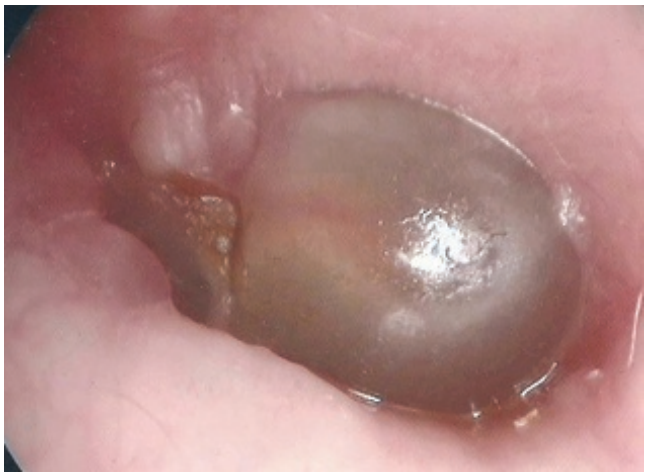

Figure 75.1 A large single bulla arising from the posterior aspect of the left tympanic membrane.

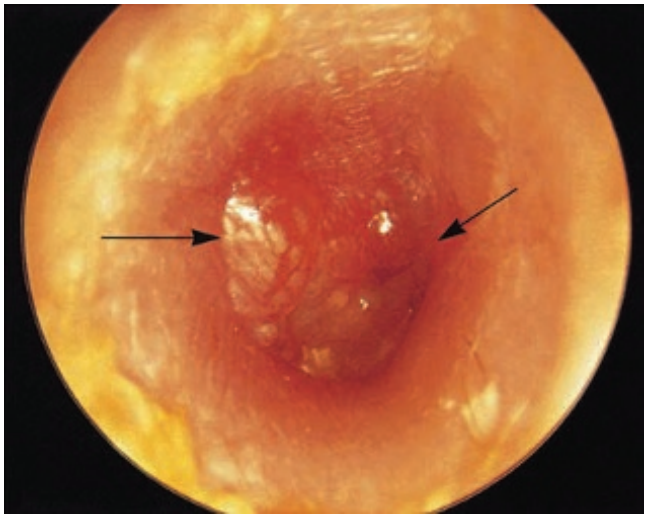

Figure 75.2 Multiple bullae on a tympanic membrane. Reproduced with permission from Wormald and Browning. *Otoscopy: a structured approach.* London: Hodder Arnold; 1996.[10]

Vertigo

Other than in the earliest reports, the presence of vertigo as part of BM has received little attention. However, in 2004 a prospective study showed 7 of 13 patients with BM (54%) reported vertigo at presentation.[13] Of the 13, 11 had abnormal electronystagmography, including 4 who did not complain of vertigo. In this cohort, a sensorineural component of hearing loss was seen in 82%. Again, the aetiology is unknown.

TREATMENT

There is no consensus, nor good evidence, to inform best practice in BM. In the majority of cases it is a self-limiting disease with spontaneous resolution of symptoms. The large case series in paediatric populations, demonstrating comparable aetiology with AOM and suggesting a possible common disease process, has supported the practice of management as for AOM.[2, 3, 9] Symptomatic treatments described include analgesia, warm compresses and incision of bullae. The third of these is of unproven benefit and may have a risk of secondary infection. The use of topical local anaesthetics has also been described.[16]

The frequent finding of inner ear involvement identified in adult case series is associated with more aggressive medical treatment, usually with broad-spectrum oral antibiotics.[4] In addition, the management of sudden-onset SNHL in association with BM has been treated by some authors with high-dose oral steroids as they would for isolated sudden-onset SNHL. Eliashar et al. treated all BM patients with an SNHL component with admission, oral steroids and carbogen, with complete recovery of hearing in 86%.[13] Drendel et al. reported 13 cases of BM with a SNHL component to their hearing loss, nine received steroids, of which five made a complete recovery and four only a partial recovery.[14] The four patients with a SNHL component who did not receive steroids all made a complete recovery.

Only one study has compared systemic antibiotics alone versus systemic antibiotics and steroids.[17] This did not demonstrate improved hearing outcomes with the addition of steroids. However, given the small sample size (23 patients), this may be subject to type 2 error. Therefore, currently there is insufficient evidence to determine the effectiveness of steroids as a treatment of SNHL in BM.

GRANULAR MYRINGITIS

DEFINITION

Granular myringitis (GM) can be defined as a chronic inflammatory disorder characterized by de-epithelialization of the outer (squamous) layer of the tympanic membrane (TM) and replacement with granulation tissue, all in the absence of middle ear disease.[18, 19]

PATHOLOGY

Histology has demonstrated oedematous granulation tissue with capillaries and diffuse infiltration of chronic inflammatory cells.[20]

AETIOLOGY

Aetiology is unknown but it has been suggested that non-specific injury to the lamina propria, such as trauma or infection, may impair epithelialization and promote granulation tissue formation.[20] This theory may be supported by the high incidence of myringitis following myringoplasty (5.5%) and the fact that in some series of GM nearly all patients had had prior otological surgery (93%).[18, 21]

The common finding of positive cultures from affected ears (*Pseudomonas aeruginosa*, *Staphylococcus aureus* (including MRSA), *Corynebacterium*, *Proteus mirabilis*, fungal species), in addition to the success of antimicrobial treatment, implicates the contribution of infection to the aetiology.[20, 22, 23]

PRESENTATION

Clinically this condition may be defined as persistent inflammation confined to the squamous layer of the TM for at least 12 weeks.[21]

Most patients present with persistent or recurrent painless otorrhoea, which may be malodorous.[18] In one study 70% of these patients had had symptoms for more than 1 year.[22] Other symptoms include intrameatal itch or fullness, mild conductive hearing loss and rarely otalgia. Some patients may be asymptomatic.

Following microsuction of otorrhoea, examination reveals granulation tissue/polyp replacing normal squamous epithelium on a sometimes thickened TM. Granulation can be localized to part of the TM (focal/segmental) or diffuse (**Figures 75.3** and **75.4**).[18, 19] The segmental type is more common, with the posterosuperior segment of the eardrum most frequently affected.[24] It may also involve the skin of the adjacent medial ear canal.

It is important to differentiate GM from other causes of chronic otorrhoea. Furthermore, most definitions of GM exclude patients with perforation or cholesteatoma.

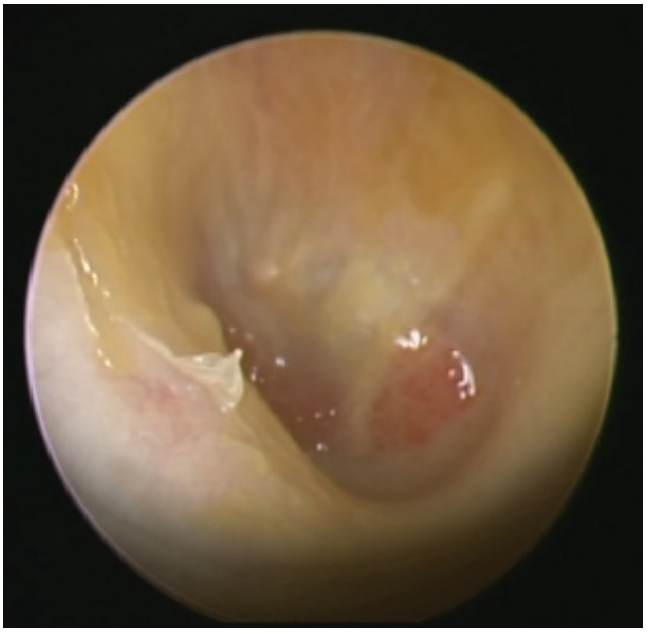

Figure 75.3 Focal areas of granular inflammation affecting the anteroinferior and posteroinferior aspects of the left tympanic membrane with active inflammation and pus.

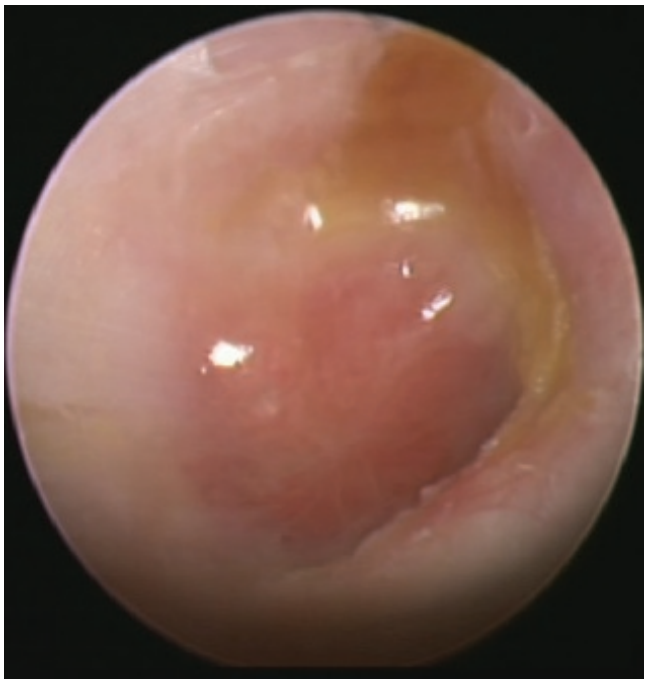

Figure 75.4 Diffuse granular myringitis affecting the entire right tympanic membrane.

INVESTIGATIONS

A swab should be taken for microscopy, culture and sensitivities to guide any antimicrobial treatment. Pure-tone audiometry and tympanometry may help to identify associated hearing loss or middle ear pathology. Occasionally, CT temporal bone may help exclude underlying middle ear/mastoid disease. Some published series include normal type A tympanogram and a normal CT as essential diagnostic criteria in GM.

Biopsy to exclude malignancy should be considered if there are concerning features such as significant otalgia or non-resolution despite treatment.

COMPLICATIONS

The natural history of this condition is difficult to determine as patients may be asymptomatic despite continued myringitis. However, we know that many patients have symptoms persisting for years.[18] This long-standing chronic inflammation of the TM and medial ear canal wall skin, in association with proliferating granulation tissue, can lead to fibrosis, scarring and stenosis of the medial ear canal with lateralization of the eardrum.[25] Although these sequelae may resolve any otorrhoea, there is likely to be a significant resultant conductive hearing loss.

MANAGEMENT

Most would agree that meticulous microscopic cleaning/debridement in combination with topical antibiotic or antiseptic agents forms the mainstay of initial management. Treatment is often more prolonged than for other types of otitis and recurrence is relatively common. A plethora of published treatment strategies exist. These can broadly be grouped into:

- topical antibiotic and antifungals, often with a steroid/anti-inflammatory agent
- topical antiseptic agents: acetic acid, aluminium acetate, phenol, hydrogen peroxide
- debulking of granulations with cold steel (curettage/cupped forceps), silver nitrate cautery or laser debridement/resurfacing
- surgical excision with grafting (onlay skin graft, temporalis fascia/perichondrium underlay technique).

A systematic review published in 2008 found 46 potentially relevant studies of which only two met the inclusion criteria.[19] The two non-randomized studies included in the review are summarized in Table 75.1.

This review concluded that, although there is insufficient evidence to support any particular management strategy, 'conventional topical antibiotic and steroid drops appear less efficacious that other treatment modalities'. In addition, dilute vinegar solution is an effective simple alternative to topical antibiotic drops.[23, 24]

Subsequent to this review, further published case series have shown good results with antiseptic topical preparations, CO_2 laser resurfacing as well as more aggressive surgical excision with overlay myringoplasty.[22, 26, 27] In addition, there has been a double-blind randomized controlled trial which compared topical 5-fluorouracil to placebo (petroleum jelly).[28] Unfortunately, as this is not a commonly used preparation and has not been compared

TABLE 75.1 Summary of the two studies included in the 2008 review of management options

Study	Design/Level of evidence	Sample size	Intervention group	Control group	Follow-up	Outcome
Jung et al. (2002)[23]	2b	30	Topical vinegar (acetic acid pH 2.43)	Topical ofloxacin	>6 months	Faster symptom resolution and reduced recurrence with topical vinegar
El-Seifi and Fouad (2000)[24]	2c	74	Surgical excision of granulation tissue with tragal cartilage underlay graft	Topical acetic acid with antibiotic/steroid drops	>6 months (average 6.25 years)	Reduced recurrence with surgery compared with topical treatment

with other more commonly used treatment modalities, it is of limited clinical utility.

In summary, there is a wide range of potential treatment modalities which have been found to be effective, but unfortunately all have reported problems with recalcitrant or recurrent cases. More recently, published studies are demonstrating the benefits of antiseptic agents in preference to antibiotic drops. Many clinicians may use more than one strategy, reserving more aggressive surgical management for recalcitrant cases as there may be a higher rate of subsequent perforation with these techniques.

FUTURE RESEARCH

- ➤ Further research is required to identify optimal treatment of BM especially when complicated by SNHL.
- ➤ Given the association of GM following otological surgery, research to identify operative risk factors for development may help reduce the incidence.
- ➤ Quality randomized controlled trials are required to compare the topical treatments most commonly used in GM.

KEY POINTS

- Bullous myringitis represents an acute severe inflammatory reaction affecting the TM.
- Aetiological pathogens in BM are similar to those in AOM.
- Inner ear involvement with SNHL (and vertigo) is not uncommon in BM and usually resolves spontaneously.
- As BM is usually a self-limiting disease, the mainstay of treatment is symptomatic. The optimal management of associated hearing loss, however, remains to be elucidated.
- Granular myringitis is a chronic condition usually presenting with otorrhoea.
- In GM, de-epithelialization of the outer layer of the TM and replacement with granulation tissue occurs in the absence of middle ear disease.
- Treatment of GM usually involves topical antimicrobial or antiseptics often for prolonged periods.
- More aggressive physical debulking or surgical excision and grafting is usually reserved for recalcitrant cases of GM.

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CHAPTER 76

KERATOSIS OBTURANS, PRIMARY AUDITORY CANAL CHOLESTEATOMA AND BENIGN NECROTIZING OTITIS EXTERNA

Tristram H.J. Lesser

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: keratitis obturans, wax keratosis, external auditory canal cholesteatoma, external auditory meatus cholesteatoma, external ear cholesteatoma, osteomyelitis of the ear, benign otitis externa, benign necrotizing otitis externa, osteonecrosis and ear canal necrosis, tympanic bone and epithelial migration of the ear. This was supplemented by obtaining all the references quoted in the papers. Sixty-six papers were considered after removing non-relevant papers and repeats. The only evidence found was in observational studies and from expert opinions.

DEFINITIONS

Keratosis obturans (KO) is a different clinical and pathological entity from primary auditory canal cholesteatoma (ACC) and benign necrotizing otitis externa (BNOE) (Table 76.1). There is a less clear distinction between ACC and BNOE. While ACC and BNOE are different diseases, they may have similar aetiologies and are not separated from each other by an identified abnormality. Whereas KO, is separated by having a specific deficit of the epithelial migration.[1,2]

The 1980s saw the definition of the difference between KO and ACC, and articles before then on KO contained some cases that were probably primary ACC and vice versa. More recent articles on necrotizing otitis externa (NOE) and ACC still contain cases that could be NOE or ACC in the same series and this may represent a clinical and pathological overlap.

Keratosis obturans is the accumulation of a large plug of desquamated keratin in the external auditory meatus.

Primary auditory canal cholesteatoma is the invasion of squamous epithelium into a localized area of bony erosion with or without bony necrosis.

Benign necrotizing otitis externa is the formation of an avascular bony sequestrum of the inferior tympanic bone with secondary inflammation of the overlying soft tissue and skin.

PATHOLOGY

In KO, a geometrically patterned keratin plug within the lumen of an expanded external auditory canal is seen (Figure 76.1). The keratin squames are shed from the complete circumference of the deep ear canal forming a lamina (onion skin) arrangement.

In primary ACC, the keratin is derived primarily from a sac that involves the bone of the ear canal with bony fragments within it and random keratin in the lumen of the ear canal. Keratin is found deep to the bone fragments.[3]

In BNOE the necrotic sequestrum of bone appears to involve the superficial cortical layer primarily.[4] Histology of the bone reveals dead lamellar bone with inflammatory

TABLE 76.1 Differential diagnosis of non-neoplastic conditions eroding the bony external auditory canal, with their clinical characteristics

	Keratosis obturans	Auditory canal cholesteatoma	Benign necrotizing otitis externa	'Malignant' necrotizing otitis externa
Aetiology	Abnormal epithelial migration	Abnormal bone leading to epithelial migration into bone	Avascular bone leading to inflammation of overlying skin	Immunocompromised Patient with necrotic bone in ear canal
Symptoms and findings	Severe otalgia Conductive hearing loss Lung or sinus disease Younger Occasionally bilateral	Otalgia mild No hearing loss Itchiness Older Usually unilateral Blocked feeling	Chronic painless infected otorrhoea Partial response to previous treatment Localized exposed bone in canal 3–10 mm diameter Dehiscent skin	Severe penetrating pain Cranial nerve palsy Diabetic/renal failure or otherwise immunosuppressed Raised inflammatory markers
Pathology	Keratin plug Tympanic membrane thickened Widened deep canal Hyperaemia of skin canal with granulations	Keratin in random pattern Tympanic membrane normal Localized osteitis/erosion of ear canal usually posterioinferior Sequestration of bone	Chronic inflammation with no associated keratin and no cholesteatoma deep to sequestrum Commensals on bacteriology	Chronic inflamation *Pseudomonas aeruginosa*
Treatment	Remove plug Treat granulations Occasionally biopsy	Surgically remove cholesteatoma graft with cartilage and fascia Biopsy	Conservative initially Surgical removal of sequestrum	Treat cause of immunosuppression High-dose antibiotics Long-term antibiotics Surgical debridement
Differential diagnosis	Wax impaction with infection Otitis externa Neoplasm	Necrotizing otitis externa Neoplasm	Auditory canal cholesteatoma Neoplasm Malignant otitis externa	Malignant neoplasm

Note: Modified from Shire JR, Donegan JO. Cholesteatoma of the external auditory canal and keratosis obturans. *Am J Otol* 1986; **7**: 361–4, by kind permission of Lippincott, Williams & Wilkins.[2]

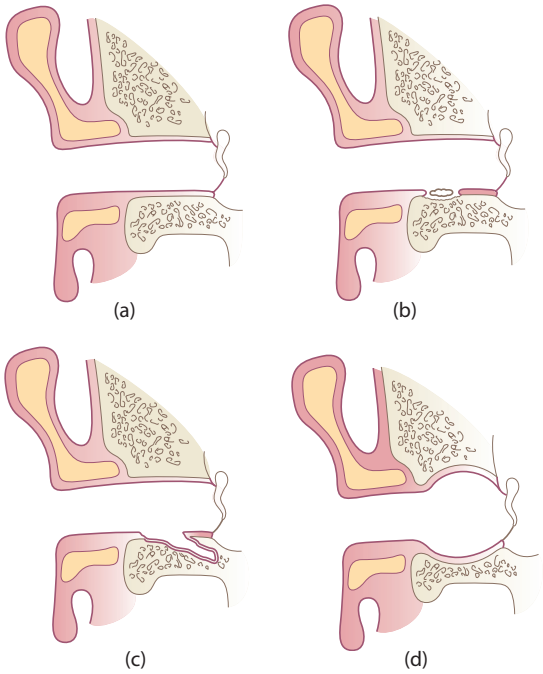

Figure 76.1 **(a)** Normal external auditory canal. Cartilage is shown in yellow, bone is stippled, and canal skin is shown as a line. **(b)** Benign necrotizing otitis externa. Note the deficient area of skin, and bony sequestrum. **(c)** Canal cholesteatoma. A sac of canal skin invades bone. **(d)** Keratosis obturans. The bony canal is 'ballooned' out.

cells filling the marrow spaces.[5] There are limited chronic inflammatory changes of the adjacent skin and subcutaneous tissue.

BACTERIOLOGY

In all three conditions skin flora and a wide range of bacteria may be cultured: *Proteus mirabilis*, *Staphylococcus epidermidis*, *Klebsiella pneumoniae* and betahaemolytic streptococci are found, but generally no *Pseudomonas* species. *Staphylococcus aureus* is the most frequent isolate.

AETIOLOGY

It is thought that KO is due to abnormal epithelial migration of the ear canal skin.[6] One case report found that the epithelium moved in an anterior direction across the whole drum. Another case that was not typical of KO but had a need for repeated aural cleaning had a grossly abnormal migratory pathway. The movement of the surface epithelium of the pars flaccida was reversed such that it migrated downwards to the pars tensa and then moved inferiorly across the whole drum.[7]

A condition called 'keratosis tympanicum' has been described with similar abnormal epithelial migration

associated with unilateral tinnitus.[8] It is not certain that these two diseases are related or that all cases presenting with KO are the same disease.

It has been suggested that there may be two types of KO. One is of an inflammatory nature which occurs secondary to an acute problem, such as a viral infection, causing inflammation of the ear canal which temporarily alters the epithelial migration. This is cured by removal. The second or the silent type is a disease that persists and is caused by abnormal separation of the keratin that continues even after the first removal and will need subsequent removals.[6]

The aetiology of external ACC is uncertain, but in some of the series primary ACC is post-traumatic or post-surgical (e.g. stapedectomy cases). It has been postulated that a piece of exposed bone of the primary auditory canal becomes infected and sequests, the epithelium migrates into this bony abnormality and the cholesteatoma is formed. Primary ACC is distinguished from cholesteatoma that arises secondary to a previous ear canal insult. Many authorities believe that idiopathic external ACC results from a reduced migratory capacity of the canal epithelium, which leads to 'keratinization *in situ*'.[9–15] This view has been challenged, however, by a study which showed no difference in the rate of epithelial migration between normal ears and those affected by external ACC.[16]

In some cases the occurrence of external ACC has been linked to branchial arch anomalies, which result in the retention of epithelial masses and lead to cholesteatoma formation in the floor of the external auditory canal.[17]

The cause of the necrotic bone in BNOE is unknown.[18] Theories relating to vascular insufficiency began with Goufas in 1954.[19] It is often stated that the tympanic bone is particularly susceptible to osteonecrosis because of its 'relatively poor blood supply'. The microangiopathy of diabetes has been advanced but there is only a little evidence that BNOE is more common in diabetics, as opposed to the 'malignant' form. Small arterial emboli have been suggested. Repeated local trauma, for example ear bud abuse, picking of the ear or the use of hearing aids, is a popular theory.[20] Bharadwaj et al. suggested association with respiratory tract inflammatory conditions is difficult to support. Bottari proposed 'neurotrophic disturbances'.[18, 21]

The overlap between ACC and BNOE if it exists is uncertain and has yet to be defined fully.[22]

The aetiology of BNOE may have some similarity with 'malignant' NOE.[23] As the tympanic plate appears to have a relatively poor blood supply, the additional microangiopathy in diabetes, as mentioned above, may predispose it to avascular necrosis and the formation of bony sequestra. The high sugar content of the bone may encourage *Pseudomonas* to grow. A similar pathogenesis is found in radionecrosis of the tympanic bone with a slowly progressive obliterative endarteritis.[24] Although diabetics may have a slightly higher incidence of BNOE as well as 'malignant' NOE, the pathogenesis of the avascular necrosis of the tympanic bone is not clear.[25]

CLINICAL SYMPTOMS

The clinical symptoms are different in KO and ACC/BNOE.

KO occurs more commonly in younger patients. It classically presents with acute severe otalgia and a conductive hearing impairment. Infrequently, the disease is bilateral. There may be an associated bronchiectasis or sinusitis.[26, 27] Many of the patients in the historical papers had a condition called 'wax keratosis', which is thought to be becoming less common as the associated lung disease and sinusitis are now better controlled. These are historical papers that may not agree with the current clinical presentation of KO.

ACC and BNOE have a similar set of clinical findings. The most common presentation is chronic otorrhoea with dull pain or itching. It is not associated with hearing impairment. Bilateral cases account for around 1 in 6–12 cases.[28, 29] A review of published case series concluded that the most common presenting symptoms of idiopathic external ACC are unilateral otorrhoea with mild to moderate otalgia.[12] A minority of patients complained of unilateral hearing loss, or were asymptomatic with the cholesteatoma being discovered on routine otoscopy performed for a separate indication.

INVESTIGATION

The primary investigation of these patients is microscopic examination of the ear either in the clinic or under general anaesthetic. In KO, the ear canal can become grossly widened or ballooned such that the tympanic membrane is left standing out in relief in a widened ear canal (**Figure 76.2**). In ACC the cholesteatoma is able to be suctioned (**Figure 76.3**) and has fragments of bone within it, and there may be some granulation tissue which needs biopsy. In BNOE the covering on the floor of the ear canal is deficient with granulations around the edges of the epithelial defect, yellow necrotic bone in the bare area with small necrotic fragments (**Figure 76.4**).[30]

Computed tomography of the temporal bones has become accepted as the gold standard for staging and preoperative planning in external auditory canal destructive disease.[32] This method allows accurate evaluation of the extent of local bone erosion and involvement of adjacent structures. Should surgery be contemplated for BNOE, a CT scan may be indicated in order to identify the extent of bone necrosis.

If gross infection is present, a pus swab may be taken. If *Pseudomonas* is cultured, the diagnosis should be queried in favour of 'malignant' NOE. If prominent inflammatory or granulation tissue coexists, chronic 'granulomatous' conditions including syphilis and tuberculosis should be excluded.

Audiometry should be normal or show a mild conductive hearing impairment in ACC and BNOE but will show a marked conductive hearing loss in KO.

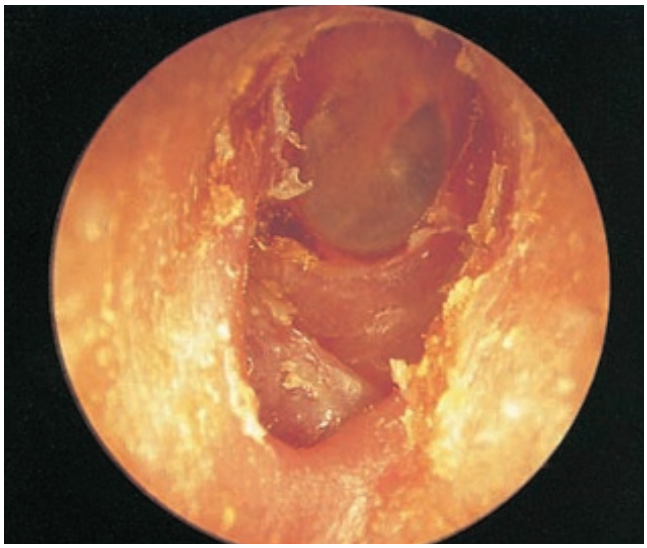

Figure 76.2 Keratisis obturans. The keratoma has been removed from the right ear with KO and shows expansion of the bony canal just lateral to the tympanic membrane. Reprinted with permission from Wormald and Browning. *Otoscopy: a structured approach.* London: Hodder Arnold; 1996.[31]

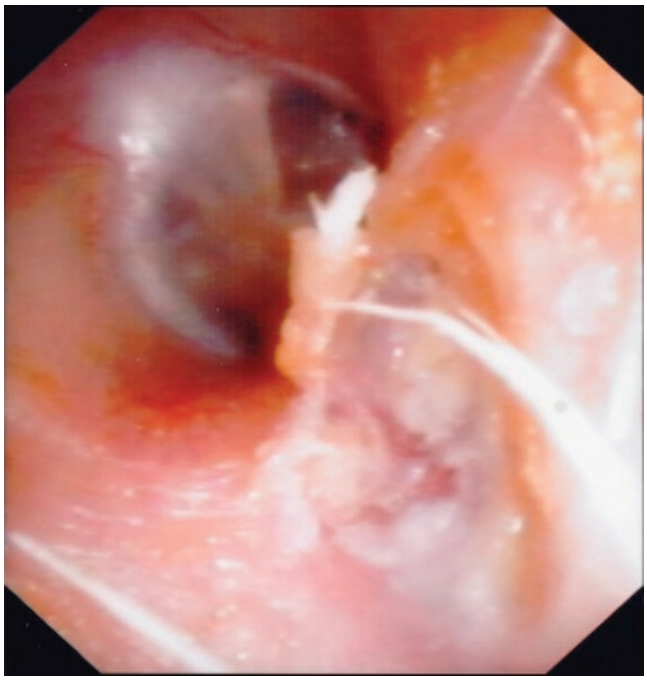

Figure 76.3 Cholesteatoma of the auditory canal after suction.

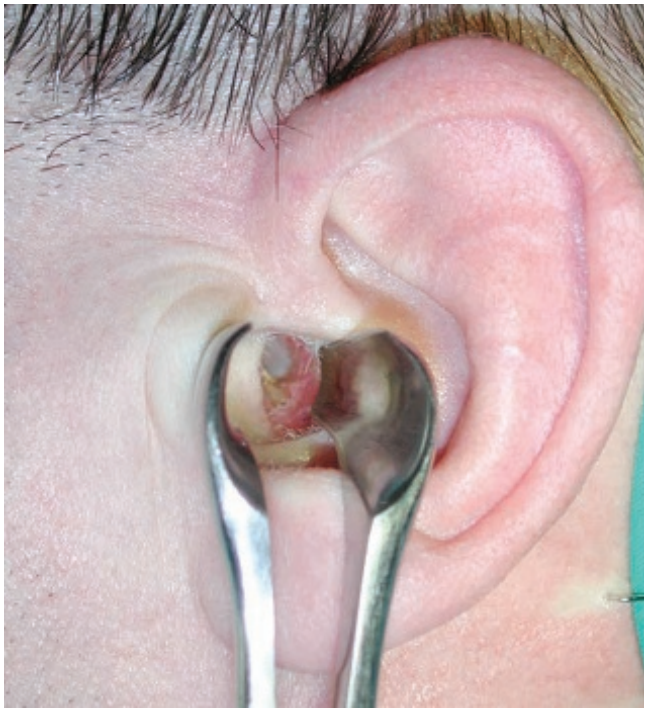

Figure 76.4 Typical appearance of benign necrotizing otitis externa. An area of denuded necrotic bone is visible in the floor of the bony external auditory canal.

BIOPSY

Histological examination of any granulation tissue is required to exclude malignancy, as the differential diagnosis will include carcinoma of the ear canal, 'malignant' NOE and benign neoplasm that has secondary infection in the external auditory canal.

EPIDEMIOLOGY

The frequency of primary ACC has been estimated as one in 1000 new otological cases and for every case of primary ACC there are four or five cases of KO.[33] BNOE is probably the most common of the three diseases.

NATURAL HISTORY AND COMPLICATIONS

Little is known of the natural history of these diseases. Sporadic reports demonstrate that normal ear canals can suddenly develop these conditions; for instance, KO can occur in either previously normal ears or in ears that have had plugs of keratin needing removal beforehand. KO can cause extensive bony erosion, including automastoidectomy.[7] There are no reports of intracranial complications from this disease. In ACC erosion through the anterior wall of the canal may affect the temporomandibular joint and rarely, in advanced cases, extension into the posterior fossa has been reported with resulting intracranial abscess.[34]

EXTERNAL AUDITORY CANAL CHOLESTEATOMA STAGING

There are two staging systems for ACC but none for the other two diseases.

Nairn et al. external ACC staging is based on the proposal that there is a preclinical disease. Stages I and II will not usually present as the disease of ACC.[15]

Nairn et al. staging:[15]

I	Epithelial hyperplasia
IIa/b	Periostitis hyperplasia with erythema (a), or denuded but not eroded bone (b)
III	Canal wall erosion and bony sequestrum
IV	Invasion into adjacent structures

Subclasses of disease stage IV include: mastoid (M), skull base and sigmoid sinus (S). temporomandibular joint (J), and facial nerve canal (F).

Seung-Ho Shin et al. clinical and radiological staging:[32]

I	Limited to the external auditory canal
II	Invades the tympanic membrane as well as ear canal
III	Creates a defect of the EAC and involves the cortex of mastoid bone
VI	Involves areas beyond the temporal bone (**Figure 76.5**)

This classification also includes treatment suggestions, as follows:

I	with local care or canaloplasty
II	with canaloplasty + tympanoplasty
III	with the above and mastoidectomy and canal wall reconstruction
IV	with removal of cholesteatoma using various techniques.

MANAGEMENT OPTIONS

The pain and deafness associated with KO mean that it is necessary to remove it, often under general anaesthetic. Canaloplasty has been suggested for recurrent KO with good results.[29] For ACC, conservative treatment is used where the extent of the cholesteatoma erosion can be seen (**Figure 76.6**). When this is not possible, patients are treated with excision of necrotic bone and cholesteatoma via the mastoid and repair of the defect using temporalis fascia.[35] The only other treatment suggested is a canal wall-up procedure with repair of the defect, but no long-term follow-up is available of such patients.

In BNOE conservative management consists of removing the bony sequestrum once it separates spontaneously,

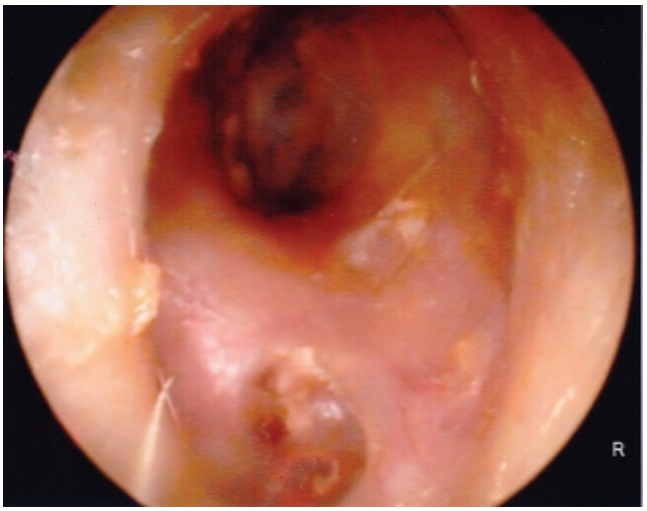

Figure 76.6 Healing cholesteatoma of the ear canal after conservative treatment.

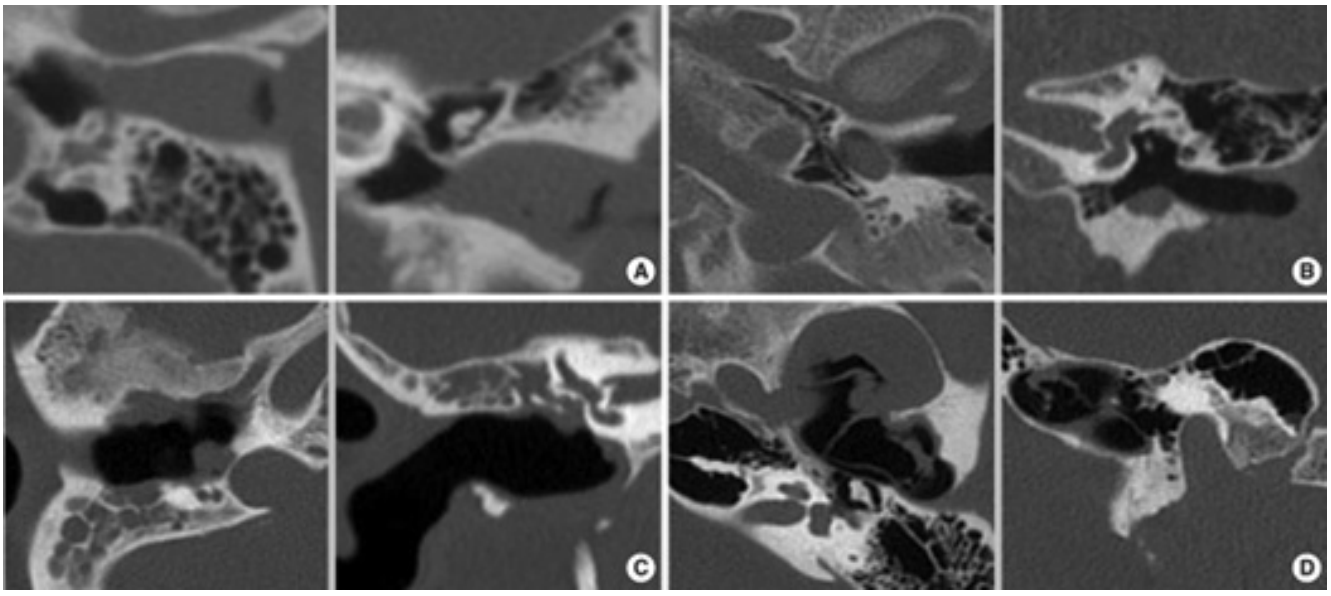

Figure 76.5 Radiology of the stages of ACC: A = I; B = II; C = III; D = VI. Reproduced from Shin et al. Classification of external auditory canal cholesteatoma by computed tomography. *Clin Otorhinolaryngol* 2010: **3**: 24–6.[32]

with local toilet and local treatment to control any infection. An oral antibiotic may be used.[22] Speculation based on a series of eight patients is that younger patients (less than 60 years) are more likely to respond to conservative management. Separation of the sequestrum, followed by epithelial growth to cover the bony defect, as encouraged by conservative management, is the most likely outcome.[21]

A more aggressive surgical approach has been advocated, with early surgical removal of the sequestrum down to healthy bone.[5, 25] Adjunctive hyperbaric oxygen may be considered when there is progression despite intensive local and systemic treatment and when there is necrosis beyond the tympanic plate.[4]

Treatments for these conditions are reported to be effective.

BEST CLINICAL PRACTICE

- ✓ Microscopic examination should be carried out in the clinic or under general anaesthetic.
- ✓ CT scan should be used for primary ACC.
- ✓ Biopsy should be undertaken to exclude carcinoma.
- ✓ Removal of the plug of keratin should be carried out in KO.
- ✓ Surgical removal and repair should be performed in primary ACC.
- ✓ Conservative treatment of BNOE is usually adequate providing 'malignant' otitis externa has been ruled out.
- ✓ Osteoradionecrosis, chronic inflammatory conditions and benign tumours should be excluded.
- ✓ These conditions may all resolve spontaneously or with local toilet and care.

FUTURE RESEARCH

- ➤ The true incidence of these diseases is not known.
- ➤ The clinical courses are not well defined.
- ➤ Further work needs to be undertaken to determine the aetiologies of these diseases and any relationship to abnormal epithelial migration and vascular insufficiency.
- ➤ The relationship between ACC and BNOE is uncertain.
- ➤ The relationship and possible shared aetiology between BNOE and malignant NOE is likewise uncertain.
- ➤ The rarity of the conditions makes level 1 or 2 evidence for treatment difficult to obtain.

KEY POINTS

- Primary ACC, KO and BNOE are different diseases.
- KO occurs in younger patients, presents with pain, may be associated with sinusitis or bronchitis, may be associated with disordered epithelial migration, either temporary or permanent, and is treated with removal of the keratin plug.
- Primary ACC is more common in the elderly, may be traumatic, presents with otorrhoea and itching and minimal hearing loss, and is treated with permeatal or mastoid surgery to remove the disease.
- BNOE is probably more common and has similar clinical presentation to ACC but may need less radical treatment.

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CHAPTER 77

ACQUIRED ATRESIA OF THE EXTERNAL EAR

Jonathan P. Harcourt

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: external ear, external ear canal, acquired and atresia.

DEFINITION

Atresia is defined as the absence of or closure of a passage of the body. This covers both congenital and acquired lesions. Tos[1] defines acquired atresia of the external ear as 'intraluminal sequelae of either intraluminal or extraluminal processes of varying aetiology, resulting in a blind sac in the external acoustic meatus'.

Atresias may be solid or membranous.

- **Solid atresia** consists of a continuous block of fibrous or fibrous and bony material which is continuous with the structure of the tympanic membrane and is of variable extent. The face of the solid atresia may be blunt or tapering, producing a funnel-shaped medial aspect to the lumen of the ear canal (Figures 77.1 and 77.2).
- **Membranous atresia** is typified by fibrous tissue that has a covering of ear canal skin on both sides, thus separating the ear canal into a medial and lateral segment (Figure 77.3). The medial part inevitably collects keratin from desquamation of the skin; this may become an erosive process and thus be defined as an external canal cholesteatoma.

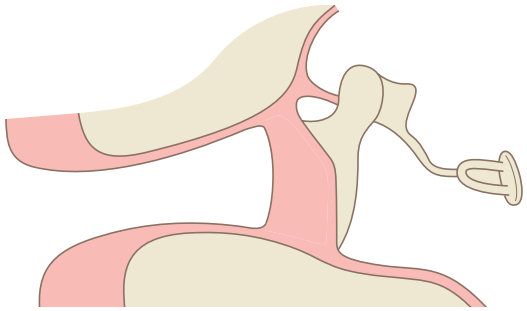

Figure 77.1 Solid atresia, obliterating the medial aspect of the bony external ear canal.

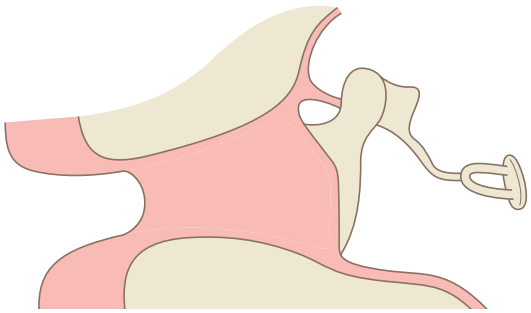

Figure 77.2 Extensive funnel-shaped solid atresia.

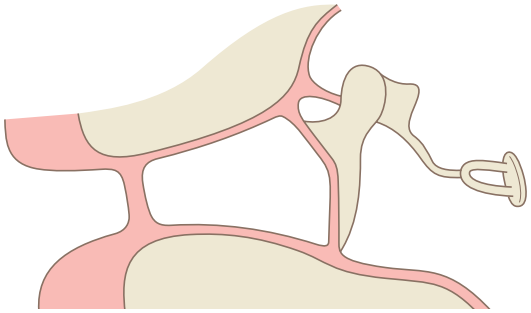

Figure 77.3 Membranous atresia in lateral external ear canal.

DIAGNOSIS

The clinical diagnosis of acquired atresia is supported by the use of CT scanning which gives a very detailed image of the bony and soft-tissue structure of the external ear. Figures 77.4 and 77.5 show examples of medial and mid-canal atresias. It particularly helps in the differentiation of solid and membranous atresia. This is an important distinction as there may be a substantial divergence of management between these two entities. Solid atresia is a safe form of ear disease, whose surgical treatment is very challenging. Membranous atresia will inevitably produce associated cholesteatoma and therefore erosion of local structure. Surgical outcome is superior to solid atresia.

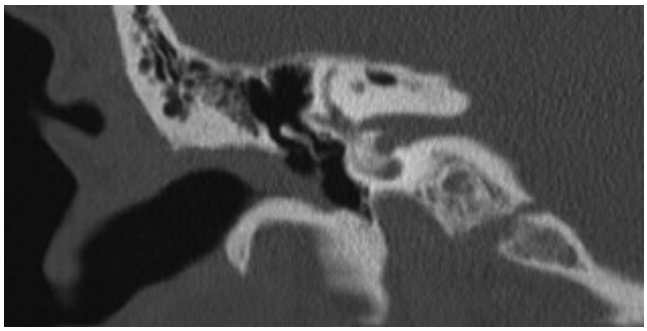

Figure 77.4 Coronal CT of right external ear canal showing medial atresia.

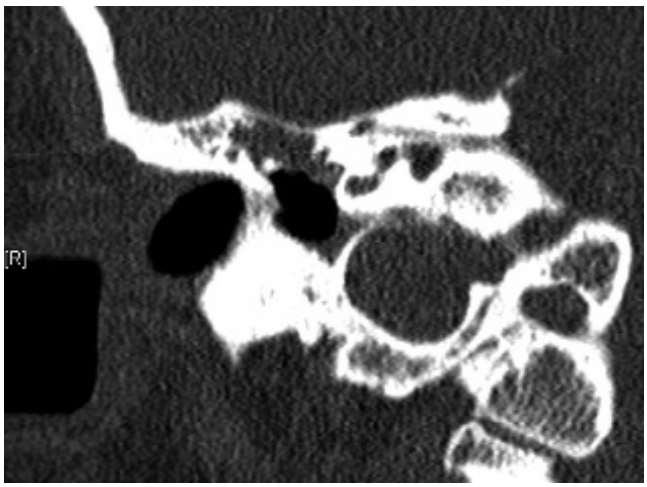

Figure 77.5 Coronal CT scan of right external ear canal showing lateral predominantly membranous atresia. The patient had undergone previous surgery for chronic otitis media.

AETIOLOGY

Acquired atresia may be caused by the following processes:[2]

- **Inflammation**, which may be as a result of :
  - otitis externa
  - psoriasis, eczema and other dermatological conditions
  - active chronic otitis media
- **Trauma**, by various mechanisms:
  - open injury, especially gunshot wounds
  - closed fracture of the tympanic plate, particularly associated with frontal facial injuries when the mandibular condyle is forced backwards through the anterior wall of the external ear canal
- **Burns**, which may be thermal, chemical, electrical or post-irradiation in nature
- **Surgery**. Any operation involving a meatal approach (tympanoplasty, etc.) has a remote risk of solid atresia but particularly with on-lay techniques. Meatal surgery (removal of an osteoma) may also precipitate membranous atresia in the lateral canal.

Pathogenesis

The pathogenesis of solid and membranous types differs.

SOLID ATRESIA

In cases associated with otitis externa or media the key development is of granular medial otitis externa with granulations of the tympanic membrane that persist for many months in spite of treatment. The granulations become fibrotic and the eardrum becomes thickened as the medial meatal mass is re-epithelialized. This process can be repeated again and again. If it is associated with active chronic otitis media, the granulations appear around the tympanic membrane perforations and eventually lead to closure of the defect before the process extends laterally as described above.

MEMBRANOUS ATRESIA

This originates in the lateral meatus as a web formation[2] which is precipitated by a circular irritation from inflammation, trauma or burns and ulceration of the skin around the entire circumference of the external ear canal. The web-like stenosis forms after fibrosis and re-epithelialization as with solid atresias. Repeated attacks or one massive injury such as a tympanic plate fracture leads to a complete atresia.

EPIDEMIOLOGY

Becker and Tos[3] estimated an annual incidence of 0.5 per 100 000 based on clinical presentation of cases over 26 years in a centralized otology practice in Denmark. The vast majority of cases were solid fibrous atresias and only a few were membranous, making the incidence of typical membranous atresias 20 times smaller than that of the solid form.

NATURAL HISTORY AND COMPLICATIONS

Once solid atresia has formed, though there may be further episodes of medial granulating otitis externa, fibrosis and re-epithelialization, overall there is a change from a 'wet' to a 'dry' phase. In the latter situation the principle

complaint is of conductive hearing loss and this is generally a stable situation. Membranous atresia is associated with medial cholesteatoma, which can potentially produce local erosion and complications. This is usually of a broad slow erosive nature, similar to keratosis obturans.

MANAGEMENT OPTIONS

Medical

During the wet phase, the medial granulations can be removed by aspiration and cauterization with silver nitrate or trichloroacetic acid and the ear packed with ribbon gauze or a wick. This local treatment may turn the ear dry and prevent further progression of the atresia.[4]

The conductive hearing loss (if bilateral) may be managed by an air-conduction hearing aid though the presence of a mould in the external ear canal can aggravate the process and lead to the ear becoming or persisting in an active state. A bone-anchored hearing aid is an alternative when a conventional air conduction device is not tolerated.

Surgical

FIBROUS ATRESIA

The principle of surgery for fibrous atresia is to remove the fibrous tissue by elevating it from the ear canal bone, the fibrous annulus and lamina propria of the tympanic membrane (Figure 77.6a). In most cases access is adequate via a speculum inserted into the external ear canal, though an endaural or retroauricular approach may be utilized. A circumferential incision is made lateral to the blunt face of the atretic plate and a plane of dissection developed between the bone of the ear canal and the canal skin, followed by the atretic plate and finally lateral to the fibrous annulus and lamina propria of the tympanic membrane (Figure 77.6b). The epithelial defect is repaired by a fine split-skin graft (SSG) which may be laid in single or multiple pieces (Figure 77.6c). A silastic disc or tube may be inserted to stabilize the epithelial surface and finally the ear canal is packed with ribbon gauze soaked in antiseptic. The ear canal requires regular suction toilet and may need repacking to prevent medial granulation and early recurrence of the atresia. This is also prevented by careful removal of all fibrous tissue with exposure of the entire circumference of the fibrous annulus. This allows stable long-term results.[3]

MEMBRANOUS ATRESIA

Similar to fibrous atresia, membranous atresia can be approached trans-canal using an ear speculum. This is satisfactory for a small atretic plate (Figure 77.7a) but, if the fibrous lesion is very thick, a retroauricular approach may be superior, allowing preservation of the lateral and medial epithelial coverings to aid repair of the ear canal skin. In the trans-canal approach the fibrous plate is excised via a circumferential incision just lateral to its margin. The whole lesion is excised with sacrifice of the minimum

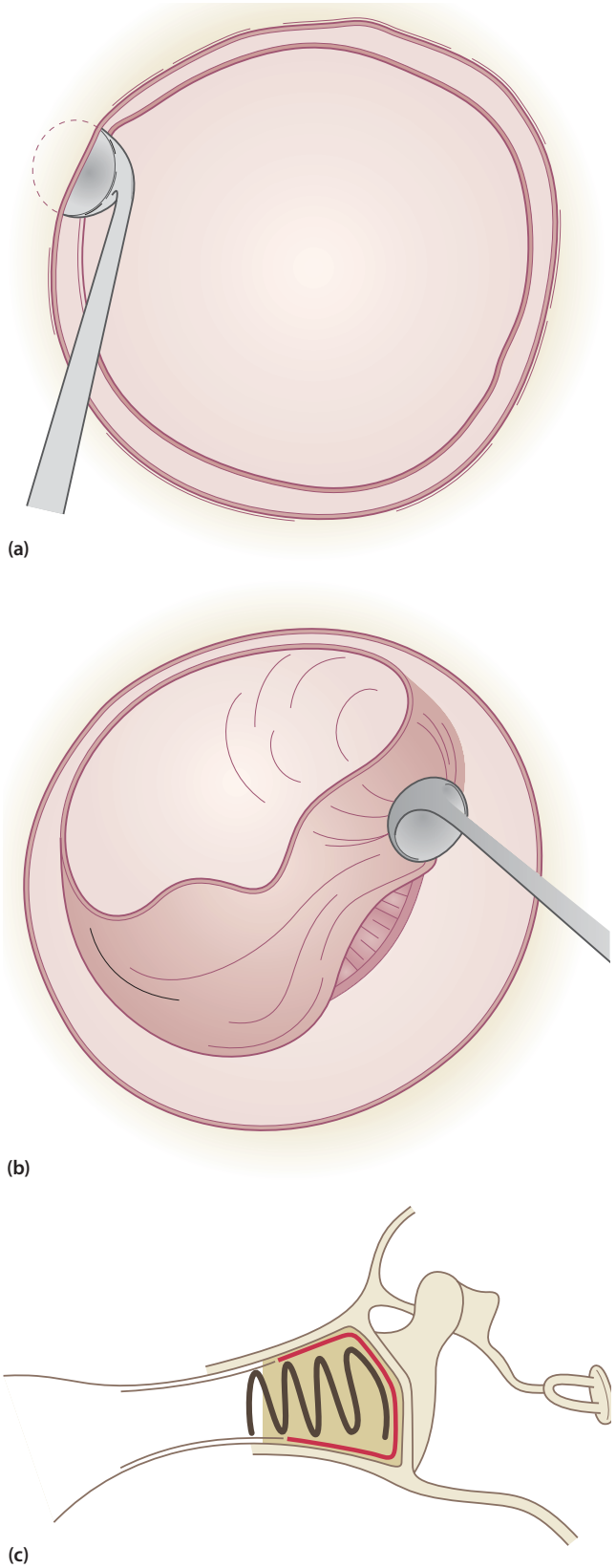

Figure 77.6 Surgery for solid atresia. **(a)** Circumferential canal incision lateral to fundus. **(b)** Dissection of the fibrous plate continues down to the lamina propria and the plate is excised. **(c)** Split-skin graft is applied to the bare medial bony canal wall and over the fibrous annulus and lamina propria and the canal is packed with ribbon gauze.

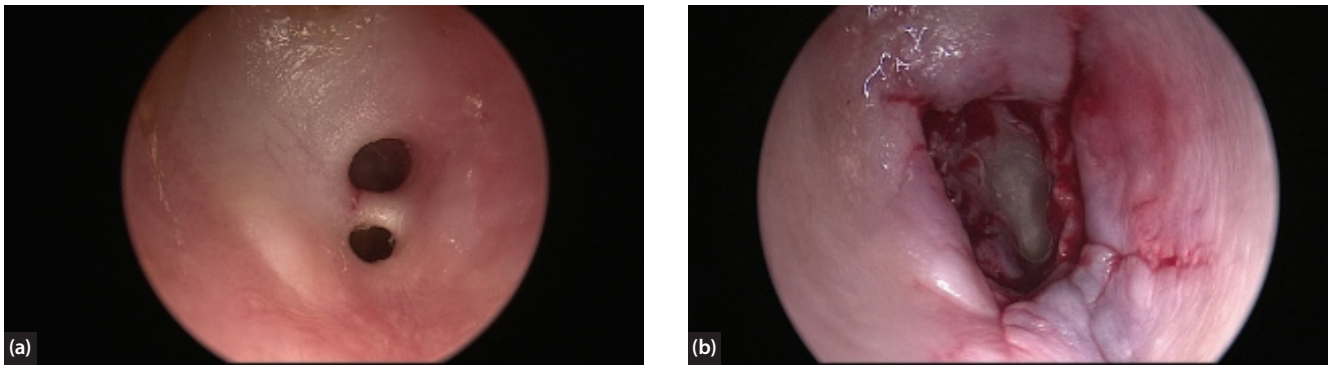

Figure 77.7 Surgery for membranous lateral atresia. (a) Predominantly membranous atresia with two small defects. **(b)** Lateral and medial flaps interleave to aid post-operative epithelialization.

of surrounding epithelium. Silastic sheets are overlaid, holding the lateral and medial skin edges against the bone of the ear canal. With thicker plates the retroauricular approach provides access to lift off the outer skin, remove the atretic plate and dissect it away from the medial skin covering. This aids the final reconstruction, providing skin flaps which can be turned to cover the bare canal bone at the site of the membranous atresia (**Figure 77.7b**).

Atresia surgery combined with tympanoplasty

As the underlying condition of atresia, particularly the solid form, is associated with middle-ear disease, such as chronic otitis media, it is not surprising that Becker and Tos[3] found that in 40% of their surgical cases there was an associated middle ear problem such as an ossicular discontinuity or tympanosclerosis. A tympanotomy may be combined with atresia surgery, especially in solid cases where the delicate fibrous layer of the tympanic membrane can be lifted to examine the ossicular chain and give access for reconstruction.

OUTCOMES

There are few published large series of long-term results in surgery for ear canal atresia. This is of particular relevance to this form of surgery because recurrence may be a late development, as the processes that drive the condition, such as otitis externa, may persist. The principal outcome measure is residual conductive hearing loss as the aim of surgery is to provide an open and stable ear canal with a relatively thin and mobile tympanic membrane.

Becker and Tos[3] published a series of 53 ear cases with follow-up of up to 27 years (average >10 years), Herdman and Wright[5] of 9 cases with about 5 years' follow-up and Magliulo[6] of 41 ears with 5 years' follow-up in the majority. The recurrence rates were 11%[3], 33%[5] and 36%.[6] The residual air–bone gap was less than 20 dB in 90%[3] in the Danish series but there was a recurrence of about a third of a clinically significant air–bone gap in the latter report.[6]

These results suggest that surgery can offer stable long-term results with good hearing in the majority but long-term recurrence is a significant risk.

BEST CLINICAL PRACTICE

- ✓ During the wet phase, the ear should be managed with regular suction toilet and local medical treatment to attempt to render the ear dry.
- ✓ Hearing loss may be managed with air-conduction or bone-anchored hearing aids.
- ✓ Atresia (particularly membranous) can be complicated by cholesteatoma and cases should undergo CT scanning.
- ✓ Surgery to relieve conductive hearing loss is possible and in expert hands may lead to stable long-term results.

KEY POINTS

- External ear canal atresia may be solid or membranous.
- It is caused by local irritation by inflammation or trauma.
- Assessment should include CT scanning of the temporal bone.
- It may be complicated by ear canal cholesteatoma.
- If in a wet phase, local treatment may render it dry.
- Auditory rehabilitation with air- or bone-conduction hearing aids should be considered.
- Ear canal surgery to relieve the conductive element and deal with any medial cholesteatoma is effective and stable in expert hands over the long term.

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CHAPTER 78

OTITIS EXTERNA AND OTOMYCOSIS

A. Simon Carney

SEARCH STRATEGY

Data in this chapter may be updated by a Medline (Ovid) search using the keywords: otitis externa, external otitis, external auditory canal and limiting the search to human, English language, full papers.

OTITIS EXTERNA

DEFINITION

Otitis externa is a generalized condition of the skin of the external auditory canal. It is characterized by oedema and erythema associated with itch, pain and discharge.

CLASSIFICATION

There is no universally accepted classification for otitis externa and it has been put into many subcategories in the past. In fact, most of these (e.g. eczematous otitis externa) are actually just predisposing factors (Table 78.1).

PATHOLOGY

The clinical course of diffuse otitis externa is extremely variable but has been divided into the following stages:[1]

Stage 1: Pre-inflammatory
Stage 2: Acute inflammatory (mild, moderate or severe)
Stage 3: Chronic inflammatory

TABLE 78.1 Predisposing factors for otitis externa

Type	Factor
Anatomical	Narrow external auditory meatus (EAM) (hereditary, iatrogenic, exostoses, trauma, etc.) Obstruction of normal meatus (kerratosis obturans, wax, foreign body, hearing aid, in-ear head phones, hirsute canal, etc.)
Dermatological	Eczema, sebhorrhoeic dermatitis, psoriasis
Allergic	Atopy, non-atopic allergy, exposure to topical medications
Physiological	Humid environment, immunocompromisation
Traumatic	Skin maceration (bathing or irrigation), ear probing, laceration, radiotherapy, ear candling
Microbiological	Active chronic otitis media, exposure to *P. aeruginosa* or fungi

In stage 1, the protective lipid/acid balance (normal pH 4–5) of the ear is lost and the stratum corneum becomes oedematous, blocking off the sebaceous and apocrine glands and producing aural fullness and itching.

With further oedema and scratching, there is disruption of the epithelial layer and invasion of resident or introduced organisms. This results in stage 2, with

a progressively thickening exudate, further oedema, obliteration of the lumen (mild: little or no obliteration; moderate: sub-total obliteration; severe: complete obliteration) and increasing pain. In the severe stages, auricular changes and cervical lymphadenopathy are often seen. After 6 months, by definition, chronic otitis externa occurs. Stage 3 is characterized by thickening of the external canal skin and this is covered in Chapter 77, Acquired atresia of the external ear.

DIAGNOSIS

Otitis externa is a clinical diagnosis based on the following symptoms and signs: pain, itch, oedema and erythema of the external auditory canal with purulent otorrhoea and debris in the meatus (**Figure 78.1**). An active chronic otitis media may be identifiable in some cases. There are no studies evaluating the accuracy of clinical diagnosis in otitis externa.[2]

EPIDEMIOLOGY

Otitis externa is estimated to have a prevalence of 0.4% per year, affecting approximately 10% of the population during their lifetime.[3]

AETIOLOGY

Any condition or situation that disturbs the lipid/acid balance of the ear will predispose an individual to otitis externa.[4] These conditions can be classified as in **Table 78.1**.

Water and moisture are thought to cause a change from a predominantly Gram-positive skin flora to a Gram-negative one. As the ear becomes inflamed, healthy cerumen (with its bactericidal properties) is rapidly removed from the ear and is no longer produced.

Secondary bacterial infection

Secondary bacterial infection is a major feature of the disease. The bacteriology of otitis externa has not changed significantly over the last few decades[5] and most patients will culture multiple organisms (**Table 78.2**). Case reports of methicillin-resistant *Staphylococcus aureus* (MRSA) in otitis externa do not appear to show it to be a management problem unless systemic involvement occurs[6] as most cases settle with topical treatment, whether the bacteria is sensitive to the topical antibiotic or not.[5] There is some evidence that the *Pseudomonas aeruginosa* strains in ear disease are different from those found elsewhere in the human body. These strains may have special adherence properties that allow the bacteria to enhance their pathogenicity.[4, 7]

Bathing

Current opinion would suggest that, although water is a well-established risk factor for the development of otitis externa, bacterial contamination is not required for the development of the condition[5] although bathing in freshwater lakes containing *Pseudomonas* contributed to a large outbreak of the condition in the Netherlands, whereas bathing in rivers, swimming pools or the sea were not shown to be risk factors.[9]

TABLE 78.2 The microbiology of otitis externa (from Agius et al.[8] and Anonymous[5])

Bacteria	Percentage
Pseudomonas spp.	50–65
Other Gram-negative organisms	25–35
Staphylococcus aureus	15–30
Streptococcus spp.	9–15

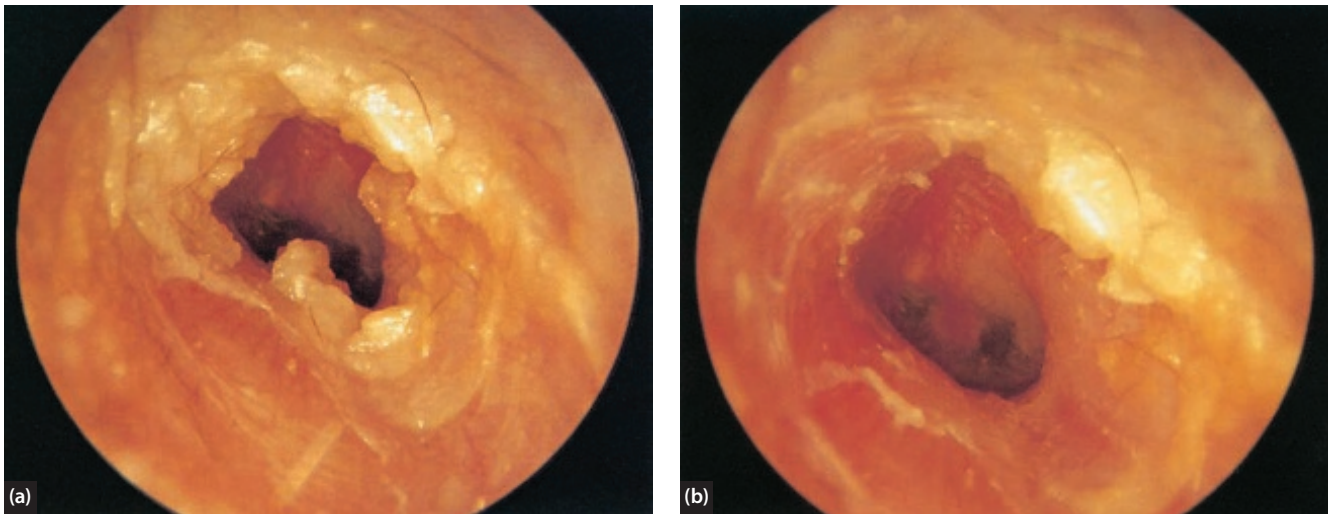

Figure 78.1 Acute otitis externa. (a) Debris inflammation in the left external auditory meatus. **(b)** After removal of the debris the swollen oedematous canal skin of the otitis externa can be seen.

Irritant/allergic reactions

Treatment of otitis externa is often with topical medications. Around 40–58% of patients have been shown to be sensitive to ingredients in topical agents on patch testing although clinical reactions may only develop in half that figure.[10, 11] There is increasing evidence that steroids may also sensitize the ear and steroid-only drops can still be a major exacerbating factor in some patients. This hypersensitivity can be through both atopic and non-atopic 'allergic' mechanisms and may or may not involve IgE.[12] In cases of resistant otitis externa, a patient should be investigated for topical hypersensitivity to possible therapeutic agents.

OUTCOMES AND COMPLICATIONS

If untreated, mild attacks of otitis externa often spontaneously resolve as the epithelial barrier becomes reestablished, the piloapocrine units produce normal secretions and the pH of the canal returns to normal. If the inflammation progresses faster than repair, increasing pain, otorrhoea and oedema of the canal occurs and the patient's condition will deteriorate. Due to the rich lymphatic drainage of the area, lymphadenopathy often occurs and soft-tissue infection can progress rapidly. This can lead to perichondritis, chondritis, cellulitis, parotitis and/or erysipelas. In the immunocompromised host, malignant otitis externa (periostitis/osteomyelitis of the skull base) can develop with significant associated morbidity and mortality.[3]

MANAGEMENT OPTIONS

The principles of treatment of otitis externa are as follows:

- thorough and regular aural toilet
- topical medication to the external auditory canal, with or without a wick
- analgesia
- treatment of regional and/or systemic complications with systemic antibiotics
- prevention of aetiological factors that could lead to exacerbation or recurrence.

Expert opinion is divided on the role of routine swabbing of the ear in otitis externa. Most otolaryngologists tend to reserve microbiological investigation for resistant or high-risk cases.[5]

Toilet remains the most effective single treatment for otitis externa. Although one primary care review claims irrigation of the ear canal is effective for the removal of debris,[2] expert opinion is generally against this and most specialists will perform aural toilet with or without microscopic assistance. There have been case reports of severe complications as a result of irrigation.[13] As microscopic toilet is not readily available to most general practitioners, patients are often treated with antibiotic/steroid medication in the form of drops or sprays without prior toilet. Aural medication commonly causes stinging or burning which may decrease compliance[14] and topical sensitivity is a common feature, especially in resistant or recurrent cases. There is no evidence for the efficacy of systemic antibiotic therapy for uncomplicated diffuse otitis externa.[15]

The use of a wick such as 1 cm ribbon gauze or a Pope otowick is often used to hold medication in the EAM. Glycerol and ichthammol (90% : 10%) used to be commonly used with an aural wick for moderate and severe cases of otitis externa, although it is now difficult to source. It has proven dehydrating and anti-inflammatory properties and antibacterial activity against *Streptoccocus* and *Staphylococcus* but poor activity against *Pseudomonas*.[16, 17] The dehydrating effect reduces canal oedema and also helps reduce pain but oral analgesia is usually necessary in moderate or severe cases. Non-steroidal anti-inflammatories, if not contraindicated, are excellent analgesics for otitis externa.

In patients who are prone to recurrent attacks, avoidance of water penetration into the ear is a major management issue. Cotton wool with petroleum jelly (e.g. Vaseline) will work well in the bath or shower and custom-made ear moulds can be made. Neoprene head bandages are a useful adjunct with the above for children in swimming pools. The use of alcohol ear drops or proprietary preparations (e.g. ear calm) after swimming will help remove any water that has penetrated into the canal. Blow-dryers (note: not on 'hot' setting) can also help remove moisture from the EAM.[5, 18]

Where dermatological conditions exist, multidisciplinary input is often required and tar preparations may be required. Any topical agent should be suspected as an exacerbating factor for eczema around the EAM.

In a small minority of patients who have recurrent attacks of otitis externa exacerbated by conventional hearing aids, insertion of a bone-anchored hearing aid can result in a spectacular and gratifying resolution of the condition.[19]

EFFECT OF MANAGEMENT ON OUTCOMES AND COMPARISON BETWEEN MANAGEMENTS

Randomized trials comparing interventions for the treatment of otitis externa are few in number. Scientific design of trials is difficult as the disease is heterogeneous in presentation, has a high rate of resolution with little or no intervention, endpoints are difficult to ascertain and often subjective and compliance with medication is known to be poor.[20]

A consensus panel convened by the American Academy of Otolaryngology – Head and Neck Surgery found no evidence for the use of systemic treatment in the absence of known risk factors or systemic signs and/or symptoms.[21] Although the choice of antibiotic used is controversial and toilet was not performed, in one randomized trial, addition of clotrimoxazole to Kenacomb ointment provided no benefit over the ointment alone.[22] The best available evidence shows little or no difference between the various topical agents, once thorough toilet has been performed,[2] although these studies are usually of low statistical power.

Likewise, toilet and topical hydrocortisone with an acidification agent (acetic acid) gives equivalent results to combination antibiotic/steroid preparations[23] and an acidification agent alone (aluminium acetate) produces similar outcomes to antibiotic (gentamicin) alone.[24] An early study compared steroid/aminoglycoside drops to placebo alone, showing a significant benefit with topical therapy at 10 days ($p < 0.001$).[25] Likewise, budesonide drops have been shown to produce better clinical outcomes than placebo.[26] Addition of any form of topical agent does seem to be better than toilet alone.[27] The sensitivity of the bacteria to the antibiotic in topical medication does not seem to influence outcomes. The fluoroquinolones ciprofloxacin and ofloxacin have been shown to be as effective as combination steroid–aminoglycoside drops[5, 28] and have the attraction of being non-ototoxic.[29] They are expensive but only need to be given twice daily, which has an advantage for compliance, especially in paediatric populations.[5] It is worth noting that many fluoroquinolone preparations still contain potentially ototoxic preservatives, although the question of ototoxicity is perhaps less relevant for otitis externa unless there is perforation of the tympanic membrane. The issue of topical ototoxicity is discussed at greater depth in Chapter 83, Chronic otitis media.

There is some evidence that spray-based medication systems provide better drug delivery to the meatus[30] although this remains controversial. In two studies from the same authors demonstrating improved outcomes from spray when compared to drops, one was non-blinded.[31, 32] It is also worth noting that the sprays used in these trials ('Otomize') also contained acetic acid, in contrast to the antibiotic/steroid drops.

TABLE 78.3 Randomized controlled trials in otitis externa

Treatment vs placebo	Trials	Result
Aural toilet	None	
Acetic acid	None	
Aluminium acetate	None	
Antibiotic, oral	None	
Antibiotic, topical	None	
Antibiotic and steroid, topical	Ref 25	80% vs 20% benefit
Antifungal, topical	None	
Ichthamol and glycerol	None	
Steroid, topical	Ref 26	Benefit
Tar	None	
Method of administration		
Drops vs spray	None	
Drops vs pack	None	
Drops vs wick	None	
Drops vs ointment	Ref 38	No difference
Wick vs gauze	Ref 36	No difference
Comparison of different treatments		
Multiple trials	The majority show no difference but are mostly underpowered.	

Self-administered powder was shown to cure otitis externa in 74% of patients when compared to drops (53%) in a randomized, non-blinded trial from Israel[33] and there may prove to be benefits from using sprays or powder, although more research is needed before firm conclusions can be drawn on this.

Compliance with medication has been shown to rise from 25% to over 90% if the medication is administered by a third party[20] and only 40% of self-medicating patients were able to get within 25% of the correct dose after 3 days of treatment.[34] Insertion of a Pope wick can cause trauma to the EAM[35] and there is only limited evidence of any enhanced efficacy for wicks over drops alone[5] although many experts find these useful in tight ear canals. In a randomized trial involving 94 patients, there was no difference in resolution rates when wicks were compared to medicated ribbon gauze.[36]

The results of randomized controlled trials comparing treatments for otitis externa are summarized in Table 78.3 and have now also been the subject of other systematic reviews.[37]

OTOMYCOSIS

Otomycosis (or fungal otitis externa) accounts for approximately 10% of all cases.[3] It is more common in hot, humid climates and is often secondary to prolonged treatment with topical antibiotics. Diabetes and other causes of immunocompromise also predispose to the condition. The diagnosis must be considered in patients with otitis externa who fail to respond to topical antibiotic/steroid drops.

Aspergillus accounts for 80–90% of cases with *Candida* being responsible for the remaining 10–20%.[3] Other fungi are rarely involved.

The commonest finding is a black, grey, green, yellow or white discharge with debris that is often said to resemble wet newspaper. Occasionally, debris is seen with visible fungal hyphae (Figure 78.2). Treatment is similar to that for diffuse

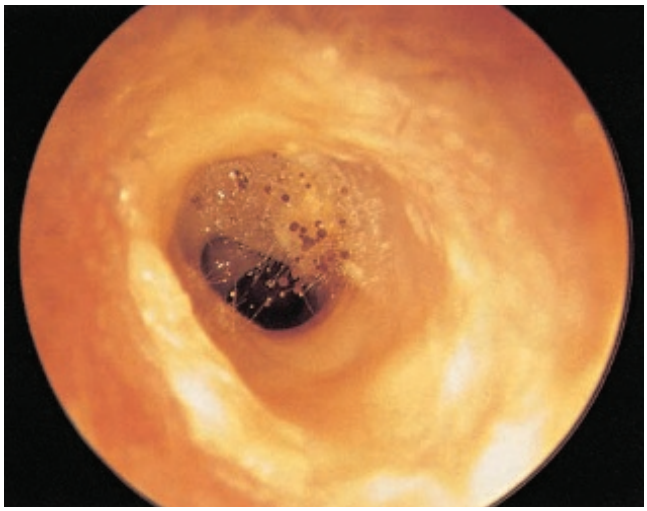

Figure 78.2 Otomycosis with *Aspergillis niger*.

otitis externa, namely toilet and removal of the debris but topical antifungal drops (e.g. clotrimazole or flumethasone with clioquinol) are usually used to expedite recovery.

In cases of resistant otomycosis, it is essential to exclude fungal infection elsewhere in the body. The 'foot and ear'[39] dermatophytid (i.d.) reaction can occur from a fungal infection in a remote location. Immunotherapy with dermatophyte (*Trichophyton*, *Oidiomycetes* and *Epidermophyton*: TOE) extracts and dust mite is the treatment of choice in this condition.[40]

Rarely, fungi can cause invasive otitis externa, especially in immunocompromised patients. Aggressive systemic antifungal therapy is required in these patients[41] who often have a high mortality from the condition.[42]

BEST CLINICAL PRACTICE

- ✓ Addition of any form of topical agent is better than toilet alone. [Grade A]
- ✓ Topical combination antibiotic/steroid drops or spray (with or without the addition of acetic acid) would be regarded as best practice for first-line treatment, given the current evidence. [Grade A]
- ✓ Regular toilet remains the most effective single treatment for otitis externa.
- ✓ Water avoidance is essential in the acute phase and to prevent recurrence. Consider hypersensitivity to topical medication in resistant cases.
- ✓ Think of otomycosis and treat with topical antifungal agents, especially if topical antibiotics have been previously used. Bone-anchored hearing aids can provide excellent results in chronic disease.

FUTURE RESEARCH

- ➤ More powerful prospective randomized controlled trials are necessary to compare different interventions for otitis externa.
- ➤ Accepted grading systems and outcome measures for interventions for otitis externa would greatly facilitate research in this area.

KEY POINTS

- Otitis externa occurs because the protective lipid/acid balance of the ear is lost.
- It affects up to 10% of the population in their lifetime.
- Up to 25% of patients may be clinically hypersensitive to topical medication.

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CHAPTER 79

PERICHONDRITIS OF THE EXTERNAL EAR

James W. Loock

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keyword perichondritis. This was augmented by references from these articles. No level 1 or 2 evidence was identified.

DEFINITION

The term correctly refers to infection or inflammation involving the perichondrium of the external ear: auricle and external auditory canal. However, it is commonly used to describe a continuum of conditions of the external ear, from erysipelas (infection of the overlying skin), through cellulitis (infection of the soft tissue) and true perichondritis to chondritis (infection involving the cartilage itself).

Classification and staging

See the definition above. A useful practical classification might be:

- erysipelas of the external ear
- cellulitis of the external ear
- perichondritis
- chondritis.

Prasad et al.[1] suggest a simple and logical staging of perichondritis/chondritis as:

Stage 1: early perichondritis without fluctuant abscess
Stage 2: perichondritis with fluctuant abscess
Stage 3: perichondritis with fluctuant abscess and cartilage destruction.

AETIOLOGY

The thin skin, minimal subcutaneous tissue and vulnerable anatomical position make conchal cartilage particularly susceptible to trauma with subsequent infection. Perichondritis usually happens secondary to trauma. Such trauma may include laceration of the auricle, surgery to the external ear, frostbite, burns, chemical injury, infection of a haematoma of the pinna, aspiration or incision of a haematoma and, in recent years, 'high' piercing of the (cartilaginous) portion of the auricle for the insertion of earrings.[2] Superficial infections of the skin (erysipelas) or subcutaneous tissue (cellulitis) of the external auditory meatus or pinna may spread deeply to involve the perichondium (perichondritis) or cartilage (chondritis).

In an analysis of 36 patients the organisms most commonly isolated were *Pseudomonas aeruginosa* (69%), polymicrobial (22%), *Streptococcus* spp. (22%) and *Staphylococcus aureus* (20%).[3] However, this may represent a selected subgroup of severe cases as in most (milder) cases no culture is taken. Other organisms cultured include Gram-negatives (*Proteus*, *Enterococcus* and *Escherichia coli*).

PATHOLOGY

Hyperplasia of the dermal layers, thickened subcutaneous tissue, intense infiltration with polymorphonuclear

leukocytes, thickening of the perichondium and destruction of the cartilage by phagocytes is described.[4]

DIAGNOSIS

The presentation is with a dull pain increasing in severity and the classical signs of inflammation involving the cartilaginous pinna (**Figure 79.1**). The lobule, which contains no cartilage, is spared. The severity of the pain and swelling of the pinna are indicators for true perichondritis as opposed to the more superficial conditions of erysipelas and cellulitis. The diagnosis is clinical and special investigations are not routinely required. A background history of underlying trauma to the external ear should be sought.

Differential diagnosis

Relapsing polychondritis may present with similar signs of inflammation, involving the pinna and fever, but it is differentiated on the basis of the systemic nature of the condition. This manifests in the involvement of cartilaginous structures at multiple sites, possibly ocular conditions (scleritis, iritis and keratitis) and, occasionally, vasculitis. See also Volume 1, Chapter 18, Connective tissue diseases: ENT complications.

Rare cases of extranodal non-Hodgkin lymphoma of the pinna, both with[5] and without[6] the presence of human immunodeficiency virus, have been reported to present similarly to perichondritis.

OUTCOMES

If untreated, a subperichondrial abscess may develop, leading to avascular necrosis of the underlying cartilage and marked deformity of the pinna. The infection may spread to the cartilage itself. Rare reported complications of perichondritis include fatal septicaemia secondary to streptococcal infection, subacute bacterial endocarditis and necrotizing fasciitis of the neck.

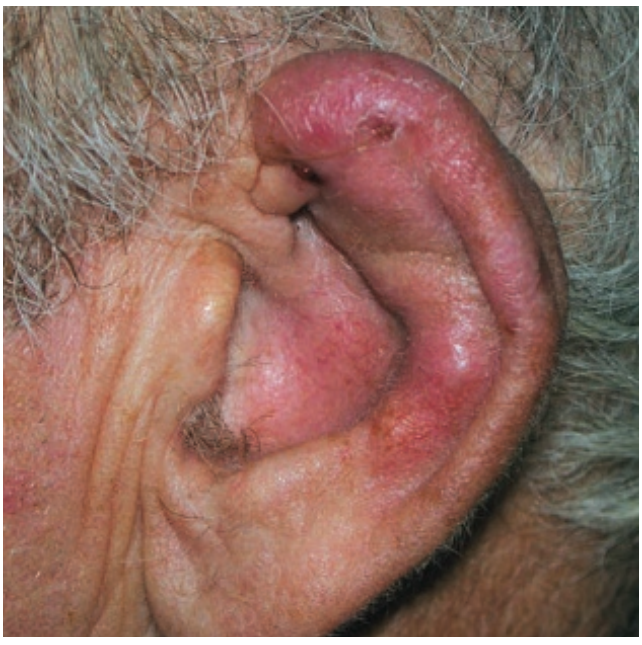

Figure 79.1 Perichondritis of the left ear. There is an associated subperichondrial abscess in this case.

MANAGEMENT OPTIONS

Prevention

Acute perichondritis should be prevented by careful placement of ear piercings away from the cartilaginous pinna. Surgery in and around the ear should avoid trauma to cartilage and tight head bandages. Haematomas of the auricle should be drained promptly and using careful aseptic techniques. The meticulous management of burn injuries to the ears should include the use of prophylactic antibiotics against Gram-negative bacteria and diligent local care including daily dressings and the removal of eschars and crusts.

First-line management

The mildest forms (cellulitis and Prasad stage 1) are adequately managed by the use of topical and oral antibiotics. Prompt treatment with a broad-spectrum antibiotic at a high dose, possibly intravenously, should be designed to cover common organisms and, in particular, *P. aeruginosa*.

The presence of subperichondrial abscess as evidenced by fluctuation requires drainage, but only when definite fluctuation is present, as premature invasive intervention may result in further spread of the infection. If pus is obtained, a pus swab should be sent for culture and sensitivity; however, pending the result, intravenous antibiotic treatment should not be delayed. Standard drainage would be by incision; Pattanaik[7] reports success with a procedure involving aspiration, syringing the cavity two or three times with streptomycin solution, and then refilling the cavity with a premixed solution of streptomycin, triamcinolone and hyaluronidase.

Resistant cases

Non-response to the above treatment, accompanied by persistent pain, suppuration and extensive signs of inflammation, necessitates further intervention.

Various authors advocate aggressive excision of necrosed cartilage including the overlying skin and subcutaneous tissue.[8, 9] However, it is difficult to decide how much cartilage to excise, and repeated debridement may be required. Furthermore, this procedure usually results in deformity, especially if the peripheral cartilagenous framework has to be removed. In severe cases, where the entire area is involved, these authors advocate total chondrectomy via an incision in the helical margin, the ear being split in bivalve fashion, the necrotic cartilage resected, and a layer of fine mesh gauze placed between the flaps and changed daily.

An alternative is a system of continuous drainage and irrigation with an antibiotic and steroid solution in order to preserve the structure and form of the auricle.[10–12] Fenestrated polyethylene tubes are placed in subperiosteal tunnels on either side of the cartilage, and aminoglycoside/cortisone solution used to irrigate these twice daily. The authors report good results and minimal deformity.

The principle of preservation of the perichondrium is supported by experimental work on rabbit ears (animal evidence), which showed that new cartilage formed when the subperichondrial space was preserved.[13] These results could however not be reproduced in monkey auricles (animal evidence).[14]

Other forms of management

The difficulty of delivering adequate antibiotic levels to devascularized cartilage, particularly in burn injuries, led to the investigation of iontophoresis (electromotive drug administration) as a means of effective local antibiotic delivery without systemic absorption. This technique creates an electric field to drive medication (antibiotics in this case) through the skin to deliver high-tissue concentration. This form of treatment is rarely used despite compelling animal and human clinical evidence. A number of authors have demonstrated experimentally the effectiveness of iontophoresis in delivering high levels of penicillin and gentamicin, respectively, to burn-injured rat and rabbit ears (animal evidence).[15–18]

In perichondritis resistant to antibiotic treatment alone, low-dose radiation has been successfully used, based on the lethal effect of such radiation, on three or four sessions of approximately 0.8 Gy of radiation over a period of 2 days.[19]

Ultraviolet radiation has been employed; however, the side effects can be significant and the efficacy of this form of treatment has subsequently been questioned.[20]

Effect on outcomes

All the above case series report resolution of the condition using the therapy they advocate. Aggressive surgery, while it may at times be necessary, may aggravate the ultimate deformity.

BEST CLINICAL PRACTICE

The available clinical literature constitutes Grade D recommendations. Consequently, recommendations must be guarded but the following would seem logical.

- ✓ Consider broad-spectrum (including antipseudomonas) antibiotic prophylaxis in severely traumatized or burnt pinnas.
- ✓ Make early use of local and systemic broad-spectrum, anti-pseudomonal antibiotic if perichondritis is suspected.
- ✓ Fluctuation indicative of pus collection requires drainage with or without irrigation and/or an indwelling drain.
- ✓ In resistant cases, add effective local antibiotic delivery by irrigation or iontophoresis.
- ✓ If further surgery is needed for excision of necrotic cartilage, preserve the perichondrium and a cartilage framework wherever possible.

FUTURE RESEARCH

- ➤ The relative rarity of this condition and the need to individualize management mitigate against level 1 and 2 evidence.
- ➤ Burns units are best placed to provide data.

KEY POINTS

- Trauma, including piercing, may contribute to perichondritis of the pinna.
- Pseudomonas is the commonest organism, but the infection may be polymicrobial.
- Cartilage necrosis and deformity may result.
- First-line management is in the form of (anti-pseudomonal) antibiotics.
- Severity, pus collection, and failure to respond may call for surgical or other forms of treatment.

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CHAPTER 80

EXOSTOSIS OF THE EXTERNAL AUDITORY CANAL

Philip J. Robinson and Sophie J. Hollis

SEARCH STRATEGY

Data in this chapter may be updated by Medline and PubMed searches, both using the keywords ear and exostosis.

DEFINITION

An exostosis (Figure 80.1) of the external auditory canal (EAC) is a benign growth of periosteal bone, which forms a smooth, sessile, hemispherical swelling in the deep part of the meatus, adjacent to the tympanic membrane. Exostoses are usually multiple, occurring in a group of three, and are bilateral. They may arise from the anterior and posterior walls of the EAC. They are usually found as an incidental finding during the examination of an asymptomatic patient. Internal auditory canal (IAC) exostoses have been described, but these are rare clinical entities.[1]

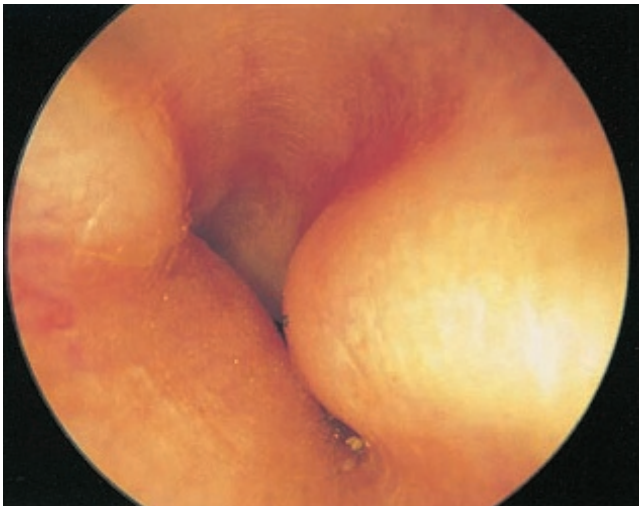

Figure 80.1 Multiple exostosis of the right external auditory canal. One exostosis is anterior and two are posterior.

PATHOLOGY

Histopathological studies of exostoses are few, as a result of the lack of suitable specimens available from the drilling method of surgical excision. However, Graham[2] described exostoses as broad-based, dense and composed of lamellated bone, covered with periosteum and its overlying squamous epithelium with an internal structure formed by concentric, dense layers of subperiosteal bone with abundant osteocytes. A lack of fibrovascular channels and the features mentioned here were proposed as a histopathological method of differentiating exostoses from the other bony swelling seen in the ear canal, an osteoma. However, a later histopathological study[3] demonstrated a considerable overlap of histological features between the two clinical entities.

AETIOLOGY AND EPIDEMIOLOGY

The relationship between cold water exposure and exostoses is now widely accepted. Exostoses are common among water sports enthusiasts, with a prevalence as high as 73.5% in a surfing population.[4] The incidence rises with length of exposure to cold water, from 55.3% for individuals who had surfed for 10 years or less to 90.9% for individuals who had surfed for longer than 20 years.

In a study of two similar groups of Japanese divers, exostoses were significantly more common and more severe in the group working in the cold water area and again showed a significant increase in incidence as the diving career progressed.[5]

Laterality of exostoses is also thought to be related to the cooling effect of wind direction in those who surf. A Californian study proposed that surfers spent most of their time in the water facing west, waiting for waves, which corresponded with the right ear being exposed to more evaporative cooling. Accordingly, the study showed that severe exostoses were twice as likely to be found in the right ear.[6]

An anthropological study of over 1000 prehistoric crania from northern Chile demonstrated a significantly higher prevalence (30.7%) in the coastal area, compared with 2.3% in the valley area and 0% in the highland population, which may be a consequence of habitual fishing in the cold waters of the Pacific ocean.[7] Fowler and Osman,[8] working with guinea pigs, were able to demonstrate the formation of new bone on the inner surface of the tympanic bulla following irrigation of the external canal with cold water. Harrison[9] carried out similar experiments with guinea pigs and found histological evidence of new bone formation in the deep meatus.

The formation of exostoses may represent a rudimentary, evolutionary response to protect the middle ear against immersion in cold water. In the hooded seal (*Cystophora cristata*), there is a broad-based exostosis in the floor of the EAC, lateral to the tympanic membrane, which helps to obstruct the EAC. In addition to cavernous tissue in the middle ear, this feature allows the seal to dive to depths of greater than 1000 m, where it stays for close to 1 hour at pressures of 100 atm, without damage to the middle ear or tympanic membrane.[10]

DIAGNOSIS

The diagnosis of exostoses (**Figures 80.1** and **80.2**) is usually made clinically from the characteristic otoscopic appearances of multiple and usually bilateral sessile, hemispherical, bony swellings arising deep in the EAC, adjacent to the tympanic membrane. It is usually straightforward to differentiate them from an osteoma, which is generally a unilateral, solitary, discrete, pedunculated mass, arising from the lateral part of the bony EAC.[11]

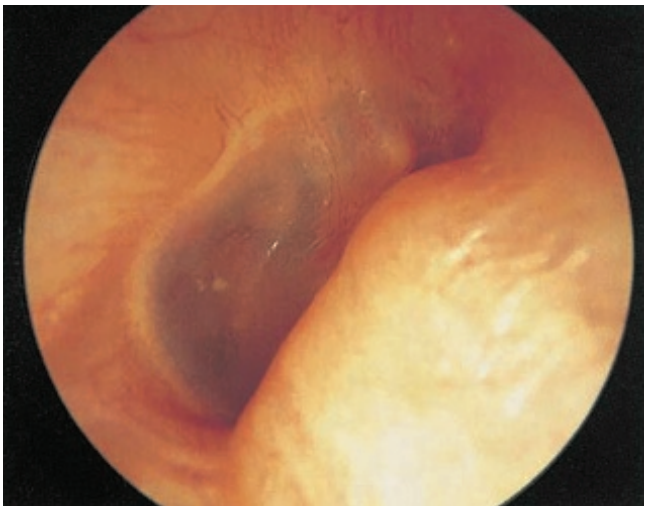

Figure 80.2 Single anterior exostosis of the right external auditory canal.

Exostoses are generally an incidental finding and asymptomatic when small. However, when the exostoses enlarge to cause a stenosis of greater than 80% of the canal lumen, there may be a history of recurrent otitis externa, chronic infection, wax and debris accumulation and conductive hearing loss. As noted above, exostoses are common among water sports enthusiasts.

In the presence of a tight stenosis of the deep ear canal, a high-resolution computed tomography (CT) scan will help differentiate large exostoses from other causes of stenosis, such as chronic otitis externa. A scan will also demonstrate complications, such as a canal cholesteatoma, developing medial to the exostoses.[12]

OUTCOMES AND NATURAL HISTORY

The incidence of exostoses and their size increases with duration of exposure to cold water. In a population of surfers, 44.7% of those who had surfed for 10 years or less had normal ear canals and only 6% had severely obstructed ear canals. In comparison, in the group that had surfed for greater than 20 years, only 9.1% had normal ear canals and 16.2% were severely affected.[4]

There are no longitudinal studies of individuals with exostoses, but it seems unlikely that there would be any significant growth in the absence of continued water exposure.

In most cases, exostoses are an incidental finding and symptoms are rare, with mild to moderate stenosis only. However, with greater than 80% canal stenosis, debris may accumulate medial to the obstruction, leading to recurrent episodes of otitis externa, conductive hearing loss and occasionally a canal cholesteatoma.

MANAGEMENT OPTIONS

In the majority of cases, no treatment is required as the patient is asymptomatic. However, general advice about avoidance of cold water should be given, with a recommendation to use earplugs or a wetsuit hood for water sports.

Hearing loss due to debris collection, or otitis externa, can be managed medically, by meticulous aural toilet using a microscope and suction. Topical application of steroid, antibiotic, antifungal or combination ear drops, may be necessary to treat inflammation or infection.[13]

Surgery

Surgery to remove the exostoses and enlarge the meatus by a meatoplasty procedure is indicated for cases refractory to medical treatment, causing recurrent or persisting otitis externa, frequent cerumen obstruction causing hearing loss and cases where wider access is required for middle-ear surgery.

Surgery is carried out, via a postaural, endaural or permeatal approach, with very careful elevation and preservation of the skin overlying the exostoses. The bone of the exostoses is removed by high-speed drill, using both cutting and diamond burrs. Great care is necessary to avoid damaging the tympanic membrane and facial nerve.

COMPLICATIONS OF SURGERY

Sheehy[11] has recommended a postaural approach in all cases of diffuse exostoses of the EAC, because of the incidence of complications and recurrence of the lesions in patients operated on transmeatally. Of the transmeatal group 25% required revision procedures (6 of 24) compared to 0/55 in the postaural group.

In some series of cases, the permeatal approach seems to be favoured, particularly in the hands of an experienced surgeon,[14] although House and Wilkinson[15] conclude from a series of more than 400 ears that the postaural approach results in complications being kept to a minimum.

Complications of surgery can include infection, tympanic membrane perforation, facial palsy, hearing loss from damage to the ossicular chain or inner ear, exposure of the temporomandibular joint with chronic pain or subluxation and early or late soft-tissue stenosis of the ear canal.

BEST CLINICAL PRACTICE

- ✓ Most exostoses are asymptomatic and are incidental findings. These are best managed by advice to minimize exposure to cold water by using swim plugs or a wetsuit hood for water sports.
- ✓ Recurrent episodes of otitis externa or cerumen impaction may be associated with exostoses and should be managed medically in the first instance with microsuction and antibiotic ear drops.
- ✓ Cases of severe exostoses may require meticulous surgical removal via a postaural approach using a high-speed drill.

FUTURE RESEARCH

- ➤ There are currently inadequate histological data.
- ➤ Further studies are required to establish the true natural history of untreated exostoses.

KEY POINTS

- Exostoses are common in water sports enthusiasts.
- Exostoses are usually an incidental finding and require no treatment.
- There is evidence that prolonged exposure to cold water in the EAC leads to increasing size and incidence of exostoses.
- Exostoses causing greater than 80% stenosis may lead to recurrent episodes of otitis externa, hearing loss and, occasionally, canal cholesteatoma.
- Treatment is usually unnecessary in small exostoses, but advice to avoid further cold water exposure may be appropriate.
- Meticulous medical management will often control the symptoms but, in cases refractory to medical treatment, excision of the exostoses may sometimes be necessary.

ACKNOWLEDGEMENTS

Figures 80.1 and 80.2 are reprinted from Wormald and Browning, *Otoscopy: a structured approach*. London: Hodder Arnold, 1996.[16]

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CHAPTER 81

OSTEORADIONECROSIS OF THE TEMPORAL BONE

James W. Loock

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: osteonecrosis/osteoradionecrosis and temporal bone/petrous temporal bone/ear. Most of the evidence is level 3 or 4 and is based upon the more frequent mandibular form of the disease.

DEFINITION

Osteoradionecrosis of the temporal bone is defined as exposure and necrosis of a variable portion of previously irradiated petrous temporal bone which fails to heal over a period of 3 months.

INCIDENCE, AETIOLOGY AND PATHOGENESIS

Because of its density, bone absorbs a greater proportion of radiation than soft tissues. Osteoradionecrosis and chondroradionecrosis may occur in various sites in the head and neck following high-dose radiotherapy, despite the relative radioresistance of bone and cartilage.[1] Osteoradionecrosis of the mandible (see Volume 3, Chapter 19, Principles and practice of radiotherapy in head and neck cancer) occurs far more frequently than in the petrous temporal bone. Chondronecrosis of the larynx, and osteonecrosis of the maxilla and nasal bone, nasopharynx/skull base, zygoma, palate,[2] clavicle and hyoid[3] have all been described.

Osteoradionecrosis of the petrous temporal bone occurs as a result of high-dose radiotherapy administered to and around the petrous temporal bone for malignancies of the parotid gland, external auditory canal, middle ear, maxilla, nasopharynx[4] and pituitary.

The radiation causes inhibition of mitosis and the capacity for tissue repair, and a vasculitis leading to obliteration of blood vessels and avascular necrosis.[5, 6] Marx et al.[7, 8] characterized the tissue as hypoxic, hypocellular and hypovascular.

The compact, rather than cancellous, nature of the petrous temporal bone, and poor blood supply of the tympanic ring, may increase susceptibility.

Radiotherapeutic techniques which have been developed to reduce the risk of osteoradionecrosis include increased energy of the beam (megavoltage versus kilovoltage) which reduces the dose to bone, the use of multiple fields to contain dose distribution, intensity-modulated radiotherapy, and the use of heavy charged particles (Hadron therapy) where the dose-distribution avoids exit dose.

The occurrence of osteoradionecrosis may be increased in patients with microvascular disease (atherosclerotics and diabetics), and as a result of trauma after radiotherapy – classically dental extractions in the case of the mandible. High local doses of brachytherapy may give an increased incidence.

PATHOLOGY

The tissues affected include bone, overlying subcutaneous tissues and skin. Auricular cartilage is seldom affected due to the low superficial radiotherapy dose received in all but irradiation of skin tumours.

The histological changes in bone include death of osteocytes and osteoblasts resulting in empty lacunae,

preponderance of osteoclasts, demineralization, osteolysis, loss of marrow substance, reparative fibrosis and often secondary infection.[6, 9] Soft-tissue histological changes include epithelial hyperplasia, atrophy of dermal structures, dermal fibrosis and soft-tissue necrosis with replacement by fibrosis.[9]

Macroscopically, there is loss of skin and soft tissue exposing bone, bony sequestration and frequently the complication of secondary infection. Of the parts of the temporal bone, the tympanic ring appears particularly susceptible.[9]

The effects of radiation on the middle and inner ears and hearing are not discussed here. The reader is referred to the publications of Borsanyi et al.,[10] Anteunis et al.,[11] Gyorkey and Pollock[12] and Jereczek-Fossa et al.[13]

DIAGNOSIS, CLINICAL PICTURE, NATURAL HISTORY AND OUTCOMES

The time interval between radiotherapy and clinically evident osteoradionecrosis can vary considerably – from less than 12 months to 23 years.[14]

Ramsden et al.[14] usefully divided cases into localized and diffuse (extensive) forms. The localized form presents mild otalgia and otorrhoea, with small areas of exposed bone in the external auditory canal (**Figure 81.1**). It generally occurs when the petrous bone was in the periphery of the irradiated field. Computed tomography (CT) scanning should show not more than small areas of sequestration. This type can heal if managed conservatively, with resolution occurring typically over 1–4 years, after spontaneous separation of the sequestrum.

The diffuse or extensive form occurs generally when irradiation is directed at the petrous temporal bone, and has more severe symptoms of pain and otorrhoea (**Figure 81.2**). CT imaging may show widespread bony destruction. Erosion of the facial canal and extension to the inner ear can occur, as well as intracranial complications, brain abscesses, meningitis and death. Radical surgical debridement and repair is often necessary to prevent complications and effect healing.

There are no studies analyzing the reliability of CT scanning in indicating the extent of bony non-viability.

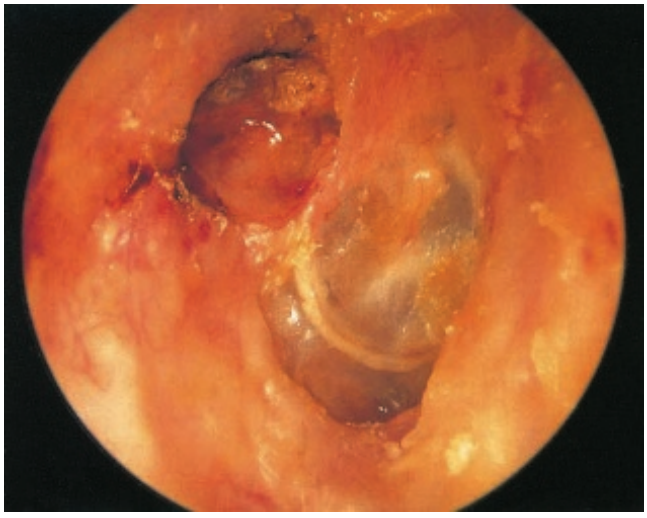

Figure 81.1 Radionecrosis of the right ear. In this ear, there is a bony defect of the posterior canal wall, a bone sequestrum having been extruded. Reprinted from Wormald and Browning, *Otoscopy: a structured approach.* London: Hodder Arnold; 1996.[15]

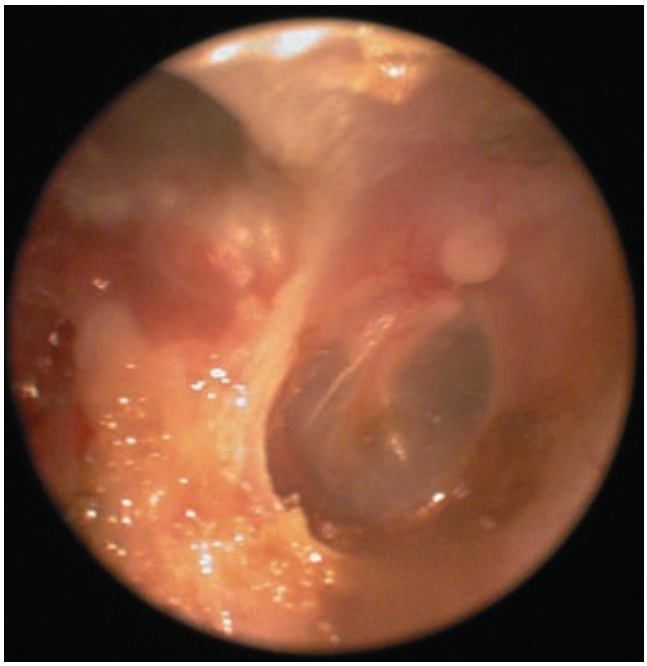

Figure 81.2 Osteoradionecrosis of the right petrous temporal bone. There was extensive bony destruction, multiple small sequestra, granulation tissue and superinfection.

MANAGEMENT OPTIONS

Prevention

The likelihood of osteoradionecrosis should be reduced by careful planning of the radiotherapy, by the scheduling of any surgical intervention prior to radiotherapy, and by waiting for full wound healing before irradiation. A relatively large case series has suggested that, when treatment for parotid neoplasms requires mastoidectomy, a situation in which the risk for radionecrosis is high, subtotal petrosectomy with mastoid obliteration and oversewing of the external ear canal should be performed *ab initio* as a better option than simple mastoiodectomy.[16]

Treatment

In an established case, the first step should be to exclude an underlying recurrence of malignancy. Thereafter, the severity of the problem guides management.

LOCALIZED NECROSIS

Cases, which just leave an area of exposed dead bone in the floor of the external auditory canal can successfully be managed conservatively, with toilet careful removal of

sequestra, local antibiotics and analgesics, although healing may take up to 4 years. Hill et al.,[17] and subsequently Metselaar et al.,[18] describe the use of a local rotational flap from postauricular skin to cover small exposed areas of bone in the external auditory canal.

DIFFUSE NECROSIS

Conservative management is inadequate for severe diffuse necrosis of the temporal bone. However, the poorly vascularized irradiated field is less than ideal for surgery. In Ramsden et al.[14] and Thornley et al. series,[19] radical surgical debridement alone required revision in half the cases.

For this reason, subsequent authors[20] recommend bringing in a vascularized soft-tissue flap at the time of debridement, as well as radical mastoidectomy or subtotal petrosectomy until healthy vascularized bone is reached. Careful placement of incisions is required in order to optimize blood supply.

The use of hyperbaric oxygen in radiation-injured tissue and osteoradionecrosis is controversial. There is a paucity of evidence in relation specifically to the petrous temporal bone but extrapolation from related literature suggests it might be helpful. In a randomized controlled trial, Marx reported four to five times reduced tissue-related complications in a series of 160 heavily irradiated head and neck patients receiving combined treatment with hyperbaric oxygen in support of debridement and surgical repair.[21] Two reviews have concluded that the available trials constitute a modest level of evidence but suggest an improved outcome with hyperbaric oxygen therapy for late radiation injury in tissues of the head and neck (*inter alia*).[22, 23]

BEST CLINICAL PRACTICE

- ✓ Radiotherapy should be carefully planned to avoid osteoradionecrosis.
- ✓ In making the diagnosis, underlying recurrent malignant disease should be excluded.
- ✓ Mild localized forms of osteoradionecrosis are best managed conservatively.
- ✓ Severe diffuse forms require aggressive surgical debridement to healthy tissue and covering with well-vascularized soft tissue.
- ✓ Hyperbaric oxygen is an adjunct worth considering in severe forms.

FUTURE RESEARCH

- ➤ The prevalence of temporal bone osteoradionecrosis is unknown but is likely to be falling because of improved radiotherapeutic techniques.
- ➤ The value of imaging in assessing the extent of osteoradionecrosis warrants study.
- ➤ The rarity of the condition makes evidence in support of management options difficult.

KEY POINTS

- Radiotherapy to and around the petrous temporal bone may cause osteoradionecrosis.
- This may occur months to years after the radiotherapy.
- Careful planning of surgery and radiotherapy can prevent this complication.
- Underlying malignancy should be excluded.
- Mild cases can be managed by local care.
- Extensive osteoradionecrosis may require radical debridement and vascularized flaps.

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CHAPTER 82

ACUTE OTITIS MEDIA AND OTITIS MEDIA WITH EFFUSION IN ADULTS

Anil Banerjee

SEARCH STRATEGY

Data in this chapter may be updated by PubMed searches using the keywords mentioned here. The first search used the keywords acute otitis media and adults, limited to human. The second search used the keywords otitis media with effusion, adults, limited to humans. These were assessed for relevance and quality. Further articles were identified from citations and other publications.

Acute otitis media and otitis media with effusion are often temporally related due to pathology also seen in childhood. They are also encountered due to specific adult-related aetiologies.

ACUTE OTITIS MEDIA IN ADULTS

DEFINITION

'Acute otitis media' (AOM) translates as acute middle ear inflammation. It is generally seen in infective conditions with the causative organism being viral or bacterial. It is a relatively common childhood condition and is seen less often in adults.

PREVALENCE AND INCIDENCE

An international multicentre primary care setting study recorded the total number of patients seen with symptoms consistent with a diagnosis of AOM (n = 3224). Sixteen per cent of the total number was over the age of 15.[1] This condition is therefore not as uncommon in the adult population as was previously thought. It remains, however, predominantly a disease of childhood and more specifically infancy.

A separate study calculated the relative risk of getting AOM to be about 200 times higher during the first 2 years of life than as an adult.[2]

AETIOLOGY

Bacterial infection accounts for the majority of adult AOM cases presenting to ENT doctors (Table 82.1). The organisms found are similar to those in paediatric cases.

TABLE 82.1 Bacteriology of middle ear aspirates from adults with acute otitis media (reprinted from Celin et al.)[3]

Bacterium	Percentage*
Haemophilis influenzae	26
Streptococcus pneumoniae	21
Moraxella catarrhalis	3
Streptococcus aureus	3
Other bacterium	26
No growth	26

* This includes multiple growths (n = 36).

DIAGNOSIS

History

Unlike presentation in the paediatric population, the affected adult can usually describe symptoms in detail and seek treatment of his or her own volition. Despite this, some may still delay treatment until a fulminating middle ear infection results in perforation of the tympanic membrane. The pain experienced together with the resultant mucopurulent otorrhoea should be distinguished from bullous myringitis, which produces a similar history of hearing loss and increasing otalgia but ends in a bloody otorrhoea secondary to bursting of blood blisters on the tympanic membrane. The two conditions occasionally occur together.

In those cases of AOM presenting before perforation occurs, hearing loss, tinnitus and otalgia are the cardinal symptoms.

Secondary symptoms include balance disturbance, general malaise, pyrexia and headache.

Examination

Otoscopy may be challenging as the bulging red tympanic membrane may prove difficult to focus on until the examiner realizes the drum is more lateral than is usually the case and withdraws the otoscope slightly to allow the drum to appear in focus. If the tympanic membrane has already perforated, it will have reverted to its usual anatomical position and the perforation may be visible. Pus may be seen in the external auditory meatus and on the tympanic membrane. Microsuction is often required to allow adequate inspection of the perforated drum.

Confusion can arise between a normal tympanic membrane with a profusion of blood vessels radiating from the umbo and a case of AOM. The most reliable otoscopic indicator of AOM has been found to be tympanic membrane bulging.[4] The diagnosis should therefore be made on a combination of history and otoscopy. Pure-tone audiometry is usually only performed if the diagnosis of AOM has been missed, but it typically shows a significant conductive hearing loss in the affected ear.

MANAGEMENT

Most cases will resolve spontaneously and only analgesia is required.

Although antibiotics are often given for this condition, there is no evidence to suggest efficacy in the adult population. Extrapolation from a Cochrane Database review of antibiotics for AOM in childhood suggests that treatment may reduce pain and the incidence of tympanic membrane perforation but this remains untested by clinical research in an adult population.[5] Studies have been bedevilled by diagnostic uncertainty. Definitive diagnosis of otitis media involves tympanocentesis and this is almost never done so that many cases of otalgia are characterized as otitis media in both adults and children.

Approximately 10% have a perforation with otorrhoea at presentation.[1] Adults with AOM are at higher risk of intracranial complications than adults with chronic otitis media.[6] While all complications of AOM are rare, acute mastoiditis, labyrinthitis, sigmoid sinus involvement and intracranial abscesses have been described as the commonest. Facial palsy accounts for 30% of these complications.[7] Full recovery of the facial nerve is the expected outcome in most cases.[8] Unlike childhood disease, meningitis in adults is an uncommon complication.

OTITIS MEDIA WITH EFFUSION IN ADULTS

DEFINITION

Otitis media with effusion (OME) describes a collection of fluid in the middle ear often extending into the mastoid air cells. This may be secondary to a severe upper respiratory tract infection (URTI). It may also follow on from, or precede, AOM. Most episodes of OME in adults will resolve untreated, but in some cases they may persist for months or longer. In adult cases it is important to ensure that other pathology has not been missed. Patients will often describe hearing loss, crackling or popping of the ears, tinnitus and sometimes balance disturbance.

PREVALENCE AND INCIDENCE

For those with both a paediatric and adult ENT practice it is well known that adults make up a very small proportion of the overall number of OME patients seen. Robinson described a prevalence of 0.6% over the age of 15.[9]

AETIOLOGY

Infection

Most adults report a URTI preceding an episode of OME.[10] Sinus infections often occur in affected individuals.[11–13] As in childhood, OME can follow on from AOM or precede it.

Liederman et al. reported that, when cultures of effusions were matched with polymerase chain reaction (PCR) detection, the organisms found were the same as in childhood disease. PCR detected *Streptococcus pneumoniae* and *Haemophilus influenzae* in 15 of 19 samples. Other organisms found were *Moraxella catarrhalis* and adenovirus.[14] Fungi have been found in the middle ear fluid of 100% of individuals with OME (n = 12) when effusions were collected and stained. Whether they also exist in the middle ear cavities of normal individuals is unknown.[15]

HIV has been reported as predisposing to a high rate of middle ear problems. In a study of 155 HIV-positive adults 18% were identified as having chronic middle ear disease – most with effusion.[16]

Allergy

The evidence for allergy as a causative factor in OME is mainly reported in paediatric studies. In a large Norwegian study, the authors found surgery for otitis media to be more common in subjects who reported an allergy.[17] Pelikan reported 71 of a group of 87 adults having positive responses to nasal allergen challenges, and 119 of the 131 positive challenges resulted in Eustachian tube dysfunction leading to significant audiometric changes. He concluded that nasal allergy can lead to Eustachian tube dysfunction.[18]

Barotrauma

Barotrauma from air flights, typically during descent, is a common cause of OME in adults, particularly when travelling with a URTI. Spontaneous resolution within a few days of landing is the usual course of events but, if this fails to occur, medical evaluation is required. There are no reliable data on the incidence of glue ear in adults following air travel.

Hyperbaric oxygen treatment can also cause OME although in most cases this will resolve without the need for ventilation tube insertion.[19]

Eustachian tube obstruction

In the paediatric population adenoidal hypertrophy or inflammation is a common cause of poor Eustachian tube function. Although this is not the case in adults, a middle ear effusion can be due to an obstructing tumour of the Eustachian tube.

A skull base tumour such as a meningioma can obstruct the upper part of the Eustachian tube leading to a middle ear effusion.[20] Although still rare, a more common cause for Eustachian tube obstruction is a tumour of the nasopharynx occluding the lower end of the tube.

Radiotherapy of the skull base can lead to impaired Eustachian tube function and induce long-term OME, in one or both ears. A retrospective study of 81 patients with nasopharyngeal carcinoma found 52% of patients had an effusion at presentation and 26% developed an effusion after radiotherapy.[21]

Eustachian tube dysfunction may also be caused by reflux. In one study, 40% of effusions taken from adults were positive for *Helicobacter pylori* (HP) by PCR assay. Of these, seven grew HP when cultured and had a positive urease test.[22] Sone et al. found that in 24 adults with high pepsinogen levels in unilateral middle ear effusions a low-frequency audiometric bone-conduction threshold elevation was present in the affected ear when compared with the healthy ear and matched controls. This led them to postulate that this may be a diagnostic sign of high pepsinogen level effusions. Unfortunately, the authors did not have sufficient data after resolution of effusions to evaluate whether this was a temporary or permanent audiometric finding.[23]

Miscellaneous

Cerebrospinal fluid in the middle ear secondary to a skull-base defect may be mistaken for OME. Ventilation tube insertion can lead to persistent otorrhoea and a route for intracranial infection.

Prolonged endotracheal intubation is a risk factor for post-operative OME. The condition has also been described in approximately 20% of patients undergoing head and neck surgery.[24]

Rare conditions producing OME include amyloidosis[25] of the nasopharynx, Wegener's granulomatosis[26] (now called vaculitis), multiple myeloma,[27] cystic fibrosis,[28] polyarteritis nodosa[29] and immune deficiency syndrome. Nasal polyposis can also be associated with OME. A history of previous surgical treatment for nasal polyps or Samter's triad (a chronic condition of asthma, recurrent sinus disease with nasal polyps, and a sensitivity to aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs)) is associated with an increased risk of synchronous OME.[30]

PRESENTATION

The majority of adults seeking treatment do so because of hearing loss. The condition is bilateral in between 42% and 69% of those affected.[9, 10, 12] In a case-control study[12] symptoms in OME sufferers were:

- hearing loss: 97%
- aural fullness: 77%
- pulsatile or crackling tinnitus: 60%.

Balance disturbances are also sometimes reported.

Subjects frequently have predisposing factors which include smoking, childhood ear infections and nasal symptoms. A recent URTI, AOM and/or barotrauma is often a feature.

Unilateral OME in adults, unexplained by past history, should always be treated with suspicion.

EXAMINATION

Features on otoscopy described in childhood disease apply equally to adult disease. The tympanic membrane is usually retracted with an abnormal light reflex and the membrane may appear dull or a fluid level may be seen.

It is important to examine not only with otoscopy but also with flexible fibre-optic nasopharyngolaryngoscopy and/or a 0 degree Hopkins rigid nasendoscope. The nose and nasopharynx should be inspected. Evidence of rhinosinusitis will direct treatment. Postnasal space lesions will require imaging and biopsy while simultaneously dealing with the aural symptoms.

INVESTIGATIONS

Audiology

A pure-tone audiogram will show the level of impaired hearing function and typically reveal a conductive hearing loss. Experienced clinicians will usually make

the diagnosis of OME from tympanic membrane appearance and tympanometry is often not necessary. However, tympanometry does have a high correlation with MRI evidence of middle ear effusion[31] and may be used for diagnosis and monitoring of OME. Pre-operative tympanometry has also been shown to have a high correlation with myringotomy findings when gas displacement of fluid is controlled for.[32]

Myringotomy

The presence of fluid at surgery confirms the condition of OME but the absence of fluid does not necessarily refute it. Although the displacement of middle ear fluid by anaesthetic gases is thought to be minimal or absent, MRI scans have shown fluid in the mastoid air cells but not in the mesotympanum.[31] Immediate pre-operative tympanometry has been compared with tympanometry once a general anaesthetic was applied. In a group of 93 patients 30% of tympanograms were found to change under general anaesthetic. A type B pre-operative tympanogram was found to be predictive of a middle ear effusion in 92%.[33]

MANAGEMENT

There are four management options in adults: (i) non-medical treatment, (ii) medical treatment, (iii) hearing aids, and (iv) surgical treatment.

Non-medical treatment

Using a Toynbee manoeuvre or Valsalva technique can be beneficial. It is particularly useful in the perennial sniffer who needs to be educated against continuing this practice and encouraged instead to increase middle ear pressures. The Valsalva technique should be performed several times a day and the patient warned that the first time air enters the middle ear space may be uncomfortable and noisy. This tends to become less dramatic as the middle ear space is gradually aerated with continued application. In children, or in adults who fail to clear their effusions using the Toynbee or Valsalava techniques, mechanical devices such as the Otovent™ balloon and Ear Popper™ can be employed to achieve the same effect.

Medical management

Nasal decongestants such as xylometazoline are widely advocated for OME in adults but there is little evidence to indicate that they alter the natural course of the disease, which is to resolve without treatment in most cases.

Most research into antibiotic use for OME has been in the paediatric population. No large studies of adults were identified in the literature searches. Using a combination of both culture techniques and confocal laser scanning microscopy, a study of middle ear effusions in children found approximately 92% to contain live bacteria. A high proportion showed biofilm morphology. This strengthens the evidence for bacteria in the aetiology of OME in children but requires further investigation in the adult population.[34]

There has been no strong evidence to indicate that N-acetyl cysteine is a reliable form of therapy for OME in adults. Although in theory a mucolytic would appear to hold promise as an alternative form of treatment, laboratory studies show that the concentration of the drug reaching the mesotympanum together with the time it remains there would be critical in determining efficacy.[35] These variables remain difficult to control in a clinical setting.

Eosinophilic otitis media (EOM) has been defined as an intractable otitis media characterized by a highly viscous effusion containing eosinophils and high levels of immunoglobulin E. A pilot study found that long-term anti-IgE therapy produced significant benefits in patients. Larger clinical trials are awaited.[36]

Hearing aids

Hearing aids are highly effective for any conductive hearing loss depending upon the underlying sensorineural function, and should be offered as a form of treatment for hearing loss in adults with long-term OME.

Surgical treatment

Several studies have shown evidence for the short-term efficacy of ventilation tube insertion in adult OME. Unfortunately, once tubes extrude, the condition may return. Sade and Fuchs found that, in 50 adult ears treated with ventilation tube insertion, the majority reverted to the disease state within 3 months of tube extrusion.[37] Similar results have been reported in a more recent study.[38] The problems of infected ventilation tubes and chronic otorrhoea have led some authors to caution against the insertion of ventilation tubes (VTs) in patients treated for nasopharyngeal carcinoma.[21]

Different types of tube design and material are used depending upon the surgeon's intentions but all have a risk of long-term perforation. Recently, the subannular tube has been advocated as a method of reducing this risk.[39]

LASER MYRINGOTOMY

The use of a laser to produce fenestration of the tympanic membrane produces a short-term solution. A mean of 15–22 days for a functioning myringotomy has been reported.[40, 41]

MASTOID VENTS

Mastoid vents bypassing the need to perforate the tympanic membrane have been shown to have good long-term efficacy in chronic OME patients with significant atelectasis. In a multicentre trial of 23 subjects, 20 of the 23 vents were

still patent after 18 months and 18 of the 23 patients had improved hearing.[42]

LASER EUSTACHIAN TUBOPLASTY

Eustachian tuboplasty using a laser has been found to confer significant benefit on a small group of patients with OME when reviewed after a year. Practised as an outpatient technique under local anaesthetic, the authors reported it to be safe and well tolerated.[43]

BALLOON DILATATION OF THE EUSTACHIAN TUBES

Dilatation of the Eustachian tubes has been proposed as a treatment by some authors.[45] A recent meta analysis of studies to date which included 1155 patients in total concluded that the treatment offers short-term benefit in the majority of cases and medium to longer term benefit in a smaller number of patients.[45] There remains a need for large placebo controlled trials.

BEST CLINICAL PRACTICE

- ✓ Acute otitis media is diagnosed on symptom history and otoscopy. Pure-tone audiometry and tympanometry are not required.
- ✓ Otitis media with effusion in adults is uncommon. Treatment options, as described, should be discussed with the patient together with the attendant risks and benefits.

KEY POINTS

- Although relatively uncommon, AOM in adults is usually bacterial and is typically caused by the same organisms found in the paediatric form of the condition.
- Vascularity of the normal tympanic membrane should not be confused with the bulging red tympanic membrane seen in AOM.
- An unexplained middle ear effusion in an adult requires endoscopic visualization of the Eustachian tube entrance in order to exclude an obstructing lesion.
- Balloon dilatation of the Eustachian tubes may be an alternative treatment to ventilation tube insertion in adult OME.

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CHAPTER 83

CHRONIC OTITIS MEDIA

George G. Browning, Justin Weir, Gerard Kelly and Iain R.C. Swan

SEARCH STRATEGY

A PubMed search was carried out using the search terms cholesteatoma, middle ear/ or mastoiditis/ or otitis media, suppurative/ or tympanic membrane perforation; randomized controlled trial; controlled clinical trial; randomized controlled trials/ random allocation/ double-blind method/ single-blind method. Comparative study/ exp evaluation studies/ follow-up studies/ prospective studies. Placebos/random. Limited to animal; limited to human; animal and human. An additional search for inactive squamous COM used the search terms: tympanic membrane and/or retraction.

DEFINITION

George G. Browning

The diagnosis of chronic otitis media (COM) implies a permanent abnormality of the pars tensa or flaccida, most likely a result of earlier acute otitis media, negative middle ear pressure or otitis media with effusion. COM equates with the classic term chronic 'suppurative' otitis media (CSOM) that is no longer advocated as COM is not necessarily a result of 'the gathering of pus'. However, the distinction remains between **active COM**, where there is inflammation and the production of pus, and **inactive COM**, where this is not the case though there is the potential for the ear to become active at some time. A third clinical entity is **healed COM** where there are permanent abnormalities of the pars tensa, but the ear does not have the propensity to become active because the pars tensa is intact and there are no significant retractions of the pars tensa or flaccida. 'Healed COM' can also be the end result of successful surgery. The differences are summarized in Table 83.1.

Our current ability to accurately assess an individual's ear, particularly with magnification, has made redundant the earlier, mainly anatomical, distinction between 'tubotympanic' and 'atticoantral' disease. The terms 'safe' and

'unsafe' are incorrect and misleading as complications can occur from any ear with active COM irrespective of its pathology.

PATHOLOGY

Justin Weir

INTRODUCTION

It is widely believed that COM often starts with episodes of acute otitis media (AOM) or otitis media with effusion (OME) in childhood. OME may lead to thinning of the tympanic membrane, hearing loss and delayed speech development, and it can impact on the child's educational development.[1] COM can be characterized histopathologically by middle ear pathology such as granulation tissue, cholesterol granulomas or cholesteatoma formation.[2]

Active COM is chronic inflammation of the middle ear and mastoid mucosa, with recurrent discharge (at least 2 weeks) through a chronic perforation of the tympanic membrane.[3] The World Health Organization (WHO) estimated that 65–330 million people worldwide are affected by CSOM, of whom 50% suffer from hearing impairment and approximately 28 000 deaths per annum are attributable to the complications of OM. Some of these figures have been confirmed by Monasta et al.[4] who recorded a CSOM incidence of 31 million cases globally. The highest incidence occurs in the first year of life (15.4 per thousand) and Oceania is the geographical area with the highest incidence (9.37 per thousand). They also found that OM-related hearing impairment has a prevalence of 30.8 per 10 000, and that 21 000 people died annually from complications of otitis media.

MOLECULAR PATHOLOGY

OM and COM are complex multifactorial diseases with no single genetic defect, which makes detection of those genes responsible for the disease process difficult to ascertain. Furthermore, it is likely that the multifactorial nature of this disease is in part due to innate immunity (toll-like receptors, cytokines, surfactant), adaptive immunity (immunoglobulins), non-specific immunity (epithelial barriers and mucin production), inflammatory regulation and craniofacial abnormalities. Towards the end of the last century several authors showed a genetic component to both AOM and OME.[5–7]

The exact molecular pathways by which persistent inflammation occurs are now beginning to be unravelled. OM is frequently caused by bacteria, which enter via the Eustachian tube, though sterile OM is not uncommon and the initiation of inflammation in this scenario is unclear. A number of murine models of OM have been developed[8] to resolve this conundrum and, in particular, two non-syndromic mouse models of COM have analyzed the heterozygous *Jeff*[9, 10] and *Junbo*[11] mutant mice.

Jeff carries a mutation in the F-box only protein 11 gene (*Fbxo11*) and *Junbo* a mutation on the zinc finger domain at the ecotropic virus integration site 1 (*Evi1*) gene. Both mutant models demonstrate hypoxia and hypoxia-inducible factor (HIF) mediated responses (more so in *Junbo* than *Jeff*).[12] HIF signalling is regulated at the transcriptional level by interactions with the master regulator of inflammation – nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) – and at the translational level by cytokines, which are glycoproteins produced by inflammatory cells and epithelial cells, such as interleukin-1 (IL-1β) and tumour necrosis factor alpha (TNF-α or TNFA) which induces the acute phase of the inflammatory response and releases other cytokines.[13, 14] Indeed, both IL-1β and TNF-α act synergistically and have similar functions in activating neutrophils, promoting fibroblast proliferation and stimulating prostaglandin and leukotrienes, all of which are important in the pathogenesis of OM.[15] NF-κB can be activated by a range of factors, other cytokines, including bacterial lipopolysaccharides, viral pathogens and growth factors.[16]

The downstream HIF signalling protein vascular endothelial growth factor (VEGF) has been shown to play a role in OME[17] and the link between HIF and VEGF was further investigated and confirmed by Cheeseman et al.[12] Essentially, hypoxia drives inflammation by activation of NF-κB, IL-1β and TNF-α and also increases angiogenesis,

TABLE 83.1 Classification of COM and synonyms used in this chapter

COM classification	Synonyms	Otoscopic findings
Healed COM	Tympanosclerosis; healed perforation	Thinning and/or local or generalized opacification of the pars tensa without perforation or retraction
Inactive (mucosal) COM	Perforation	Permanent perforation of the pars tensa but the middle ear mucosa is not inflamed
Inactive (squamous) COM	Retraction	Retraction of the pars flaccida or pars tensa (usually posterosuperior) which has the potential to become active with retained debris
Active (mucosal) COM		Permanent defect of the pars tensa with an inflamed middle ear mucosa which produces mucopus that may discharge
Active (squamous) COM	Cholesteatoma	Retraction of the pars flaccida or tensa that has retained squamous epithelial debris and is associated with inflammation and the production of pus, often from the adjacent mucosa

COM, chronic otitis media.

vascular permeability and recruitment of neutrophils through activation of VEGF. The introduction of tympanostomy tubes (grommets) alters the oxygen tension and this might be an important mechanism in the downregulation of HIF signalling.

The recruitment of inflammatory cells, whether neutrophils, mast cells, lymphocytes, plasma cells or monocytes/macrophages, is integral to the initiation and subsequent chronicity of OM.[15] Once inflammation is initiated, there is an accumulation of fluid and inflammatory cells in the middle ear cavity, causing conductive deafness and rarely secondary cochlear dysfunction through diffusion of cytokines through the round window.[18] Moreover, cytokines, such as TNF-α and IL-8, induce upregulation of mucin genes within the middle ear and the altered viscosity impairs mucociliary clearance.[15, 19] Both TNF-α and IL-8 can increase inducible nitric oxide synthase (iNOS) in the middle ear mucosa and nitric oxide stimulates mucin production.[20]

Fbxo11 and *Evi1* also interact with the transforming growth factor beta (TGF-β or TGFB) signalling pathway in mice[21] and in humans.[22] Tateossian et al.[23] identified a further link between TGF-β and COME in mutant TGF-β-induced factor homeobox 1 (*Tgif1*) mice, highlighting the importance of the TGF-β signalling pathway and its effects on the responses to hypoxia in the chronically inflamed middle ear. There is considerable crosstalk between TGF-β and HIF-1α pathways as both SMAD-3 (which is one of the many mediators of the TGF-β pathway) and HIF-1α are coactivators of VEGF expression.[24] Furthermore, TGF-β /SMAD signalling leads to downregulation of p38 by including MAPK phosphatase-1 and the subsequent suppression of the mucin protein MUC5AC,[25] resulting in the impaired mucociliary defence. Conversely, NTHi strongly induced upregulation of MUC5AC via activation of the Toll-like receptor 2-MyD88-dependent p38 pathway in a middle ear epithelial cell line.[25] In addition, *MUC5AC* rather than *MUC5B* or *MUC2* was shown to be associated with OME,[26] though this has been challenged by Preciado et al.[27] who showed that MUC5B is the predominant mucin in middle ear effusions from children with OME. However, Kerschner et al.[28] showed that the *MUC5AC* gene was upregulated by more than 150 times in OME samples compared with controls. Either way, the upregulation of mucins, whether by microbial pathogens, cytokines, growth factors, cigarette smoke[29] or gastric acid,[30] results in overproduction of mucin within the middle ear and the subsequent conductive deafness.

Toll-like receptors (TLR) are a group of pattern-recognition receptors that are involved in the innate immune system against microbial pathogens. In particular, Toll-like receptor 4 (*Tlr4*) responds to and recognizes the lipopolysaccharide (LPS) of Gram-negative bacteria such as nontypeable *Haemophilus influenzae* (NTHi), *Streptococcus pneumoniae* and *Klebseilla oxytoca*.[31] Thus, a lack of *Tlr4* results in a poor response to Gram-negative bacteria. The innate immune system is the first line of defence against invading pathogens and has been widely studied in OM.[32, 33] Several studies have shown that TNF-α is important in the regulation of inflammation in the middle ear. Downregulation of TNF-α results in the formation of mucosal polyps,[34] the lack of activation of TLRs and downstream proteins such as CC chemokine ligand 3 (CCL3) and the subsequent lack of recruitment of inflammatory cells.

The human homologues *FBXO11* and *TLR4* of the mouse genes *Fbxo11* and *Tlr4* have been investigated in genetic association studies of human OM. The Minnesota OME/rOM Family Study cohort looked at 142 families with 248 children diagnosed with recurrent or chronic OM.[35] They were genotyped using 13 single-nucleotide polymorphisms (SNPs) across the *FBXO11* gene[36] and a significant association with univariate but not multivariate analysis was found. However, in the larger Western Australian Family Study of Otitis Media, Rye et al.[22] found a significant association with two *FBXO11* polymorphisms on both univariate and multivariate analyses. Interestingly, *EVI1* was not associated with OM in three independent predominantly Caucasian cohorts,[22, 37] suggesting that this gene does not exert the same effect on OM susceptibility in humans as it does in mice.

In a Dutch population of 348 children aged less than 7 years with two or more episodes of AOM, Emonts et al.[38] found that there was a significant association at the *TLR4* D299G polymorphism with 'otitis-prone' (four or more episodes of AOM in the preceding year) when compared to 'non-otitis-prone' children (two to three episodes of AOM in the preceding year).

Genome-wide linkage studies have identified OM susceptibility loci at several regions of linkage on chromosomes 3p25, 10q22, 10q26, 17q12 and 19q13.[35, 39, 40] To date, the susceptibility genes underlying these linkage regions have not been mapped, though Casselbrant et al.[39] proposed a cluster of chemokine genes on 17q12 and several surfactant protein genes near 10q26, while Daly et al.[35] proposed *ADAM8* gene (a disintegrin and metalloproteinase domain), an allergy-associated gene, as a possible candidate for 10q22 linkage peak and Chen et al.[40] suggested potential candidate genes at 19q such as *ZNF71*, an endothelial zinc finger gene induced by TNF-α, and *ZNF304*, which activates lymphocytes.[41] Other candidate genes included members of the inflammasome protein complex which are key regulators of the innate immune response to harmful exogenous or endogenous stimuli.

In summary, the genetic studies, whether from mouse to human or vice versa, have highlighted the importance of regulating the pro-inflammatory and anti-inflammatory effects of pathogens. No doubt the next-generation sequencing methods such as exome sequencing and whole-genome sequencing will help to identify the candidate genes and clarify the molecular pathogenesis of this disease.[8]

EOSINOPHILIC OTITIS MEDIA

Eosinophilic otitis media is a relatively new subgroup of OM/COM which was first described in Japan.[42] It occurs mainly in patients with bronchial asthma who have T–helper type 2 dominant predisposition, and a patulous Eustachian tube which allows entry of

antigenic material into the middle ear resulting in an eosinophilic dominant inflammatory infiltrate.[43] IL-5 is one of the key cytokines in this entity as it has a direct chemotactic effect on eosinophil recruitment. In COM there can be either a simple perforation with a thick yellow viscous effusion or a proliferation of granulation tissue extending into the external ear canal which can often be intractable.

PATHOLOGY OF SUBTYPES OF CHRONIC OTITIS MEDIA

Inactive mucosal COM (dry perforation)

WHO includes inactive mucosal COM (dry perforation) under CSOM.

There is permanent perforation of the pars tensa but the middle ear and mastoid are not inflamed (Figure 83.1). The mucocutaneous junction is usually located at the margin of perforation which can extend up to the fibrous annulus.

Active mucosal COM (perforation with otorrhoea, CSOM)

There is chronic inflammation within the mucosa of the middle ear and mastoid with varying degrees of oedema, submucosal fibrosis, hypervascularity and an inflammatory infiltrate including lymphocytes, plasma cells and histiocytes (Figure 83.2). There is also an increase in the number of goblet cells and basal cell hyperplasia in the middle ear epithelium.[44] Granulation tissue can occur (Figure 83.3) and this is often clinically described as 'aural polyps' which have protruded through the perforated tympanic membrane. Some areas with active COM (both mucosal and cholesteatomatous subtypes) demonstrate focal areas of cholesterol granuloma formation, which microscopically consists of a giant cell reaction surrounding cholesterol clefts (Figure 83.4).

Chronic inflammation can affect the whole of the middle ear cleft including the mastoid antrum and some surgeons believe it is important when a perforation is repaired that the whole of the infected mucosa and granulation tissue from the mastoid and middle ear space is removed in order to control the disease. There is, however, no good evidence that this is necessary and many surgeons only close the perforation even in active disease (see role of adjuvant mastoidectomy in the discussion of management below).

Active mucosal COM is often associated with destruction of the ossicular chain.[45] The affected ossicles typically show areas of hyperaemia with proliferation of capillaries and prominent granulation tissue (Figure 83.5). The long process of the incus, stapes crura, body of incus and manubrium are involved in decreasing order of frequency. Bone resorption or destruction occurs by osteoclast activity. There are a number of bone-modelling molecules/proteins such as receptor activator NF-κB (RANK) and RANK ligand (RANKL) that are expressed in COM which can activate osteoclasts, whereas osteoprotegerin acts as an antagonist to RANKL.[46, 47] Kuczkowski et al.[45] also investigated the expression of TNF-α, IL-1α, IL-6 and IL-10 (an immunosuppressive regulator of acute inflammation) in COM with cholesteatoma formation and bone destruction and found a significant correlation with TNF-α, IL-1α and IL-6. IL-10 is a key anti-inflammatory cytokine and inhibits the production of TNF-α, IL-1, IL-6 and IL-8 as well as inhibiting macrophages and the production of oxygen radicals by neutrophils.[48]

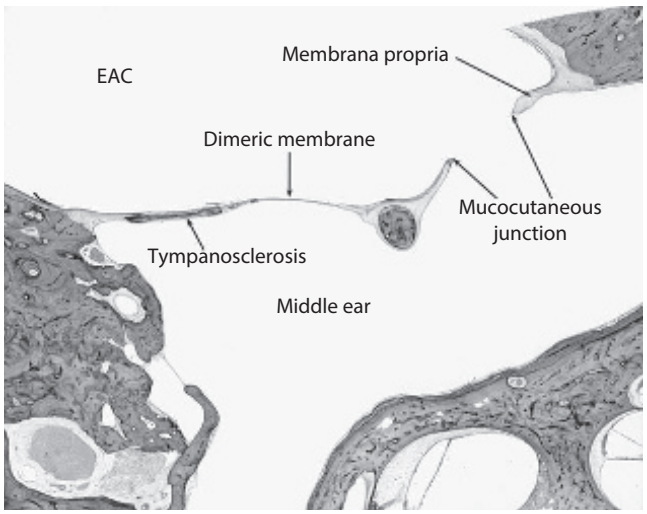


Figure 83.1 Axial temporal bone section from a 43-year-old man. There is a dry perforation of the anterior part of the pars tensa. The mucocutaneous junction is located at the margins of the perforation. The drum remnant anterior to the perforation shows fibrous thickening affecting its middle layer, the membrana propria. There is also a dimeric membrane and tympanosclerosis in the posterior part of the tympanic membrane. EAC, external auditory canal. (*Magnification ×13.*)

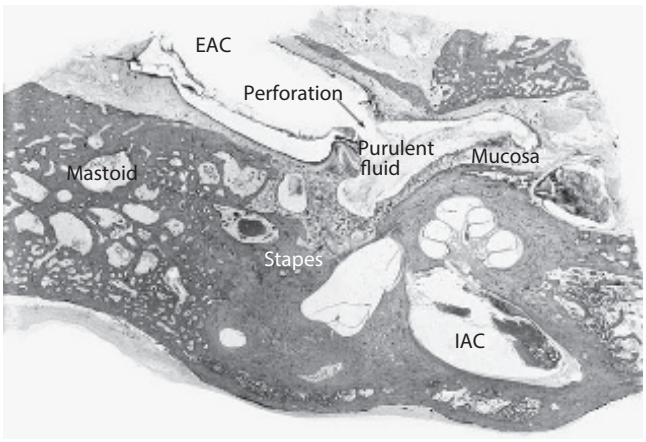


Figure 83.2 Axial temporal bone section from a 77-year-old woman with active mucosal COM. There is a perforation of the pars tensa anterior to the manubrium. The middle ear mucosa is markedly thickened with hypervascularity and active chronic inflammation. There is purulent fluid in the tympanic cavity that is draining through the perforation. The mastoid air cells also show chronic inflammation. EAC, external auditory canal. IAC, internal auditory canal. (*Magnification ×4.*)

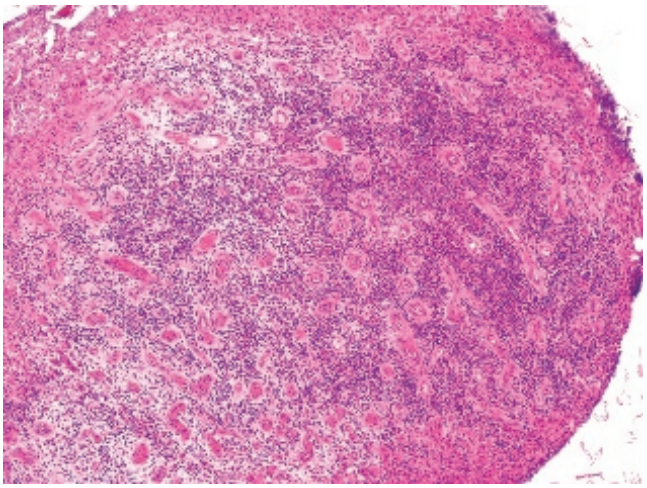


Figure 83.3 Granulation tissue consisting of numerous blood vessels and an inflammatory infiltrate of neutrophils, lymphocytes and plasma cells. (*Magnification ×100.*)

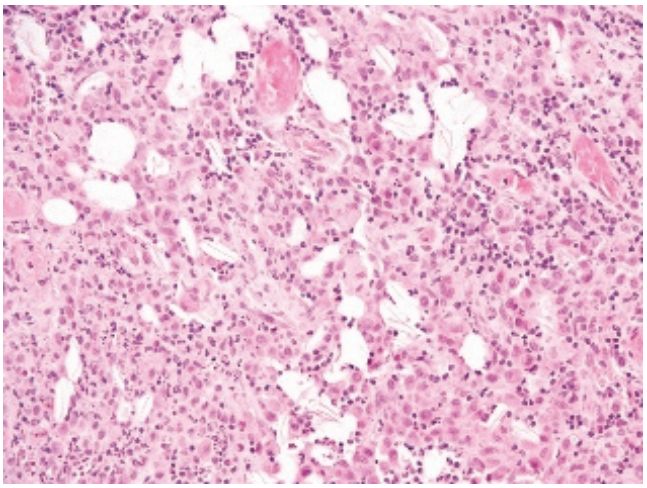


Figure 83.4 Cholesterol clefts (++) surrounding flakes of keratin. Around the cholesterol clefts are numerous macrophages as well as the smaller lymphocytes and neutrophils. (*Magnification ×200.*)

It most likely contributes to the elimination of middle ear inflammation and provides a negative feedback mechanism to the pro-inflammatory effects of TNF-α.

Bacteria also play a role in the bone destruction seen in COM and infected cholesteatoma. Nason et al.[49] showed that *Pseudomonas aeruginosa* LPS (the main antigenic component of the bacterial cell wall) stimulates RANKL-primed precursor osteoclasts into bone-resorbing osteoclasts by an autocrine/paracrine mechanism involving at least 11 cytokines including TNF-α, IL-1α, IL-1β, IL-9 and IL-10, granulocyte-colony stimulating factor (G-CSF), monocyte chemotactic protein-1 (MCP-1) and macrophage inflammatory protein (MIP-1α) among others.

Inactive squamous epithelial COM (retraction, atelectasis and epidermization)

Negative static middle ear pressure can result in retraction (atelectasis) of the tympanic membrane. A 'retraction pocket' consists of an invagination into the middle ear space of part of the tympanic membrane and this may be **fixed**, when it is adherent to the structures in the middle ear, or **free**, when it can move medially and laterally depending on the state of inflation of the middle ear. 'Epidermization' is a more advanced type of retraction and refers to replacement of the middle ear mucosa by keratinizing squamous epithelium without retention of keratin debris.[50]

Active squamous epithelial COM (acquired cholesteatoma)

Cholesteatoma is a benign keratinizing epithelial-lined cystic structure found in the middle ear and mastoid (Figure 83.6). It can cause destruction of the local structures – ossicular chain and otic capsule, thereby

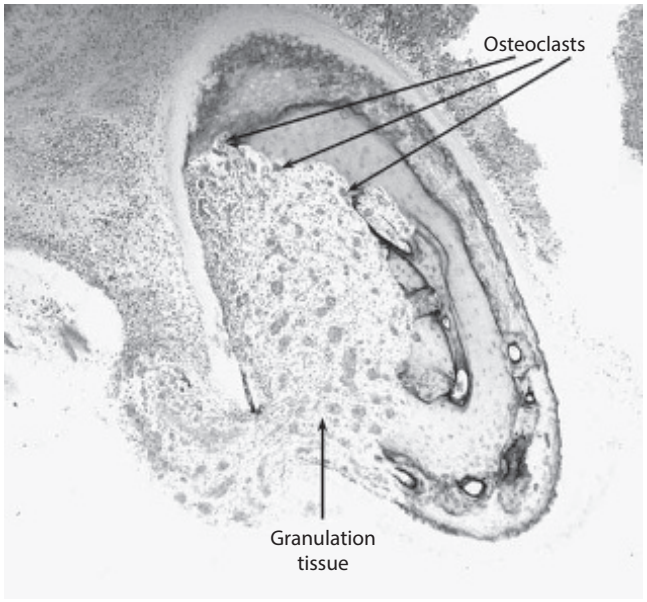


Figure 83.5 High-power view of cross-section of manubrium from a 23-year-old woman with active mucosal COM, showing resorptive osteitis with replacement by granulation tissue. (*Magnification ×81.*)

leading to complications such as hearing loss, vestibular dysfunction, facial paralysis and intracranial disease or infection. The term 'cholesteatoma' was first coined by the German physiologist Johannes Muller in 1838.[51]

The annual incidence of cholesteatoma was found to be approximately 3 per 100 000 in children and 9.2 per 100 000 in an adult Caucasian population in Northern Europe.[52, 53] There is variability of prevalence across racial types, however, with Inuit Eskimos having a significantly lower rate, of 5 per 100 000.[54] Moreover, an Australian study of Aboriginal children and adults reported a low incidence of cholesteatoma (1–3%) compared to higher rates of COM (25–45%), suggesting that the anatomical location of the perforation may have a bearing on the development of a cholesteatoma.[55]

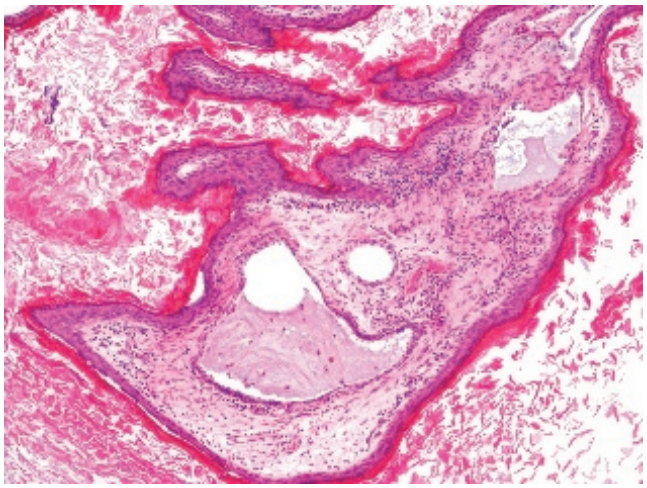


Figure 83.6 Cholesteatoma consisting of keratinizing squamous epithelium. In the submucosa there are a few dilated glands (+) containing mucus. (*Magnification ×100.*)

The pathogenesis of cholesteatoma is due either to the retraction of Shrapnell's membrane (pars flaccida) or the posterior superior quadrant of the pars tensa, or to retraction of the entire pars tensa[56, 57] – the so-called 'retraction pocket theory' first described by Bezold in 1890.[58] This was developed by Sudhoff and Tos[59] who proposed a combined retraction and proliferation model. Key to this theory is Eustachian tube dysfunction which leads to retraction of the pars flaccida into the epitympanum, and subsequent cholesteatoma formation.[60, 61]

A number of other theories relating to the pathogenesis of cholesteatoma, in addition to the retraction pocket theory, have been proposed:[56]

- **basal cell hyperplasia:** proliferation of papillary cones in the basal layer of the squamous epithelium of the pars tensa or flaccida
- **immigration:** based on the ingrowth of squamous epithelium through a pre-existing perforation
- **metaplasia:** of colonies of epithelial cells in the middle ear from cuboidal to keratinizing squamous epithelium.

Cholesteatoma can also be classified according to its topology. Thus, attic cholesteatoma is a mixture of retraction and papillary proliferation as proposed by Sudhoff and Tos,[59] whereas sinus cholesteatoma is a posterosuperior retraction or perforation of the pars tensa extending to the tympanic sinus, posterior tympanum and beyond. Tensa cholesteatoma is retraction and adhesion of the entire pars tensa and may involve the tympanic orifice of the Eustachian tube. On occasions it may result in an acquired epidermal remnant behind the intact tympanic membrane. The pathogenesis of such a remnant remains elusive, but it is thought to develop either from a resolved retraction of the pars tensa, where residual squamous epithelium remains in the middle ear cavity, or from an ingrowth of meatal squamous epithelium.[59, 60] Of note, those individuals who have a perforation of the tympanic membrane rarely have a cholesteatoma on the posterior superior quadrant of the pars tensa or in the pars flaccida.[1]

Recently, Yamamoto-Fukuda et al.[62] performed an elegant study using a hybrid gerbil model to demonstrate that the epithelial cells in cholesteatoma are derived from the tympanic membrane and not from the epithelial cells within the middle ear or epithelium from the external auditory canal. Indeed, the molecular pathology of cholesteatoma has been investigated by a number of authors. Using DNA chip analysis, 282 genes were found to be differentially expressed in comparison to the control samples[63] and Klenke et al.[64] identified 3558 new cholesteatoma-related transcripts. Of those, 811 were upregulated and 334 downregulated more than twofold. The genes involved are found in a number of different biological processes including signal transduction, cell growth, cell communication, metabolism, transport and the immune response. Hamajima et al.[65] determined the role of inhibitor of DNA-binding (Id1) in the proliferation of cholesteatoma keratinocytes. They found that Id1, a protein that leads to cell immortalization, induces up regulation of NF-κB/cyclin D1/keratin 10 in the keratinocytes. The authors concluded that Id1 contributed to the thickening of the middle ear mucosa, cell cycle progression and removal of cell cycle inhibition.

The role of keratinocyte proliferation has also been described in animal models of cholesteatoma[66] and in humans the proliferation rate of cholesteatoma in comparison to external auditory skin has been investigated and been shown to be 2.3 times higher.[67] More detailed studies on keratinocyte proliferation including the *p53* tumour suppressor gene, c-jun and c-myc protein were all found to be upregulated in cholesteatoma.[56, 68, 69] This is coupled with the increased apoptotic rate of cholesteatoma leading to the accumulation of keratinous debris.[70, 71]

Others, such as Huisman et al.[72] have explored the function of TGF-β in cholesteatoma from 12 patients. They ascertained that, while TGF-β is not upregulated in the keratinocytes, it is upregulated in the stroma. They concluded that cholesteatoma behaves as a chronic wound healing process. Further support for this argument has been provided by Lee et al.[73] who demonstrated an increased expression of some pattern recognition receptors (PRRs) mRNA including those encoding for TLRs, TLR-2, -3, -4, -6, -7 and -10, and nucleotide-binding oligomerization domain-containing protein 2 (NOD-2). PRRs, which recognize conserved microbial structures, activate the innate immune system and the activation of TLRs lead to the mobilization of cytokines, chemokines and interferons as well as proteases, defensins, collectins, lysozyme and lactoferrin.[74] Furthermore, downstream mediators of inflammation such as IL-1 and IL-8 were also upregulated. Indeed, TLRs can induce NF-κB as well as TNF-α.[75]

The interplay between the epithelium of cholesteatoma and the surrounding stroma is key to understanding its destructive effects. There are defects in the regulation of epidermal growth factor receptor (EGFR) system,[76]

as well as IL-1 and TGF-α[77] – all important factors in the inflammatory process. Furthermore, TGF-α has been shown to upregulate matrix metalloproteinase-9 (MMP-9),[78] which has been demonstrated to cause bone destruction.[79]

The inflammatory nature of cholesteatoma has gained credence and some authors believe that inflammation rather than retraction is the precursor event required for acquired cholesteatoma formation:[80] when a perforation has occurred, the normal epithelial migration on the external aspect of the tympanic membrane is altered, resulting in a proliferation of squamous epithelium through the perforation into the middle ear cavity. If infection intervenes, migration ceases and squamous hyperplasia with the resultant keratin formation commences, leading eventually to the formation of a cholesteatoma.[60] However, as noted, perforations per se are not often associated with cholesteatoma and it may well be that there are different pathological processes involved in the formation of cholesteatoma secondary to perforated tympanic membranes compared to cholesteatoma derived from an intact tympanic membrane.

In the rare instances of cholesteatoma occurring behind an intact tympanic membrane it has been shown that the cholesteatoma is derived from the tympanic membrane.[62] Whether it is due to a hyperproliferation of squamous epithelium which forms protrusions into the tympanic cavity and, with repeated bouts of chronic inflammation, these turn into cholesteatoma,[72, 81] or whether there is a proliferation of squamous cones or papillary ingrowths from the epidermal basal layer within the retraction pockets[57] remains to be determined.

Healed chronic otitis media

Jensen et al.[82] observed a 39% spontaneous healing rate among a long-term population-based cohort of Greenlanders. Of those healed ears, circular atrophy indicating a healed perforation was the commonest finding. The presence of circular atrophy can lead to a higher risk of reperforation from further episodes of AOM or barotraumas. De Beer et al.[83] followed up 358 subjects from a birth cohort with and without OM histories and/or ventilation tube insertion. They found that at 8 and 18 years of age the prevalence of abnormalities (tympanosclerosis, atrophy, atelectasis, pars tensa retraction pockets and pars flaccida retraction) fell from 92% to 46%. By 18 years of age, many of the tympanic membrane abnormalities had completely resolved, though the prevalence of tympanosclerosis remained high in those treated with tubes.

In OME the tympanic membrane can be damaged by matrix metalloproteinases within the effusion.[84] Tympanosclerosis develops in the lamina propria between the epidermis and mucosal epithelium. It consists of hyaline deposits of acellular material visible as white plaques and white nodular deposits. Pathologically, these hyaline deposits are composed of thickened collagen fibres I, II and III admixed with calcium phosphate deposits[50] and over time osseous metaplasia can occur. Tympanosclerosis surrounding the ossicles in the epitympanum and the stapes superstructure or footplate in the oval window causes varying degrees of immobility of the ossicular chain and it is a well-recognized adverse factor in tympanoplasty (**Figure 83.7**).

PATHOLOGY OF COMPLICATIONS OF CHRONIC OTITIS MEDIA

Routes of spread of infection

The prevalence rates for the extracranial and intracranial complications of COM have been reported as ranging between 0.69% and 5%.[85–87] The most common extracranial complication remains a mastoid abscess. In cases with both extra- and intracranial complications, cholesteatoma was frequently found in the middle ear and mastoid cavity. Facial nerve paralysis can complicate OM in the absence

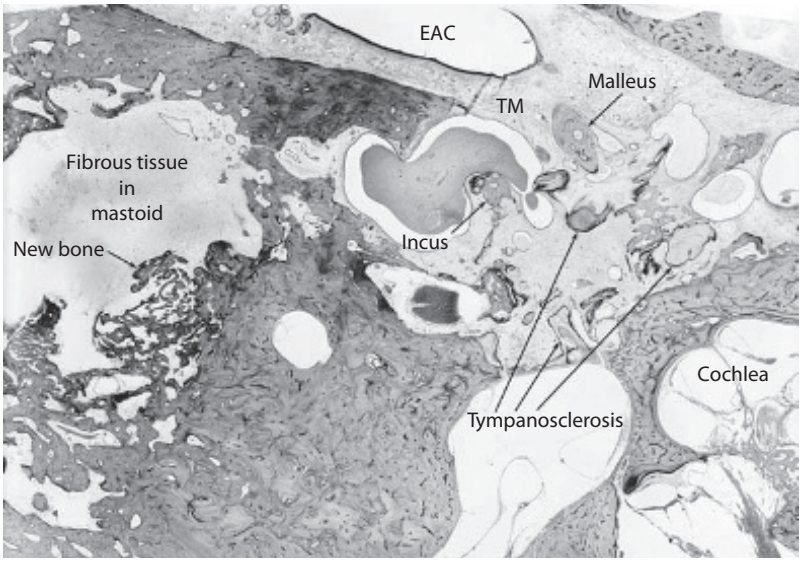


Figure 83.7 Axial temporal bone section from a 77-year-old man with healed COM. The tympanic membrane (TM) is markedly thickened due to proliferation of fibrous tissue. The middle ear and mastoid spaces have been overrun by fibrosis and cyst formation ('fibrocystic sclerosis'), as well as deposition of new bone ('fibro-osseous sclerosis'). There are extensive deposits of tympanosclerosis within the middle ear. It is very difficult to restore hearing by tympanoplasty surgery in such cases of end stage pathology. EAC, external auditory canal. (*Magnification ×9.*)

of cholesteatoma. Patients with COM and cholesteatoma were more likely to develop complications than those with just COM.[86] The most frequently isolated pathogen from ear swabs was *Proteus mirabilis* in 33.3% of cases.

Ibrahim et al.[88] analyzed the incidence of meningitis secondary to suppurative OM in adults. They found that acute and chronic suppurative OM accounted for 13% and 3% of cases of meningitis respectively and calculated that the incidence of otogenic meningitis was 0.42 per 100 000 per year.

Labyrinthine fistula

Labyrinthine fistula can be caused by active mucosal COM or cholesteatoma. The lateral semicircular canal is the most commonly affected site and the reported incidence of fistula formation is 4–13% of all cases.[89] Histologically, cholesteatoma matrix or granulation tissue becomes apposed to the endosteum of the inner ear or directly to the membranous labyrinth. In many fistulae reactive inner ear changes are absent thus a protective walling off phenomena appears to occur (**Figure 83.8**). The margins of some labyrinthine fistulae show evidence of new bone formation and this probably explains the clinical observation that many fistulae show spontaneous bony closure after removal of the offending cholesteatoma or granulation tissue.

Labyrinthitis

Labyrinthitis, whether serous or suppurative, can cause sensorineural hearing loss by affecting various cochlear structures including the hair cells, spiral ganglion cells and striae vascularis. Adams[90] demonstrated that the type I fibrocytes within the spiral ligament expressed NF-κB, which may alter the function of the ion channels within the spiral ligament, resulting in hearing impairment. Suppression of cochlear NF-κB activity by steroids before antibiotic treatment may suggest a role for steroid therapy in recovering from sensorineural hearing loss although there is no evidence for their efficacy in clinical practice.

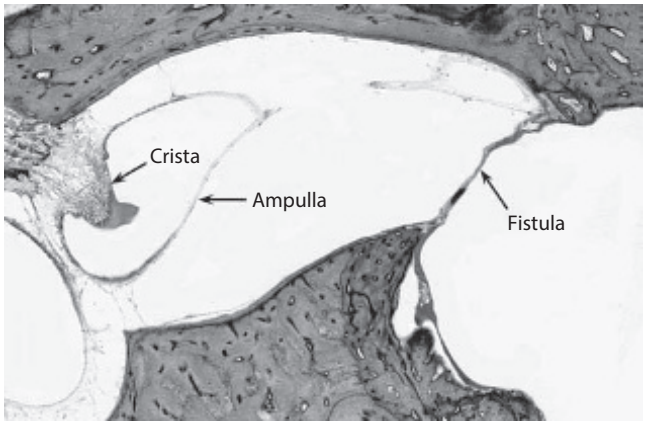


Figure 83.8 High-power view of temporal bone section from a 76-year-old woman with active mucosal COM that resulted in resorption of bone over the lateral semicircular canal with resulting fistula. Only the endosteum separates the perilymphatic space from the middle ear space. Note the absence of reactive inner ear change at or adjacent to the fistula site. (*Magnification ×34.*)

Facial nerve paralysis

The frequency of facial nerve paralysis ranges from 0.16% to 2.62%.[87, 91, 92] Granulation tissue and/or cholesteatoma may cause facial nerve paralysis with a dehiscent or eroded bony facial canal.[92] The nerve and surrounding vascular plexus can become inflamed and swollen and result in degeneration of the axonal fibres. Of note is the fact that the prognosis of the paralysis is worse in COM than in paralysis from trauma, Bell's palsy or AOM.[92]

Otogenic intracranial complications

Although death from intracranial complications of COM has decreased in the developed world,[93] it still remains problematic in developing countries,[94] where Dubey et al. reported a mortality rate of 31.2% in their series. Intracranial complications include meningitis, otitic hydrocephalus, lateral sinus thrombosis, cavernous sinus thrombosis and intracranial sepsis (e.g. extradural, epidural, subdural, perisigmoid sinus and cerebral abscess formation).[87, 91, 95] The routes of infection are via osteitis of the mastoid or temporo-occipital bone, resulting in thrombophlebitis of the venules with or without bone erosion, or by thrombosis of the sigmoid sinus by infected cholesteatoma.[94]

Hearing loss

COM can produce inflammatory changes at the round window and inflammation in the adjacent scala tympani.[96] This can rarely result in loss of both inner and outer hair cells in the basal turn as well as a reduction in the area of the stria vascularis leading to sensorineural hearing loss. The pathogenesis of the inner ear inflammation has been linked to the spiral ligament fibrocytes (see 'Labyrinthitis' above) which release chemokines in response to the middle ear pathogens, in particular monocyte chemoattractant protein-1 (MCP-1/CCL2).[97] Using the C3H/HeJ mouse model which lacks the gene for TLR4, MacArthur et al.[98] observed disruption of inner ear ion and water transport functions as well as alteration in tissue remodelling genes. As many of these channels and transporters are located on the lateral wall of the cochlea, both endolymph production and maintenance are at risk when COM occurs.

AETIOLOGY AND EPIDEMIOLOGY

Gerard Kelly

PREVALENCE OF CHRONIC OTITIS MEDIA

The prevalence of adult middle ear disease in the British population was obtained from the UK National Study

of Hearing,[99] a prospective clinical study of a randomly selected UK population (Table 83.2). An otoscopic diagnosis was made in over 2000 individuals. The overall prevalence of healed, inactive and active COM was 11.9%, 2.6% and 1.5% respectively. The prevalence of active and inactive COM was 4.1%, with 3.1% of individuals having unilateral and 1.0% bilateral disease.

The UK National Study of Hearing[99] also examined the relationship between COM and age, sex and socioeconomic group. There was no sex difference in the prevalence of COM.

Individuals in the age group 41–80 years were twice as likely to have COM as those in the age group 18–40 years. COM has a higher prevalence in lower socioeconomic groups, with manual workers having twice the prevalence of non-manual workers.

Unfortunately, in this study, it was not possible to separate patients with COM into those with mucosal and those with squamous disease. Surgical data is all that is available to give the relative frequencies of mucosal and squamous disease.

Alho et al.[100] reported the rates of surgery in the general population in 1992. The surgery rates were 13 per 100 000 for inactive COM, 7 per 100 000 for active mucosal disease and 4 per 100 000 for active squamous disease. These figures clearly underestimate the true incidence of this disease in the population as not all patients with COM will be seen by a physician or undergo surgery. A similar study[101] identified an incidence of chronic squamous otitis media to be 9.2 per 100 000, with a bilateral incidence of 4.4% within this subgroup. This study showed no socioeconomic difference in incidence; however, unlike the UK National Study of Hearing, these individuals were not randomly selected but presented with ear symptoms and therefore the sample may have been biased with patients in higher socioeconomic groups being more inclined to seek medical intervention.

AETIOLOGY OF CHRONIC OTITIS MEDIA IN GENERAL

Acute otitis media and otitis media with effusion

Both childhood AOM and OME can cause long-term changes of the tympanic membrane.[102] Histological degeneration of the tympanic membrane occurs in the outer and inner fibrous layers of the lamina propria and in the submucosal layer.[103] These changes may reduce the elastic properties of the tympanic membrane making it more susceptible to chronic perforation or retraction. Cases of adults acquiring COM are not uncommon but, again, this could be the result of adult episodes of AOM.

Why some individuals progress from AOM to COM is not clear but the risk factors for this occurring are likely to include some of those for AOM and OME. What is required is for one of the cohorts of children that have been studied for OM to be followed up into adulthood. Unfortunately, none has yet been reported. An alternative is to study a group of adults with COM and record risk factors in comparison to a group of adults that do not have COM. In this type of study a multifactorial analysis would be required. The only study in this category was the

TABLE 83.2 Population prevalence (%) of adult chronic otitis media.[99] The 95% confidence intervals are in parentheses

	Healed otitis media	Inactive chronic otitis media	Active chronic otitis media
Overall	11.9 (10.2, 13.6)	2.6 (1.8, 3.4)	1.5 (1.1, 1.9)
Age (years)			
18–40	10.1 (8.6, 14.4)	2.5 (1.0, 4.0)	0.9 (0.2, 1.6)
41–60	11.5 (9.3, 13.7)	2.1 (1.2, 3.0)	2.1 (1.3, 2.9)
61–80	16.2 (12.8, 19.6)	2.7 (1.6, 3.8)	2.1 (1.3, 2.9)
Sex			
Male	12.6 (9.8, 15.4)	2.8 (1.4, 4.2)	1.9 (1.1, 2.7)
Female	11.3 (9.3, 13.3)	2.4 (1.7, 3.1)	1.2 (0.8,1.6)
Occupation			
Manual	13.5 (11.0, 16.0)	3.3 (2.3, 4.3)	2.2 (1.5, 2.9)
Non-manual	10.1 (7.7, 12.5)	1.9 (0.8, 3.0)	0.8 (0.4, 1.2)

UK National Study of Hearing and the factors included in this were limited to those in Table 83.2. This leaves studies that report on single factors as the highest level of evidence available for these factors.

Genetics and race

The incidence of COM varies in different populations and, in the developed world, is highest in Eskimos, American Indians, New Zealand Maoris and Australian Aborigines.[104] It appears that the prevalence of COM, at least in populations predisposed to it, is declining. In one study of New Zealand Maori children,[105] the prevalence of COM decreased significantly from 9% in 1978 to 3% in the corresponding months of 1987 ($p < 0.02$).

It is difficult to answer the question of whether genetic factors influence COM because of confounding variables such as low socioeconomic grouping of some genetic groups with a high incidence of COM. It is known, however, that there is a high incidence of COM in American Indians, and this incidence varies considerably among different tribes of American Indians, a finding that is likely to have a genetic basis.[106] In a prospective population-based, 2-year cohort study on the incidence of both active and inactive COM in a high-risk Greenlandic population,[107] being of Inuit descent was identified as a risk for the condition, with a HR of 5.56.

In a review of COM in developing countries[108] high levels of COM were noted in some countries, but rates varied considerably. This is likely to be due to population characteristics and environmental factors rather than antibiotic usage.

Environment

As has already been stated, the prevalence of COM is greater in lower socioeconomic groups. The reason for this is multifactorial. In a cohort study, with results on 12 000 children[109] factors significant for ear discharge (although not necessarily COM) were general health scores, maternal smoking and day-care attendance. While sometimes quoted as a factor, the effect of breastfeeding was weak and did not show statistical significance. The decrease in prevalence of COM in New Zealand Maori children from 1978 to 1987 is thought to be due to improvement in both health care and housing conditions.[105] In Koch's prospective population-based 2-year cohort study[107] on the incidence of both active and inactive COM, identified risk factors included: attending childcare (hazard ratio (HR) = 3.18) and household smokers (HR = 4.56).

Eustachian tube dysfunction and upper respiratory tract infections

Eustachian tube dysfunction is more common in patients with COM than in individuals free from middle ear disease.[110] It is not known, however, if the Eustachian tube dysfunction is the initiating factor in COM or whether it is a result of COM. Koch et al.[107] also showed that upper respiratory tract infections (URTIs) increased the risk of COM, but whether URTI is an independent risk factor in COM was unclear and, whereas there are many studies which examine the relationship with AOM and URTIs, studies which examine this relationship with COM are scant.

Gastro-oesophageal reflux disease (GORD)

There has been interest in the role of GORD in ear disease but only anecdotal evidence exists that there may be a relationship between GORD and COM.[111] A systematic review concluded that there may be a higher prevalence of GORD in children with OME and recurrent AOM and that the presence of pepsin or pepsinogen in the middle ear could be related to physiologic reflux, although a cause and effect relationship was unclear.[112]

Craniofacial abnormalities

The incidence of COM in cleft palate patients followed up to 10 years of age is around 20%, with 2% of them having a cholesteatoma.[113] The tensor veli palatini muscle is hypoplastic in cleft palate children and may predispose to Eustachian tube dysfunction.[114]

Autoimmune disease

It is not known if autoimmune disease predisposes to COM. In one study, however,[115] COM was present in 29% of consecutive patients with ankylosing spondylitis.

Immune deficiency

AIDS is associated with higher levels of COM compared to the human immunodeficiency virus (HIV)-negative population. This had been suggested[116] and was the subject of previous debate, although it was known that AIDS could present as aural polyps due to *Pneumocystis carinii* infection.[117] Higher-level evidence has been presented[118] in a case control study of children in Sub-Saharan Africa (Angola) which found a rate of active COM of 26% in HIV-positive children versus less than 4% in the HIV-negative group (with similar findings of dry tympanic membrane perforation rate of 9% versus 1% and bilateral hearing loss of >25 dB of 13% versus 1% in the HIV-positive versus HIV-negative groups). Antiretroviral treatment is associated with a lower prevalence of COM in HIV-infected individuals.[119]

FACTORS INFLUENCING ACTIVITY OF CHRONIC OTITIS MEDIA

Infection

The mucopus removed from ears with active COM is rarely sterile.[120] Microbiology cultures frequently yield multiple organisms and these vary depending on climate, patient population and whether antibiotics have or have

not been used recently. Studies therefore report different isolates in differing proportions. In a prospective study of patients whose active ears were swabbed and cultured in the clinic,[121] 64% cultured only aerobes, 32% both aerobes and anaerobes, and 5% had no growth. In those with aerobes (Table 83.3) most ears had several isolates with a mean of 2.5 different aerobes. None of the patients in this study had been treated with oral or topical antibiotics for the previous 4 weeks.

There is debate about whether the presence of a cholesteatoma influences microbiological findings. Some studies have shown no difference in the microbiological cultures between squamous epithelial disease and mucosal disease[121] whereas other studies have suggested that *Pseudomonas* is less common in squamous epithelial disease.[122] It seems obvious and logical to assume that the activity of the ear in COM would be caused by pathogenic organisms. However, cultures from almost 50% of patients with inactive COM yield an identical flora to that found in active COM.[120] Furthermore, although anaerobes can be isolated from 32% of ears, their elimination by metronidazole does not cause the ear to become inactive.[123] *Pseudomonas aeruginosa* is infrequently found in the normal ear and rarely initiates acute infection. *Pseudomonas* is ubiquitous in our physical environment and has a predilection for moist areas. It is thought to infect tissues first by adherence to epithelial cells by means of pili or fimbriae.[124] In common with *Pseudomonas* infections in other sites of the body, normal tissues usually resist such attachment, unless there is cellular injury such as in chronic lung disease in cystic fibrosis. This phenomenon of 'opportunistic adherence' may represent an important step in the pathogenesis of middle ear infections as it does in respiratory infections. Thus it could be argued that the bacteria in COM are secondary invaders with the mucosal inflammation caused by other factors.

Biofilms

Bacteria preferentially exist in complex, surface-attached organizations known as biofilms which confer advantages over their planktonic counterparts and express markedly different phenotypes. Biofilm bacteria have greater antimicrobial resistance and host defences and can best be thought of as 'self-assembling multicellular communities'. These biofilms are important in chronic infections. Studies to examine the presence of biofilms in active COM have shown a 60% biofilm incidence as opposed to 10% in the control, uninfected group.[125] Biofilms are more abundant in squamous OM,[126] where 82% of cholesteatoma ears were found to have biofilms as opposed to 42% of the mucosal COM and 9% of the control, normal middle ear (cochlear implant) group.

TABLE 83.3 Aerobic bacteria isolated from patients with active COM who had had no antibiotic therapy in the previous 4 weeks; *n* = 83 (from Sweeney et al.)[120]

Bacteria	Number of isolates	% ears
Proteus spp.	79	95
Staphylococcus aureus	33	40
Pseudomonas spp.	25	30
Coagulase-negative staphylococci	24	30
'Coliform' bacilli	21	25
Other*	23	28
Total	**205**	

* Other includes *Corynebacterium* spp., *Escherichia coli*, *Streptococcus faecalis*, *Streptococcus pyogenes*.

Upper respiratory tract infections

Although many patients report activity of COM with a URTI, this has not been examined scientifically. URTIs produce transient Eustachian tube dysfunction in healthy individuals[127] and, as the respiratory mucosa of the Eustachian tube continues into the middle ear, this may become infected, resulting in activity of the mucosa either primarily or secondary to bacterial superinfection.

AETIOLOGY OF CHRONIC MUCOSAL OTITIS MEDIA

It is generally believed that mucosal COM arises from an episode of AOM where, after rupturing, the tympanic membrane fails to heal. Before immunization was practical, COM resulting from a single infection of measles was common, and it has been shown that acute measles may cause severe necrotizing otitis media.[128] A permanent perforation of the pars tensa can also result from the insertion of a ventilation tube in the tympanic membrane, which fails to heal. Long-stay ventilation tubes (T tubes) increase the risk of this occurring over simple grommets, with a perforation resulting in 2.2% of children treated with grommets compared with 16.6% treated with T tubes. The relative risk of long-term ventilation versus simple grommets was 3.5 (CI 2.6, 4.9).[129]

If COM is a sequela of AOM, the predisposing factors of AOM and COM should be the same. If there is a small but tangible risk of the tympanic membrane failing to heal after an episode of AOM, the number of attacks of AOM would increase the risk of COM developing, the risk of perforation being cumulative with each acute infection. There is evidence that the number of siblings, the type of day care, sex, duration of breastfeeding, maternal socioeconomic class and prematurity are all independent factors in the development of AOM in the first year of life (Table 83.4)[130] It would seem reasonable to assume that these factors are likely to be associated with the development of COM and there is evidence of association of some of these factors with COM (see above).

AETIOLOGY OF CHRONIC SQUAMOUS EPITHELIAL OTITIS MEDIA (CHOLESTEATOMA)

There is general acceptance of the theory that OME predisposes to chronic retraction of the pars tensa or flaccida and that this subsequently progresses to cholesteatoma.

TABLE 83.4 Variables associated with the parental report of acute otitis media during the first year of life, when the preceding variables have been taken into account, with the respective odds ratio[130]

Variable		Odds ratio	95% confidence interval
Number of siblings	≥3 vs 0	2.5	1.9, 3.4
	1–2 vs 0	2.0	1.3, 2.9
	≥3 vs 1–2	1.3	1.0, 1.7
Type of day care outside home vs at home		1.6	1.4, 1.9
Male vs female		1.3	1.2, 1.5
Duration of breastfeeding (months)	<3 vs ≥9	1.5	1.2, 1.8
	3–5 vs ≥9	1.4	1.3, 1.6
	6–8 vs ≥9	1.3	1.1, 1.5
Maternal socioeconomic status	Class 3 vs class I	1.8	1.3, 3.1
	Class 2 vs class 1	1.7	1.2, 2.3
	Class 3 vs class 2	1.1	1.0, 1.2
Prematurity yes vs no		1.4	1.1, 1.8

In a retrospective study of almost 46 000 Australian children who had a ventilation tube (VT) insertion operation,[131] 460 children developed cholesteatoma. The cumulative percentage of children who developed cholesteatoma within 15 years after one VT was 0.9%, after two VTs it was 2.1%, after three VTs it was 3.8%, and after four or more VTs it had risen to 5.2%. The rate of developing cholesteatoma increased 10% for each additional year in age before the first VT. For children who underwent two or more VTs, the rate of cholesteatoma increased 21% with each additional year between VTs. Adenoid removal was associated with a 27% reduction in the rate of developing cholesteatoma. This study concluded that 'children with persistent or refractory middle ear disease who required multiple VTIs were at increased risk of cholesteatoma'. First VTs inserted at an early age, subsequent VTs inserted without delay, and adenoid removal were associated with a reduced rate of cholesteatoma development.

VTs are not a panacea for cholesteatoma prevention but their use by aerating the middle ear may play a part in the reduction of cholesteatoma rates, perhaps by preventing retraction. Even if this is the case, why some cases of retraction progress and others do not is uncertain. Several other factors in cholesteatoma genesis have been postulated including the following.

Squamous metaplasia

There has been long-standing debate over the aetiology of chronic squamous epithelial OM. One theory suggests that cells from which a cholesteatoma arise originate from metaplasia of the middle ear mucosa. Another theory suggests that a cholesteatoma arises from the skin of the tympanic membrane. Although squamous metaplasia of respiratory epithelium occurs in the lower respiratory tract, it is unlikely to be a source of middle ear cholesteatoma. The best evidence suggests that cholesteatoma arises from skin cells of the tympanic membrane. All cells contain a cytoskeleton made from filaments comprised of protein subunits. The cytokeratins are a family of these proteins found in epithelial cells and middle ear cholesteatoma has a cytokeratin pattern typical of skin and closely resembling skin of the external auditory meatus.[132] Cholesteatoma sacs are found in close proximity to the tympanic membrane and are not encapsulated but are connected to the tympanic membrane by a neck of invaginated squamous epithelium, and the tympanic membrane appears to follow progressive changes from normal to retraction pockets and then to cholesteatoma.[133] This inference in the progression to cholesteatoma comes from histological studies of temporal bones. A large cohort study is needed to identify if there is a real progression from normal to retraction pockets and then to cholesteatoma. This would require subjecting thousands of children to otoscopic examinations for many years, and until this study is attempted the question of whether retraction pockets form cholesteatomas is unanswered.

Misplaced epithelium

If cholesteatomas are derived from the skin of the tympanic membrane, there are various ways in which this skin might become trapped in the middle ear and mastoid. Cholesteatomas may form from retraction pockets, from papillary ingrowth through the tympanic membrane, from ingrowth of squamous epithelium through a perforation or from implantation of squamous epithelium in the middle ear.

Cholesteatomas are most likely to arise from a retraction pocket in the pars flaccida or the posterosuperior part of the pars tensa and the initiating factor is probably dysfunction of the Eustachian tube resulting in negative middle ear pressure. Because of their greater blood supply compared with the rest of the tympanic membrane, the pars flaccida and the posterosuperior quadrant of the pars tensa are more affected by inflammatory cell infiltration in AOM and in OME.[134] This may leave the fibrous

layer in these areas thinner than the fibrous layer in the remainder of the tympanic membrane. Further evidence that cholesteatomas arise from retraction pockets comes from the fact that retraction pockets are frequently found after surgical removal of a cholesteatoma and grafting of the tympanic membrane. Retraction pockets and cholesteatoma can also be induced in some experimental animals by electrocautery to the Eustachian tube orifice.[135]

Ingrowth of skin through a tympanic membrane perforation has been suggested as a cause of cholesteatomas. These 'perforations', however, are more likely to be the misdiagnosed opening of a retraction pocket. It is assumed that the retraction continues to grow and the sac fills with the desquamated cells leading to the accumulation of keratin and cholesteatoma formation.

It is the case, however, that retraction pockets are common whereas cholesteatomas are uncommon. There are factors in the development of cholesteatoma other than just Eustachian tube dysfunction. Ruedi[136] suggested that papillary ingrowth of squamous epithelium through its own basement membrane in the pars flaccida could result in a cholesteatoma. Inflammation in the middle ear in addition to retraction pocket formation is likely to be an important factor and the retraction pocket formation and papillary ingrowth of squamous epithelium may coexist as a mechanism for the aetiology of cholesteatoma.[137]

In cholesteatoma, as in a normal wound, there is hyperproliferation and migration of the epithelium but, unlike the situation in a wound, this growth pattern persists.[138] It may be that the area of maximum growth is found in the neck of the cholesteatoma sac.[139]

Cholesteatomas may result from implantation of squamous epithelium into the middle ear. This could occur as a result of trauma to the tympanic membrane, either through injury or by surgery. Although likely to exist as a mechanism for their development, it could only account for a small proportion of cholesteatomas.

DIAGNOSIS AND ASSESSMENT

Iain R.C. Swan

INTRODUCTION

Examination of the ear with a microscope is the 'gold standard' for the diagnosis of COM although to reach an acceptable standard requires training, aided by operative experience exploring ears that have previously been otoscopically assessed. History taking and investigations are an aid to management rather than to diagnosis.

OTOSCOPY

Whenever there is a suggestion of COM, otoscopy is improved by using a microscope and appropriate aural speculum. This also greatly facilitates aural toilet, which is almost always required to fully visualize all areas. Such toilet can be any combination of suction, irrigation, mopping or instrumental removal (see Chapter 73, Clinical examination of the ears and hearing).

An otoscopic camera linked to a monitor gives a good overall view of anatomy and pathology that is particularly applicable if there is an open mastoid cavity. It is also helpful in viewing the anterior recess of the tympanic membrane, which is often blocked from view by the anterior canal bulge. A camera is extremely useful for teaching and to explain disease to the patient.

After any aural toilet, the clinician has to assess all areas of the external ear and the tympanic membrane to decide if there is pathology and if so what the pathology is (see **Table 83.1**). Before illustrating examples of various pathologies in different areas, some aspects that are generally applicable are discussed.

OPERATION SCARS

Prior to otoscopy, operation scars should be looked for. Endaural scars (see **Figure 73.2** in Chapter 73, Clinical examination of the ears and hearing) can be difficult to detect but suggest previous middle ear surgery which may have included canal wall-down mastoid surgery. Postauricular scars (see **Figure 73.3** in Chapter 73, Clinical examination of the ears and hearing) suggest previous surgery requiring access to the middle ear or mastoid singly or in combination.

SITE OF PATHOLOGY

Anatomically the pars tensa can be divided into four quadrants (**Figure 83.9**) but pathology, such as perforations, tends to be anterior, posterior or inferior (**Figure 83.10**). Hence, division into thirds rather than quarters is preferred. To record the proportion of the pars tensa involved by a specific condition, percentages are preferred to non-defined terms such as small, large and subtotal. By definition, all perforations of the pars tensa are 'central', indicative of 'tubotympanic disease'. The pars flaccida in the attic has to be cleared of any debris and assessed for pathology which may occur alone or along with pars tensa disease. By definition, all attic disease is 'atticoantral' and 'marginal'. The attribution of the term 'marginal' goes along with the absence of an annulus, which is not normally present in the attic/pars flaccida. If the term 'marginal' is applied to pars tensa pathology, its interpretation becomes confusing and should be avoided. The annulus is almost invariably present in pars tensa perforations unless it has been previously removed surgically.

OPEN MASTOID CAVITIES

These are usually created surgically but can occur spontaneously by the natural resolution of attic cholesteatoma, albeit the resultant cavity is usually small and confined to the atticoantral region (**Figure 83.11**). Open mastoid cavities can be difficult to detect if there is a narrow external auditory meatus or the cavity is not in continuity with the attic/antrum (**Figure 83.12**). If an ear has been operated on, and in particular if there is a postauricular scar, the

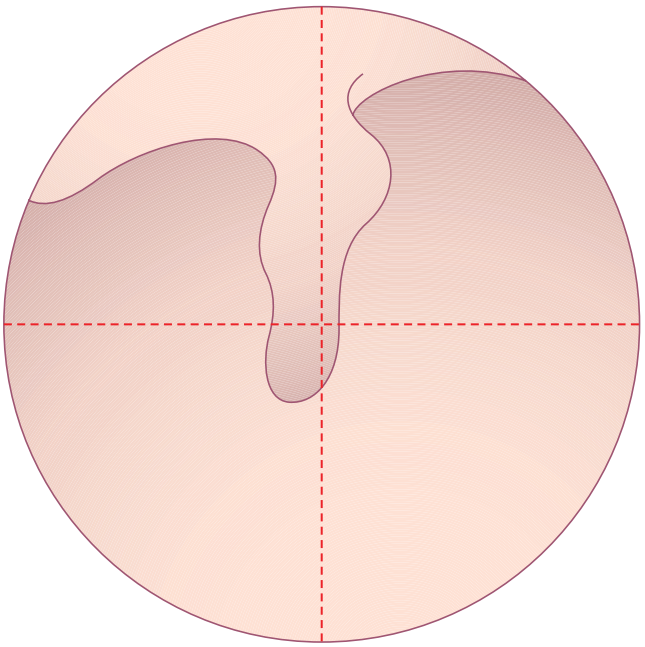


Figure 83.9 The four quadrants of the pars tensa (right ear).

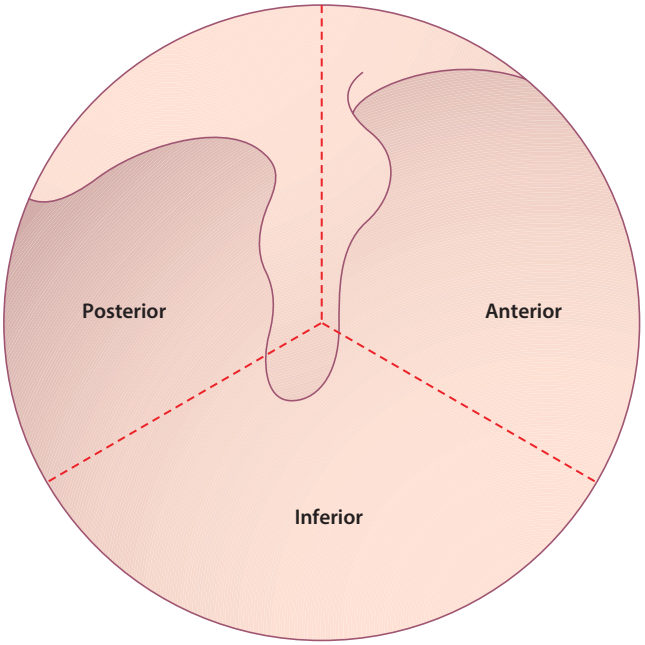


Figure 83.10 The three thirds of the pars tensa (right ear).

posterosuperior canal wall should always be closely examined. Sometimes, because of a narrow external auditory meatus or a high, residual posterior canal wall, an open cavity cannot be fully viewed.

ACTIVE OR INACTIVE?

A decision as to whether an ear is currently active, i.e. inflamed with the production of inflammatory products including pus, is primarily based on visualization of an inflamed mucosa and secretions. In squamous epithelial disease that is active with a cholesteatoma, there is almost invariably associated

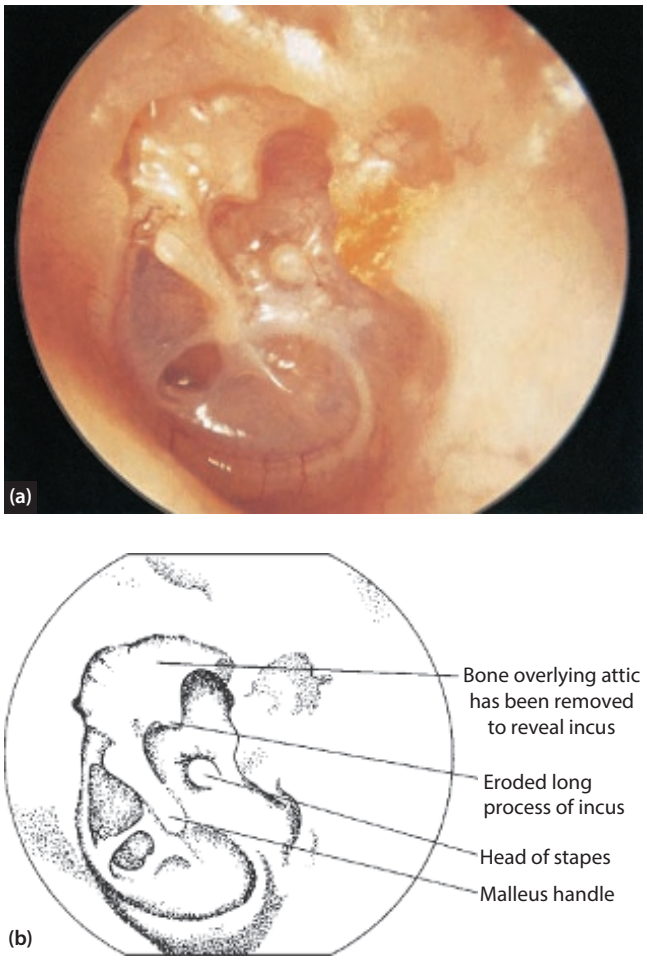


Figure 83.11 Left atticotomy. The attic has been exposed by drilling and is lined by a dry retraction pocket, part of which is out of vision. The malleus handle and body are present, as is the body of the incus. The long process of the incus has been eroded. The pars tensa is intact but retracted onto the head of the stapes.

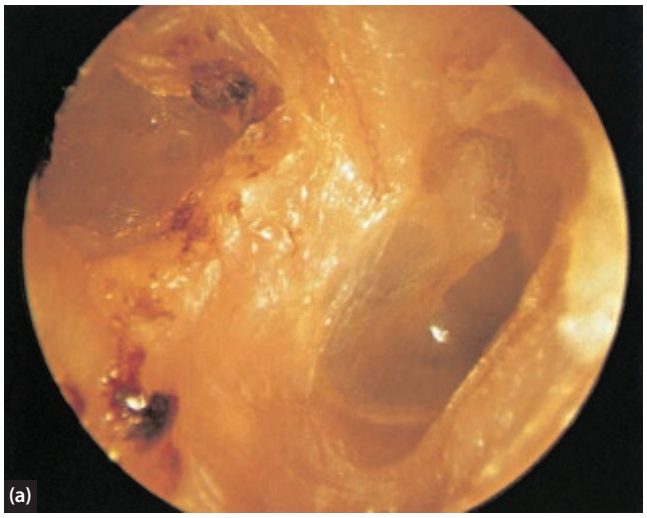
mucosal disease that can be seen and produces the secretions, perhaps along with squamous epithelial debris. Secretions, and in particular mucopus, can dry and be mistaken for wax. Once removed, the underlying disease may still be active or have become inactive (Figures 83.13 and 83.14).

OTOSCOPIC DIAGNOSTIC CATEGORIES

In an ear with COM that has not previously been operated upon, it should be possible otoscopically to put the ear into one of four diagnostic categories (see Table 83.1).

Healed otitis media

This term is given to an ear where the pars tensa is intact but abnormal. Such a diagnosis can be, and often is, in association with other middle ear conditions such as OME. The most common abnormality of the pars tensa is chalk patches/tympanosclerotic plaques, there being no



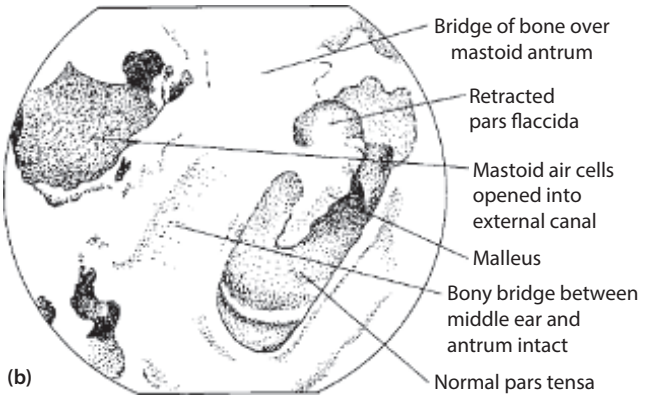


Figure 83.12 Right inactive modified (Heath) mastoidectomy. The pars tensa is normal. The pars flaccida is retracted but inactive. Posteriorly, the mastoid air cells have been surgically opened into the external canal by partial removal of the posterior canal wall. The bridge of bone over the incudal fossa and the mastoid antrum is normally removed in a modified radical mastoidectomy (and in an attico-antrostomy). It has not been removed in this case. There is no evidence of activity.

clear distinction between these two terms (Figure 73.17 in Chapter 73, Clinical examination of the ears and hearing; and Figure 83.15). The other abnormality covered by the definition of healed otitis media is thin replacement membranes, usually circular in outline and suggestive of an old perforation that has healed without the middle, fibrous tissue layer (Figure 83.16). When there is uncertainty as to whether such an area is a perforation or not (Figure 83.17), pneumatic otoscopy can be of value, or the patient can be asked to perform a Valsalva manoeuvre. Replacement membranes may be slightly retracted (Figure 83.18), when the additional diagnosis of OM with effusion should be considered. The distinction between these localized and more generalized, posterior marginal retractions is discussed below.

Inactive (mucosal) COM

This diagnosis implies a permanent perforation of the pars tensa and that the middle ear mucosa, as seen through the perforation, is inactive (Figures 83.19, 83.20 and 83.21).

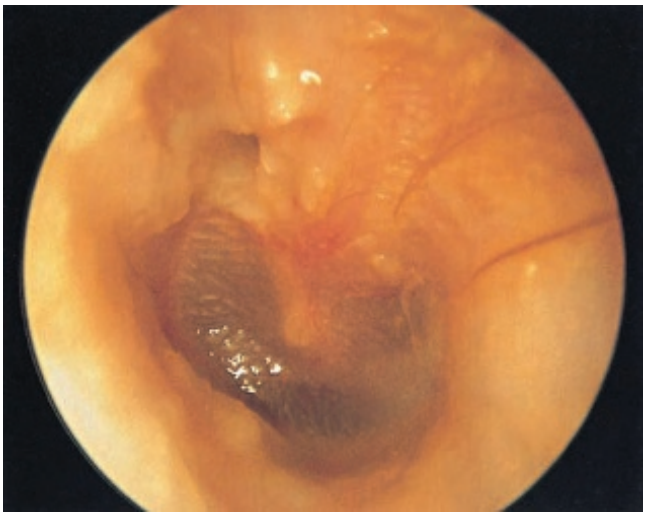


Figure 83.13 Left active COM. Pars flaccida obscured by pus. The pars tensa is normal.

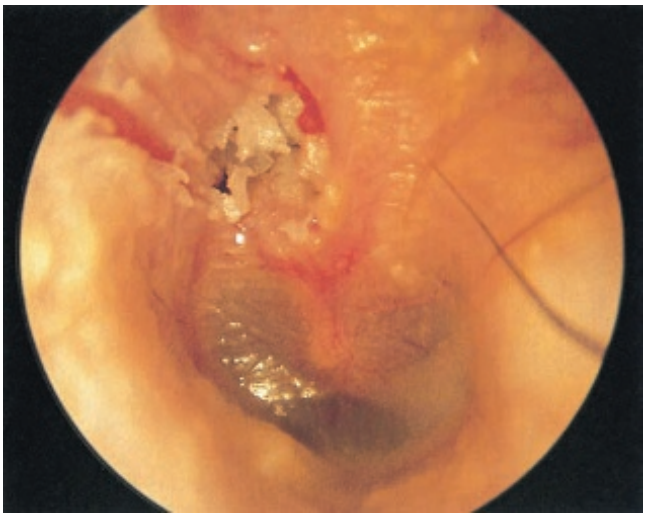


Figure 83.14 Same ear as Figure 83.13 after aural toilet. Active COM clearly visible affecting pars flaccida in the attic. The white debris is squamous epithelial debris, indicative of cholesteatoma.

Active (mucosal) COM

Activity is evident, usually with a generally inflamed middle ear mucosa, but sometimes with granulation tissue that is localized (Figure 83.22) and which can become polypoidal (Figure 83.23).

In both active and inactive COM, particularly when the defect involves the posterior third, the intactness or otherwise of the ossicular chain should be assessed and recorded (Figures 83.21, 83.24 and 83.25). Surgical classifications for these have been proposed but most prefer to record what the defects are, if any.

Inactive (squamous) retractions

These can occur in the pars tensa or the pars flaccida. Pars tensa retractions are primarily of the posterior tympanic membrane, the classification most used to document their

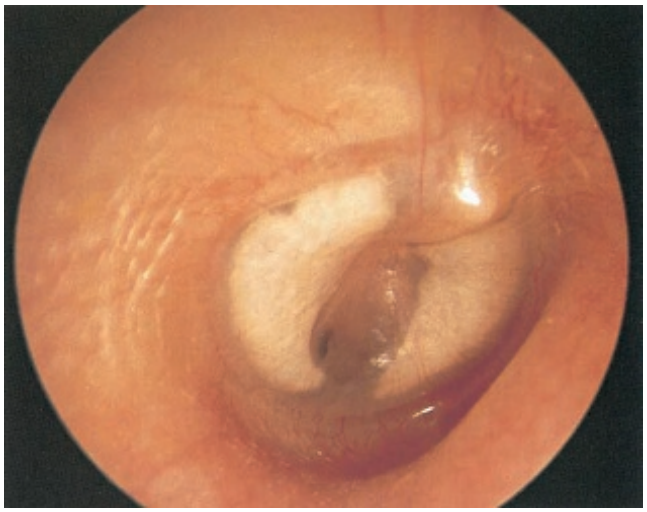


Figure 83.15 Tympanosclerotic plaques, one anterior, one posterior (right ear).

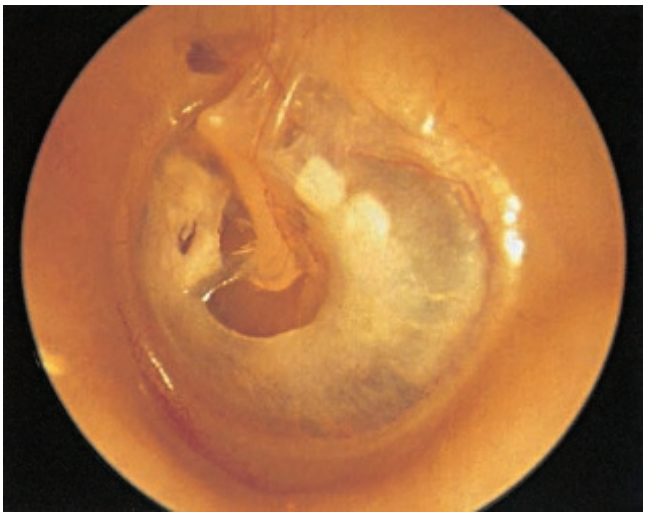


Figure 83.17 Scarred pars tensa associated with left healed otitis media.

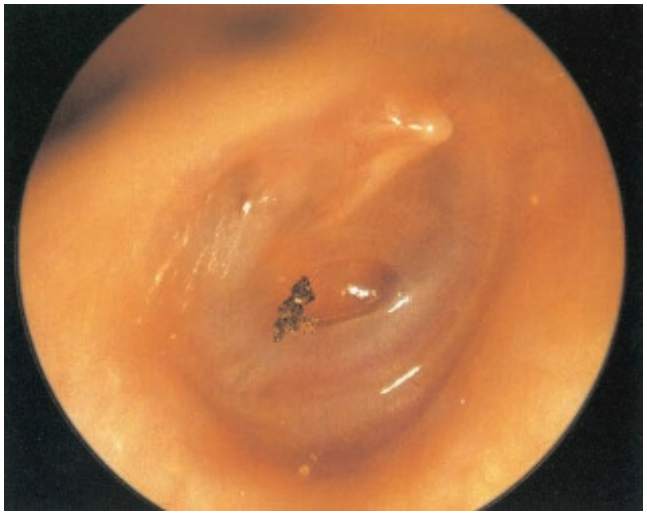


Figure 83.16 Healed otitis media (right). In this ear there is a thin replacement membrane over what is presumed to be an old inferior perforation.

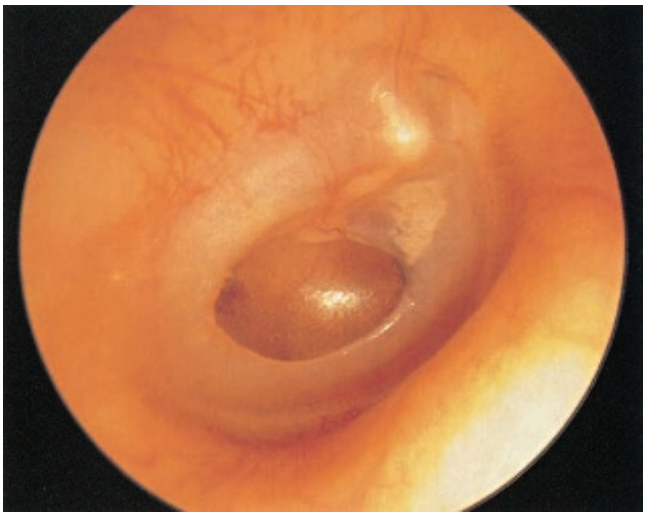


Figure 83.18 Localized retraction of pars tensa affecting central area (right ear).

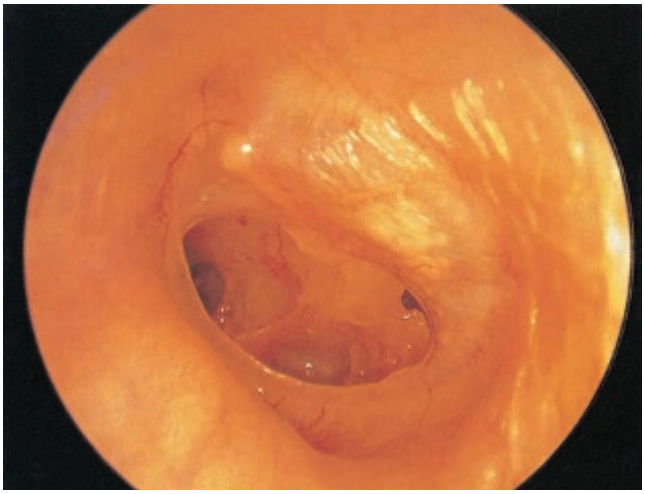


Figure 83.19 Inactive left COM. There is anterior inferior pars tensa defect through which the middle ear mucosa can be seen to be normal, i.e. not inflamed.

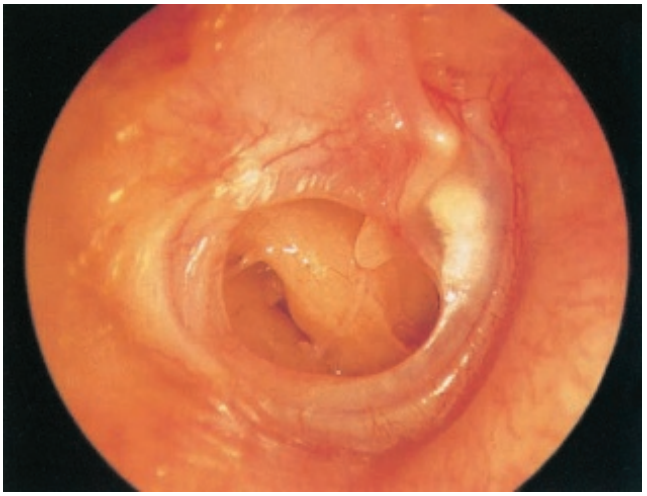


Figure 83.20 Inactive (mucosal) chronic otitis media, right ear.

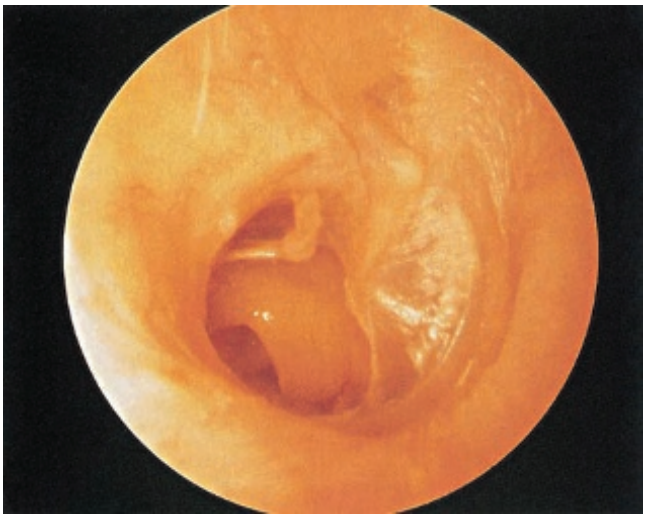


Figure 83.21 Not eroded long process of incus in inactive (mucosal) COM (right ear).

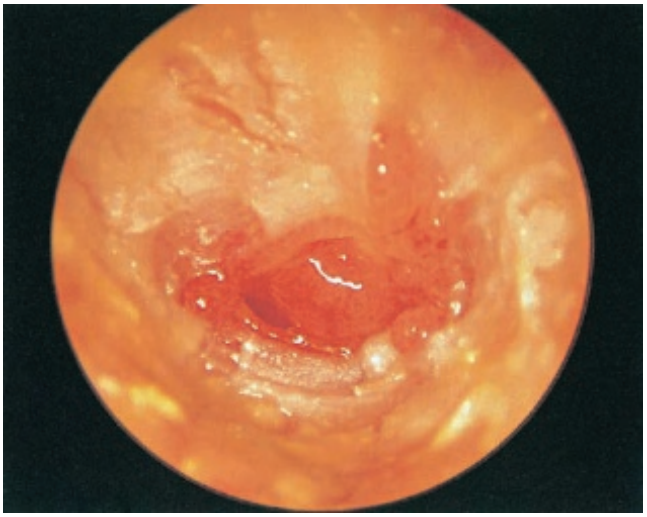


Figure 83.23 Left active mucosal COM. There is pus and debris on the canal wall. The tympanic membrane cannot be fully visualized but there appears to be an inferior defect. The main finding is a polyp protruding through the perforation and granulation tissue on the remaining tympanic membrane.

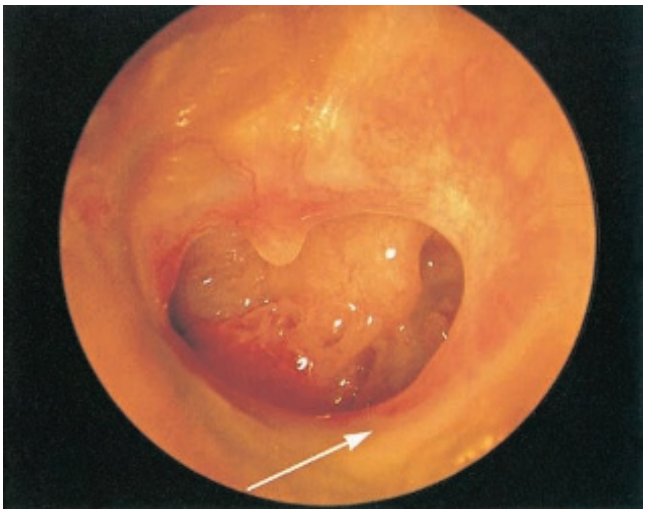


Figure 83.22 Left active mucosal COM. There is pus on the canal wall. The middle ear mucosa, seen through a 60% inferior pars tensa perforation, is minimally inflamed. The activity is mainly from granulation tissue on the edge of the perforation (arrowed).

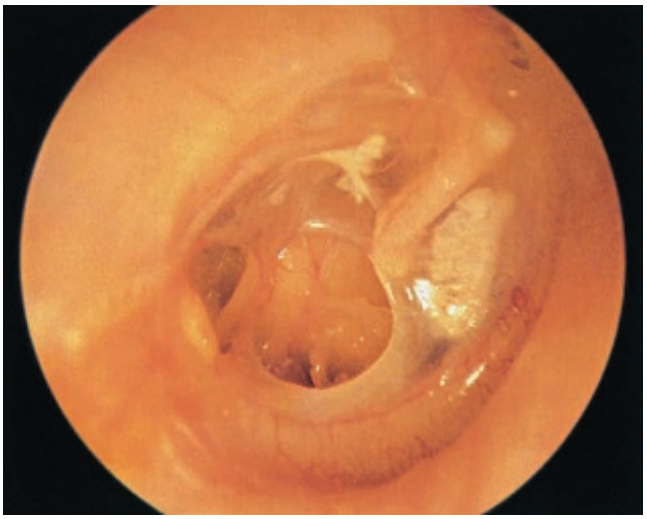


Figure 83.24 Posteroinferior perforation in inactive (mucosal) COM (right ear).

degree being that of Sadé and Berco.[140] In essence, what requires to be recorded is what structures the pars tensa is retracted onto and whether the pars tensa is adherent to them. Most important is whether the retraction is totally in view or whether there are areas out of view that might not be self-cleansing and have the potential to become active with a cholesteatoma (Figures 83.26, 83.27, 83.28, and 83.29).

Pars flaccida retractions have been diagrammatically classified into four stages by Tos et al.[141] (Figure 83.30). In stage 1, the pars flaccida is dimpled and more retracted than normal but not adherent to the malleus (Figure 83.31). In stage 2, the retraction is adherent to the neck of the malleus and the full extent of the retraction can be seen (Figure 83.32). In stage 3, part of the retraction is out of view and there may be partial erosion of the bony attic wall (Figure 83.33). In stage 4, there is definite erosion of the attic wall with the full extent of the retraction being uncertain because it is out of view (Figure 83.34). Tos's classification is relatively simple to apply, the only difficulty being making a distinction between stages 3 and 4. Hence, these are often grouped together as stage 3/4.

Cholesteatoma (active squamous disease)

Cholesteatomas are the end stage of (squamous epithelial) retractions of the pars tensa (Figure 83.35) or flaccida (Figure 83.33) that are not self-cleansing, retain epithelial debris and often elicit a secondary, inflammatory mucosal reaction. In the majority of cases the extent of the cholesteatoma cannot be determined otoscopically because the retraction pocket containing the debris is not fully in view.

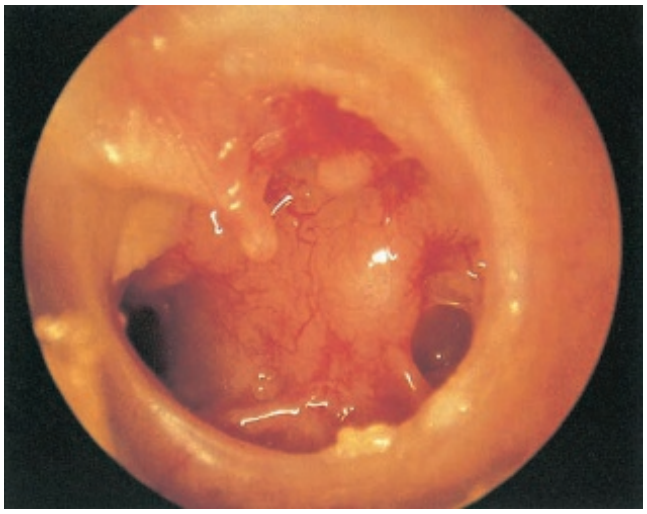


Figure 83.25 Active left mucosal COM. In this ear the stapes is seen through the perforation. The long process of the incus has been eroded.

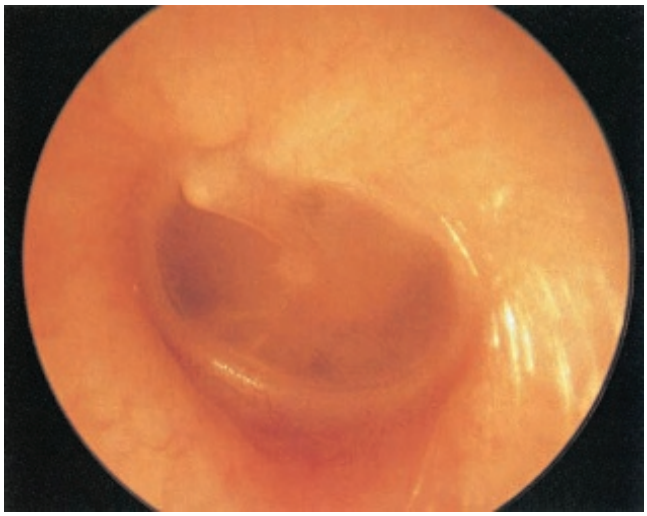


Figure 83.26 Stage 1: pars tensa retracted. There is no middle ear fluid (left ear).

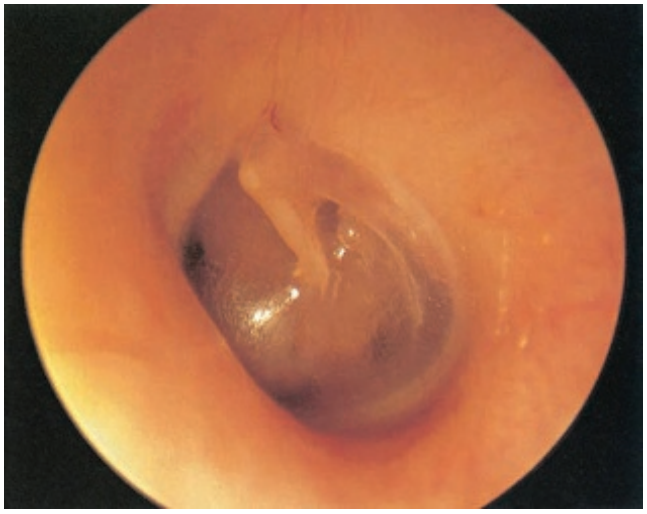


Figure 83.27 Stage 2: Pars tensa severely retracted. The tympanic membrane is in contact with the long process of incus (left ear).

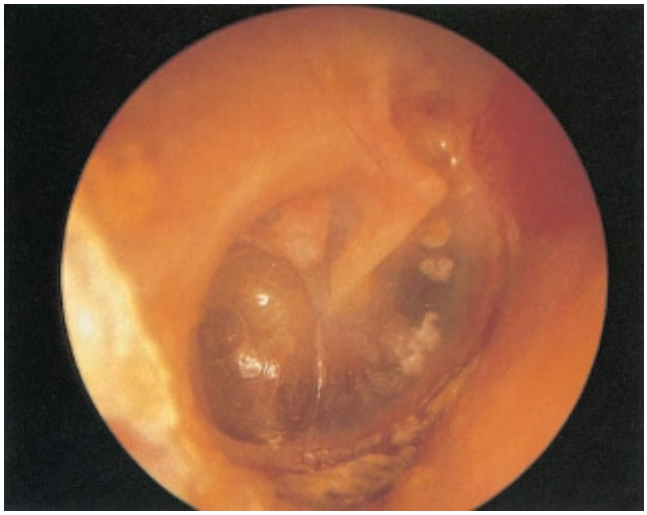


Figure 83.28 Stage 3: Posterior retraction of tympanic membrane onto promontory. Ossicular chain intact. Small anterior chalk patch (right ear).

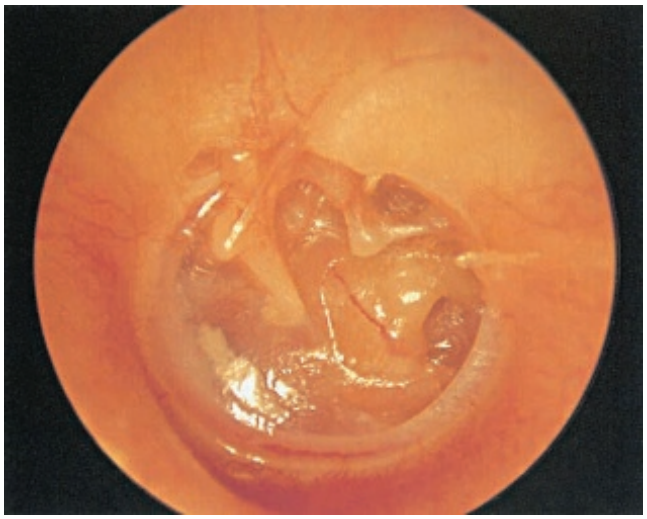


Figure 83.29 Stage 4: Adhesive otitis. the pars tensa is adherent to the promontory and draped around the long process of the incus and stapes (left ear).

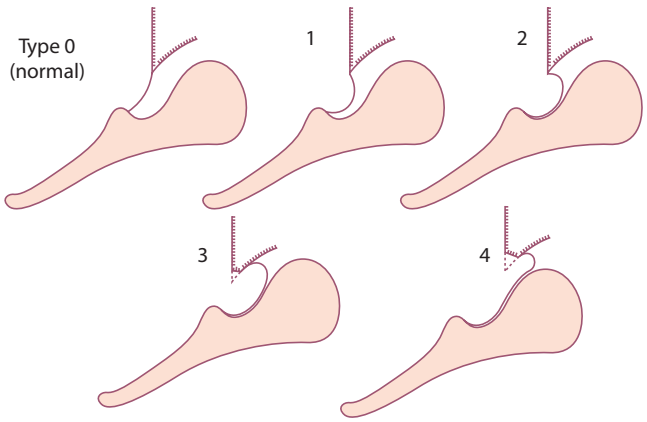


Figure 83.30 Staging of attic retraction. Redrawn with permission from Tos et al.[141]

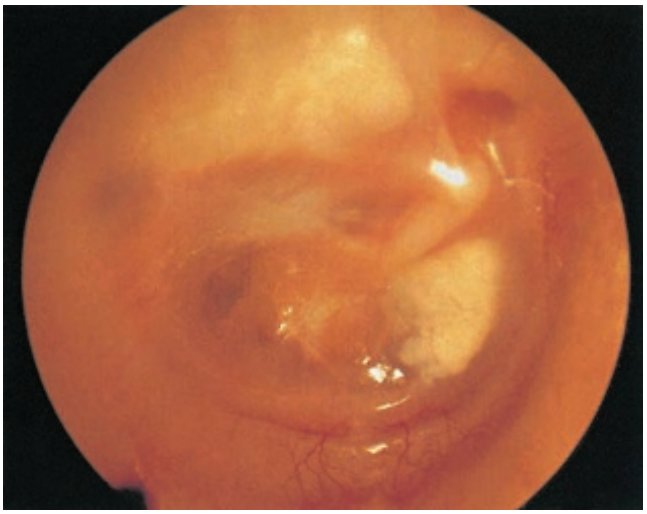


Figure 83.31 Stage 1 retraction of pars flaccida. Simple attic dimple. Coincident anterior tympanosclerotic patch of pars tensa (right ear).

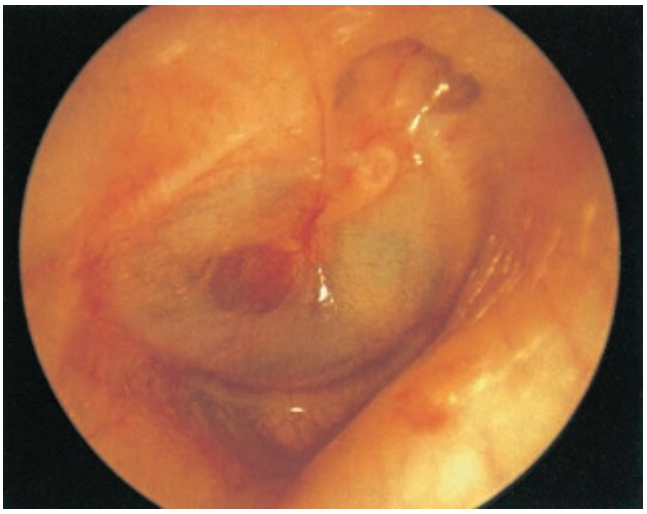


Figure 83.32 Stage 2 retraction of pars flaccida. Retraction adherent to neck of malleus (right ear).

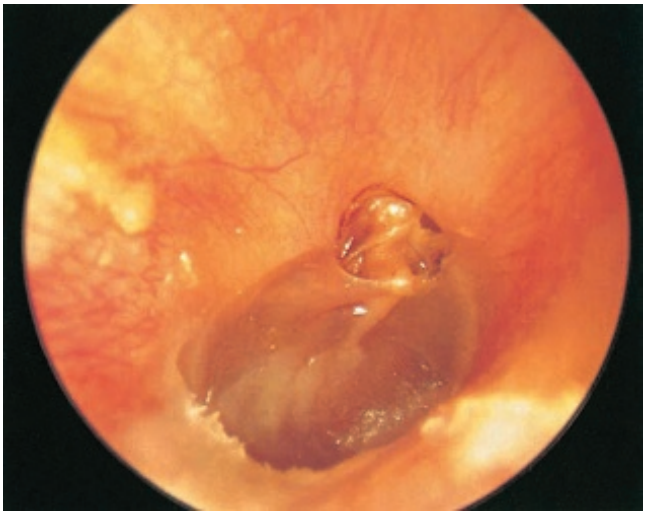


Figure 83.33 Stage 3 retraction of pars flaccida. Part of retraction out of view. Suggestion of middle ear fluid (right ear).

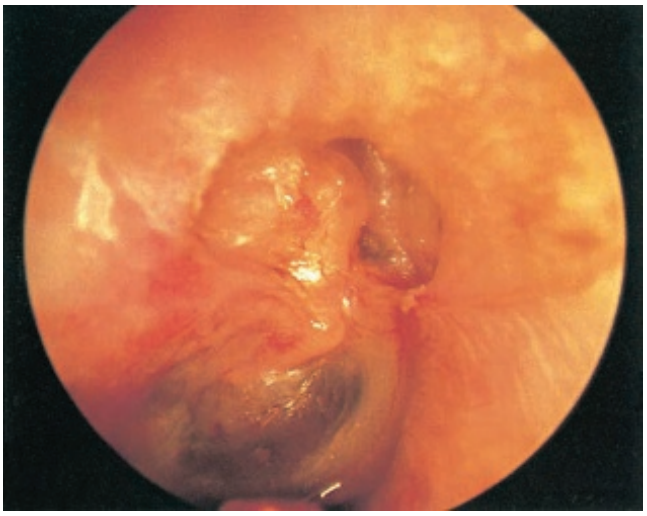


Figure 83.34 Stage 4 retraction of pars flaccida. Erosion of bony attic wall and part of retraction out of view. No activity (right ear).

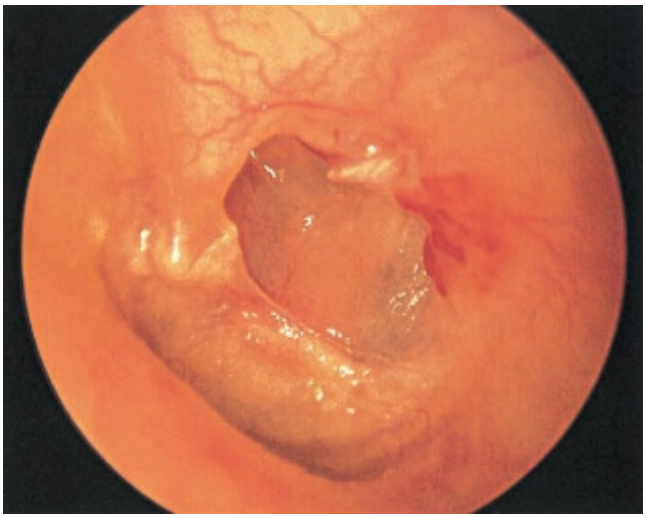


Figure 83.35 Posterior atelectactic pars tensa with erosion of posterior canal wall, as well as long process of incus and stapes superstructure. Prominent granulations on posterior canal wall suggestive of progressive cholesteatoma (left ear).

HISTORY

As COM will be diagnosed in the majority of cases by otoscopy, history taking should focus on symptoms and previous management. This allows future management and potential outcomes to be discussed more appropriately. An exception to this attitude is when there is a history of peripheral type vertigo. If present, this merits more detailed assessment (see 'Labyrinthine complications' below).

The majority of adults (~80%) presenting with COM report a hearing impairment and approximately 70% an ear discharge (Table 83.5).[142] Even in those with currently active COM, only around 75% will report a current discharge and there is no difference in this report whether a cholesteatoma is present or not. There also is no apparent difference in the smell associated with cholesteatoma compared with active mucosal disease.[143]

TABLE 83.5 Symptoms of active COM, broken down into mucosal disease and cholesteatoma (squamous disease)

Symptom	Percentage	
	Active mucosal	Cholesteatoma
Hearing loss	74	83
Otorrhoea	69	56
Otalgia	37	39
Childhood ear disease	26	43

Reprinted from Sheahan et al.,[142] with permission.

Enquiry will be made as to any previous surgery and about recent topical aural medications and how effectively they were used.

AUDIOLOGY

Pure-tone audiometry, air and bone conduction with appropriate masking will provide numerical values to the degree of hearing impairment, the magnitude of the air–bone gap and whether there is an associated sensorineural impairment for each of the two ears. Such information is important to inform decisions regarding management.

ADDITIONAL INVESTIGATIONS

Additional investigations are only relevant if they modify, to a material extent, decisions that have been previously made based on otoscopy, history and pure-tone audiometry.

Vestibular assessment

Vestibular assessment will be performed on those with episodes of peripheral-type vertigo and some patients undergoing revision surgery. A fistula test, if positive with the production of acute vertigo accompanied by nystagmus, is suggestive of a semicircular canal fistula created by a cholesteatoma or previous mastoid surgery. A negative fistula test does not exclude such conditions. Caloric testing to determine whether there is residual vestibular function after previous surgery can be helpful in determining which surgical procedures are applicable.

Imaging

High-resolution computed tomography (CT) scanning in both the coronal and axial planes of the temporal bone is recommended in the pre-operative evaluation of cholesteatoma.[144] CT may help to assess the extent of disease in a partially aerated mastoid. However, cholesteatoma appears as a homogeneous mass with similar density to oedematous mucosa and to brain tissue. In the absence of aeration, the extent of disease is rarely visible, though it may be suggested by erosion of air cells. CT shows the pneumatization of the mastoid which may influence surgical approach and will demonstrate any anatomical variants. It may demonstrate erosion of the bony labyrinth, most commonly the lateral semicircular canal, the tegmen tympani, or of the facial canal, but cannot be relied upon to do so.[145]

Diffusion-weighted magnetic resonance imaging (DW-MRI) differentiates cholesteatoma and inflammatory tissue and brain. It has been shown to be reliable at detecting small residual or recurrent cholesteatoma after surgery, and at assessing the intracranial extension of cholesteatoma.[146] As DW-MRI becomes more widely used, it is likely to replace second-look operations in some patients after intact canal wall mastoid surgery.

Endoscopy

The endoscope is sometimes useful in the outpatient clinic. It may allow assessment of the extent of a retraction pocket in a patient who is not particularly fit for surgery. It may help to visualize the middle ear in patients with very narrow ear canals.

Bacteriology

Bacteriological and fungal cultures are of potential value only when the ear is active or if there are infective complications. If systemic antibiotic therapy is being contemplated, culture of any secretions with antibiotic sensitivity pattern of any growths being assessed can be of value in deciding which antibiotic to prescribe as most do not cover the full range of bacteria that can be isolated as potential pathogens from the ear. The same could be said for topical antibiotic therapy although, if gentamicin or ciprofloxacin is chosen, their spectrum is broad enough to cover most probabilities.

NATURAL HISTORY, MANAGEMENT AND OUTCOMES

Iain R.C. Swan

INACTIVE MUCOSAL CHRONIC OTITIS MEDIA

Natural history

Inactive mucosal COM (see **Figure 83.19**) is the condition of the middle ear where the structure and often the hearing are impaired by the presence of a permanent tympanic membrane defect, but in which there is no active infection or mucoid discharge. Such an ear may remain inactive, become active or even occasionally heal.

PROGRESSION TOWARDS HEALING

The progression towards healing is presumably impaired by the disease that resulted in COM in the first place. This is usually recurrent episodes of acute infection with

perforation of the tympanic membrane, which initially heals successfully within a few days, but after a variable number of attacks the tympanic membrane fails to heal. This is regarded as a result of failure of the blood supply to the perforation edges due to endarteritis, but there may be other factors related to repair mechanisms at cellular level. If for any reason the blood supply improves, this may tip the balance in favour of healing. There are no data on the probability of this occurring but observation and experience suggest that natural healing is a relatively rare event in adults though it appears to occur more often in children. Lehmann et al.[147] reported a significant reduction in the prevalence of tympanic membrane perforations in Aboriginal children due to improved hygiene after the opening of a community swimming pool. It is probable that closure will only occur following a period of disease inactivity and this is the goal of medical therapy in mucosal disease and indeed the goal of surgical treatment is to achieve a healed state.

PROGRESSION TOWARDS ACTIVITY

Progression towards activity is more common, theoretically provoked by factors such as a URTI or the ingress of water, particularly if contaminated by bacteria or irritants. The diverse flora occurring in active ears and the fact that the bacterial flora are similar in mucosal and squamous epithelial disease suggest that bacterial contamination is not the primary event in most cases.[121] It is the increased mucus production that provides the culture medium for opportunist organisms to flourish. The fact that the same organisms may be isolated from inactive as from active ears in 50% of cases would also support this contention.[120] Traditional concepts about the role of sinonasal disease in the precipitation of activity in COM are not supported by convincing evidence.

Presentation

Inactive COM presents with a hearing impairment or may be an incidental finding in older patients with a mixed hearing impairment. Some patients present because of discomfort in the ear during swimming when water gets into the middle ear. A careful history of discharge should be sought. If the only history of discharge is many years previously, this may not influence management. However, many patients have more recent episodes of discharge and this does influence management.

Examination

Pure-tone audiometry assesses the magnitude of the conductive hearing impairment due to the disease. The degree of air–bone gap depends on:[148]

- the size of the perforation in the tympanic membrane
- erosion of the ossicular chain, most commonly the long process of the incus and sometimes also the stapes superstructure
- significant granulation tissue around the ossicular chain which can reduce its mobility
- tympanosclerosis around the ossicular chain.

If surgery is contemplated, microscopic examination is important as this may give some information about the state of the ossicular chain.

Management

Management options are surgery, a hearing aid or no treatment. Hearing aids should always be considered in the management of hearing disability (see 'Hearing aids in chronic otitis media' below).

OBJECTIVES OF SURGERY

The aim of middle ear surgery for hearing is reduction in the patient's hearing disability, not just closure of the air–bone gap. Hearing disability is largely dependent on the hearing in the better-hearing ear, therefore the hearing thresholds in the non-operated ear need to be taken into account when considering the likely benefit to the patient from reconstructive surgery. If successful closure of the air–bone gap still leaves the patient with significantly poorer hearing in the operated ear, then benefit from successful surgery is dubious. The objectives of any surgery should be carefully considered. Dry perforations that are symptom-free do not usually require closure. If the only symptom is a hearing impairment, the chances of improving hearing with surgery should be considered carefully, not just the hearing in the operated ear but the overall hearing ability of the patient. In patients with a history of intermittent activity, surgery to close the perforation is probably indicated to minimize future activity. Those patients whose main symptom is discomfort when swimming should be encouraged to wear ear plugs. These are usually extremely effective at preventing discomfort and are a simpler and safer option than surgery.

MYRINGOPLASTY

Tympanoplasty refers to any operation involving reconstruction of the tympanic membrane and/or the ossicular chain. Myringoplasty is a tympanoplasty without ossicular reconstruction. Over the years many methods have been used for closing perforations. The most widely used and accepted method is underlay graft of temporalis fascia or sometimes perichondrium. Cartilage has become increasingly popular as a graft material, particularly when the tympanic membrane is retracted (see discussion of myringoplasty in 'Inactive squamous chronic otitis media' below). The basic procedure is to excise the rim of the perforation so that there is a raw surface from which new tissue will grow. The mucosa on the undersurface of the remaining tympanic membrane near to the perforation is removed or scraped with a sickle knife or similar instrument to provide a bed for the graft. This is then placed under the tympanic membrane remnant and acts as a scaffold for new growth of the squamous epithelial layer. The mucosa over the promontory should be carefully preserved to reduce the likelihood of post-operative adhesions between the graft and the promontory.

Outcomes: tympanic membrane take rate

The success rate in achieving an intact tympanic membrane in expert hands is often quoted as around 95%. However, when results of large numbers of operations in the hands of many surgeons are reported, the success rate is much lower (**Table 83.6**). Palva and Ramsay[149] looked at the outcome of 281 myringoplasties in their department. The closure rate in Palva's hands was 97%, while in the hands of other members of the department it was only 74%. Similarly, Vartiainen[150] reported that the successful tympanic membrane closure rate for trainees was 78% compared to 95% for the senior staff. Successful outcome seems to be significantly influenced by the expertise of the surgeon. Many reports of results are based on relatively short follow-up of 6–12 months. However, longer-term follow-up suggests that some ears which are initially intact develop recurrent perforation.[151]

The closure rate is reported to be higher in small perforations (74%) than large perforations (56%).[154] Numerous authors have reported that the failure rate in anterior perforations is higher. However, this failure rate can be greatly reduced by anchoring the anterior margin of the graft beneath the annulus.[156]

There is no evidence that prophylactic antibiotics influence closure rate or other outcomes. A Cochrane review found 11 randomized trials of prophylactic antibiotics in middle ear surgery. None of these trials reported significant difference in outcomes between the prophylactic antibiotic and control groups.

Revision surgery can be considered in those ears where the graft fails. The possible reasons for failure should be considered and, if necessary, the surgical method can be modified. Halik and Smyth[151] found that only 60% of tympanic membranes were intact after revision surgery, which is a much lower success rate than usually claimed for primary surgery.

Outcomes: hearing

Successful closure of the tympanic membrane usually gives only a small improvement in hearing (Table 83.7).

It is uncommon to get total closure of the air–bone gap in myringoplasty, as closure of a tympanic membrane perforation does not make the ear a normal ear. In those patients in whom the air–bone gap is 35 dB or more, there will be either erosion or fixation of the ossicular chain.[148] Here, surgery would require myringoplasty and ossiculoplasty (see below).

TABLE 83.6 Successful closure rate in myringoplasty

Reference	No. of cases	Closure rate (%)
Kotecha et al.[152]	1070	82
Wielinga et al.[153]	555	88
Lee et al.[154]	423	64
Black and Wormald[155]	211	78

Complications

The complication rate in myringoplasty is low in all series. Kotecha et al.[152] reported one facial nerve palsy in 1070 patients and one extradural abscess.

OSSICULOPLASTY

The most common pathology in the middle ear is erosion of the long process incus. This is reasonably straightforward to correct surgically. The preferred option is to place a prosthesis between the handle of malleus and the head of stapes. Various materials are used, most commonly autograft incus or head of malleus and alloplastic prostheses. When the stapes superstructure is also missing, the malleus handle has to be connected to the stapes footplate and autograft materials are rarely suitable. Occasionally there is also erosion of the malleus handle; here the prosthesis connects the tympanic membrane directly to the stapes superstructure or footplate. The choice of material is largely dependent on the situation in the operated ear and the surgeon's personal preferences. Homograft materials are not recommended because of the theoretical risk of transferring prion disease.

Outcomes

There are many reports in the literature of the outcome of ossiculoplasty. Iurato et al.[157] reviewed 20 published reports of the results of ossiculoplasty when the malleus and stapes superstructure were present. In expert hands, a post-operative air–bone gap of 0–10 dB is achieved in only 50% of patients while 80% have an air–bone gap of 0–20 dB. Iurato found no reported difference in hearing outcome between different types of prosthesis.

When there is erosion of the stapes superstructure as well, the success rates of surgery are generally lower. Mills[158] reported a mean hearing improvement after ossiculoplasty of 14 dB when the stapes arch was intact and 6 dB when it was eroded. Shinohara et al.[159] reported 68% 'success' rates at 1 year with partial ossicular replacement prostheses where only the incus needs to be replaced. This compares with 46% for total ossicular replacement prostheses where the incus and the stapes superstructure are absent, though 'success' was not defined.

Most authors report the results of surgery after 3–12 months. Those who look at long-term results report that success rates are lower: at 5-year follow-up, Shinohara's 'success' rates had fallen to 60% (from 68% at 1 year) and 34% (from 46%).[159]

Myringoplasty and ossiculoplasty can be carried out as a one- or two-stage operation. It is generally accepted that the success rate of ossiculoplasty is higher if the procedure is staged, but this is to be expected as only those ears that have a closed aerated middle ear are chosen for the second-stage procedure. Staging does require two separate operations, and most surgeons would carry out a one-stage procedure if it seemed feasible in that particular ear. It would seem much more efficient to attempt a one-stage procedure and revise it if it fails.

TABLE 83.7 Hearing after successful myringoplasty

Reference	No. of cases	Mean hearing improvement (dB)	Residual air–bone gap (dB)
Lee et al.[154]	261	8.1	–
Palva and Ramsay[149]	281	8.0	9.3

TYMPANOSCLEROSIS AND SURGERY

Tympanosclerosis is found in the middle ear in around 25% of ears at surgery. In some cases, the mobility of the ossicular chain is reduced by tympanosclerosis in the attic or in the oval window. If the ossicular chain is intact and only the incus and head of malleus are fixed, this can be corrected by removing the incus and head of malleus and reconstructing the ossicular chain between handle of malleus or tympanic membrane and stapes. Alternatively, the outer attic wall can be removed and the malleus and incus mobilized. This is often effective in the short term, but there is a tendency for refixation of the ossicles by fibrous tissue or bone.

When the stapes is involved, surgery involves mobilization of the stapes or stapedectomy. Results of stapes surgery in tympanosclerosis are not as good as in otosclerosis with a post-operative air–bone gap of 20 dB or less reported in only 72% (111 of 154 operations)[160] and 70% of cases (45 of 64 operations).[161] The complications of surgery, such as dead ear, are reported to be more common; Albu et al.[162] reported a 4% (1 of 25) and Gormley[163] a 5% (3 of 67) incidence of post-operative sensorineural loss.

THE EUSTACHIAN TUBE AND SURGERY

An aerated middle ear is necessary for middle ear function. Sometimes reconstructive middle ear surgery that appears technically successful at the time of surgery subsequently has a poor outcome because of non-aeration of the middle ear. A functioning Eustachian tube is necessary for an aerated middle ear. Assessment of Eustachian tube function pre-operatively is a poor predictor of the successful closure of the tympanic membrane.[164] If the contralateral ear is atelectatic, suggesting poor Eustachian tube function, it is unlikely that the Eustachian tube will function in the operated ear.

New methods of improving Eustachian tube function have been tried in recent years. In laser tuboplasty, soft tissue in the wall of the Eustachian cushion is ablated. Kujawski and Poe reported improved tubal function in 65% of patients,[165] but long-term outcomes are not yet known. In balloon Eustachian tuboplasty, a balloon catheter is inserted into the tubal ostium and inflated for 2 minutes. Sudhoff et al. reported that 87% of 351 patients were satisfied with the improvement in tubal function after 12 months;[166] long-term results are awaited. In actively inflamed ears, it is possible for Eustachian tube function to improve when the middle ear mucosa reverts to a more normal state after closure of the tympanic membrane. It may sometimes be worthwhile inserting a VT in the tympanic membrane, or in the graft, as a temporary method of improving aeration, hoping that the function of the Eustachian tube will improve.

KEY POINTS

- The degree of hearing impairment depends on the size of the perforation and the state of the ossicular chain.
- Myringoplasty closes perforations in 64–95% of cases, depending on the experience of the surgeon.
- As the hearing improvement from ossiculoplasty when the malleus and stapes are present is only 14 dB, hearing aids should always be considered in management.

ACTIVE MUCOSAL CHRONIC OTITIS MEDIA

Natural history

Active mucosal COM (see **Figure 83.25**) may remain active, become inactive or progress to complications. Continuing activity may be the result of infection with a particularly virulent or persistent organism, commonly *Pseudomonas*. Impaired immunity plays a role in some groups of patients such as diabetics but the increased incidence of active COM in deprived communities in the developed world (see 'Aetiology of chronic otitis media in general' above) suggests that nutritional and environmental factors including hygiene play a part in predisposing individuals to COM.[147]

PROGRESSION WITH CONTINUING ACTIVITY

Continuing activity of COM is likely to result in increasing damage to the ossicular chain and potentially to the inner ear. The former is common but the latter seems to be relatively rare. The precise incidence of ossicular damage in COM is unknown but if there is significant ossicular involvement a substantial deterioration in hearing results. The otorrhoea, particularly with multiple infecting organisms,[167] may be a factor relevant to more rapid deterioration. The inflammatory reaction in the middle ear associated with granulation tissue is agreed to be the most likely factor for ossicular damage occurring. The non-specific changes in bone associated with the inflammatory reaction include osteoclastic and osteoblastic activity which results in the resorption and remodelling of bone. Frequently, permanent damage to the most finely constructed parts of the chain occurs, mainly to the incus long process and the stapes superstructure where there is abundant osteoclastic activity but osteoblastic influences appear weak. The same process may play a part in the development of a sclerotic mastoid in COM where osteoblastic activity predominates.

HEARING IN ACTIVE MUCOSAL COM

One of the cardinal symptoms of COM is hearing loss and usually this is conductive in type although sensorineural loss may occur (see 'Sensorineural hearing loss' below). In the early stages of disease, conductive hearing impairment occurs in most cases but this is usually mild and often only causes significant handicap if disease is bilateral. As the disease process advances only slowly, the patient appears to adapt to the loss so that thresholds of 30–40 dB HL are common with little complaint from the patient. In mucosal disease, the size of the perforation in the pars tensa is relevant to the hearing loss but other important factors such as the presence of granulation tissue, mucus, adhesions and tympanosclerosis are also of importance in determining the hearing level. If the ossicular chain loses continuity, there may be a substantial increase in hearing impairment with thresholds increasing up to 50–60 dB HL in such cases. In bilateral disease this constitutes a significant handicap and hearing rehabilitation including reconstructive surgery may be a priority for the patient.

Presentation

The two main symptoms of active mucosal COM are otorrhoea and hearing impairment. The discharge varies in quantity and character. It may be continuous or intermittent, mucoid or purulent. In patients with intermittent otorrhoea, an increase in discharge may follow a URTI or entry of contaminated water into the middle ear, most commonly when swimming. However, many patients present with hearing difficulty as their only symptom. Though they have active mucosal COM, they are unaware of otorrhoea as the quantity is insufficient to appear at the external auditory meatus. The small amounts of discharge dry up at the medial end of the external auditory canal and form crusts. These crusts are sometimes mistaken for wax by inexperienced otoscopists. The hearing impairment is conductive, though older people may present primarily with age-related sensorineural hearing impairment but have an additional unilateral conductive component. On questioning, these patients will often report that they had otorrhoea when they were younger.

Examination

The hearing should be assessed by pure-tone audiometry. As potentially ototoxic agents are commonly used in the management of active mucosal COM, it is important to record the hearing before treatment. There is usually associated hearing impairment which is mainly conductive. Bacteriology is usually not necessary unless complications are suspected or initial antibiotic therapy fails to reduce the inflammation. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most commonly reported pathogens, most of the other organisms being Gram-negative coliforms (see 'Factors influencing activity of chronic otitis media' above).

Management

AURAL TOILET

The initial stage in management is thorough aural toilet. This is most effectively carried out with a microscope and suction which also allows accurate assessment of the extent of ear pathology. However, some clinicians use gentle syringing with saline or antiseptic agents. In the past, aural toilet was carried out with cotton wool on probes, but this is probably not as effective. It is, however, an effective way for the patient to clean his or her own ear between clinic visits prior to the insertion of topical medication.

TOPICAL MEDICATION

Numerous studies have been carried out over many years comparing various topical agents: antibiotics, steroids, antifungals and antiseptics. Topical antibiotics with steroids are significantly better than dry mopping alone,[168] dry mopping in combination with a topical saline solution[169] or topical aluminium acetate solution.[170] Topical antibiotics are more effective than oral.[171, 172] or intramuscular antibiotics.[173]

Gentamicin or neomycin, usually with hydrocortisone, has been the most popular topical agent for many years. More recent studies have compared topical quinolone antibiotics (ciprofloxacin or ofloxacin) with these more traditional agents. Miró et al.[174] compared topical ciprofloxacin with topical polymyxin B, neomycin and hydrocortisone suspension and found no significant difference in effectiveness (91% and 87%, respectively) in a study of 322 patients. Tong et al.[175] reported a significant difference in the effectiveness of topical ofloxacin (93%) compared with neomycin, polymyxin B and hydrocortisone (71%, $p = 0.04$) in a small study with 52 patients.

SUMMARY

Topical antibiotic therapy is the most effective means of treating active otorrhoea in COM. Topical aminoglycosides have been shown to be ototoxic in animals and can be ototoxic when administered parenterally in humans. There have been several anecdotal reports of possible ototoxicity from topical preparations in humans, though it is difficult to separate the effects of treatment from the effects of the disease. There is no conclusive evidence that topical aminoglycosides are ototoxic when used in treatment of COM.[32] The consensus view in the UK is that their use is acceptable but they should only be used in actively discharging ears and for a limited time.[176] The available evidence suggests that quinolones are at least as effective at reducing otorrhoea as aminoglycosides. As they do not appear to be ototoxic in animal experiments, quinolones may be preferable to aminoglycosides in active COM. An overview of the scientific literature on the management of active mucosal COM is provided by Cochrane reviews.[177, 178]

Though medical management is effective in reducing otorrhoea in most cases, it recurs in many patients. Recurrence of activity 4–6 weeks after completion of treatment was reported in 5%[174] and 43%[179] of patients.

SURGERY

In those cases that do not become inactive on medical management, surgery is required to heal the ear. Those cases that become inactive should have closure of the perforation (see 'Myringoplasty' above) to prevent recurrence of activity, together with ossiculoplasty if appropriate.

Myringoplasty

Though it is preferable to make active ears inactive before surgery, this is not always possible, and surgery should not be postponed because of this. Activity in the ear has been suggested as a cause of failure of tympanoplasty. However, Kotecha et al.[152] and Black and Wormald[155] found no influence of the condition of the ear at the time of surgery on the subsequent graft take rate. A Cochrane review found no evidence that the success rate of surgery is influenced by prophylactic antibiotic therapy.[180]

Role of adjuvant cortical mastoidectomy

Many authors suggest that a cortical mastoidectomy should be carried out at the same time as myringoplasty in active ears. Mishiro et al.[181] compared 104 ears treated by tympanoplasty alone with a previous group of 147 ears treated by tympanoplasty with mastoidectomy. There was no significant difference in tympanic membrane closure rates between groups (94% in tympanoplasty alone and 91% in tympanoplasty with mastoidectomy). Balyan et al.[182] reported 81 ears that were actively discharging at the time of surgery treated with tympanoplasty without mastoidectomy (53 ears) and tympanoplasty with mastoidectomy (28 ears). There was no significant difference in the graft success rates between these groups (91% and 86% respectively). Hall et al.[183] reviewed five studies comparing tympanoplasty with and without mastoidectomy and found no evidence that mastoidectomy increases the success rate of surgery in these ears.

AURAL POLYPS

In some cases, aural polyps are found protruding from the middle ear. In compliant patients, these can sometimes be removed or partially removed in the clinic with suction or perhaps small aural forceps using microscopic vision. It should be remembered that polyps can be attached to the stapes superstructure or to the facial nerve, and that damage to these structures can occur. Cauterization of polyps with silver nitrate on a stick may be helpful, though this should be done with care as damage to the facial nerve can occur. Both methods should be followed by topical treatment as outlined above.

In those with persistent otorrhoea and an aural polyp not managed in the outpatient clinic, the polyp should be removed. If this requires an anaesthetic, it would seem more efficient to perform the definitive surgery at the same time whenever possible, rather than simply removing the polyp and listing the patient for further surgery at a later date. Removal of polyps usually causes bleeding in the ear that interferes with surgical access, but this can be greatly reduced by the use of a laser in the removal of the polyp.

KEY POINTS

- In many patients with active mucosal COM, the only symptom is hearing impairment.
- Initial management is aural toilet and topical antibiotics with or without topical steroids.
- Quinolones are probably preferable to aminoglycosides because of the theoretical risk of ototoxicity, though there is no evidence that they are more effective.
- Definitive management is surgery, at least to close the perforation, but preferably to improve hearing as well.
- There is no evidence that prophylactic antibiotics influence the outcome of surgery.
- There is no evidence that the outcome of surgery is poorer in active ears.
- There is no evidence that concomitant mastoidectomy improves outcomes after tympanoplasty.

HEALED OTITIS MEDIA

Natural history

Healed otitis media (see **Figure 83.16**) may be the end result of episodes of AOM or OME. It may also be the end result of natural healing of ears with either mucosal or squamous COM. It is also the aim of surgery in most cases of COM irrespective of its type or activity.

PROGRESSION OF HEALED OTITIS MEDIA

The usual outcome in healed otitis media is a stable ear which does not accumulate debris and in which the hearing impairment does not increase. Such ears frequently have tympanosclerosis in the tympanic membrane that does not progress or result in any hearing impairment. In a few cases, tympanosclerosis affects the ossicular chain, particularly in the attic, and may result in a conductive impairment that is difficult to treat surgically. The incidence of and risk factors for tympanosclerosis have been studied by several authors. The incidence of tympanosclerosis in all cases of COM is estimated at 25%.[184] The incidence of attic tympanosclerosis fixing the ossicular chain is low and the factors which trigger this in otherwise currently healed ears is unknown. Tympanosclerosis of the pars tensa is reported to resolve in some cases, but this is not common.[185] It is generally thought that tympanosclerosis occurs less commonly in squamous epithelial disease and in active mucosal disease, but supporting evidence is lacking.

PROGRESSION TOWARDS ACTIVITY

Reperforation of the tympanic membrane may occur if there is a subsequent episode of AOM or minor trauma. The most likely causes for the latter are barotrauma and ear syringing but there is no evidence that defines the frequency of this occurring. Episodes of AOM are most likely to occur in children but may occur occasionally in adults, particularly if there is a predisposition to chronic ear disease. The tympanic membrane rarely heals normally. Although the

membrane may heal to a state of intactness, the supporting fibrous layer of the drum may be weakened or fail to regenerate, resulting in a thin scar at the site of the previous perforation or indeed the whole membrane may be thin and attenuated. If chronic Eustachian tube dysfunction persists, as it often will, the drum becomes retracted and may become draped over and adhere to the structures in the medial wall of the middle ear, a condition known as adhesive otitis media. This condition may be exacerbated or precipitated by inflammatory adhesions within the middle ear.

HEARING IN HEALED OTITIS MEDIA

The hearing in healed otitis media may be normal or there may be a mild conductive hearing impairment unless there is ossicular damage or fixation. There may also be an underlying sensorineural hearing impairment from any of the causes of this or specifically as a result of cochlear damage related to previous infection. Once the healed state has occurred, further increase in either conductive or sensorineural hearing impairment is unlikely but there is no evidence that looks at this issue specifically.

Presentation

Patients with healed otitis media may present with a hearing impairment. In elderly patients, it is commonly an incidental finding when they present with age-related hearing impairment. Some patients give a history of ear problems many years previously, often in childhood, but many do not recollect ever having had otorrhoea.

Examination

Diagnosis is made on otoscopy. As the only symptom is hearing impairment, the hearing thresholds in each ear must be assessed. Pure-tone audiometry determines the magnitude of the conductive hearing impairment. Many cases have a minimal air–bone gap, but in ears where there is fixation of the ossicular chain by tympanosclerosis or by adhesions in the middle ear, or erosion of the ossicular chain, most commonly of the long process of incus, the air–bone gap can be up to 60 dB.[148]

If there is a significant air–bone gap and surgery to improve the hearing is contemplated, careful microscopic examination of the ear should be carried out as this may give information about the extent of pathology, particularly tympanosclerosis, and the likelihood of reconstructive surgery being successful (see **Figure 83.7**).

Management

Management is only indicated in the presence of significant hearing disability and hearing aids should always be considered (see 'Hearing aids in chronic otitis media' below).

SURGERY

Many patients, particularly younger ones, prefer surgery, which will usually include ossiculoplasty. It should, however, be borne in mind that the success rates of surgery are limited. Successful surgery requires a well-aerated middle ear, but careful examination of the ear will usually give appropriate information about aeration. Significant adhesions in the middle ear limit the success of surgery as these frequently recur after surgery. Tympanosclerosis may also reduce the chances of successful surgery (see 'Inactive mucosal chronic otitis media' above).

KEY POINTS

- As hearing impairment is usually the sole symptom, hearing aids are often the optimal management option.

INACTIVE SQUAMOUS CHRONIC OTITIS MEDIA

Inactive squamous COM is defined as retraction of the pars tensa or pars flaccida with the potential to be active with retained debris (cholesteatoma). There may be associated damage to the ossicular chain and other middle ear structures. It is commonly referred to as 'tympanic retraction' or a 'retraction pocket'. Typical examples of inactive squamous COM in the pars tensa and pars flaccida can be seen in the section on 'Diagnosis and assessment' above (see **Figures 83.26–83.30**).

The majority of evidence is from personal case series that use a number of different classifications of retractions. Consequently, it is difficult to make meaningful comparisons between series. Furthermore, the retractions are frequently reported in case series in association with OME. The results of treatment for such retractions can be impossible to disentangle from the effects of treatment for the OME.

Examination

The ear should be carefully examined when a retraction is present and particular attention should be drawn to the following possible changes. Where possible, a clinical photograph should be obtained to enable comparisons to be made over time, because diagrams and staging systems, such as those developed by Sadé and Tos, have been shown to be unreliable.[186–188]

RETRACTION OF THE PARS FLACCIDA

Classify the retraction according to Tos. Can I see the fundus of the retraction pocket or not? Is this thought to be self-cleansing or not? Whether a retraction pocket is self-cleansing or not is a qualitative judgement based upon size and appearance. A small, clean retraction pocket in the pars flaccida or pars tensa is likely to be self-cleansing, but such judgements can only be confirmed over time by clinical review.

RETRACTION OF THE PARS TENSA

Is this retraction pocket thought to be self-cleansing or not? What is the relationship of the tympanic membrane to the incudostapedial joint? Is there partial or complete

erosion? What effect has this had upon hearing thresholds? Has the bony ear canal at the level of the tympanic membrane been eroded by long-standing retraction of the pars tensa and become wider? This can be evaluated because structures not normally visible, such as the stapedius tendon and facial nerve, becoming visible. Is the pars tensa adherent to the promontory or not? Whether or not the tympanic membrane is adherent to the promontory may be difficult to evaluate, but Charachon[189] and Gersdorff and Garin[190] argued that autoinflation may provide evidence of such adherence.

Tympanometry may be helpful. An unusually high peaked tympanogram, type A_d, is suggestive of tympanic membrane hypermobility or ossicular discontinuity and may provide further evidence of adherence of the tympanic membrane to the promontory or not. Sadé[191] reported a long-term series of 59 patients with 'hyperinflated' tympanic membranes, in which the middle ear pressure is elevated above atmospheric pressure resulting in ballooning out of the tympanic membrane, so-called hyperectasis. A type A tympanogram with a peak above atmospheric pressure would be indicative of hyperectasis. Sadé[191] noted that hyperectasis was preceded by atelectasis and that this hyperinflated state could persist for weeks, months or even years. If the pars tensa is adherent to the promontory, the perceived wisdom is that the retraction is likely to be long standing although this has not been formally tested in studies. A type B, or flat, tympanogram will suggest the presence of a middle ear effusion, in association with a retraction, and if accompanied by an associated hearing loss, may be a factor in deciding management.

OTHER FACTORS

The role of allergy and sinonasal infection is traditionally thought to be important and usually is included in the treatment of middle ear disease. The precise role of these other factors is not clear other than a general interference with Eustachian tube function. Any relationship between sinonasal factors and tympanic retraction has not been formally examined in clinical studies, but clinical examination of the nose would have a place if symptoms, such as obstruction or discharge, are present.

Natural history

The first assumption is that pars tensa and pars flaccida retractions are clinical consequences of the same predisposing factors. If so, then pars tensa and pars flaccida retraction should coexist. There is good case series evidence that pars tensa and pars flaccida retractions coexist. In a series of 250 adults and children with atelectatic tympanic membranes, Luntz et al.[192] found evidence of pars tensa retraction in 60% and pars flaccida retraction in 86%. Both sites of retraction were found in 49% and only one site in 53%. Another large case series (n = 327) also found a similar association between pars tensa and pars flaccida retraction; if pars tensa retraction was Sadé grade 1, then pars flaccida retraction was present in 43%, and if grade 2 then in 61%, respectively.[193] The lesson here is that, if pars tensa retraction exists, a careful examination should be made to see if pars flaccida retraction is present and vice versa.

PROGRESSION OF RETRACTION POCKETS

Once a retraction of either site is present, the key clinical question is whether such a retraction is likely to progress, remain static or resolve. They may reach such a size and configuration that they cease to become self-cleansing and accumulate inactive squamous debris. This debris may become infected and the clinical picture can then be characterized by repeated episodes of discharge, often with symptom-free intervals in between: intermittently active squamous COM. There is evidence that tympanic retraction can behave in this way, although reliably identifying those ears that will progress from those that will remain stable is not possible. Consequently, regular review is necessary. Retraction may lead to histological changes in the tympanic membrane with loss of elasticity and rigidity so that the tympanic membrane no longer 'drives' the ossicular chain or areas of the tympanic membrane may be eroded leaving a perforation. Tympanic retraction may also damage middle ear structures, for example erode the long process of incus.

There is evidence from follow-up of pars tensa retractions in children with OME that it is a dynamic condition with around 70% resolving spontaneously.[194] Studies of retraction of the tympanic membrane in children and adults over a longer period usually include surgical and medical treatment groups which makes it much more difficult to infer the natural history of this condition. Certainly the balance of evidence when a retraction is in association with otitis media in children is that VTs do little to affect the condition.[195,196] Indeed, the insertion of a VT may significantly increase the chances of retractions and atrophy of the pars tensa.[197] Charachon,[198] in a study of adults and children (n = 95) of stage 1 and 2 (Charachon classification) tympanic retractions followed up over a period of 5 years, found that 16% deteriorated to stage 3 (follow-up 82%) and underwent surgery.

RETRACTION POCKETS AND CHOLESTEATOMA

That there is a relationship between tympanic retraction and significant pathology, such as cholesteatoma, is suggested by several temporal bone studies[199–202] and experimental animal work.[203,204] Longitudinal population studies indicate that there is a significant association between cholesteatoma and pars flaccida retraction in adults and pars flaccida and pars tensa retraction in children.[205,206]

Certain clinical groups have a greater chance of middle ear pathology leading to significant changes to the tympanic membrane. Children with a cleft palate have an approximately 20% chance of developing retraction in the pars tensa[207,208] and those with Turner syndrome have approximately a 50% chance of tympanic pathology.[209] There is, somewhat surprisingly, no evidence that those with cystic fibrosis are more likely to develop tympanic or middle ear changes compared with the general population.[210]

No studies were found that specifically examined the natural history of tympanic retraction and erosion of the ossicular chain, particularly in relation to any change in hearing.

Management

The general assumption is that the complications described above have a reasonable chance of occurring despite the lack of research evidence that this actually happens. A wide variety of treatments have been proposed, but none has been submitted to a randomized controlled trial. Consequently, there is only case series evidence of the efficacy of various treatments.

MANAGEMENT OF NASAL DISEASE

There is evidence that a poorly functioning Eustachian tube plays a role in the pathogenesis of tympanic retraction, so it is common practice to look for and treat any sinonasal disease such as infection or allergy. This practice seems reasonable but no case series could be identified of such management of retraction pockets. Small case series examined the usefulness of tubal insufflation in the management of tympanic retraction. One series (n = 13) politzerized atelectatic middle ears with either carbon dioxide, oxygen, air or nitrogen.[211] The tympanic retraction did disappear, only to slowly reappear at a speed corresponding to the diffusion coefficient of the gases used. No long-term benefit was seen.

AURAL TOILET

Sadé[212] maintains that small retraction pockets can be managed by regular suction cleaning and many experienced otologists would agree with this view. However, no case series has reported its efficacy.

SURGICAL TREATMENTS

Surgical treatments have been undertaken to prevent complications such as discharge, progression of tympanic retraction and restoration of hearing. They are conveniently divided into:

- management of the tympanic membrane
- ventilating the middle ear.

MANAGEMENT OF THE TYMPANIC MEMBRANE

Surgical management of the tympanic membrane is essentially an anatomical approach designed to restore the normal anatomical appearance. The thin retracted tympanic membrane, lacking its normal elastin and collagen component, is unable to withstand any negative middle ear pressures and can become more retracted over time. This has led to a wide variety of surgical approaches.

Excision, no graft

Some have argued that the retracted tympanic membrane is abnormal, should be excised and a new 'normal' eardrum will naturally grow in its place. Sharp and Robinson[213] found that after one excision there was no recurrence in 65% of cases with a mean follow-up of 14 months, but 8% (5 of 66) of ears had persisting perforations. Others have combined excision with insertion of a VT in the remaining tympanic membrane.[214–216] All were small personal case series of less than 40 ears. The incidence of recurrence of the tympanic retraction and persisting perforation were of the same order. The evidence is not of good quality so it is difficult to make a case for inserting a VT at the same time as excising the retraction pocket.

Excision, myringoplasty

A number of larger case series combine excision of the tympanic retraction with a conventional myringoplasty using a variety of graft materials: temporalis fascia,[217–221] dura[222] and reinforcement with cartilage.[205, 223–230] These studies have variable follow-up periods and frequently include both children and adults and other treatments such as insertion of a VT, reconstruction of the ossicular chain or mastoid exploration. These case series suggest that recurrent retraction may be more reliably prevented with cartilage than with temporalis fascia grafts alone. However, there is no good evidence that myringoplasty has any benefit over a watch-and-wait policy in the management of retraction pockets.[231]

Excision, myringoplasty with cortical mastoidectomy

The role of mastoid surgery, undertaken at the same time as the tympanoplasty, seems to suggest that no further benefit is gained.[232–234] However, there may occasionally be a place for removal of small quantities of osteitic bone in the posterosuperior quadrant of the pars tensa to 'marsupialize' a tympanic retraction that is beginning to become no longer self-cleaning.[235]

VENTILATION TUBES

At first sight, to many clinicians, the use of VTs for tympanic retraction would seem obvious. Assuming that the basic pathophysiology is Eustachian tube dysfunction, if air could once again gain access to the middle ear, normal pressures would be restored and the tympanic retraction stabilized or reversed. Evidence that VTs play a temporary role was demonstrated by Sadé et al.[236] They closed a long-term VT used in the management of retraction and showed that retraction returned within 1–2 hours in 89% (33 of 37 cases). Despite this, the evidence seems to suggest that long-term benefit from VT insertion in established retraction is not so straightforward.

Much of the evidence to support or refute the use of VTs has been gained from studies that have been principally concerned with the treatment of OME. Such studies suggest that the use of VTs[195, 237, 238] had no long-term effect on the tympanic membrane. Indeed, the use of VTs in OME seems to increase the prevalence of pars tensa atelectasis and attic retraction. A meta-analysis of both randomized controlled trials and case series of OME showed that long-term VTs increased the risk of perforation

by 3.5 (95% CI, 1.5–7.1) and cholesteatoma by 2.6 (95% CI, 1.5–4.4).[197] The apparent lack of success of VTs in the management of tympanic retraction may be because histological changes have taken place in the tympanic membrane rendering the situation irreversible.

In ears with very poor aeration, Yung[239] has devised a method of inserting a permanent titanium vent into the mastoid antrum at the time of tympanoplasty. This allows aeration of the middle ear and has been successful in a significant proportion of patients. The technique requires surgical expertise and regular long-term follow-up to unblock the vent. It is not yet commercially available.

HEARING LEVELS AND RETRACTION

No studies have tried to associate hearing levels and degree of retraction. Such an association is unlikely to exist with pars flaccida retractions. Significant retractions of the pars tensa are likely to interfere with sound conduction, but erosion of the ossicular chain, usually the incus, will have a greater effect. In addition, no studies were found on the use of hearing aids in tympanic retraction, but this management makes sense, is by definition safe, and is likely to be how many patients are managed.

RECOMMENDATIONS FOR MANAGEMENT FOR AN INACTIVE RETRACTION

In an adult patient

If the patient is an adult (over the age of 12), the Eustachian tube function is likely to be normal and the retraction has a substantial chance of being stable. If there is no significant hearing loss and the retraction pocket is self-cleansing, then follow-up on an occasional basis would be appropriate until it seems clear that it is not progressing. If the retraction pocket is not self-cleansing, then it may be managed with regular microscopic suction clearance.

If there is a conductive hearing impairment, this may be due to loss of effectiveness of the atelectatic tympanic membrane or an ossicular problem. The decision to manage this surgically will depend upon the wishes of the patient, the hearing in the other ear and the expertise of the surgeon. The eardrum may be reconstructed with a graft with a cartilaginous component to help prevent recurrence of retraction. An ossiculoplasty would also be performed where relevant.

In a child under 12 years

In a child under 12 years there is a greater likelihood that a retraction will be unstable and it is important that such children are kept under review. If the hearing is normal, or near normal, then intervention is probably not necessary. If there is modest retraction and a hearing loss due to the presence of a middle ear effusion, then the usual guidelines for managing OME should be followed. There is no evidence that ears with OME and a retraction should be managed any differently as spontaneous resolution is common.[194]

If the retraction is progressing, with, for example, clinical evidence that the incudostapedial joint is beginning to be eroded, or the fundus is beginning to disappear out of view, then most otologists would recommend surgery. The situation is an exercise in damage limitation because the feeling is that, left untreated, this particular retraction will progress to incudostapedial joint erosion or a cholesteatoma. There is an argument for simply excising the abnormal atelectatic tympanic segment and hoping that a more normal tympanic membrane will grow back. The child and their guardians need to be advised that there is a good chance of leaving a tympanic perforation, but that this may be preferable to ossicular erosion or a cholesteatoma. There is little evidence that inserting a VT at the same time influences the outcome. Many otologists would argue that it is possible to go further and consider a tympanoplasty with thin cartilage or pallisades to reinforce the tympanic membrane and prevent a recurrence. There is an increasing body of evidence that this can be accomplished with good hearing and with an eardrum that can remain stable for a good period of time.

There is no evidence that concomitant exploration of the mastoid improves the outcome and this should, by and large, not be considered unless the possibility of unexpected cholesteatoma needs to be ruled out.

KEY POINTS

- Self-cleaning retraction pockets are usually stable in adults but they should be followed carefully in children.
- There is no evidence that surgical management of self-cleaning retraction pockets influences the natural history.

ACTIVE SQUAMOUS CHRONIC OTITIS MEDIA (CHOLESTEATOMA)

Natural history

Active squamous epithelial disease (**Figure 83.36**) is a retraction pocket filled with keratinous debris which may remain active or become inactive. In the former case the disease may or may not anatomically extend. The factors upon which this depends are not clear, but the issue of whether the degree of sclerosis of the mastoid is relevant is controversial. In well-pneumatized temporal bones, such as in children, the disease is frequently extensive, expanding down the well-formed air cell tracts. Squamous epithelial disease is more commonly found in poorly pneumatized sclerotic bones, but whether the sclerosis is relevant to the aetiology of the disease or is caused by it has also not been fully resolved. The evidence suggests that the most important factor in the development of mastoid sclerosis is poor Eustachian tube function. In a prospective study of cleft palate children in whom one ear only was managed with a VT, the mastoid air cell system was noted to be larger on the ventilated side in 86% (19/22) of ventilated ears.[240] Poor Eustachian tube function and reduced middle ear cleft volume has been shown to be characteristic of ears with cholesteatoma.[241]

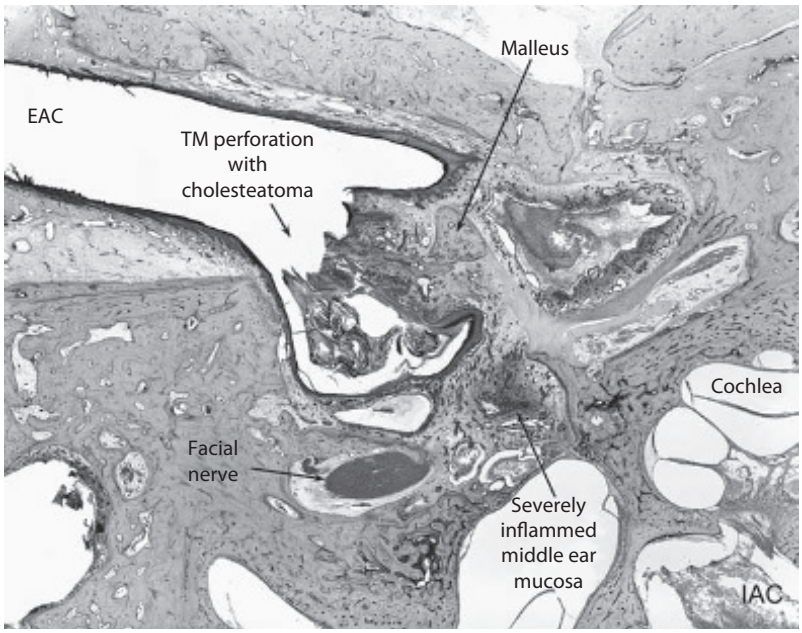


Figure 83.36 Axial temporal bone section from an 18-year-old woman with active squamous epithelial COM (cholesteatoma). There is a posterior perforation of the pars tensa extending to the annulus with ingrowth of squamous epithelium into the middle ear forming a cholesteatoma. Note the retained keratin within the cholesteatoma sac. There is granulation tissue within the middle ear that surrounds the cholesteatoma sac. EAC, external auditory canal. IAC, internal auditory canal. (*Magnification ×8.*)

PROGRESSION TOWARDS HEALING

There are no figures available which define the proportion of cases of active squamous epithelial disease which heal but cases are occasionally encountered where the patient has a well-formed 'atticotomy' or 'mastoidectomy' cavity but denies ever having surgery. In these cases presumably the disease process has selectively resulted in bone erosion of the outer attic wall and in some cases the whole posterior meatal wall. The epithelial migration pattern is restored from medial to lateral and the ear develops a 'normal' albeit widened external meatus or 'automastoidectomy' cavity.

In a proportion of cases, also undefined in the literature, there is a change from an active keratin producing retraction pocket to one that no longer produces or accumulates squamous epithelium but reverts to a clean, non-progressive retraction. This is only likely to occur if the retraction pocket is small and in the situation of established cholesteatoma, by definition active squamous epithelial COM, spontaneous reversion to inactivity must be rare but its frequency has not been documented.

PROGRESSION OF ACTIVE DISEASE

The natural history of cholesteatoma is for anatomical progression of disease over a variable timescale with inevitable involvement of the ossicular chain and possible involvement of the labyrinth by erosion of the lateral semicircular canal. The serious and potentially life-threatening sequelae of intracranial and intratemporal complications are discussed below (see 'Intracranial complications'). The timescale for this is extremely variable and it is likely that many patients live with active squamous epithelial disease with minimal disability or inconvenience. Bacteriology is non-specific with a wide range of organisms frequently cultured. Madana et al. found *Pseudomonas* in 32%, *Proteus* in 20% and *Staphylococcus aureus* in 19% in children with cholesteatoma.[242] As with mucosal disease, these organisms are likely to be opportunistic rather than primarily pathogenic (see 'Factors influencing activity of chronic otitis media' above). As the disease process advances, erosion of bone takes place as the lesion enlarges, by the mechanisms of osteoclastic and osteoblastic remodelling discussed in 'Active mucosal chronic otitis media' above. Although bone erosion in cholesteatoma takes place in the absence of acute inflammation and granulation tissue formation in some cases, the norm would be for the disease process to be associated with chronic granulation tissue formation with osteitis in the adjacent bone.

HEARING IN ACTIVE SQUAMOUS COM

It is well recognized that hearing is often preserved until a very late stage in ears containing cholesteatoma in spite of the ossicular chain being disrupted. Severe erosion of the incus with absence of the long process is common in established cholesteatoma and frequently the disease engulfs the whole incus and the malleus head. The stapes superstructure is also often involved and may be eroded. Fortuitously for the patient, hearing preservation occurs because the cholesteatoma sac bridges the gap between the functioning part of the ossicular chain and the inner ear. The unfortunate consequence is that removal of the disease surgically may reduce the hearing by increasing the air–bone gap. Involvement of the incus in cases of cholesteatoma is almost universal but precise figures are not available. Fortunately, in many cases it is possible to reconstruct the middle ear in such a way that hearing loss is minimized.

Presentation

Classically, active squamous COM presents with foul-smelling otorrhoea and hearing impairment. However, many patients complain only of hearing impairment and

are unaware of any discharge from their ear as the quantities of pus are small and these dry up and form crusts. Sometimes, the inexperienced otoscopist can miss the disease as the pars tensa appears normal, but a small crust obscures the attic (see **Figure 83.11**). The crust can be mistaken for wax, though wax only occurs in that site if the patient pushes it there with a cotton bud.

Examination

Microscopic examination is usually required to allow thorough cleaning of the discharge and to confirm the diagnosis. In very inflamed ears, a cholesteatoma may not be visible at first presentation. Sometimes there is an aural polyp obscuring the attic or posterior pars tensa; such a case should be assumed to be a cholesteatoma until proven otherwise. Removal of crusts can be uncomfortable and, particularly in children, may require an anaesthetic. When debris is removed from a retraction pocket in the attic or posterior pars tensa, the extent of the retraction pocket may not be visible with a microscope. Examination with a rigid endoscope may be helpful if knowledge of the extent is important for management decisions.

IMAGING

Many clinicians favour radiology before undertaking surgery for cholesteatoma. CT has been the standard method of imaging for many years. It provides very good resolution of anatomical landmarks. Its disadvantage is poor differentiation of cholesteatoma from other soft tissues, such as granulation tissue, cholesterol granuloma[243] or brain tissue. Bone erosion of the scutum and the incus and malleus though rarely the stapes can be demonstrated. CT can often demonstrate erosion of the inner ear with fistula formation or dehiscence of the facial nerve, but a negative CT does not rule out a fistula. Fistulae are reported to occur in 10–15% of cases of cholesteatoma but the sensitivity of CT at identifying fistulae is not reliable (**Table 83.8**). Dehiscence of the facial nerve is identified surgically in up to 19% of cases of cholesteatoma,[244] most commonly in the horizontal portion.[244] Fuse et al. reported that facial nerve dehiscence was detected on CT in only 66% of 29 cases.[245] Yu et al. found that the condition of the facial canal on CT corresponded with surgical findings in only 67 of 76 ears (88%).[246] The surgeon should not rely on CT but should assume that there is a fistula and that the facial nerve is dehiscent in all cases to minimize the complications of surgery.

Conventional MRI shows cholesteatoma as a soft-tissue mass but does not differentiate this from other soft tissues. It does not provide enough bony detail to be useful on its own. More recently, non-echoplanar DW-MRI has been shown to be very reliable at detecting cholesteatoma and differentiating it from other soft tissues.[250] It has been shown to be of value in detecting residual cholesteatoma and reducing the necessity for second-look surgery.[251]

If intact canal wall surgery is to be considered, knowledge of the anatomy, in particular the pneumatization of the mastoid, is important. If the mastoid is acellular, intact canal wall surgery is more difficult. If canal wall-down surgery is planned, some experienced surgeons do not consider radiology necessary, unless intracranial complications of disease are suspected. There is no evidence that pre-operative CT influences the surgical management of cholesteatoma in canal wall-down surgery.[252, 253]

TABLE 83.8 Surgically proven fistulas identified on CT

Reference	No. of cases	Fistulae identified on CT (%)
Herzog et al.[247]	8	38
Vanclooster et al.[248]	48	90
Kvestad et al.[249]	20	55

Management

The aims of management of active squamous COM are to relieve the patient's symptoms and to minimize the risks of complications of the disease. However, complications are rare (see 'Complications of surgery' below). Surgical removal is the only effective treatment for cholesteatoma, but surgery has potential complications too. Are the risks of the treatment greater than the risks of the disease? The likelihood of complications of the disease varies with the life expectancy of the patient, while the risks of surgery vary inversely with the skill of the surgeon. When surgical treatment is considered appropriate, topical treatment for granulations and associated mucosal disease while awaiting surgery may lessen the otorrhoea and therefore be socially beneficial (see 'Active mucosal chronic otitis media' above). Some patients, particularly the elderly, may be unfit for surgery and the risks of the disease may be minimal. In these cases, careful aural toilet with removal of squamous debris from the retraction pocket and topical treatment at regular intervals may keep the symptoms at a level acceptable to the patient. Hearing aids should always be considered when there is hearing disability (see 'Hearing aids in chronic otitis media' below).

The aims of surgery for active squamous COM are:

- eradication of disease
- an epithelialized, self-cleaning ear
- hearing maintenance or improvement.

The principle aim of surgery for cholesteatoma is to completely remove disease and minimize the risk of recurrence, but, in addition, the ear should be returned to as near normal as possible. The ear should be self-cleaning and should not require regular aural toilet, and the hearing should be restored, although this is not always possible. The idea that the aim of surgery is simply to remove disease in order to create a safe ear is obsolete. Many patients present because of hearing impairment and will not be satisfied with management that provides no apparent benefit.

There are many different surgical techniques for managing active squamous COM, which can largely be categorized as open cavity (canal wall-down) and closed cavity (canal wall-up) mastoidectomy. Over the last 30 years

there has been much discussion among otologists about the comparative benefits of these techniques, and there is no more agreement now than there was 30 years ago.

CANAL WALL-DOWN MASTOIDECTOMY

The traditional method for removal of cholesteatoma was modified radical mastoidectomy using the posterior to anterior approach. The mastoid was opened behind the external auditory canal, the cholesteatoma identified and followed forwards through the aditus into the attic with removal of the posterior bony wall of the canal. This usually resulted in a large cavity, much larger than is required to control the disease. Large cavities can be problematic: many continue to discharge and, even if well epithelialized, they often do not self-clean so regular clinic attendance is required for removal of squamous debris and wax from the cavity.

Small cavity mastoidectomy, or atticoantrostomy, the anterior to posterior approach, has become more popular. The cholesteatoma is identified in the epitympanum or posterior mesotympanum and followed backwards. Sadé[254] gave a very clear description of the surgical method. Smyth and Brooker[255] showed that this technique resulted in a much smaller cavity with a mean volume of 1.4 cm^3 compared with 2.4 cm^3 after modified radical mastoidectomy, and that there was no difference in the number of ears that continued to discharge between the two techniques. In addition, when the cholesteatoma is small, surgery can be limited to atticotomy and the defect in the attic wall can be closed with tragal or conchal cartilage with its perichondrium attached.

Wormald and Nilssen[256] evaluated the mastoid cavities in 101 patients attending an outpatient clinic between 6 months and 20 years after mastoidectomy. The cavity was actively discharging in 52% and dry in 48% of patients. They found the following significant differences in the active cavities:

- high facial ridge
- sump in cavity below floor of external auditory canal
- perforation in tympanic membrane
- small external auditory meatus.

The problems of mastoid cavities can be reduced by good surgical technique and by partial obliteration of cavities, either with cartilage or prosthetic materials. The cavity must be rounded and smoothly contoured with no overhanging ridges and no facial ridge in order to allow migration of epithelium. The tympanic membrane should be repaired to close all communication between the mastoid cavity and the mesotympanum and Eustachian orifice. The meatus should be an adequate size relative to the size of the cavity, so a meatoplasty is almost always required. The conchal cartilage removed from the meatus should be used to reduce the size of the cavity.

Canal wall-down surgery has lower rates of recurrence of cholesteatoma (5–15%) and recurrences are usually easily identified in the outpatient clinic, so second-look operations are rarely necessary. Residual cholesteatoma should be a rarity in competent hands. A significant proportion of patients (20–25%) continue to have otorrhoea, either intermittent or continuous, after mastoid surgery.[257–259] Experienced otologists of repute have much higher success rates at creating dry ears. Smyth and Brooker[255] reported that only 5% of ears were moist 5 years after surgery. This is probably an indication that attention to detail in these operations results in much better outcomes for the patients.

CANAL WALL-UP MASTOIDECTOMY

Canal wall-up mastoidectomy (combined approach tympanoplasty) has the advantage of leaving an intact external auditory canal and no mastoid cavity. However, the incidence of recurrent and residual cholesteatoma is high (20–50%), therefore second-look operations after 12–18 months are necessary in most cases, and some cases require further procedures subsequently. Second look can often be avoided nowadays by the use of DW-MRI.

The advantage of canal wall-up mastoidectomy is the preservation of a (relatively) normal external auditory canal and the absence of a mastoid cavity. It has been claimed that post-operative hearing thresholds are better, but there is no evidence for this as all reports are case series and outcomes depend on selection of patients. Many authors claim that their hearing outcomes after canal wall-down mastoidectomy are comparable.

A minority of surgeons, most of whom are experienced otologists, favour this procedure. It is technically more difficult and requires significantly longer operating time. In addition, at least one further operation may be required. Patients must be made aware of this. More recently, some surgeons have recommended canal wall-up surgery with obliteration; these ears are followed up with diffusion-weighted MRI to exclude residual cholesteatoma.[251]

CANAL WALL-UP VERSUS CANAL WALL-DOWN MASTOIDECTOMY

Reconstruction of the middle ear can be achieved with either technique and there is no evidence that the long-term hearing results differ between procedures. It has been claimed at times that post-operative hearing results are better following canal wall-up mastoidectomy. These claims are usually based on an author's comparison of cases that have undergone one of these procedures. It must be remembered that the procedure is not randomized but is the one thought most appropriate for the patient. Some authors have pointed out that, though the post-operative hearing thresholds are worse after canal wall-down mastoidectomy, the pre-operative hearing thresholds are also worse.[260] Karmarkar et al.[261] found no significant difference in post-operative hearing results between 176 cases of canal wall-down mastoidectomy and 257 cases of canal wall-up procedures. Toner and Smyth[262] reported better hearing outcomes 1 year after surgery for canal wall-up compared with canal wall-down mastoidectomy. However, at long-term follow-up (mean of 9 years), there was no significant difference between groups. Many

surgeons, by doing canal wall-down surgery but partially obliterating the cavity, achieve an outcome that is similar to canal wall-up surgery.

PARS TENSA CHOLESTEATOMA

Cholesteatoma arising from the pars tensa may be confined to the middle ear, most commonly growing into the facial recess and sometimes spreading anteriorly beneath the pars tensa and malleus handle. This can be removed by opening the facial recess, which is more easily accessible than inexperienced surgeons sometimes think. When the cholesteatoma grows anteriorly, care must be taken not to leave some under the tympanic membrane remnant. Complete clearance from the oval window, especially when there is an intact stapes superstructure, can be difficult. If there is doubt over clearance of disease, the tympanic membrane can be closed and the ear reopened after 12–18 months.

OSSICULOPLASTY IN ACTIVE SQUAMOUS COM

The incus is probably the most commonly used prosthesis for ossicular reconstruction. The possibility of an allograft incus from an ear with cholesteatoma containing squamous cells has been explored. Rupa et al.[263] examined histologically 60 mallei and 53 incudes from ears with cholesteatoma and found no evidence of squamous epithelial cells, while Dornhoffer et al.[264] examined 11 incudes removed at the time of surgery in ears with cholesteatoma and found evidence of squamous epithelial cells in seven incudes (64%). There is thus the theoretical risk that the use of such an incus could cause a recurrent cholesteatoma. The possibility that these cells could regenerate without a blood supply seems remote. No case of recurrent cholesteatoma arising from an allograft incus has been reported in many extensive surgical series.

COMPLICATIONS OF SURGERY

Complications of mastoid surgery are not uncommon. In an audit of results in the UK, facial palsy occurred in 1% and dead ear in 2% of 365 canal wall-down mastoidectomies.[258] Wormald and Nilssen[265] reported the outcome of mastoid surgery in 1024 patients. The incidence of intra-operative facial nerve palsy was 2% and of total loss of hearing was 2%. The incidence of facial palsy is widely accepted to be rare in the hands of expert surgeons. However, total loss of hearing also occurs in the hands of experts, usually in ears where there is a fistula into the inner ear.

PROBLEM MASTOID CAVITIES

Mastoid cavities that continue to discharge can usually be corrected surgically. Regular aural toilet over many years with frequent antibiotics is ineffective and is poor medical practice in the modern world. Most commonly the problem arises because of poor surgical technique at the initial mastoidectomy: the meatus may be too small, a high facial ridge may have been created, there is a sump in the mastoid tip or the tympanic membrane has not been closed. If the cavity is well epithelialized but debris collects, correction of the cause of poor drainage – narrow meatus, high facial ridge – may result in significant improvement. For cavities with more extensive disease, revision surgery requires meticulous surgical technique. Jackson et al.[266] give a careful description of the principles of management of problem cavities. In their series of 541 ears, 89% were clean, healed and dry after revision surgery.

However, many surgeons nowadays prefer to obliterate, at least partially, large cavities that are not epithelialized. Revising these cavities and making them even larger rarely succeeds in creating a dry ear. Skin does not readily grow on bare bone and the naturally moist environment in the ear encourages the growth of respiratory mucosa. The cavity can be made smaller by obliteration which can be achieved by filling the cavity with bone pâté [267]or hydroxyapatite granules.[268] Both of these materials must be covered by a vascularized fascioperiosteal flap. Alternatively, the posterior canal wall can be reconstructed with a hydroxyapatite prosthesis.[269] The different methods of mastoid obliteration have not been directly compared. In numerous case series using these and other techniques, the proportion of patients who have dry ears following obliteration is reported as 80–95%.[270] Irving et al.[271] reported better symptom scores in patients who had mastoid obliteration than in patients who had revision mastoidectomy. Meticulous surgical technique is considered necessary to avoid leaving squamous epithelium in the obliterated cavity, though cases of this have not been reported.

KEY POINTS

- Cholesteatoma continues to enlarge in most patients, but the rate of progression on average is very slow.
- The preferred management in patients who are otherwise fit is surgery.
- The aims of surgery are to remove disease, to create a trouble-free ear and to improve the hearing.
- At least 1% of patients get a facial palsy and 2% a dead ear after mastoid surgery in the UK. The incidence is very much lower when the surgery is performed by experienced surgeons.

HEARING AIDS IN CHRONIC OTITIS MEDIA

Healed COM

Hearing aids are straightforward and effective forms of management. When listening in low- and medium-level environments, a person with a conductive hearing impairment will have poorer speech recognition ability than someone with a sensorineural impairment of the same degree. The person with the conductive hearing impairment will, however, derive more speech recognition benefit from hearing aids than the person with the

sensorineural hearing impairment.[272] There is no evidence to compare successful surgery with provision of hearing aids in this patient group. For many patients, hearing aids are the more acceptable form of management. Their success rate in lessening disability is much greater than that of surgery and the complication rate is much smaller. In patients with hearing disability and bilateral healed COM, a hearing aid is appropriate even if surgery is planned for the poorer-hearing ear. Unless surgery is very successful, they will still have a hearing disability afterwards.

Inactive COM

Many people believe that closure of the perforation in inactive COM is necessary prior to fitting a hearing aid, though there is no evidence to confirm this. It is accepted that some patients with inactive COM who are fitted with a hearing aid then develop active COM and otorrhoea. However, the likelihood of this happening is not known. Adults who have a history of intermittent otorrhoea are probably likely to develop further otorrhoea when using a hearing aid. However, the chances of otorrhoea in a patient with a totally inactive ear and no recent history of otorrhoea are probably small, though there is no evidence to confirm this. A sensible management plan in such a patient would be to try a hearing aid. If the ear becomes active, the tympanic membrane should be repaired. If the ear remains inactive, then the patient has avoided an unnecessary operation.

The only presenting symptom in patients with inactive squamous disease is hearing impairment. If they have a hearing disability, a hearing aid is often the most effective management.

Active COM

Hearing aids are effective in patients with hearing disability, as in inactive mucosal COM. However, closure of the external auditory canal with a hearing aid usually exacerbates the otorrhoea, so the otorrhoea should be managed first and the preferred option is usually surgical repair of the tympanic membrane. In some patients, for example patients who are medically unfit for surgery and patients with only one hearing ear, surgery is better avoided. Such patients can often be managed by regular aural toilet and occasional topical treatment.

All otologists have some problem discharging mastoid cavities that are resistant to all attempts at treatment. Occasionally, such a patient has bilateral problem cavities or has a profound hearing loss in the opposite ear. If such a patient requires hearing amplification, conventional air conduction hearing aids cause problems: they exacerbate the activity and the otorrhoea interferes with the function of the hearing aid. These patients can often be effectively managed with a bone-anchored hearing aid (BAHA) (see Chapter 93, Bone-conduction hearing aids) that does not interfere with the disease.[273] Such management often has the additional benefit of reducing the amount of discharge from the cavity.

KEY POINTS

- In many patients with COM, the main symptom is hearing disability and this should be managed at an early stage.
- Conventional hearing aids are effective management of patients with hearing disability and inactive COM.
- Bone-anchored hearing aids can be very effective management of patients with hearing disability and active COM which does not respond to treatment.

COMPLICATIONS OF ACTIVE CHRONIC OTITIS MEDIA

Classification of complications

The complications of active COM may be classified as intratemporal (cochlea, labyrinth and facial nerve), sometimes expressed as extracranial, and intracranial. Extracranial complications are postauricular abscess, facial palsy, petrous apicitis and Bezold abscess (neck abscess as a result of direct extension from suppuration in the mastoid tip). Intracranial complications are meningitis, brain abscess, extradural abscess subdural abscess, lateral venous sinus thrombosis and otitic hydrocephalus.

RELATIVE INCIDENCE OF COMPLICATIONS

In a large series of 268 patients with complications of COM, the incidence of extracranial complications was 32%, intracranial complications was 56% and combined intracranial and extracranial was 12% (Table 83.9).

RISK OF COMPLICATIONS

Traditionally, ears with squamous epithelial disease have been regarded as being more at risk of serious complications as opposed to those with mucosal disease. In fact, the evidence confirms that there is a significant risk with both types of disease. Singh and Maharaj[274] report an incidence of 41% squamous epithelial versus 59% mucosal disease in their group of extracranial complications and 59% squamous versus 41% mucosal disease in the intracranial group. In the combined group, 58% had squamous epithelial disease and 42% had mucosal disease.

Otorrhoea as an obvious symptom may or may not be present and there is no evidence that ears with COM are more or less likely to suffer complications if they are

TABLE 83.9 Relative incidence of complications in active mucosal and squamous COM

Extracranial	%	Intracranial	%
Postauricular abscess	75	Brain abscess	51
Facial palsy	6	Subdural abscess	20
Bezold abscess	2	Extradural abscess	10
Petrous apicitis	0.2	Lateral sinus thrombosis	20
Meningitis	12		

Reproduced from Singh and Maharaj,[274] with permission.

actively discharging. However, the development of pain may indicate that an acute infection has supervened and that there may be a build-up of pus under pressure in the middle ear or mastoid. Although there is no direct evidence that such ears have a higher incidence of complications, the clinician should bear this possibility in mind. As discussed above, the incidence of brain abscess arising from mucosal disease is significant and indeed otogenic abscess may occur from ears previously treated by mastoidectomy.[275] The annual risk of developing an otogenic brain abscess has been estimated at 1 in 10 000, making the lifetime risk of a 30-year-old patient with chronic ear disease of the order of 1 in 200.[276]

MORTALITY FROM COMPLICATIONS

The intracranial complications of COM are serious, with a mortality of 8% in the series of Singh and Maharaj.[274] Of the 15 deaths, 7 were in ears with squamous epithelial disease and 8 in ears with mucosal disease. There was 1 death from meningitis, the others being from brain abscess (12) and subdural abscess (2). There were no deaths from extracranial complications.

Extracranial complications

SENSORINEURAL HEARING LOSS

It has been suggested that toxins in COM can damage the cochlea. However, comparison of the two ears in patients with unilateral COM and no history of any factors predisposing to hearing loss have shown no difference in bone-conduction thresholds between the diseased ears and the contralateral normal ear (Dumich and Harner,[277] 200 patients; Noordzij et al,[278] 69 patients). Browning and Gatehouse[279] found no difference in bone-conduction thresholds between 395 ears with COM and 920 control ears after correcting for the Carhart effect. It has been suggested that the risk of sensorineural hearing loss may increase with age.[280] One recent study found a strong association between COM and sensorineural loss, but the authors comment that their data showed extreme variability, which implied that there may by a group of patients particularly vulnerable to sensorineural loss.[281] On the evidence available it seems reasonable to conclude that sensorineural hearing loss may occur as a result of COM, but that this is a rare occurrence and does not affect the great majority of patients. Sensorineural hearing loss may result from the treatment of active COM with potentially ototoxic eardrops, but most practising otolaryngologists regard this as rare, probably at least as rare as sensorineural hearing loss due to the disease.

SUDDEN SENSORINEURAL HEARING LOSS

Sudden sensorineural loss may also occur, but the incidence and precise reasons for this have not been defined nor has the precise relationship to the COM as distinct from other causes.

LABYRINTHINE COMPLICATIONS

Acute bacterial labyrinthitis or cochleolabyrinthitis is a serious complication that often results in a dead ear. Fortunately, in the context of such a common disorder as COM, it is a relatively rare event to lose all the hearing from mucosal disease and the main risk to the inner ear may be from surgery. Similarly, balance disturbance is a serious complication due to labyrinthine involvement by the infective process and may be the first sign of the development of a labyrinthine fistula, almost invariably into the lateral semicircular canal. Chronic low-grade imbalance, with or without detectable nystagmus, implies the development of a labyrinthine fistula. This entity can occasionally result in sudden acute vertigo although this is rare. Erosion of the bone overlying the lateral canal arises in both mucosal and squamous epithelial disease, particularly if there is extensive granulation tissue formation. The frequency of fistulae at surgery is usually reported as 10–15%. The mechanism is likely to be the inflammatory reaction provoking osteitis in the labyrinthine bone which is then subject to the forces of osteoclastic and osteoblastic activity with the osteoclastic element predominating. When the inflammatory process is eliminated by surgery, bone regeneration may occur over such a fistula.

FACIAL NERVE COMPLICATIONS

The incidence of facial palsy is small in the context of the commonness of the disease and it is usually associated with dehiscence of the fallopian canal. Erosion of the bony fallopian canal can occur in active mucosal COM but probably more commonly in squamous epithelial disease where it has been reported in up to 19% of cases,[244] particularly in the presence of granulations, and granulation tissue may form on the nerve sheath itself. Removal of this granulation tissue, which may be exuberant enough to form a polyp, is extremely hazardous to the nerve and should only be carried out under direct vision.

MANAGEMENT OF EXTRACRANIAL COMPLICATIONS

Labyrinthine complications

Acute labyrinthitis should usually be managed medically with bed rest, intravenous antibiotics and labyrinthine sedatives such as prochlorperazine. The patient should be observed carefully for early signs of meningitis. When the general condition has improved, usually after several days, the middle ear and mastoid should be formally explored and appropriate surgery carried out.

Patients with active squamous COM and a suspected labyrinthine fistula should have early surgical management to prevent deterioration of inner ear function. Most surgeons recommend a canal wall-down mastoidectomy. The cholesteatoma matrix should be left undisturbed over the semicircular canals until all other disease is removed and all other aspects of the procedure such as meatoplasty are completed. The matrix should then be carefully lifted and the fistula identified. It is

then peeled off the membranous labyrinth and the fistula is immediately sealed with fascia and bone dust. The fascial graft for the tympanic membrane provides a further layer of closure. Though the risks of loss of cochlear function are higher in large fistulas, Herzog et al.[247] reported no loss of cochlear function in 17 fistulas not exceeding 2 mm.

Facial nerve complications

In the presence of a facial nerve palsy, active COM should be managed urgently and almost always surgically. Appropriate intravenous antibiotics should be commenced on admission. Squamous COM should be managed by the appropriate surgical approach and the cholesteatoma matrix should be carefully dissected off the fallopian canal and facial nerve. Active mucosal COM should be managed by cortical mastoidectomy and exploration of the middle ear with careful removal of granulation tissue from the fallopian canal. Some surgeons believe that the canal should be widely decompressed and the nerve sheath opened, but others think that removal of disease is adequate and that opening of the nerve sheath increases the risk of surgical trauma to the facial nerve. Complete recovery of facial function can be expected in most cases after careful surgical management within a few days of onset. Delay in management results in poorer outcomes.[282]

Intracranial complications

ROUTES OF INFECTION OF THE CRANIAL CAVITY

There are several routes by which sepsis may spread to the cranial cavity from an infected ear and, indeed, considering the proximity of the dura and sigmoid sinus to the infective process, in many cases, it is surprising that intracranial complications are not more common. These routes are most commonly by direct erosion of osteitic bone by the inflammatory process or via infected thrombophlebitis of the emissary veins traversing the bone and also the dura. Infection may also reach the cranial cavity via fractures and surgical defects. Normal anatomical points of weakness, such as the oval and round windows and the internal auditory meatus and cochlear aqueduct, are other possible routes for infection entering the cranial cavity.

OTOGENIC INTRACRANIAL SEPSIS

The main intracranial septic complications are meningitis and intracranial abscess. The latter may be subdivided into extradural abscess, subdural abscess and intracerebral or cerebellar abscess. Thrombophlebitis of the sigmoid sinus and otitic hydrocephalus are the other main complications.

MENINGITIS

Meningitis usually presents as an acute illness with severe headache, neck stiffness and in the later stages drowsiness and coma in a systemically ill patient. Early diagnosis is essential to minimize the risk of death and serious sequelae such as sensorineural hearing loss. The suspicion of meningitis should be raised in any otherwise fit individual with a severe acute pyrexial illness with headache who has a history of a discharging ear, particularly if there is neck stiffness. The diagnosis is confirmed by lumbar puncture, and culture of cerebrospinal fluid will identify the organism.

INTRACRANIAL ABSCESS

In intracranial abscess the presentation is often much more insidious, with low-grade headache, occasionally more severe, mild pyrexia and in the later stages drowsiness, lethargy and weakness. Subdural abscess tends to present more acutely and may be accompanied by fits and focal neurological signs depending upon site, whereas abscess within brain tissue has a notoriously insidious onset with symptoms developing over several days, and neurological signs, dependent upon site, relatively infrequent. Classically, there is an early period of more acute symptoms due to a localized encephalitis with associated brain oedema. The predominant symptoms are headache and vomiting with fever and general malaise. These symptoms then settle as the abscess develops and the more insidious symptoms supervene. The most common sites for otitic intracranial abscess are temporal lobe and cerebellum, as would be expected from their proximity to the temporal bone. The frequency of and mortality from brain abscess have declined markedly in recent years, with mortality of 6–14% quoted in one series.[283] The diagnosis is made by CT scanning, which should be undertaken early if any of the above symptoms develop in a patient with COM.

LATERAL VENOUS SINUS THROMBOSIS

Lateral venous sinus thrombophlebitis is a rare but extremely serious complication of COM requiring urgent recognition and treatment. Infection spreads to the venous sinus directly from the mastoid or via any of the venous channels draining the middle ear and mastoid. Prior to the development of infected thrombus within the lumen of the sinus, there may be abscess formation in the close vicinity of the vein. Initially, mural thrombus forms in the sinus which gradually propagates and organizes. Septic embolization frequently occurs which may result in metastatic abscess formation and occlusion of the sinus may result in raised intracranial pressure. The clinical features will frequently be modified by antibiotic therapy but pyrexia, otalgia and mastoid and neck tenderness in a systemically ill patient are suggestive. Drowsiness and lethargy supervene as the illness progresses and the disease is frequently complicated by other intracranial septic complications such as meningitis or brain abscess. Papilloedema is frequently present and highly suggestive of the diagnosis. The investigation usually undertaken first is CT scanning but MRI may add further information, particularly about venous flow in the sinus.

OTITIC HYDROCEPHALUS

Otitic hydrocephalus (benign intracranial hypertension) is the rarest of the intracranial complications of ear disease and may occur after an episode of AOM, as well as complicating COM. The aetiology remains obscure but the consensus view is that it results from lateral sinus thrombosis, presumably with concomitant obstruction of other intracranial venous channels.[284] Symptoms are the same as those mentioned above, which may raise the suspicion of any intracranial complication, and the presence of papilloedema is suggestive. Early CT scanning is necessary to make the diagnosis and rule out more serious intracranial septic complications.

MANAGEMENT OF INTRACRANIAL COMPLICATIONS

General principles

The basic principles of management of intracranial sepsis resulting from COM are:

- antibiotics
- full neurological observations
- neurosurgical advice
- management of the ear.

Broad-spectrum intravenous antibiotics in effective dosage should be started. A bacteriology swab of the ear should be taken but choice of antibiotic agent should not await the results of culture and sensitivity, especially as ear swabs do not necessarily correlate with abscess swabs. Choice of antibiotic depends on the location of the patient, as the likely organisms vary in different parts of the world. In addition, the range of drugs available and the likely resistance of organisms change with time.

Full assessment of the neurological condition of the patient should be recorded and regularly monitored. The neurosurgeon will usually decide on the management of the patient, but this decision may be influenced by the neurological condition and its progress.

Meningitis

Treatment is antibiotic therapy and observation. Management of the ear should be deferred for a few days until the patient's condition improves. However, if the patient's condition does not improve after 48 hours, or if it deteriorates, then immediate exploration of the ear is indicated.

Intracranial abscess

Abscesses usually require drainage. Otogenic extradural abscesses usually lie adjacent to the temporal bone. The most appropriate surgical approach to the abscess is through the mastoid, therefore the ear disease should be managed at the same time.

Subdural and intracerebral abscesses were traditionally managed by the neurosurgeon, by aspiration through a burrhole, which may require to be repeated, or by craniotomy and excision of the abscess. More recently, these abscesses have been managed by transmastoid drainage of the abscess with mastoidectomy, either canal wall-up or wall-down depending on the pathology in the ear.[285, 286]

Lateral venous sinus thrombosis

Most clinicians advocate early surgical management of the ear. It used to be thought that the lateral sinus should also be opened. After clearing disease from the mastoid, the bone covering the lateral sinus is removed, the sinus opened and the infected clot removed. However, more recent case series have recommended mastoidectomy and antibiotics without opening the sinus.[287, 288]

Otitic hydrocephalus

Otitic hydrocephalus may result from raised intracranial pressure associated with lateral venous sinus thrombosis.

Management is reduction of the raised intracranial pressure by steroids, diuretics and hyperosmolar dehydrating agents. Treatment may need to be continued for many weeks. Occasionally a ventriculoperitoneal shunt may be required.

BEST CLINICAL PRACTICE

- ✓ Complications should be considered in any patient with COM who is generally unwell and in particular with symptoms such as pyrexia and headache.
- ✓ Early and effective management of complications is important. Expert, non-otolaryngological advice may be required.

FUTURE RESEARCH

- ➤ Advances in sequencing technologies and mass spectrometry for gene expression and proteomics.
- ➤ Use of bioinformatics to anlayze gene networks.
- ➤ Development of mouse models for CSOM and cholesteatoma.
- ➤ Development of bacteriophages, small interfering RNA (siRNA) in treatment of COM.
- ➤ Novel methodologies for middle ear drug delivery.

KEY POINTS

- Chronic otitis media (COM) implies a permanent abnormality of the pars tensa or flaccid.
- Active mucosal COM is often associated with destruction of the ossicular chain.
- Cholesteatoma is a benign keratinizing epithelial-lined cystic structure found in the middle ear and mastoid.
- Epithelial cells in cholesteatoma are derived from the tympanic membrane.
- In the rare instances of cholesteatoma occurring behind an intact tympanic membrane it has been shown that the cholesteatoma is derived from the tympanic membrane.
- The prevalence of COM is greater in lower socioeconomic groups.
- COM in cleft palate patients followed up to 10 years of age is around 20%, with 2% of them having a cholesteatoma.
- Studies to examine the presence of biofilms in active COM have shown a 60% biofilm incidence as opposed to 10% in the control, uninfected group.
- OME predisposes to chronic retraction of the pars tensa or flaccida and this subsequently progresses to cholesteatoma.
- Tympanosclerosis is found in the middle ear in around 25% of ears at surgery.

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Figures 83.9–83.29 and 83.31–83.35 are reprinted from Wormald PJ and Browning GG. *Otoscopy: a structured approach*. London: Hodder Arnold; 1996.[289]

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CHAPTER 84

MYRINGOPLASTY

Charlie Huins and Jeremy Lavy

SEARCH STRATEGY

Data in this chapter may be updated by a Medline and Embase search using the keywords: myringoplasty, tympanoplasty, tympanic membrane, perforation, chronic otitis media and focusing on surgery and management.

INTRODUCTION

Myringoplasty can be defined as the surgical repair of the tympanic membrane.[1] In the majority of cases the damage is likely to be a persisting perforation of the drum but there are also situations where a thin or retracted drum may need to be reinforced. This chapter will focus on the perforated eardrum but some of the techniques described are also applicable to reinforcement myringoplasty. Wullstein in 1956[2] classified tympanoplasty, with myringoplasty being classified as a Type I tympanoplasty.

HISTORY

Descriptions of artificial animal-based plugs being used to cover perforated tympanic membranes date back to the 1640s.[3] Such plugs probably served the purpose of keeping the ear dry and therefore reducing the risk of infection, but it is unlikely that there would have been any positive effect on the hearing acuity of the ear. For the first accounts of more sophisticated treatment one has to wait until the 1850s when Yearsley described an artificial eardrum consisting of moistened cotton wool.[3] This was inserted into the perforation and plugged it, often affording a noticeable improvement in hearing. Toynbee describes an artificial eardrum comprising a gutta percha disc and a silver wire. Around this time William Wilde and Roosa were advocating the use of cautery to the remnant tympanic membrane to encourage healing. Silver nitrate and trichloracetic acid were commonly used agents. Joynt (1919) combined cautery with the use of a paper patch overlying the perforation; Blake first described the paper patch on its own in 1887. In 1878 Berthold described his technique of using a full-thickness skin graft, describing this alongside 'freshening' or excision of the perforation edges to 'render these parts into a wound'; he is also credited with being the first to use the term 'myringoplasty'. Ely described a similar technique but his work was not published until a year later in 1879.

Although these techniques were being described in the medical literature, they were not consistently successful and it was not until the 1950s with Wullstein's split skin graft and Zollner's pedicled skin graft that higher rates of successful repair were being reported, albeit only up to 71% in ideal cases.[4] The other crucial development that was occurring around this time was that of the operating microscope. The availability of illumination and magnification afforded by the operating microscope transformed this area of surgery probably more than any other.

The use of skin grafts was associated with a relatively high rate of reperforation, inflammation and cholesteatoma formation.[5] Attention passed to other graft materials, with Zollner describing fascia lata (1956), Heerman temporalis fascia (1958) and Shea vein grafts (1960). Since then the list of potential graft materials has expanded to include perichondrium, cartilage, periosteum, fat, subcutaneous tissue, amniotic membrane, dermal matrix, fibroblasts, animal pericardium and sclera!

AETIOLOGY

Infection

The commonest cause of an acute perforation is following an episode of acute otitis media. Spontaneous healing of such perforations is the norm, with 70–80% healing within 30 days,[6, 7] with pre-existing tympanosclerosis, malleus injury, infection and large perforations negatively influencing spontaneous closure rates.[8] Loss of contact inhibition of the squamous epithelial cells is postulated to be the driver for repair of acute injuries to the membrane. When a perforation becomes chronic, the margin of the perforation can be seen to be stable with the squamous epithelial cells coming into contact with the epithelial cells of the mucosal layer, creating a barrier against further vascular proliferation.[9]

Trauma

A direct blow to the ear can result in rupture of the tympanic membrane. This can be an isolated injury or, in cases of more severe trauma, can be associated with fractures of the temporal bone and damage to other structures in the middle ear. Barotrauma related to air pressure changes with air travel or water pressure and diving can similarly cause rupture, as can direct trauma such as with a cotton bud.

Iatrogenic

Iatrogenic trauma from middle ear surgery or following the extrusion of a ventilating tube (VT) should be evident from the history. The risk of a chronic perforation following short-term VT is 2.2%, with long-term VTs increasing the risk to 16.6%.[10]

PRESENTATION

Perforations may be completely asymptomatic and can be found incidentally. The majority of patients, however, will present to the ENT surgeon as a result of their symptoms, the commonest being discharge and hearing loss.

Discharge

A mucoid discharge from the ear, be it simple mucus or mucopurulent, should always alert the clinician to the likelihood of a tympanic membrane defect. There are no mucous glands in normal ear canal skin whereas they are in abundance within the middle ear mucosa. Discharge, in most cases, is associated with infection. This can be from ingress of potentially infective organisms from the outside into the middle ear through a pre-existing perforation or from mucosal reaction to a systemic infection (e.g. an upper respiratory tract infection), with the rapid build-up of mucopus resulting in an acute perforation.

Common pathogens include *Pseudomonas*, *Staphylococcus aureus* and *Moraxella*.[11] A swab for microscopy, culture and sensitivity is not routinely sent, being reserved for cases of recurrent infections not responding to 'standard' topical antibacterial medications, in immunocompromised individuals or where suspicion of unusual bacteria is present.

Management of mucopurulent discharge from the ear would follow guidelines set by NICE,[12] with first line being thorough microsuction to reduce the bacterial load followed by regular application of topical antibiotic preparation to the external ear canal. It is acceptable to use short courses of a topical antibiotic with or without corticosteroid, but careful consideration must be given to potential risk of aminoglycoside-induced ototoxicity in patients with a suspected or confirmed perforation.[13] In such circumstances many ENT surgeons would use quinolone-based drops as they are not ototoxic.[14] An ENT-UK position paper stated that a short course of topical aminoglycoside-based drops in the presence of a perforation was acceptable since pus in the middle ear associated with otitis media carries a higher risk of ototoxicity than the drops themselves. This course must be short and stopped as soon as the infection has cleared.[15] An oral antibiotic may also be given in severe or unresponsive infections. An ear wick may be used for severe infections, but the duration of use of each wick should be kept to a minimum.

Hearing loss

Hearing loss can vary depending on the size and location of the perforation. More severe hearing loss should alert the clinician to the possibility of coexistent ossicular involvement/discontinuity. Very small perforations may not cause any hearing loss, but larger defects can cause moderate conductive hearing loss (CHL) due to loss of surface area available to absorb sound energy.[16]

Perforations tend to affect the lower frequencies, having less of an impact as frequency increases.[16]

The site of the perforation has not been seen to correlate with the magnitude of hearing loss, except for those affecting the posterosuperior quadrant.[16] Complete ossicular discontinuity can result in a maximal CHL of around 60 dB.

INDICATIONS FOR MYRINGOPLASTY

The three principal indications for myringoplasty are recurrent otorrhoea, hearing loss due to a chronic perforation, and the desire to swim without having to waterproof the ear.[17]

Infection

The presence of a perforation exposes the middle ear to the risk of recurrent infection from external sources. This can have a significant effect on the quality of life, together with a risk of progression of the middle ear pathology.[18]

Hearing loss

The repeated insult of infections is not only unpleasant for the patient but can affect hearing through both the presence of mucopus and the potential destruction of the ossicular chain. The distal aspect of the long process of the incus is the most vulnerable part of the chain, due to its tenuous blood supply. Erosions at this point can lead to loss of continuity with the stapes and hence a CHL.

Small perforations under 25% may not lead to any significant hearing deficit. Perforations greater than 25% have been shown to cause a greater CHL as size increases.[16] Post-operative audiometric gain has been shown to correlate well with increasing size of the repaired perforation,[19] with those >50% demonstrating a greater pre-operative loss and greater post-operative gain.[20] Exposure of the ossicular chain appears to be more of a factor for hearing loss than loss of the round window baffle effect; perforations in the posterosuperior quadrant have a larger CHL than other sites. Perforation-induced hearing losses appear greatest at lower frequencies with less influence on higher frequencies.[16]

Social

In the presence of a perforation, the general advice is to protect the ear from water to prevent pain and infection, though there does not appear to be any high quality evidence to support this. To enable swimming without the need to protect the ear from water, particularly in children, is a relative indication for myringoplasty.

CONTRAINDICATIONS TO MYRINGOPLASTY

Cholesteatoma

The presence of cholesteatoma is an absolute contraindication to myringoplasty alone. All squamous epithelium must be excised from the middle ear prior to closure of the tympanic membrane defect to prevent further progression of the cholesteatoma and its subsequent well-recognized complications.

Contralateral hearing

Relative contraindications include a contralateral dead ear. Hearing loss from myringoplasty is rare at 1.5%, potentially from infection or manipulation of the drumhead and ossicular chain during surgery.[21]

Bilateral perforations

Should bilateral perforations be present, most would advocate operating on one ear at a time. While the incidence of severe hearing loss from myringoplasty is rare,[21] unilateral surgery avoids any risks to the contralateral ear, leaving this side available for hearing and communication, certainly while the post-operative packing is present (in the other). However, other studies have suggested that bilateral myringoplasty is safe, reduces costs and increases patient satisfaction, with post-operative packing causing only a modest CHL that is readily acceptable to patients.[22]

Eustachian tube dysfunction

Severe Eustachian tube dysfunction can be extremely challenging to treat. Attempting to elevate a Sade grade IV retraction from the ossicular chain can increase the risk of hearing loss. There is also an increased chance of an iatrogenic cholesteatoma should any epithelial cells be left *in situ*.[23] Reconstructing the tympanic membrane using cartilage can provide more resilience against the negative middle ear[22] but, despite this, recurrence of the retraction can occur.[18]

As when considering all surgery, the general medical fitness of the patient must be taken into account. Multiple factors adversely affect wound healing and can potentially influence the surgical result and should therefore be optimized prior to surgery. Chronic general medical conditions, such as diabetes and cardiovascular disease, lead to poor oxygenation of tissues, with infection and stress disrupting neuroendocrine immune equilibrium. Medications, obesity, smoking and alcohol consumption and poor nutrition should be optimized prior to surgery.[24] The insult of a general anaesthetic must also be taken into account for patients with multiple medical comorbidities. Myringoplasty can frequently be performed under local anaesthetic and particular consideration for this should be made in this patient group. Day-case surgery for tympanoplasty is increasingly the norm without compromising patient care and safety.[25]

FACTORS INFLUENCING TREATMENT OPTIONS

Various tympanoplasty prognostic scoring systems have been proposed, including SPITE (surgical, prosthetic, infection, tissues and Eustachian tube) and MERI (Middle Ear Risk Index), to try to stratify possibilities of success.[26] Other factors to consider prior to surgical intervention include patient age, presence of infection, status of the other ear, reperforation rates, the influence of the mastoid and smoking.

Timing and age

There is a debate as to whether age plays a part in success rates following myringoplasty. Some would advocate avoiding such surgery in younger children, awaiting Eustachian tube (ET) maturity prior to contemplating perforation repair. Morphological changes in the ET that accompany improvement in function are most marked after the age of 7 years,[27] with many managing these patients conservatively until after this age, assuming these patients were relatively asymptomatic. Others, however, suggest that age does not play a part in surgical outcomes

and will offer surgery to children younger than 7 years old. The state of the contralateral ear is an important guide as to overall function of the ET. Problematic perforations, such as those with recurrent infections or marked hearing loss causing developmental delay, may warrant earlier operative intervention.

Adenoidectomy

Evidence regarding the contribution of adenoidectomy to myringoplasty success is conflicting,[17] with the majority of reviews suggesting that prior adenoidectomy confers no benefit in success rates of myringoplasty.[28–31]

Infection

The literature has differing opinions regarding the influence of infection present at the time of surgery on outcomes. Up to 20% of perforated ears (both wet and dry) have been shown to grow pathogens on culture[32] and infection is one of the most common causes of failure in myringoplasty.[33] Some studies demonstrate that the presence of infection at time of surgery negatively influences outcomes, with higher rates of failed perforation closure, retraction pocket formation and myringitis.[18] The majority of studies, however, have shown that the presence of infection does not negatively influence surgical outcomes and therefore most surgeons would not be deterred from proceeding in the presence of active infection.[34, 35]

Other ear

A normal contralateral ear is a positive predictor of success of tympanoplasty as this suggests favourable overall Eustachian tube function.[26]

Conversely, abnormalities in the opposite ear should be checked to exclude the possibility of bilateral hearing loss or even the presence of cholesteatoma. With the presence of abnormalities in the other ear, success of graft uptake has been found to be poorer.[26, 36]

The presence of a bilateral perforation may influence the choice of graft material. Though there is little evidence to support any one particular graft material producing more favourable results over another,[17, 25] the use of cartilage is becoming more popular, particularly in this group, subtotal perforations and revision surgery, due to its perceived superior resilience over temporalis fascia alone and therefore potential higher closure success rates.

Reperforation rates

The literature quotes success rates of 60–99% in adults and 35–94% in children.[37] Most studies have short follow-up periods yet reperforation can occur several years after the initial surgery. There are relatively few long-term studies, with some suggesting that success rates fall over time from around 85% at 1 year to 78% at 10 years.[36] Reperforation rates in children under 15 years have been quoted at 18%, over double the rate of that in adults.[18]

Most failures occur in the early post-operative period, mainly due to graft failure from infection with graft necrosis or failure of the anterior aspect of the graft – the most tenuous area due to this region's apparent hypovascularity compared to the rest of the tympanic membrane.[5, 18, 38] Following initial failures, there are no clear guidelines as to whether surgical revision is indicated and, if so, how long one should wait before reoperating, though 3 months would seem a reasonable time to allow for the postsurgical changes to resolve.

Mastoid

The influence of the mastoid air cell system on chronic otitis media (COM) is still subject to debate. Poor pneumatization of the mastoid, together with Eustachian tube dysfunction, often predispose to chronic suppurative otitis media.[7] It is thought by some that mastoidectomy can improve outcomes in non-cholesteatomatous COM surgery by creating a reservoir of aerated bone to buffer pressure changes in the middle ear and by eradicating residual mucosal disease hidden in the mastoid air cells.[33, 39] While a recent study comparing myringoplasty alone with the same in combination with mastoidectomy did not show any statistically superior advantage with the latter, that group obtained better hearing results and required fewer subsequent ear procedures.[40] Other studies have demonstrated the presence of residual mastoid disease on CT scans of the temporal bones in patients whose graft had failed,[33] with mastoidectomy being advised in cases of COM not responding to pre-op intensive medical treatment[41] or in revision cases.[39] Although mastoidectomy has been claimed to be a safe procedure that neither significantly increases operative time nor results in further complications,[17] others argue that mastoidectomy does not improve surgical outcomes and exposes the patient to increased surgical risks.[42, 43] A recent literature review did not show any benefit of performing mastoidectomy with tympanoplasty for uncomplicated perforations.[44] More complicated otological disease, such as active mucosal COM or repeat perforations, show worse outcomes and may benefit from concurrent mastoidectomy, but there is insufficient evidence to recommend this.[45]

Social

The influence of smoking on surgical outcome is not clear. Some studies suggest no statistically significant effect on graft take rate[19] whereas others have noted the local, regional and systemic negative effects of smoking on the middle ear and Eustachian tube.[26, 46] Locally, nicotine causes cutaneous vasoconstriction, and increases thrombosis risk with carbon monoxide reducing the oxygen carrying capacity of blood. Regionally, chemical irritation leads to increased mucous viscosity and reduced mucociliary clearance with Eustachian tube obstruction. The systemic negative effects of smoking are well documented in the literature, particularly on the respiratory system.

INVESTIGATIONS

Ear swab

The value of microbiological culture of all discharging ears has not been shown to be statistically beneficial over empirically treated ears.[47]

Audiometry

All patients with a perforation or perceived hearing loss should undergo audiometric testing at the time of their clinic visit. This allows for quantification of the degree of hearing loss and can assist the surgeon in predicting what may be found in the middle ear at the time of surgery. Certainly, audiometry pre- and post-operatively allows for analysis of surgical outcome, both for surgeons to audit their results (and perhaps change their practice) and to demonstrate to the patient a successful outcome. The hearing in the contralateral ear is an important factor in guiding decision making in myringoplasty.

Imaging

Most myringoplasties do not require pre-operative imaging. In those in whom the history is unusual, or examination findings suggest further pathology, a fine-cut CT of the temporal bone can reveal unexpected opacification or unusual bone erosion, together with providing some insight into the state of the ossicular chain.

In cases with sensorineural asymmetry, a difference of greater than 20 dB at two adjacent frequencies is an indication for screening for the rare possibility of a concurrent vestibular schwannoma. T1-weighted MRI with gadolinium of the internal acoustic meatus is the gold standard investigation of choice.[48]

GRAFT MATERIALS

Since the full-thickness skin graft, first used by Berthed in 1878, many graft materials have been tried.[17] From autologous, to allogenous and heterogeneous, a wide spectrum of alternatives is available and there is no one ideal material.[17, 25]

The least invasive and perhaps simplest is the paper onlay technique, using a thin cigarette paper or similar placed onto the tympanic membrane as an outpatient procedure. This has been used with reasonable success to assist closure of small perforations, occasionally requiring repeat applications for a successful outcome. It is least successful for large perforations.[26]

Of the autologous materials, temporals fascia is the most frequently utilized for all perforations given its availability, the abundance of tissue and ease of use. Success rates of 77–99% in adults and 35–94% in children are quoted,[37] depending on experience and technique,[38] though multiple other factors may be influential. Easily harvested via a postauricular or endaural approach, a separate scalp incision, hidden in the hairline, may also be used during a permeatal approach. Treating the fascial graft prior to use with formaldehyde[18] does not appear to enhance successful closure rates, while the topical application of adhesive following graft placement is claimed to do so, although the median follow-up was relatively short at 4 months.[49]

Perichondrium from either the tragus or concha provides an alternative material, with the former being easily accessed either via a small and cosmetically acceptable retrotragal incision or by extending an existing end aural incision (if used as the approach). Several surgeons prefer tragal perichondrium due to its ease of harvest, particularly for the permeatal approach, and its long-term reliability.[50]

Cartilage, either from the tragus or concha, is gaining popularity as a more reliable material. A composite graft from the tragus provides a very practical material with a good thickness and curvature for use in tympanoplasty, together with a very low metabolic rate.[50] Keeping the cartilage attached to the perichondrium helps placement and aids graft stabilization and is now considered one of the best materials for use in larger perforations (greater than 50%),[17] adhesive otitis media and revision surgery for recurrent perforations, with quoted closure rates of up to 100%.[50]

Fashioning a cartilage 'butterfly' is a technique that has been proposed for smaller perforations less than 6 mm, with the cartilage disc being circumferentially incised by 1 mm. This groove is engaged into the perforation rim, thereby stabilizing the graft. Mild myringitis was encountered in 11%, resolving within 3 months, with a quoted closure success rate of 94%.[51]

There is some debate as to whether the hearing gain obtained with cartilage is inferior to that of fascia or other more flexible material. Short-term post-operative hearing with cartilage is not as good as that with temporalis fascia or perichondrium, but results at 1 year were the same,[50] with long-term hearing outcomes of cartilage and fascia being equivalent.[52, 53] This is presumed to be due to the partial resorption of cartilage over time[50] which causes it to lose its rigidity.[54]

Other autologous materials have been used, either locally accessible such as periosteum, subcutaneous tissue, ear canal or other skin graft and fat, the latter usually being harvested from the lobule or post auricular region[55] though umbilical fat has also been used.[56] Fascia lata and vein[57] provide a more distant autograft. Autograft and xenograft have been combined using fat and a hyaluronic acid ester (Epidisc) with quoted overall closure rates being 92.7%.[55, 58]

Experimental investigations of allogeneic materials include extracellular matrix in the form of urinary bladder matrix (in 14 animals with a closure in 13 out of 14 ears at the end of the experiment at 12 weeks)[59] and stem cells.[60] Results were encouraging though numbers were very small in both studies.

Alloderm, processed from human allograft skin and rendered immunologically inert, can provide an alternative when temporalis fascia is not available, with a success rate of 87.5%, equivalent to that of temporalis fascia.[61]

Several xenogenous materials have been investigated. Equine and bovine pericardium were found to be inferior

to temporalis fascia.[38] Basic fibroblast growth factor (FGF) has been studied since exogenous bovine FGF stimulates the proliferation of fibroblasts and vascular cells, induces endothelial cell migration, releases matrix-degrading proteases and forms tubular structures resembling blood capillaries.[62, 63] FGF has been used either in combination with atelocollagen, a type 1 collagen material derived from calf dermis, with closure achieved in 92% of 87 patients,[64] or to large (greater than 50%) traumatic perforations applied either via a Gelfoam patch over the perforation, or as drops alone with very encouraging results of 97% and 100% closure respectively within 10 days, compared to 55% in the control group within 41 days.[65]

TECHNIQUES

Two main techniques have been described for placement of graft materials, namely overlay and underlay. Overlay derives its name from the graft being placed lateral to the fibrous layer of the drumhead and hence over the fibrous annulus, the epithelial layer having been elevated alone and then replaced onto the graft. The underlay technique involves placement of the graft medial to the entire tympanic membrane, with elevation of a flap of ear canal skin together with the drumhead being most commonly used for access, stabilizing the graft under the fibrous annulus. A prospective randomized controlled study of both techniques did not show any difference in temporalis fascia graft uptake rates between the two techniques.[23] The authors concluded the underlay technique to be superior due to its technical ease, shorter post-operative healing time, fewer complications and better hearing gain.

There is debate as to correct placement of an underlay graft, particularly with a medialized handle of malleus. Usually the graft should pass under the malleus though, with a subtotal or central perforation with an exposed umbo, some advise a small hole in the centre of the graft through which the umbo can pass to try to prevent the 1.4% risk of graft lateralization.[18]

Access can be achieved permeatally or utilizing a cartilage-avoiding incision – endaural or postaural – depending on the location of the perforation and size of the ear canal. Since the development of the binocular microscope in the 1950s, this has become the standard for all middle and inner ear surgery. Recently, endoscopic techniques have been gaining popularity with the advantages of minimal access surgery and avoidance of visible scars.

COMPLICATIONS

Risks of reperforation have been discussed earlier in this chapter.

Retraction of the drumhead following grafting can occur in up to 10%,[18] with some suggesting the use of cartilage to try to prevent this.[50, 52, 53, 66]

Elevation of the anteroinferior aspect of the tympanic membrane runs the risk of anterior blunting, a risk with both overlay and underlay techniques.[23] Various techniques or packing methods have been proposed to try to prevent this as it can impact on hearing outcomes.

The incidence of iatrogenic cholesteatoma, particularly with the overlay technique which runs a higher risk of leaving some squamous epithelium medial to the graft, can be as high as 4.4%.[67, 68]

Myringitis can occur, influenced by the presence of infection[18] or choice of material,[51] though most cases resolve within 3 months with short-term topical medication and observation.

BEST CLINICAL PRACTICE

- ✓ Most surgeons wait until the patient is at least the age of 7 years before considering myringoplasty.
- ✓ The presence of infection at the time of surgery does not negatively impact success rates.
- ✓ Adenoidectomy confers no benefit on success rates for myringoplasty.
- ✓ There is insufficient evidence to support concurrent mastoidectomy during tympanoplasty.
- ✓ Temporalis fascia is the most frequently used autologous material, with the use of cartilage increasing in popularity for larger perforations (greater than 50%).
- ✓ Cartilage tympanoplasty has equivalent long-term hearing outcomes to temporalis fascia or perichondrium.
- ✓ Underlay and overlay techniques have similar outcomes.

FUTURE RESEARCH

- ➤ The quality and quantity of randomized controlled trials are limited.
- ➤ Further research should involve levels 1 and 2 evidence with regard to:
  - ➢ the role of mastoidectomy with tympanoplasty in chronic otitis media
  - ➢ ideal minimal age for surgery
  - ➢ the role of tissue engineering and growth factors should be a productive area for future research.

KEY POINTS

- Around 70–80% of acute perforations heal spontaneously within 30 days.
- The risk of chronic perforations following short-term ventilation tubes is 2.2% rising to 16.6% with long-term tubes.
- Aminoglycoside antibiotics are ototoxic but quinolone-based are not; a short course of topical aminoglycoside-based drops in the presence of a perforation is acceptable but, if used, this should be stopped as soon as the infection has cleared.
- Three indications for myringoplasty are recurrent infections, hearing loss and social impact such as pain on swimming.
- Success rates for myringoplasty are 60–99% in adults and 35–94% in children.
- Post-operative retraction of the drumhead can occur in up to 10%.
- The risk of iatrogenic cholesteatoma is 4.4%.

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CHAPTER 85

OSSICULOPLASTY

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: ossiculoplasty, ossicular chain, reconstruction, prosthesis, middle ear, hearing, with additional searching of secondary sources.

INTRODUCTION

This chapter covers the principles and practicalities of surgery to correct ossicular chain abnormalities with the aim of improving hearing. The surgical priorities when treating chronic middle ear disease are first to make the ear safe, then to make it dry, and finally to make it work. The last of the three is often the most difficult – and of great concern to the patient – which is why ossiculoplasty can be both challenging and rewarding.

AETIOLOGY/PATHOLOGY

Conductive hearing loss due to ossicular chain abnormalities may be either congenital or acquired, and is due to either ossicular chain discontinuity or fixation.

Congenital

Deformities of the ear occur in approximately 1 in 15 000 births with isolated middle ear abnormalities or 'minor' malformations being less common than 'major' malformations which may also involve the tympanic membrane and external ear.[1, 2] Favourable results following surgical reconstruction of major malformations are dependent on the severity of the abnormality. The status of the ossicles, presence of the round window, pneumatization of the middle ear space, and course of the facial nerve are key determinants.[3] Prognostic grading systems such as the Jahrsdoerfer score can be used to predict the likelihood of achieving good hearing outcomes.[4]

A diverse range of isolated middle ear deformities has been described, the most common being fixation of the stapes footplate which may occur in isolation (which is often bilateral) or in association with stapes superstructure or other ossicular abnormalities.[5] Epitympanic fixation of the ossicular heads and ossicular discontinuity are described less frequently.[6] The most challenging cases involve aplasia of the oval or round window; however, fortunately these are rare. Surgery for congenital ossicular chain abnormalities should only be attempted by experienced otologists after careful consideration of alternatives which include air- or bone-conduction hearing aids.

Acquired

The majority of ossicular chain defects arise as a consequence of chronic otitis media with or without cholesteatoma. Ossicular chain erosion is much more common in the presence of cholesteatoma (**Table 85.1**). The most common acquired abnormality is erosion of the long process of the incus, which may be confined to the incudostapedial joint (ISJ) or extend a variable distance superiorly. The stapes superstructure may be partially or completely eroded, whereas the malleus handle is the most frequently preserved. Shortening or absence of the malleus handle is generally associated with subtotal perforations.

Ossicular disruption secondary to trauma may occur following direct injury to the tympanic membrane,

TABLE 85.1 Ossicular chain defects in 1211 consecutive chronic middle ear cases

Defect	% Incidence with cholesteatoma *n* = 692	% Incidence without cholesteatoma *n* = 519
Ossicular chain intact	27	71
Incus alone eroded	26	18
Incus and stapes eroded, malleus intact	24	7
Incus, stapes and malleus eroded	11	2
Incus and malleus eroded, stapes intact	8	2
Stapes alone eroded	2	0.4

TABLE 85.3 Modifications to classification system by Kartush[9]

Group	Ossicular status
O	Intact ossicular chain
E	Ossicular head fixation
F	Stapes fixation

TABLE 85.5 Middle Ear Risk Index 2001[13]

Otologic factor	Maximum score
Otorrhoea	3
Perforation	1
Cholesteatoma	2
Ossicular status	4
Middle ear granulation	2
Previous surgery	2
Smoking	2

barotrauma or temporal bone fracture. These defects are further described in Chapter 91, Ear trauma. Idiopathic cases of resorption of the long process of the incus in the absence of active suppurative ear disease have been described in the literature but are rare.[7]

CLASSIFICATION OF DEFECTS

The value of a classification system is to enable a systematic description of pre-operative ossicular status to facilitate meaningful analysis of surgical outcomes. Given the multitude of surgical approaches for correcting ossicular chain abnormalities, it is essential when evaluating results that the pathologies are comparable. While each patient will present a subtly unique anatomical situation, defects can be broadly characterized by the presence or absence of different components of the ossicular chain.

The most widely used classification system is the Austin–Kartush system which applies to situations without an intact incus. First proposed by Austin in 1971,[8] four distinct

TABLE 85.2 Austin classification of ossicular chain defects with absent incus[10, 11]

Group	Ossicular status	Abbreviation	Prevalence (%)
A	Malleus handle and stapes superstructure present	M+ S+	60
B	Malleus handle present, stapes superstructure absent	M+ S–	23
C	Malleus handle absent, stapes superstructure present	M– S+	8
D	Malleus handle and stapes superstructure absent	M– S–	8

TABLE 85.4 Belluci classification of otorrhoea[12]

Otorrhoea	Risk value
Dry ear	0
Occasionally wet	1
Persistently wet	2
Persistently wet + cleft palate	3

anatomical situations are described (Table 85.2). This was modified by Kartush in 1994,[9] with the addition of three further categories to include a normal ossicular chain, and cases of fixation (Table 85.3). Situations not covered by the Austin–Kartush classification are rare and include isolated malleus handle fracture and fracture of the stapes superstructure. The classification also makes no specific allowance for partial incus erosion where incus remnant preservation is attempted.

PROGNOSTIC FACTORS

The ideal scenario in which to perform ossiculoplasty is in a stable well-ventilated middle ear, with an intact tympanic membrane, in the absence of ongoing middle ear infection or cholesteatoma. Absence of any of the above factors increases the risk of failure, as do patient factors such as smoking status.[13]

The Middle Ear Risk Index (MERI) was devised by Kartush in 1994 and generates a numeric value which corresponds to severity of disease, and the likelihood of a successful outcome following surgery.[9] This can be used to guide case selection and counselling of patients pre-operatively but is perhaps most useful for research purposes. It is an amalgamation of the Austin–Kartush classification of ossicular defects, the Belluci classification of otorrhoea (Table 85.4),[12] and takes into consideration the presence of tympanic membrane perforation, middle ear granulation, and cholesteatoma. The MERI was originally scored 0–12, and was later modified in 2001 to include smoking and increase the weighting for granulation and cholesteatoma thus giving a score of 0–16 (Table 85.5).[13] Alternative risk stratification or scoring

systems include the Ossiculoplasty Outcome Parameter Staging (OOPS) index,[14] or SPITE factors (surgical, prosthetic, infection, tissue, Eustachian).[15]

KEY POINTS

- Use of a classification system such as the Austin–Kartush allows a meaningful analysis of results and comparison of results between surgeons.
- Ossiculoplasty results are significantly affected by the status of the middle ear.

MATERIALS FOR RECONSTRUCTION

The ideal material for ossicular reconstruction should be biologically stable (resistant to resorption and non-reactive), of the correct mass and stiffness, be easy to handle, and ideally low cost. There are many options for reconstruction which can be broadly divided into autografts, homografts and alloplastic materials.

Autograft

Autografts are tissues that are harvested from the same patient on which they are to be used, and can include ossicles, cortical bone and cartilage. Their primary advantage is excellent biocompatibility with low risk of extrusion. When available, an autograft offers a low-cost solution compared to ossicular prostheses.

Incus interposition is an example of a well described and popular technique in situations with an intact malleus handle and stapes superstructure.[16, 17] Cartilage tends to be less stable due to displacement or resorption and is less commonly used.[18, 19]

Limitations to the use of autologous ossicles are that the incus is not uniformly present in diseased ears, while technical skill and time are required to sculpt the incus to the required shape. There is a risk of implanting residual disease if the ossicle has been enveloped in cholesteatoma, therefore careful assessment of its integrity is required. Some surgeons recommend autoclaving ossicles prior to reimplantation to reduce the risk residual disease[20] but this is not widely practised.

Homograft

Homograft material is derived from human donor tissue. A wide choice of pre-prepared graft material is available with options including cortical bone, cartilage, ossicles, and *en bloc* ossicular chain with tympanic membrane attached.[21, 22]

Benefits over autografts include a shortening of the operative time as pre-prepared prostheses can be inserted directly or with minimal modification. Homografts offer reconstructive options that may be absent or eroded in diseased ears, and do not carry the risk of residual cholesteatoma provided they are harvested correctly.

The major barrier to the use of homograft materials is the potential risk of disease transmission from donor to recipient, with viral infections and the transmissible spongiform encephalopathy Creutzfeldt–Jakob disease (CJD) of particular concern.

The majority of cases of iatrogenic CJD transmission have occurred following neurosurgical procedures using infected dural grafts.[23] Two cases of CJD transmission have occurred following ear surgery, one as a result of cadaveric dura mater, and another due to the use of pericardium. There are no reported cases of CJD transmission from the use of homograft tympanic membranes or ossicles while they have been used in thousands of procedures.[24, 25]

A combination of serological donor screening, and appropriate methods for ossicle preparation can reduce the risk of disease transmission to a very low level. However, ongoing concerns about potential infectivity combined with significant infrastructure required to maintain an ossicle bank, and the improvement in artificial materials mean that homografts have fallen out of favour in many countries.

Alloplastic materials

The use of alloplastic materials for ossiculoplasty was first described in 1952 by Wullstein who used a 'palavit' (vinyl–acrylic resin) columella prosthesis to connect a mobile stapes footplate with the tympanic membrane.[26]

Since that time, a wide range of materials have been used in the search for a prosthesis that retains its structural integrity yet can be easily shaped or modified. Of equal importance is that the prosthesis does not induce unwanted inflammatory reactions in middle ear tissues yet bio-integrates in such a way that it is not extruded.
Materials that have been used include:

- solid plastics: polytetrafluoroethylene, polyethylene
- solid metals: stainless steel, gold, titanium
- porous sponge-like plastics: Proplast®, Plasti-Pore®
- ceramics: aluminium oxide, hydroxyapatite.

Solid plastics and stainless steel were some of the earliest materials used but were largely abandoned due problems with absorption at bony interfaces and extrusion.[27] Plasti-Pore® became one of the most widely used artificial materials following its introduction in 1976, but it has high extrusion rates when placed in contact with the tympanic membrane therefore cartilage interposition is required.[28] Histopathological studies have also shown porous plastics can elicit a foreign body giant cell reaction with evidence of implant degradation.[19]

Hydroxyapatite is a calcium-based bio-ceramic with a mineral composition similar to bone and continues to be a popular and proven material with low extrusion rates.[29] Some prostheses are compound designs to take advantage of the different properties of the materials, for example a hydroxyapatite head that can be placed directly against the tympanic membrane with a composite shaft that can be easily trimmed to length.[30]

Titanium implants were introduced in the early 1990s,[31] and have excellent mechanical properties due to high rigidity allowing low-weight prosthesis designs.

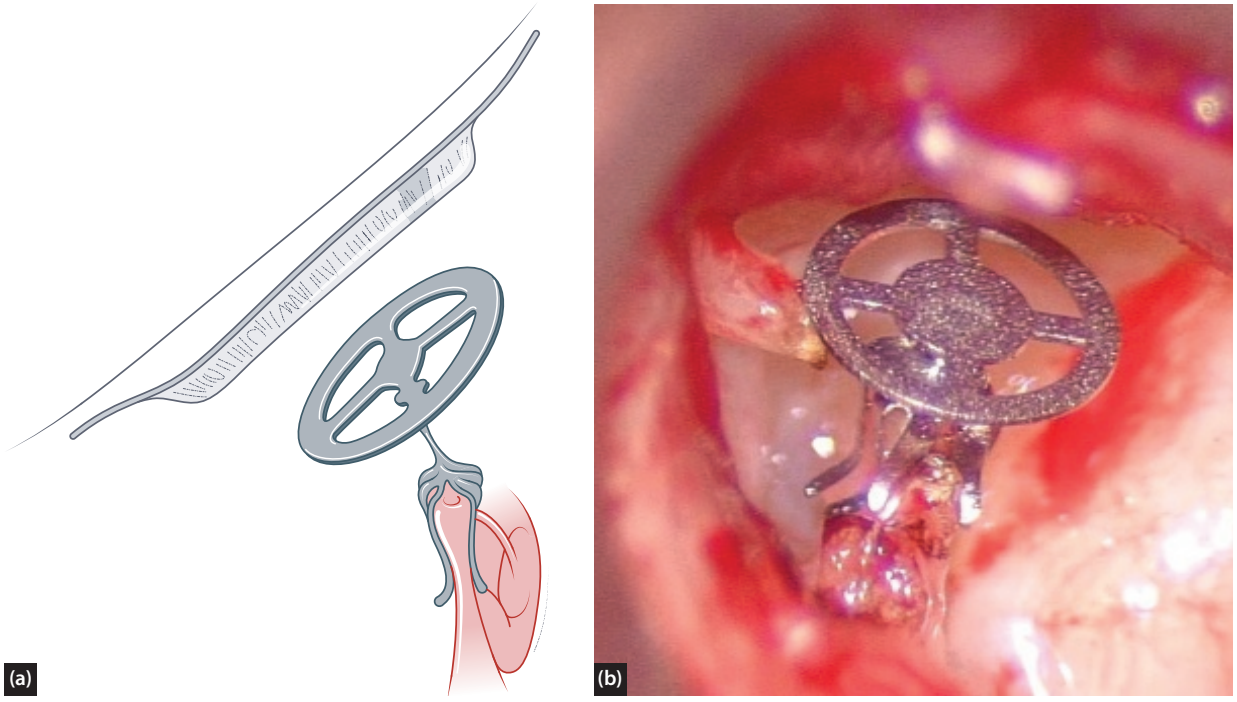

Figure 85.1 PORP on intact stapes. (a) Partial ossicular replacement prosthesis *in situ* on intact stapes superstructure. The cartilage and perichondrium graft lies between the prosthesis and the tympanic membrane. **(b)** Partial clip prosthesis sitting on stapes inferior to eroded incus long process which remains in place.

Complex designs are possible with open head configurations to improve visualization during placement, and delicate 'claw' attachments to fasten securely to the stapes head (Figure 85.1a). Titanium is biocompatible with low extrusion rates of less than 5%.[27] While most surgeons interpose cartilage between a titanium prosthesis and the tympanic membrane, Pringle has questioned whether this is necessary.[32]

KEY POINTS

- Autograft incus continues to be a widely used material for ossicular reconstruction.
- Ideal prostheses should not induce reaction in the middle ear.

BOX 85.1 Terminology

PORP = partial ossicular replacement prosthesis. Generally used to mean a prosthesis that is designed for situations with an intact stapes superstructure.
TORP = total ossicular replacement prosthesis. For use in situations where there is no stapes superstructure and the prosthesis restores a connection with the stapes footplate.

Ossicular reconstructions are referred to as **columellae** when the sound transmission is restored with an ossicle to tympanic membrane connection, and **assemblies** where there is an ossicle-to-ossicle connection.

SURGICAL OPTIONS TO CORRECT SPECIFIC DEFECTS

Due to the wide variation in surgical practice and increasingly large range of prostheses available it is not possible to give an exhaustive account of all surgical options for each reconstruction. What follows are illustrative examples of proven surgical strategies.

Box 85.1 introduces ossicular reconstruction/replacement terminology.

Eroded long process of the incus

This is the most common ossicular chain defect encountered in patients with chronic middle ear disease of all aetiologies.[33] Early attempts to restore hearing in cases of ISJ separation included stapediopexy where the tympanic membrane is brought into direct contact with the stapes head.[34] This approach has the obvious disadvantage of losing the amplification and dampening functions of the ossicular chain. Preservation of the natural anatomy is preferable and can be achieved by the following methods.

BRIDGING WITH AUTOLOGOUS TISSUE

Where there is a small distance of separation between the stapes head and incus long process remnant, interposition bridging may be attempted.[34] Materials that are most frequently used for this purpose include autologous cortical bone – harvested from the mastoid or external auditory canal – or cartilage.[35] Reconstruction of longer defects may be unstable and can lead to unpredictable results.[16] Bridging material may be partially resorbed, displaced, or form bony ankylosis with the canal wall.

PROSTHESIS

The first dedicated ISJ replacement prosthesis was reported in 1993 and consisted of a basic cuboidal hydroxylapatite design with a circular aperture for the stapes head and a groove to accommodate the long process remnant.[36] A variety of other prostheses have been developed over time, differing in both material and design. The interface with the stapes head may be a simple cup although more recent adoption of titanium and improved manufacturing techniques allow more complex designs such as self-securing clips.[37] The prosthesis may accommodate the incus long process remnant with a groove, wire coil or circumferential crimping attachments.

BONE CEMENT/BONE PATE

The use of bone cement to reconstruct the long process of the incus is a more recent development and has been shown to give good hearing results at least in the short term. Studies show 80% of patients achieve air–bone gap closure to within 20 dB at 1 year.[38, 39] Care must be taken when applying bone cement to avoid spillage onto the stapes footplate or unintended fixation to the posterior canal wall.

An alternative to cement is the use of bone pate which can be collected by drilling healthy mastoid cortex. This option works best where there is still a partial connection between the long process of the incus and the stapes head (Figure 85.2). Some surgeons mix the bone dust with blood and/or fibrin glue to aid adhesion.

Eroded incus with malleus and stapes present (Austin–Kartush type A)

In cases where the incus is partially or completely eroded and anatomical reconstruction of the ossicular chain is not

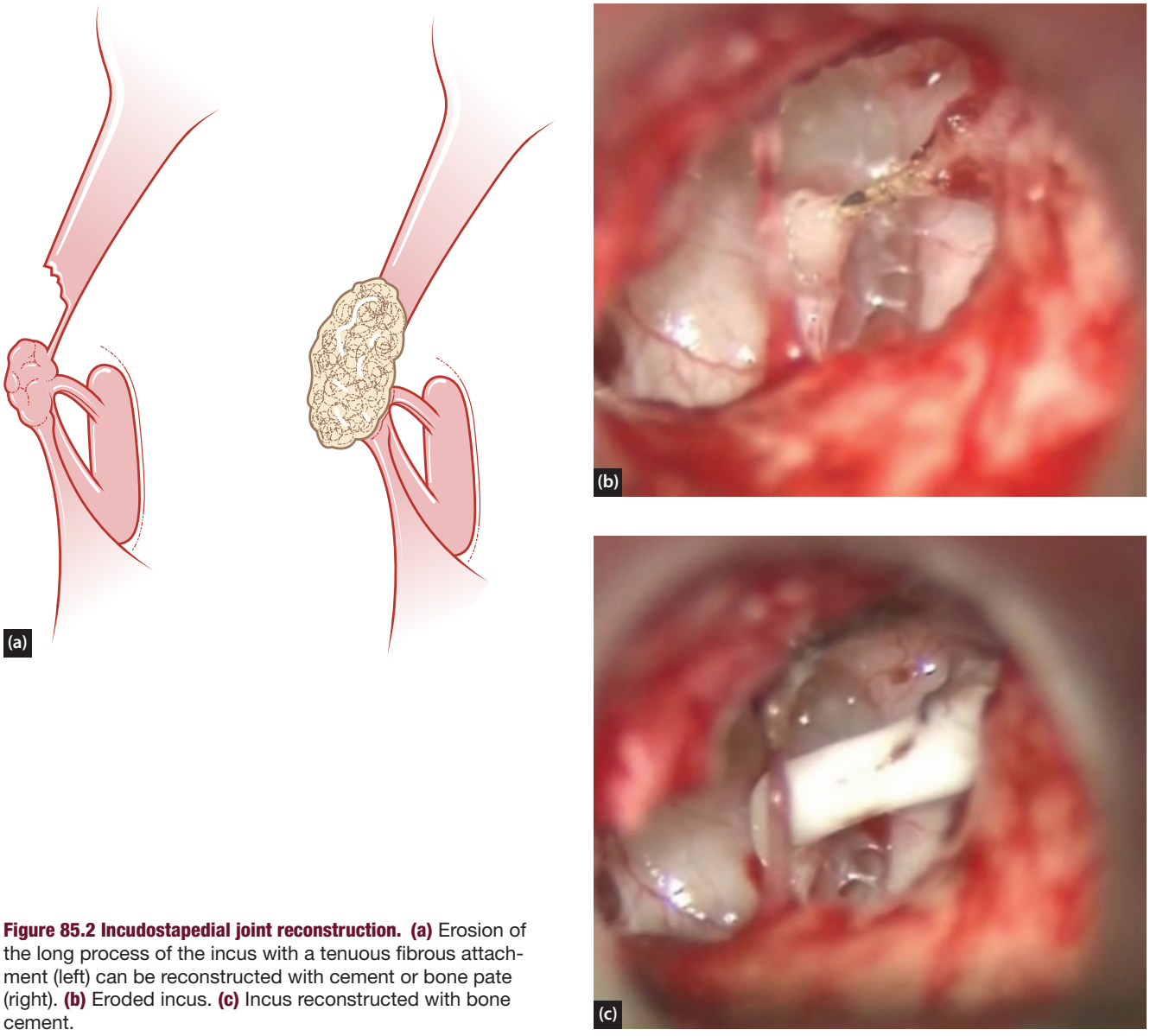

Figure 85.2 Incudostapedial joint reconstruction. (a) Erosion of the long process of the incus with a tenuous fibrous attachment (left) can be reconstructed with cement or bone pate (right). **(b)** Eroded incus. **(c)** Incus reconstructed with bone cement.

possible, there are several alternative options for restoring hearing when the malleus handle and stapes superstructure remain intact.

AUTOLOGOUS OSSICLE INTERPOSITION

Repositioning the incus as a method for restoring the function of the ossicular chain was first described in 1957 by Hall and Rytzner,[40] since which time it has been shown to be a stable option for reconstruction.[41]

When the body and short process of the incus are intact, it may be used for reconstruction provided the surgeon is confident it harbours no residual disease. Ossicle forceps and a microdrill are used to sculpt the ossicle into the desired shape with a variety of configurations possible.

The classical method involves placing the body of the incus on the stapes head with the short process directed towards the malleus handle and medial to it.[16] Modifications of the technique include creating a groove in the short process so that it rests against the malleus handle, or alternatively lateral to the malleus handle.[39] The malleus head may be used where the incus is not available (**Figure 85.3**), although usually it is brought into direct contact with the tympanic membrane, in contrast to the incus assembly which aims to rest against the malleus handle. Cartilage and sculpted cortical bone can be used although these are more prone to resorption or ankylosis.[18]

The use of homograft ossicles or cortical bone has also been described[22, 42] and continues to be used in some countries, with up to 90% of patients achieving <20 dB air–bone gap in one series of cases receiving sculpted homograft incus interposition.[43]

PARTIAL OSSICULAR REPLACEMENT PROSTHESIS

Selecting an appropriate ossicular replacement prosthesis requires careful consideration of the anatomical configuration of the middle ear and ossicles. The two main options for prosthesis placement are stapes to malleus or stapes to tympanic membrane.

Stapes to malleus

Advantages of this configuration are preservation of the catenary lever mechanism of the tympanic membrane.[44] Placing the prosthesis medial to the handle of the malleus may also reduce the rate of extrusion as compared to prostheses in direct contact with the tympanic membrane.[45]

A significant drawback is that in most situations the malleus–stapes offset means the vector of force is never perfectly in the line of the stapes, thereby resulting in inefficient energy transfer (**Figure 85.4**). When the malleus–stapes offset is of sufficient magnitude for the interposition prosthesis to have an angle greater than 45 degrees relative to the vertical axis of stapes movement, significant tilting movements occur at the footplate with resultant marked loss of sound transmission.[46]

This can be improved by malleus relocation, which involves separating the malleus handle from the tympanic membrane, division of the tensor tympani at its insertion, and stretching or avulsing the anterior suspensory ligament by pulling posteriorly on the neck of the malleus. The superior ligament is left in place to support the malleus. The malleus handle is placed more posteriorly towards a position overlying the stapes head (**Figures 85.5** and **85.6**).[47]

Stapes to tympanic membrane

This approach can be used in cases where the malleus handle orientation is unfavourable due to anterior angulation or medial displacement. The disadvantage of this method is that the catenary lever mechanism is lost, and the prosthesis may be unstable as it does not have any fixed lateral attachment other than the relatively compliant tympanic

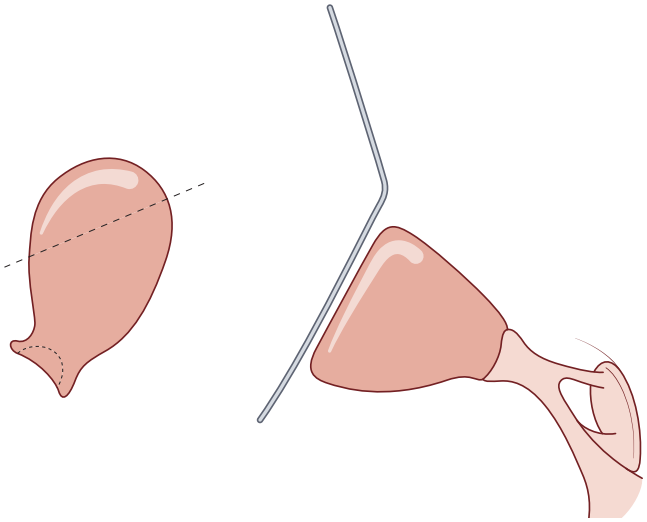

Figure 85.3 Malleus head reconstruction with intact stapes. The malleus head can be used in a stapes-to-drum configuration to reconstruct Austin–Kartush type A or C defects. The left-hand image indicates the reshaping required prior to use.

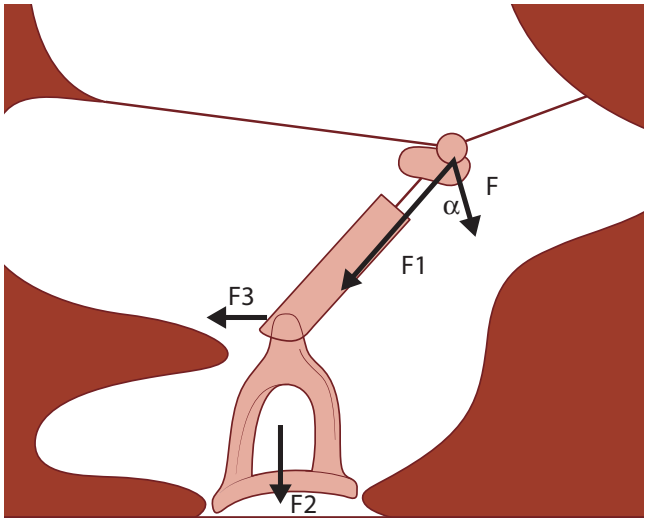

Figure 85.4 If the malleus is very anterior and medial, angle α increases. As angle α gets larger the desirable force through the footplate F2 decreases and the undesirable tilting force F3 increases (Courtesy of Robert Vincent).

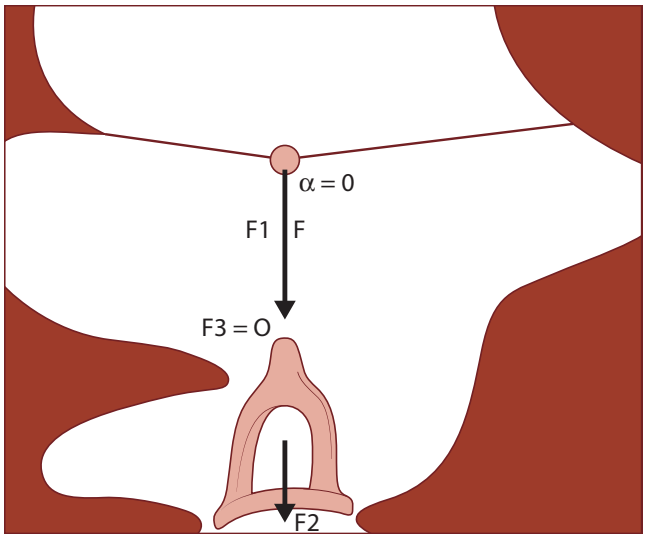

Figure 85.5 When the malleus is repositioned over the stapes, the undesirable tilting force F3 is reduced (Courtesy of Robert Vincent).

membrane. Some prostheses require interposition of a thin cartilage strip between the tympanic membrane and the head of the prosthesis to reduce the risk of extrusion although not all surgeons feel this is necessary.[27, 32]

Most prosthesis designs are in the shape of a drawing pin with a strut which attaches to the stapes head, and a perpendicular flat disc which may be centred on the strut or eccentrically placed. Some newer designs have an open head which allows the surgeon to visualize the stapes during insertion thereby facilitating this manoeuvre.

Interestingly, some surgeons advocate using TORPs in the presence of an intact stapes. The prosthesis shaft is placed between the stapes superstructure and the facial nerve directly onto the stapes footplate. This aims to improve prosthesis stability and energy transfer.[48]

Malleus present, stapes absent (Austin–Kartush type B)

When the stapes superstructure is absent, mechanical coupling between the stapes footplate and the tympanic membrane or malleus handle must be achieved. This type of reconstruction is inherently less stable due to the distance that must be bridged and the absence of a fixed attachment point on the stapes footplate. Several studies using multivariate analysis have identified presence of the stapes superstructure as being a key determinant of success following ossiculoplasty, with poorer hearing outcomes to be expected when it is absent.[49–51]

HOMOGRAFT OSSICLE

Autologous incus is rarely available as a reconstructive option in this situation as absence of the stapes superstructure will almost invariably be accompanied by a degree of long-process erosion. Homograft incus has been used extensively for this purpose with most reports describing the long process resting on the footplate and a sculpted notch at the opposite end to accommodate the malleus handle.[22, 42, 52] Results for this technique are highly variable.

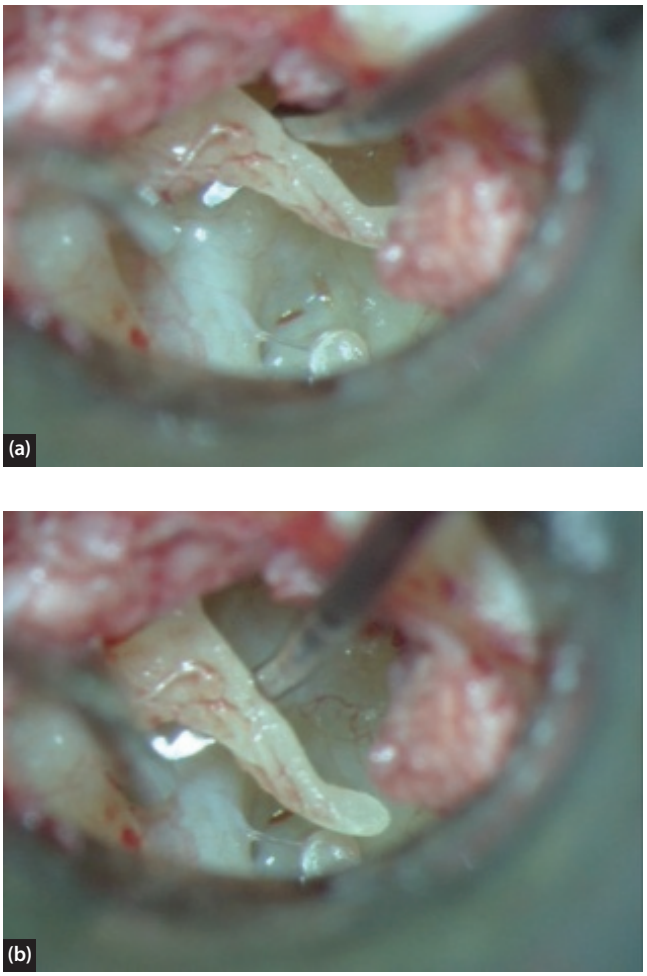

Figure 85.6 (a) A heavy hook is placed anterior to the neck of the malleus, which has been separated from the tympanic membrane and divided from the tensor tympani. It is then pulled posteriorly and the anterior malleolar ligament gives way to allow the malleus to be placed more posteriorly. (Robert Vincent.) **(b)** The repositioned malleus now lies directly over the stapes. (Robert Vincent.)

TOTAL OSSICULAR REPLACEMENT PROSTHESIS

TORPs bear structural similarity to PORPs with the range of head designs often shared, however the strut is longer to reach the stapes footplate, and the medial end of the prosthesis is often flattened to rest on the footplate rather than cupped. As with PORPs, some designs of TORP are shaped specifically to accommodate the malleus handle with a notch or groove, whereas others have a flat disc leaving both footplate-to-malleus and footplate-to-tympanic membrane options open.

One of the challenges of this type of reconstruction is the tendency for prosthesis displacement. TORPs can be placed directly on the stapes footplate, although stability may be improved with a cartilage ‘shoe’ or a

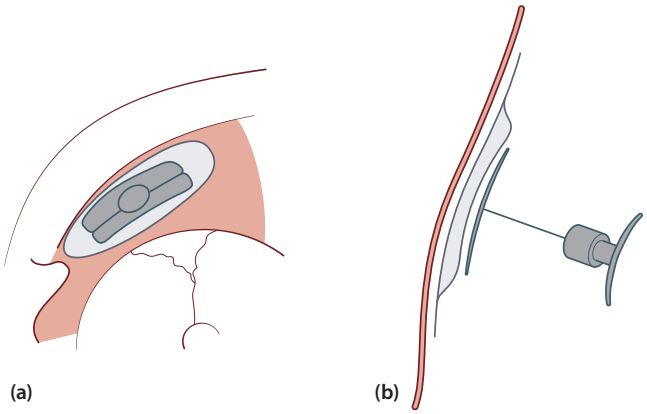

Figure 85.7 TORP with footplate shoe. (a) The footplate prosthesis in position on the oval window beneath the facial nerve. **(b)** A typical configuration with a cartilage and perichondrium graft between the prosthesis and tympanic membrane.

specially designed footplate prosthesis.[53, 54] The footplate shoe acts as an anchoring point for the medial end of the prosthesis, thereby reducing displacement while also helping to direct the vector of force through the centre of the footplate improving sound transmission (Figure 85.7).[55]

Malleus absent, stapes present (Austin–Kartush type C)

Several retrospective analyses have shown absence of the malleus handle to be a major independent prognostic factor resulting in poorer hearing outcomes following reconstruction.[56, 57] This is partly due to the loss of the amplification produced by the tympanic membrane–malleus handle complex, and loss of a solid point of fixation for any reconstructed assembly.

The simplest surgical option is to proceed with a stapes-to-tympanic membrane reconstruction as described above for type A defects. An alternative approach is to recreate the malleus handle, either with autologous material or with a prosthesis. Homograft tympanic membrane with attached malleus handles have also been used widely.[58]

NEOMALLEUS

Creation of a neomalleus strut can be achieved with incus, cortical bone or cartilage. Black showed superior hearing outcomes with a neomalleus assembly technique as compared to collumella only approach.[59] He described a neomalleus strut being placed medial to the tympanic membrane graft with the preferred source being a strip of cartilage from the root of the helix.

MALLEUS REPLACEMENT PROSTHESIS

The design and use of a malleus replacement prosthesis is a recent development described by Vincent et al. Patients receiving the malleus replacement prosthesis showed improved hearing results as compared to using a footplate to tympanic membrane TORP (12.5 dB air–bone gap and 23.3 dB respectively) and reduced prosthesis displacement.[60]

Malleus and stapes absent (Austin–Kartush type D)

This is the most challenging ossicular defect and is likely to lead to the poorest outcomes. It may be managed with a combination of the above techniques and will require reconstruction with autologous tissue, ossicle interposition or TORP. The reconstruction may be footplate-to-tympanic membrane, or alternatively a neo–malleus or malleus replacement prosthesis may be used to improve stability.

OPERATIVE CONSIDERATIONS

Length of prosthesis

Several studies have investigated the effect of the tension of the ossicular reconstruction on sound transmission at the oval window. Lower-tension reconstructions with a short prosthesis resulted in better sound transmission than higher-tension reconstructions with a long prosthesis.[46, 61] The beneficial effect of a more loosely fitting prosthesis on hearing must be balanced against the potential increased risk of displacement.

Staged reconstructions

As the majority of ossicular chain defects arise as a consequence of chronic suppurative otitis media, tympanic membrane retraction or cholesteatoma, the primary goal of the initial operation is generally to achieve a safe, dry ear. The decision whether to attempt ossicular chain reconstruction at the first operation or whether to perform a staged reconstruction at a later date depends on several factors.

The most important issues to consider are the risk of recurrent or residual disease. Eustachian tube function is a key determinant of outcome following tympanoplasty surgery,[62, 63] and the associated tympanic membrane retraction causes specific problems in ossiculoplasty due to increased risk of prosthesis displacement or extrusion. Similarly, where there is judged to be a significant risk of residual cholesteatoma, performing primary ossiculoplasty can complicate potential revision surgery if the recurrence involves the reconstructed ossicular chain.

In ears at higher risk of retraction or residual disease it may be prudent to delay reconstruction until a disease-free, aerated middle ear space has been achieved. However, it is often possible to offer primary reconstruction, particularly as improved imaging techniques with diffusion-weighted magnetic resonance imaging allow the option for radiological cholesteatoma surveillance without necessitating second-look surgery.[64, 65]

AUDIT AND RESEARCH

One of the challenges facing ossiculoplasty surgeons is being able to predict what outcome is likely to be achieved with a particular type of reconstruction or prosthesis. While published series may give an indication of the range of outcomes that can be expected, it is essential that surgeons are aware of their own results when consenting patients for surgery. Individual data collection and self-audit may be facilitated by specialized software or internet-based data entry.[66, 67]

There is a paucity of randomized controlled trials for evaluating ossiculoplasty methods or prostheses. Most results published in the literature are case series from a single surgeon or institution, with comparisons often occurring at the time of transitioning between an established method and a newer approach. Comparing results between studies may be confounded by several uncontrolled variables such as population differences, case complexity (although previously mentioned risk scoring systems may help adjust for this) and, perhaps most importantly, surgical technique.

It is important to be aware of variation in the way results are reported as there is no universally accepted measure of a 'successful outcome'.[68] The main considerations following ossiculoplasty are hearing results, and complication rates which may be prosthesis-related (extrusion, displacement, inflammatory reaction) or general (graft failure, taste disturbance, etc.). Most studies report short observation periods of 1 year; however, it has been established that audiometric results frequently deteriorate over time, and complications may present after many years.[56, 69]

KEY POINTS

- While prosthesis design and surgical technique undoubtedly affect results, the status of the middle ear is probably the most significant factor in outcome.
- Surgical results from ossiculoplasty tend to deteriorate over time.

BEST CLINICAL PRACTICE

✓ As ossiculoplasty results are variable, surgeons should endeavour to record their own results to enable accurate consent of their patients.

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CHAPTER
86

EUSTACHIAN TUBE DYSFUNCTION

Holger H. Sudhoff

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: Eustachian tube, Eustachian tube dysfunction, imaging, chronic otitis media focusing on diagnosis, surgery and management.

INTRODUCTION

The Eustachian tube (ET) is part of a system including the nose, palate, rhino-pharynx and middle ear spaces.[1] This comprises the tympanic cavity, which includes the bony ET and the mastoid air cell system (**Figure 86.1**). The tympanic cavity and mastoid cells are interconnected and allow for gas exchange and pressure equalization. The ET is a complex organ consisting of a dynamic, mucosal lined canal, cartilage, surrounding soft tissue, peri-tubal muscles, superior bony support and the sphenoid sulcus. Clinical experience as well as numerous patient studies and animal models prove that the ET plays an important role in various middle ear pathologies.[2–4] Despite improvements in the understanding of ET function, significant uncertainties remain due to its complex anatomy, multiple functions as well as the impact of intrinsic and external factors.[5,6] Intermittent transitory tubal dilation is probably the major mechanism for equalizing middle ear cleft and ambient atmospheric pressure.[7] Barometric and chemical receptors within the middle ear cleft are assumed to provide autonomic nervous system feedback that impacts on the frequency of involuntary tubal opening.[8,9] Our understanding of the anatomy and physiology of the ET still continues to evolve. Recently, McDonald et al. demonstrated that the ET might have a sequential peristaltic-like mechanism.[10]

Currently, there are various medical and surgical interventions available for chronic obstructive ET dysfunction

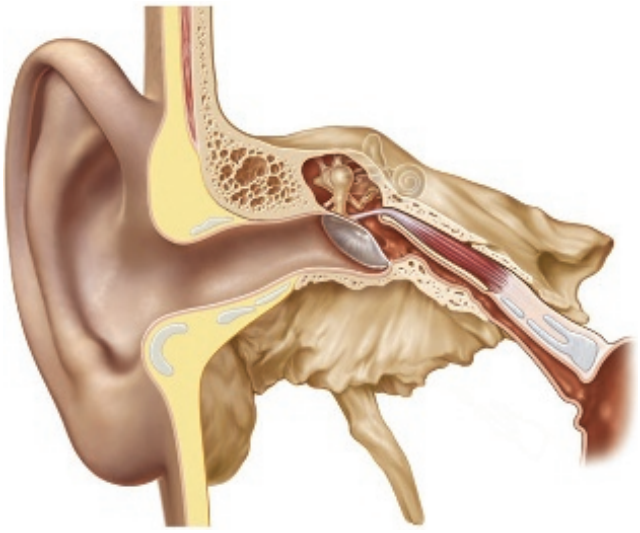

Figure 86.1 Temporal bone drawing of the cartilaginous and bony portion of the ET and middle ear spaces.

including balloon Eustachian tuboplasty (BET) and laser or microdebrider tuboplasty.[11–17] However, the small sample sizes in the reviewed literature represent a significant limitation when assessing their efficacy. The majority of available studies are underpowered and unable to detect a significant effect.[18] Long-term results with these procedures still have to be established.

DEFINITION

The term Eustachian tube dysfunction (ETD) describes impairment of ET function and leads to a variety of symptoms and physical findings. The condition does not necessarily lead to detectable middle ear pathologies. Dysfunction of the ET can be either acute or chronic. Acute ETD can occur during nasal congestion due to a common cold or allergic rhinitis, for example, and is generally transient. ETD lasting longer than 3 months consecutively is considered chronic. Chronic ETD can be due to obstruction or to a patulous (branching) Eustachian tube (PET). ETD is nevertheless a poorly defined condition.[18]

AETIOLOGY

Allergic disposition with accompanying mucosal hyperplasia and nasopharyngeal acid reflux may play an important role in ETD. ETD can lead to clinical symptoms such as aural fullness, impaired pressure equilibration, altered middle ear aeration, hearing loss and autophony (the unusually loud hearing of a person's own voice).

ETD is estimated to be present in about 1% of the general population.[19] Because the most common cause of obstructive dysfunction is mucosal inflammation within the cartilaginous ET, patients should be questioned about inflammatory processes such as allergic rhinitis, chronic rhinosinusitis, laryngopharyngeal reflux (LPR) and smoke exposure.[20, 21] ETD has been found to be associated with a higher number of nasopharyngeal reflux events and higher reflux finding score in adult patients.[22] Paediatric ETD may be caused by adenoidal hypertrophy and mucosal swelling due to acute or chronic upper respiratory tract infections. Cleft palate, granulomatous diseases, cystic fibrosis, Samter's triad and Kartagener syndrome are predisposing factors. ETD may be a contributing factor to vertigo.[23, 24] It is important to distinguish ETD from other causes of aural fullness such as temporomandibular joint (TMJ) disorders, superior semicircular canal dehiscence syndrome, Ménière's disease and increased intracranial pressure employing a tailored assessment. Almost 40% of all children up to the age of 10 years develop temporary ETD.[25, 26] Studies accessing paediatric and adult patient cohorts demonstrate that ETD is detectable in up to 70% of patients undergoing middle ear surgery.[27] Good ET function is believed to be important for the successful outcome of middle ear surgery.[28, 29] Patients with a PET usually present with positional autophony and hearing both voice and breathing sounds or aural fullness.[26] The precise distinction between the obstructive and 'patulous' ET is essential for appropriate medical or surgical treatment but is often challenging. Patients with PETs may benefit from augmentation or reconstructive procedures.[30, 31]

ASSESSMENT

A large variety of methods have been employed to assess ET function,[31–39] with more than 40 described in the literature.[31] None is able to give detailed insight into all aspects of ET physiology and pathology. Clinical tests such as otoscopy, endosocopy, Politzer test, Valsalva (exhaling into a closed airway by pinching the nose and closing the mouth) and Toynbee manoeuvre (pinching the nose and swallowing) may give initial guidance. Manometric testings (tympanometry, reflex decay tympanometry, nine-step inflation deflation test, modified inflation deflation test, forced response test and tubomanometry (TMM)) have some value.[31–39]

TMM was described by Estève in 2001[36, 37] and is a tool to measure the opening of the ET tube and the transportation of gas into the middle ear by registering pressure changes (**Figure 86.2**). A stimulus of a controlled gas bolus is applied to the nasopharynx during swallowing and recorded by a pressure sensor in the occluded external ear canal. If ET opening is registered, the time of opening in relation to pressure application can be measured (opening latency index or index R). An R value of <1 indicates early opening of the ET, which is considered optimal.[36]

TMM R values have been used together with clinical symptoms to generate an ET score, a semi-objective rating system used for quantification and inter-individual as well as prospective comparison of ET function (**Table 86.1**).[12] The ET score can range from 0 (= complete obstruction) to 10 (= normal tubal function). The clinical symptoms 'clicking sound when swallowing' and 'positive Valsalva manoeuvre' are rated with 0 points for 'never', 1 point for 'sometimes' and 2 points for 'always'. TMM results at 30, 40 and 50 mbar are incorporated in the ET score as well. An immediate opening of the ET ($R \leq 1$) is weighted with 2 points, a delayed opening ($R > 1$) with point and no opening (negative or not measurable R) with 0 points. The ET score gives a quantitative assessment of ET function and allows inter-individual as well as prospective comparison.

The pressure chamber is a useful device for assessing ET function under varying pressure conditions, regardless of whether the eardrum is intact or perforated.[31] However, pressure chambers are complex, expensive and not widely available.

For the technique of sonotubometry, sound is applied via a probe in the nose. Sound is then measured in the external auditory canal and fluctuations during swallowing are recorded.[31]

There are numerous other approaches to assess ET function such as phototubometry, scintigraphy, ultrasound, application of dye and taste-bearing substances, electromyography, flowmetry, and (opto)tensometry.[31] At present, none of these methods has produced data of clinical significance.[18, 33]

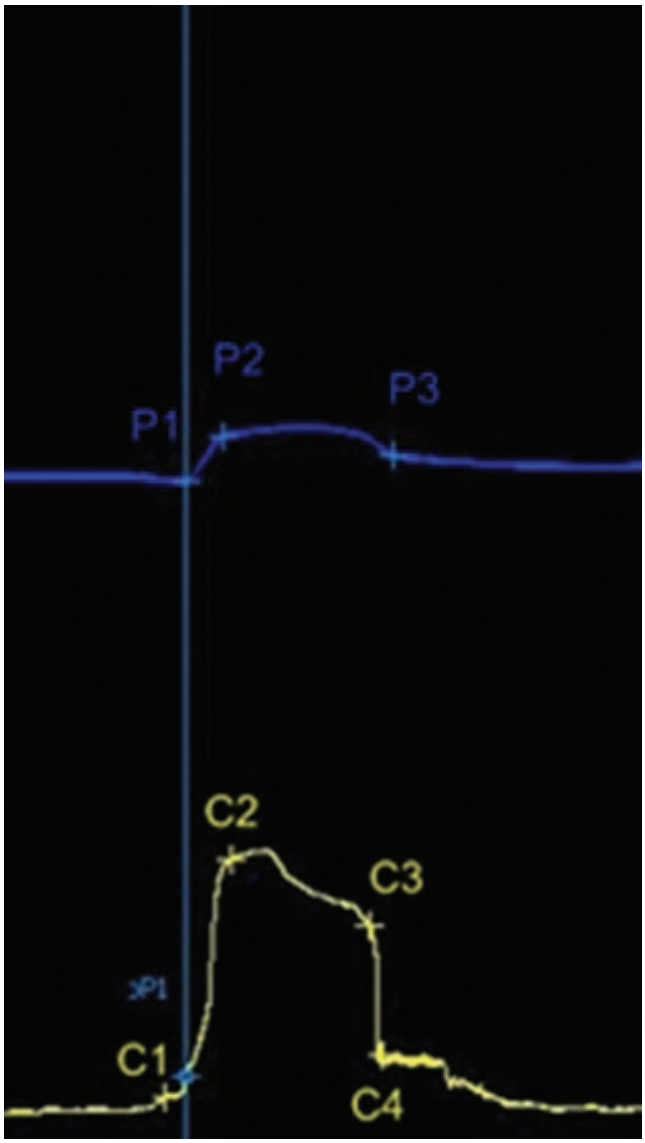

Figure 86.2 ET measurement. The yellow line represents the pressure in the nasopharynx, the blue line the pressure in the external ear canal.

Imaging with computed tomography (CT), cone beam tomography and magnetic resonance (MR) has long been used to examine anatomic and functional deficiencies as well as to rule out pathology in the nasopharynx or superior canal dehiscence syndrome (SCDS)[4, 20] (see Chapter 65, Superior semicircular canal dehiscence).

TABLE 86.1 The Eustachian tube score

Symptom/finding	2 points	1 point	0 points
Clicking sound when swallowing	Always	Sometimes	Never
Positive Valsalva manoeuvre	Always	Sometimes	Never
TMM 30 mbar	R<1	R≥1	No R
TMM 40 mbar	R<1	R≥1	No R
TMM 50 mbar	R<1	R≥1	No R

A seven-item ETD questionnaire (ETDQ-7) was recently developed to assess patient symptoms (**Table 86.2**).[38, 39]

The lack of high-quality studies means multiple gaps remain in the evidence base for assessment of ETD.[18, 40]

PATULOUS EUSTACHIAN TUBE

A patulous Eustachian tube (PET) (tuba aperta, hyperpatent ET) may lead to an enormous reduction in quality of life. Symptoms of PET include autophony, breath synchronous tinnitus, pressure sensation in the ear, and hearing loss. In combination with so-called 'sniffing', it may rarely lead to the development of cholesteatoma.[41] Due to the diffuse symptoms, the correct diagnosis of this disease and especially the distinction from obstructive ETD can be challenging. The movement of the tympanic membrane in synchrony with respirations is not always present but is diagnostic when seen. PET disorders may occur in two types: the PET type, in which the lumen remains anatomically open, even at rest. The other type, the semi-patulous Eustachian tube, is a less severe form. In the latter the tube lumen is anatomically closed at rest but, due to low tubal resistance to airflow, it may open during exercise. It may then become patent due to a decrease in peritubal extracellular fluid volume attributable to disease, exercise, weight loss (leading to reduction of Ostmann's fat pad which lies inferomedial to the ET) or concurrent medical treatment for another condition.

TABLE 86.2 The ETDQ-7 questionnaire – a tool for the evaluation of chronic obstructive Eustachian tube dysfunction[37]

Over the past 1 month, how much has each of the following been a problem for you?	No problem		Moderate problem			Severe problem	
1. Pressure in the ears?	1	2	3	4	5	6	7
2. Pain in the ears?	1	2	3	4	5	6	7
3. A feeling that your ears are clogged or 'under water'?	1	2	3	4	5	6	7
4. Ear symptoms when you have a cold or sinusitis?	1	2	3	4	5	6	7
5. Crackling or popping sounds in the ears?	1	2	3	4	5	6	7
6. Ringing in the ears?	1	2	3	4	5	6	7
7. A feeling that your hearing is muffled?	1	2	3	4	5	6	7

The incidence of PET has been reported with 0.3% of the general population.[42] Münker diagnosed this condition in 6.6% of 100 women with normal ears.[43] Pulec reported on 41 cases identified at the Mayo Clinic in 19 years in 1964.[44] Clinicians' awareness of patients with PET generally results in a higher recognition of this disorder. Only 10–20% of the patients seek medical help for their complaints.[44]

A PET can be best diagnosed through a well-structured examination including patient history, physical examination with thorough observation of movements of the tympanic membrane, and tympanometry with reflex decay. Tympanometry with reflex decay is helpful in the diagnosis but it requires an intact tympanic membrane and it should be evaluated in comparison with the contra lateral side. TMM does not require an intact tympanic membrane and is a valuable tool in diagnosing ET disorders. TMM allows a definite distinction of patulous and obstructive ET dysfunction.[36, 37] TMM regularly reveals an immediate opening with $R < 1$.

When the diagnosis of patulous ET is made, thorough counselling of the patient is important. It is important for the patient to acknowledge that the disease is annoying but harmless. All treatment options have to be outlined to the patient and conservative treatment should be regarded as the first choice. If conservative measures do not lead to an improvement of the symptoms, there are several surgical or interventional treatment options.

Oestrogen nasal drops or oral administration of saturated solution of potassium iodide has been used to induce swelling of the ET opening. Nasal medication containing diluted hydrochloric acid, chlorobutanol and benzyl alcohol has been demonstrated to be effective in some patients. This has been reported to be well tolerated with little or no adverse effects.[41, 44]

Myringotomy and grommet insertions have demonstrated ability to reduce symptoms but are not definitive therapy.[45] In a retrospective analysis of 46 patients (60 ears) with patulous ET, grommets significantly reduced the symptoms in 53% of the ears.[46] An additional option for symptomatic treatment is the augmentation of the tympanic membrane with cartilage especially in severely atrophic eardrums. The effect of augmentation can be tested by placing a small piece of paper on the tympanic membrane prior to surgery.

There are different surgical strategies such as the PET reconstruction with, for example, cartilage, the Kobayashi plug or the injection of Vox® implants into the torus tubarius.[28–30] In patients with ETD that is refractory to medical management, newer surgical techniques may provide symptomatic relief with a reasonable duration.[29, 30] Continued basic science research into the cause of dysfunction, the mechanisms of benefit from intervention and long-term clinical outcomes are necessary.

MEDICAL MANAGEMENT

Medical management of ETD should be directed at the underlying cause. There is currently low evidence of any efficient medical therapies for ETD.[18] Pharmacological interventions include application of nasal steroids, antihistamines, inhaled and systemic decongestants.[47–49]

A randomized, double-blind, placebo-controlled trial studied the effect of a decongestant agent (xylometazoline chloride 0.1%) and placebo (saline 0.9%) applied directly to the pharyngeal opening of the ET. The study concluded that a topical decongestant improves ET function but only at unphysiologically high pressures.[48] Another trial investigated the efficiency of intranasal aqueous triamcinolone acetonide in treating the tympanometric signs and symptoms of ETD.[47] Their findings did not support the use of intranasal steroid sprays to treat the manifestations of ETD.[47]

POLITZERIZATION/OTOVENT™/ EAR POPPER®

No statistical difference in equalization of the middle ear pressure was found between Valsalva manoeuvres, Toynbee manoeuvres and Ear Popper®. The Ear Popper® is an automated device that is applied to the nose and delivers a regulated flow of air into the nasal cavity in healthy adults under physiological conditions.[50, 51] The automated device's ease of administration and its ability to control airflow suggest that it has the potential to be an effective home treatment that can be administered by the parents or guardians of children suffering from otitis media with effusion.[52, 53] Autoinflation using the Otovent™ system was found to be an effective short-term treatment for children with OME when used regularly under supervision.[52] However, available data are too limited to draw any definite conclusion.

LASER TUBOPLASTY

Kujawski, Poe and Caffier reported on their results of laser Eustachian tuboplasty. It seems to be a feasible, safe and in suitable cases effective treatment of chronic obstructive ETD. Using a KTP-laser, inflamed or hyperplasic tissue and sometimes also cartilage is resected from the pharyngeal orifice of the ET. This technique is reported to be successful in almost 70% after 1 year.[13–15]

BALLOON DILATION EUSTACHIAN TUBOPLASTY

Balloon dilation Eustachian tuboplasty (BET) is a minimally invasive interventional method to treat chronic obstructive ETD. It is usually performed with the patient under general anaesthesia.[54] A balloon catheter is introduced into the ET via the nose, under transnasal endoscopic vision.[11, 12] Once the balloon is correctly positioned in the cartilaginous portion of the ET, it is filled with saline up to a pressure of 10 bars. The pressure is maintained for 2 minutes (**Figure 86.3**). BET can be performed as a unilateral or bilateral procedure in adult patients and children

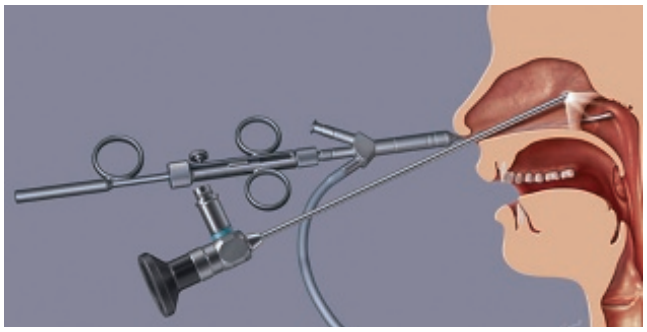

Figure 86.3 Instruments for balloon dilatation Eustachian tuboplasty (Spiggle & Theis Medizintechnik, Overath, Germany).

Figure 86.4 Novel insertion tool with three angled extensions: 30°, 45° and 70°, colour-coded according to Hopkins endoscopes.

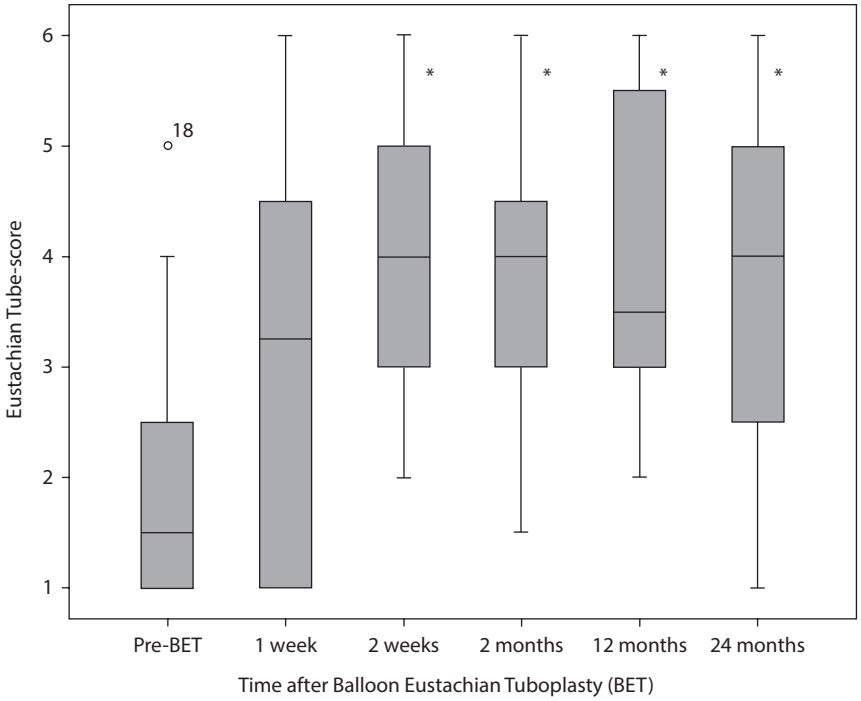

Figure 86.5 Eustachian tube score (see Table 86.1) at the 2 months follow-up. Patients with 24 months follow-up data available were included ($n = 22$). (Asterisks indicate $p \leq 0.001$ in Wilcoxon's test.)

from the age of 7 years. For younger children, additional data are required and currently under investigation.[55] BET is indicated for symptomatic patients with an ET score of ≤5 and the presence of at least one of the following clinical symptoms of obstructive ETD:[56]

- uncomfortable sensation of pressure in the ears especially with changes of atmospheric pressure (e.g. on an aeroplane)
- inability to perform Valsalva manoeuvre
- chronic otitis media with effusion
- middle ear atelectasis
- recurrent middle ear diseases (e.g. perforation, cholesteatoma)
- failed tympanoplasty (e.g. protruding middle ear prosthesis).

In a series of more than 400 patients suffering from obstructive ETD, approximately 80% reported a subjective benefit from BET, and had a significant improvement of their ET score without serious side effects.[56] Significant scarring in the nasopharynx, for example following radiotherapy for nasopharyngeal tumours or after injury of the torus tubarius during adenoidectomy, can be technically challenging. Cleft palate patients do not seem to benefit from BET since the underlying pathology in these cases is a muscular dysfunction rather than obstruction of the ET.[56] Poe et al. described a quite similar method of BET with a modified catheter in 2011 and 2014.[16, 57] They performed the dilatation with a modified sinuplasty balloon with 12 atm for 1 minute and later 2 minutes. Post-operatively all treated patients were able to perform the Valsalva manoeuvre.[16] BET does not seem to require

imaging in normal cases.[58, 59] The results of the present data seem to reveal BET as a safe and effective method.

DISCUSSION

ETD is often regarded as a 'black box' in which the function of the system remains unclear.[18] It has become increasingly clear that there are a variety of underlying reasons leading to ETD. Their identification and treatment is crucial for clinical improvement. Over many years, a variety of different treatment options for chronic obstructive ET dysfunction have been proposed. They range from nasal decongestives and steroids to golden tube conductor wires, grommet insertion and tympanoplasty. Convincing evidence of long-lasting benefit is absent. More recent publications focus on balloon catheter dilation of the ET, microdebriders and laser tuboplasty and these appear more promising.[11–17]

BET as a minimally invasive treatment for obstructive ETD was presented in 2008.[11] A balloon catheter with a newly designed endoscope to widen the cartilaginous portion of the ET was introduced. The available results for the treatment of obstruction of the ET are promising. There are uncertainties about the use of the procedure in children due to the obvious anatomical differences. Additional studies are necessary to identify patients who are most suitable candidates for this procedure and defining cut-off levels for the procedure. Patient selection is the most crucial point and requires more clinical data.[56]

The results of the present data seem to prove BET as a safe and effective method. BET may have potential to improve the long-term results of tympanomastoid surgery through the enhancement of middle ear ventilation.[60–62]

CONCLUSIONS

ETD is still a poorly defined condition. Due to the limited and poor-quality evidence, it is difficult to draw definite conclusions on the effectiveness of any therapy. Consensus on diagnostic criteria for ETD is required to define inclusion criteria of future trials. There is, however, emerging work with encouraging, but preliminary, results that suggest evidence for safety in the surgical management of ETD. As with many newly introduced techniques, the current data remain limited to non-controlled case-series, with heterogeneous data collection methods and lacking substantial long-term outcomes. Nevertheless, short-term data provide favourable results. Recent treatment options including BET and patulous ET surgery may be offered as a treatment option to selected patients.

ACKNOWLEDGEMENTS

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BEST CLINICAL PRACTICE

- ✓ Clinical assessment will vary what investigations are available. Ideally assessment should include otomicroscopy, tympanomatry, Rinne's and Weber's tuning fork tests and pure tone audiometry and nasopharyngoscopy (to visualize the orifice of the Eustachian tube). There is no single test to diagnose Eustachian tube dysfuntion. Therefore at this stage we have to rely on the clinical observations (symptoms and signs) detailed above.
- ✓ A number of tests for Eustachian tube function have been described, including tubomanometry, sonotubometry, nine-step inflation-deflation test and pressure chamber tests. At the current time, these tests can be useful research tools.

FUTURE RESEARCH

- ➤ Our understanding of ET anatomy and physiology still remains incomplete, including the epidemiology of Eustachian tube dysfunction, development and validation of patient-reported symptom scores and subjective and objective pressure tests, the development of a core set of outcome measures and further randomized controlled trials of treatments for Eustachian tube dysfunction.
- ➤ There is a strong requirement for consensus on the definition of ETD and for the development of precise diagnostic and treatment criteria.
- ➤ All current studies suggest that balloon dilation of the Eustachian tube is beneficial to patients with Eustachian tube dysfunction. Additionally, placebo controlled trials are still needed.

KEY POINTS

- Sound conduction requires a stable air compartment within the middle ear spaces maintained by a functioning ET.
- ETD plays a significant role in various middle ear pathologies.
- There are a number of methods of assessing ET function, but none provides detailed insights into all aspects of ET physiology and pathology.
- Management of any underlying allergies or reflux is necessary for long-term success in patients with obstructive dysfunction.
- Patients with problems with pressure equilibration or chronic otitis media may be potential candidates for balloon dilation of the cartilaginous portion of the Eustachian tube (BET).

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CHAPTER 87

OTOENDOSCOPY

David A. Bowdler, Annabelle C.K. Leong and David D. Pothier

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: ear, endoscope, otoendoscopy, endoscopy, microscope, surgery and otology.

INTRODUCTION

In otology, the operating microscope revolutionized ear surgery by improving the accuracy and safety of operative procedures. Indeed, the use of the microscope with microinstruments led to otology being one of the first fields of minimally invasive surgery. The advantages of the operating microscope are obvious: it delivers a stable image in the familiar head-on view with the ability to vary magnification while freeing both of the surgeon's hands to operate. However, its straight-line view is also the microscope's main limitation as it is unable to navigate around anatomical corners to provide a wide and variable direction of view, unlike the endoscope. Modern advances in endoscope design have provided a new tool for the examination of anatomical structures in the middle ear and more challenging applications extend to neuro-otological operations such as the removal of acoustic neuromas. A spectrum of approaches currently exists between totally microscopic ear surgery and totally endoscopic ear surgery, with an increasing number of otologists using the endoscope to some extent during an otologic procedure. This chapter deliberately concentrates on the otoendoscope, often to the exclusion of the microscope, as traditional or conventional methods are covered elsewhere. The authors vary in their views from mixed usage to a totally endoscopic approach but all believe that the otoendoscope is an essential piece of equipment for the best practice of otology. Each individual must decide his or her own position with respect to the degree of usage of the otoendoscope.

HISTORY OF OTOENDOSCOPY

Although the fibre-optic endoscope was invented in 1954 by Hopkins,[1] otoendoscopy only began with the use of the fibre-optic hypodermic microscope by Long in 1965.[2] Subsequent forays by Mer[3] in 1967 involved practical issues with manoeuvring the great mass of the microscope to attempt safe passage into the middle ear space. Around the same time, Proctor, Donaldson and Wigand were all undertaking detailed studies of the middle ear spaces and their significance, especially the sinus tympani, epitympanic sinus and protympanum, which were the anatomical blind spots for the operating microscope.[4–6]

From the early 1980s onwards, otoendoscopy was increasingly used to inspect and diagnose middle ear disease, particularly residual disease after canal wall up mastoidectomy procedures.[7–11] Second-look operations in patients who had previously undergone intact canal wall mastoidectomy with tympanoplasty operations were performed with the aid of otoendoscopes to exclude residual epitympanic or mastoid cholesteatoma.[9–11] Thomassin strongly influenced the field of endoscopic middle ear surgery by emphasizing the use of endoscopes to search for and remove disease in the anterior epitympanic recess, tubal orifice and sinus tympani with special microinstruments and observed a distinct reduction

of residual cholesteatomas as a result. He also advocated the otovideoendoscopic technique, which involved coupling of the endoscope to a camera and performing the operation while looking at the video image.[12]

In addition, Eustachian tube endoscopy with small fibre-optic endoscopes had begun in 1976 and was developing alongside middle ear endoscopy, with many studies initially using a nasopharyngeal approach to investigate the relationship of Eustachian tube pathology with chronic otitis media and cholesteatoma.[13, 14]

OTOENDOSCOPY VERSUS THE MICROSCOPE

Debate continues unabated as to whether the role of the otoendoscope remains that of an adjunct to the microscope or if it truly has come into its own as an alternative. On the one hand, otomicroscopy with magnification and a sharp image is advantageous whenever it is possible to get the entire area of surgery into the field of view. On the other hand, the advantages of the otoendoscope are clear in terms of its manoeuvrability, proximity of image, wide field of vision and angle of view (Figure 87.1). Its direction of view is also variable and is influenced by the angulation of endoscope employed, usually 0, 30, 45 or 70 degrees (Figures 87.1 and 87.2). It represents a more advanced form of minimally invasive surgery than the microscope alone and is hence associated with reduced surgical morbidity.

Proponents of entirely transcanal endoscopic ear surgery argue that, although there is a spectrum of use of the endoscope as described previously, the reduced morbidity afforded by the endoscope arises from the fact that no postauricular or endaural incision is required to gain appropriate access to the middle ear space. Moreover, there is a reduced requirement to violate healthy tissue purely to access a relatively limited area of disease. When the endoscope is used as an adjunct to microscopic surgery,

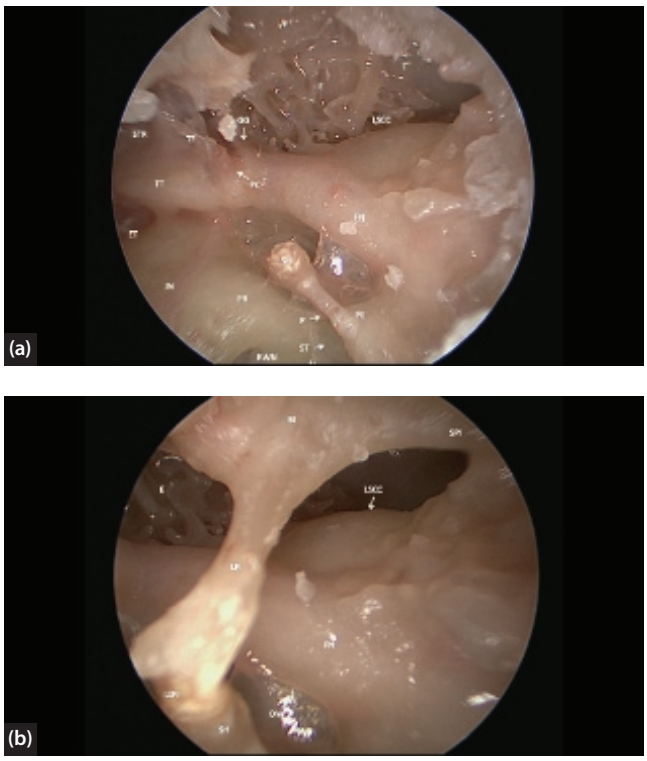

Figure 87.1 **(a)** Anatomy of the middle ear as viewed with a 0° endoscope. **(b)** Anatomy of the tympanic isthmus region as viewed with 0° endoscope. T – tympanic isthmus; E – epitympanum; LSCC – lateral semicircular canal; FN – facial nerve; PE – pyramidal eminence; P – ponticulus; ST – sinus tympani; RWN – round window niche; SH – stapes head; PR – promontory; JN – Jacobsen's nerve; ET – Eustachian tube; TT – tensor tympani; STR – supratubal recess; TF – tensor fold; GG – geniculate ganglion; PC – Processus cochleariformis; OW – oval window area; LPI – long process of incus; LtPI – lenticular process of incus; BI – body of incus; SPI – short process of incus.

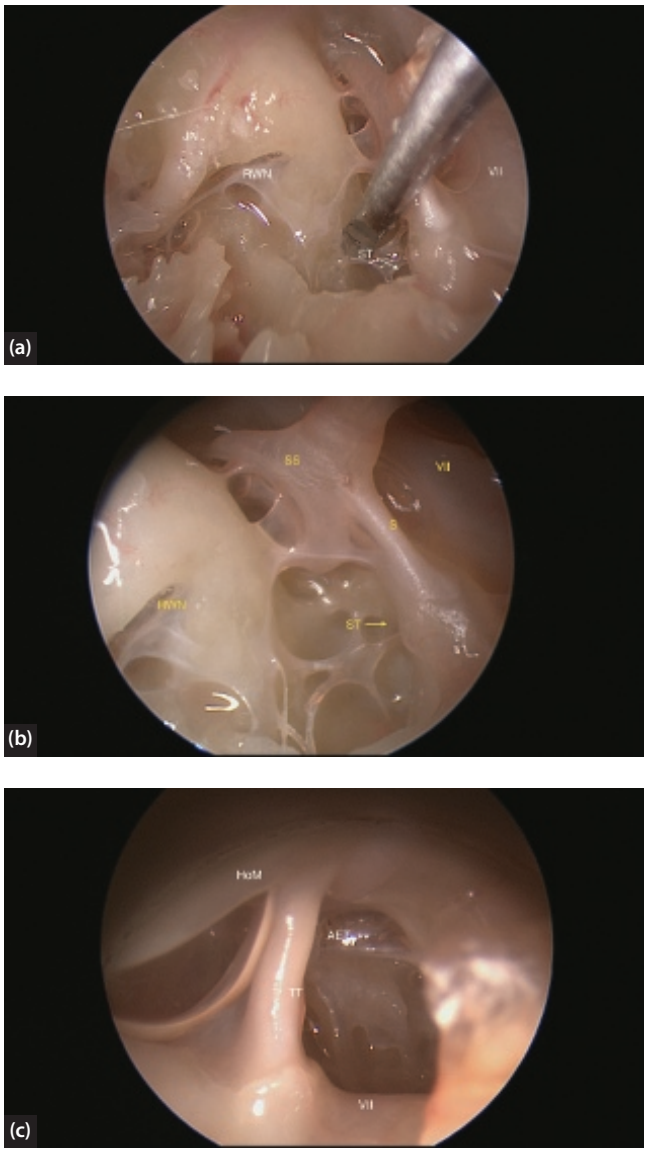

Figure 87.2 **(a)** 30° endoscopic view of the sinus tympani. **(b)** 45° endoscopic view of the sinus tympani. **(c)** 70° endoscopic view of the anterior epitympanum and tensor tympani. JN – Jacobsen's nerve; RWN – round window niche; ST – stapedius tendon; S – stapes; VII – facial nerve; SS – stapes superstructure; HoM – handle of malleus; AET – anterior epitympanum; TT – tensor tympani.

although there are clear clinical gains in terms of access, these advantages of reduced morbidity are largely lost.

It is acknowledged that the operating microscope does not allow good surgical control of the hidden areas in the middle ear such as the sinus tympani, the anterior epitympanum, the protympanic recess and the facial sinus recess. Bowdler and Walsh compared the accessibility of different middle ear subsites in canal wall-up and canal wall-down temporal bone dissections, using the 0 degree 4.0 mm diameter and 70 degree 2.7 mm diameter Storz® rigid otoendoscopes and operating microscope.[15] In canal wall-up dissections, the sinus tympani, facial recess, protympanum, attic and posterior tympanotomy could be seen with the 0 degree otoscope and good views of the sinus tympani and Eustachian tube were obtained with the 70 degree otoscope. In comparison, the microscope failed to give a view of the sinus tympani either through the posterior tympanotomy or via the ear canal (**Figure 87.3**). In canal wall-down dissections, the otoendoscopes were able to offer a good view of all sites but once again, the microscope provided poor views of the sinus tympani. Karhuketo reported similar advantages with 1.7 mm diameter 0, 30 and 90 degree endoscopes over the microscope.[16] In fact, the view offered by the endoscope so differs from that of the microscope that Marchioni published

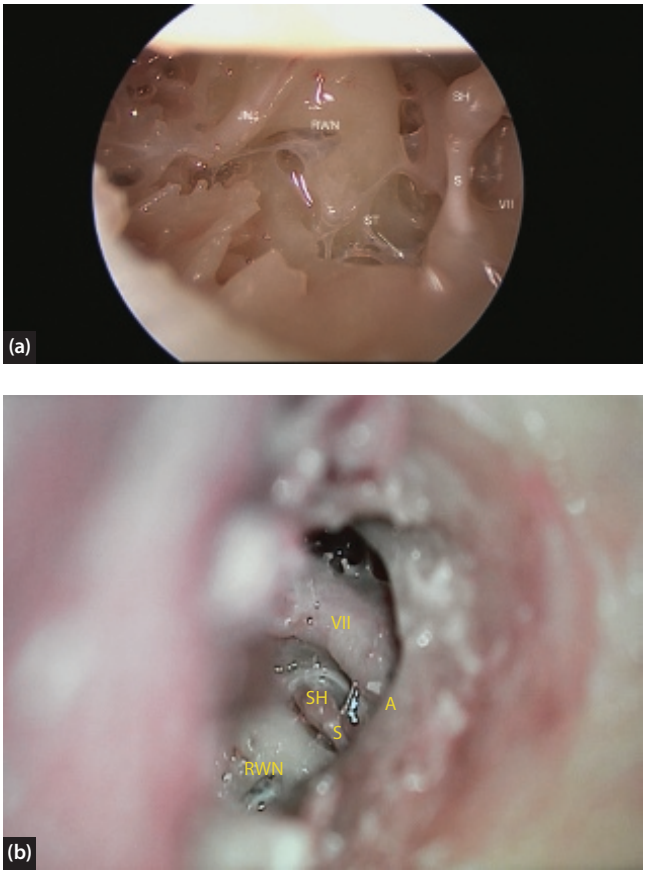

Figure 87.3 **(a)** View of the sinus tympani obtained with 0° endoscope. **(b)** View obtained with the microscope with optimal positioning through the ear canal. S – stapes; ST – stapedius tendon; SH – stapes head; JN – Jacobsen's nerve; RWN – round window niche; VII – facial nerve; A – bony annulus.

a detailed anatomical report of the sinus tympani using the transcanal endoscopic approach, classifying the sinus tympani into various types based on morphology and depth (**Figure 87.4**).[17] A new term 'finiculus' was also devised to describe the ridge of bone that marks the border between the retrotympanum and hypotympanum.[17]

Another example of this difference in access between the two techniques is the facial recess. If approached through transcanal endoscopy, it ceases to be a recess and becomes merely a small depression on the posterior wall of the mesotympanum that can be reached within minutes of the start of the operation. In contrast, microscopic technique requires a cortical mastoidectomy and subsequent identification of the facial nerve, providing a limited keyhole access in the space between the chorda tympani and the facial nerve.

The use of the otoendoscope is, however, accompanied by several disadvantages. For example, using the otoendoscope leaves only one hand free to operate. Another perceived disadvantage is the lack of true three-dimensional (binocular) vision during the operation, but with sufficient experience, this appears to have limited impact. The more common limitation for otoendoscopy tends to be peri-operative haemorrhage that leads to fogging and smearing of the endoscope tip, hence it has to be cleaned often. Frequent irrigation can be helpful in clearing the field of blood but may often be inadequate in clearing the sinus tympani and epitympanum.[18] New instruments are in development which address the limitations of standard instruments when used with an endoscopic approach (**Figure 87.5**). Less frequently, due to the inherent rigidity of the instrument, otoendoscopy may be limited by the extreme curvature of the external auditory canal (EAC). Anatomical structures such as the mallear body and lateral semicircular canal may also be difficult to see.[19] Thomassin found that 2.7 mm diameter endoscopes had an advantage over their 1.7 mm cousins in this respect.[12] Current transcanal endoscopic ear surgery relies on 3 mm or 4 mm endoscopes for most applications. Furthermore, smaller diameter endoscopes are extremely fragile; the shorter its working length, the less the bending torque achievable with the same force, but the 1.7 mm endoscopes are unable to tolerate any bending.[20]

Safety issues

Safety issues surrounding endoscopy have focused on the risk of thermal injury to the middle ear. An *in vivo* canine study found that the temperature rise at the lateral semicircular canal increased in relation to endoscope diameter and the Hopkins rods (3.0 mm and 1.9 mm diameter) produced the same or greater heating effect as a warm 44 °C water caloric test.[21] More worrying findings were the discovery of a 5 mm burn on the medial wall of the middle ear when using a 3 mm Hopkins rod and charring effects on the edge of the myringotomy. MacKeith et al. measured the temperature reached by the tip of the endoscope and found that, although temperatures at the tip of the endoscope were sufficient to cause thermal injury, measurements taken 5 mm from the tip were far lower

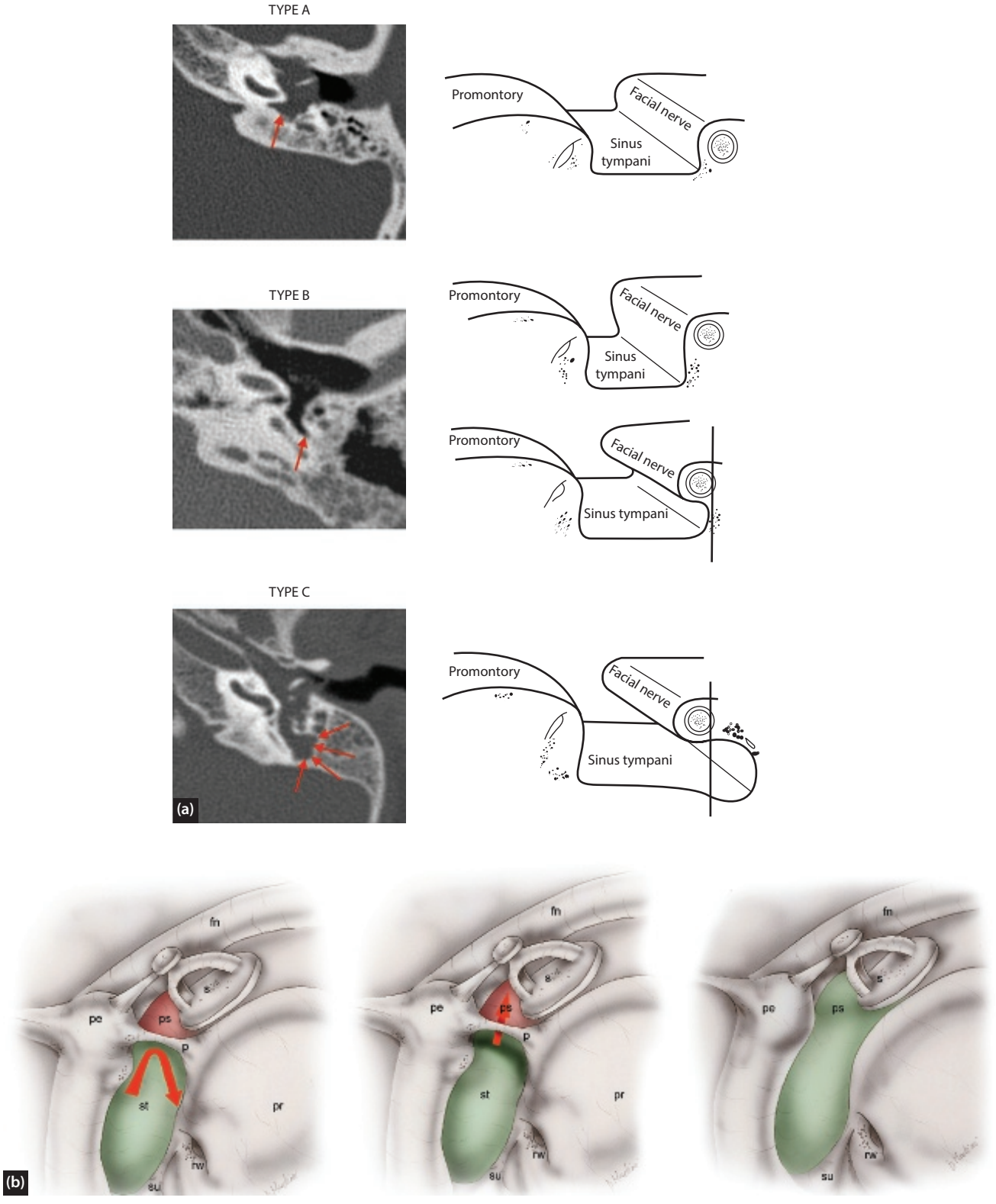

Figure 87.4 (a) Anatomical classification of the sinus tympani based on morphology and depth on axial CT scan. Type A – limited sinus tympani; Type B – deep sinus tympani with medial extension with respect to the facial nerve; Type C – deep sinus tympani with posterior extension with respect to the facial nerve. **(b)** The sinus tympani lies medial to the pyramidal eminence, stapedius muscle and facial nerve and it lies lateral to the posterior semicircular canal and vestibule. The superior limit of this space is represented by the ponticulus, while the inferior anatomical limit is represented by a prominent ridge extending from the styloid eminence to the posterior rim of cochlear window niche: the subiculum. Different morphologies of the ponticulus are shown here. fn – facial nerve; pr – promontory; rw – round window; st – sinus tympani; p – ponticulus; ps – posterior sinus; s – stapes; pe – pyramidal eminence; su – subiculum. Images reproduced with kind permission of Dr Daniele Marchioni.

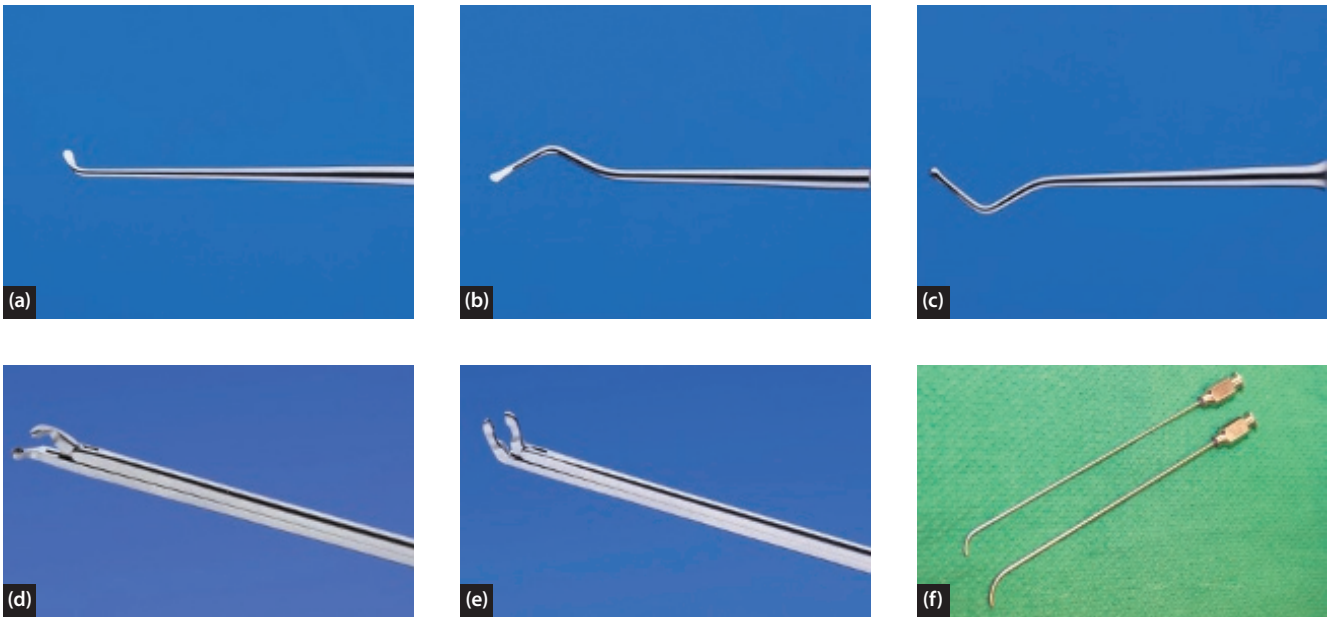

Figure 87.5 Different types of instrument used in endoscopic ear surgery. **(a)** Single curved dissector, **(b,c)** double curved dissector, **(d)** left-angled forceps, **(e)** up-angled forceps, and **(f)** curved suction cannulae.

and cooling took place rapidly when the endoscope was removed.[22] In addition, the learning curve in otoendoscopy means that it will take some time for the surgeon who is accustomed to an entirely microscopic technique to adapt accordingly. Lack of endoscopic experience or indelicate tissue handling may lead to unsafe advancement during otoendoscopic exploration and possible forceful dislocation or fracture of ossicles.[19]

GENERAL REQUIREMENTS

Pre-operative imaging with high-resolution computed tomography (CT) is recommended before any middle ear procedure where the endoscopic and microscopic approach is planned, but for many surgeons this is equally true of any procedure for middle ear cleft disease. Standard axial, sagittal and coronal views are not as helpful in the true endoscopic setting as they are in the microscopic setting. The best series of views to use are reconstructed along the plane of the external auditory meatus to allow the surgeon to anticipate what he/she will duly encounter endoscopically (Figure 87.6).

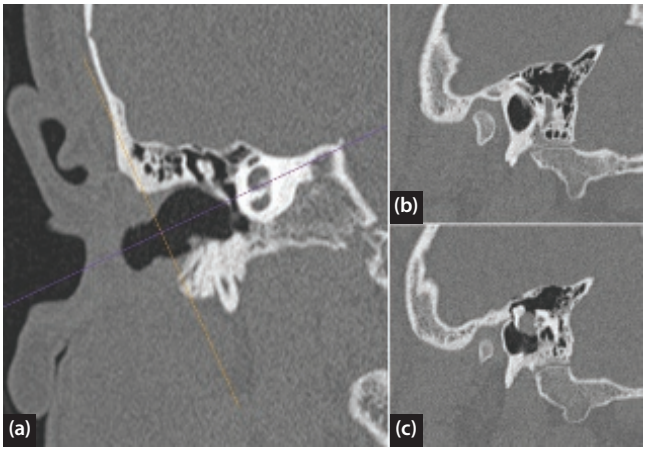

Figure 87.6 Reconstruction of CT scan images along plane of external auditory meatus, best used for pre-operative planning in endoscopic ear surgery.

Endoscope specifications

There are two schools of thought when it comes to selecting which type and size of endoscope to use for ear surgery. Many otologists will use both operating microscope and endoscopes symbiotically, performing part of their surgery with 2.7 mm diameter 0, 30 and 45 degree endoscopes and rarely, using the 70 degree endoscope as well as the 1.9 mm endoscopes, especially to pass through the posterior tympanotomy. Others may undertake the majority of their surgery using a 14–18 cm long 4 mm diameter 0 degree Hopkins rod and endoscope, the very same endoscope used for sinus surgery (Figure 87.7). The latter practice has been termed endoscopic ear surgery (EES) to denote its distinction from the former and is steadily gaining popularity among some otologists.[17, 23, 24] The advantages of using a longer and wider endoscope include a wider field of view, as well as the fact that the surgeon's hands are farther away from the ear canal and hence less likely to interfere with one another intra-operatively.

Digital camera specifications

Although using a high-quality Hopkins rod is essential in otoendoscopy, the digital camera attached to the endoscope also needs to be of high specification. One of the most important considerations is that it should be a camera whose imaging system uses three charge-coupled devices (CCDs), where each one takes a separate measurement of the primary

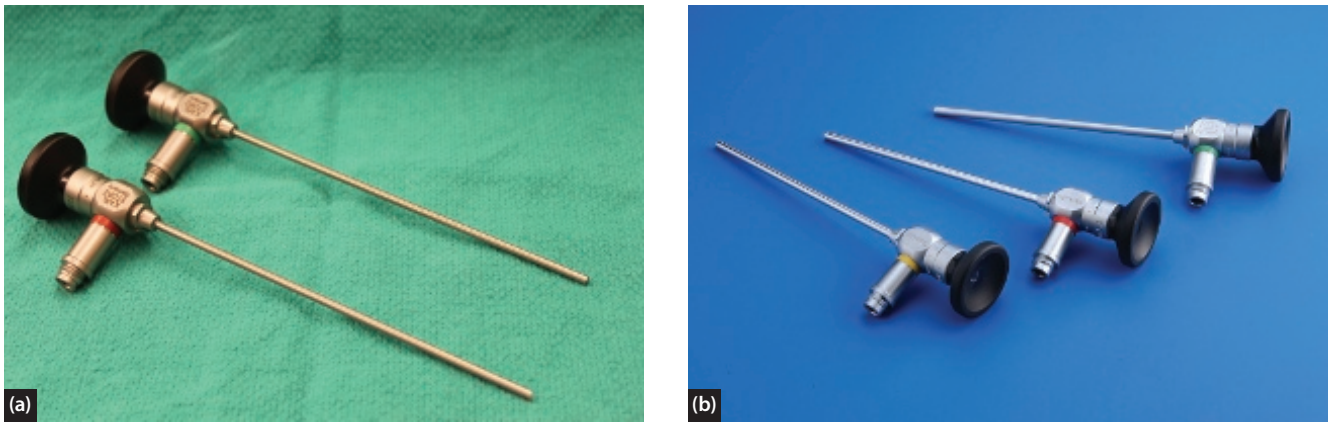

Figure 87.7 (a) Straight and angulated endoscopes (length 14 cm, 4 mm diameter) used in endoscopic ear surgery. **(b)** Straight and angulated endoscopes (length 11 cm, 2.7 mm diameter) more suitable for diagnostic purposes in ear surgery.

colours, red, green or blue light for each pixel, rather than a single CCD camera which can only detect one-third of the colour information for each pixel.[25] Three CCD cameras generally provide superior image quality through enhanced resolution and lower image noise. Single CCD cameras are prone to 'red-out' when they are used in a very small area with a lot of bleeding.[25] Even though there is not much bleeding during EES, the field tends to become reddened, causing complete saturation of the camera. The entire field assumes an orange hue that makes the identification of anatomical structures extremely challenging.

DIAGNOSTIC INDICATIONS

Extent of retraction pockets and cholesteatoma

The diagnostic potential of the endoscope lies most commonly in the evaluation of retraction pockets and cholesteatoma, particularly in blind spots such as the sinus tympani, attic, protympanum and hypotympanum.[7–10] Endoscopy can be performed in the clinic setting as part of the otological examination to assess the extent of middle ear disease and assist in planning the surgical approach. Serial photodocumentation of retraction pockets over a follow-up period may help the otologist to decide whether to adopt a conservative management approach or embark upon surgical intervention.[26]

Ossicular continuity through perforation

Evaluation of ossicular chain continuity may be undertaken endoscopically through an existing tympanic membrane perforation, as demonstrated by Nomura.[27] This procedure may be performed in the outpatient setting with the application of local anaesthesia if required.

Otoendoscopy through myringotomy

Middle ear endoscopy may also be carried out through a myringotomy for many indications such as unexplained conductive hearing loss,[20] perilymphatic fistulas[28] or occult cholesteatoma.[29] Fabinyi and Klug reported on the pathological findings in the middle ear of 60 patients using the transtympanic endoscopic approach, concluding that this method could be used to rule out ossicular anomalies and check for displaced stapes prostheses.[30] Ogawa made the diagnosis of idiopathic perilymphatic fistulas with a 45 degree 1.2 mm diameter Olympus® endoscope through a myringotomy and went on to close the fistulas with fascia and fibrin glue after elevating a tympanotomy flap.[31]

Laser-assisted tympanostomy assisted by otoendoscopy was first performed by Silverstein to examine the relationship between healing of secretory middle ear disease and the tympanic membrane.[32] He went on to use endoscopy to evaluate round window patency as the presence of adhesions might affect the instillation of intratympanic medication in cases of Ménière's disease and sudden sensorineural hearing loss, noting that 17% of patients had partial round window obstruction while 12% had total obstruction.[33] More recently, Kakehata used a similar technique in the outpatient setting to insert the endoscope through a 2 mm laser-assisted myringotomy for assessment of the ossicular chain and stapedial fixation in otosclerosis.[34] The location of the perforation was made between the oval and round windows with a single pulse of 10 watts from the Otoscan™ carbon dioxide laser. Diagnosis of stapes fixation with this technique involved direct endoscopic observation of the stapedial reflex, which was achieved by evaluating the mobility of the stapes in response to contralateral sound stimulation.[34]

THERAPEUTIC USES

Tympanoplasty/ossiculoplasty

The least complicated therapeutic application of endoscopy in ear surgery is probably that of tympanoplasty. Endoscopic type I tympanoplasty (myringoplasty) was first described in 1992 with a graft take rate of 92% and air–bone gap closure to less than 10 dB in 83% of cases.[35] Subsequent studies of endoscopic transcanal myringoplasties followed, with similar success rates as microscope-assisted cases.[36, 37] Tarabichi described his endoscopic technique in a series

of 165 patients and felt that its greatest potential was in tympanoplasty and cholesteatoma surgery.[38] Endoscopic transtympanic tympanoplasty and ossiculoplasty with columella reconstruction or interposition with tragal cartilage was later described in another study, albeit small, with acceptable post-operative hearing results.[24]

Retraction pocket surgery

The use of endoscopy in the surgery of retraction pockets imparts the ability to 'see round corners' to ensure that no epithelium has inadvertently been left in the middle ear cleft after the retraction pocket has been dissected free. It enables the surgeon to retrace the sac, starting from the mesotympanum and continuing through its twists and turns around the ossicles and ligaments. This improved access also facilitates preservation of the ossicles while ensuring the complete removal of the matrix, rather than piecemeal and through different access portals.[23] Tarabichi described an endoscopic transcanal tympanotomy with extended atticotomy and tragal cartilage reconstruction technique in 168 patients with retraction pockets/cholesteatoma and reported a recurrence rate of 7%.[39] He concluded that, while this approach allows the use of the ear canal as the direct and natural access point to cholesteatoma within the mesotympanum, attic, facial recess, sinus tympani, hypotympanum and Eustachian tube, it does not improve access to mastoid disease. Endoscopic access through a mastoid antrostomy may still be required to evaluate an extensive retraction pocket from a posterior perspective.[40]

Mastoid surgery

Numerous techniques have been proposed to facilitate removal of cholesteatoma from the sinus tympani, such as the use of intratympanic mirrors or the retrofacial approach to the sinus tympani, but these methods have not been widely accepted.[41, 42] The last 20 years have seen a myriad of reports on the use of rigid endoscopes to inspect and clear disease in the middle ear.[8, 11, 40, 43] The most detailed studies originated from Thomassin et al.,[10] where the most of the operation was performed with the microscope and the endoscope was employed only in certain situations: at the end of primary canal wall-up mastoidectomy procedures to verify the degree of eradication, when the cholesteatoma had reached the posterior region of the tympanic cavity, the epitympanic recess, or when there was extension to the level of the orifice of the Eustachian tube. Thomassin used a camera coupled to the endoscope whenever it was possible to perform true endoscopic surgery.

Otoendoscopy can also be helpful in canal wall-down mastoid procedures. Yung studied 92 such cases, consisting of small cavity mastoidectomies, canal wall reconstruction and primary obliteration following open cavity mastoidectomies, with 2.7 mm and 4.0 mm diameter (30 and 70 degree) rigid endoscopes.[43] He found that more than one-third of cases had disease extending into the sinus tympani, which was made visible and accessible with the use of side-viewing endoscopes.[43] He did not use the otovideoendoscopic technique recommended by Thomassin et al.[10] as the attachment of the video camera to the endoscope increased the weight of the endoscope and made it more difficult to be manoeuvred. Yung concluded that routine use of endoscopes to control the sinus tympani gives the otologist more confidence at the end of the operation that eradication of the disease is complete as it provides direct vision and also allows better documentation of operative findings.

Minimally invasive second-look combined approach tympanoplasty

Second-look surgery to check for residual and recurrent cholesteatoma is common practice after canal wall-up mastoidectomy operations, as the rate is reported to be higher than with canal wall-down procedures, varying from 10% to 43%.[44–46] One major reason for this is poor access, particularly to the sinus tympani and anterior epitympanum with the operating microscope, leading to increased residual disease. Thomassin et al. showed that the rate of residual disease detected at second-look surgery could be reduced from 47% to 5% with the routine use of otoendoscopy at primary surgery.[10] More recently, Ayache et al. reported the use of otovideoendoscopy to identify and excise residual disease overlooked by otomicroscopy in canal wall-up procedures.[47] Otoendoscopy revealed rates of 44% residual disease in the epitympanum and 34% in the retrotympanum with conversion to canal wall-down procedure avoided in many cases. Their study also suggested that the need for a second-look look combined approach tympanoplasty (CAT) procedure after endoscopic removal at primary surgery would be influenced by the quality of excision achieved with endoscopy.

With the aid of endoscopes, the morbidity of second-look procedures can be reduced by using a minimally invasive approach. A 1 cm stab incision is made anteriorly to the original postauricular incision in the sulcus that allows insertion of a 2.7 mm endoscope into the mastoid cavity to search for residual disease (**Figure 87.8**). Any residual pearls of disease may then be removed without resorting to wider exposure. The posterior tympanotomy may also be reopened through this approach to allow insertion of the endoscope, although a 1.7 mm endoscope is usually required. The accuracy of detecting residual cholesteatoma with this endoscopic technique was verified by performing conventional second-look mastoidectomy procedures with the microscope on the same patients; the results after both techniques were similar.[48] Moreover, the operating time with this approach is shorter than reopening the original incision.[18] McKennan reported that patients find it more comfortable and also reduces the time taken off work.[9] Factors that may require reopening of the original postauricular incision, however, include excessive bleeding, extensive recurrence, reossification over the mastoidectomy site, scar tissue in the mastoid or middle ear cleft, dehiscent facial nerve and lateral semicircular canal fistula. More experienced surgeons would not deem any but the first two factors to be absolute contradictions.

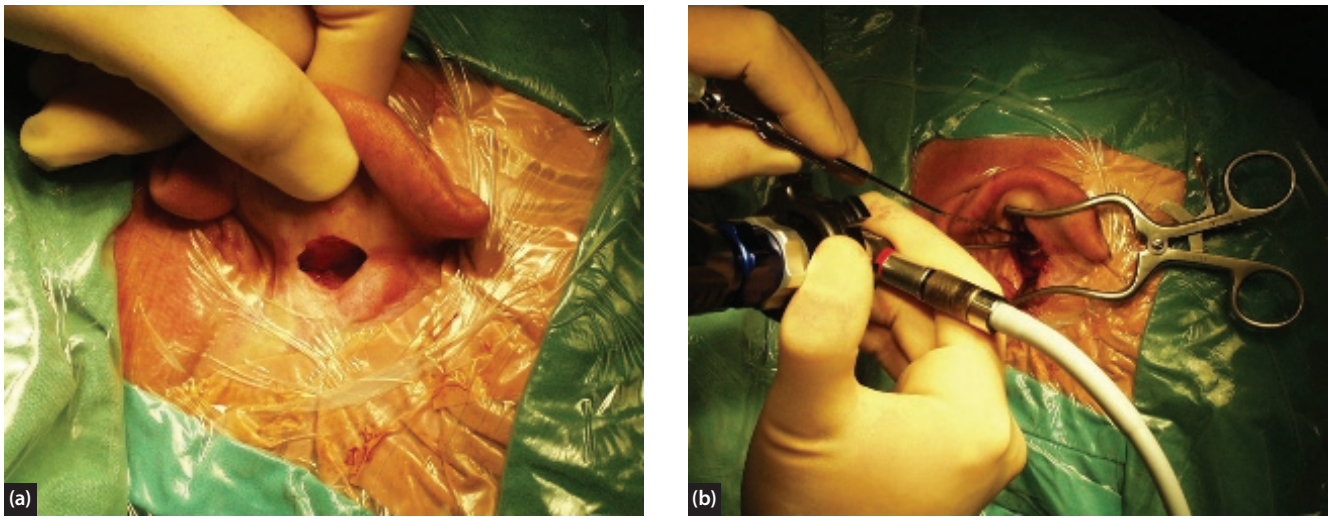

Figure 87.8 **(a)** Performing a minimally invasive stab incision at second-look combined approach tympanoplasty (CAT) surgery. **(b)** Insertion of a 0° (and subsequently a 30°) rigid endoscope into the stab incision to assess for residual disease.

Newer applications

NEUROTOLOGIC SURGERY

Endoscopy of the cerebellopontine angle is not new, but Magnan first described its use in patients with vestibular schwannoma, trigeminal neuralgia hemifacial spasm and incapacitating vertigo.[49] He inserted 1.7mm and 4.0mm 0 degree and 30 degree angled Hopkins rods through a small retrosigmoid craniotomy to access the cerebellopontine angle endoscopically to help identify the relationship between nervous and vascular structures. Endoscopic assistance also helped to prevent cerebrospinal fluid leak after vestibular schwannoma surgery by helping to find patent air cells so that these could be sealed with bone wax and fat grafts.[18]

The role of the endoscopic surgery in the inner ear and internal auditory canal (IAC) is limited and usually used as an adjunct to the microscopic approach. The endoscopic approaches of the inner ear and petrous bone may be summarized as combined transmastoid approaches (translabyrinthine suprameatal, transotic, infralabyrinthine approaches); combined retrosigmoid approach; and exclusive endoscopic transcanal approach.[50, 51] With the combined transmastoid approach, after the microscopic step in the translabyrinthine and transotic approaches, the introduction of the endoscope into the mastoid cavity gives a good view of the geniculate ganglion, medial and anterior portion of the intralabyrinthine facial nerve and removal of residual disease without manipulation of the nerve. With the combined retrosigmoid approach, the aim is to obtain good control of the intrameatal portion of the nerve endoscopically, removing the residual acoustic neuroma within the inner canal, and it is similar to the use of endoscopy in the retrosigmoid neurosurgical approach.

The third approach is the exclusive endoscopic transcanal approach which is still in its infancy.[51] This approach allows endoscopic access to the inner ear from the EAC, preserving facial nerve function and avoiding the need for mastoidectomy or external incisions. After removal of the tympanic membrane and ossicular chain, access to the medial wall of the vestibule is possible. This wall lies adjacent to the fundus of the IAC, representing a portal to access the inner ear and IAC. Endoscopic removal of the bone between the geniculate ganglion and the medial wall of the vestibule will give direct access to the intralabyrinthine path of the facial nerve all the way to the IAC. The use of high-speed drills as part of the endoscopic approach provides a number of challenges, namely the accumulation of bone dust and the need for constant irrigation. Although an otologic drill can be used, for this surgery, it is usual to make use of piezoelectric cutting instruments to remove bone without injury to soft tissues and minimize the production of bone debris. Removing the medial wall of the vestibule will allow direct access to the intrameatal portion of the facial nerve, obtaining entire control of the first segment of the facial nerve.

Although there are currently few indications for the entirely transcanal approach to the inner ear, the technique has been used successfully to remove cochlear schwannomas and small intracanalicular acoustic neuromas. The necessity to approach the lesion through the labyrinth and/or the cochlea makes the technique suitable only in situations where the preservation of hearing is not planned. While far less invasive than a traditional translabyrinthine approach, an endoscopic excision of a lesion of the inner ear or IAC has few indications as the technology currently stands. The risk of bleeding following the removal of the tumour in the IAC makes the endoscopic approach a risky proposition, as there is no way to control haemorrhage under these circumstances owing to the limited access to the IAC at its medial end.

ENDOSCOPIC STAPEDOTOMY

Endoscopic stapedotomy is another novel application of EES. Poe performed stapedioplasties (stapedotomies without prosthesis insertion) in 11 patients by making argon ion laser cuts under endoscopic assistance in the anterior crus and footplate, so as to mobilize the posterior segment

of the stapes while the anterior portion remained fixed.[52] He reported that these patients' hearing improved with air–bone gap closure to a mean of 8.3 dB. More recently Nogueira published a series of 15 patients who had undergone fully endoscopic stapedotomy using a transcanal approach.[53] He used 4.0 mm 0 degree and 30 degree endoscopes, the former to elevate a tympanomeatal flap and the latter to inspect the middle ear and for subsequent stapes work. The advantages associated with the use of endoscopy during stapes surgery include achieving excellent exposure of the oval window niche without removal of healthy bone from the EAC, avoiding any manipulation of the chorda tympani and obtaining a good view of the anterior crus of the stapes to allow its removal without blind manoeuvres.[53]

ENDOSCOPIC COCHLEAR IMPLANTATION

Currently, the use of an endoscopic approach in cochlear implantation is controversial. No case series have yet been published regarding this application of otoendoscopy, but there have been a number of individual cases presented at conferences on EES. The surgical technique involves the routing of the electrode through the epitympanum after a 'well' has been created for the receiver. A small cortical mastoidectomy is fashioned to allow access to the middle ear via the epitympanum after which the ear canal skin is raised from the bony portion of the EAC without the requirement for transection. Once the middle ear has been reached, the implant is guided into the cochleostomy under endoscopic guidance. Another technique involves the passing of the electrode down the ear canal within a bony groove into the middle ear after which the groove is filled with bone wax or other material.

Supporters of these techniques claim that the electrode can thus be placed in a minimally invasive fashion without risk to the facial nerve that is inherent in a technique that requires access through a posterior tympanotomy. The elevation of the tympanic membrane and the skin of the posterior canal wall, however, may lead to an additional route for infection of the mesotympanum and there have been a number of cases of extrusion of the electrode from its groove in the posterior EAC wall through the skin of the EAC, all requiring explantation.

FUTURE DIRECTIONS AND INNOVATIONS

3D otoendoscopy

The disadvantage of the two-dimensional view that comes with an endoscopic approach has been of little hindrance to the development of EES. This mirrors the development of endoscopic sinus surgery in this regard. The development of 3D endoscopy is an area that shows promise; the limited dimensions of the EAC make the use of twin endoscopes very challenging and the 3D view that is achieved by the Da Vinci® robot system cannot be achieved in the ear canal with current technology. To overcome this limitation, 3D CCD chips have been developed to allow a 3D image to be generated with a chip with a diameter of 3.3 mm. This may pave the way for the routine use of 3D camera systems for this purpose.

SUMMARY

Fibre-optic technology, endoscopic expertise, microinstrumentation and laser equipment have all greatly improved over the past few years. It is likely that otoendoscopic surgical techniques will prove increasingly important in otologic surgery. Most of the anatomical spaces in the middle ear that are considered challenging to access with the microscopic technique can easily be approached with endoscope-assisted surgery. The inclusion of the endoscope in microscopic procedures on middle and inner ear pathology, as well as in neuro-otological procedures, could potentially help the surgeon to achieve improved results with regard to the preservation of important structures, limitation of injury to healthy bone for access and allowing a minimally invasive approach in certain situations. At present, opinion continues to be divided as to whether the role of endoscopy in otology should be that of an all-encompassing technique or more as a useful adjunct to the microscope. Regardless, exciting developments in technology and expertise mean that otoendoscopy is likely to remain a key tool of technique in the otologist's armamentarium into the future.

KEY POINTS

- The microscope has traditionally been the workhorse of ear surgery but modern advances in endoscope design and endoscopic surgical techniques have ushered in a new era for the rigid endoscope as a key tool in otology.
- New anatomical terms to describe detailed middle ear anatomy have been devised to accommodate the different view obtained endoscopically.
- There are currently two schools of thought when it comes to selecting size and type of endoscope for ear surgery, divided between shorter 2.7 mm diameter endoscopes, and longer 3 or 4 mm diameter rigid endoscopes. The latter practice has been termed Endoscopic Ear Surgery (EES).
- A wide range of diagnostic indications exist for endoscopic ear surgery, most commonly the assessment of the extent of retraction pockets and cholesteatoma.
- Multiple therapeutic applications exist for the endoscope in middle ear surgery, ranging from endoscopic tympanoplasty and retraction pocket surgery, to minimally invasive second look canal wall up mastoid surgery.
- Newer applications include endoscopic stapedotomy, endoscopic cochlear implantation and total transcanal approaches to the inner ear.
- The role of endoscopy in otology continues to grow in importance but debate remains as to whether the endoscope in ear surgery should be exclusively used with the omission of the microscope or if the endoscope will endure instead as a useful adjunct to the microscope.

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CHAPTER 88

TUBERCULOSIS OF THE TEMPORAL BONE

Ameet Kishore

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: tuberculosis, otitis media and temporal bone.

DEFINITION

Tuberculosis is a chronic granulomatous infection caused by *Mycobacterium tuberculosis*. Other mycobacteria such as *Mycobacterium bovis*, *Mycobacterium avium* and *Mycobacterium fortuitum* can also cause infection referred to as 'atypical tuberculosis' or non-tuberculous mycobacterium (NTM) (see also Chapter 37, Cervicofacial infections). While tuberculosis (TB) is predominantly pulmonary, 12–15% of reported cases of TB involve extrapulmonary sites.[1] Rarely the temporal bone may be involved with TB – tuberculous otitis media or tuberculous otomastoiditis.

PREVALENCE

The WHO estimates there are 8 million cases of TB reported annually.[2] The majority of these occur in Asia (55%) and Africa (31%). TB of the temporal bone, however, is extremely uncommon and constitutes less than 1% of all cases of chronic otitis media.[3, 4]

Tuberculous otitis media is even rarer in developed countries and its incidence in the UK is said to be only 0.04% of cases of chronic otitis media.[5, 6] The advent of BCG vaccination and the use of effective antituberculosis therapy have led to a significant reduction in incidence of TB particularly in developed countries.[2] In a previous review of the literature, of the 320 cases of tuberculous otitis media reported in the medical literature between 1986 and 1990, 83% were from Africa.[7]

In developing countries, where TB is still endemic, tuberculous otitis media remains an important differential diagnosis of chronic otorrhoea that is unresponsive to conventional treatment. In a study from Africa, of over 11 000 patients with TB identified over a 6-year period, 43 (0.37%) were diagnosed as having tuberculous otitis media.[4]

PATHOGENESIS

Tuberculous otitis media occurs frequently in ears with pre-existing chronic middle ear infection where the organisms enter the middle ear through an existing tympanic membrane perforation.[8, 9] There are two other potential routes through which the tubercle bacilli may reach the middle ear: either through the Eustachian tube or by haematogenous spread from another focus.[10, 11] Pulmonary tuberculosis may predispose to the development of tuberculous otitis media by providing a source for haematogenous spread to the temporal bone.[12] Tuberculous otitis media in children has been reported to be secondary in up to 50% of cases.[8]

Tuberculous otitis media may present in different pathological phases. In the acute phase there is congestion

followed by thickening of the tympanic membrane and the appearance of tubercles and perforations. The chronic form is slow and painless with perforations and pale pink granulation tissue. The necrotic or caseous form destroys the bone with sequestrum formation.[13]

DIAGNOSIS

The clinician needs to have a high index of suspicion of tuberculous otitis media in patients living in highly endemic areas who present with otorrhoea not responsive to conventional treatment. Up to 50% of patients with tuberculous otitis media may give a history of exposure to TB.[14–16] The initial symptoms and signs are frequently non-specific and similar to those of chronic otitis media. The patients may have symptoms and signs of pulmonary tuberculosis such as cough, night sweats and fever, and should have a thorough clinical examination and a chest X-ray.[17] The prevalence of active or inactive pulmonary tuberculosis in patients with tuberculous otitis media can range from 14% to 93%. However, a number of patients may not present with findings suggesting pulmonary tuberculosis if the disease is inactive.[8, 12]

CLINICAL PRESENTATION

The classical description of tuberculous otitis media is painless otorrhoea, multiple perforations, pale granulations, early severe hearing loss and bone necrosis.[4, 18–20] Otoscopic examination reveals a tympanic membrane perforation through which the middle ear mucosa may appear pale or denuded.[13–15] The bone of the middle ear cleft may be denuded of mucosa in up to 30% of patients.[12]

Multiple tympanic membrane perforations were once considered a hallmark of the disease, but this is seldom reported and is thought to be rare.[21, 22] Small perforations may coalesce to form a single, large perforation.[19, 20] Ng has suggested a triad of signs for tuberculous otitis media: regional lymphadenopathy in the absence of typical systemic features of TB refractory otitis unresponsive to conventional antimicrobial agents, and the presence of complications such as facial nerve palsy or sensorineural hearing loss relatively early in the course of the disease.[23] The hearing loss is usually conductive due to tympanic membrane perforation, although it is not uncommon to have a mixed hearing loss which is disproportionate to the disease due to the occurrence of labyrinthitis. Hearing loss out of proportion to otoscopic findings, the absence of otalgia and the presence of complications such as a facial nerve paresis should alert the clinician to the possibility of tuberculous otitis media.[3, 16, 24] Facial palsy is reported in 10–20% of patients and occurs early in the disease process.[11, 16, 25] It has been suggested that the presence of a facial palsy in the absence of a cholesteatoma should alert the clinician towards the possible diagnosis of tuberculous otitis media.

BACTERIOLOGY

While a positive culture for the acid-fast bacillus *Mycobacterium tuberculosis* confirms the presence of tuberculous otitis media, ear discharge provides a poor yield for positive cultures. This is believed to be due to the low bacterial count in the ear discharge.[11, 26] A positive swab for culture and sensitivity is diagnostic in less than 20% of cases of tuberculous otitis media.[8, 27] Polymerase chain reaction (PCR) has been used to detect mycobacterium tuberculosis in pus or tissue specimens to confirm the diagnosis.[28]

HISTOPATHOLOGY

Histopathological examination of a biopsy specimen is the most definitive way of confirming the diagnosis of tuberculous otitis media.[4, 28] This necessitates a biopsy of granulation tissue, middle ear polyps from the external canal or tissue removed at mastoidectomy. The microscopic finding of granulomata with caseous necrosis, epithelioid cells and Langerhans giant cells is a strong indicator of TB. The false-negative rate of histopathological diagnosis has been suggested to be 10%.[4] In one series of patients, however, the diagnostic yield from histology of middle ear biopsy and aural polypectomy was only 30% and 35% respectively.[15]

IMAGING

Plain skull X-rays are non-specific. They may demonstrate haziness or erosion within the mastoid air cells that are similar to the findings in any other form of chronic otitis media.[29] **A CT of the temporal bone is the radiological investigation of choice** and will usually demonstrate the presence of soft tissue in the middle ear cleft with a relatively well-preserved mastoid air cell system. There is typically minimal sclerosis of the mastoid, mucosal thickening of the bony external auditory canal, or soft-tissue extension within the external auditory canal without erosion of the scutum.[11, 21, 30] With advanced disease, CT may demonstrate diffuse destruction of the temporal bone in contrast to selective destruction of the scutum seen in active squamous chronic otitis media.[20] A CT is important when assessing the degree of involvement of the temporal bone and the likelihood of any complications such as facial nerve involvement, erosion of the semicircular canals or labyrinthine ossification.

DIAGNOSTIC CHALLENGES

TB of the temporal bone is seldom considered as the initial diagnosis in a patient with a discharging ear owing to its rarity. This, however, explains the frequent delay in diagnosis.[18] This is particularly true in developed nations. In developing countries in Africa and Asia, the index of suspicion should be higher. Many patients have no previous history of TB infection and have a normal chest X-ray.[3]

The absence of disease-specific clinical findings and the very high false-negative rate of bacteriological culture makes it difficult to confirm the diagnosis of tuberculous otitis media early in the disease process.[11] **The widespread use of neomycin- and gentamicin-containing ear drops can mask the clinical features of tuberculous otitis media as these drugs have a weak antituberculous effect.**[15, 26, 31]

As early treatment can prevent complications such as irreversible hearing loss and facial nerve palsy, the clinician needs to have a high index of suspicion.[11]

The differential diagnosis of tuberculous otitis media includes other chronic conditions affecting the temporal bone such as Wegener's granulomatosis, histiocytosis X, chronic otitis media, cholesteatoma, histoplasmosis, blastomycosis, syphilis and lymphoma.

COMPLICATIONS

Complications of tuberculous otitis media are commoner and tend to be more severe in children. Facial nerve paralysis has been reported in 16% of adults and 35% of children with tuberculous otitis media.[4] Profound hearing loss can occur following spread of infection into the cochlea.[5, 19, 20, 32] Granulation tissue invading the Fallopian canal and compressing the facial nerve results in a facial nerve palsy in 10–20% of patients.[11, 24, 25, 33, 34] Other complications reported are postaural fistula, temporomandibular joint involvement,[34] intracranial complications such as meningitis, tuberculomata,[35] otitic hydrocephalus[36] and multiple cranial nerve palsies.[4, 31]

MANAGEMENT

The two components of treatment are antituberculous therapy and surgery. Medical management with antituberculous therapy is the mainstay of treatment once the diagnosis has been confirmed.[4, 5, 11, 12, 18, 26, 28] Antitubercular treatment using the current standard medication of isoniazide, ethambutol, pyrazinamide and rifampicin may be required for a minimum period of 6 months. Treatment over a longer period may be required in cases of disseminated TB and meningitis.[37] Patients may only require medical treatment.[38, 39]

Surgery may be required to obtain tissue for histology, drain a subperiosteal abscess or remove a bony sequestrum.[4, 18] The incidence of sequestrum formation may be as high as 30%.[27] Surgery may be indicated in the presence of facial nerve palsy for the purposes of a facial nerve decompression if medical management fails to demonstrate clinical improvement in facial nerve function.[4, 18]

Resolution of the otorrhoea with medical management alone can begin to be seen after 2–3 weeks of treatment and the disappearance of granulation tissue can be observed in 1–5 months.[12, 17] Some authors have suggested that combined modality treatment of surgery and antituberculous therapy is likely to be more effective and result in quicker healing with better outcomes.[11, 16, 20, 24] The role of surgery for facial nerve palsy in tuberculous otitis media is contentious as similar results are reported with medical management alone.[4, 14] In the case of bilateral tuberculous otitis media resulting in bilateral profound hearing loss, cochlear implantation is an option for hearing restoration. However, the labyrinthine ossification that follows tuberculous otitis media can make surgery difficult.[40]

KEY POINTS

- Tuberculous otitis media is a rare condition and constitutes 0.3–0.9% of all patients with chronic otitis media.
- Most cases have been reported from countries where TB is endemic such as in Africa and Asia.
- There are no specific clinical features as symptoms and signs are similar to chronic active otitis media.
- The confirmation of diagnosis is difficult as bacteriology is insensitive. Histopathology is often required to confirm the diagnosis.
- Complications such as profound hearing loss and facial nerve paralysis can occur early in the disease process.
- The mainstay of management is medical using antituberculous treatment for 6 months or longer.
- Surgery in the form of mastoidectomy with or without a facial nerve decompression is reserved for patients who do not respond to medical treatment, for removal of sequestrum, drainage of a subperiosteal abscess or facial nerve decompression.
- The clinician should have a high index of suspicion in patients with persistent otorrhoea that is resistent to standard medical treatment or where complications occur disproportionately early in the disease.

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CHAPTER

89

OTOSCLEROSIS

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SEARCH STRATEGY

Definition and pathology

Data in this section may be updated by a Medline search using the search string ("Temporal Bone/pathology"[Mesh]) AND "Otosclerosis/pathology"[Mesh].

Aetiology

Data in this section are may be updated by a search in PubMed, Embase, CINAHL and the Cochrane Library using synonyms for 'otosclerosis' and 'aetiology' in title and abstract.

Incidence

Data in this section may be updated by a Pre-Medline and Medline search using the keywords otosclerosis and incidence, and otosclerosis and prevalence.

Diagnosis

Data in this section may be updated by a Medline search using the keywords otosclerosis and diagnosis.

Natural history
Data in this section may be updated by a Medline search using the keywords otosclerosis; audiometry, pure-tone; hearing loss, otosclerosis and natural history.

Management options: fluoride
Data in this section may be updated by a Medline search using the keywords otosclerosis and sodium fluoride.

Management options: hearing aids
Data in this section may be updated by a Medline search using the keywords otosclerosis or stapes surgery, and hearing aid.

Management options: surgery
Data in this section may be updated by a Medline search using the keywords otosclerosis or stapes surgery, and 5015 references were identified. Each key topic was cross-referenced independently (e.g. antibiotic prophylaxis, steroids, etc.).

DEFINITION AND PATHOLOGY

Thanos Bibas

DEFINITIONS

Otosclerosis is a localized hereditary disorder of bone metabolism of otic capsule enchondral bone that is characterized by disordered resorption and deposition of bone.[1–2] It is thought to result from increased and pathologic bone remodelling and the basic lesion consists of areas of bone resorption by osteoclasts and new bone formation by osteoblasts, accompanied by vascular proliferation and tissue stroma.

Clinical otosclerosis refers to lesions that affect the stapes, stapediovestibular joint or round window membrane and thus cause conductive hearing loss. In cases of mixed hearing loss it is assumed that there are lesions affecting the cochlear endosteum as well. **Cochlear otosclerosis** refers to lesions involving the cochlear endosteum without affecting the stapes or the stapediovestibular joint, thus causing pure sensorineural hearing loss, with no conductive element. It is considered very rare, but prevalence is difficult to judge as some authors include cases with mixed hearing loss. **Histologic otosclerosis** refers to histopathological lesions that do not affect the stapes, stapediovestibular joint or cochlear endosteum, and thus remain asymptomatic during life.[2] Although the prevalence of histologic otosclerosis has been estimated as high as 8.3%, an unselected series of temporal bones has found a prevalence of 2.5%.[3]

HISTOPATHOLOGY

Bone remodelling in the otic capsule and animal models

The otic capsule is unique compared to the rest of the bony skeleton in that it exhibits limited remodelling. There is a gradient of decreased remodelling rate from the periphery of the otic capsule towards the membranous labyrinth. It has been hypothesized that otic capsule remodelling is related to the ratio of two cytokines, osteoprotegerin (OPG) and RANKL (receptor activator nuclear-kb ligand).[4] OPG is a potent inhibitor of osteoclast maturation and functions in competition with RANKL (an activator) for the osteoclast RANK receptor. OPG is highly expressed within the spiral ligament and perilymph and may easily diffuse into the lacunocanalicular network of bony otic capsule through intercellular gaps of the inner ear lining. Impedance of the patency of this signalling pathway may lead to increased bone remodelling and development of the abnormal otosclerotic pattern.[5] Although there are no good animal models for otosclerosis, OPG knockout mice demonstrate progressive loss of hearing, stapes fixation and abnormal focal bone remodelling with many histological similarities to human otosclerosis.[4] However, active remodelling in these mice occurs throughout the entire skeleton and diffusely within the otic capsule. It also involves the incus and malleus, which is rare in otosclerosis, and the effects are reversed by administration of bisphosphonates.[6]

Light and electron microscopy findings

The earliest indication of otosclerotic process is resorption of enchondral bone around blood vessels, with consequent enlargement of perivascular spaces followed by deposition of immature (woven) bone. Through continuous remodelling, more mature bone (lamellar bone) is deposited, mediated by osteoblasts. Active otosclerotic foci are characterized by increased vascularity and increased bone turnover, while inactive (sclerotic) foci consist of dense mineralized bone. Both types may coexist in the same focus.[2] The connective tissue stroma in otosclerotic foci consists of fibroblasts and osteocytes, while there is complete absence of acute inflammatory cells. Electron microscopy studies usually describe osteoclasts in the centres but not in the periphery of otosclerotic foci, thus possibly indicating a lesser role in bone resorption in the advancing front.[7]

Origin, sites of involvement and distribution of lesions

The most common site of involvement is the cochlear wall anterior to the oval window. This is followed by the round window niche and the cochlear apex.[8] Less frequent sites include foci posterior to the oval window, the walls of the internal auditory canal, around the cochlear duct and the semicircular canals, the entire footplate (**Figures 89.1** and **89.2**), and involvement of the middle ear ossicles.[9] Invasion of labyrinthine spaces and the vestibular aqueduct are rare, while invasion of the internal auditory canal or the facial nerve canal have not been reported.

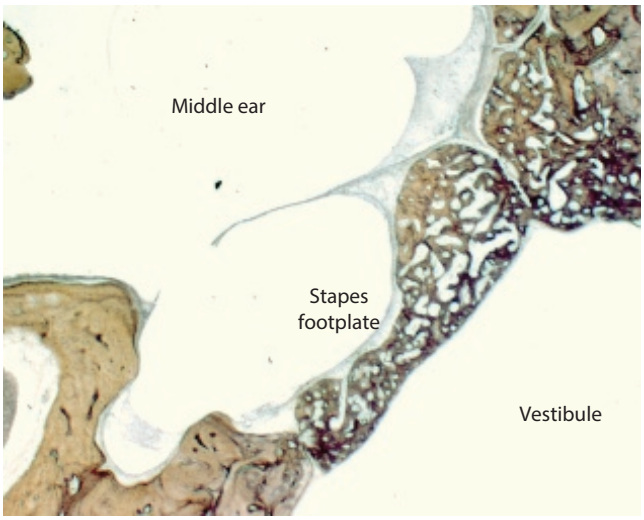


Figure 89.1 Left temporal bone of a 27-year-old female patient with a history of bilateral otosclerosis and Hodgkin disease. The entire stapes footplate is replaced by otosclerotic bone and is fixed both anteriorly and posteriorly. (UCL Ear Institute Temporal Bone collection, specimen F23.)

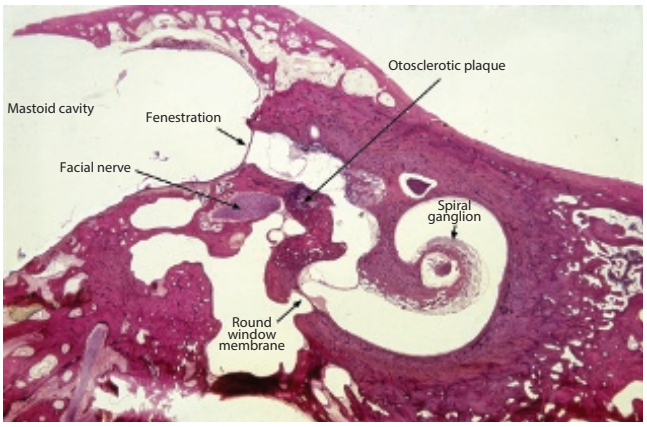


Figure 89.2 Right temporal bone of a 49-year-old female patient with bilateral otosclerosis and bilateral surgical fenestration of the lateral semicircular canals. This specimen is unique as it is sectioned in the vertical plane to demonstrate the fenestration, as well as the oval and round windows in a single section. There is a surgically created window of the LSSC measuring 1.3 mm in the vertical diameter, which is bridged by a thin layer of squamous epithelium. The ampulla appears normal. There is a large otosclerotic plaque causing thickening of the footplate of the stapes. Otosclerotic bone at the superior and inferior margins of the oval window overlaps and partially obliterates the oval window. Round window niche and membrane and spiral ganglion in the basal turn appear normal. (UCL Ear Institute Temporal Bone collection, specimen F267R.)

Michaels and Soucek studied in detail the development of the otic capsule in relation to the origin of the otosclerotic plaques.[10] In all but 2 of the 65 temporal bones studied, a single plaque of otosclerosis occupied much of the otic capsule posterior to the cochlea. Each of the posterior plaques had a well-defined edge at the periosteum lining the otic capsule, extending from the level of the posterior edge of the processus cochleariformis to a level of approximately one-third of the distance along the tensor tympani muscle from the processus. It is the progression of this that will eventually involve the stapes footplate, leading to fixation and conductive hearing loss. In addition, in 42 of these temporal bones there is also a plaque of otosclerosis in the anterior cochlear part of the otic capsule, showing a wide area of contact with the periosteal surface bordering the canal for the internal carotid artery. In both types of plaques, the pattern of change suggests that they commence at the periosteum and, as the immature advancing front of the plaque grows outwards, the tissue that is left behind matures with time, so that the most mature bone in the plaque is near the periosteum.

Very rarely, large cavities may form within otosclerotic foci, a condition termed cavitating otosclerosis.[11] These cavities may act as a 'third window' in cases where the cavitation is in contact with the endosteum of the scala tympani, and may be implicated in persistence of the air–bone gap following a successful stapedectomy. Cavitating foci may also communicate with the CSF space in the internal auditory canal, and may result in gushers during cochlear implantation. There is also an increased risk of the implant electrode being misplaced through a cavitating lesion to the pericochlear cavity.[11]

Conductive hearing loss

Conductive hearing loss is usually related to pathology (narrowing or ankylosis) of the annular ligament, especially the posterior part. A recent study showed that the size of the air–bone gap appeared to be determined by the extent and degree of this pathologic change, and that bony ankylosis was associated with an air–bone gap greater than 30 dB. However, the degree and extent of bony footplate ankylosis could not be reliably predicted by the size of the air–bone gap. Since a lack of bony ankylosis increases the risk of a floating footplate during stapes surgery, one should be aware of this complication even in cases with large air–bone gaps.

Other factors that may contribute to conductive pathology in cases of otosclerosis include complete obstruction of the round window niche (this is frequently associated with a persistent air–bone gap following stapes surgery, and if recognized pre-operatively may be a contraindication to surgery), cavitating otosclerosis (due to a 'third window' effect) and malleus fixation (see 'Surgical pathology' below).

Sensorineural hearing loss

Although the effect of otosclerosis on cochlear function has been controversial in the literature, most temporal bone studies show that, in cases with otosclerosis and sensorineural hearing loss, the hair cells, stria vascularis and spiral ganglion cells either are unaffected or their loss is insufficient to account for the recorded hearing thresholds.[2] Some studies have shown that, when sensorineural hearing loss occurs, it is often in cases with otosclerotic involvement of the endosteum, where it tends to induce hyalinization and atrophy of the spiral ligament.[12] In contrast, in a study of five temporal bones with pure cochlear otosclerosis, one case had normal hearing, while in the rest,

the reduction in the population of cochlear elements was not related to the extent and location of endosteal involvement.[13] However, a temporal bone study by Doherty and Linthicum using objective estimates of stria vascularis width and quantification and localization of spiral ligament hyalinization within the cochlea demonstrated a direct relationship between stria vascularis atrophy and sensory hearing loss that correlated well with the amount of spiral ligament hyalinization.[14] It is worth mentioning that, although temporal bone pathology studies have demonstrated that pure cochlear otosclerosis does occur, its incidence appears to be quite low and that otosclerosis as a cause of idiopathic sensorineural hearing impairment in individuals without clinical evidence for otosclerosis in the form of stapedial fixation is rare.[2]

Vestibular symptoms

Vestibular symptoms may be experienced by 10–30% of patients with otosclerosis but its pathophysiology is obscure in most cases. In a comprehensive temporal bone study by Saim and Nadol, the incidence of vestibular symptoms was correlated with the degree of sensorineural hearing impairment.[15] These cases also demonstrated degeneration of Scarpa's ganglion, which was independent of the severity of otosclerotic involvement of the vestibular end organs. Conversely, almost half of temporal bones in the same study demonstrated involvement of the superior vestibular canal or cribrose area, regardless of vestibular symptoms.

Vestibular symptoms may also be caused by comorbid pathology, such as Ménière's disease. Otosclerotic foci may rarely involve the vestibular aqueduct, but it may also occur without any prominent associated pathology. Yoon et al. looked at 128 temporal bones with otosclerosis, and direct involvement of the vestibular aqueduct was observed in four temporal bones from two patients.[16] In all four, the vestibular aqueduct was filled with active otosclerotic foci. The lumen of the endolymphatic duct and sac was narrowed as a result of fibrosis, and endolymphatic hydrops was observed, which was more severe in the pars inferior than the pars superior. Collapse of the ductus reuniens and dilated saccule was seen in three temporal bones. Issa et al. studied the position of the saccular and Reissner's membranes in relation to the stapes footplate in eight temporal bones from patients with otosclerosis and Ménière's disease. It was found that the saccular and Reissner's membranes did not contact the stapes footplate in cases where pre-operative bone-conduction levels were 35 dB or better at 500 Hz and there was no high-frequency loss. Stapedectomy was reported successful and it was therefore concluded that surgery does not increase the risk of sensorineural hearing loss when these criteria are met.[17]

SURGICAL PATHOLOGY

Stapes surgery

In a histologic human temporal bone study, Pauw et al. measured the distances between the medial surface of the stapes footplate and the utricle and the saccule in normal and otosclerotic bones.[18] No statistical difference was found between the two groups and they concluded that the safest place for a stapedotomy is in the central and inferior-central thirds of the footplate. However, a 0.4 mm stapedotomy piston can be introduced relatively safely to a depth of 0.5 mm in the vestibule over the entire surface of the stapes footplate. Although stapes experiments in animal studies have showed an association between saccular rupture and hair cell loss in the basal and middle turns, it is not clear whether these are associated with the rupture itself, or by shock waves in the perilymphatic spaces following aggressive manipulation of the footplate. However, collapse of the saccular wall by a contact injury from the piston can lead to endolymphatic hydrops postoperatively, presumably by interfering with the longitudinal flow of endolymph.[19]

Although closure of the air–bone gap to within 10 dB is observed in the majority of primary stapedectomies, a residual or recurrent conductive hearing loss may occur. In a comprehensive human temporal bone study by Nadol, it was found that the most common histopathological findings related to conductive hearing loss after stapedectomy included resorptive osteitis of the incus at the site of prosthesis attachment, obliteration of the round window by otosclerosis, and a malpositioned prosthesis at the oval window.[20] Round window obliteration resulted in the largest air–bone gap, but in most of the temporal bones there were more than one finding that could account for this.

Although malleus fixation may be a cause of residual conductive hearing loss, its isolated incidence in temporal bone studies is 1–8%.[21, 22] In an otopathological study of 1108 bones, fixation of the malleus was observed in only 1% of the cases, was usually unilateral and involved the lateral epitympanic wall rather than the anterior mallear ligament.[22] However, temporal bone studies have shown that the incidence of malleus fixation seems to have a higher incidence in patients with otosclerosis. In a temporal bone study by Nandapalan et al. it was apparent that otosclerotic bones have a significantly higher incidence of hyalinization of the anterior malleal ligament (AML), which seems to be related to the duration rather than the severity of otosclerosis.[23] In another study by Oktay et al., although no relationship between hyalinization of the AML and otosclerosis was found, otosclerosis seemed to be a predisposing factor for bony fixation of the head of the malleus to the lateral epitympanic wall.[21] It is therefore prudent to evaluate mobility of the malleus in all stapes surgery.

Cochlear implantation

Cochlear implantation in otosclerotic patients may be complicated by round window obstruction and/or facial nerve stimulation. The round window may be partially or completely obstructed by otosclerotic foci. In rare instances, there is formation of new bone in the scala tympani of the basal turn of the cochlea.[24] Intraoperatively this can potentially cause difficulties at

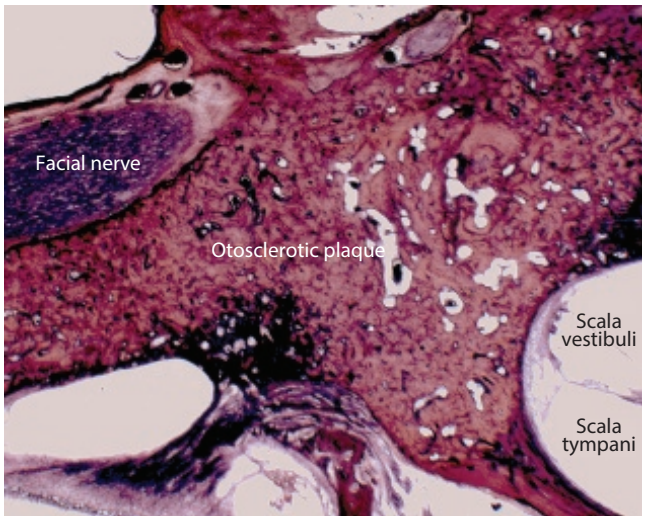


Figure 89.3 Left temporal bone of an 86-year-old male patient with otosclerosis. A large otosclerotic plaque is extending from the cochlea endosteum to the medial aspect of the facial canal in the horizontal segment. (UCL Ear Institute Temporal Bone collection, specimen F41.)

inserting the electrode arrays, necessitating a cochlear drill-out. The incidence of unintentional facial nerve stimulation is significantly higher in patients with otosclerosis than in the general population, especially when a straight electrode is used.[25] Full-thickness involvement of the otic capsule between the cochlea endosteum in the basal turn and different parts of the facial canal may explain the incidence of facial nerve stimulation in these cases, possibly due to altered spread of the current (**Figure 89.3**). It is therefore suggested that a perimodiolar electrode should be preferred, especially in cases in which the pre-operative CT scan suggests that the otic capsule is involved between the facial nerve canal and the upper basal turn of cochlea.

Facial nerve dehiscence

The histopathological incidence of facial nerve dehiscence in otosclerosis was studied by Nomiya et al. in 84 cases compared to 102 age-matched controls.[26] No significant difference was found between temporal bones with and without otosclerosis. Interestingly, the otosclerotic focus did not invade the inside of the canal and did not show any deformity of the canal or injury of the nerve, thus explaining the lack of facial nerve palsy in otosclerosis. It is also suggested by the authors that otosclerotic lesions have the potential to close dehiscences of the facial canal in the oval window area.

AETIOLOGY

Arnold J.N. Bittermann, Inge Wegner and Wilko Grolman

In this chapter we are looking for evidence to support the aetiology of otosclerosis. Aetiology has been a topic of discussion for decades now, but in modern medicine the evidence base has rightfully gained much importance.

GENETIC PREDISPOSITION

OTSC1 (chromosome 15q25-26), *OTSC2* (chromosome 7q34-36), *OTSC3* (chromosome 6p21.3-22.3), *OTSC4* (chromosome 16q21-23.2), *OTSC5* (chromosome 3q22-24) and *OTSC7* (chromosome 6q13-16.1) are monogenetic otosclerosis loci.[27] A recent study has shown mutations and altered expression of the *SERPINF1* gene in patients with familial otosclerosis. This gene encodes PEDF (pigment epithelium-derived factor) which is a known regulator of bone density and is the first disease-associated gene to be identified in otosclerosis.[28]

Monogenic otosclerosis is relatively rare and in most patients otosclerosis occurs without a clear familial background or with only a few affected family members, suggesting the involvement of both genetic and environmental factors.[29] Genes associated with this complex form of otosclerosis include *COL1A1*, *TGFB1* and *RELN*.

A systematic literature search reveals different association and family studies of a genetic cause of otosclerosis. However, the number of studies with low risk of bias is limited. Risk of bias concerns the methodological strengths and limitations of a study. The fewer the methodological limitations, the lower the risk of bias. High-quality studies show that otosclerosis in Japanese patients is not linked to the *NOG* gene[30] and that a polymorphism in the Sp1 binding site located on the *COL1A1* gene is associated with otosclerosis[31] as well as *OTSC1*.[32] Studies with a moderate risk of bias show a statistically significant association of otosclerosis with the *ACE* gene,[33] the *AGT* gene,[33] *OTSC2*,[34] the *RELN* gene,[35, 36] the *TGFB1* gene[36] and 11q13.1.[36] Family-based studies of moderate quality show a statistically significant association of otosclerosis with *OTSC2*,[37] *OTSC5*,[38] *OTSC8*[27] and *OTSC10*.[39] It is important to note that results from studies with moderate to high risk of bias may report spurious associations due to their bias and low statistical power. Interestingly, sex-specific association of *COL1A1* to otosclerosis could be found in one study.[40] The same goes for the *RELN* gene.[36] One single-nucleotide polymorphism (SNP) in the *COL1A1* region was associated with female gender (odds ratio 1.395) and one SNP in the same region with male gender (odds ratio 0.865).[40] One SNP in the *RELN* gene was identified that was associated with male gender (odds ratio 1.392). These findings suggest that both the *COL1A1* and *RELN* gene association with otosclerosis might be influenced by gender, which we should expect since the dominance of presentation is in women.

KEY POINTS

- Despite the extensive availability of studies on the genetic aetiology of otosclerosis it is not possible to assign one or more responsible genes that play a key role in the pathophysiological pathway that leads to otosclerosis.

VIRAL INFECTION

The possibility that a persistent viral infection of the otic capsule may cause otosclerosis was first proposed based on the histological similarity between otosclerosis and Paget's disease, along with mounting evidence of a viral aetiology of Paget's disease.[41, 42]

Otosclerotic foci show all the characteristics of chronic inflammation.[43] An initial active and lytic phase of bone resorption, with proliferation of blood vessels, osteoclasts and mononuclear cells, is followed by the formation of new bone. Support for this hypothesis comes from immunohistochemical evidence of measles virus proteins and antigenicity in active otosclerotic lesions.[44, 45] More recently, two studies have shown an increased expression of specific measles virus receptor CD46 isoforms in otosclerotic footplates.[46, 47] Furthermore, lower levels of anti-measles virus IgG were found in serum from otosclerosis patients with virus-positive footplates compared to healthy controls without otosclerosis and otosclerosis patients with virus-negative otosclerotic footplates.[48–50] In this context, Karosi et al. have shown that combining the assessment of anti-measles virus IgG serum level and the presence of conductive hearing loss results in high diagnostic specificity of 90% and high sensitivity of 96% during the pre-operative evaluation of patients suspected of otosclerosis.[50] Elevated levels of anti-measles virus IgG have been detected in perilymph.[48, 51] Others have found measles virus RNA in archival and fresh frozen footplate specimens with otosclerosis.[52–55] However, failure to do so has also been reported.[56–58] The complete measles virus RNA sequence has never been reported, nor has the isolation of measles virus from otosclerotic samples been successful. It may be argued that the reason is that measles virus titres in otosclerotic samples are too low to be detected. This in turn raises the question whether such a low level of virus could ever cause disease.

Decreasing numbers of stapes surgery and a shift towards older patients following the introduction of vaccination programmes in the US and Europe have been reported by various surgeons.[59–61] Epidemiological surveys of hospitalized otosclerosis patients showed a significant decrease in otosclerosis among the vaccinated population.[62] Interestingly, the decrease in the vaccinated female group was minor in comparison with the male group, which may indicate gender-specific differences in susceptibility or reactivity to measles virus. However, the measles virus hypothesis does not explain why otosclerosis is extremely rare among Africans,[63] despite the fact that the measles virus does occur frequently in African children.

KEY POINTS

- Inconsistencies between current research studies mean that the role played by the measles virus in otosclerosis remains uncertain.

AUTOIMMUNE DISEASE

It has been suggested that otosclerosis represents a form of autoimmune disease with humoral autoimmunity to type II collagen or a closely related antigen that is abundantly present in the regions of predilection. The available evidence is somewhat conflicting. Elevated circulating antibodies against type II collagen[64–66] and type IX collagen[66] in the blood of patients with otosclerosis have been reported. Others, however, have not found a difference in the circulating autoantibody levels between otosclerosic patients and healthy controls.[67–69] A subgroup of patients with disease duration of between 3 and 5 years did show increased autoantibody concentrations in one of these studies.[68] Animals immunized with type II collagen have been found to produce lytic bone lesions in the otic capsule that strongly resemble otosclerosis.[70–72] In similar animal models such otogenic lesions have not been identified.[73, 74]

Criticism of this hypothesis is based on the ubiquitous presence of type II collagen in other sites and the concurrent production of joint lesions in type II collagen-immunized animals, which is not a feature of otosclerosis. Also, patients with relapsing polychondritis have extremely high titres of circulating antibodies against type II collagen, with involvement of multiple organ-sites, but without evidence of otosclerosis.[75]

CYTOKINES

As mentioned above under 'Genetic predisposition', several genes encoding for cytokines have been associated with otosclerosis. These cytokines are transforming growth factor β1 (TGF-β1) and bone morphogenetic protein (BMP).

Bone morphogenetic protein, an inflammatory cytokine that is part of the TGF-β superfamily, may be involved in pathological bone remodelling in otosclerosis. BMPs play a pivotal role in bone formation as well as the healing cascade of bone.[76, 77] Various isoforms, such as BMP2, BMP4, BMP5 and BMP7 have been detected in fresh frozen footplates with active otosclerotic foci.[78–80] Significant expression of BMP receptors 1B and 2 has been shown, whereas BMP receptor 1A was always absent within otosclerotic foci.[78]

HORMONAL FACTORS

Since angiotensin II stimulates the secretion of TNF-α, the renin–angiotensin-aldosterone system (RAAS) may play a role in the regulation of bone remodelling. This theory was first presented by Imauchi et al. in 2008.[33] There is conflicting evidence regarding the association between genes encoding RAAS and otosclerosis.[33, 81] To date, active expression of members of the RAAS family has not been confirmed in otosclerotic stapes footplates.[82]

INCIDENCE

George G. Browning, Arnold J.N. Bittermann, Inge Wegner and Wilko Grolman

GENERAL

It is important to distinguish histological otosclerosis from clinical otosclerosis. In case of histological otosclerosis, otosclerotic foci could be present within the temporal bone without clinical symptoms such as hearing loss and vertigo.

Literature reporting the incidence of otosclerosis is limited. Prospective studies, exclusively designed to identify the incidence of histological and clinical otosclerosis, are rare. Recent studies, describing otosclerosis incidence, mostly present the epidemiology of a variety of otologic disorders including otosclerosis as a subpopulation.[83] This could result in biased results and conclusions. The publication of Declau et al. is the best available evidence reporting the incidence of histological otosclerosis.[84] The incidence of clinical otosclerosis is best described in the publication from the British National Study of Hearing.[85]

HISTOLOGICAL OTOSCLEROSIS

The 'gold standard' for the reporting of the incidence of histological otosclerosis would be a prospective study of the histology of bilateral temporal bones removed consecutively from a population. Such a study has been reported from the University of Antwerp, Belgium, where harvesting of the ossicular chain is routine, as everyone is classified as a donor candidate unless otherwise indicated.[84] The study was of 118 consecutive pairs of temporal bones from white individuals whose mean age was 63 years. The bones were processed and the gross sections visually screened to identify possible bones with otosclerosis. These bones, along with any others that had a suggestion of otosclerosis on microradiography, proceeded to conventional histology. Four of the 118 individuals were found to have histological otosclerosis, an incidence of 3.4%. Two of the patients had bilateral otosclerosis. In none of the four bones where the stapes was still present was it fixed. The limited size of this study did not allow for gender and age to be investigated. This incidence is considerably lower than that of approximately 8% reported from larger temporal bone collections.[86–88] The reason for this is almost certainly a bias to process bones likely to have ear pathology. In these collections, the proportion of males to females is about equal. Age makes no difference to the incidence of histological otosclerosis over the age of 10 years.[86] The percentage of bones with histological otosclerosis that have ankylosis of the stapediovestibular joint is only approximately 12%. Taking these two figures together, it makes the likelihood of clinical otosclerosis in the white population to be approximately 1%. Insufficient data have been reported from temporal bone collections to calculate the effect of gender and age on the incidence of clinical otosclerosis.

One collection had 576 bones from black individuals and only 5 (0.9%) had histological otosclerosis.[86] Ohtani et al evaluated a total of 1011 temporal bones from an unselected series of temporal bones from 507 Japanese persons without signs of otosclerosis. Histologic otosclerosis was found in 15 out of the 1011 ears (1.48%).[88]

CLINICAL OTOSCLEROSIS

Despite the existence of histological otosclerosis, in daily practice, only otosclerosis resulting in complaints such as hearing loss will be clinically relevant. Many prospective studies have reported the incidence of audiometrically assessed hearing impairments in a sample of the population. Unfortunately, few have included otoscopy and bone-conduction thresholds, which are essential to identify patients with clinical otosclerosis. However, the British National Study of Hearing included these measures. They defined presumptive clinical otosclerosis as an ear where the tympanic membrane was normal, the tympanogram was peaked with normal pressure range and associated with an air–bone gap of 15 dB or greater over 0.5, 1 and 2 kHz.[85] In adults, the overall prevalence of otosclerosis was 2% (confidence interval 1.5 to 2.7) with an equal distribution between men and women (Table 89.1). It was only when the air–bone gap was 30 dB or greater that women were (×3) more likely to have otosclerosis than men. The incidence increased with age, those aged 41–60 years were twice and those aged 60–80 years were four times as likely to have clinical otosclerosis.

The proportion of patients that had had surgery was less than 10% and this explains the relatively low population prevalence of otosclerosis reported from clinical series. These are considerably influenced by the proportion of patients with an impairment that seek advice, the referral pattern and the attitude of the specialist to surgery and hearing aids. Studies that report audiometric outpatient data are likely to be less biased. In one such study

TABLE 89.1 Population prevalence per 100 of the presumptive diagnosis of otosclerosis (reprinted from Browning and Gatehouse,[85] with permission)

	Otosclerosis (%)	95% CI
Overall	**2.1**	**1.5, 2.7**
Age (years)		
18–40	1.6	0.6, 2.6
41–60	2.2	1.3, 3.1
61–80	3.0	1.7, 4.3
Sex		
Women	2.0	1.3, 2.7
Men	2.2	1.2, 3.2
Occupational group		
Non-manual	1.5	0.8, 2.2
Manual	2.7	1.9, 3.5

from Copenhagen, the prevalence over a 5-year period of clinical otosclerosis was 2% of patients seen with a hearing impairment.[89, 90] When the proportion of individuals that have bilateral as opposed to unilateral otosclerosis is examined, both clinical and temporal bone case series are likely to be biased towards reporting a higher proportion having bilateral disease. From these, approximately 75% of patients have bilateral disease. Unfortunately, the UK National Study of Hearing[85] did not report its results in this format. In 2012, Hannula et al. presented an epidemiological study on the prevalence of ear diseases in Finland. A total of 850 native Finnish subjects with an age between 54–66 years old were randomly selected. Within this group, the prevalence of otosclerosis was 1.3%.[83] Declau et al. also included an extrapolated estimation of clinical otosclerosis, based on their temporal bone findings and indicated that clinical otosclerosis has a prevalence of 0.3–0.4% among the white ethnic population.[84]

The incidence of clinical otosclerosis in non-Caucasians must be considered unknown because of their dependence on surgical series. These report that surgery for otosclerosis is uncommon in Mongoloid races and is extremely rare in Negroid races.

DIAGNOSIS

George G. Browning and Christopher P. Aldren

OTOSCOPY

Otosclerosis is the presumptive aetiology of a conductive hearing impairment in the presence of a normal, mobile tympanic membrane. The 'gold' reference standard of diagnosis is made at surgery, when it should be possible to exclude the considerably rarer causes of such an impairment, such as congenital ossicular chain abnormalities and other diagnosis (5% and 3% of cases respectively).[91] Ossicular chain discontinuity subsequent to head trauma will give a similar presentation but can be diagnosed by the temporal relation of the hearing loss to the trauma in the history. A 'flamingo flush' or Schwartz sign, a red blush of the tympanic membrane over the promontory, is said to be due to the vascularity of an active otosclerotic focus but is rarely seen.

Otosclerosis can also occur when the tympanic membrane is abnormal, such as in chronic otitis media. This is because otosclerosis will occur in the same percentage of patients with such a condition as it does in the general population (approximately 2%).[85] Thus, in patients with chronic otitis media, around 2% of them will have otosclerosis as an additive component to their conductive hearing impairment. This additive component only becomes apparent when stapes fixation is identified at surgery for pathology other than otosclerosis.

SURGICAL DIAGNOSIS

On raising a tympanomeatal flap, the middle ear will appear anatomically normal. The bone around the oval window may be whiter than normal but no clear junction between otosclerotic and non-otosclerotic bone will be apparent, as in histological sections (Figure 89.4). The mobility of the stapes and other ossicles will be assessed. Minor degrees of fixation are difficult to assess as long as the ossicular chain remains intact, which is the case until the incudo stapedial joint is divided. After surgical removal of part of the bony attic wall to visualize the stapes footplate, it will usually be seen to be thicker than normal. Occasionally, the oval window will be filled with obliterative otosclerosis. If the footplate is found not to be fixed, alternative causes of the conductive hearing loss such as fixation of the malleus should be sought.

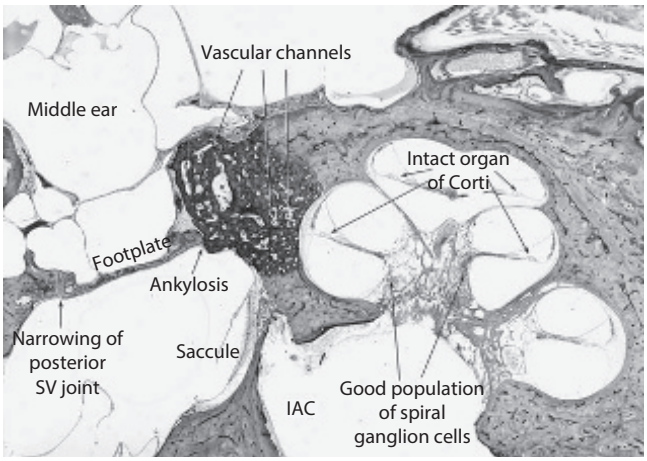


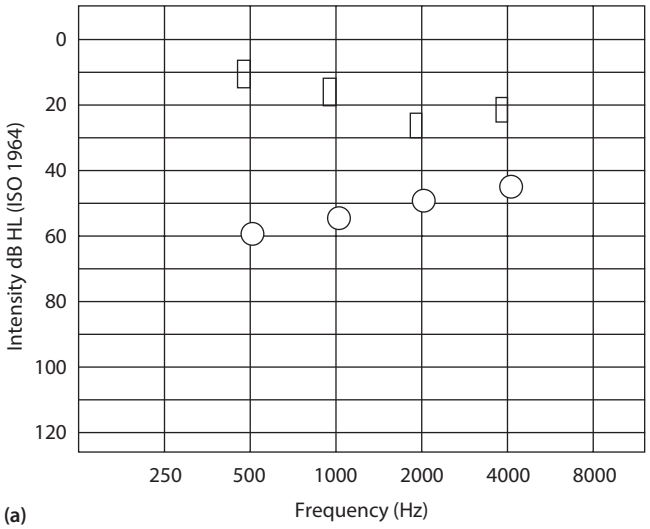
Figure 89.4 Temporal bone section in the axial plane from an 85-year-old man with clinical otosclerosis. There is a single focus of otosclerosis anterior to the oval window, which contains many vascular channels. The focus has caused ankylosis of the anterior portion of the stapes footplate and has also pushed the footplate posteriorly, resulting in narrowing of the posterior stapediovestibular (SV) joint. The otosclerotic focus has also reached the endosteum of the basal turn of the cochlea. Note that the sensory and neural elements of the cochlea are intact, including the organ of Corti, stria vascularis and spiral ganglion cells. IAC, internal auditory canal. (**Magnification ×13.**)

HISTOLOGICAL DIAGNOSIS

Histological confirmation of otosclerosis is more readily obtained if a total stapedectomy is performed. However, now that stapedotomy is the favoured surgical procedure, the stapes superstructure is the only material available. As fracturing of the crura to remove it occurs in non-otosclerotic bone, histology of this specimen is usually valueless.

PURE-TONE AUDIOMETRY

Pure-tone audiometry with appropriate masking will be required to confirm, by the presence of an air–bone gap, any clinical suggestion of a conductive hearing impairment. In those with normal bone-conduction thresholds, the air–bone gap will usually have the classical pattern of being greater at the low frequencies (Figure 89.5) with a Carhart notch.



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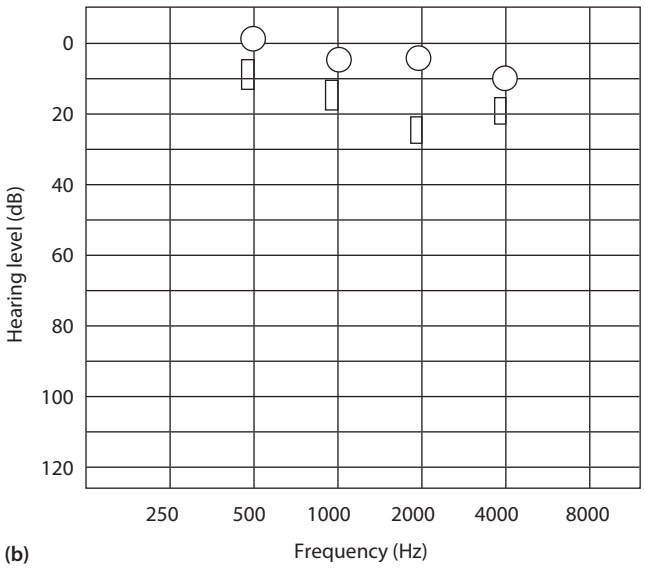

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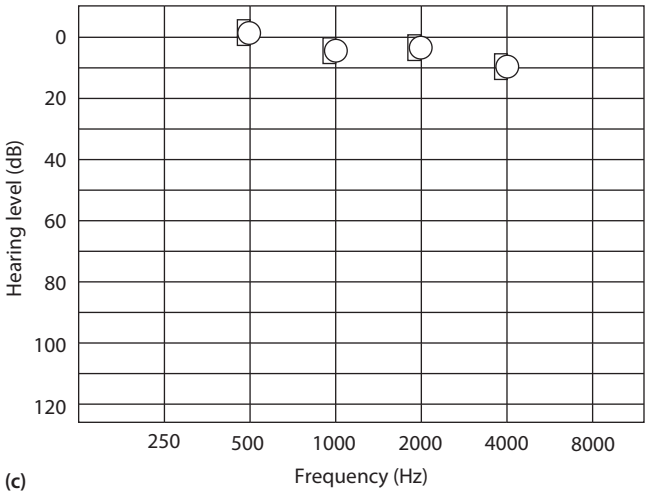

(c)

Figure 89.5 **(a)** Pre-operative audiogram showing classical appearance of a conductive impairment in clinical otosclerosis. The air–bone gap in the right ear is greater at the lower frequencies and a Carhart notch is present at 2 kHz. **(b)** Audiogram of the same patient following successful stapes surgery using the pre-operative bone-conduction thresholds. The air–bone gap has been overclosed. **(c)** Audiogram of the same patient using the post-operative bone-conduction thresholds. The air–bone gap has been closed and the bone-conduction thresholds are better than the pre-operative ones, with elimination of the notch at 2 kHz.

Air–bone gap

The magnitude of the middle ear conductive impairment can only be measured by magnitude of the air–bone gap; the difference between the average air-conduction thresholds and the average bone-conduction thresholds. Traditionally, a three-frequency average over 0.5, 1 and 2 kHz has been recommended, primarily as the air–bone gap is greatest at these frequencies. Others use a four frequency average over 0.5, 1, 2 and 4 kHz, as the air-conduction average of these more accurately reflects the monaural hearing disability. The technical criticism of using this four-frequency average is that the bone-conduction thresholds at 4 kHz are less reproducible than at the lower frequencies. The American Academy of Otolaryngology and Head and Neck Surgery[92] recommends that a four-frequency average over 0.5, 1, 2 and 3 kHz be taken. In practical terms it probably does not matter what air-conduction four-frequency averages are taken as they are usually within 2–3 dB.[93, 94]

What the magnitude of the air–bone gap has to be to diagnose a conductive impairment is usually taken as 10 dB irrespective of what frequencies are averaged. This is because any lesser gap might be due to test/retest error of the audiometric assessment. What the magnitude of the air–bone gap has to be to justify consideration of surgery as a management option has historically been taken as 20 dB. However, many recent series include patients with smaller air–bone gaps down to 10 dB. The assertion is that, if an air–bone gap of between 10 and 20 dB can be closed to the pre-operative bone-conduction, the patient will materially benefit. Before patients with such a small air–bone gap are operated upon, it is essential for a surgeon to audit his results to ascertain how often this occurs in otosclerotic individuals with larger air–bone gaps.

Carhart notch

The Carhart notch is closely related to the Carhart effect. This effect was initially described following successful stapes surgery where overclosure of the air–bone gap occurred when the post-operative air–bone gap was calculated using the pre-operative bone-conduction

thresholds. However, on testing the post-operative bone-conduction thresholds, these had improved, particularly at 2 kHz, where the Carhart notch had been eliminated (Figure 89.5). The magnitude of this effect has been variously calculated (Table 89.2) but averages an improvement over 0.5, 1 and 2 kHz of at least 12 dB.

The reason this occurs is that, when the skull is vibrated by bone-conduction sound, the sound is detected by the cochlea via three routes. In Figure 89.6 route A is by direct vibration within the skull, route B is by vibration of the ossicular chain, which is suspended within the skull, and route C is by vibrations emanating into the external auditory canal as sound and being heard by the normal air-conduction route. In a conductive hearing impairment the latter two routes are deficient but are regained by successful reconstruction surgery. Hence the bone-conduction thresholds improve following surgery. The reason that there is a Carhart notch at 2 kHz before the surgery is that the Carhart effect is greatest around that frequency.

Coincidentally, though the notch was initially described in otosclerosis, it occurs in all ears that have a conductive impairment irrespective of the aetiology. Although in non-otosclerotic ears there is the potential for the Carhart effect to occur following surgery, this seldom happens because the surgery is usually less effective at correcting the conductive hearing impairment than it is for otosclerosis.

Many otosclerotic patients will have a mixed hearing impairment, the potential aetiologies of the sensorineural component being discussed below. In mixed impairments the Carhart notch tends to disappear (Figure 89.7). With increasing sensorineural hearing impairments it becomes increasingly difficult to mask the bone-conduction thresholds (Figure 89.8) and in severe, profound and total hearing impairments (Figure 89.9) to decide whether there is a conductive

TABLE 89.2 The magnitude of the Carhart effect (dB) from various authors (reprinted from Browning,[99] with permission)

Study	kHz			
	0.5	1	2	4
Carhart (1950)[95]	5	10	15	5
Gunderson (1973)[96]	12	12	12	9
Ginsberg et al. (1978)[97]	15	17	18	17
Gatehouse and Browning (1982)[98]	5	8	12	5

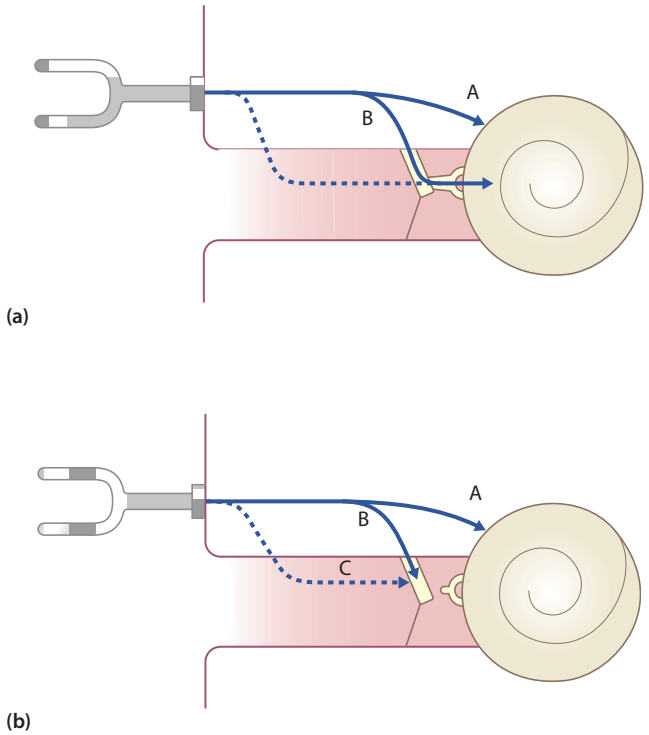

Figure 89.6 (a) The three normal routes of bone-conduction of sound vibrations to the inner ear: route A: via the skull bone; route B: via the ossicular chain; and route C: via the external auditory canal. In a normal ear, when the skull is vibrated by bone-conduction, it not only vibrates the cochlea via route A, but it also vibrates the tympanic membrane and ossicular chain (route B) and the air in the external auditory canal (route C). **(b)** In the presence of a conductive defect, the osseous route A is the only route for sound vibrations to reach the inner ear. When there is a middle-ear conductive defect, routes B and C are materially diminished in magnitude. Redrawn from Hannula et al.[83] with permission.

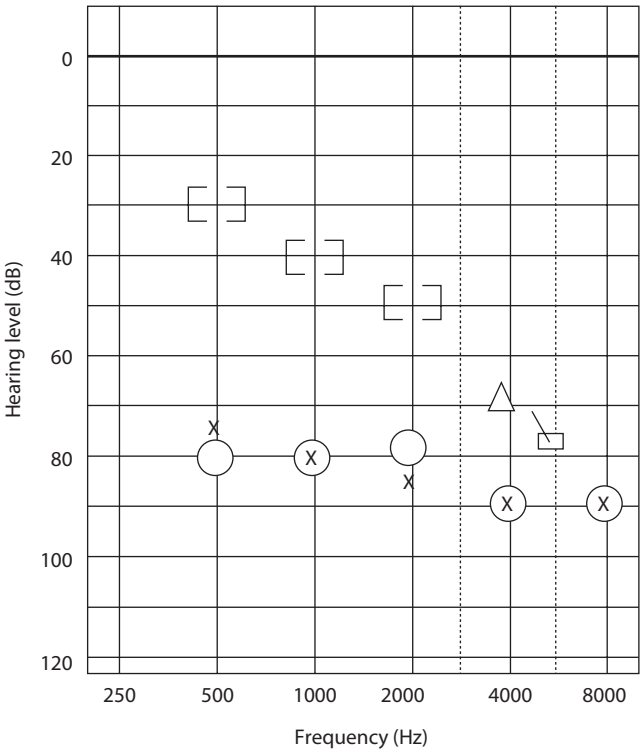

Figure 89.7 Audiogram showing a mixed hearing impairment, the conductive component being presumed due to clinical otosclerosis because the tympanic membrane is normal on otoscopy. The Carhart notch is hidden by the associated sensorineural hearing impairment. Redrawn from Browning,[99] with permission.

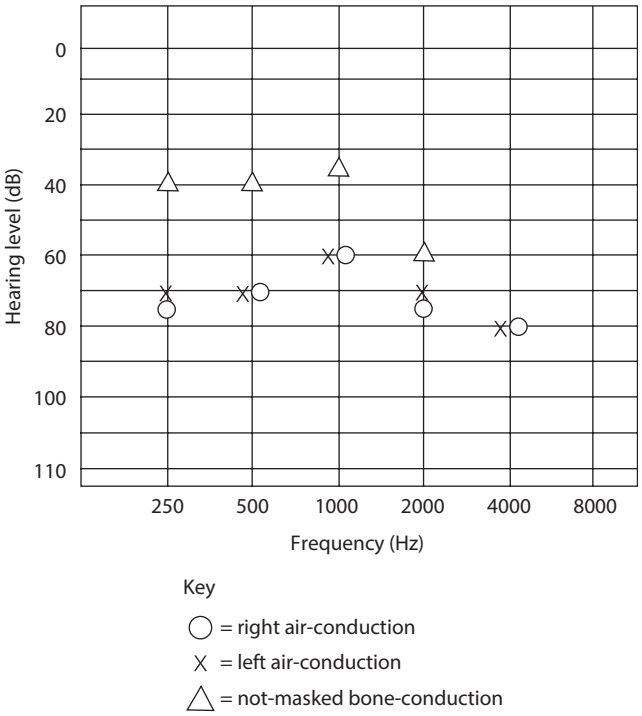

Figure 89.8 Audiogram of a patient with a bilateral severe impairment where it is not possible to mask the bone-conduction thresholds. One or both ears may have a conductive component to the impairment. Redrawn from Browning,[99] with permission.

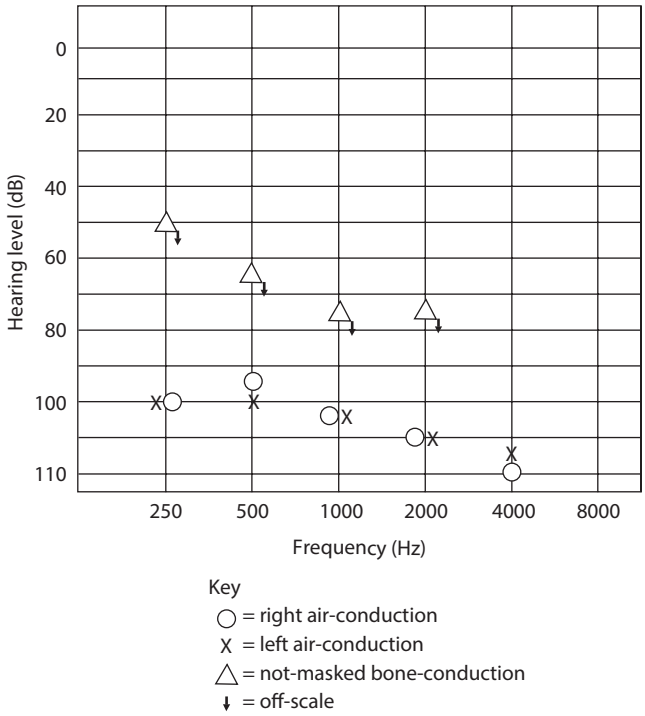

Figure 89.9 Audiogram of a patient with a bilateral profound impairment where bone-conduction thresholds are not recordable but there could be a 30 dB conductive impairment in one or both ears due to otosclerosis. Redrawn from Browning,[99] with permission.

component or not.[100] In these circumstances, various factors in the history or investigations can increase the certainty with which clinicians can come to a diagnosis of otosclerosis.

Given that the Carhart notch can be seen in any case of ossicular chain fixation it is perhaps not surprising that a recent literature review showed little to support the predictive value of the Carhart notch in the diagnosis of otosclerosis.[101]

HISTORY

The classic history is of a progressive hearing loss in early adulthood. In those with a severe or profound impairment, an earlier audiogram showing a mixed impairment or a history of a previous operation to improve the hearing as an adult will be suggestive of otosclerosis. A family history of hearing problems, unless it is clearly identified as being an otosclerotic history, covers too many potential aetiologies to be of value. A history of deterioration of the hearing during pregnancy is often cited to occur and indeed 50% of those with bilateral and 25% of those with unilateral otosclerosis will report such a change.[102] However, no data are available on how many individuals with hearing impairments due to other causes report such deterioration. The audiometric evidence for deterioration is retrospective and uncontrolled for time.[103] Certain features of a patient's history may suggest a diagnosis other than otosclerosis. These are early age of onset, no history of progression, associated discharge or trauma, associated vertigo.

TYMPANOMETRY

As might be expected, the compliance in ears with subsequently surgically confirmed otosclerosis is less than normal but the range is such that in an individual ear it does not add to the diagnosis.[104] The same comments also apply to multifrequency/multicomponent tympanometry.[105] If there is any doubt about there being otitis media with effusion as an alternative diagnosis, tympanometry is obviously then of value.

RADIOLOGY

High-resolution CT (HRCT) scanning is able to detect abnormal bone densities within the otic capsule. HRCT shows active otosclerosis as hypodense or lucent areas within the otic capsule, typically anterior to the oval window (**Figure 89.10**). The stapes footplate may be seen to be thickened. Other typical findings are narrowing of the oval and round window niches and a classic double ring sign around the cochlea. During the inactive sclerotic phase of disease, bone densities increase towards normal and CT diagnosis may be more difficult. Quesnel et al. compared HRCT with histology in cadaveric temporal bones from patients with known otosclerosis. Two blinded

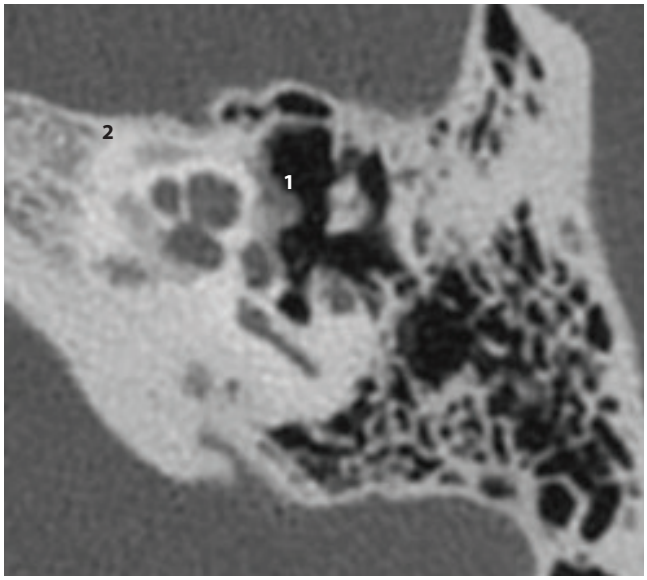

Figure 89.10 Axial CT scan of the left middle ear through the stapes footplate showing lucency anterior to the stapes footplate (1) and around the cochlear (2).

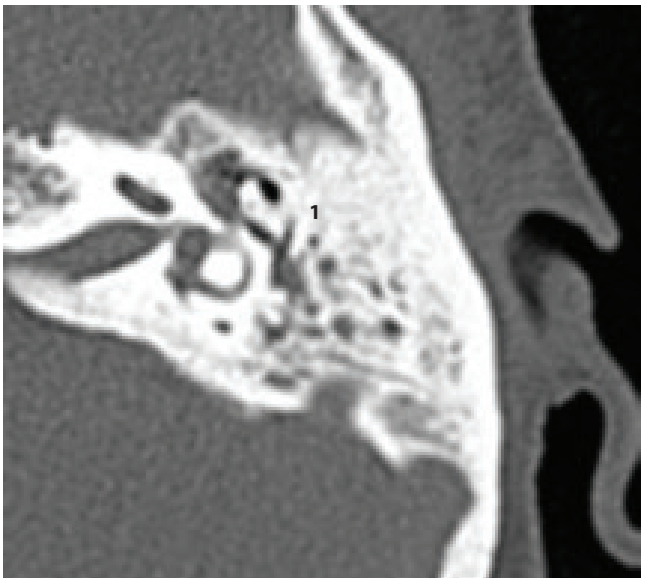

Figure 89.11 Axial CT scan of the left temporal bone showing the incus fused to the lateral wall of the attic (1).

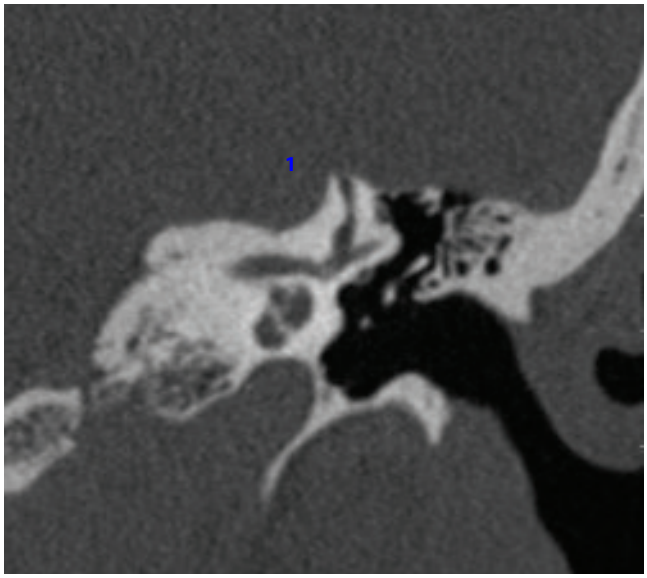

Figure 89.12 Coronal CT scan of the left temporal bone showing superior semicircular canal dehiscence (1).

neuroradiologists correctly identified 8 of 10 otosclerotic temporal bones from a group including 36 control non otosclerotic bones. There were three false positives where an area of lucency anterior to the oval window was due to soft tissue and not otosclerosis. This gives a sensitivity of 80% and specificity of 91.6% against the gold standard of histological diagnosis.[106] Various studies have compared CT and surgical findings with typical sensitivity of 70–80%. More recent studies with better CT scanning techniques using smaller pixel sizes have shown sensitivity for fenestral otosclerosis of over 90%.[107] With these improved sensitivities the case for routine CT scanning is growing, although many surgeons would not use CT scanning for classic cases of otosclerosis given the accuracy of the clinical assessment. CT does, however, have the ability to detect other pathologies such as malleus head fixation, incus fixation (**Figure 89.11**), superior semicircular dehiscence (**Figure 89.12**) and widened vestibular aqueduct as well as the extent of disease and anatomical variants. HRCT is therefore recommended if the diagnosis is in doubt, for example with early-age onset or associated vertigo. It is also of value if cochlear implantation is being contemplated. Pre-operative CT scanning is now obligatory in France prior to stapes surgery.

Cone beam CT scanning has the ability to resolve very thin slices down to 0.3 mm but with lower radiation doses than HRCT. Sensitivities appear similar to HRCT.[108, 109]

MRI scanning is useful if cochlear implantation is contemplated.

AUDIOLOGICAL ELIGIBILITY FOR SURGERY

Because clinical otosclerosis is a presumptive diagnosis in patients with a conductive hearing impairment and no evidence of other middle ear pathology, it is important that one is certain that there is indeed a conductive hearing impairment before deciding that an individual patient might benefit from surgery.

In the majority of patients, the pure-tone audiogram will be the audiological deciding factor provided this can be relied upon, particularly in the appropriate masking of bone-conduction thresholds. Traditionally, it was felt that there had to be at least an air–bone gap of 20 dB or more to benefit from surgery and the majority of stapes surgeons still use this cut-off. However, experience would suggest that an improvement in the hearing of less than 20 dB is appreciated by patients, particularly if they have a bilateral hearing impairment. Hence, experienced stapes surgeons may operate on ears with an air–bone gap of

10–20 dB, knowing that in a high proportion of them the air–bone gap will be closed.

More recently, some surgeons have been operating on patients with an air–bone gap of 10 dB or less. The concept here is that in reality there is the potential for a greater improvement in the air-conduction thresholds than 10 dB because of the Carhart effect.[110] The problem with this approach is that air–bone gaps of 10 dB or less may be artefacts of the audiometric test method. Hence, these authors suggest that there should be other evidence of a conductive hearing impairment, such as multiple audiograms, an absent acoustic reflex or appropriate tuning fork test results.

DIAGNOSIS OF COCHLEAR OTOSCLEROSIS

Two distinct situations exist when the diagnosis of cochlear otosclerosis may be made. The first is where there is a mixed impairment and the conductive component is due to clinical otosclerosis. The second is where there is a pure sensorineural impairment and aetiology is being sought.

In association with clinical otosclerosis

There is no reason why otosclerosis should protect against the majority of recognized aetiologies for a sensorineural impairment with the possible exception of noise trauma. It is therefore possible to compare individuals' bone-conduction thresholds with age-, sex- and socioeconomic-controlled population values. However, before doing this, they have to be corrected for their artificial depression due to the Carhart effect. The majority of papers do not do this. In addition, surgery can cause a sensorineural hearing impairment so the judgement can only be made on unoperated ears. When this is carried out, the data are again conflicting. Browning and Gatehouse found, on average, individuals with otosclerosis have no poorer thresholds than expected in the population.[111] However, both Topsakal et al. and Redfors and Moller also showed significantly greater sensorineural loss in non-operated otosclerotic ears than in age-matched controls.[112, 113] In post-operative studies examining progressive sensory hearing loss over time the data are again conflicting, with one 20-to-30-year-longitudinal study[114] showing the bone-conduction thresholds in patients after fenestration surgery for otosclerosis deteriorating with time at the same rate as the general population (1 dB every 2 years) but another with follow-up at 30 years showing significantly greater loss.[113, 115] Whatever the cause, there are undoubtedly a number of otosclerotic patients with a mixed hearing impairment, where the sensorineural impairment is considerably greater than expected from population data. Indeed, in cochlear implantation programmes, such patients make up approximately 1% of the population (see 'Cochlear implantation' below).

In the absence of a conductive impairment

To date, from the hundreds of temporal bones reported with histological otosclerosis, only three patients have been reported with a sensorineural impairment and no clinical otosclerosis in one or both ears. In these patients, the otosclerotic focus surrounds the cochlea without involvement of the oval window.[116, 117] On the other hand, there are many case reports of cochlear otosclerosis being diagnosed radiologically in individuals with a bilaterally normal middle ear and a pure sensorineural impairment. Evaluation of CT scans to identify differing areas of density is subjective and methods that calculate the density of various anatomical areas are superior. If this is carried out, the range of normal values overlaps that of patients with suspected pure cochlear otosclerosis.[118]

KEY POINTS

- Otosclerosis is the presumptive aetiology of a conductive hearing impairment in the presence of a normal, mobile tympanic membrane.
- Tympanometry does not generally aid the diagnosis of clinical otosclerosis.
- The case for pre-operative CT scanning is growing as scanning becomes more accurate.

NATURAL HISTORY

George G. Browning

CONDUCTIVE HEARING IMPAIRMENT

Ideally, to study the natural history of otosclerosis, one would like to follow up a cohort of young adults with serial audiometry over many years. This would enable the clinician to answer the following three questions that would be of clinical interest in the management of patients:

- How likely is unilateral otosclerosis to become bilateral with time?
- What is the average rate of progression of the magnitude of the air–bone gap in the better and poorer ears?
- Are there some individuals in whom the air–bone gap deteriorates and others in whom it does not?

Unfortunately, no study of this type has been identified. The main body of data available as an alternative way of trying to address these questions are surgical series that have been followed up for some years and report the non-operated otosclerotic ear as well as the operated ear. It is unfortunate that the operated ear, which in many instances will start as the poorer hearing ear, cannot be used to describe the natural history because the operation itself can have an effect on both the air- and bone-conduction thresholds. Reporting the natural history in the non-operated ear is likely to underestimate the magnitude of change in the air- and bone-conduction thresholds because in many instances it will be the better, and hence less affected, ear.

For an average of 9.5 years, Vartiainen et al.[119] followed up a series of patients that they had operated on one ear for

otosclerosis. In 122 of them, the other ear had clinical otosclerosis and their interest in reporting these ears was to see whether fluoridation of the water supply made any difference to the progression of the disease (see 'Fluoridation of drinking water' below). The 91 patients that had low levels of water fluoridation are those that are of particular interest because they are the larger group. Taking threshold averages over 0.5, 1 and 2 kHz, there was a yearly deterioration in the air-conduction thresholds of 2.1 dB, in the bone-conduction of 1.2 dB and the air–bone gap of 0.9 dB. Hence, one could postulate that the air–bone gap in an otosclerotic ear would deteriorate by around 10 dB every 10 years. The deterioration in the bone-conduction thresholds is just slightly greater than that which might be expected due to ageing and could be partly related to the Carhart effect.[120]

KEY POINTS

- From the limited data available in patients with unoperated otosclerosis, the air–bone gap and the bone-conduction thresholds both deteriorate by around 1 dB per year. Hence, the air-conduction thresholds will deteriorate by around 2 dB per year.

MANAGEMENT OPTIONS: FLUORIDE

George G. Browning and Christopher P. Aldren

FLUORIDATION OF DRINKING WATER

Sodium fluoride is a known inhibitor of osteoclast activity and so a stabilizer of bone turnover. It also leads to increased calcium deposition in otospongiotic foci and decreased bone remodelling.[121] This property makes it a potential treatment for otosclerosis and its use was first reported in 1964.[122] The release of cytokines from bony remodelling adjacent to the cochlear spiral ligament may be responsible for the sensorineural hearing loss sometimes seen in otosclerosis. Sodium fluoride has the potential to reduce this.

Flouridation of the drinking water to 1 mg/L in the town of Kuopio, Finland, between 1959 and 1992 allowed Vartiainen to compare patients exposed to fluoridated drinking water for an average of 21 years with those in the surrounding areas who had a natural low level 0.1 mg/L of fluoride in the drinking water with no added flouride. They found no difference in the prevalence of clinical otosclerosis over a 25-year period.[123] They also followed the change in hearing over an average of 9 years in the operated ears of patients who had had surgery for otosclerosis from the two populations. They found no significant difference in deterioration of bone-conduction or air-conduction over time in the operated ears. In the same patient population they were able to assess hearing loss in the non-operated ears. At presentation the hearing in the non-operated ear in the patients from the fluoridated water area was significantly better. Looking at those patients with >10 dB AB gap in the non-operated ear for an average of 9 years they noted a non-significant reduction in progression of the hearing loss in those in the area with fluoridated water.[120]

In another study comparing patients from areas of low and high water fluoride levels, those from the low area had a ×4 incidence of clinical otosclerosis.[124] However, their exposure was for all of their lives averaging 21 years and the level of the fluoride in the water was nearly twice as high at 1.9 mg/L as the low-fluoride areas. Targets levels for optimum flouride for dental health in the UK are 1 mg/L. It must be concluded that fluoridation of tap water to 1 mg/L has no impact on the prevalence of clinical otosclerosis but may slow the rate of deterioration of hearing in non-operated ears.

ORAL FLUORIDES

Flouridation of tap water gives a daily intake of 0.53 mg. However, oral fluoride supplements allow much higher doses to be given.

A number of case controlled series comparing patients with and without sodium fluoride supplementation are suggestive of benefit.[125, 126] In a double-blind Danish randomized controlled trial 43 untreated otosclerosis patients were given 40 mg sodium fluoride daily together with 500 mg of calcium gluconate and 400 units of vitamin D. The control group of 52 otosclerosis patients had the calcium gluconate and vitamin D but not the sodium fluoride. All patients had between 12 and 24 months of treatment. In the control group 13 of 52 saw their average air-conduction reduce by over 10 dB during the study which was significantly greater than 3/43 in the treatment group.[127] Unfortunately, no data were reported on the bone-conduction thresholds. It would appear that high-dose oral fluoride may decrease the rate of hearing loss in otosclerosis patients. There are no studies looking specifically at the optimum time period of treatment, however typically 2 years is recommended.

Data on side effects from the use of long-term high-dose sodium flouride come from the literature on osteoporosis treatment. Synovitis, gastrointestinal disturbance with pain and vomiting, painful plantar fasciitis and anaemia are commonly seen.[128]

The highest strength of sodium fluoride tablet available in the UK is 2.2 mg. This means that, to emulate the Danish study above, 20 tablets would need to be taken each day. This combined with the risk of side effects, the limited data on efficacy and the excellent results from stapedotomy mean that few UK surgeons currently use sodium fluoride. However, it may be considered in otosclerosis patients with progressive sensory hearing loss.

BIPHOSPHONATES

Biphosphonates are frequently used in the treatment of osteoporosis and Paget's disease. They are known to reduce bone remodelling and as such like sodium fluoride

may offer benefit in patients with otosclerosis. Early studies showed little benefit however a recent study using new third generation biphosponates showed a reduction in rate of progressive sensory hearing loss in patients with cochlear otosclerosis.[129] These drugs require further investigation but may reduce the deterioration of sensorineural hearing loss over time.

MANAGEMENT OPTIONS: HEARING AIDS

Peter A. Rea and Christopher P. Aldren

CONVENTIONAL HEARING AIDS

The importance of conventional hearing aids is not reflected in the number of publications on the subject: they make up less than 2% of the literature on otosclerosis.

Conventional hearing aids offer one of the four options in otosclerosis management, the others being no treatment, surgery and rarely bone-anchored hearing aids.

As a primary treatment, hearing aids are a particularly effective method of managing conductive hearing impairments. Hearing thresholds obtainable compare favourably with surgical outcomes. The choice of surgery or hearing aids in pure conductive hearing impairment depends on other factors: attitude to risk, aesthetic and comfort considerations, hearing-specific functional status and quality of life. Surgical risk is discussed under 'Management options: surgery' below. The perceived aesthetic disadvantages of hearing aids are particularly important in otosclerosis because of the relatively young population being treated. However, modern hearing aids can be very discreet and patients are often pleasantly surprised if they try them. Surprisingly little is published on hearing-specific health status and quality of life outcomes in the treatment of conductive hearing impairments. The limited literature available suggests that hearing-specific health status may be significantly improved by hearing aids. In contrast, quality of life measures are typically at population averages pre-treatment and, perhaps surprisingly, do not improve further.[130] Randomized trials comparing hearing aids to surgery are not available.

As the patient ages, the conductive impairment may become mixed with sensorineural impairment secondary to both age-related and cochlear otosclerosis. In this situation, recruitment may become a problem. Eventually, the level of hearing impairment may exceed the power of hearing aids alone. Suitable comparisons between hearing aids for mixed conductive and sensorineural impairments and surgical outcomes are not available.

FAR-ADVANCED OTOSCLEROSIS

Far-advanced otosclerosis (FAO) was first described by House and Sheehy in 1961 as a patient with otosclerosis with average air-conduction of over 85 dB and bone-conduction unmeasurable due to limits of audiometric equipment.[131] These patients are beyond the help of conventional air-conduction aids alone and can be managed in one of three ways: stapedectomy and subsequent conventional hearing aids, cochlear implantation or the new direct acoustic cochlear stimulation (DACS) device. A careful history to distinguish FAO from a pure sensorineural hearing impairment is essential. Clues include the timescale of the hearing impairment, family history, previous audiograms showing an air–bone gap, normal speech and CT evidence of cochlear otosclerosis.

A patient with FAO may, for example, have a sensorineural impairment of 65 dB HL with an air–bone gap of an additional 60 dB. This may show a complete hearing impairment on an audiogram. Stapedectomy, however, may raise the air-conduction threshold to 65 dB HL. This could be satisfactorily aided. Case series report successful hearing aid use post-stapedectomy in 46–82% of these patients.[132] While cochlear implantation gives the best overall results in these patients, it is much more expensive and so in many cases stapedotomy with conventional hearing aid offers a good first-line treatment, with cochlear implantation reserved for failures.[133] Following a review of the literature, Merkus et al. produced an algorithm to aid decision-making. Patients with pre-op speech discrimination <30%, more severe changes on CT scanning and small air–bone gaps do worse with stapedotomy and should be considered for primary cochlear implantation.[134]

During post-stapedectomy rehabilitation with hearing aids it is likely to be the sensorineural rather than conductive hearing loss that is being aided. Functional recovery, as demonstrated by word recognition scores, may continue for months or years post-surgery. It has been proposed that this reflects acclimatization or recovery from auditory deprivation.[135] Thus, both improved auditory thresholds and recovery from auditory deprivation may be noted with dual therapy.

As a 'rescue' treatment many years after surgery for otosclerosis, hearing aids are likely to be needed frequently. Truly long-term figures are notoriously difficult to obtain. From their series of large fenestra stapedectomy, Smyth and Hassard[136] estimated a requirement for a hearing aid on average 13 years after surgery and at 21 years after small fenestra surgery. Shea's figures[137] showed the need for a hearing aid at 30 years post-surgery in 30% of patients in whom initial stapedectomy had been successful. In a study following up stapedectomy patients at 30 years after surgery Redfors and Moller found that 66% of ears had moderate to profound hearing loss worthy of aiding. They also noted that the progression of sensorineural hearing loss was greater in operated compared with than the non-operated ears.[113]

It has been argued that all patients considering surgical treatment of otosclerosis should undergo a reasonable trial of hearing aid use to allow a fully informed consent to be obtained,[138] though this view is far from universally held. Informed consent requires available options to be discussed in a manner a patient will understand, so a trial of an aid may be the best method of addressing this. It is certainly a luxury to be able to offer a 'risk-free trial' of one of the options.

BONE-ANCHORED HEARING AIDS

Bone-anchored hearing aids (BAHA) have been proposed as an alternative method of managing otosclerosis in a limited number of situations. Selection criteria are similar to those typically used in BAHA programmes for other conditions. A specific benefit is that they do not produce the risk of a dead ear that may result from stapedectomy. An only hearing ear with otosclerosis combined with difficulty using a conventional aid, or a post-fenestration cavity, would be typical scenarios. Outcome data are limited. Objective testing of free-field thresholds and speech discrimination scores appears similar to conventional aids. Subjective outcomes including comfort and sound quality have been reported in a small series of patients with otosclerosis to be better with a BAHA than with a conventional aid.[139]

DIRECT ACOUSTIC COCHLEAR STIMULATION

The direct acoustic cochlear stimulation (DACS) device is of use in patients with mixed hearing loss where a successful stapedotomy alone would not allow the patient to manage without a hearing aid. The device consists of an active middle ear implant attached to a stapes prosthesis. First described by Hausler et al. in 2008,[140] the DACS allows direct acoustic stimulation of the perilymph via the stapes prosthesis. Subsequently developed by the Cochlear company, the Codacs™ has recently been reported to give good hearing in 14 patients. Indications were a minimum average bone-conduction of over 30 dB and with an additional air–bone gap of over 30 dB. Average pre-op unaided hearing and conventional hearing aided thresholds were 86 dB and 52 dB respectively. Post-operative aided Codacs™ thresholds were 37 dB.[141]

COCHLEAR IMPLANTATION

Patients with FAO or failed stapedotomy may be candidates for cochlear implantation and these patients make up approximately 10% of adult cochlear implant programmes. Their audiological results are comparable to those of non-otosclerotic patients receiving cochlear implants. Rea showed speech discrimination scores (using binaural CID sentences) improved from 12% (range 0–52%) pre-operatively to 88% (range 22–100%) post-operatively,[142] results which are mirrored in other series.

However, there may be problems in electrode placement due to otosclerotic ossification of the round window or basal turn of the cochlear which may necessitate extra drilling. Ossification of the apical region of the cochlear can lead to incomplete electrode placement. Non-auditory stimulation from the cochlear implant is also reported to be commoner in otosclerosis patients. Most commonly this is facial twitching but also can be otalgia and dizziness. This is thought to be due to demineralization of the otic capsule.[143] These pitfalls are summarized in Table 89.3.

TABLE 89.3 Pitfalls of cochlear implantation in otosclerosis

Source	Pitfalls
Resulting from previous otosclerosis surgery	Incus subluxation Severe middle ear adhesions Tympanic membrane vulnerable at site of bony curettage Ossification of scala tympani from post-stapedectomy labyrinthitis
Resulting from disease process	Obliteration of round window by spongiotic bone Incomplete electrode placement 'Looping' of electrode through soft spongiotic bone in cochlea Facial nerve stimulation by electrodes within cochlea

BEST CLINICAL PRACTICE

✓ For best clinical practice in relation to hearing aids, see Chapter 54, Hearing aids, and Chapter 93, Bone-conduction hearing aids.

FUTURE RESEARCH

➤ No randomized trials can be found comparing outcomes using hearing aids versus stapedectomy.
➤ Evidence for the role of bone-anchored hearing aids remains limited.

KEY POINTS

- Conventional hearing aids are effective in the management of hearing loss in otosclerosis.
- Their role is likely to increase with technological advance.
- A trial should at least be discussed prior to contemplating surgery.
- They may be used in addition to stapedotomy in FAO.

MANAGEMENT OPTIONS: SURGERY

Peter A. Rea and Rinze A. Tange

HISTORICAL PERSPECTIVE

Three distinct phases can be identified in the development of surgery for otosclerosis: mobilization and extraction of the stapes, in late 19th-century Europe; fenestration of the horizontal semicircular canal in the first half of the 20th century; and mobilization of the stapes revisited, along with stapedectomy and stapedotomy with prostheses in the latter half of the 20th century.[144, 145]

In 1876 Kessel described his work on the columella of pigeons, and the stapes of dogs and humans. He removed the footplate 'allowing a new membrane to form'. He, and

other early otological adventurers, also removed the malleus, incus and tympanic membrane to 'free up' the footplate. Miot and Boucheron from Paris reported cases in the 1880s in which the stapes was rocked to mobilize it after removal of part of the tympanic membrane. They noted the technique to be most successful in early ankylosis. Their efforts were limited by poor surgical equipment, poor illumination, lack of magnification, lack of antibiotics and consequent risk of deaths from meningitis, lack of adequate or standardized audiometry and lack of understanding of the functioning of the ossicles as shown by the 'ossiculectomy' technique described. While these surgeons were perhaps ahead of their time, not surprisingly due to the limited success and risks of serious complications stapes surgery fell into disrepute and in 1900 Siebenmann, Politzer and Botey stated 'mobilization of the stapes in otosclerosis is not only useless, but often harmful'. This was to remain the consensus view for the next 50 years.

Fenestration of the horizontal semicircular canal can be traced back to 1897, and was developed by Sourdille (1930) through his multistage operations. It was Julius Lempert in 1938 who described a single-stage endaural technique that became the mainstay of otosclerosis surgery for two decades. There was a 65% chance of the fenestration remaining patent and a 2% risk of serious complication. On long-term follow-up over half the patients had hearing better than prior to surgery.

Modern stapes surgery re-emerged in 1952 when Rosen had a patient whose hearing was restored following 'palpation' of the stapes. Stapes mobilization became accepted as the treatment of choice for those with only partial ankylosis, though re-ankylosis tended to develop a few years later. Fenestration was reserved for footplates that could not be mobilized. John Shea rediscovered the stapedectomy procedure and reconstructed the sound transmission system with a prosthesis. The first prosthesis inserted in 1956 was a replica of a normal human stapes. A huge backlog of untreated otosclerotic ears was operated on in the following decades, during which time the technique evolved. In the first decade of stapedectomy, the fenestration procedure fell from favour. In the next 10 years, the use of prostheses and a living oval window seal gained popularity, and in the subsequent decade the debate over small versus large fenestra surgery emerged. More recently, technological advances and research contributions have refined our approach, but the caseload is diminishing.

CONTRAINDICATIONS TO SURGERY: CONTROVERSIES IN OTOSCLEROSIS SURGERY

The smaller number of operative cases, coupled with increasing numbers of otolaryngology trainees with some exposure to this potentially demanding surgery, raises the question, 'who should be performing stapes surgery?' Opinions vary widely. The evidence suggests that there is a significant association between experience and both technical ability and surgical outcomes for stapes surgery.[146] While rules are not established, it seems sensible that only a limited number of surgeons need training in this operation, and only a limited number need to perform it. A requirement for individuals to audit their results is emphasized in the literature.

Returning to the patient, the indications for surgery have been discussed under 'Diagnosis' above. Controversies, or 'when not to operate' above, will be reviewed here. Caution should be exercised when interpreting the survey figures quoted for current practice: they do not necessarily equate to best practice.

Age

Large series of stapes surgery report cases between 6 and 92 years of age. Surgery in children represents only a very small proportion of operations. This reflects both the common use of hearing aids to manage otosclerosis in children and the rarity of cases in this age group. We reviewed the five largest paediatric series covering 200 cases, and found post-operative air-conduction was within 10 dB of pre-operative bone-conduction in 89%. One series followed their children for a mean 11.6 years post-operatively. None redeveloped a conductive impairment, and sensorineural thresholds deteriorated at a mean 0.7 dB (range 0–2.3 dB) per year.[147] Special precautions are required when contemplating surgery on children with a conductive hearing impairment, however, in particular the risk of congenital middle and inner abnormalities. In the presence of a mixed hearing impairment, CT imaging of the temporal bone is advised to rule out inner ear abnormalities that may be associated with a cerebrospinal fluid gusher, in particular X-linked progressive mixed hearing impairment. The incidence of obliterative otosclerosis, at 26–41%, is also reported to be much higher in children than adults having stapes surgery. The results of surgery at the other end of the age spectrum, aged 70–92 years, are reported to be similar to those in a younger adult population.[148] In summary, caution is required when considering surgery in children, while no upper age limit needs to be applied in adults on technical grounds alone.

Occupation and leisure activities

Occupation and leisure activities that may predispose to barotrauma are important. Historically, military pilots were grounded after surgery, but they may now fly military jets in several countries post-stapedectomy. Commercial air travel, snorkelling, scuba diving, strenuous activities and parachuting have also been cautioned. Clinical evidence of the feasibility of such activity was suggested by a study from The House Ear Clinic. Questioning 208 patients who had snorkelled, scuba dived or parachuted following stapes surgery, no immediate relationship to otological difficulties was identified.[149] No consensus exists between surgeons regarding advice to patients. In the UK, 18% of otolaryngologists give no flying restrictions, while 82% suggest avoidance for between 1 and 24 weeks.[150] In a survey of members of the American

Otological Society, 12% gave no restrictions on flying post-stapes surgery, 20% recommended a 2-day restriction and 60% suggested 2 weeks or more. Similarly, with scuba diving, 35% recommended restrictions for between 1 and 6 months, while more than 50% recommended permanent abstinence.[151] The suggested time delay is said to allow the connective tissue seal time to mature. A post-operative test has now been proposed: applying tympanometric pressure of 400 mm H_2O to the ear while recording nystagmus matches the maximal possible displacement of the prosthesis. If pathological eye movements are not evoked, and the appearances of the tympanic membrane are normal, it is suggested diving or parachuting can be safely performed.[152]

Ménière's disease and general vestibular symptoms

Ménière's disease is often stated as a contraindication because of the proximity of the distended saccule to the footplate. A small clinical and temporal bone study suggested that the saccule did not contact the footplate in patients with bone-conduction levels of 35 dB HL or better at 500 Hz and with no high frequency impairment, concluding surgery could be performed within these constraints.[17] Caution is, however, clearly required. More general vestibular symptoms do not appear to be a contraindication to surgery. This is supported by a large temporal bone study that found a strong association between loss of Scarpa's ganglion cells and vestibular symptoms in patients with otosclerosis, suggesting neuronal degeneration and not hydrops to be the cause.[15] Clinical studies have shown no difference in hearing outcomes between patients with or without pre-operative vertigo.

Unilateral otosclerosis

Whether to operate on unilateral otosclerosis is contentious. It is worth remembering that unilateral conductive hearing impairment is less likely to be caused by otosclerosis than bilateral impairment. A survey in the UK revealed 81% of consultants may operate for unilateral otosclerosis.[139] However, a patient's disability is mainly determined by the hearing threshold in the better hearing ear. So, to be of maximum benefit, surgery will have to provide symmetrical hearing in this group: in effect closing the post-operative air–bone gap to within 10 dB. The initial bone-conduction will also have to be near normal, or be able to be normalized after surgical correction of the Carhart effect. Most papers quote this degree of closure being achieved initially in 80–95% of procedures but, as will also be shown under 'Hearing outcomes' below, longer-term results may not be as good. Patients may still, however, have some benefit in certain circumstances even when symmetrical hearing is not achievable.

Second-side surgery

Second-side surgery is equally controversial. Seventy-five percent of UK consultants surveyed would perform bilateral stapes surgery.[150] The perceived risk is of delayed bilateral cochlear impairment. Total cochlear impairment may occur many years after a stapes procedure, but the risk is low, at around 1%. The potential benefits are twofold. A second-side operation gives both a greater chance of obtaining one normally functioning ear, and also of gaining binaural hearing. This has been demonstrated by de Bruijn et al. and is clearly illustrated in **Figure 89.13**.[153] The incremental benefits to the individual appear significant,

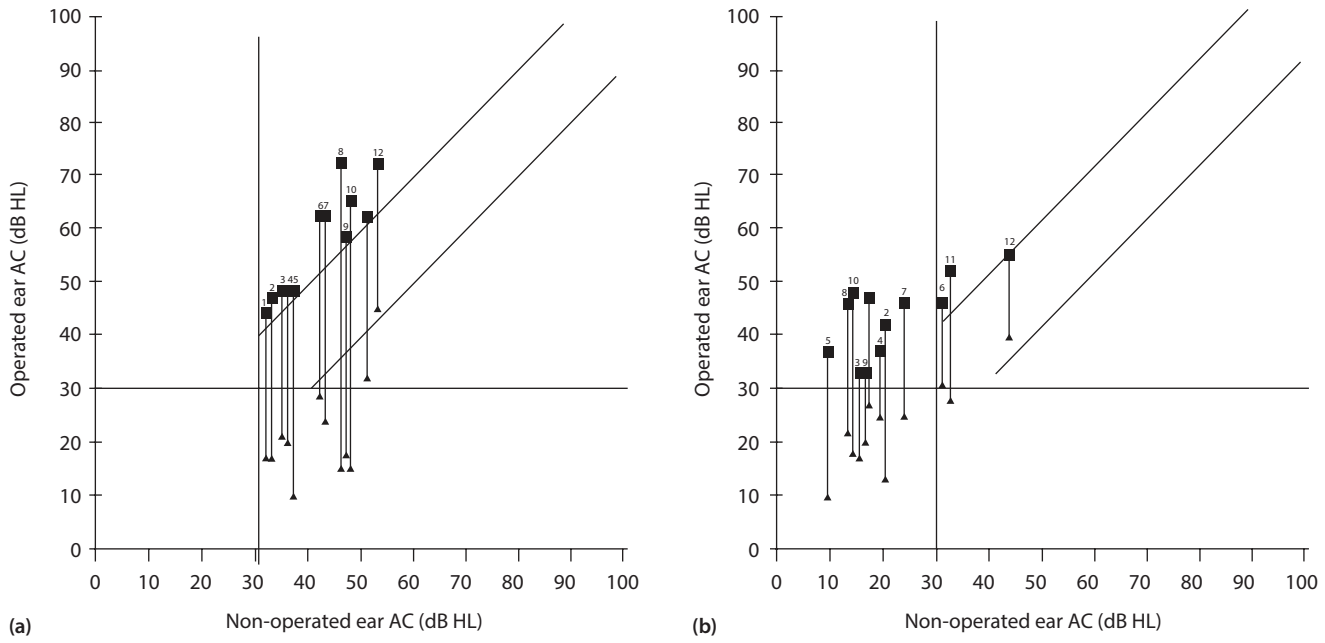

Figure 89.13 Pre- (■) and post-operative (▲) air-conduction (AC) thresholds. Each patient is indicated by an Arabic numeral. **(a)** Results from stapedotomy on the first side. **(b)** Results after stapedotomy on the second side. Reproduced from Vartiainen et al.,[119] with kind permission of S. Karger AG, Basel.

but are less with second-side surgery than with first.[154] Using the American Medical Association (AMA) criteria it was found that the 'Binaural Hearing Impairment Score' fell from 26% to 10% after surgery to one side, and from 11% to 7% after second-side surgery. The 'Impairment of the Whole Person Scores' fell from 9% to 4% and 4% to 2%, respectively.

Air–bone gap

Twenty dB is traditionally taken as the minimum air–bone gap before considering surgery. Some expert stapes surgeons will operate on patients with air–bone gaps of as little as 10 dB in the belief that overclosure will allow a relatively greater improvement in air-conducting thresholds. One series of 136 stapes procedures on patients with air–bone gaps of 10 dB or less equalled or overclosed the pre-operative bone-conducting threshold in 90% of cases, producing a mean air-conduction improvement of 17 dB. It is worth noting that a further 18 patients in this series did not have stapes surgery performed at all at the exploratory tympanotomy, suggesting that diagnosing otosclerosis may be more difficult in this group.[110]

Other factors

A number of other factors are frequently cited. General health and safety of anaesthesia may be significant. Active infection in the outer or middle ear and pregnancy are absolute contraindications to surgery. Whether surgery should be deferred until no further childbirth is planned is debatable. Lippy et al. looked at the hearing results before and after surgery for otosclerosis in women with and without children and found those with children were slightly better. No correlation between the number of children or breastfeeding with hearing loss was seen.[155] Eustachian tube dysfunction is cited as a potential contraindication though quantifying this is not clearly described. Active otosclerosis as indicated by the 'Schwartze sign' is quoted as a contraindication, though much of the evidence is anecdotal. Diabetes has been considered a relative contraindication, though this is not supported by a literature review.

SURGICAL TECHNIQUES

Medical prophylaxis

The ear is prepared with an aqueous antiseptic solution. There is no evidence to support the use of steroids or antibiotics peri-operatively. Indeed, the use of prednisolone has been reported to increase post-operative vertigo.[156]

Anaesthesia

Stapes surgery may be performed under either local or general anaesthesia. A surgeon's personal experience strongly influences the decision. In the UK, over 90% of procedures are performed under general anaesthesia but local anaesthesia is much more popular in Europe. There is no evidence to support superior hearing results or differences in post-operative vertigo with either anaesthetic technique.[157]

General anaesthesia has the advantages of flexibility if complications or difficulties are encountered, and of a motionless operative field. Hypotensive anaesthesia is useful to reduce bleeding.

Local anaesthesia is also generally well tolerated. Short-acting intravenous analgesia and sedation may be given at the beginning of surgery, while infiltration of local anaesthetic (1% lidocaine) and dilute adrenaline (1 : 30 000–1 : 100 000) is performed. Initial infiltration of the posterior wall of the external auditory meatus via the postaural sulcus is followed by slow direct infiltration of the canal skin just lateral to the bony and cartilaginous junction. A pretragal injection may also be made to reduce discomfort if a retractor is used. Some surgeons recommend sedation throughout the procedure; others prefer the patient fully awake to prevent movement on sudden arousal. Local anaesthesia allows the patient to report dysequilibrium, which may be useful in revision surgery where adhesions can extend into the vestibule. Confirmation of hearing restoration after prosthesis placement is also possible as the surgeon talks to the patient. Difficulty may result if complications are encountered during surgery, in particular those that may induce vertigo. Transient facial palsies may result from the infiltration. Patients may complain of the noise, dizziness, anxiety, backache, claustrophobia and discomfort.

Exposure

The surgery can usually be performed through a purely permeatal approach although some surgeons use an endaural incision. When using a permeatal approach a speculum holder is very useful to stabilize the speculum and give a stable platform to allow the surgeon to stabilize his or her hands. A tympanomeatal flap is elevated from 7 o'clock to 12 o'clock (in the right ear), hinging forwards just posterior to the handle of the malleus. The chorda tympani nerve is gently freed from any mucosal folds. The posterosuperior bony annulus is reduced with curettes, drill or hammer and gouge, further releasing the chorda tympani if required. A heavy hook can be useful to remove the bony covering of the chorda tympani and liberate the nerve. Enough bone should be removed from the annulus to expose the stapes, oval window, facial nerve and the base of the pyramid.

Establishing the diagnosis

Anatomical anomalies which may compromise surgery, such as a persistent stapedial artery or overhanging facial nerve, should be identified, as should alternative causes of the hearing impairment such as tympanosclerosis. The stapes superstructure should be gently palpated to check for fixation of the footplate. The diagnosis is often clearer after disarticulation of the incudostapedial joint. The footplate and round window should be examined for evidence of otosclerosis, in particular very extensive disease.

If there is complete obliteration of the footplate, a drill-out of the footplate will be required and inexperienced surgeons may choose not to proceed. Total round window obliteration is rare, occurring in less than 1% of operative cases, not easily corrected, and associated with poor outcome. The malleus should be palpated to test for fixation of the malleus head, anterior ligament and malleoincudal joint. Again, this assessment is more easily performed after disarticulation of the incudostapedial joint.

Restoring the sound transmission mechanism

The historical review described many ways in which sound transmission may be restored across the stapes footplate. While variations on all these themes are still practised, stapedotomy is now used most widely. The surgical methods will be outlined first. A more detailed outcomes review of specific technical aspects is made under 'Hearing outcomes' below.

Stapedectomy and partial stapedectomy

The steps in a stapedotomy are shown in Figure 89.14. First, the incudostapedial joint is divided using a joint knife. This should be inserted from the posterior aspect of the joint and moved anteriorly as the stapedius tendon will reduce movement of the stapes superstructure. The mobility of all ossicles is then reassessed to make sure the stapes is indeed fixed and that a fixed malleus is not missed. The stapedius tendon is now divided with a laser, scissors or microhook. The stapes superstructure may now be removed by fracturing the crura down, away from the facial nerve, but it is better to first divide the posterior crus with a laser or crurotomy scissors to reduce the risk of mobilizing the footplate. If possible, the anterior crus should also be divided prior to removing the stapes. This may be hidden from view but can be accessed by feel using a handheld laser. The laser should be angled away from the facial nerve. The distance between the footplate and the incus should now be measured. It is most common to measure from the undersurface of the incus to

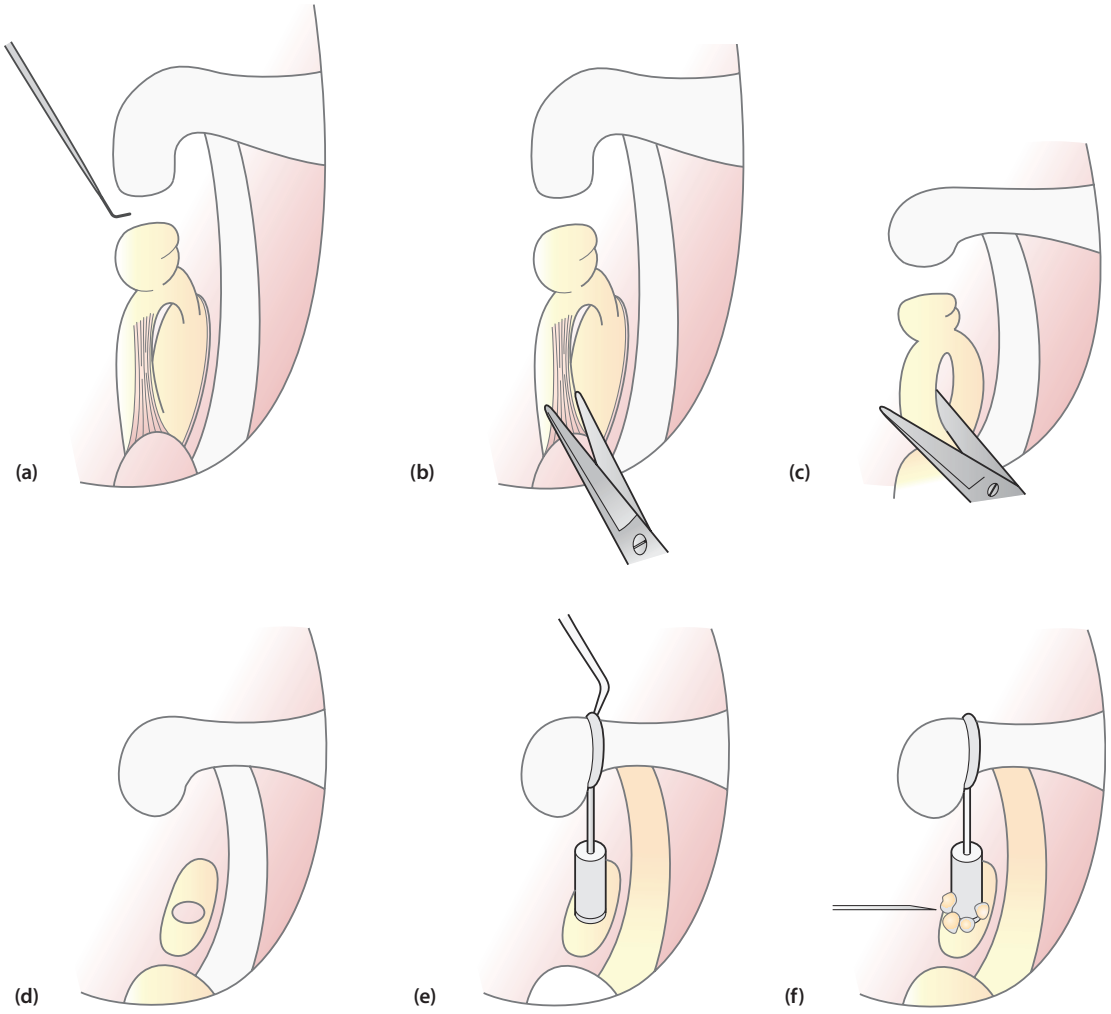

Figure 89.14 Steps in stapedotomy. **(a)** Following disarticulation of the incudostapedial joint, a fixed footplate is confirmed. **(b)** Division of the stapedius tendon. **(c)** Division of the posterior crus of the stapes using crurotomy scissors or a laser followed by down fracture of the crura. **(d)** Stapedotomy drilled in posterior third of the footplate. **(e)** Following insertion of the prosthesis, final adjustments are made and crimping carried out if required. **(f)** Packing around the footplate with fat or connective tissue.

the footplate. If the footplate is thickened, the measurement should be made again after the footplate is thinned just before the stapedotomy is performed. Manufacturers do differ in their labelling of prostheses, though the length is usually from the bottom of the loop. The functional length of the piston is from the upper surface of the lower half of the loop to the tip of the shaft. It therefore is the sum of the shaft length and the thickness of the loop material. For wire pistons the thickness of the loop material is negligible; for the Teflon loop piston this is 0.5 mm and has to be taken into consideration when cutting the shaft. The prosthesis selected should be 0.25 mm longer than the distance from the undersurface of the incus to the surface of the perilymph to allow sufficient penetration. This will usually result in a 4.25 mm, 4.5 mm or occasionally 4.75 mm prosthesis being selected.

The stapedotomy should be made at the junction of the middle and inferior thirds of the central portion of the footplate where the distance between the underside of the footplate and membranous labyrinth is greatest.[18] It may be made with a laser, electrical microdrill or handheld perforator. The perforation should be slightly wider than the prosthesis. If a 0.4 mm prosthesis is being used, it is usual to fashion a perforation of approximately 0.5–0.6 mm. The tighter the fit, the less the need for a connective tissue seal. However, if too tight, the hearing will be reduced as movement of the prosthesis will be impaired. In thick footplates the perforation should be of sufficient size to prevent the prosthesis touching the side of the hole, especially if it cannot be suspended absolutely perpendicular to the footplate. An interposition graft is placed over the footplate perforation at this point if used. If a Teflon loop is chosen, it must first be opened out on the shaft of a middle ear needle and then positioned on the incus with the help of crocodile forceps or an otological suction tube, where it will close around the long process of the incus. The shaft is simultaneously positioned in the footplate perforation. Wire loops will need crimping, or closing with laser or diathermy in the case of certain alloys. The piston is then assessed for adequate tightness at the incus and length at the footplate. Blood, fat or a connective tissue seal is usually then placed around the footplate perforation in an attempt to seal it, if a vein graft has not been placed over the stapedotomy first (this is discussed further below under 'Hearing outcomes'). The tympanomeatal flap is then replaced and the external ear canal packed.

Stapedectomy has fallen in popularity as stapedotomy has risen, though it was still the technique of choice for 19% of UK otolaryngologists in 2002.[150] The approach to the footplate is the same as for stapedotomy (**Figure 89.15**). A control hole is made in the footplate. The whole footplate or more typically the posterior third is removed with picks. The defect is covered with a connective tissue graft, most commonly vein from the forearm, and the prosthesis placed on the graft and suspended from the long process of the incus.

Footplate mobilization

In the 1950s, Rosen developed the stapes mobilization technique, but refixation occurred in months. In 1956, Fowler developed the anterior crurotomy technique with similar results. A recent variation is the laser stapedotomy minus prosthesis (STAMP) procedure. All these techniques depend on a lack of ankylosis at the posterior stapediovestibular joint. The laser procedure described by Silverstein et al. uses a handheld laser probe to vaporize the anterior crus of the stapes and perform a linear stapedotomy across the anterior third of the footplate. The stapes mobilizes if otosclerosis is confined to the anterior third of the footplate. It is claimed to be possible to achieve this in one-third of operative cases.[158, 159]

Revision surgery

Revision surgery is more technically challenging than primary stapes surgery. The clinical indications for revision operations are summarized in **Table 89.4**, while the discussion that follows will outline the possible findings at revision surgery. Three themes emerge from reviewing the literature. First, local anaesthetic is more frequently, though not exclusively, described as being advantageous. This is because the presence of adhesions between the prosthesis or footplate graft and the membranous labyrinth may induce vertiginous symptoms on manipulation of the prosthesis during revision surgery under local anaesthetic. This may prevent the surgeon further traumatizing the membranous

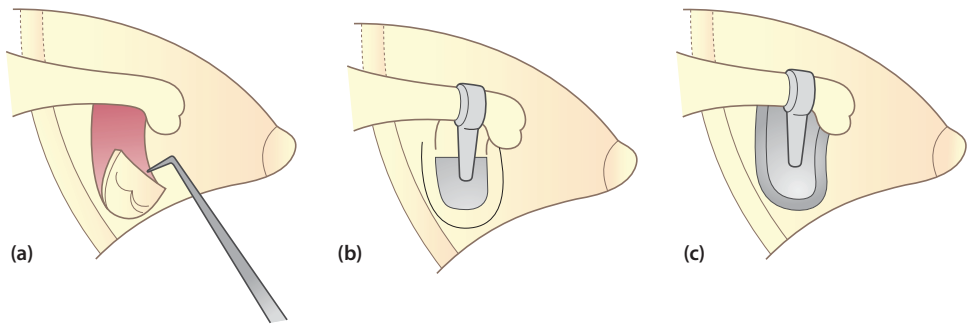

Figure 89.15 Steps in stapedectomy. **(a)** After division with picks, the posterior footplate fragment is removed. **(b)** If the anterior fragment remains fixed, the partial oval window defect is covered with vein or fascia and the prosthesis positioned. **(c)** If the anterior footplate has become unstable, it is removed and a larger graft used to cover the oval window.

TABLE 89.4 Pre-operative indications for revision stapes surgery in 522 cases (reproduced from Lippy et al.[160] with permission)

Indication	Cases (%)
Conductive hearing loss	92.5
Dizziness	2.5
Sensorineural hearing loss/perilymph fistula	1.9
Far-advanced otosclerosis	1.7
Distortion or vibration	1.1
Previous fenestration	0.2

labyrinth and so prevent a dead ear. Second, a much wider variety of surgical techniques may need to be employed to deal with the related ossicular pathology. Third, many centres recommend the use of lasers for revision surgery. Advocates state that vaporizing middle-ear adhesions with a laser allows more accurate assessment of the underlying pathology, aids removal of a non-functioning prosthesis, and allows a new fenestration to be fashioned without manipulating the footplate. These variables will be analyzed under 'Hearing outcomes' below.

PERI-OPERATIVE HAZARDS

Surgical approach

The external auditory canal may be excessively narrowed by pathology such as exostoses. While on occasions it may be necessary to correct these in a separate operation, it is frequently possible to do both operations at once.

Tympanic membrane perforation is reported to occur during approximately 2% of stapes operations. The procedure need not be abandoned as the perforations are usually small tears which can easily be repaired with an underlay myringoplasty. A spare piece of vein from a vein graft makes an ideal repair material but tragal perichondrium can also be used. Long-term results are unchanged.[161]

Anatomical

The chorda tympani nerve needs to be gently displaced from the operative field. This may require extended bony curettage. The facial nerve is dehiscent above the oval window in approximately 10% of ears. It may rarely herniate down over the oval window. In the former case, caution is needed. In the latter, surgery may need to be abandoned although a bucket handle prosthesis which sits under the lenticular process often allows a better angle with the shaft of the prosthesis coming from further inferiorly than a standard prosthesis. Care should be taken at revision surgery where a dehiscent nerve may be embedded in fibrous tissue and vulnerable as this is cleared. The facial nerve canal may also overhang the footplate limiting surgical access. Again, a bucket handle prosthesis can be useful in this situation.

Major vascular anomalies are rare. An aberrant internal carotid artery needs no further elaboration. A persistent stapedial artery may run from the facial canal between the stapedial crura. This may obstruct safe access and cause troublesome bleeding. There are reports of safely dividing smaller vessels and proceeding with surgery. Anatomical accounts of the stapedial artery giving segmental supply to the facial nerve and even brainstem are noteworthy for the brave contemplating dividing larger vessels.

Access to a narrow oval window niche can be improved in selected cases by drilling on the promontory with a microdrill, without evidence of significant sensorineural impairment in published series.

Other diagnoses

Congenital abnormality, fracture or post-inflammatory fixation or erosion of the ossicles must be identified. Their management is beyond the scope of this chapter.

The management of tympanosclerotic fixation of the stapes footplate remains controversial and to some is a contraindication to surgery. It has been historically considered to have a high rate of post-operative sensorineural hearing impairment, the highest reported being 26%, though this assumption stems from only a small proportion of the published series. We reviewed 14 case series totalling 382 stapedectomies and stapedotomies. Dead ears are reported in 2.6%. Surgery may need to be staged as tympanic membrane perforation frequently coexists. Surgical techniques are also varied because of the frequent associated fixation of the other ossicles. Consequently, a total ossicular replacement prostheses is often required. Hearing outcomes are inevitably not as good as with surgery for otosclerosis. Vincent et al.[162] clearly reported series showed closure of the post-operative air–bone gap to 10 dB in 39% and 10–20 dB in a further 31%. Only 22% achieved normal bilateral hearing on the Glasgow Benefit Plot.

Osteogenesis imperfecta has also traditionally been associated with poorer stapedectomy outcomes than for otosclerosis. This in part reflects the progressive mixed nature of the hearing impairment that has been shown to worsen late outcomes.[163] There are also higher risks of a floating footplate and unusual ossicular or tympanic ring fractures. Authors of the larger case series conclude surgery is a reasonable alternative to hearing aids, particularly when hearing aid use alone does not provide adequate amplification.[164]

Ossicular problems

Ossicular problems may arise as a complication of surgery or be identified in combination with footplate fixation. The incus may be displaced during curettage of the bony annulus or instrumentation of the oval window. If it can be maintained in its anatomical position, an incus to footplate prosthesis can still be employed, otherwise a malleostapedotomy will be required. Congenital or inflammatory fixation of the incus may be encountered. Incus–malleus fixation has been reported in 1% of stapedectomies.

Malleus head fixation is typically reported in primary otosclerosis surgery at a rate of 1%, though Causse quoted 10.6%.[165] This may reflect how carefully it is sought. It has become an area of particular interest following the work of Fisch who reports partial or total malleus fixation in 46% of his revision stapedectomies. This is seven times the rate of most other authors. He employs an epitympanotomy to examine the anterior malleolar ligament, as well as the incudomalleolar joint, both sites of potential fixation. A malleostapedotomy is recommended in most cases.[166] Biomechanical evidence emphasizes the importance of a particularly firm attachment of the wire loop to the malleus handle to prevent tilting movements of the angulated prosthesis.[152]

Stapes footplate

Peri-operative difficulties with the stapes footplate increase the risk of sensorineural hearing damage. Minimal stapes fixation or a previous mobilization procedure predispose to a floating footplate. This occurs in less than 1% of procedures. A preliminary burr hole in the footplate prior to fracture of the crura may reduce the risk of a floater. If it does occur, it may be possible to drill an inferior marginal burr hole to aid extraction of footplate fragments. Others advise placing a tissue graft and prosthesis on the footplate. If in doubt, it may be safest to place a large tissue graft over the footplate and not revisit for at least 6 months to allow refixation.

In 3–11% of cases the footplate may be solid or obliterated. Otosclerotic foci within the footplate itself may produce a thick 'rice grain' footplate. This situation is also associated with an increased risk of a floating footplate. The oval window may become extensively involved with new bone in obliterative otosclerosis. Wide saucerization of the footplate has been associated with high rates of sensorineural hearing damage. A stapedotomy technique is recommended, but the perforation should be wide enough to prevent lateral contact of the prosthesis onto surrounding bone, which would cause attenuation of sound transmission.[165] If the footplate reobliterates, revision surgery has been associated with very high rates of sensorineural hearing damage.

A cerebrospinal fluid 'gusher' is rarely encountered. Causse and Causse [165] quoted 0.03% in his series. It presents as a rapid flow of fluid on entering the vestibule. It is most commonly seen in congenital mixed hearing impairment. There are reports of it originating from either an abnormally wide cochlear aqueduct or an internal auditory canal defect. No individual has large experience of this condition. The patient should immediately be positioned head up. It is then most commonly managed by a tissue graft over the oval window with a prosthesis to anchor it. The use of a lumber drain has been advocated by a minority. There were occasions when the flow could only be stemmed by ablation of the cochlear aqueduct or packing the internal auditory canal.

The operative field should be dry enough to prevent blood entering the oval window. The aspiration of blood or perilymph from the oval window is significantly associated with high-frequency sensorineural hearing damage.

POST-OPERATIVE COMPLICATIONS

Conductive hearing impairment

Post-operative conductive hearing impairment may present immediately after surgery, suggesting the sound transmitting mechanism was never successfully restored, or months or years later. Statistical analysis of published data is difficult in part because the exact nature of the previous surgery is often in doubt, as it is difficult at revision surgery to assess the entire footplate, which is often encased in fibrous tissue. This is important as the literature does not clearly distinguish the differing risks of each complication between stapedectomy and stapedotomy techniques, despite the use of lasers in revision surgery having improved assessment of the footplate. However, we have reviewed 19 major series published between 1980 and 2003, adequately describing 2670 revision stapedectomies and stapedotomies. Three causes of failure were particularly frequently reported. Prosthesis displacement out of the footplate was identified in 953 cases (36%, range 18–82%), and incus erosion in 549 (21%, range 5–32%). Bony regrowth over the fenestration was less consistently quoted but where stated it was found in 1–24% of each series.

Displacement of the prosthesis out of the oval window fenestration has a number of possible causes. A short prosthesis may be displaced from the vestibule simply by Valsalva or sneezing. A short piston may result not only from incorrectly measuring the distance from long process to footplate, but also from the distortion of the loop around the long process of the incus that may result from the variable diameter of the long process, different loop properties and different crimping techniques.[167] Contracture of the connective tissue seal over the fenestration appears capable of pushing the prosthesis out of the vestibule. There is anecdotal evidence to suggest that the thicker the oval window sealant, the greater the lateralization of the prosthesis. This would imply that a vein graft, being very thin, would be most suitable, followed by perichondrium, fat and fascia. In theory, better still is a tight laser stapedotomy. This may require no seal and so may reduce the risk of lateralization.[168] Traction from adhesions between the prosthesis and adjacent structures appears capable of displacing a prosthesis, so minimizing surgical trauma around the oval window is recommended. Anecdotal evidence also suggests that middle ear adhesions, lateralization of the oval window neomembrane and prosthesis migration are more severe following stapedectomy than stapedotomy. Finally, an intact footplate that was never fenestrated is frequently reported. No conclusions can be drawn from the literature as to whether any specific prostheses are particularly prone to these complications.

Necrosis of the long process of the incus causes loosening of the attachment of the prosthesis and a conductive

hearing impairment. The hearing impairment may fluctuate. Although often attributed to a reduction in blood supply secondary to cutting the stapedial tendon, and pressure on the long process from the prosthetic loop, some authors have claimed two other observations make this unlikely. The marrow of the incus may be able to provide adequate blood supply, and the frequent findings of a circumferential bony defect filled with granulation tissue are said to be more typical of a foreign body reaction.[165] It is common for both long process erosion and displacement from the vestibule to coexist. Necrosis should be distinguished from loose attachment of the prosthesis to the long process of the incus through faulty crimping, a complication that may be easily corrected.

Bony regrowth is more common in cases that initially demonstrated obliterative otosclerosis. It is reported both within a year of primary surgery and many years later.

Fibrous adhesions fixing either the ossicles or prosthesis are reported in 8–24% of revision operations. Such fixation develops independently of the incus or malleus fixation discussed previously, though both should be sought at revision surgery.

Footplate refixation may be encountered following mobilization procedures, though these are performed rarely now.

Sensorineural hearing damage

This may occur peri-operatively or present many years after surgery. Quoted results are subject to publication bias and an absence of randomized trials. Caution is also required as the largest series reflect the results of established experts. The majority of recent publications on stapedotomy quote no dead ears or cases of severe sensorineural damage in their series. One of the largest series of stapedotomies identified 13/1911 (0.7%) cases of sensorineural damage, combining early and late failures.[169] Rates for stapedectomy are generally higher and range from 0 to 11%, though are not necessarily directly comparable. However, one of the largest series reported no immediate cases of permanent sensorineural impairments in over 4000 procedures.[170] Revision surgery is usually associated with higher rates of sensorineural hearing damage. Reviewing 20 papers analyzing 2585 revision procedures, we identified 113 cases of severe sensorineural hearing impairment, a rate of 4.4%. Sensorineural impairment was identified in 0–20% of each series, while a dead ear rate of 0–14% was quoted. Length of follow-up was variable. This is significant as approximately half the episodes of acute sensorineural hearing impairment in both primary and revision cases were delayed, often by very many years.

Early mild sensorineural hearing loss is common. Sperling et al. noted 62% of patients had some sensorineural threshold shift in at a least one frequency when measured at day 5 post-operatively. This reduced to 32% at 6 months.[171]

Causes of peri-operative sensorineural damage are most often attributed to surgical trauma, in particular, extensive drilling associated with obliterative otosclerosis (particularly revisions), floating footplates and perilymph aspiration. Congenital footplate fixation and cerebrospinal fluid (CSF) gushers make up a second group. Delayed sensorineural damage is often unexplained. Causes include barotrauma from air travel and blast injury, reparative granuloma, perilymph fistula and suppurative labyrinthitis. An association with influenza has been quoted.

These late conductive and sensorineural failures, which could total several per cent of procedures, may influence the decision to proceed to surgery. In addition to the slow progressive cochlear impairment, they are discussed under 'Natural history' above.

Facial nerve injury

Immediate temporary facial nerve palsy may occur immediately post-operatively as a result of local anaesthetic infiltration. Delayed temporary facial palsy is well described between days 4 and 10 post-operatively. Rates of 0.1–0.5% are quoted. The cause is unknown but in some cases it may result from facial nerve swelling, resulting from the nerve being heated by a drill or laser. Full recovery is always reported over days or weeks. The role of steroids is not clear.

Permanent injury is very rare in stapes surgery (0.07% in the largest series). It is reported in association with aberrant nerves crossing the footplate, with laser or burr injury in the presence of a dehiscent canal and while clearing fibrous tissue from the footplate during revision surgery.

Vertigo

Transient dysequilibrium or vertigo post-operatively is not uncommon and can be managed with vestibular sedatives. Vertiginous symptoms combined with sensorineural hearing impairment and tinnitus occurring in the first week post-operatively most commonly result from a 'serous labyrinthitis' from which a rapid recovery can be expected. No treatments have been shown to improve outcomes.

Should dysequilibrium persist or arise later, a cause should be sought. Benign positional paroxysmal vertigo was reported in 4/63 post-stapedectomy patients in one study, all successfully treated with the Epley manoeuvre.[172] Vertigo is reported in 20–35% of patients with reparative granuloma and one-third of patients with a perilymphatic fistula. Both conditions are discussed below. An overlong prosthesis may cause vertigo and may be diagnosed by a positive fistula test on pneumatic otoscopy. Other causes described include a depressed footplate, bony fragments compressing the saccule, suppurative labyrinthitis, endolymphatic hydrops and vestibular schwannoma. Careful neuro-otological examination is required. Diagnosis of the labyrinthine cause is reported to be possible in many cases using HRCT scanning.

Perilymphatic fistula

A primary perilymphatic fistula is, by definition, present at the end of stapedectomy, a secondary fistula develops

months or years later. The largest series quote oval window fistula rates of 0.25–2.5% following stapedectomy. Rates appear significantly lower following stapedotomy. Fistulae are reportedly identified at 1.5–12% of revision operations. In many ways, symptoms are similar to those of endolymphatic hydrops: a persistent or fluctuating hearing impairment in 71–87% of cases, which may be sensorineural, mixed or conductive in nature; vertigo in approximately one-third of patients and dysequilibrium in a further third; tinnitus in 28–45%; and sometimes a sense of fullness in the ear. Some patients with a fistula have presented with meningitis. A positive fistula test may be present in two-thirds of cases. The greatest risk factor for a fistula is repeatedly reported as having been the use of gelatin sponge to seal a stapedectomy, a technique now largely abandoned. Treatment should be prompt. At re-exploration, if the prosthesis is displaced, the defect should be grafted and anchored with a new prosthesis. If the prosthesis still enters the vestibule, there may be adhesions with the membranous labyrinth and it may be safest to pack the footplate with fat without disturbing the vestibule.

Reparative granuloma

This is a well-recognized cause of early post-stapedectomy hearing impairment. The term granuloma is a misnomer. It refers to granulation tissue formation around a stapes prosthesis and the oval window which may extend into the vestibule. Early stapedectomy series quoted rates of 1.3–5%. A more recent postal survey of American otologists suggested an incidence of 0.1% post-stapedectomy and 0.07% post-stapedotomy,[173] though this is likely to be an underestimate. They are associated with the type of graft material used, most commonly Gelfoam or fat, and rarely with perichondrium, fascia or vein. Reparative granuloma usually presents 1–2 weeks post-stapedectomy, though a recent paper had one severely destructive case occurring 2 years after surgery.[174] It should be suspected when the commoner symptoms of 'serous labyrinthitis' fail to settle. They present with deterioration in hearing after an initial post-operative improvement in 70–100% of cases. The hearing impairment is progressive or sudden and sensorineural or mixed. It is associated with vertigo in 20–35% of cases and sometimes tinnitus.[161] There may also be otalgia.[174] Examination shows a dull red tympanic membrane, particularly in the posterior–superior quadrant. Management is controversial. Most papers advise early surgical intervention within 2 weeks of stapedectomy. It is uncertain whether the granulation tissue and prosthesis or granulation tissue alone should be removed. Outcomes are split evenly between hearing improvement, stabilization and profound impairment.

Many surgeons would now advocate a more conservative policy of steroids and antibiotics initially and some would consider delayed surgery if no improvement occurred. CT and MRI can be useful in assessing the extent of the granuloma which can rarely be very large and destructive.[174] Evidence-based conclusions cannot be drawn.

Discomfort to loud noise

This symptom has been reported in 35–41% of patients following stapes surgery and, although it frequently settles, it can persist on long-term follow-up.[175] It may, of course, reflect solely the improved hearing in the operated ear as normal hearing subjects will experience noise intolerance at certain volumes and loudness discomfort levels seem little changed. The role of stapedius tendon reconstruction is discussed under 'Hearing outcomes' below.

Alteration in taste

Damage to the chorda tympani nerve is reported in up to 30% of procedures, while in revision series the nerve has been quoted as being found intact in as few as 20% of cases. Sectioning or stretching the nerve may result in a metallic taste, impairment of taste, dry mouth and soreness of the tongue, typically for 3–4 months following surgery, though on occasion much longer. Cutting the nerve appears to lead to greater and longer-lasting symptoms than preserving it.[176] Bilateral damage will produce severe symptoms. For similar levels of damage, altered taste is noted more commonly after otosclerosis surgery comparted with cholesteatoma surgery as it is thought the chorda may often have pre-existing damage in cases with cholesteatoma.[177]

Cholesteatoma

Cholesteatoma has been reported in the oval window secondary to skin elements implanted during harvesting of a fat graft.

Meningitis

Meningitis and death have been reported, particularly in the older literature, following stapedectomy with fistula formation. Some authors have advocated exploratory tympanotomy in any patient with meningitis who has a stapes prosthesis to exclude a fistula.

HEARING OUTCOMES

Background

Reviewing outcomes data for middle ear surgery is not straightforward and is discussed under 'Conductive hearing impairment' above. The techniques used for stapes surgery have evolved gradually over four decades, with multiple variables to contend with including fenestration size and technique, graft material, prosthesis diameter and design, stapedius tendon repair, pathological severity and surgical expertise. Published series often combine several techniques. Reporting methods have also evolved making direct comparisons difficult. Randomized trials are notable for their scarcity. Furthermore, several series have quoted converting approximately 20% of stapedotomies into stapedectomies because of technical difficulties. This may introduce further bias as the results of stapedectomy

are made to appear worse as they reflect more difficult cases. Meta-analyses either are not possible or have not been attempted.

When comparing technical factors such as the type of prosthesis or biomaterial, closure of the air–bone gap is often a satisfactory measure. Cochlear damage may be broadly assessed by comparing pre- and post-operative bone-conduction or speech discrimination. The hearing gain experienced by the patient in one ear is best assessed by the air-conduction thresholds. However, from a patient's perspective, two other outcomes matter. First, the reduction in their auditory disability. This depends very much on the hearing in the better ear, information that historically was rarely presented. Second, 'average' outcomes become meaningless. It is the relative likelihood and implication of good, bad or very bad results that are important, which explains the role of presenting data in audiometric 'bins' of 10 dB, or graphically, to highlight extreme outliers.

Comparison of different techniques

STAPEDECTOMY VERSUS STAPEDOTOMY

As the debate between small or large fenestra techniques evolved, there were many series published from excellent centres quoting closure of the air–bone gap to less than 10 dB in over 90% of cases using either stapedectomy or stapedotomy techniques, though typically pre-operative bone thresholds have been used.[178–180] When comparing their stapedectomy series to their subsequent stapedotomy series, it is apparent that more than the size of the fenestra had changed. Often the piston and grafting technique altered making direct comparison difficult. However, a trend began to emerge that suggested stapedotomy was less traumatic to the membranous labyrinth, resulted in fewer complications and offered potentially better hearing gain in frequencies of 4 kHz and above. The benefits that have been claimed are shown in **Table 89.5**.

In 1978, Smyth and Hassard[181] offered a more direct comparison that supported the developing consensus. Reviewing results of 750 stapedectomies and stapedotomies, the immediate hearing outcomes were similar in the two groups except for sensorineural impairments of greater than 20 dB, which occurred in 1.5% of stapedectomies but no stapedotomies. Most impairments could be related to surgical trauma while trying to remove the footplate. The rate of fistulae was also higher in the stapedectomy group (2.0% versus 0.6%).

TABLE 89.5 Suggested benefits of small versus large fenestra techniques

Technique	Suggested benefits
Stapedectomy	Better low-frequency hearing gain May be only method technically possible
Stapedotomy	Better high-frequency hearing gain Lower incidence of: • perilymphatic fistula • sensorineural hearing impairment • lateralization of graft • post-operative vertigo • revision surgery More stable hearing gain Less 'labyrinthine trauma'

In reviewing the literature, we identified only one randomized controlled trial comparing stapedectomy (59 cases) and stapedotomy (32 cases).[182] This supported the consensus that higher-frequency hearing outcomes tend to be better with stapedotomy. In keeping with many studies, the need for revision was greater in the stapedectomy than stapedotomy group (7% versus 3%).

Direct comparison between the case series that make up the rest of the literature is difficult. The majority of publications show a similar degree of early closure of the air–bone gap in lower frequencies with both large and small fenestra techniques. Short-term closure to within 10 dB (most papers using pre-operative bone-conduction) occurred in 54% to over 95% of cases, with the majority of the published series quoting 80–95%. However, there is a clear majority that report better high frequency (4–8 kHz) outcomes for stapedotomy over stapedectomy. This has been shown to be associated with better speech discrimination in a small number of publications. The clinical significance of this has been questioned. A minority of papers report better low-frequency gain for stapedectomy, but this is not always maintained on longer-term follow-up.

Long-term hearing outcomes are addressed in several papers. The largest cohort has been followed by Shea.[137] He reviewed more than 4100 primary stapedectomies in his series of 14 449. Although the details of follow-up are unclear, the size of the series makes the findings influential. Both total and partial stapedectomies were performed with a variety of grafts. Averaging hearing at 0.5, 1 and 2 kHz, and identifying those with an air–bone gap of 10 dB or less and no loss in speech discrimination of greater than 10%, he quoted success in 95% at 1 year post-operatively, 90% at 6–10 years, and 63% at greater than 30 years. Most importantly, he believed that sufficient sensorineural impairment would be present in 30% of patients by 20 years post-operatively and that a hearing aid would be required.

A long-term follow-up in Finland comparing stapedectomy and stapedotomy obtained an impressive 63% follow-up at an average 20 years post-operatively.[175] Mean hearing results were not statistically different between the groups on short- or long-term follow-up. Air- and bone-conduction thresholds fell at a similar rate of 0.9 dB per year in both groups, which matches other publications that have previously quoted 0.6–1.2 dB per year. These numbers imply there is little worsening of the conducting mechanism on longer-term follow-up in the 'average' patient, but does not address individual failures. At an average 20 years after surgery, 37% of the group were occasional or regular hearing aid users, results very similar to those of Shea.[137]

STAPEDOTOMY TECHNIQUES

Stapedotomy techniques have been compared in a number of studies. No differences in outcomes were identified in

a prospective study between the use of a microdrill and handheld microperforator.[183] KTP, CO_2, erbium:YAG and argon lasers have all been frequently used in stapes surgery since initial results were published in 1980. There are potential risks to the membranous labyrinth with their use including photothermal, photochemical and photoacoustic damage. There are reports of temporary threshold changes using the CO_2, KTP and erbium:YAG lasers. The authors of a study using the erbium:YAG discontinued its use on the basis of their findings. The use of lasers versus the microdrill was reviewed in 550 cases at The House Ear Clinic in Los Angeles and similar results were reported,[184] the same finding to a review of the use of picks, drills and lasers in Marquet's series of 1681 procedures.[169] Despite this report, there is evidence to suggest that laser stapedotomy may have a lower complication rate than traditional methods. Rauch and Bartley[185] published a comparison between argon laser fenestration and traditional techniques and demonstrated a fivefold greater rate of footplate fracture using conventional fenestration methods. CO_2 and argon lasers have been compared and no outcome differences found. A recent systematic review was inconclusive on which was the optimum laser to use for stapes surgery.[186]

CONNECTIVE TISSUE SEALS

The use of connective tissue seals to cover the fenestration is another area of controversy. They will increase the surface area to transmit energy (this needs to be remembered when considering piston diameter outcomes which are discussed under 'Prosthesis types' below), may prevent perilymph leakage and restore the stiffness of the annular ligament in theory. It has already been mentioned that vein appears to be the most suitable material for stapedectomy. For stapedotomy it is not easy to compare series because of multiple variables, in particular the size of the stapedotomy is often not reported. Certainly, Causse[187] has reported excellent results using vein. Many otologists prefer not to interpose a graft but fashion a tight-fitting stapedotomy and seal the fenestration with blood or fat placed around the prosthesis.

ENDOSCOPIC STAPEDOTOMY

With the current interest in endoscopic ear surgery it is not surprising there are an increasing number of studies looking at endoscopic stapes surgery. These studies have demonstrated that endoscopic stapes surgery is safe and has similar audiologic outcomes to microscopic stapes procedures. Advantages compared to peraural stapes surgery would appear to be few but possibly a reduced amount of resection of the bony annulus is required.[188, 189]

PROSTHESIS TYPES

Prostheses vary in their design, material (Teflon, steel, gold, platinum, titanium and alloys), weight, diameter and anchorage to the long process of the incus. There are many good publications comparing piston diameter. Theoretical constructs would favour larger piston diameters, particularly in frequencies below 1.5 kHz. (If this argument sounds familiar, remember that a larger fenestration will effectively increase the sound-transmitting area of the end of the piston, and the largest fenestration is a stapedectomy.) This has to be balanced against the perceived risk of increased labyrinthine trauma and the technical limitations of larger fenestrations.[165] A minority of studies show no difference in hearing outcomes between different piston sizes, a majority appear to show benefit for larger pistons, particularly for frequencies up to 2 kHz. Teig and Lindeman[190] attempted to avoid the many confounding variables and demonstrated a 0.6 mm piston produced mean hearing results 4–10 dB better than a 0.4 mm piston, while a 0.8 mm piston was better than the 0.6 mm piston by 5–7 dB. While temporal bone studies have also suggested superiority of larger pistons,[191] a recent systematic review showed no evidence to support the superiority of large pistons over smaller diameter pistons.[192]

There are some published data to suggest that heavier pistons (steel – 12.5 mg, or gold – 10 mg) may produce better results in the lower frequencies, while lighter pistons (Teflon – 3 mg) may be better in higher frequencies,[165] a trend well illustrated by de Bruijn et al.[193] At present, there is insufficient evidence to confirm these differences are of clinical significance.

The material used is important only in that it must attach firmly to the incus and not incite a foreign body reaction. There are a number of individual case series of different products but most studies fail to show significant differences in hearing results between the prostheses as the majority are small and lack statistical power.

There has been a growth in use of self-crimping pistons made of thermally triggered alloys, of which a number of varieties are available. The piston is placed as normal but then heated with diathermy or a laser which causes it to self-crimp. Early results suggest these prostheses may be easier to use as satisfactory crimping is often felt to be one of the most difficult parts of the operation.[194] It is also felt that these pistons perhaps give more consistent results. Although long-term hearing results are not yet available, mid-term results appear stable.[195]

PRESERVATION OF THE STAPEDIUS TENDON

This is proposed as a method of preserving the blood supply to the long process of the incus, of reducing discomfort at high sound pressure levels and of improving speech intelligibility. Evidence regarding the benefits to blood supply is limited and it is likely much may be obtained from the marrow in any case. Causse et al. series[196] of 3457 tendon reconstructions was published in 1997 and claimed to show improved speech intelligibility in noise and reduced intolerance of loud noise, but the analytical methods used make it difficult to draw conclusions. A large questionnaire study by another group failed to show any difference in outcomes. Of note is that the surgeons at the Causse clinic no longer reconstruct the stapedius tendon due lack of perceived benefit to the patients.

Revision surgery

Revision surgery is associated with a greater risk of sensorineural hearing impairment, as described above, and with poorer hearing outcomes than primary stapes surgery. It is particularly difficult comparing case series because of the variables involved. However, we have reviewed 24 series and found closure of the air–bone gap (using old reporting guidelines) to within 10 dB was achieved in 54% (mean value unweighted for series size, range 17–81%).

While there are many claims that revision surgery is safer under local anaesthetic, it is difficult to establish this from the literature.

The use of a laser is often advocated for revision surgery to allow adhesions to be cleared from the oval window, to free an ankylosed prosthesis from the incus, to sculpture the incus or to control bleeding. Most papers comparing revision surgery with and without a laser do not report any differences in hearing outcome. However, in Lippy et al. series of 483 revisions,[160] it was noted that in the period the laser was not available, closure to within 10 dB was achieved in 70% of cases and when it could be used, if required, this increased to 80%.

Malleostapedotomy is usually reserved for cases of severe incus erosion.

The more revisions an ear has undergone, the less likely a good result can be expected. Lippy et al.,[160] for example, quote closure to 10 dB in 76% of first revisions, 66% of second, 57% of third and 38% of fourth revisions.

TINNITUS OUTCOME

Tinnitus is common in those undergoing stapes surgery, being reported in 56–79% of cases pre-operatively. Surgery is a successful method of alleviating this symptom. The results of seven series involving 696 patients with tinnitus were looked at. Post-operatively, 44% (mean unweighted for series size, range 27–64%) of patients had no tinnitus, 34% (16–56%) had less tinnitus than pre-operatively, 16% (8–27%) had equal symptoms and 5% (1–11%) had more tinnitus.[197] Looking at those who had no tinnitus pre-operatively, symptoms are reported to occur in 0–16% post-operatively, with most papers quoting no new cases.

Several authors have reported that the prognosis for low-pitched tinnitus is particularly good after surgery, while the prognosis for high-pitched tinnitus is poor. This has not been corroborated by all studies.

COCHLEAR IMPLANTATION

Cochlear implantation is a potential management option for those patients with FAO in whom other modes of sound amplification have failed. Otosclerosis accounts for approximately 10% of implants in adult programmes. Most patients being considered will have had surgery for otosclerosis previously, either stapes procedures or fenestration. If not, stapedectomy in combination with conventional aiding should be seriously considered prior to proceeding to implantation.

This population has its own unique surgical challenges, due to both previous surgery and the disease process. These have been summarized in **Table 89.3**.

In a large series presented by one of the authors,[142] speech discrimination scores (using binaural CID sentences) improved from 12% (range 0–52%) pre-operatively to 88% (range 22–100%) post-operatively, results which have been mirrored in other series.

BEST CLINICAL PRACTICE

- ✓ A trial of a hearing aid should be discussed before proceeding to stapes surgery.
- ✓ Stapes surgery should be performed only by those who undertake it regularly.
- ✓ Appropriate outcome data should be audited by individual surgeons.

FUTURE RESEARCH

The surgical correction of hearing impairment caused by otosclerosis has a long and interesting history. It is currently one of the most successful operations we have to improve hearing. Large gaps remain in our knowledge, however.

- ➤ More accurate and standardized outcomes data will allow comparisons between techniques and refinement of the indications for surgery.
- ➤ Further exploration of patient-orientated outcomes, both for hearing aids and surgery, will help the debate over treatment of unilateral disease and bilateral surgery.
- ➤ Randomized trials rather than case series are desirable and possible for stapes surgery and hearing aid use, but they may require multicentre studies. These are required to assess variations in technical aspects of surgery, such as prosthesis design, dimensions and graft material. These will eventually allow meta-analysis of results and clearer guidelines, something still not currently possible on evidence-based criteria.

KEY POINTS

- Stapes surgery is an effective treatment for both the hearing loss and tinnitus of otosclerosis.
- Debate continues over indications for stapes surgery, in particular its role in unilateral disease and in second-side surgery.
- Revision surgery carries higher operative risks than primary surgery.
- Stapedotomy seems to be associated with fewer complications than stapedectomy.

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CHAPTER 90

OTOLOGICAL EFFECTS OF PAGET'S DISEASE

Ian D. Bottrill

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search and a search of the Cochrane and Bandolier libraries using the keywords: osteitis deformans, Paget's disease of bone, temporal bone, deafness, hearing loss, tinnitus, vertigo, imbalance, dizziness and focusing on pathogenesis, aetiology, diagnosis and management.

DEFINITION

Sir James Paget gave the first account of the disease which bears his name in 1877.[1] The disease was initially termed 'osteitis deformans'. Paget's disease of bone (PDB) is a progressive, focal disorder of bone remodelling and is the second most frequent metabolic bone disorder. There is an increase in osteoclastic activity producing bone reabsorption, with reactive stimulation of osteoblasts producing increased bone deposition, resulting in bone that is architecturally unsound. This leads to bone pain, deformity and fragility. Affected individuals typically have enlargement of the skull with involvement of the pelvis, tibia or femur. It is interesting to note that skeletons from archeological sites in Western Europe are the only ones to show evidence of Paget's disease.[2] This chapter will focus on the impact of Paget's disease on the temporal bone. [Level 1 evidence]

EPIDEMIOLOGY

PDB is the second most common bone disease in the world. It has a 3:2 male predominance. The disease is more common in Britain, North America, Australia and New Zealand. It is rare in Scandinavia, Asia and in non-white races.[3] The UK prevalence in the over 55 year age group is 0.3%; incidence rates for clinically diagnosed PDB rise steeply with age.[4] The same study found that, over the 10-year study period, the incidence of PDB disease declined significantly with time.

AETIOLOGY

The exact cause of PDB is unknown. The current opinion and evidence support an interplay between genetic and environmental factors, possibly viral infection of the bone cells, as the cause. The first gene found to be affected in PDB is the *SQSTM1* gene; currently more than 25 mutations have been identified in this gene. This gene encodes p62, a protein that is involved in regulating osteoclast function. Those patients who carry the abnormal gene are more likely to develop more advanced disease than PDB patients who do not express this abnormal gene. Other candidate genes have also been isolated in recent years.[5]

Polyclonal antibodies reveal paramyxovirus antigens in pagetic osteoclasts compatible with measles and respiratory syncytial virus infections. Studies with monoclonal antibodies implicate measles, simian virus and human parainfluenza virus. Electron microscopic studies have shown that the nuclei in pagetic osteoclasts have a fingerprint pattern, which supports a viral infection as a possible aetiological agent.[6] However, not all studies have found paramyxovirus particles or RNA in pagetic bone. In addition, there have been no convincing viral particles isolated from the cells of pagetic osteosarcoma, and it has not been possible to pass the disease to uninfected cells in culture.

PATHOPHYSIOLOGY

Bone changes

The basic abnormality is increased bone turnover in the involved bones. PDB can exist in monostotic and polyostotic form, with 10–30% of patients having monostotic disease. Any bone can be involved, with the most frequently affected bone, in decreasing order, being the pelvis, femur, skull, tibia, vertebrae, clavicle and humerus.

The changes in bone occurring in PDB can be divided into three phases: osteolytic, mixed and osteoclastic.[7] In the temporal bone a fourth phase has been described: a lamellar remodelled phase, in which the osteoblastic pagetic bone may undergo a process of remodelling into quite normal-appearing lamellar bone with distinct Haversian canal systems. This process is particularly seen in relation to the internal auditory canal, producing bossing of pagetic bone. In the temporal bone the endochondral bone is more resistant to resorption.[8, 9]

Different histological phases may coexist within a single temporal bone specimen.[7] Within the temporal bone, histological studies have shown that PDB involves the periosteal bone first. With increasingly aggressive disease, the process may extend into the enchondral layer and may finally invade the endosteal layer. [Level 1 evidence]

Symptoms and signs

In the early stages, the disease may be asymptomatic. Symptoms gradually progress, frequently starting with pain, stiffness and fatigability. The bone pain of PDB is typically constant, deep and boring. The cause of the pain is likely to be related to the increased periosteal blood flow exerting intraosseous pressure and stimulating bone pain fibres.

HEARING LOSS IN PAGET'S DISEASE

Sir James Paget, in his original publication, recognized hearing loss as a complication. The prevalence of hearing loss in PDB is quoted has varying between 13% and 40%. Van Staa et al.,[4] in their large epidemiological study, found that patients with PDB had a greater risk of hearing loss compared to age and sex matched controls (relative risk 1.6; 95% confidence intervals 1.3–1.9). This study was based on questionnaire data and did not include audiometric testing. A study by Young et al.[10] compared audiometric data in a group of patients with PDB selected at random from a tertiary hospital database and compared this with age- and sex-matched controls. They found the PDB group had significantly elevated auditory thresholds when compared to the control group: 41/75 PDB had a pure-tone average threshold of >40 dB compared to 8/76 controls. The hearing loss is typically of a high-frequency sensorineural nature.

It has also been noted that PDB may be associated with a low-frequency air–bone gap. Baraka[11] attempted to determine the rate of progression of hearing loss in patients with PDB. He reported that, on average, patients with PDB experience a greater reduction in hearing over time compared with age-matched controls. The pagetic ears deteriorated by approximately 2 dB per annum compared to 0.5 dB per annum in controls. His conclusions are limited by the very small sample size (4 patients with a minimum of 4 years of regular testing out of an initial study population of over 100 patients with proven PDB). Tinnitus is also slightly more common in Paget's than in controls, with a relative rate of 1.5 (95% confidence intervals 1.1–2.2).

The majority of pathological studies published relate to isolated case reports. Khetarpal and Schuknecht[7] have reviewed reported cases and tabulated the proposed mechanisms of sensorineural and conductive hearing losses, demonstrating the wide variation in suggested aetiology for the two types of deafness. Of the 26 temporal bones in 16 individuals, the only consistent feature they demonstrated was age-related histological changes. Pagetic lesions were present in the periosteal layer in all 26 temporal bones. In 22, they demonstrated extension to the enchondral layer and the endosteal layer was involved in 14. They found no evidence of ossicular fixation to account for the air–bone gap that was documented in seven individuals. The essence of their study was that 'both the conductive and sensorineural components of the hearing loss in Paget's disease are caused by changes in bone density, mass and form that dampen the finely tuned motion mechanics of the middle and inner ears'.[12] However, Dimitriadis et al.,[13] in their temporal bone study of eight subjects showed stapes fixation in two bones and a fractured stapes footplate in one specimen. The conductive component does not improve surgically even if otosclerosis coexists.

Historically, the hearing loss has been attributed to narrowing of the internal auditory canal[14] with compression of the vestibulocochlear nerve. Latterly this association has been brought into question. Monsell et al.[15] also looked for evidence of nerve compression as a cause of the sensorineural deafness. In a study of 64 ears with radiographically confirmed PDB of the skull, they demonstrated no relationship between the mid canal diameter and minimum diameter of the internal auditory canal and the hearing thresholds. In addition, auditory brainstem responses were normal in 56 out of the 64 ears, indicating that a retrocochlear lesion is unlikely to be the source of the hearing loss. However, this study did not look at tests for cochlea hearing loss (e.g. recruitment) to support their hypothesis. In a separate study Monsell et al.[16] also demonstrated a strong and statistically significant relationship between the bone mineral density of cochlea capsule versus both the high-frequency pure-tone air-conduction thresholds and the air–bone gap in subjects with Paget's disease of the skull. This latter study supports the conclusions from Khetarpal and Schuknecht's earlier histological study. In Dimitriadis et al. study they found occlusion of the inferior cochlear vein in 78% of cases leading to secondary changes in the stria vascularis and postulated fluid homeostasis abnormalities.

VESTIBULAR DISTURBANCE IN PAGET'S DISEASE

The literature regarding vestibular disturbance in PDB is not as extensively reported as studies on hearing loss.

The incidence is generally reported to be in the region of 20–30% of individuals with PDB suffering from vestibular dysfunction, but this is not compared to age-matched controls.[9] However, van Staa et al.[4] compared the frequency of reported dizziness/giddiness in 2456 patients with PDB compared to 7395 age- and sex-matched controls. They found rates of 5.0% and 3.7% respectively, producing a crude relative rate of 1.3 (95% confidence interval 1.2–1.5).

In Khetarpal and Schuknecht's study, vertigo was recorded in 4 of the 16 subjects investigated. The symptoms have the characteristic of motion-provoked imbalance. Histological analysis of these patients with imbalance did not reveal any changes such as loss of hair cells in the maculae or cristae. Even with histological evidence of pathology of the vestibular system, not all patients with changes had a history of imbalance. They found that losses of vestibular nerve fibres, greater than normal for age, occurred in nine ears of six subjects, three of whom had a history of vertigo.

DIAGNOSIS

PDB is often found incidentally on X-ray or laboratory tests performed for other reasons. It can be diagnosed through radiology, radionuclide bone scanning, and biochemical tests of bone resorption or formation. Plain X-ray findings in the early stages of the disease may be confined to osteolytic lesions in the involved bones. As the disease progresses, further radiographic changes occur, including increased bone density, abnormal architecture, cortical thickening, bowing and overgrowth. Microfractures may be seen in long bones. Laboratory testing should include renal function and liver function tests, calcium, albumin, alkaline phosphatase and 25-hydroxyvitamin D.

Computed tomography may show the involvement of the temporal bone (**Figures 90.1** and **90.2**) and in extreme cases may show complete obliteration of the otic capsule. When PDB affects the temporal bone, it typically spreads from the petrous apex laterally, producing a washed-out appearance of the involved bone caused by extensive demineralization. The process frequently affects the internal auditory canal first, progressing to involvement of the otic capsule. In advanced disease, the deposition of irregularly mineralized bone occurs, resulting in thickening of the petrosa and narrowing of the internal auditory canal. Nuclear medicine scans using technetium-labelled phosphonates show increased nuclide localization to the pagetic sites and can be a useful screen for disease extent.

Abnormal laboratory investigations include an elevated serum alkaline phosphatase (or bone-specific alkaline phosphatase). This enzyme is a marker of new bone formation and not resorption. The degree of osteoclastic activity can be assessed by measuring urinary hydroxyproline/creatinine (a measure of collagen breakdown) as well as measurements of urinary and serum deoxypyridinoline, N-telopeptide and C-telopeptide. Serum calcium and phosphorus levels usually are normal, but serum calcium may increase during bedrest.[16] [Level 1 evidence]

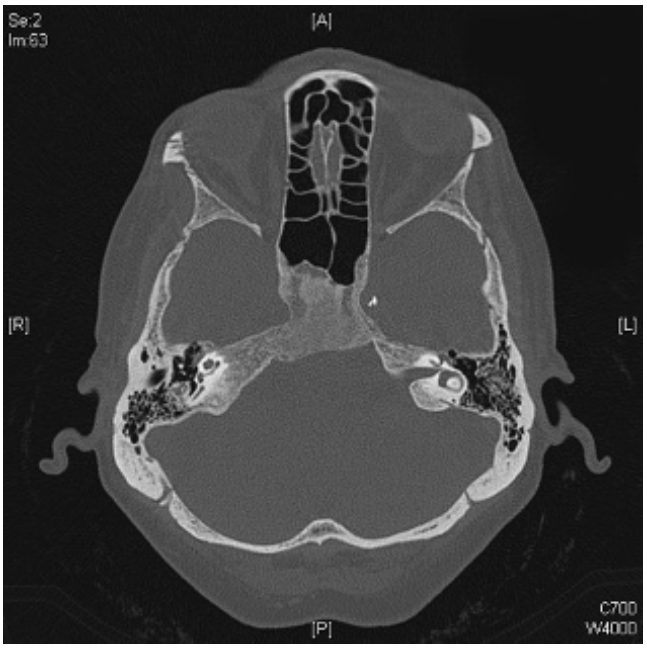

Figure 90.1 CT Paget's axial.

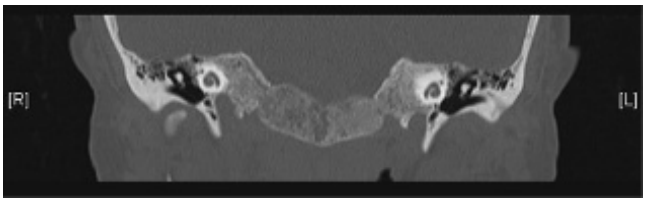

Figure 90.2 CT Paget's coronal.

MANAGEMENT OPTIONS

From the clinical descriptions and research findings it would appear that early PDB is not associated with significant otological complications. With advanced disease, otological complications do occur but with only modestly increased rates compared to the normal population. It is unlikely that the otolaryngologist is likely to pick up a new, early case. The patient will usually be under the care of the rheumatologists and combined management will be required. The dilemma is what to do with the known case who may present in the otolaryngology clinics.

Four main methods of treatment exist for PDB: physiotherapy, antiresorptive therapy, analgesics and surgery. Drug therapy is the mainstay of treatment for the non-otological aspects of the disease but may have beneficial effects on the otological aspects of the disease as well.

The current criteria for treating Paget's disease vary, ranging from those who treat only advanced disease to those who intervene early, to try to prevent the development of any complications, with no conclusive evidence to support either strategy. Crisp[17] lists his indications for the treatment of PDB (**Box 90.1**). He quotes skull disease as an indication for treatment but does not expressly mention audiovestibular symptoms.

Drug therapy is based on antiresorptive therapy. The mainstays of drug treatment are the biphosphonates.

BOX 90.1 Indications for treatment (reproduced from Crisp,[17] by permission of Oxford University Press)

1. Pain arising from the site of known PDB
2. Early, potentially deforming disease
3. Osteolytic lesions, especially in weight-bearing bones
4. Skull disease
5. Complications:
   a. progressive neurological syndrome
   b. fissure fractures (avoid etidronate)
   c. immobilization hypercalcaemia
   d. high-output cardiac failure
6. Disease in patients aged under 55 years
7. Serum alkaline phosphatase and/or urine hydroxyproline concentration more than twice the normal upper limit
8. Patients likely to undergo joint replacement at involved sides within 6 months, primarily to reduce blood loss due to hypervascularity present in active pagetic bone

These drugs act to reduce bone turnover and normalize the raised biochemical markers. Early biphosphonate use required daily treatment for 6 months, but as newer drugs have been introduced current recommendation is for a single 5 mg intravenous dose of zolendronic acid. Reid et al.[18] double-blind randomized trial showed a single infusion of zoledronate produced greater level of biochemical disease control when compared to daily treatment of risedronate for 2 months. In an open follow-up, of up to 6.5 years, the relapse rate with risedronate was 20% compared to 0.7% with zolendronic acid. [Grade A evidence]

Reid et al.[19] did, however, report a single case of potential otic toxicity related to pamidronate infusions. Their patient received five infusions of the drug and immediately after the second to fifth infusions the patient reported problems with tinnitus, vertigo and hearing loss. With the exception of the tinnitus, his symptoms resolved completely. No other report of potential otic toxicity exists in the literature with regard to biphosphonate treatment.

The results of middle-ear reconstruction in PDB are generally poor due to the lack of a consistent pathology to explain the conductive hearing loss. Modern hearing aids offer a useful modality in the management of both the conductive and sensorineural loss. There are other surgical modalities mentioned in the literature, including the use of a bone-anchored hearing aid in one subject.[20] Because of the vascularity of the bone, the procedure was performed in two stages, to allow the fixture to osseointegrate. There are also case reports of the use of cochlear implantation with reasonable results.[21]

OUTCOMES

There is no direct evidence that aggressive treatment of PDB is associated with the prevention of progression or a reduction in risk of future complications.[17] However, indirect evidence, as shown below, suggests that this may be the case. The evidence for this includes:

- the failure to treat PDB has been associated with further destruction of bone and progression of bony deformities
- successful treatment of PDB has been associated with restoration of normal patterns of bone deposition.

Lando et al.[22] reported the use of calcitonin and etidronate in two patients with polyostotic PDB with rapidly progressing sensorineural hearing loss demonstrating stabilization of hearing in one patient and improvement in the other. Other studies (references 13–18 in their paper) confirm these findings with calcitonin alone.

Complications of clinical conditions

The most devastating complication of PDB is the development of osteosarcoma. This occurs in less than 0.1% of patients with PDB but at a significantly higher rate than in non-affected individuals. It tends to occur more frequently in the polyostotic variant of the disease. In van Staa et al. study[4] the incidence rate was found to be 0.1 per 100 person-years.

Skull expansion may lead to disfigurement, typically frontal bossing. Extensive involvement of the skull base, producing softening of the bone, may lead to platybasia – the descent of the cranium on the cervical spine – which may lead to vertebrobasilar compromise. Skull involvement may also lead to headaches and other cranial nerve involvement.

Pain, osteoarthritis, deformity and fractures are commonly associated with PDB. Other rarer complications include high-output cardiac failure, when more than one-third of the skeleton is affected, hypercalcaemia and hyperuricaemia.

Although remission after treatment is related to the degree of biochemical control, and very strong histological evidence that effective suppression promotes more normal bone remodelling, evidence is lacking that intensive treatment inhibits the development of long-term complications.[17]

KEY POINTS

- Paget's disease commonly affects the skull.
- It is a condition of abnormal osteoclast activity.
- Otological sequelae occur more commonly than in age- and sex-matched controls.
- The weight of evidence supports direct involvement of the otic capsule as the cause of the otological symptoms.
- Treatment with biphosphonates can suppress osteoclastic activity although the long-term benefits on the otological complications remain unproven.

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CHAPTER 91

EAR TRAUMA

Stephen C. Toynton

SEARCH STRATEGY

All searches were performed using Medline Plus, Embase using Ovid, PubMed, Google Scholar, and the Cochrane database. Original or definitive references have been given priority over more recent ones that do not add significantly to the knowledge base.

Auricular haematoma and associated injuries

Ear surgery, ear external, external ear, pinna, auricle, auricular, helix and concha were all searched against, individually: trauma, haematoma, pseudocyst, cyst, chondritis and chondromalacia. Specific terms also searched were: auricular haematoma, otohaematoma, haematoma auris, wrestler's ear, asylum ear, cauliflower ear, hyperchondroplasia auris traumatica, auricular pseudocyst, benign idiopathic cystic chondromalacia, endochondral pseudocyst.

External ear canal trauma

Ear surgery, ear external, external ear canal, external auditary canal and external auditary meatus were all searched against, individually: trauma, injuries, wounds, lacerations and fractures. Specific terms also searched were: meatal step fracture and canal cholesteatoma.

Traumatic tympanic membrane perforations

Tympanic membrane and ear drum were searched against, individually: trauma, perforation, acute injury. Specific terms/phrases also searched were: traumatic perforations of the tympanic membrane, blast injury, primary blast injury, caustic ear injury, caustic trauma, batteries, CSF otorrhoea and cerebral spinal fluid.

Ossicular trauma

Ossicles, ossicular chain, malleus, incus and stapes were searched against, individually: trauma, fracture, dislocation, conductive hearing loss, hearing loss, head injury and temporal bone fracture.

Temporal bone trauma

Temporal bone, fracture, injury, head injury, trauma, craniocerebral trauma, epidemiology, CSF leak, vertigo, imbalance, otorrhoea, perilymph, fistula, deafness, hearing loss and evaluation using the keywords ossicle, ossicle and dislocation, middle and (ear and adhesions), middle and (ear and trauma), traumatic and tympanic and (membrane and perforation).

Whiplash injuries

The same terms as were used for temporal bone trauma were searched, but adding: whiplash injuries, whiplash-related disorder, therapy, vertigo, hearing loss, physical therapy techniques, neck and rehabilitation.

Otitic barotrauma and otitic decompression illness

There are a number of different clinical conditions that are included under the umbrella term of ‘otitic barotrauma’. Each has been searched separately with the primary search terms: diving, scuba, SCUBA, diving medicine, hyperbaric medicine, decompression illness, flight, aviation and aviation medicine in all the subgroups.

External ear barotrauma (external ear squeeze, reversed ear, reverse ear squeeze)

Ear external, external ear canal, ear canal, external auditary canal and external auditary meatus were searched against the primary search terms. Specific terms: external ear barotrauma, external ear squeeze, reversed ear, reverse ear, reverse ear squeeze. Neither original research papers nor specific reviews were found.

Middle ear barotrauma (barotitis media, middle ear squeeze)

Middle ear barotrauma, barotitis media, middle ear squeeze, middle ear trauma, haemotympanum and perforation were searched against the primary search terms. This delivered several hundred results, almost all of which are review articles, adding little to the overall knowledge. Additional specific terms: prevention of middle ear barotrauma, otalgia, decongestants, pseudoephedrine, xylometazoline, oxymetazoline. This identified four randomized controlled trials.

Caloric vertigo

Caloric vertigo was searched against the primary search terms. Searches failed to reveal any reports or research specifically targeting this.

Inner ear barotrauma (compression inner ear barotrauma)

Inner ear and inner ear barotrauma were searched against the primary search terms. Specific terms: perilymphatic fistula, round and oval window fistula(e/s), fluorosceine and cochlin-tonoprotein. Numerous citations were found, including review articles, but no randomized controlled trials.

High-pressure nervous (neurological) syndrome (isobaric gas counterdiffusion)

High-pressure nervous syndrome, high-pressure neurological syndrome, isobaric gas counterdiffusion were searched against the primary search terms. Despite numerous references, very few were relevant to otology.

Alternobaric vertigo

Alternobaric vertigo, asymmetric pressure, pressure difference and differential middle ear pressure were searched against the primary search terms.

Barotraumatic facial palsy (facial baropareisis, alternobaric facial palsy)

Barotraumatic facial palsy, facial baropareisis, alternobaric facial palsy, were searched against the primary search terms. Additional searched terms included facial palsy, facial paresis, neuropraxia, nerve injury. Sporadic case reports were identified and several animal studies.

Decompression illness

For detailed accounts of the physiology and practice of decompression illnesses extensive general texts are available relating to both diving and aviation medicine. Highly recommended are: 'The physiology and medicine of diving' in *Bove and Davis' Diving medicine*[1] and *Fundamentals of aerospace medicine*.[2] Diving texts usually refer to the effect of altitude in aviation when relevant. Searches including the above terms failed to locate any randomized controlled trials. Level 1 evidence was available in both pathology and physiology studies.

Cerebral air gas embolism

Searched against primary terms also with additional search terms including: intracranial embolism, air embolism, CAGE and accidents.

AURICULAR HAEMATOMA AND ASSOCIATED INJURIES

The following are covered in this section:

- auricular haematoma (otohaematoma, haematoma auris, wrestler's ear)
- cauliflower ear (hyperchondroplasia auris traumatica)
- auricular pseudocyst (benign idiopathic cystic chondromalacia, endochondral pseudocysts).

AURICULAR HAEMATOMA

Definition

An auricular haematoma is a collection of blood occurring in the subperichondrial layer or an intracartilagenous space of the pinna.

Aetiology and natural history

The most frequent modern associations are wrestling, boxing and rugby union.[3–5] There is a very important link with non-accidental injury in children.[6, 7] Spontaneous haematomas are extremely unusual although possibly occur in patients with hypertension or with severe coagulopathies.[8, 9] Folding the helix into the concha may lead to auricular haematoma formation.[10] In the veterinary literature auricular haematoma was thought to have an autoimmune aetiology. This theory has now been discarded in favour of trauma.[11]

Auricular haematomas usually occur on the anterior (lateral) surface of the pinna. Here the skin is firmly attached to the perichondrium. The shearing of the perichondrium and an attached thin underlying cartilage layer creates a potential space, the plane of cleavage being within the cartilage itself, that is filled with blood following the rupture of small vessels[4, 12–14] (**Figure 91.1**). Any haematoma within the posterior soft tissues is readily absorbed with minimal effect on the cartilage.

Early evacuation results in good resolution with minimal cosmetic deficit. If the auricular haematoma is not removed, there is an invasion of chondroblasts into the organizing haematoma, forming granulation tissue which results in new cartilage formation.[15] As the perichondrium is the source of new cartilage growth, this occurs on the anterior surface, from the side of the separated perichondrium. Breeches in the perichondrium result in the cartilage buckling over the haematoma and causing the typical irregularities associated with a 'cauliflower ear' (see 'Caulifower ear' below).[15] Trauma to the thinned skin overlying the helix may result in infection, pain, cosmetic deformity and meatal stenosis. In the most chronic cases ossification or 'petrification' may occur between the cartilage layers resulting in a bone hard area.[16, 17]

Reports of auricular haematoma occurring in Morquio-Brailsford disease (osteochondrodystrophia deformans, mucopolysaccheridosis type IV) and Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy (SHML)) do not describe a convincing association.[18, 19]

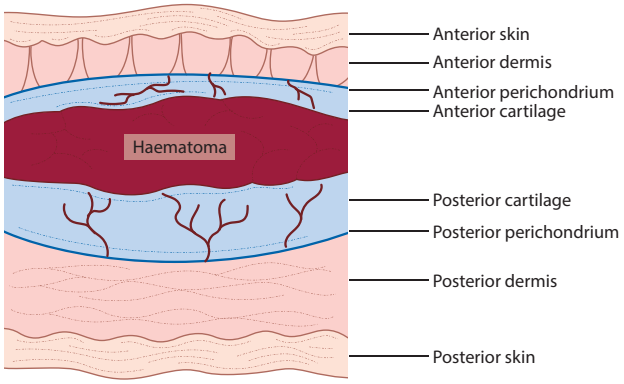

Figure 91.1 Splitting of cartilage layer by haematoma. (Modified with permission from Bull and Lancer.[12])

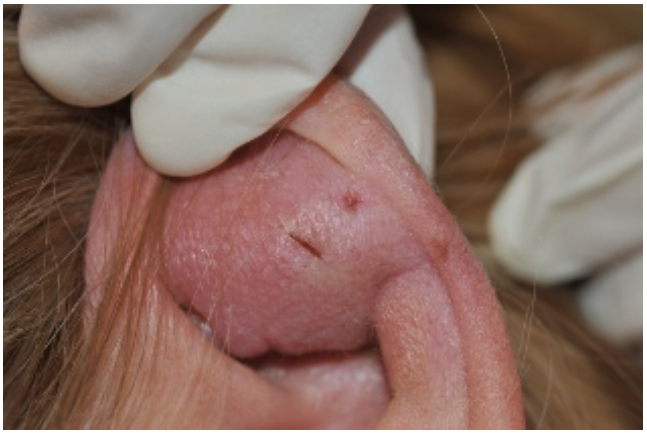

Figure 91.2 Recurrent auricular haematoma, previously incised and aspirated.

CAULIFLOWER EAR

Cauliflower ear is hyperplastic proliferation of the external ear cartilage following repeated episodes of trauma (typically auricular haematoma) or perichondritis from infection or other causes of inflammation. Improvement of this deformity is difficult. Specialist texts on plastic surgery to the pinna should be consulted.

AURICULAR PSEUDOCYST (BENIGN IDIOPATHIC CYSTIC CHONDROMALACIA)

Definition

An auricular pseudocyst is an intracartilaginous cystic collection, devoid of any epithelial lining, containing viscous, straw-coloured, sterile fluid, similar to an auricular haematoma in its anatomical location and its treatment. It is more often seen by dermatologists due to its association with local irritation and dermatoses.

Aetiology and natural history

Intrachondral pseudocysts are swellings of straw-coloured, slightly gelatinous fluid, high in glycosaminoglycans, occurring in cartilage spaces with no epithelial lining.[20] There is a low risk of progression to a cauliflower ear, unless acute trauma or infection intervene. They are usually located in the triangular fossa.

The pathoaetiology is thought to be a chondromalacia probably caused by repeated minor trauma, although often there is no such history. They usually occur in adult men between 30 and 40 years of age.[21] There appears to be an increased incidence in motorcycle helmet wearers but not due to a single episode of trauma.[22]

CLINICAL FEATURES OF AURICULAR HAEMATOMA AND PSEUDOCYST

Auricular haematomas present as a painful acute swelling, usually of the anterior surface of the conchal bowl, antihelix or helix. After several days the tenderness decreases leaving a non-tender, slightly fluctuant, bluish-coloured lump. Rarely, infection may intervene, particularly if associated with local cuts or abrasions. A specific history of trauma is almost always present. If this is not forthcoming, then assault and non-accidental injury must be strongly suspected. The condition is so unusual in children and so strongly associated with local trauma that, almost regardless of the alleged history, a Child Protection Team should be asked to investigate.

Auricular pseudocysts are painless and symptom-free, usually with no history of preceding trauma. Local areas of skin irritation are a frequent association.

MANAGEMENT OF AURICULAR HAEMATOMA

There are no formal comparative studies.[23] All recommendations are based on level 4 evidence.

Treatment regimens are based on the requirement to:

- evacuate the haematoma
- remove granulation tissue
- compress or obliterate the dead space to prevent reaccumulation.

Evacuation of haematoma and granulation tissue removal

ASPIRATION

Aspiration is performed under sterile conditions from the anterior surface in the area of maximum fluctuation. It may be attempted for up to 48 hours post trauma. There is, however, an apparent high recurrence rate. If aspiration has been delayed, appears incomplete or there is a recurrence, or if granulation tissue has formed, formal incision and curettage will be required.[4] A closed liposuction method has been described,[24] but the anterior and posterior approaches are both frequently used.

Anterior approach

The incisions are made along the inferior border of the helix along the scapha, in the antihelical fold, or along the conchal fold, as necessary.[3, 25] The skin and elevated periosteum and any associated anterior cartilage layer are incised along the same line. The flap is elevated, the underlying haematoma evacuated and the granulation tissue curetted off the underlying cartilage, including any damaged or necrotic cartilage. Care must be taken not to perforate the posterior skin. The flap is then returned and the incisions carefully closed (**Figure 91.3**).[4, 26] Measures to prevent reaccumulation are required.

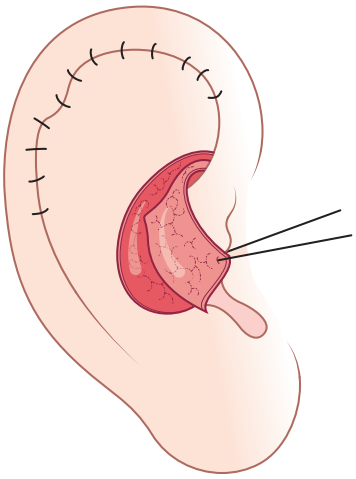

Figure 91.3 Anterior approach. (Modified with permission from Giffin.)[3]

Posterior approach

This approach is preferred in patients who wish to continue to play sport straight away and in those who already have a degree of cauliflower ear following repeated trauma. It may provide better cosmesis. An incision is made opposite the haematoma, on the posterior aspect, down to the surface of the cartilage. A 5 mm window of cartilage is removed, releasing the haematoma, taking care not to perforate the anterior skin.[27] Any granulation tissue on the anterior cartilage surface is easily curetted via this window, which may be enlarged if necessary. The incision does not require closure. Measures to prevent reaccumulation are mandatory (**Figure 91.4**).

Non-surgical methods and compression or obliteration of the dead space

Alternative methods include the injection of sclerosants, such as OK-432, steroids, streptomycin with hyaluronidase, triamcinolone or even fibrin glue, although two or three treatments per ear are often required.[28–33]

Recollection must be prevented but simple bandages and bolsters do not work well. Sutureless compression techniques include the use of moulded silicone, thermoplastic splints, swimmer's nose clip.[34–37] Suction drainage via a posterior incision or an indwelling 18-gauge catheter with a pressure dressing is an alternative.[12, 37–39] Despite their effectiveness, these drains may be accidentally removed and interfere with continuing sport. Compression suture methods with absorbable, or non-absorbable, through-and-through mattress sutures are most commonly used over bolsters and are probably the most effective (**Figure 91.5**).[40] The bolster material enables the application of even pressure to both sides. Bolsterless techniques using sutures alone, or with silicone moulds, plastic tubing or buttons on both sides are alternatives.[40–45] The author prefers using dental rolls as their sponginess enables better definition of the contours and helps to prevent overtightening of sutures. The patient may return to contact sports although a head guard to provide extra protection is advised.

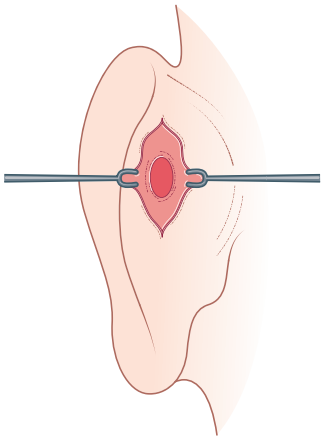

Figure 91.4 Posterior approach with cartilage window.[27]

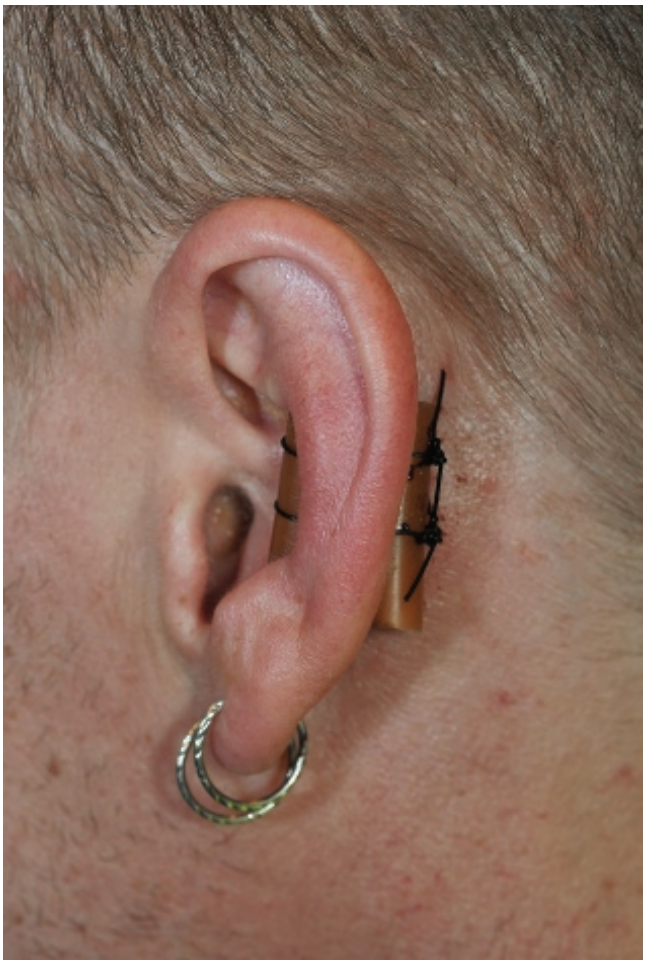

Figure 91.5 Through-and-through sutures over bolsters (dental rolls or soft tubing).

TREATMENT OF AURICULAR PSEUDOCYST

The treatment principles are the same as above but, as there is no granulation tissue, curettage is unnecessary. Recurrence approaches 100% for simple aspiration without compression.[46, 47] A popular technique is deroofing by removal of a disc of anterior skin and the underlying perichondrium. The exposed cartilage is allowed to granulate with a bolster compressing the surrounding areas.[48] A simple method of achieving this is with a skin biopsy punch.[49] The anterior and posterior drainage techniques described above are equally applicable to auricular pseudocysts. The success of bolsterless techniques is widely described,[42, 43] and superior to sutureless compression.[50]

PREVENTION OF AURICULAR HAEMATOMA AND PSEUDOCYST

The use of headgear in wrestlers approximately halves the rate of haematomas from 52% to 26%; 10.6% of those regularly using headgear, and 26.6% of those who do not, develop them.[51]

The use of tape around the head covering both ears and/or the application of lubricants are frequent preventative measures used by rugby union players, although these measures are relatively ineffective. Wearing headgear gives a relative risk of about 0.59, demonstrating reasonably effective protection.[52]

KEY POINTS

Auricular haematoma and associated injuries

- Early haematoma evacuation is recommended.
- Curettage of granulation tissue is important if drainage is delayed.
- Whichever surgical approach is used, compression sutures are recommended.

EXTERNAL EAR CANAL TRAUMA

MILD TRAUMA

Minor bruising, lacerations or small subcutaneous haematomas are often caused by the use of cotton buds or sharp implements in an attempt to remove wax or to alleviate irritation. External ear barotrauma may cause similar injuries. Such injuries are usually inconsequential. No specific treatment is usually required; however, if there are any signs of infection, then an appropriate topical antibiotic drop should be prescribed. In those who cannot keep their ears dry for the following 14 days, prophylactic acetic acid ear drops may be used.[53, 54]

MODERATE AND SEVERE TRAUMA

Moderate or severe trauma may present with bleeding from the external meatus. A history of trauma should always be sought, especially if the patient is found unconscious. Soft-tissue lacerations may result in canal stenosis (see Chapter 77, Acquired atresia of the external ear).

Association with mandibular fractures

Ear canal bleeding with pain is a frequent presentation of temporal bone fractures and also of those of the tympanic plate associated with mandibular trauma and condyle fractures. The association of trismus with bleeding and pain is highly suggestive of such injuries.[55, 56] Mandibular trauma, particularly posterior dislocation of the condyle, may result in damage to the cartilaginous parts of the external auditory canal with laceration and bleeding and, more rarely, fracture of the tympanic plate. This may occur without an associated condylar fracture. Although the initial impression may be of an external ear canal fracture, one of the mandible must be excluded.[57] Three-dimensional CT imaging is useful in fully assessing tympanic plate fractures.[58] Extreme bleeding may indicate an associated jugular bulb tear with blood coming from either a tympanic membrane perforation or a fracture line through the temporal bone. Death may result.[59]

There are no appreciable differences in presentation, or of the features of the fractures, between adults and children.[60] The management of mandibular fractures is beyond the scope of this publication.[61]

FRACTURES OF THE EXTERNAL AUDITORY MEATUS

Temporal bone fractures, with resulting tegmen defects, may be seen as a longitudinal step defect extending medially and including the annulus. They are usually associated with a haemotympanum. A tympanic membrane perforation with ossicular disruption may coexist. Severe displaced fractures may result in herniation of brain and meninges (meningoencephalocele) into the external canal.[62, 63]

Management

As most cerebrospinal fluid (CSF) leaks close spontaneously, initial conservative management is indicated. Rarely, when they do not, surgical intervention is required, usually via a middle fossa approach. If there is a superior meatal roof defect associated with the presence of granulation or polypoid soft tissue, MRI is recommended to exclude prolapsed intracranial contents. A mastoid approach may be considered for access to the ossicles or facial nerve, in which situation the opportunity should be taken to smooth off any meatal step deformities and to reinforce or fill any wide fracture lines to prevent the potential formation of canal cholesteatoma.

Canal cholesteatoma

Trapped non-migratory keratin may result from the growth of an inclusion dermoid caused by superficial trauma or irregularities within the walls of the external canal interfering with skin migration. Trapped keratin acquires the features of tympanic cholesteatoma with local bone destruction and may erode adjacent structures.

Unlike non-traumatic cases, which are often self-limiting (see Chapter 76, Keratosis obturans, primary auditory canal cholesteatoma and benign necrotizing otitis externa), surgical intervention is usually necessary. The cholesteatoma should be removed and the canal bone smoothed, enlarging the defect as necessary to create a flat profile. An associated soft-tissue meatoplasty may also be required to aid self-cleansing. Bone pâté and thinned cartilage sheets may be used to fill bone defects, particularly if the fracture, or drilling, has resulted in a posterior canal wall defect into mastoid air cells. Such repairs should be covered with temporalis fascia or perichondrium.

KEY POINTS

External ear canal trauma

- Minor abrasions usually require no treatment.
- Blood from the external meatus requires that both temporal bone and mandibular fractures are excluded.
- If a fracture is suspected, any meatal soft tissue should be left alone pending imaging to exclude herniation of brain/meninges.

FOREIGN BODY TRAUMA

Foreign body trauma is covered elsewhere in this volume (see Chapter 34, Foreign bodies in the ear, nose and throat).

TRAUMATIC TYMPANIC MEMBRANE PERFORATIONS

Tympanic membrane perforations may occur as the result of a pressure wave in the external ear canal, or by direct penetration. About 50% are attributable to slap injuries or direct blows. Self-inflicted penetrating injuries account for about 25%, with 25% being due to causes that include diving and aviation barotrauma, foreign bodies such as button batteries, other caustic substances, insects, welding debris and blast injury. Associated tinnitus and vertigo have been reported in 30.8% and 8.1%, respectively, but only in 2.0% and 0% during follow-up.[64]

TYMPANIC MEMBRANE PERFORATION AS A MARKER OF PRIMARY BLAST INJURY

Primary blast injury (PBI) is defined as: 'A combination of tympanic membrane perforation, pneumothorax, pulmonary contusion, non-penetrating facial sinus injury and bowel perforation'. The presence of tympanic membrane perforation has been considered a significant predictor of PBI. A study of US soldiers demonstrated, unexpectedly, that only 16% of all blast exposure patients had perforations, 50% of these being bilateral. Only 7% of blast injuries had PBI and only half of these had tympanic membrane perforations. Therefore, the presence of a perforation would appear to be a poor predictor of PBI.[65]

TYMPANIC MEMBRANE PERFORATION AS A MARKER OF CONCUSSIVE HEAD INJURY

The presence of a perforated tympanic membrane, from head trauma, is a strong predictor for concussive head injury. The relative risk appears to be about 2.76.[66]

CAUSTIC PERFORATION

The most common cause of caustic membrane perforation is button batteries in children. There were an estimated 3748 battery-related emergency department visits among children in the USA between 1990 and 2000.[67] This may be a presentation of non-accidental injury.[68] Electrical shorting between the battery terminals from mucosal contact, and possibly cerumen, causes battery leakage. The battery may become corroded at the crimp area, resulting in a permanent short, considerably speeding up the leakage and consequent trauma. Severe burns may result. Ear drops act as an electrolyte, rapidly enhancing the process, and therefore must not be used.[70] Local inflammation and erosion may extend into surrounding structures and cause deafness, facial palsy, meatal stenosis and even death.[68, 71] As these complications may occur quickly, removal of the button battery, thorough irrigation of the meatus with sterile water and any necessary debridement, should be performed urgently.

Damage from button batteries can occur quickly and they should be removed as a matter of urgency. The reader is referred to the section entitled 'Batteries and magnets' in Chapter 34, Foreign bodies in the ear, nose and throat.

CLINICAL ASPECTS

A careful history of the trauma modality is required, with attention given to concomitant injuries such as those associated with penetrating injury, temporal bone fractures, blast injury and lightening strike. Examination should include the pinna and canal, with microscopy as necessary. Microsuction may be required to observe the tympanic membrane in detail.

Injuries range from mild injection of the vessels over the malleus handle, to actual perforation. These changes may be classified in the same way as those resulting from barotrauma (see **Table 91.8** below). CSF otorrhoea requires exclusion.

Any foreign body should be removed. If a general anaesthetic is necessary, the opportunity should be taken to apply cigarette paper or absorbable gelatin sponge to any perforation. Infections should be treated with aural toilet and topical quinolone antibiotic drops. In the outpatient situation, if the patient is tolerant, clearance of blood, wax and keratin debris by microsuction is appropriate. Application of a paper patch or absorbable sponge is straightforward with the aim of speeding up spontaneous healing. In the intolerant patient, when no foreign body is present, no active treatment is appropriate.

A 3-month interval should pass before considering a formal repair as early surgery may have worse outcomes than conservative treatment or paper patches.[72] A reasonable exception to this policy might be when a quick, strong repair is desirable, such as in elite water sport athletes or commercial divers.

PROGNOSIS

Spontaneous resolution rates are high, typically 80–94%. Poorer outcomes are observed with increasing age and perforation size[73, 74] and are significantly lower in blast injury.[75] The worst follow welding injuries.[64]

Large studies have shown that the mean time for spontaneous healing is about 1 month, and a majority will have healed within 3 months. A slower speed of healing occurs if there is a middle ear infection. The site of the perforation is, however, insignificant. Penetrating injuries, and a

history of ear syringing post trauma, are the only risk factors important in predicting non-healing.[76, 77]

Office treatments, such as paper or gelfoam patches, are unlikely to increase the likelihood of healing but increase the speed of healing by up to 17 days (28.2±3.6 days in the spontaneous healing group 11.1±2.1 days, $p = 0.0017$ for sponge patching).[78] The biocompatibility, and lack of tissue toxicity, of cigarette papers has been validated.[79] There appears to be no extra advantage in formally repairing in the acute stage (12.5±1.9 days),[80] with no advantage in painstakingly aligning the perforation edges.[81, 82] Small underpowered studies of new interventions, such as the application of epidermal growth factor or hyaluronic acid, may enhance the rapidity of healing but not the chance of healing.[83, 84] Nanofibrillar patches, similar in structure to spiders' webs, have also given promising results.[85]

KEY POINTS

Traumatic tympanic membrane perforations

- Caustic substances, particularly batteries, should be removed straight away.
- No liquid, including drops, should be administered if a battery is present.
- Primary blast injury is a clinical condition whose definition includes tympanic membrane perforation, but this is a poor predictor for the condition.
- Tympanic membrane perforation is a good predictor for concussive head injury.
- Application of a cigarette paper patch or gelfoam increases speed of healing but not the likelihood.
- Surgical repair is only indicated after 3 months as over 80% of perforations heal spontaneously.

OSSICULAR TRAUMA

Most ossicular injuries are dislocations that are identifiable radiologically.[86] Any of the joints may be affected but dislocation of the incus is the most frequent (**Figure 91.6**; **Table 91.1**).[87–90] This may simply be disruption of the incudostapedial joint with minimal incus displacement, although with more severe trauma there may be complete separation.[91] Dislocation out into the ear canal may be associated with a tegmen fracture.[92]

Fractures of the ossicles are much less frequent,[86] being mostly of the incus long process.[93] Studies of cadavers following severe head injuries have noted a variety of damage that includes disconnection of the malleoincudal or incudostapedial joints and fractures of the malleus or stapes.[94] The malleus handle may be fractured, particularly in cases of middle ear barotrauma.[95, 96] Complete malleus dislocation has also been described.[88] Isolated fracture dislocation of the stapes footplate is very rare[97] and almost always the result of penetrating injuries, with associated pneumolabyrinth and perilymphatic fistula.[98] Trauma to the stapes may result in fracture of the arch,[88, 91, 93] or dislocation of the whole stapes.[99] In some cases, a combination of these lesions may be found and there may also be fractures of the bony external auditory meatus or fixation of the incus and/or malleus.[93, 100] Ossicular disruption following trauma may occur without perforation of the tympanic membrane.[101]

TRAUMA MODALITIES

Skull trauma from blows to the temporal, parietal or occipital region (with or without fracture of the temporal bone)

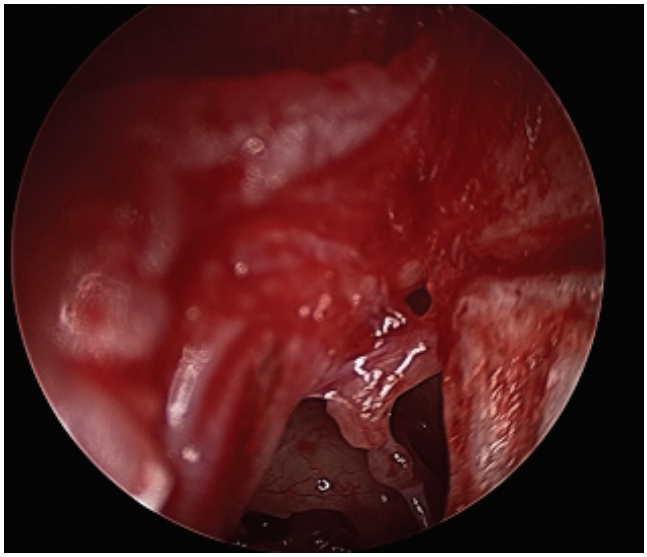

Figure 91.6 Dislocated incus; showing adjacent canal fracture.

TABLE 91.1 Frequent sites of injury

Author(s)	Year	Ears	Incus dislocation	Stapes fracture	Malleus fracture	Stapes luxation	Incus fracture	Ossicular fixation	EAM fracture
Hough[91]	1969	31	26	9	3	0	0	8	20
Rohrt[89]	1973	8	1	2	0	2	3	1	0
Spector et al.[93]	1973	28	10	7	1	0	8	5	0
Mills and Starriit.[120]	2002	12	12	2	0	0	0	2	1
Yetiser et al.[90]	2008	40	13	5	0	6	7	2	-
Total		119	62	25	4	8	18	18	21

Modified from Robert Mills, Scott Brown's *Otorhinolaryngology, Head and Neck Surgery,* 7th ed. Volume 3, Table 237g.1, p. 3493.

is the main cause; other modes of injury are rare.[102] About 60% occur without a concomitant temporal bone fracture.[101] Hearing loss occurs in about 22.5% of temporal bone fractures.[103] Around 16–30% of these have a conductive component, of which some will be due to transient causes such as a haemotympanum.[103, 104] Direct penetrating trauma is less common[105, 106] and may be iatrogenic as a result of intratympanic injections, particularly if there has been previous middle ear surgery or stapedectomy.[107] Other causes include middle ear barotrauma, surgical trauma and lightening strike.[108] Several large studies identify similar aetiologies. Drill-induced trauma to the incus during tympanomastoid surgery usually causes incudostapedial joint dislocation and a corresponding conductive hearing loss. Permanent sensorineural hearing loss is also highly likely in this situation but prophylactic disarticulation of the incus does not protect against it in a standardized guinea pig model.[109] Simple manipulation of the ossicles during surgery should, however, not result in a sensorineural deficit.[110] Digital pressure applied to the external auditary meatus may result in a sudden pressure change resulting in an isolated malleus fracture.[96] A comprehensive forensic post-mortem study looking at head injury victims using multislice CT methods suggests that the type of energy imparted is more important than simply the amount.[111] Damage to the ossicular chain may also occur secondary to osteoradionecrosis.[112] Congenital incus dislocation has also been described.[113]

DIAGNOSIS

A conductive component to the hearing loss following trauma of any sort should alert the surgeon to the possibility of ossicular injury. It may be difficult to diagnose ossicular disruptions that occur without perforation of the tympanic membrane, or once it has healed. Once acute sequelae, such as a haemotympanum, have resolved, further evaluation is necessary. Patients may present at variable times after the traumatic event, sometimes many years later.

INVESTIGATIONS

An initial audiometric assessment should be performed as soon as is practical after the injury. The initial conductive loss is often due to a haemotympanum or tympanic membrane perforation. A concomitant sensorineural loss may partially resolve (cochlear concussion). Rarely, however, audiometry may be normal,[114] or become so following healing despite a lack of reduction of the dislocation or fracture.[115] Any haemotympanum should be allowed to clear and time given for natural healing processes to take place before repeating the audiometric assessment, as excellent spontaneous hearing resolution may take place.[115] A varying degree of conductive impairment may therefore be present, often accompanied by a high-frequency impairment due to cochlear trauma. A tympanogram may show unusually high compliance, with a high peaked type A_D tympanogram, although this may occur in normal ears.

High-resolution CT is the imaging of choice for investigating ossicular trauma. Both axial and coronal images are needed for the evaluation of fractures and dislocations of all three ossicles. Reformated images are useful.[86] Three-dimensional CT imaging gives better information about the spacial orientation of the ossicles,[101] but virtual endoscopy enables even more of the ossicular chain to be seen, particularly the stapes crura.[116] This technique has given excellent predictive results of 100% in a small series of 17 patients.[117]

MANAGEMENT

Conservative management

Since surprisingly good hearing recovery may take place with fibrous healing when the incudostapedial joint is disrupted, even if the incus is entirely displaced,[115] a 3-month period is recommended prior to surgical exploration. Those patients who do not wish to undergo surgery should be offered aiding. Results from ossiculoplasty are inversely related to the degree of ossicular disruption. Coexisting sensorineural losses with major ossicular disruption may make surgical intervention unjustifiable, particularly if there is normal hearing in the contralateral ear. Detailed CT scanning is therefore recommended to aid this decision. Before undertaking surgery for a unilateral conductive deficit, consideration should be given to the likelihood of an adequate surgical result providing true benefit.[118] An exception may be when the air conduction thresholds in a mixed loss are sufficiently high that aiding would give poor results. In such cases, provided speech discrimination is adequately preserved, ossiculoplasty with the intention to aid post-operatively is a justifiable approach ('surgery for aiding').

Surgery

After elevating the tympanic membrane, identification of the nature and exact location of the ossicular injury is essential. After major trauma there is usually little doubt, although minor dislocations and fractures may be difficult to locate with confidence. A methodical process should be used whereby the malleus, incus and stapes head are palpated in turn while carefully watching the stapes footplate under high power. The impression of a lag, or failed transmission of movement, is indicative of the site of injury. Adhesions may be present around the specific site of injury. Watching the stapes superstructure rather than the footplate may result in missing subtle crural fractures. Delay in operating makes little difference to the long-term results.[119]

Since 1957 many surgical techniques have been described.[88] The displaced incus may be replaced by any standard ossiculoplasty method (see Chapter 85, Ossiculoplasty). Fixing it in its anatomical position via a posterior attic approach, combined with a tympanotomy, may be very successful.[120] Good results have been

described for the repair of simple incudostapedial subluxation with cartilage tip interposition, cement[121] or cyanoacrylate glue.[122, 123] Disappointing results using incus tip techniques may occur due to an unrecognized subluxation of the malleoincudal joint. Such cases may be identified at revision surgery where consideration should be given to an incus replacement technique. Cartilage repair of an isolated malleus fracture is straightforward and should give good results.[124] In cases of isolated stapes crural fractures, a strut or piston may be placed between the incus and footpate.[88, 93] A laser stapedotomy technique, however, gives more stability and is also useful for cases of stapes luxation.

RESULTS

There are no published randomized controlled trials (RCTs) addressing any aspect of ossicular chain trauma surgery. Numerous publications give the results of small series of specific interventions, or larger ones giving their overall results. The larger series available are presented in Table 91.2. These all include cases with a range of middle ear pathology and treatments, resulting in small numbers and therefore making conclusions difficult. Physiological repositioning of the incus has been described in several small series as giving the most impressive results,[91, 93, 120] the transmastoid posterior attic approach achieving the best.[120] Conventional ossiculoplasty techniques should give better results when performed for trauma than chronic suppurative otitis media in that there is usually no associated middle ear pathology and Eustachian function is normal. Soft-tissue adhesions within the middle ear and attic may compromise the outcome of treatment.[120] Cases with a greater degree of damage to the middle ear structures represent a greater reconstructive challenge than those with isolated incus dislocation.

TABLE 91.2 Hearing results (case series only)

Author(s)	Year	Ears	Technique(s)	Air–bone gap<10dB post-operatively (%)
Hough[91]	1969	31	Bone chip	100
			Per-meatal repositioning	80
			Ossiculoplasty	88
			Other	29
			Overall	78
Spector et al.[93]	1973	28	Per-meatal repositioining	
			Ossiculoplasty	
			Other	
			Overall	66
Mills and Starriit[120]	2002	12	Posterior attic approach repositioning	71
			Ossiculoplasty	25
			Overall	54

KEY POINTS

Ossicular trauma

- A variety of fracture/dislocation combinations is possible.
- The tympanic membrane may be intact.
- A conductive hearing impairment that persists following head trauma is most likely to be due to incus dislocation (62%).
- High-definition 3D CT scanning, or CT virtual endoscopy, is helpful in establishing the diagnosis.
- The cause may only be definitively determined by exploratory tympanotomy.
- The results of reconstructive surgery are generally better than those obtained in chronic suppurative otitis media, as the middle ear space is healthy.

TEMPORAL BONE TRAUMA

EPIDEMIOLOGY/AETIOLOGY

The overall incidence of temporal bone injuries is not determinable, and that reported for fractures varies widely. One estimate is that 8.5/100 people have either lost consciousness or suffered temporary confusion as a result of a head injury.[125] Blunt trauma to the temporal bone is much more frequent than penetrating injury. Skull base fractures occur in 3–30% of head injury attendances to Emergency Departments, 9–40% of these having temporal bone fractures.[126–128] About 7.9% are bilateral.[129] Men in their late twenties and early thirties predominate (male : female 2.8–4 : 1).[127, 129–131] Temporal bone trauma without fracture has similar aetiologies. Road traffic accidents probably account for about 50%, other frequent causes being falls (16–40%), assaults (10-37%) and, in the US, gunshot wounds (3–30%).[132–134] The profile may be different where medicolegal proceedings are taking place, when as many as 45% of cases may be due to work related injury.[131]

About 15% occur in children (males : females 2 : 1), the peak incidence being at approximately 5 years of age. Falls from a height predominate as the cause (40%) in children, with road traffic accidents accounting for only 34%.[60]

INNER EAR TRAUMA WITHOUT TEMPORAL BONE FRACTURE

Inner ear concussion (labyrinthine concussion, cochlear concussion, inner ear concussive syndrome) and mild traumatic brain injury

'Concussion' describes a temporary unconsciousness or confusion, with other symptoms, caused by a blow to the head. The term is often used synonymously with mild traumatic brain injury. This has been defined as: 'A traumatically induced physiological disruption of brain function

characterized by brief loss of consciousness (30 minutes or less), any alteration in mental state at the time of accident, anterograde or retrograde amnesia, negative neuroimaging [CT], Glasgow Coma Scale [GCS] score of 13–15 and post traumatic amnesia of not more than 24 hours'.[135, 136] The terms 'mild' and 'minor' are often used interchangeably although minor head injury is sometimes used to indicate extremely mild injuries in patients with an initial GCS of 15.

Head injuries account for about 1.4 million Emergency Department attendances per annum in the UK, approximately 90% of all traumatic brain injury being classified as mild. About 80% are discharged directly from the Emergency Department.[137] Although CT scans may be normal, MRI scanning has demonstrated a high incidence of parenchymal injury even when the GCS was as high as 14.[136, 138]

HEARING LOSS

About 52% of patients suffering from mild traumatic brain injury experience a subjective short-term transient hearing loss for several hours to 2 days immediately after the trauma.[139] Despite this, several studies have found no evidence of permanent hearing loss, as measured by pure-tone audiometry.[149, 150] More detailed audiometric evaluation has, however, suggested abnormal amplitude differences of transiently evoked otoacoustic emissions and absent stapedial reflexes in 12/31 patients.[139] Despite the implication that almost all concussive symptoms and signs recover, any associated hearing losses may very rarely be permanent even in those whose other symptoms have resolved.[131, 141] Histological analysis has demonstrated microfractures involving the otic capsule when imaging has been negative, suggesting an explanation for this.[141] No accounts of hearing loss, without dizziness, could be found.

A study of 100 consecutive head injury patients found 44% of those with mild traumatic brain injury to have auditory symptoms; this figure increased to 75% in the moderate/severe brain injury group. In both groups, about 75% of patients were found to have measurable vestibular abnormalities. Those few patients having a conductive loss all had a sensorineural component. Auditory abnormalities were shown to increase with the severity of the head injury whereas vestibular abnormalities were no more frequent in those with more severe injuries.[131]

TINNITUS AND HYPERACUSIS

Fifty-three percent of all patients suffering from traumatic brain injury develop tinnitus, particularly following trauma directly to the ear. Hyperacusis occurs to some degree in 87%. These symptoms may be due to direct cochlear injury, trauma to the auditory nerve and to brain parenchyma. Tinnitus and hyperacusis may be present in as many as 21% of those injuries where there is no measured hearing loss.[131, 142]

DIZZINESS AND VERTIGO

Dizziness may be described within four categories: vertigo, pre-syncopal light-headedness, multisensory dizziness, and psychophysiologic dizziness. Of these, only the symptom of vertigo may be clearly linked to the vestibular system.[143] This affects about 24% of patients with mild traumatic brain injury.[134] Possible specific sites of injury include the vestibular nuclei, the labyrinth or the upper cervical spine.[144, 145] Symptoms almost always resolve within 10 days.[146]

MANAGEMENT

A careful history, with particular reference to witnesses, is important in determining the modality and severity of any head injury. The initial assessment and investigations are in the domain of the emergency physician and, as necessary, the neurology and neurosurgical teams. The evaluation should, however, include a full neuro-otological examination. A policy of no active treatment for an isolated sensorineural hearing loss is appropriate. In patients with vertigo, undefined dizziness and tinnitus, CT of the temporal bones is indicated. Bed rest, head elevation and avoidance of straining are advised. A diagnosis of perilymphatic fistula should be considered (see below). Other causes of sensorineural loss, which may be coincident, may require exclusion with MRI.

No studies have specifically addressed the use of steroids although, given the likely aetiological factors of shear, microfractures and the assumed consequent inflammation, their use in cases of mild traumatic brain injury and cochlear concussion might seem persuasive. Large RCTs have not, however, found any benefit for the overall outcome with steroid treatment in any level of traumatic brain injury.[147]

Audiovestibular symptoms with or without hearing loss are a major component of traumatic brain injuries. A full range of supportive and rehabilitative measures should be provided, including hearing aids, vestibular rehabilitation, tinnitus and hearing therapy as well as general psychosocial rehablitation.[148] The evidence for psychogenic causes for audiovestibular symptoms is weak.[131]

PROGNOSIS

During the first week following their injury most patients report a range of symptoms that include headaches, dizziness, fatigue, memory deficits, anxiety and depression.[149] Up to 40% of patients have persistent residual symptoms one year later.[150, 151] Those with three or more symptoms beyond 3 months are defined as having postconcussive syndrome.[152] There is some evidence to suggest that there is the rare occurrence of a progressive hearing loss. This may be immunologically mediated via the HSP 70 antigen.[153]

Perilymphatic fistula

Rupture of the round or oval windows may occur with or without a temporal bone fracture. The management is as for other causes of perilymphatic fistulae (see 'Inner ear barotrauma' below).

Benign paroxysmal positional vertigo

Benign paroxysmal positional vertigo (BPPV) is the most common cause of vertigo post trauma, affecting 61% of the

patients who consult for persistent symptoms.[131] In a large retrospective study, 67% required multiple repositioning manoeuvres in the post-traumatic group compared to only 14% in the idiopathic.[154] It has been hypothesized that this worse prognosis may be due to an increased incidence of bilateral involvement and the occurrence of additional labyrinthine injuries, such as microscopic haemorrhages or tissue shearing[154, 155] (see also Chapter 64, Benign paroxysmal positional vertigo).

Delayed endolymphatic hydrops (post-traumatic Ménière's syndrome, secondary Ménière's disease)

Symptom combinations indistinguishable from Ménière's disease, either in the same or the contralateral ear, may develop some years after the initial onset of a sensorineural hearing loss following trauma of almost any sort, including acoustic trauma, head injury with and without fracture, infectious sequelae of measles, mumps and syphilis, and acoustic trauma.[156–158] Symptoms may also develop following surgical trauma, particularly stapes (and historically fenestration) surgery.[159] The prevalence is uncertain but it would appear to be uncommon. One study of patients with endolymphatic hydrops found a history of trauma in 5/31 patients (16%) including in contralateral ears.[157] The management of this condition should be as for idiopathic Ménières disease (see Chapter 63, Ménière's disease).

KEY POINTS

Mild traumatic brain injury

- Around 90% of traumatic brain injury is classified as mild.
- About 52% with mild traumatic brain injury have subjective hearing loss.
- Persistent measurable hearing loss is very rare.
- Tinnitus and hyperacusis may occur without hearing loss.
- Around 24% have dizziness or vertigo that has usually resolved within 10 days.
- Benign paroxysmal positional vertigo (BPPV) is the most common vestibular condition but it may be more resistant to repositioning manoeuvres than the idiopathic type.
- Perilymphatic fistula is a rare consequence.
- Clinical features of endolymphatic hydrops may occur in both the affected or contralateral ear many years later.

EAR TRAUMA WITH TEMPORAL BONE FRACTURE

Classification

The most commonly used system classifies temporal bone fractures according to their orientation relative to the axis of the petrous ridge: longitudinal or transverse.[160, 161] Most series describe 80–90% of fractures as longitudinal and 10–20% as transverse.[133] Although a convenient system, it has not been proven to correlate well with clinical signs or outcomes. Fractures have been found to be randomly placed or comminuted, and they are often not adequately described by the traditional classification.[162] True longitudinal fractures are uncommon so alternative classifications attempt to include oblique and complex fracture orientations.[91, 163]

An alternative system considering fractures as otic capsule violating or sparing is becoming more widely adopted.[60, 126, 132] This system emphasizes the structures involved rather than simply describe the fracture orientation.[127] Otic capsule fractures are associated with an increased incidence of serious sequelae.[126] Facial nerve paralysis, CSF leak and profound hearing loss were twice, four times and seven times, respectively, more likely in otic capsule violated cases. Some caution is, however, required as others have found no statistical difference using this differentiation.[127, 129] An attractive approach is simply to differentiate between petrous and non-petrous fractures. In one study CSF leak was only 1.1 times more common in transverse than in longitudinal fractures but was 9.8 times more common in petrous than in non-petrous fractures. Facial nerve injury is also more strongly correlated with fractures through the petrous temporal bone than with other fracture types. Sensorineural hearing loss did not correlate with the transverse fracture classification but was significantly more prevalent in petrous fractures.[164]

No convincing new classification system has evolved that repeatedly achieves reliable reproducibility to justify standard adoption. Therefore, a more descriptive strategy is suggested where the clinician combines the classifications by describing the fracture both in terms of its predominant orientation and whether it involves the petrous bone, otic capsule and brain parenchyma.

Temporal bone fractures in children

In children there is a relative increase in transverse fractures with 59% being longitudinal and 41% transverse.[60] This may be due to the different stress and resistance lines in the paediatric skull as a result of non-fused sutures and different bone density.

Clinical features of temporal bone fractures

HEARING LOSS

Any pattern of loss – immediate, delayed, transient, permanent or progressive – may be seen in cases of temporal bone fracture.[133] A conductive hearing loss of greater than 20 dBHL is likely to occur in two-thirds of patients tested within 72 hours of injury, with 17% persisting 6 weeks afterwards.[165] The management of conductive injuries is discussed above (see 'Ossicular trauma'). Although a persistent hearing loss is rare in cases of mild head injury, a sensorineural loss is often found in patients who have sustained a temporal bone fracture. The affected frequencies are usually at 4 kHz and higher.[131, 140] The degree of hearing loss is proportional to the degree of head injury.[130]

Complete loss of hearing in the affected ear is reported in about 17% of patients with a fracture.[165] Tinnitus and hyperacusis are frequent symptoms, and their management should be supportive.[131]

SYMPATHETIC HEARING LOSS

A delayed and progressive loss, without vestibular symptoms, may occur many months or years following the injury. It is thought to occur in 1–11% of ears following temporal bone fracture and to be immunologically mediated.[166] Similar occurrences have been identified after revision stapes surgery,[167] and vestibular schwannoma surgery.[168] Exposure of antigens from traumatized cochleovestibular membranes is thought to lead to immune sensitization and hence an attack on the contralateral ear. The same mechanism has been hypothesized as the cause of delayed progressive hearing losses occurring in the injured ear.[169] Animal studies have supported this mechanism.[170, 171]

VERTIGO

Similar rates of post-traumatic dizziness occur following severe temporal bone trauma and after minor head injuries. It occurs in at least three-quarters of cases.[131] Where the petrous bone/otic capsule are spared then a mechanism of vestibular concussion is thought to occur and resolution should be relatively fast, taking a matter of days.[146] This is unlike the destructive process with fractures through the otic capsule where resolution as a result of central adaptation may take up to 12 months.[133]

Clinical examination

A complete neuro-otological examination should be performed including a conscious state assessment (Glasgow Coma Scale), and examination of the cranium looking for evidence of penetrating injury, lacerations and mastoid bruising (Battle's sign) indicative of a skull base fracture. The absence of external injuries, particularly soon after the injury, does not preclude an underlying fracture. Cranial nerve examination is mandatory, with particular reference to facial nerve function. Examination of the neck, and the rest of the body, should be performed in conjunction with emergency physicians as appropriate. Tuning fork tests may be useful until formal audiometry is practical. Clinical tests of balance, gait and cerebellar function should be performed as soon as the patient's general state permits.

Otoscopic examination may reveal cerumen, blood, oedema, a canal step fracture, CSF, haemotympanum and tympanic membrane perforation. A good view may be difficult to obtain. Syringing and irrigation methods of cleaning are contraindicated due to the risk of ascending infection via open fractures and tympanic membrane perforations. Microsuction is rarely useful in the early stages of management; imaging usually gives sufficient information for the necessary decision-making. It is, however, indicated if infection is observed in the meatus. CT images should be available enabling any risk to be evaluated. Any soft tissue encountered should be left alone. Packing the meatus should be performed only in cases of uncontrolled haemorrhage. If this is required, a pack without a radio-opaque marker should be used to prevent interference with subsequent imaging.

Investigations

IMAGING

High-definition CT scanning is the investigation of choice. Better CT technology will increase the diagnostic rates of both temporal bone trauma with fracture[172] and mild traumatic brain injury, where a negative CT scan forms part of the diagnostic criteria.[135] It is the recommended initial investigation for the evaluation of all head injuries in patients with a Glasgow Coma Scale score of 14 or less.[173] If available, a high-definition temporal bone scan should be obtained straight away as part of the brain scan evaluation, particularly if temporal bone trauma is suspected; if not, then scan as soon as is practicable. Where hearing loss or vertigo is evident, but with no fracture demonstrated on CT, T1-weighted MRI may demonstrate a hyperintense signal in the labyrinth indicative of haemorrhage,[174] and may also identify temporal lobe contusion.[175] In the recovery phase labyrinthine enhancement may also be seen on MRI suggestive of an inflammatory process.[172] Targeted imaging may be necessary to examine specific injured structures, such as gadolinium-enhanced MRI of the facial nerve, or angiography for vascular injury. Despite CT findings, patient management is primarily guided by symptoms and clinical signs.[176]

HEARING ASSESSMENT

Clinical speech and whisper tests and tuning fork tests give useful initial hearing information long before the patient is sufficiently well to undergo formal audiometry. Early baseline audiometry is useful so that subsequent progress or deterioration may be monitored. In cases of bilateral temporal bone fracture, urgent hearing assessment is indicated and an audiometer should be taken to the bedside if necessary. Formal audiometry 6 weeks following temporal bone injury usually allows sufficient time for a haemotympanum to resolve, enabling assessment of residual conductive and sensorineural deficits.

Tympanometry will assist in determining the role of middle ear fluid in any conductive impairment. Rarely, evoked response audiometry may be useful in unconscious patients or children.

VESTIBULAR ASSESSMENT

Following head injury of any type, dizziness is a predominant, but often non-specific, symptom.[143] The presence of nystagmus may provide evidence of vestibular involvement although the observed movements may be complex if there is cerebellar trauma (see Chapters 49, Physiology of equilibrium and Chapter 62, Evaluation of balance). The typical finding of a horizontal nystagmus may be observed

with the fast phase directed away from the side with the failed labyrinth. Gait testing, augmented by other clinical tests such as Romberg and Unterberger tests, is useful, particularly in documenting resolution.

Caloric testing and other electro- or videonystagmographic tests seldom influence management, but they may be important during recovery to document the extent of any deficit and to objectively document progress or deterioration, particularly in the context of ongoing medicolegal proceedings.[177]

Treatment

ACUTE GENERAL

The general management of head trauma is outside the clinical domain of the otolaryngologist. A team approach is, however, indicated.

ACUTE SPECIFIC

Steroids

Despite widespread use for otological indications, such as sudden acute idiopathic sensorineural hearing loss, there are no convincing data suggesting benefit from the use of systemic steroids.[178] The use of intratympanic steroids has attracted much recent interest and may achieve better results (see Chapter 60, Idiopathic sudden sensorineural hearing loss). These techniques are unlikely to be applicable in the acute phase following temporal bone fracture for both practical reasons and the presence of a haemotympanum. Large randomized controlled studies have demonstrated no benefits with the use of steroids in overall outcome when used in the acute setting, even finding a very significant increase in mortality in more serious cases of traumatic brain injury.[147, 173] In view of this there is no justification for their routine use.

Antibiotics

Meningitis complicates about 2% of skull base fractures.[179] The routine use of prophylactic antibiotics confers no benefit with respect to: frequency of meningitis (even in patients with a CSF leak), all-cause mortality, meningitis-related mortality, or the need for surgical correction in patients with CSF leakage.[180]

MEDIUM AND LONG TERM

The management of any conductive loss is discussed above. Persistent mild to moderate hearing losses may be fitted with conventional air-conduction aids. Unilateral profound losses may benefit from a CROS or bone-anchored hearing aid with the aim of counteracting the head-shadow effect, convincingly improving hearing in noise performance.[181] Improvements in directional discrimination have, however, proved disappointing,[182, 183] although even in the elderly 65% satisfaction was evident.[184] Cochlear implantation in such cases may soon be shown to provide the best results, although availability and funding issues may prevent it.[185] If disabling tinnitus persists, implantation may be the treatment of choice.[186] MRI, as well as promontory stimulation testing, are necessary to check the integrity of the VIIIth nerve components if no hearing is elicited. CT scans should also be examined to check the integrity of the cochlea for implantation.

Regular monitoring of patients with progressive losses is important as an obliterative labyrinthine process may compromise successful implantation in the future. If there is a significant delay between the time of the injury and that of implant surgery, repeat imaging is essential preoperatively to rule out labyrinthitis ossificans or other structural abnormalities that may prevent successful electrode insertion.[187]

In patients with bilateral otic capsule fractures, and profound bilateral deafness, bilateral implantation is indicated as soon as the patient is sufficiently well to undergo confirmatory hearing tests and to tolerate general anaesthesia.[188, 189] If returning function in one or both ears is suspected, the worse ear should be implanted and the other carefully monitored. This ear may then be implanted if subsequent deterioration is observed. Implantation provides good rehabilitation results although persistent facial nerve stimulation secondary to electrical leakage through fracture lines occasionally causes difficulties.[190]

The management of tinnitus and vestibular symptoms should be managed as for temporal bone trauma without fracture (see above).

KEY POINTS

Temporal bone fracture

- Descriptions of fractures as longitudinal or transverse have a poor correlation with actual fracture orientation or clinical features.
- Fractures in children are more likely to be transverse.
- All patterns of hearing loss are possible.
- The absence of external injuries does not preclude an underlying skull base fracture.
- Ear syringing is contraindicated as it risks ascending infection.
- High-definition CT is the investigation of choice.
- MRI is indicated if neurological or vascular injury is suspected.
- Use of steroids may increase mortality.
- There is no evidence of any benefit conferred by the routine use of antibiotics.
- In cases of complete hearing loss, cochlear implantation should be performed as soon as possible before intracochlear fibrosis or calcification preclude effective electrode placement.

Complications of temporal bone fracture

FACIAL PALSY

Facial nerve palsy complicates about 7% of temporal bone fractures, dependimg on the type of trauma and fracture pattern.[191] Penetrating trauma has a higher incidence of about 52%.[192] Facial nerve injuries occur in 10–25% of longitudinal fractures, in 38–50% of transverse,[133] and are more common with otic capsule violating fractures.[191] Sixty-six percent of fractures are located at the geniculate

ganglion, 20% at the second genu, 8% in the tympanic segment and 6% in the mastoid portion. Six percent of geniculate ganglion lesions exhibited a second site of trauma in the mastoid portion.[193]

Clinical issues

It is important to ascertain whether the onset of the facial palsy was immediate or delayed and if partial or complete. These details are often unclear due to other potentially life-threatening issues (e.g. a palsy may not be noticed in ventilated patients). The implication of an immediate palsy is that the nerve has been directly traumatized, impinged or perhaps transacted. Delayed onset, even if only by a few minutes, and any residual function, imply neural continuity. Those cases where time of onset cannot be ascertained are best considered as immediate onset.[191]

Investigation

An excellent prognosis for recovery exists in cases of partial or delayed facial nerve palsy. Elecrophysiological testing is only necessary in cases of immediate complete palsy or in those cases of complete paralysis, with an uncertain history, that were thought to have been of delayed onset but have failed to improve. The timing of electrophysiological investigations remains controversial (see Chapter 112, The facial nerve and its non-neoplastic disorders). Most protocols are derived from studies performed on patients with idiopathic, Bell's palsy. Electroneuronography performed at about 10 days post injury is advocated but in patients with severe trauma this is usually not practical.[193] If it shows no response, electromyography is indicated. There is an established standard whereby good recovery of facial function is expected if the decline in the compound action potential on electroneuronography does not reach 90%. Although this seems to have evolved into a treatment threshold, 67% of patients who reach this level of degeneration also have excellent outcomes. A comparative study between idiopathic and traumatic facial palsies only demonstrated the importance of the 90% threshold in the idiopathic group.[194]

High-definition CT should have been performed in all patients as part of the head injury assessment. In cases of complete facial palsy contrast MRI may identify the main location of injury. This may be particularly useful if there is a comminuted or double fracture, or if no fracture is seen to be in the vicinity of the nerve on CT.[195]

Treatment

There is no evidence that any intervention for incomplete palsies gives superior results to no treatment. All of these patients are expected to make a complete, or almost complete, recovery (House–Brackmann I or II).[126, 191]

Steroids Systemic steroid treatment is usual for both delayed and immediate cases of facial palsy despite there being no controlled studies specifically examining their use in this setting. As they improve the degree of recovery and reduce synkinesis in Bell's palsy, without evidence of harm,[196] until there is evidence to the contrary, their use may be justified although the degree of coexisting traumatic brain injury takes priority. This often precludes the use of steroids as their use increases mortality.[147] There is no comparative study examining the optimum dose nor duration of treatment. An appropriate dosing regimen is 1 mg per kg per day of prednisolone, or equivalent, for 1–3 weeks, with a taper for longer courses.[133]

Surgical decompression The role and timing of surgery remains controversial. There are no RCTs to assist decision-making and no direct comparisons of treatment versus no treatment. Studies have not convincingly made the case for surgery. Complete nerve transection that cannot spontaneously recover accounts for about 14% of cases[193] and complete, immediate palsies, treated conservatively, may expect a 50% chance of complete or near-complete recovery without surgery.[191] A standard has evolved whereby immediate palsies showing the requisite 90% degeneration on electroneuronography within 2 weeks of injury are considered for surgery. Further research is clearly required. Despite these uncertainties, early identification and repair of a transacted nerve, and decompression of a clearly impinged nerve, are appropriate. This will only be achieved if immediate, complete palsies are comprehensively investigated, differentiating them from other cases that are more likely to recover spontaneously.

KEY POINTS

Post-traumatic facial nerve palsy

- Facial palsy complicates 7% of temporal bone fractures.
- Only complete, immediate onset, palsies require electrophysiological testing.
- A finding of 90% degeneration on electroneuronography at 14 days is a commonly used standard for consideration for surgical intervention although 67% with this result have good resolution without intervention.
- With no treatment 50% of complete immediate-onset palsies achieve good recovery.
- About 100% with incomplete palsies achieve House–Brackmann I or II grade recovery.
- Steroids may be effective but must only be used only if there is no significant associated brain injury.

OTHER NERVE PALSIES

Additional cranial nerve injuries occur in 7.8% of cases of temporal bone fractures. These consisted of VIth nerve injury when the petrous apex was fractured, also lower cranial nerve palsies as a result of jugular foramen haematoma.[193]

CEREBROSPINAL FLUID LEAK

Clinical features

Estimates of the frequency of CSF leaks following temporal bone fracture vary widely between 11% and 33%.[191, 197] Most (81%) resolve spontaneously within 5 days and 95% within 14 days,[191] although it is likely that many go unnoticed.

The risk of meningitis in temporal bone fracture is about 2%,[179] which probably increases to 7% with a CSF leak.[191] Concurrent ear infection increases this risk to as much as 20%.[191] Low-pressure headache and increasing risk of meningitis occur if leaks persist. Larger defects are probably less likely to heal spontaneously.

Management

Although not validated, bed rest with head elevation and avoidance of straining and lifting is advocated. If the leak has not stopped within 10 days, insertion of a lumbar drain is a sensible intervention. Prophylactic antibiotics are unhelpful in the absence of an ear infection.[180]

The requirement for surgical closure is unusual. Location of a persistent leak is not necessarily straightforward, particularly with comminuted fractures. The presence of a defect on a CT scan is not necessarily the site of the leak. Peri-operative fluorescein cysternography is sometimes useful for identifying the site.[198] For larger defects there is a risk of herniation of meninges and brain into underlying spaces. An MRI scan is also recommended to establish this pre-operatively. It is probable that some cases of meningoencephalic herniation go unrecognized but, due to the risk of infection, repair is recommended.[199]

The surgical approach and method used varies according to authors' preferences; however, large defects and revision cases are best closed by a middle fossa, extradural approach, sometimes with a combined mastoid approach. Smaller defects in more accessible areas of the tegmen and posterior fossa may be successfully closed via a transmastoid approach, with or without disarticulation of the ossicular chain. Numerous different materials, including autologous cartilage, temporalis fascia, fascia lata, and porcine- and bovine-derived artificial dura have been used. No superior results have been described with any particular material. If no hearing remains in the ipsilateral ear, consideration should be given to repair with a blind sac closure.[199] Rarely this may require the addition of a subtotal petrosectomy in those cases that violate the otic capsule.[200]

KEY POINTS

Post-traumatic CSF leaks

- CSF leaks complicate 11–33% of temporal bone fractures.
- Around 95% resolve spontaneously within 14 days.
- Large tegmen defects and persistent CSF leaks should be surgically closed to prevent meningitis.

RECURRENT LATE MENINGITIS AND MENINGOCOELE/ENCEPHALOCOELE

Despite spontaneous healing, recurrent CSF leaks and meningitis may occur, even many years after the primary injury. The diagnosis is often made when CSF is found in the middle ear when ventilation tubes are being inserted for an assumed middle ear effusion, or when a defect is noted on a CT scan performed prior to a lumbar puncture for meningitis.[133] MRI is indicated if there is a large defect, or if any suspicion of herniation of intracranial contents is seen on CT. Defects should be repaired and reinforced.

VASCULAR INJURY

Fractures of the bony canals of the internal carotid artery and sigmoid venous sinuses are relatively common but publications are sparse and mainly confined to the neurosurgery and neuroradiology literature. Those patients with worse injuries and a lower GCS are more likely to have a fracture involving the carotid canal.[201] Only 4% of skull base fractures result in vascular injury despite about a quarter of fractures entering the carotid canal. Sixty-two percent occur at the junction between its lacerum and cavernous portions (the spheno-occipital suture), and about 18% of these sustain a vascular injury. Fractures through the petrous segment are less common but carry a higher, 25%, risk of vascular injury.[201] Internal carotid artery dissection with carotid–cavernous fistula is a rare consequence.[193] Intimal damage resulting in aseptic sigmoid sinus thrombosis is rare (1 in 82 temporal bone fractures).[163]

A high index of suspicion is required in those patients with more severe skull base fractures, particularly if there is evidence of otic capsule fracture or cranial nerve palsies. The jugular and carotid canals should be routinely, and carefully, examined on the CT scan with a low threshold for requesting angiography. Examples are shown in **Figure 91.7**.

WHIPLASH INJURY

DEFINITION

This is indirect injury to the neck caused by an acceleration–deceleration incident resulting in a flexion–extension injury of the cervical spine. There is no direct trauma. Whiplash injury (or whiplash-associated disorder (WAD)) is the resulting functional impairment.[202] The term whiplash implies an amplification of relatively small forces into larger ones.

CLASSIFICATION

In 1995 the Quebec Task Force (QTF) produced a landmark consensus publication that provided a useful classification of these injuries into five grades, dependent on clinical symptoms and signs (**Table 91.3**).[202] Symptoms and signs should occur within 72 hours to be considered attributable to the whiplash trauma.[203, 204]

EPIDEMIOLOGY

The incidence varies greatly between 70 and 300 per 100 000 population.[202, 204] There are estimated to be more than one million new patients per year in the US. In the UK 250 000 patients per annum cost an estimated £3 billion[205, 206] with legal submissions occurring at a rate of about 150 per day. They increased by 268% in the year following the introduction of the compulsory use of seat belts.[205]

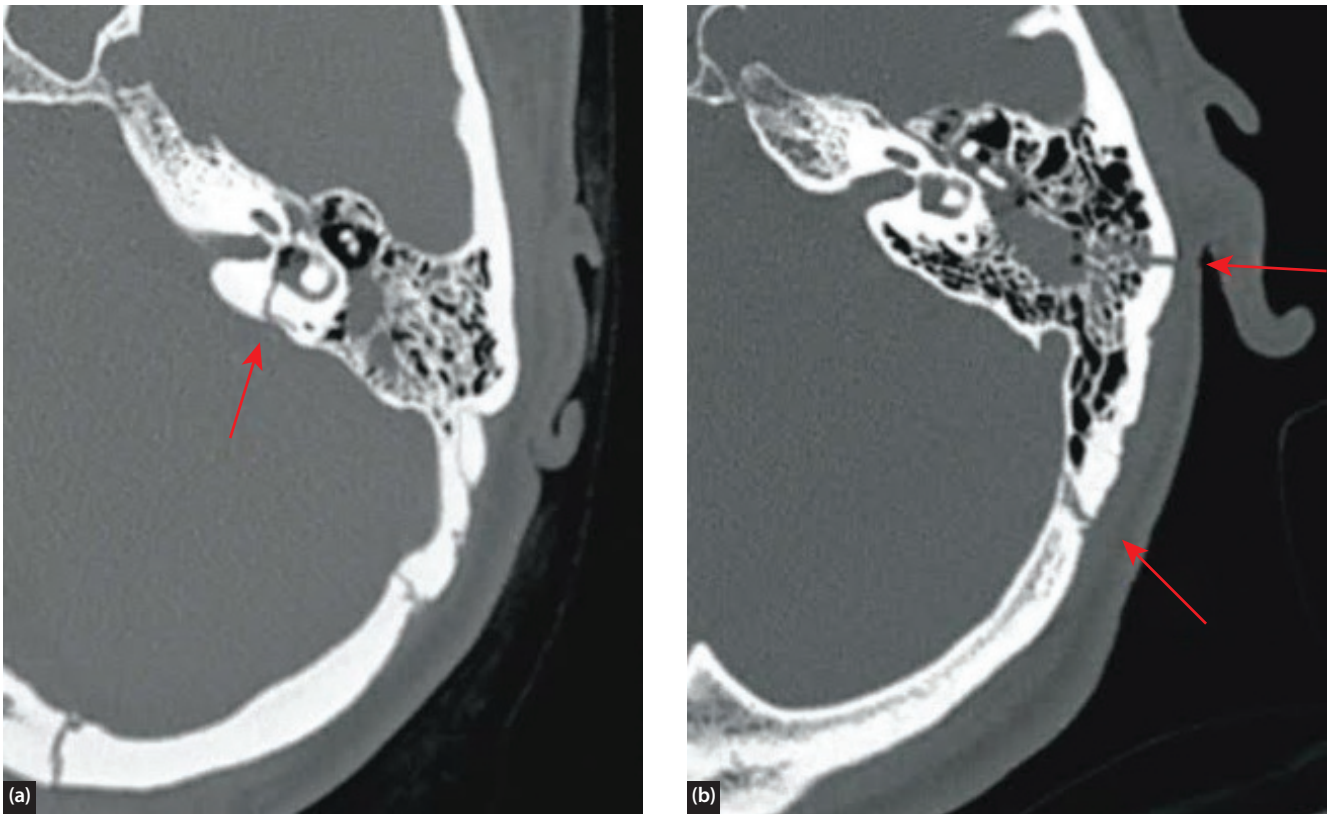

Figure 91.7 High-definition CT scans demonstrating (a) otic capsule-sparing and **(b)** otic capsule-violating fractures.

TABLE 91.3 Whiplash-associated disorder grading system after the Quebec Task Force conference

Grade	Symptoms and signs
0	Nil symptoms
I	Complaint of pain on motion, but no pain on physical examination
II	Complaint of pain on motion, with pain on physical examination
III	As grade II, but with neurological symptoms
IV	Fracture or dislocation

Adapted with permission from Spitzer et al.[202]

AETIOLOGY

Simulated accidents have shown that a 5 mph (8 km/h) rear-end car collision results in a positive acceleration of 8.3 G and 4.7 G of the head and chest, respectively. Below 3 mph (4.8 km/h) the difference between the displacement of the head and that of the chest is small or absent, causing no real whiplash movement of the head on the neck.[207, 208]

Despite what are clearly surprisingly large forces, the causes of many of the resulting symptoms remain unclear but incude soft-tissue neck trauma, skeletal spine damage and vascular or direct trauma to the spinal cord/brain stem or vestibular nuclei. Transient ischaemia or haemorrhage in the labyrinth as a result of transient compression of the vertebral artery, direct labyrinthine concussion, the noise of the collision causing acoustic trauma and psychological triggering of a pre-existing hearing disorder are also hypothesized.[177, 202]

CLINICAL FEATURES

General

Symptoms usually begin within 72 hours of the incident, the most common being neck pain and stiffness, with or without definite clinical signs such as tenderness or a decreased range of motion (grades I and II). Symptoms are shown in Table 91.4[204] and are similar to those reported in patients following head injury (see above).

Otological

In a study of 197 731 cases of whiplash 15–20% developed late whiplash syndrome with persistent complaints including headache, vertigo, instability, nausea, tinnitus and hearing loss.[209]

HEARING LOSS

Subjective hearing loss occurs in approximately 13%.[210, 211] Measurable hearing loss by pure-tone audiometry, in patients with grade I and II whiplash injury is at most rare and has not been confirmed by various studies.[212, 213] Some patients complain of hearing difficulties,

TABLE 91.4 Mild whiplash (grade I and II): most frequent symptoms experienced in the first week following injury

Symptom	Approximate prevalence (%)
Neck pain	94
Neck stiffness	96
Interscapular pain	35
Headache	44
Numbness/paraesthesia	22
Vertigo	15
Eye symptoms	12
Hearing symptoms	13
Sleeping problems	35
Memory problems	15
Signs of stress	30

Adapted with permission from Jansen et al.[204]

usually of poor speech discrimination, despite having a normal audiogram. A controlled 'speech in noise' study has shown demonstrable abnormalities in 30% of whiplash patients as compared to 5% of matched controls.[213] No study could be found associating the degree of whiplash injury to pure-tone audiometry findings or to audiological symptom scores. However, given the deceleration nature of the injury, it is reasonable to suppose that severe cases of whiplash (grade III and IV) may induce intralabyrinthine trauma similar to that found in head injury (see above). Therefore, any patient sustaining a whiplash injury who complains of hearing loss, tinnitus or vertigo should undergo a full neuro-otological assessment.

TINNITUS

Despite appearing in the list of acute symptoms, tinnitus does not appear to occur as a persisting symptom attributable to minor (grade I and II) whiplash.[212,213] More severe whiplash injury has many of the features of minor head injury, although no specific associations between audiological symptoms and whiplash-related disorders have been confidently identified.[204]

VESTIBULAR SYMPTOMS

The most common vestibular problem after whiplash injury is BPPV and it is usually a feature of more severe injury (grade III). Its management is as for the idiopathic condition (see Chapter 64, Benign paroxysmal positional vertigo).[214] As in BPPV following head injury, the condition may be more refractory to repositioning techniques requiring more treatments.[215]

Only 3.65% of those with low-grade (I and II) whiplash injury undergoing medicolegal assessment for otological and vestibular symptoms complained of non-specific dizziness symptoms in the acute phase following their original injury. Caution should therefore be exercised before attributing such symptoms to whiplash injury.[212]

TABLE 91.5 Guidelines for imaging in whiplash injury

Grade	Imaging
I	No X-ray examination **Exceptions:** Over age 65 years, concurrent skeletal disease (e.g. rheumatoid arthritis). History of neck surgery. Unsafe to examine
II	Plain X-ray or CT **Exceptions:** CT mandatory if any spinal nerve root or cord symptoms
III	CT Additional investigation with MRI often indicated

Adapted from Jansen et al.[204] and National Institute for Health and Care Excellence[218]

The nature and causes of the imbalance that often occurs in the late whiplash syndrome remains unclear. A study using electronystagmography only found abnormalities if there was a concomitant minor head injury. Posturography was, however, similarly positive in both groups, making a labyrinthine cause unlikely.[216] Comparative studies have found some evidence of vestibulopathy by VNG testing: 19% in whiplash (11% peripheral, 5% central, 3% indeterminable) compared to 60% in minor head injury.[217]

INVESTIGATIONS

Imaging

Indications depend on the clinical grade of whiplash injury (Table 91.5).[218]

Other tests

Audiometry should be performed as soon as possible in any patient complaining of hearing loss. Other tests are seldom necessary in the acute phase. Every attempt should be made not to overinvestigate as this may be linked to a poor outcome.[218] Neurophysiological tests should be reserved for use in those patients who do not make a full recovery.

TREATMENT

A Cochrane review was unable to support or refute the effectiveness of conservative treatments in grade I and II whiplash injury.[219] There is only limited evidence for mobilization strategies over immobilization collars.[218,220] In the acute phase of whiplash injury simple analgesics are recommended.[218] High-dose intravenous steroids given in the first 8 hours after injury decrease neck pain at 1 week but there was no difference in outcome at 6 months.[221,222] There is no strong evidence to support the use of any patient advice strategies.[223]

Hearing losses and tinnitus should be treated on their own merits. Dizziness, vertigo and imbalance have been shown to be effectively improved by vestibular exercises, even if differentiation between these vestibular symptoms

in various studies is unclear.[204, 224] The performance of vestibular rehabilitation exercises in patients with neck pain and limitation of neck movements is safe. Their symptoms and signs are correlated with their self-perceived dizziness handicap score.[225] Stress disorders, anxiety, sleeplessness and depression should be addressed to ensure optimum overall outcomes.[204]

PROGNOSIS

Mild (grade I and II) whiplash injury spontaneously recovers in 97–100% within 1 year.[202, 226, 227] Overall (grades I– IV) most patients recover within 8 weeks[202] but 14–50% develop WADs.[228, 229] It is possible that up to 50% of all patients have minor residual symptoms that may persist for as much as 2 years.[230] Degenerative changes seen on initial MRI scans all progress over 10 years but in over 50% of patients symptoms improve. There is no correlation between the progression of the degenerative findings and patient symptoms.[206]

Audiovestibular symptoms are uncommon initially (3.6–13%) and are expected to completely disappear within 5 months. Dizziness is, however, such a frequent complaint of more severe cases that the prognosis of this should be considered to be that of the overall condition.[212]

Systematic reviews strongly suggest that high initial pain intensity is the strongest indicator of a poor prognosis.[204, 218, 231] Other indicators are: the severity of the initial trauma, double collisions (rear-end followed by front-end collision), serious car damage, previous mental ill-health and a high grade of WAD.[206] Worse outcomes have been refuted in older patients, women, high acute psychological response, angular deformity of the neck, rear-end collision and compensation.[204, 231] The interactions between physical injury and an individual's pre-existing medical and mental condition significantly affect their illness behaviour. The worse the perception of the initial injury, the worse their neck pain at 1 month.[232] Despite most fully recovering within 2 months, not recovering by this time holds a worse prognosis. Likewise, if not resolved by 6 months, long-term difficulties are likely.

Controversy exists regarding the effects of seeking compensation, or malingering, on patient outcome. Studies from Lithuania and Greece, where there is no cultural expectation of compensation or of chronic disability, have excellent outcomes within 12 months. The very few patients with residual symptoms had them prior to their injury.[218, 226, 227] There is very little evidence to suggest that seeking compensation in itself is linked to the severity of patients' symptoms.[233] The resolution of legal cases, or the receipt of compensation, does not appear to improve outcomes.[234, 235] Ongoing research is investigating why countries such as Britain have such high numbers of claims.[236]

More high-quality research is required into the neuro-otological symptoms and outcomes following whiplash injury.

KEY POINTS

Whiplash injury

- Whiplash injury is extremely unlikely at speeds under 3 mph (4.8 km/h).
- There are persistent symptoms in approximately 20% of cases.
- Subjective hearing loss is seen in 13%.
- Objective hearing loss is rare and very rare, or absent, in grade I–II whiplash injury.
- Tinnitus is not a feature of grade I–II whiplash injury.
- Dizziness/vertigo is a rare complaint in grade I–II whiplash injury but common in more severe cases.
- Benign paroxysmal positional vertigo is the most common vestibular complaint.
- Around 97–100% of all symptoms in grade I–II whiplash injury recover within 1 year.
- Encouraging activity rather than rest and immobilization is recommended in patients with grade I–II whiplash injury.
- If vertigo or dysequilibrium is a symptom, vestibular rehabilitation should be provided. [Grade A]

OTITIC BAROTRAUMA AND OTITIC DECOMPRESSION ILLNESS

INTRODUCTION TO OTITIC BAROTRAUMA

'Barotrauma' is defined as an injury produced by mechanical forces caused by a change of pressure in a gas-filled space.[237] Otitic barotrauma, therefore, encompasses those pathological conditions of the ear induced by pressure changes. Severe cases occur from sudden large pressure changes, such as slap injuries typically sustained during an assault, when water skiing, high board diving and blast injury. Mild occurrences are common in airline passengers, scuba divers and in single-breath free diving.[237, 238]

The physics and pathophysiology behind most of the clinical entities are established. An exception is the exact role of 'bubbles' in the pathoaetiology of decompression illnesses. There is some temporal bone evidence for the various conditions described, but some of the pathophysiological explanations relating to the described inner ear conditions are incomplete. Most of the respiratory physiology, particularly relating to compression and decompression, and the fate of gases in the body, was established in the early 20th century by John Haldane.[239]

Pressure/volume relationships

The clinical conditions resulting from barotrauma are most easily described by considering the physiological events that occur during subaqua diving with scuba apparatus. Similar events occur during flight but, because of the lower pressures involved, the resulting barotraumatic injuries are usually less pronounced. Boyle's law describes the inverse relationship between the pressure of a gas and the volume it occupies (**Table 91.6**). Its importance is demonstrated by the relative bubble volume decrease observed

TABLE 91.6 Gas laws

Law	Detail	
Boyle's law	The volume (V) a gas occupies is inversely proportional to its pressure (P) at a constant temperature (T).	($V = k/P$, where k is a constant)
Dalton's law	The total pressure of a gas mixture always equals the sum of the partial pressures each gas would exert if it alone occupied the available volume.	($P_T = pP_1 + pP_2 + pP_3$ ..... pPn)
Charles's law	At a constant pressure the volume of a gas dissolved in a liquid is proportional to the temperature.	($PV = RT$, where R is a universal gas constant)
Henry's law	The amount of gas that will dissolve in a fluid, at a given temperature, is proportional to the partial pressure of that gas.	

TABLE 91.7 The effect of depth (seawater) on gas volume

Depth (m)	Atmospheres pressure	Pressure (kPa)	Volume (%)	Bubble (%) diameter
0	1	101	100	100
10	2	202	50	79.3
20	3	303	33	69.3
30	4	404	25	63.3
40	5	505	20	58.5
50	6	606	17	55

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with increased pressure (Table 91.7). The pressure increase with depth is a linear relationship of approximately 1 kPa for every 10 cm, while descent in air from 5500 m to sea level represents a pressure increase of only 0.5 atmospheres (50.5 kPa) (Figure 91.8). When diving, the largest percentage change in gas volume occurs during the first 10 m of descent (Table 91.7) (the first 1000 m of altitude for aviators), the ambient pressure doubling to 2 atmospheres and the corresponding gas volume being halved. This explains not only why a diver's impression of middle ear pressure change is maximal during the first 10 m, but also why the risk of developing otitic barotrauma is greatest in shallow dives or in low-flying, non-pressurized aircraft.

AMBIENT PRESSURE

The concept of ambient pressure is central to the understanding of the mechanisms involved. The external pressure is uniformly distributed over an object. In a system that has no air spaces within it, this pressure is transmitted equally throughout the structure. This is of particular relevance to the vasculature. If a large vein (e.g. the internal

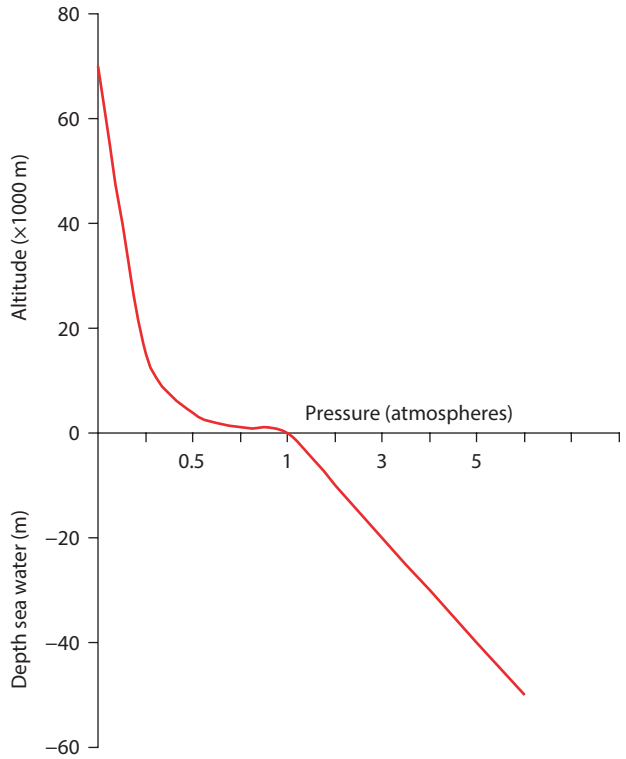

Figure 91.8 Altitude and depth versus pressure.

jugular) has pressure applied from the outside, provided that the whole body is submerged, it will transmit that pressure onwards. Head-out immersion causes a significant squeezing of blood volume from the lower limbs into the chest and into the head causing an increasing cardiac output and raised intracranial pressure with headaches.[238, 240] In the diver, or aviator, the pressure is equally applied to all body structures, there is no differential pressure across any membranes or systems so function is essentially unchanged. The exception, however, is when there is an air-filled cavity within the body. As the middle ear is a bony cavity, no distension or expansion is able to take place. The vasculature within the wall of the middle ear is, however, in continuity with that of the rest of the body, and therefore the intraluminal vascular pressures reflect the ambient pressure. If there is a relatively negative middle ear pressure due to a failure to equalize via the Eustachian tube, then there will be an increasing difference between the intraluminal vascular pressure and the middle ear pressure. If a sufficient gradient exists, then oedema and even rupture of those vessels within the mucosal lining will occur.

PHYSIOLOGICAL CONSEQUENCES OF COMPRESSION (DESCENT)

Figure 91.9 illustrates a diving model whereby the external auditory meatus is separated from the middle ear by the tympanic membrane, with the Eustachian tube connecting the middle ear cavity with the nasopharynx. During breathing, the nasopharynx is filled with inspired air from a compressed air cylinder via a regulator. This air pressure is equilibrated, by the regulator in the mouthpiece, to be equal to the ambient external pressure, provided the diver continues to breathe normally. As the diver descends, the ambient pressure increases. The middle ear pressure becomes increasingly negative compared to the ambient pressure unless equalization via the Eustachian tube takes place. This occurs by the voluntary action of the tensor and levator palati muscles opening the usually closed tube.[241] If the Eustachian tube cannot be opened effectively, the equalization of the pressure within the middle ear space with that of the external ambient pressure cannot occur. The relatively negative pressure within the middle ear will increase with further descent, resulting in a pressure differential across the tympanic membrane, which is therefore pushed inwards by the external ambient water pressure. This stretching is perceived as a sensation of external pressure and discomfort, which stimulates further attempts at equalization. If this does not prove possible, then the diver should return towards the surface to decrease the pressure gradient, thereby improving the ability to equalize. If this is not done and descent continues, then middle and inner ear barotrauma may occur.

The perception of the requirement to equalize occurs at a maximum of 86 cm (2.6 ft) reflecting a pressure change of only 8.7 kPa (60 mmHg). At this pressure, if no equalizing manoeuvre is performed, then mucosal congestion and oedema will occur. This is because the ambient pressure is reflected in the vasculature of the middle ear. This increases the transmural pressures, thus increasing transudation. Continued descent results in 'Eustachian locking', which occurs at a pressure difference of about 13 kPa (90 mmHg), an equivalent depth of approximately 1.3 m (3.9 ft).[242, 243] At this pressure, the power of the levator palati muscles is insufficient to voluntarily overcome the external closing pressures. Should this situation occur, middle ear barotrauma will follow. If the pressure gradient across the tympanic membrane is large, and occurs before the middle ear fills with an effusion or blood, then the tympanic membrane may rupture. If this occurs in one ear only, then a sudden influx of cold water into the middle ear may result in unequal thermal stimulation inducing a rigorous caloric vertigo.

The pathoaetiology of inner ear barotrauma is illustrated in Figure 91.9. The perilymphatic space is separated from the middle ear by the oval and the round window membranes. Alterations in intracranial and corresponding CSF pressures may be transmitted to the inner ear fluid compartments via the cochlear and vestibular aqueducts. If the diver or aviator fails to equalize his middle ears, then the pressure within the external ear canal will cause the tympanic membrane to be pushed inwards with a resultant inward force on the stapes footplate via the ossicles. This causes a corresponding bulging of the round window membrane into the middle ear space. The pressure gradient is also increased by the ambient pressure of the spinal fluid transmitted through the aqueducts to the inner ear fluids, this pressure being relatively positive compared to the middle ear pressure. Sufficient pressure by these mechanisms alone may be generated to cause round window membrane rupture; however, a forced Valsalva manoeuvre would certainly increase the intracranial, and therefore CSF, pressures by up to three times

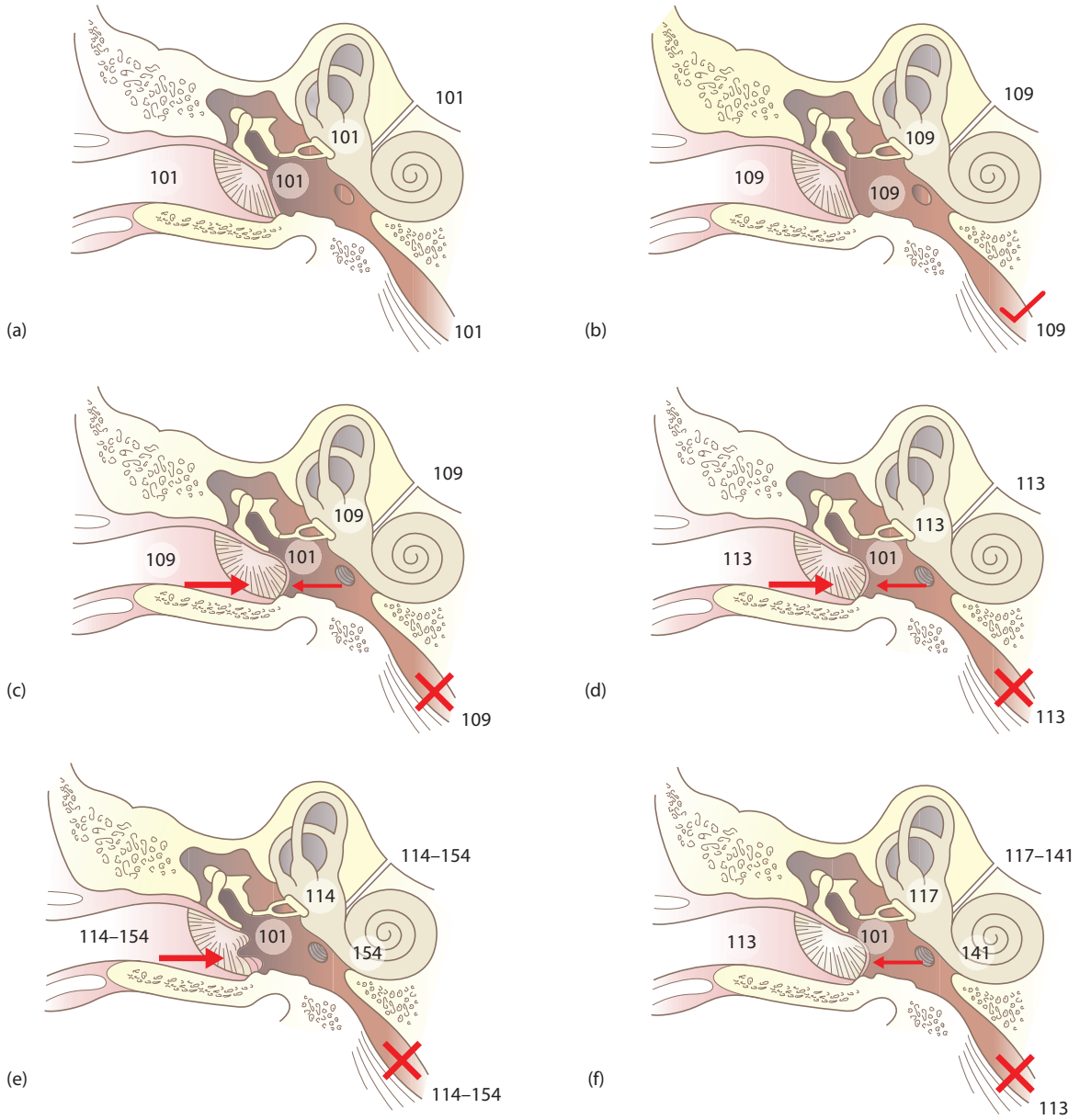

Figure 91.9 Otitic barotrauma on descent: theoretical pressure changes (kPa) and potential pathology. **(a)** Equal pressures on surface (sea level). Actual inner ear perilymph pressure is really slightly higher than ambient pressure. **(b)** Normal equalization with descent. **(c)** Depth 0.86m and pressure difference of 8 kPa, bulging tympanic membrane and round window into the middle ear. **(d–f)** Blocked and locked Eustachian tube. **(d)** 1.29 m with 12 kPa pressure difference. **(e)** Tympanic membrane ruptures at variable pressures. **(f)** Forced Valsalva increases CSF and perilymph pressure resulting in round window rupture. Adapted with permission from Farmer JC, Thomas WG. Ear and sinus problems in diving. In: Strauss R (ed.). *Diving medicine.* New York: Grune and Stratton; 1976.

that of normal. Studies in cats have demonstrated that the round window will rupture at pressure gradients of between 16 and 40 kPa (120–300 mmHg).[244] A perilymphatic fistula may therefore be expected to occur at the oval or round windows due to these implosive, or explosive, forces.[245] It is possible that these events are more likely to occur in patients with a congenital weakness of the annular ligament, or in those who have had stapes surgery, chronic middle ear disease, or perhaps have congenitally large cochlear or vestibular aqueducts.

PHYSIOLOGICAL CONSEQUENCES OF DECOMPRESSION (ASCENT)

If normal equalization of the middle ear pressures has occurred during descent, then the middle ear pressure is equal to that of the surrounding ambient pressure. During subsequent normal ascent, as the middle ear pressure exceeds that of the ambient pressure, passive ventilation of air through the Eustachian tube into the pharynx occurs.[246] When flying, this is normally every 13.25 m (43.5 ft) of ascent, regardless of the speed

of decompression.[247] If both Eustachian tubes are functioning correctly, the only conditions experienced on ascent are decompression illnesses.

During a diver's descent (or, for the aviator, during the previous flight), mild middle ear barotrauma may occur due to suboptimal Eustachian tube function, resulting in mucosal oedema and possibly haemorrhage. As a result, the usual passive ventilation, which should occur during subsequent ascent, can no longer take place. To continue ascending in these circumstances would result in a relatively positive middle ear pressure (**Figure 91.9**) compared to the ambient pressure, causing an outward bulging of the tympanic membrane. By similar mechanisms to those described during descent, the reverse effect on the oval and round windows may be seen. The tympanic membrane is pushed outwards and a traction force is applied to the oval window via the ossicles. This is accompanied by an inward force on the round window membrane. The pressure gradient is increased further as the perilymphatic pressure, reflecting the ambient pressure, has decreased with ascent. It is possible, therefore, for perilymphatic fistulae to occur during this phase of a dive. A sudden outflow of air down the Eustachian tube is sometimes described, immediately followed by the symptoms and signs of a perilymphatic fistula.

Clinical features

The manifestations of otitic barotrauma may be conveniently divided into the following three categories, which are discussed below:[248]

- compression injuries
- injuries at high pressure
- decompression injuries.

COMPRESSION (DESCENT) INJURIES

External ear barotrauma (external ear squeeze, reversed ear, reverse ear squeeze)

This occurs when a pocket of air is trapped within the external auditory meatus by cerumen, earplugs, foreign bodies or exostoses, although it is usually due to the wearing of a tight-fitting diving hood. The insertion of occlusive earplugs during aircraft descent is an uncommon cause.

If Eustachian tube function is normal, then, with increasing compression, the pressure of the trapped meatal air becomes negative compared to that of the middle ear and the external ambient pressure. As a result, the pressure gradient across the tympanic membrane results in it being displaced outwards. If with sufficient force, perforation may occur.

The main symptom is of pain, increasing with depth. The ear canal skin and tympanic membrane become injected and petechial haemorrhages, and bleeding, may be observed. The immediate remedial action is to decompress by ascending. If relevant, the diving hood should be adjusted or modified and the meatus cleaned, preferably by microsuction. The ear should be kept dry and diving avoided until the skin appears normal and the causative factor is addressed. Occlusive earplugs should be avoided when diving to more than 1.5 m and when flying.

KEY POINTS

External ear barotrauma

- External ear barotrauma involves a trapped air pocket in the external meatus.
- Pain increases in proportion to compression.
- There are tympanic membrane features as for middle ear barotraumas.
- **Prevention:** avoid occlusive earplugs and headgear.
- **Treatment:**
  - clear external meatus of blood/wax debris
  - use antibiotic drops for secondary infection
  - surgically repair any perforation if spontaneous healing fails
  - consider exostectomy.
- **Advice:** complete resolution should be observed and the causative factor corrected prior to further flying/diving.

Middle ear barotrauma (barotitis media, middle ear squeeze)

Middle ear barotrauma is the most frequent pressure-induced ear condition and may occur wherever there is Eustachian tube dysfunction resulting in a transtympanic pressure gradient.[249] Commercial flights, scuba and free diving, rollercoaster rides[250] and hyperbaric therapy are common causes. Transient evidence of middle ear barotrauma has been demonstrated in 5% of adults and 25% of young children after flying.[251]

CLINICAL FEATURES

Predicting who might be at risk during flight is difficult. Tympanometry is unhelpful as it is usually normal. Many people who have no problems with their ears when flying cannot voluntarily equalize their middle ear pressures. The sensation of equalization when performing the Valsalva manoeuvre has a poor (0%) predictive value for potential barotrauma. The Toynbee test has a positive predictive value of 25%. A nine-step inflation/deflation tympanometric Eustachian tube test has a much better chance of accurate prediction (25% positive predictive value, 75% negative predictive value).[252] Reliable (100%) predictive results have been obtained by combining the nine-step test with the Toynbee test.[253] Studies have correlated poor mastoid pneumatization with an increased chance of developing middle ear barotraumas. When estimating mastoid area by the simplified rectangular method, no patients with a mastoid area greater than 34.7 cm^3 sustain barotrauma, whereas those less than 13.6 cm^2 suffer from it.[254, 255]

For diving, the inability to 'equalize' by performing the Valsalva manoeuvre is a useful guide. Those unable to equalize both ears have a 91% chance of developing middle ear barotrauma compared with only 37% of controls.[256] Sonotuberometry and tubotympanometry have been suggested in an uncontrolled study, as methods that may accurately predict those who will develop middle ear barotrauma.[257] The speed of descent appears to be an important factor. The faster the compression, the less opportunity exists for equalization, especially if the person is distracted, working or asleep, particularly during the aircraft's descent.[258]

Initial symptoms are the sensation of a blocked ear and a strong desire to equalize. Progressive otalgia results with increased compression and there is an inability to equalize. An initial minimal conductive loss is due to the decreased compliance that results from the transtympanic pressure differential. The development of a middle ear effusion will follow quickly if the middle ear vacuum effect is maintained. This has been confirmed experimentally by introducing carbon dioxide into unilateral ears in monkeys, which results in the development of rapid negative middle ear pressures ('underpressure'). Subsequent MRI scans showed that the contrast leaked into the middle ears readily in those with induced negative pressure, but not into the control ears.[259] Mucosal oedema predictably occurs, even in those with normal Eustachian function, after repeated or long duration dives.[260] The increasing pressure differential may result in a perforation of the tympanic membrane and this is characterized by sudden severe pain. If diving, a sudden ingress of water into the middle ear may result in caloric vertigo (see 'Caloric vertigo' below). Severe middle ear barotrauma may also result in ossicular damage. Larger conductive losses may be observed with damage to the stapes footplate,[261] incus dislocation[262] and even a fractured malleus handle.[95, 263]

Examination of the tympanic membrane will reveal changes varying from a normal appearance (with mild symptoms), to free haemorrhage with a tympanic membrane perforation. These changes have been classified (**Table 91.8**)[264] and are a modification of Teed's four-grade classification.[265] Pure-tone audiometry and tympanometry are minimum investigations, a conductive hearing loss with decreased compliance and a negative middle ear pressure being expected. These tests should be used to monitor resolution in more severe cases. A treatment regimen has been suggested on the basis of a three-level clinical classification of severity.[242]

- Type 1: When there are symptoms of middle ear barotrauma, but no (or minimal) signs, no specific treatment is required.
- Type 2: When significant signs are present, but no perforation, conservative treatment is indicated with either oral or topical nasal decongestants.
- Type 3: Where there is middle ear barotrauma with perforation, an initial observation period is recommended with cleaning of the affected ear if necessary.

A myringoplasty is indicated in those cases that fail to heal spontaneously. Patients should be advised to await complete resolution of their symptoms before they return to diving or flying. Although Farmer's recommendations are of Grade C, and not specifically evidence-based, they are the result of a wide clinical experience, and are logical and consistent with established practice. As perforations secondary to middle ear barotrauma are usually found in otherwise healthy ears, the surgical results should be better than in cases following otitis media.

TABLE 91.8 Tympanic membrane appearance in middle ear barotrauma

Grade	Symptoms and signs
0	Symptoms, no signs
1	Redness and retraction
2	Intratympanic membrane haemorrhage
3	Gross tympanic membrane haemorrhage
4	Haemotympanum
5	Perforation

PREVENTION OF MIDDLE EAR BAROTRAUMA

Medical

High-quality RCTs have shown a strong effect for oral pseudoephedrine in the prevention of barotrauma when flying but not for topical xylometazoline.[266, 267] Similar results have been found in scuba divers.[268] No significant difference was found in the occurrence of otalgia between two groups of children under 6 years taking oral pseudoephedrine or placebo.[269] The use of oral psudoephedrine is recommended before flying, in those with mild Eustachian symptoms. This advice should not, however, be extended to scuba divers with acute Eustachian dysfunction due to the larger risk of middle ear barotrauma and the greater potential consequences of it.

Slowing down the rate of change of pressure is beneficial. The use of occlusive earplugs when diving or flying is contraindicated due to the risk of external ear barotraumas; pressure-equalizing earplugs are currently sold at many airports, but their benefit remains unproven. Small studies have suggested no benefit,[270] or possibly even an increase in the incidence of barotrauma.[271] A recent small double-blind, controlled pressure chamber study does, however, suggest that a 7-minute delay in the time taken to equalize the external ear canal pressure may be achieved, and that despite no measurable improvement in Eustachian tube function, symptoms are significantly improved. Slower rates of compression when delivering hyperbaric treatments may decrease the frequency.[272]

The use of nasal balloon inflation (auto-Politzerization) using Otovent™ (Abigo, Sweden) may be helpful in improving the ability to equalize by those who have difficulties performing equalization manoeuvres.[251]

Surgical

Performing myringotomies (often as a simple local anaesthetic procedure), and the insertion of ventilation tubes, may be appropriate for preventing otalgia and middle ear barotrauma in those wishing to fly. This procedure is clearly contraindicated for diving.

Eustachian tube balloon dilatation (balloon Eustachian tuboplasty) is gaining popularity and may become the treatment of choice, particularly for those who suffer from equalization difficulties flying.[273]

EUSTACHIAN TUBE DYSFUNCTION AND NASAL SEPTAL DEVIATION

The role of the nasal airway and nasopharynx in Eustachian tube function is complex and has been the subject of much research. There is, however, little knowledge regarding the effect of nasal surgery on the ability to equalize middle ear pressure. Only one controlled study has been attempted where posterior septal surgery considerably increased the ability to equalize to 10 m as compared to controls.[273] The author's experience is in marine biology students or commercial divers, who stand to lose their careers or licences because of inability to equalize their middle ear pressures. Despite some success, caution is advised, especially in those with minimal septal anomalies. More validation is required regarding the efficacy of this procedure.

DIVING AND FLYING AFTER MIDDLE EAR SURGERY

There are no specific data that precisely identify a 'safe' post-operative period after which it is safe to fly. Following reconstructive surgery most surgeons advise a restriction of any activity which might result in a sudden change in the middle ear pressure, for several weeks. Tympanic membrane grafts and ear canal healing should be complete before water sports are resumed, and flying should not be permitted until any aural packs are removed and healing verified. Slap injuries following stapes and total ossicular replacement surgery may be prevented by the use of earplugs. Evidence of adequate Eustachian function should be obtained prior to resuming diving or flying. Scuba diving after stapes surgery remains controversial and there are no good studies addressing this. Some patients insist on continuing with the sport and report no difficulties.[274] Animal experiments have shown no significant increase in inner ear barotrauma after stapedectomy when compared to control ears.[275] Safe diving should be possible in those post-tympanoplasty patients whose Eustachian function appears adequate.[249] If, however, it is poor, given the mechanisms of fistula formation, it is likely that particularly those who have undergone stapes surgery are at an increased risk of a perilymphatic fistula and even prosthesis displacement. As there are potentially fatal consequences of a perilymphatic fistula when diving, pursuing this after stapes surgery is considered by many to constitute an unnecessary risk. If patients are insistent, strict advice regarding Eustachian function and a post-operative wait of 6 months is recommended.

KEY POINTS

Middle ear barotrauma

- Middle ear barotrauma is very common during flight and scuba diving.
- The perceived ability to 'equalize' is a useful predictor for diving, but not for flying.
- Speed of compression is an important risk factor.
- Conductive hearing loss is usual.
- Oral pseudoephedrine and Otovent™ balloon may be effective preventative measures.
- Surgical repair of the tympanic membrane and even ossicles may be necessary.
- Nasal septal (vomeroethmoidal) surgery may improve the ability to 'equalize' middle ear pressures.
- Consider Eustachian tube balloon dilatation.
- **Prevention:**
  - oral decongestants [Grade A]
  - Otovent™ balloon
  - consider Eustachian tube balloon dilatation
  - no flying or diving with upper respiratory infections
  - identify those at risk
  - asymmetric equalizers
  - inability to voluntarily equalize at sea level (divers)
  - nasal obstruction.
  - treat nasal conditions
  - consider septal surgery
  - myringotomies/ventilation tubes for flying.
- **Diagnosis:**
  - obtain specific history: pain on descent
  - otoscopic appearance (Table 91.8)
  - audiometry: conductive loss.
- **Treatment:**
  - conservative/symptomatic initially
  - elective repair of the tympanic membrane and/or ossicles
- **Advice to patients:**
  - complete resolution is expected in mild cases
  - scuba adiving is contraindicated if problems persist
  - oral decongestants are helpful before flying/diving. [Grade A]

CALORIC VERTIGO

Asymmetrical contact of cold water with both tympanic membranes, or cold water ingress into one middle ear via a perforation, may result in a caloric effect. Causes include wax, exostoses, otitis externa, tight diving hoods, leaking earplugs or a foreign body in the external meatus. It is usually short-lived and mild. Cold water ingress through a tympanic membrane perforation may give severe symptoms. The colder the water, the more pronounced is the effect. On surfacing, the caloric stimulus is removed and the vertigo is self-correcting.

A history of Eustachian tube dysfunction may be present and examination may reveal a perforation or impacted ear wax. No residual audiological nor neurological signs or symptoms should be present after surfacing.[264]

KEY POINTS

Caloric vertigo

- Caloric vertigo involves the asymmetric exposure of each ear to cold stimulus.
- It is short-lived and self-correcting.
- It is very common in mild forms.
- There are no residual audiological or neurological symptoms or signs.

Inner ear barotrauma (compression inner ear barotrauma)

The pathophysiological mechanisms have been described above (see 'Physiological consequences of compression'). Histopathological studies have demonstrated three different pathological entities in the inner ear resulting from compression barotrauma:

- inner ear haemorrhage
- labyrinthine membrane tears
- perilymphatic fistula.

Various clinical matches have been proposed to explain the corresponding distinct patterns of presentation seen in temporal bone specimens.[276]

INNER EAR HAEMORRHAGE

This gives transient, or minimal, vestibular symptoms and mild to moderate sensorineural hearing loss. A good recovery is expected.

LABYRINTHINE TEARS

Tears of the labyrinthine membrane may produce similar symptoms, but any loss is permanent, often at 1–2 kHz. Patients may present with symptoms closely resembling those of an acute Ménière's disease attack, with vertigo and tinnitus, complete with the characteristic low-frequency hearing loss. Temporal bone studies have demonstrated Reissner's membrane rupture.[277] Similar occurrences have also been shown in airline passengers, either with or without labyrinthine window rupture.[278] Temporal bones from divers who died under such circumstances showed bleeding into the middle ear and mastoid. Inner ear damage consisted of haemorrhage around Reissner's and the round window membranes, as well as rupture of the utricle and saccule.[279] Implosive forces to the inner ear due to middle ear overpressure (occurring on ascent with a locked Eustachian tube) may cause more severe inner ear trauma than the more commonly occurring barotrauma on compression (descent).[280]

PERILYMPHATIC FISTULA

The diagnosis and management of perilymphatic fistula generates considerable debate. The condition was first recognized in aviators, although it has became of great interest in diving medicine.[281, 282] Detailed descriptions of labyrinthine window ruptures and inner ear trauma associated with inadequate middle ear pressure equalization were published in the early 1970s.[283, 284] Perilymphatic fistula is a well-recognized consequence of head injury, surgery, congenital anomalies, cholesteatoma and neoplasia. Spontaneous fistulae possibly occur, without any recognized aetiological factors, although controversy surrounds both their existence and management.[285–287] As many as 0.5% of divers have suffered from a perilymphatic fistula.[288]

Clinical features

The exact timing of the onset of symptoms relative to the injury is the single most helpful piece of clinical information. The dive profile is important for scuba divers and this will also assist in deciding if the dive was one from which a decompression illness could reasonably result (see below). The time of onset of these symptoms is usually definite in aviators but may only be recognized on surfacing in divers. A typical history is of difficulty equalizing the middle ear pressure during descent, particularly during an upper respiratory infection, resulting in a rigorous Valsalva manoeuvre being attempted. There is a sudden onset of vertigo, an accompanying hearing loss (sensorineural or mixed) and often tinnitus.[289] Muffled hearing and occasional, but persistent, dysequilibrium may be the only symptoms. Any acute symptoms often resolve rapidly after several days, although mild dysequilibrium (which may change to transient vertigo on straining), mild persistent nausea and motion intolerance, often with a subtle sense of 'not coping', are the most common symptoms of a chronic perilymphatic fistula. Fluctuating hearing is typical.

A perilymphatic fistula should be suspected in an otherwise healthy ear (or in one with evidence of middle ear barotrauma) if there is a sensorineural hearing loss of rapid onset, constant or intermittent dysequilibrium, positional nystagmus, Tullio phenomenon, a positive fistula sign and tinnitus. The main differential diagnosis is of inner ear decompression illness (**Table 91.9**). It is an important distinction as recompression in error may cause further middle and inner ear barotrauma. Conversely, not recompressing a patient with a decompression illness may result in permanent cochleovestibular damage, further progression of the decompression illness and even death.

Clinical signs

Examination of the tympanic membrane may reveal signs of middle ear barotrauma (see **Table 91.8**) but, unless it is an acute presentation, the appearance is often normal. A full neurological examination, including of the cranial nerves, should be performed. Nystagmus may be present, usually towards the contralateral side, but this may disappear over a few days as symptoms of vertigo often give way to the more typical dysequilibrium. The Romberg test is normal in more mild cases and, if it is possible to perform the Unterberger step test, this often yields a positive result. The 'side-step' test, a modification of the Singleton 'side-step turning test'[290] has been described, and has promising results.[291] With the eyes closed, the patient takes two consecutive broad steps sideways, and then stops with both feet together. A subsequent sway or overshoot in the same direction as the steps were taken is regarded as a positive result, the affected ear being on the side towards the direction of movement. Dix–Hallpike tests for positional vertigo are often positive but often do not give the typical results for BPPV. The nystagmus may be difficult to identify, is not usually rotatory and is often not towards the downward ear. The latency may be short or absent with little sign of any fatigability.[292]

TABLE 91.9 Differential diagnosis of inner ear barotrauma and labyrinthine decompression illness

	Middle ear barotrauma	Inner ear barotrauma	Inner ear decompression illness
Phase of dive/flight symptoms first noticed	Usually descent, possible on ascent (reverse squeeze)	Usually descent; may occur on ascent, or just after surfacing (<10 min)	Only during or after ascent; usually after surfacing; more likely near surface
Difficulty equalizing middle ear pressure	Yes	Yes	Not usual
Associated middle ear barotrauma	N/A	Usual	Not usual
Associated non-otological symptoms	None	None	Usually other symptoms of decompression illness
Vertigo	None	Usual	Usual – dysequilibrium may predominate
Sensorineural hearing loss	None	Frequent	Frequent – may be difficult to ascertain
Effect of recompression on symptoms	Worsened	Worsened	Improvement
Hearing loss	Conductive loss	Mixed loss – common (85%)	SN loss (38–66%)*

*Nachum et al.[345]

Investigations

The larger the fistula, the more likely are the clinical signs, and any special investigations, to be positive. Baseline pure-tone audiometry should be performed as soon as possible. Fistula tests are unreliable. An improvement in pure-tone thresholds when lying for 30 minutes compared to sitting (Frazer test), and external auditory meatus pressure change fistula tests using a Siegel's speculum, are only positive in 25–40% of surgically proven fistulae.[293, 294] Improved results (being positive in 90% of proven cases) have been obtained when using accurate pressure stimulation with tympanometry in conjunction with electronystagmographic recordings. The results, however, include fistulae from other causes, such as temporal bone trauma, post-surgical and congenital.[294] Unfortunately, it is the more subtle presentations, with smaller or intermittant fistulae, that cause the diagnostic uncertainty. In an attempt to address this, extensive studies utilizing transtympanic electrocochleography with tone-burst stimuli to confirm the presence or absence of surgical, post-traumatic and spontaneous fistulae have been performed.[295] Despite reasonable validation during stapes surgery, this method of investigation has not gained popularity. High-definition MRI and CT scans may prove useful. Their use may assist making the diagnosis, but the predictive value is unknown and probably low overall. The results of radiological investigations therefore should be considered only in the context of other clinical findings. Features which may be seen include intralabyrinthine air,[296, 297] fluid in an otherwise non-diseased mastoid or middle ear, and fluid in the round window niche on T2-weighted MRI.[298] Confirmatory tests at the time of surgery are considered below.

Treatment

Treatment options are based on hearing and balance restoration and preservation. Opinions vary between a conservative, expectant strategy and surgery. The results of hearing conservation and salvage are poor. This is probably because of frequent diagnostic delays that contribute to the permanence of any sensorineural hearing loss. For this reason, immediate surgery in all suspected cases has been advocated by some.[299] This approach clearly does not allow any time for spontaneous closure to take place. Many prefer an initial conservative approach, including bed rest for a minimum of 5 days. Exploration is then reserved for (i) those with progressive hearing deterioration observed on daily, or more frequent, audiometry, (ii) failure of the vestibular symptoms to improve after 5 days, (iii) failure of complete resolution after 1 month.[292] In reality there is a range of severity of the presenting symptoms and signs so, in the absence of definitive trial results, a pragmatic approach is suggested. This should be dictated by the observations that surgery seldom improves a hearing loss, although it may stabilize it, and that dysequilibrium is well treated, but the timimg of surgery for this indication is relatively unimportant. The initial management should therefore be dictated by the severity of the hearing loss. The following treatment strategies assume that a typical presentation of hearing loss with imbalance has occurred.

Moderate to severe hearing loss The overall picture is inevitably influenced by the time taken for the patient to present to the otologist. Emergency exploration is of relevance in more severe acute cases with both a significant sensorineural hearing loss and vertigo (30–40 dB HL or worse). Given the overall poor prognosis for hearing, there is no advantage in delaying and immediate exploration is therefore recommended.

Minimal hearing loss (high-frequency only, or mean 20 dB HL loss) Many patients with inner ear barotrauma do not have an obvious history and findings consistent with a perilymphatic fistula. For those with more mild sensorineural hearing losses and vestibular symptoms, an initial conservative approach is reasonable. Bed rest is

advised, with elevation of the bed head to 30–40 degrees. Raising the intracranial pressure by coughing, straining, vomiting or performing the Valsalva manoeuvre should be avoided. This is also recommended as the initial management of all cases where there is any suspicion of a perilymphatic fistula, while deciding on further action. Steroids are often prescribed, despite the lack of evidence for their use, particularly when a presumed diagnosis of an intralabyrinthine haemorrhage or tear is supposed. An initial conservative approach has become more favourable as surgical exploration appears to treat vestibular symptoms more effectively than it does improve the sensorineural hearing loss.[300] This may be because some of those reported may not have had fistulae, but intralabyrinthine pathology only. Patients should have daily audiometry performed and this should be repeated immediately if there is any subjective deterioration. If confirmed objectively, surgical exploration should be performed without delay.

Mild to moderate hearing loss (20–40 dB HL) If presentation is less than 24 hours following the event, and vestibular symptoms and signs predominate, then immediate exploration is appropriate. After 24 hours, the need for exploration should be judged predominantly on serial daily, or more frequent, audiometric findings. An ear with evidence of deteriorating hearing should always be explored, without waiting until the next day to validate the deterioration. If the hearing has spontaneously improved, it is reasonable to wait for 5 days before exploration for persistent vestibular symptoms; if there is no hearing loss, a conservative strategy may be followed for up to 4 weeks. Once stable good hearing has been verified, this may be at home provided that rest and the above-mentioned precautions are observed. Some surgeons do not perform surgery before 2 weeks have passed as spontaneous resolution is often encountered. The earlier the presentation with hearing loss, the worse the hearing loss, and the worse the vestibular component, the stronger is the indication for urgent surgery.

Despite a trend towards a conservative approach, several other issues should be considered. An exploratory tympanotomy should present very few surgical risks if performed by a specialist otologist in an otherwise medically fit patient.[301] There is little evidence to support either the conservative or aggressive surgical strategy but deterioration is necessarily a retrospective finding. The overall morbidity, inconvenience and cost of 2 weeks or more of bed rest are often ignored. Overall, a low threshold for exploration is recommended.

Future studies

The identification of idiopathic perilymphatic fistula remains controversial.[287] However, it is unlikely that any further significant progress will occur until a reliable marker of perilymph (possibly cochlin-tonoprotein) is identified and studies on those patients with sudden hearing loss and vestibular symptoms, without a suggestive fistula history, are performed.

Acute sensorineural hearing loss without vestibular symptoms

A sudden hearing loss may occur in the absence of any vestibular symptoms. An isolated intracochlear decompression illness is the main differential diagnosis, so the appropriate history, including middle ear symptoms associated with inner ear barotraumas, must be sought. An intracochlear haemorrhage is the probable aetiology and this may be apparent on MRI. Despite a lack of convincing evidence, oral or intratympanic steroids should be considered for patients with moderate and severe losses (see Chapter 60, Idiopathic sudden sensorineural hearing loss). An immediate tympanotomy would be difficult to justify unless serial audiometry suggests fluctuating hearing without overall spontaneous improvement. In those cases where there is a dead ear, alternative pathologies require exclusion (see Chapter 60, Idiopathic sudden sensorineural hearing loss).

Care should be taken that all patients are followed up, as cases of perilymphatic fistula presenting with chronic dysequilibrium are encountered many months or even years after the event.

Surgery for perilymphatic fistula

Numerous series and case reports have been published covering a broad spectrum of aetiologies, usually post-trauma or congenital fistulae in children.[300, 301] A standard tympanotomy is performed but care must be taken to avoid mucosal damage. Identification of the site of the fistula is notoriously difficult. It may be useful to place the patient in a head-down position and increase the ventilatory pressure. Unfortunately, this also encourages bleeding, which may further increase the degree of uncertainty.

Intra-operative identification using intrathecal fluoroscein is not reliable for locating perilymphatic fistulae as the timing of the injection relative to the surgery, the slow and unpredictable diffusion rate of the marker into the perilymph and the differing patencies of the cochlear aqueduct make it unreliable.[302] Intravenous fluoroscein is not useful as it appears as a transudate in the middle ear and is not taken up readily into the perilymph.[303] Mixing it with the local anaesthetic infiltration may be useful as perilymph, not being stained, will appear to displace any fluorescein containing fluid.[304]

Careful inspection of the round and oval windows, around the middle ear and the Eustachian tube orifice for a source of the leak is performed. An endoscopic technique may have the advantage of keeping the dissection to a minimum hence decreasing the amount of blood and exudate in the middle ear at the time of surgery.[305] Despite these advantages, when used alone, the method may not be adequate to exclude a perilymphatic fistula,[306] and the adequacy and interpretation of the view is more important than the method used. The round window membrane itself is usually hidden within the bony niche and it is easy to mistake mucosal folds for the true round window membrane. If this occurs, or if endoscopic methods are unfamiliar or unavailable, then curetting away the bony overhang should enable a better view. If a drill is used, it may be useful to mix fluorescein into the irrigation fluid.

Care is required not to traumatize the membrane. Any fistula found should be covered with a tissue plug and supported by absorbable middle ear packing material. If no definite fistula is observed, it is sensible to place a tissue graft in the round window and over the footplate. Fat has the advantage of filling in depressions whereas vein is useful due to the 'sticky' nature of its adventitial surface. The author usually uses both.

It is probably unwise to perform ossicular surgery at the same procedure. Given the possibility of a cochlear concussion type of injury, the inner ear may be susceptible to even minor degrees of further trauma. Repair of the tympanic membrane should, however, be performed at the time. If a delayed exploration for persisting dysequilibrium with a stable sensorineural loss is performed, appropriate ossicular surgery might be considered, provided the necessary audiological criteria are satisfied.

Confirmatory intra-operative tests

The collection of fluid for analysis as a confirmatory test for the presence of perilymph may provide retrospective evidence for a perilymphatic fistula. Beta 2-transferrin is 100% specific but its low sensitivity of 29% makes this test not worthwhile.[307, 308] Cochlin-tonoprotein is a 16 kDa protein that has been identified in human perilymph.[309] It is not present in other body fluids[310] and has been found in 92% of perilymph samples, as compared to 0% of CSF, from the same patients.[311] There is a claimed specificity of about 98%.[311] There may therefore be a confirmatory diagnostic test available in the future.

Results

The data available are difficult to interpret as some patients without surgically identified fistulae improve as a result of, or despite, their surgery. Spontaneous improvement is often seen in more mild cases, even if no surgery is performed. Despite these restrictions, surgical intervention appears to relieve vestibular symptoms (87%) and to improve the hearing in about 40% of sudden hearing loss cases.[299] Other reports suggest that hearing stabilization, rather than necessarily improvement, is achieved in most cases.[301]

KEY POINTS

Inner ear barotrauma

- There are three types of inner ear barotrauma: inner ear haemorrhage, labyrinthine tears and perilymphatic fistulae.
- The history of pressure/time profile of the incident is important.
- The most suggestive symptom is dysequilibrium with manoeuvres which increase intracranial pressure.
- Other symptoms include sensorineural hearing loss (may fluctuate), chronic dysequilibrium, mild nausea, unaccustomed motion sickness, vertigo, tinnitus, positional vertigo and Tullio phenomenon.
- Clinical fistula signs are only useful if positive.
- Otoscopy is sometimes normal.
- The decision for surgical exploration is based on the severity of the presenting hearing loss and failure of the vestibular symptoms to resolve.
- Surgical results are good for vestibular symptoms and relatively poor for hearing improvement.
- **Prevention:**
  - as for middle ear barotrauma (above)
  - avoid over-rigorous attempts to equalize middle ear pressure
  - identify those at risk:
    - as for middle ear barotrauma (above)
    - previous perilymphatic fistula.
- **Diagnosis:**
  - must distinguish from decompression illness (**Table 91.9**)
  - obtain the exact nature and timing of symptoms
  - establish the time/pressure profile
  - conduct a full neurological examination, including postural balance tests
  - pay attention to the direction and nature of nystagmus, with/without the removal of optic fixation
  - maintain monitoring with daily audiometry
  - conduct a tympanometric held pressure fistula test with electronystagmography
  - consider tone-burst electrocochleography.
- **Treatment:**
  - always consider the need for early surgery – continue to review
  - use steroids for moderate and severe hearing losses
  - carry out immediate surgical exploration if there is short presentation and moderate/severe hearing loss
  - surgical exploration for:
    - progressive hearing loss
    - persistent disequilibrium
    - close obvious fistulae, if unclear then cover both windows with fat/vein adventitia.
- **Advice to patient:**
  - complete resolution is expected in mild cases
  - scuba diving is contraindicated if problems are persistent
  - take decongestants before flying/diving
  - beware of lifting/straining/flying for 6 weeks post-operatively.

INJURIES AT HIGH PRESSURE

High-pressure nervous (neurological) syndrome (isobaric gas counterdiffusion)

High-pressure nervous syndrome may occur when divers are exposed to extremely high pressures. The characteristic symptoms are of tiredness, general dizziness and tremors (both postural and intentional, of the hands and even of the whole body) that may progress, with increasing pressure, to ataxia and myoclonus. Unlike nitrogen narcosis, psychomotor impairment exceeds intellectual impairment. The depth at which the condition occurs depends on the compression rate. Symptoms may occur at high pressure, but characteristically soon after changing the inspired gas mixture to one that includes a second inert gas. The sudden onset of vertigo and nausea with nystagmus has been reported as part of this syndrome.[312] Permanent vestibular damage has been described, but there is no hearing loss.[313, 314]

KEY POINTS

High-pressure nervous syndrome

- High-pressure nervous syndrome occurs with extreme pressure exposure.
- It usually occurs on changing inspired gas mixtures.
- It is characterized by tiredness, general dizziness and tremor.
- It may progress to include vertigo, ataxia and myoclonus.
- Psychomotor impairment exceeds intellectual impairment.
- Permanent vestibular damage may result, with no hearing loss.

DECOMPRESSION (ASCENT) INJURIES

Alternobaric vertigo

This is a condition of asymmetrical middle ear overpressure stimulation occurring in divers,[315, 316] air passengers and crew.[317] It usually occurs in those who describe unilateral equalization problems. On ascent, failure of equalization due to minor middle ear congestion and oedema, or unilateral Eustachian tube dysfunction, may lead to a relatively higher pressure in one middle ear. Of 2053 Swedish divers, 22% described symptoms consistent with alternobaric vertigo at some time during their diving careers.[318] The condition occurs on ascent or within 2 minutes of surfacing. Episodes are not usually severe, with a maximum duration of about 10 minutes. Divers may also describe a tumbling sensation, or a tilting of their surroundings, rather than simple rotation. Experimental evidence supports these clinical observations, with true vestibular nystagmus demonstrated when middle ear overpressure was present in only one ear during controlled decompression in a pressure chamber.[319, 320] Animal studies have also demonstrated an increase in vestibular neuronal impulses as a response to middle ear overpressure.[321] It is, however, not exclusively a condition of ascent. Twenty-seven percent of cases occurred during descent.[315]

KEY POINTS

Alternobaric vertigo

- Alternobaric vertigo is caused by asymmetric middle ear overpressure.
- It is common in divers and aircrew.
- It often has a preceding history of unilateral difficulties 'equalizing'.
- It usually occurs with decompression (27% with compression) or within 2 minutes of surfacing. It is rare for signs to persist for more than 10 minutes.
- There are no permanent sequelae.

Barotraumatic facial palsy (facial baropareisis, alternobaric facial palsy)

A transient facial nerve palsy may occur as a result of high middle ear pressure during ascent. It has been described in both aviators and divers.[322, 323] A correct diagnosis is important to avoid potentially hazardous, and unnecessary, recompression treatment. It is probably due to a pressure-induced neuropraxia in an individual with a congenital dehiscence of the facial nerve in its intramastoid portion (0.5–57% of all temporal bones).[324] Animal studies have demonstrated that blood flow in the vasa nervora of the facial nerve decreases if increased middle ear pressure is transmitted through a dehiscence of the facial canal.[325] A neuropraxia has also been induced by applying increasing pressures to an exposed part of the facial nerve in cats.[326] In a non-dehiscent facial canal, pressure may be transmitted through the fenestra of the chorda tympani.[327] The blood flow, and the palsy, rapidly return to normal when the middle ear pressure is relieved. The condition may be associated with alternobaric vertigo. It is important to rule out other causes of facial palsy (see Chapter 112, The facial nerve and its non-neoplastic disorders). Clinical evaluation should include complete general neurological and neuro-otological examinations, the main differential diagnosis being a decompression illness. A facial palsy due to this would be very unlikely to occur in isolation without any other neurological symptoms or signs. Patients are likely to have associated symptoms and signs of otitic barotrauma (see Table 91.8). The onset is typically rapid and the condition resolves after a few minutes. This would be very unlikely to be the case if a decompression illness were the cause.

If there is a bulging tympanic membrane, then a myringotomy should be performed, although a persisting palsy should be investigated and treated as for a decompression illness. Recompression treatment may worsen symptoms when Eustachian tube dysfunction is still present, but it is clearly not indicated when a diagnosis of isolated barotraumatic facial palsy has been made. If a decompression illness is also suspected, or if uncertainty as to the true diagnosis persists, a myringotomy should be performed and a grommet inserted prior to proceeding with recompression treatment. A full recovery is expected.

KEY POINTS

Barotraumatic facial palsy

- Barotraumatic facial palsy is caused by middle ear overpressure during ascent.
- It involves neuropraxia secondary to compression of the vasa nervora.
- No other neurological symptoms or signs are present.
- It is often associated with mild middle ear barotraumas.
- Rapid spontaneous resolution is expected.
- Myringotomy should be performed if there is persistence, when a bulging tympanic membrane is identified.

NON-BAROTRAUMA-ASSOCIATED INNER EAR PROBLEMS IN DIVERS

Frequent high pressure exposure itself has been refuted as a cause of sensorineural deafness.[328, 329] Animal studies have suggested inner ear damage,[330, 331] but with adequate controls no histological inner ear damage was then

found even after the application of extra high ambient pressures.[332] The predominant cause of increased hearing thresholds in commercial divers is noise induced with no evidence for hearing loss or vestibular impairment associated with diving itself.[333, 334] There is a similar lack of convincing evidence in sports divers.[335]

DECOMPRESSION ILLNESS AND HYPERBARIC MEDICINE

Pathophysiology

VENTILATORY EFFECTS

The exchange of oxygen and carbon dioxide between the alveoli and blood occurs down concentration gradients. Assuming normal ventilation, as oxygen is utilized by respiration, there is a continuous transfer of oxygen into the blood from the alveoli, with carbon dioxide transfer in the opposite direction. Pulmonary transfer of inert gases depends on the solubility of that gas in blood. At low ventilation rates, highly soluble gases exchange slowly as they remain more easily equilibrated with their blood concentrations across the alveolar membranes. Gases, such as nitrogen and helium, have low solubility in blood (i.e. tend to remain in gas phase rather than solution), resulting in their rapid exchange almost whatever the ventilation rate. Thus equilibration of their alveolar–arterial gas tensions readily occurs.

Henry's law states that the amount of gas dissolved in a tissue is proportional to the pressure on that tissue. During descent (compression), the increased ambient pressure results in a greater amount of nitrogen dissolved in both the arterial and venous blood. During ascent (decompression), as the ambient pressure falls, a gas phase will form within the tissue unless the gas is metabolized or removed at a sufficiently fast rate. Nitrogen and other inert gases, which cannot be metabolized, are only transferred via a concentration gradient from the tissues back into the blood stream. Nitrogen has a low partition coefficient (water/oil, 0.19) as it is more soluble in lipids than in water. Consequently, its transfer from the tissues to the vasculature is slow. Once in the blood it is transported to the lungs where the gas tensions in the pulmonary capillaries are equilibrated with the partial pressures of gases in the alveoli before exhalation. If subsequent decompression is too rapid, nitrogen bubbles will form.

BUBBLES

A bubble in the body is only absorbed when its nitrogen partial pressure exceeds the nitrogen tension in the surrounding blood/tissue.[239] If a short dive takes place, there will be little time for nitrogen to dissolve and diffuse into tissues, and therefore a rapid ascent is possible. When decompressing after a longer dive, carbon dioxide will come out of solution very quickly due to its high solubility. Provided adequate ventilation continues, it traverses the alveolar membranes and is expired so quickly that bubbles do not have time to form. Due to nitrogen's low partition coefficient, interstitial nitrogen microbubbles will form and subsequently enlarge, unless the rate of transfer through the endothelium into the vasculature exceeds the rate of their formation. Likewise, primary intravascular bubbles will form if the rate of nitrogen forming a gaseous phase is faster than the lungs' ability to remove the excess dissolved nitrogen. Doppler ultrasound has shown that bubbles are present in the venous systems of many divers during decompression, without consequence.[336] These bubbles pass through the venous system until they are trapped and filtered by the pulmonary vascular bed, where diffusion into the alveoli occurs. Pathological effects may be seen if there is: saturation of the pulmonary filter (resulting in arteriovenous shunts), a patent foramen ovale of the heart or rupture of alveoli (or a pre-existing lung bulla) causing pulmonary barotrauma.

Exercise significantly affects tissue uptake of nitrogen during compression[337] and speeds expulsion on decompression.[338] Obesity (nitrogen being more soluble in lipids than in water) and increased age may increase the tendency to develop decompression illness, although this is disputed.[339]

KEY POINTS

Hyperbaric pathophysiology

- Increased ambient pressure (compression) increases the amount of dissolved gases in blood and tissues.
- Decompression results in a gas phase, unless metabolism or removal are at a sufficient rate.
- Nitrogen transfer from tissues to blood is slow (low partition coefficient).
- Short dives give insufficient time for nitrogen to dissolve and diffuse into tissues.
- Exercise during compression increases the amounts of dissolved nitrogen.
- Vascular bubbles forming on decompression cause vascular occlusion and direct endothelial damage.

Hyperbaric oxygen treatment (therapy)

Bubbles in the blood are a common occurrence in decompression situations. They are inconsequential, unless their number or size is sufficient to cause symptoms. The two central concepts of hyperbaric medicine are the ability to (i) dissolve gas nuclei by rapid compression and (ii) increase the amount of gas in solution.

The Undersea and Hyperbaric Medical Society indications for hyperbaric oxygen treatment are shown in **Box 91.1**. A systematic review has found that convincing results have only been achieved in treating decompression illness and gas embolism.[340] This is supported by established physiology, results from animal experiments and extensive clinical experience spanning over 100 years. Using the Grading of Evidence, Assessment, Development and Evaluation (GRADE) system for reviewing evidence, the evidence level has been elevated from C to A for these indications.[341] There is a convincing physiological case for its use in carbon monoxide poisoning. In conditions such as clostridial myonecrosis, synergistic gangrenes, crush syndromes and osteomyelitis, results are difficult to assess as its role is predominantly adjuvant and, therefore, controlled studies are very difficult to perform. Anecdotal and series reports describe good results in many cases.

BOX 91.1 Approved indications for hyperbaric oxygen therapy

Air or gas embolism
Carbon monoxide poisoning
Clostridial myositis and myonecrosis (gas gangrene)
Crush injury, compartment syndrome and other acute traumatic ischaemias
Decompression illnesses
Arterial insufficiencies: central retinal artery occlusion
Enhancement of healing in selected wound problems
Severe anaemia
Intracranial abscess
Necrotizing soft-tissue infections
Osteomyelitis (refractory)
Delayed radiation injury (soft tissue and bony necrosis)
Skin grafts and flaps (compromised)
Thermal burns
Idiopathic sudden sensorineural hearing loss
(Source: Undersea Medical Society 2014, www.uhms.org. Reproduced with permission.)

Hyperbaric oxygen treatment is indicated in all cases of suspected decompression illness because failure to treat is associated with permanent functional damage, and death.

Pathological effects of bubbles on the inner ear

Obstruction of small vessels may cause damage to susceptible organs, including the inner ear. Animal experiments following forced decompression showed evidence of irritation of the semicircular canal endostea with osteoblastic and fibroblastic differentiation, finally leading to fibro-osseus labyrinthitis,[342] and also to cause both bubbles and haemorrhages in the labyrinthine fluid spaces.[343] In humans vascular obstruction, haemorrhage and exudates in the inner ear fluid spaces and bubbles within endostial bone immediately around the semicircular canals. Microfractures into the pericanal spaces and new bone growth have been described.[344]

KEY POINTS

Hyperbaric treatment

- Hyperbaric treatment increases the amount of gas in solution.
- It dissolves gas nuclei by rapid compression.
- It is highly effective for cases of decompression illness and gas embolism.
- It has an adjuvant role in gangrenes, crush syndromes and osteomyelitis.
- Failure to give hyperbaric oxygen treatment rapidly in decompression illness is associated with permanent functional damage.

INNER EAR DECOMPRESSION ILLNESS

Decompression illnesses have been classified into two types:

- Type I: Musculoskeletal pain predominates, although cutaneous features (itching, urticarial rash, burning sensation) and systemic symptoms of malaise, anorexia and fatigue are also included.
- Type II: Cardiorespiratory and/or central nervous system involvement.

As many as 70% of all divers with this condition have followed their decompression tables correctly, many reports occurring after shallow sport dives.[345] The diagnosis may be very difficult to distinguish from inner ear barotrauma, especially as both often coexist with middle ear barotrauma. A careful history of the dive profile, the timing of the onset of symptoms, and their exact nature, is essential. The verification of the dive history is usually straightforward as many divers now carry electronic dive computers that provide at least a depth/time printout. The onset of decompression illness symptoms is usually only a few minutes (but may be as long as up to 36 hours) after surfacing. A history of symptoms starting when returning from a diving holiday by air is not uncommon as flying after diving may exacerbate, or even cause, decompression illness.[346] There is an increase in the tendency for more nitrogen to come out of solution due to the lower partial pressures of the inspired air and the decreased ambient pressure at altitude.

Organs with high metabolic rates and unit blood flow, such as the stria vascularis, are more susceptible.[347, 348] Isolated vestibular or hearing symptoms are rare. A history of other symptoms attributable to a decompression illness should be sought. Localized pain (91.8%), numbness or paraesthesia (21.2 %), muscular weakness (20.6%) and skin rash (14.9%) are the most frequently described. Non-specific dizziness or vertigo was the fifth most common (8.5%) with auditory disturbance occurring in only 0.3%.[349]

The time of onset is an important factor when attempting to differentiate decompression illness from other conditions. In cases of central nervous system (type II) decompression illness, 50% of patients report the onset of their symptoms within 10 minutes of surfacing and 90% within 3 hours.[350] Type I decompression illness has a longer delay, but 90% become symptomatic within 6 hours of surfacing. Most patients presenting to the otolaryngologist following a dive or a sudden decompression aviation incident, who do not only have middle ear barotrauma, will complain of dizziness or vertigo. Very few of these, however, will have either inner ear barotrauma or inner ear decompression illness (**Table 91.10**). True vertigo is unusual,[351] as is a sensorineural hearing loss (**Table 91.11**). The low numbers of inner ear barotrauma and perilymphatic fistula patients emphasizes the relative rarity of these conditions, and also the difficulties establishing a diagnosis when frequent complex symptoms and signs coexist, with the presentation often being delayed.

Clinical signs

Otoscopy, fistula tests and a full neurological examination, Romberg, Unterberger, head-thrust and Dix–Hallpike positional tests should all be performed if possible. Nystagmus may be present and the use of Frenzel glasses

TABLE 91.10 Coexisting symptoms in 97 consecutive divers presenting to a tertiary centre with 'dizziness'

Symptom	Number of patients
Paraesthesia	26
Joint pain	25
Pain in limbs	18
Weakness in limbs	11
Hearing loss	9
Back pain	5
Abdominal pain	4
Skin rash	4
Unconsciousness	4
Blurred vision	3
Convulsions	1

Source: Primary database - Diving Diseases Research Centre, Plymouth, UK.

TABLE 91.11 Final diagnoses in 97 divers presenting with 'dizziness' to a tertiary centre

Diagnosis	Number of patients
Anxiety	1
CAGE	6
Near-drowning	2
Decompression illness, unspecified	3
Decompression illness, neurological	47
Decompression illness, joint	7
Decompression illness, skin	3
Decompression illness, musculoskeletal	3
Decompression illness, spinal	7
Decompression illness, pulmonary barotrauma	1
Decompression illness, pain	10
Decompression illness, inner ear/vestibular	4
Gas embolism	1
Hypocapnia	1
Muscle pain	3
Trauma right knee	1
No abnormality found	2

More than one diagnosis may apply. Source: Diving Diseases Research Centre, Plymouth, UK, (Bryson P./Toynton S. unpublished data).

to remove optic fixation typically enhances the nystagmus occurring with peripheral vestibular lesions. The clinical assessment should concentrate on differentiating not only between inner ear barotrauma and inner ear decompression illness, but also between a localized peripheral vestibular and a brainstem decompression illnesses. The distinction between central and peripheral causes of vertigo is discussed elsewhere (see Chapter 62, Evaluation of balance). Clinical features, which may aid in the differential diagnosis, are shown in Table 91.9.

Investigations

Investigations for general dizziness and hearing loss should be performed as appropriate, and as soon as the clinical situation allows (see Chapters 49, Physiology of equilibrium and Chapter 62, Evaluation of balance). Otological evaluation is often only practical after substantial hyperbaric and supportive treatment. An audiogram may be possible, but caloric and electronystagmographic testing is not well tolerated in the acute stage. Intracranial gas bubbles may form within any of the tissue or fluid spaces, including within the endolymph and perilymph. Probably more commonly however are embolic phenomena caused by large quantities of bubbles that have not been filtered by the pulmonary bed. Patients with evidence of an inner ear or other intracranial decompression illness should therefore undergo echocardiography to exclude a patent foramen ovale, which may occur in 48-80% of cases.[351–353]

Treatment

Recompression treatment should be instigated straight away. If there has been any suggestion of middle ear barotrauma, difficulty with middle ear pressure equalization, doubt as to the exact diagnosis, or a possibility of an overlooked perilymphatic fistula, then performing myringotomies (and preferably the insertion of grommets) beforehand is essential. The clinical features in a small series of 29 cases of inner ear decompression illness were as follows: pure vestibular involvement in 10 (34%), localized cochlear insult in 4 (14%), combined cochleovestibular event in 15 (52%). Two-thirds had a hearing loss at presentation. Consistent with most publications, they described a great difference in decompression illness resolution if treated with hyperbaric oxygen treatment within 6 hours (53% complete resolution of symptoms) as compared to those treated after this time (only 1 of 9 patients' symptoms resolved). Overall, only 6 of the 19 patients (32%) with cochlear damage made a full recovery.[345]

KEY POINTS

Inner ear decompression illness

- Many scuba divers have followed decompression tables correctly.
- Inner ear decompression illness may occur after shallow 'sports' dives, in common with other decompression illness.
- The differential diagnosis between inner ear decompression illness and inner ear barotrauma may be difficult (Table 91.9).
- Inner ear decompression illness may be precipitated by flying soon after diving.
- Isolated vestibular/cochlear decompression illness is rare; concurrent decompression illness symptoms/signs should be expected.
- All cases must be screened for a patent foramen ovale;
- Recompression within 6 hours is mandatory for all cases.
- **Prevention:**
  - avoid sudden decompression
  - ensure sufficient decompression times when diving
  - identify those at risk

  - those working/exercising under compression conditions
  - previous decompression illness
  - repeated dives
  - flying after diving.
- **Diagnosis:**
  - must distinguish from inner ear barotrauma (Table 91.9)
  - obtain exact nature and timing of symptoms
  - establish time/pressure profile
  - comprehensive neurological examination, including postural balance tests
  - echocardiography to exclude patent foramen ovale.
- **Treatment:**
  - urgent fluid resuscitation
  - early recompression hyperbaric oxygen therapy, within 6 hours
  - recompress if in doubt
  - myringotomy/grommets if impaired consciousness or equalization difficulties.

MIDDLE AND INNER EAR BAROTRAUMA SECONDARY TO HYPERBARIC OXYGEN TREATMENT

Middle ear barotrauma is the most common complication of hyperbaric oxygen therapy occurring in about 8% of patients undergoing repeated treatment dives.[354, 355] The incidence of vestibular symptoms with hearing loss is about 1.5% of dives or in 3% of those treated.[355] This is far more likely to occur in those in whom the indications included osteoradionecrosis of the head and neck region.[356] An inability to voluntarily autoinflate the middle ears prior to treatment increases the risk of developing middle ear barotrauma.[357] Unconscious patients or those with artificial airways while anaesthetized have a 94% chance of barotrauma, therefore routine insertion of ventilation tubes in such patients is indicated.[358] Other risks include the elderly, females, a history of cardiovascular disease and head and neck cancer, particularly following radiotherapy.[359]

KEY POINTS

Middle and inner ear barotrauma secondary to hyperbaric oxygen treatment

- Barotrauma is a common sequela of hyperbaric therapy.
- Risk is increased with:
  - increasing frequency of treatments
  - unconscious patients
  - osteoradionecrosis of temporal bone
  - inability to voluntarily equalize middle ear pressures
  - cardiovascular disease.
- There should be a low threshold for prophylactic myringotomies/ventilation tubes.

CEREBRAL AIR GAS EMBOLISM

Cerebral air gas embolism (CAGE) is the most serious and dramatic event for both scuba divers and aviators. It may occur during any depth of dive, even in swimming pools. It is usually seen in inexperienced divers who breath-hold when surfacing in an emergency. Ascent of only 1 m, without exhalation, is sufficient to produce microalveolar tears. Massive air gas embolism therefore occurs in the brain and the rest of the body. Involvement of the coronary arteries and brain are the predominant causes of the high rate of sudden death. Symptoms and signs are typically of very sudden onset and occur on ascent or very soon after surfacing. These include chest pain, severe dyspnoea, subcutaneous crepitus, dysphagia, dysphonia, general or focal seizures, confusion, hemiplegia, focal weakness, visual field defects and blindness. Blood-stained frothy sputum is a common feature.

Vertigo is commonly described and may be the presenting symptom in about 25% of cases. This usually occurs without either sensorineural hearing loss or tinnitus. Usually other neurological signs develop rapidly. The main differential diagnosis being of inner ear decompression illness, but the history, speed of onset, severity, associated signs and symptoms (such as surgical emphysema in the neck and on X-ray) usually prevent diagnostic difficulties. Emergency treatment is to place the patient in the Trendelenberg (head-down) position breathing oxygen. Following this, recompression takes priority over all other treatment and assessment options.[360]

FUTURE RESEARCH

➤ This chapter has provided an in-depth review of the otological conditions associated with barotrauma and hyperbaric conditions. While the underlying physics and physiology are well researched and understood, the clinical conditions, their diagnosis, treatment and prognosis are not.

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CHAPTER 92

OTALGIA

Philip D. Yates

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: earache, otalgia, referred otalgia, geniculate neuralgia, carotidynia, glossopharyngeal neuralgia, temporomandibular joint and earache and/or otalgia, and by the Cochrane Database of Systematic Reviews.

INTRODUCTION

Otalgia can arise from pathology within the ear (primary otalgia) or as a result of disease processes elsewhere (secondary or referred otalgia). While in children otalgia is much more frequently otogenic, in adults referred otalgia is the more common cause.[1]

Anatomy

The sensory supply of the ear is highly complex and not fully determined. It is this complexity that can lead to diagnostic difficulty in a patient presenting with otalgia, particularly when it is the only symptom. There are four cranial nerves and two cervical nerves that contribute to the sensory supply of the ear. The greater auricular nerve and, to a lesser extent, lesser occipital nerve supply sensation to the whole of the cranial surface of the pinna and to the lateral surface below the meatus (C2 and C3) (**Figures 92.1** and **91.2**). The auriculotemporal nerve, a branch of the mandibular division of the trigeminal nerve, supplies the lateral surface of the tympanic membrane, the external acoustic meatus and the lateral skin of the pinna above the level of the external meatus. The auricular branch of the vagus (Arnold's nerve) supplies the posteroinferior quadrant of the tympanic membrane, posteroinferior meatal skin and an area of the concha. The extent of facial nerve innervation of the ear roughly corresponds with that of the vagus, but its contribution is sparse.

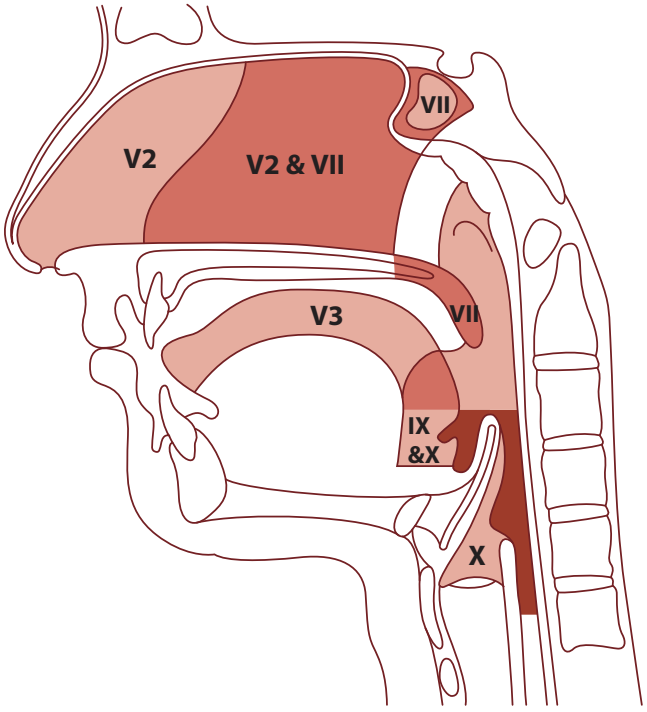

Figure 92.1 Otalgia arising from head and neck sources. Essentially any pathology residing within the sensory net of cranial nerves V, VII, IX and X and upper cervical nerves C2 and C3 can potentially cause pain referred to the ear. Adapted from Scarbrough et al. *Am J Clin Oncol* 2003; **26**(5): e157–62.[8]

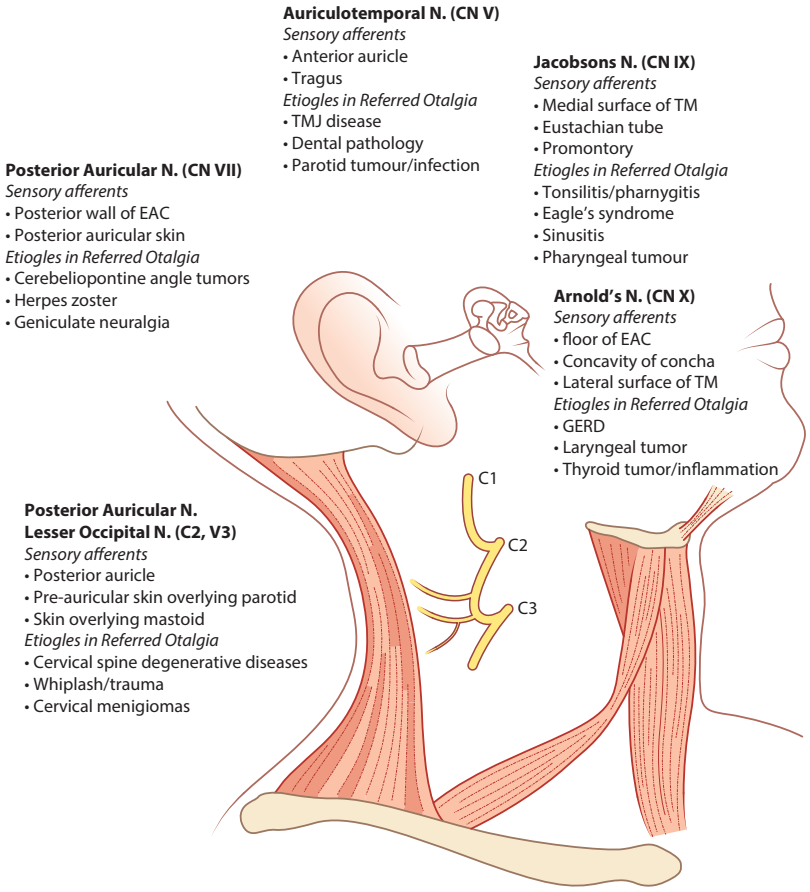

Figure 92.2 Complex sensory innervation of the ear and periauricular structures and various aetiological causes in referred otalgia. Adapted from Jaber et al. *Otolaryngol Head Neck Surg* 2008; **138**(4): 480.[22]

The middle ear is supplied by the tympanic branch of the glossopharyngeal nerve (Jacobson's nerve).[2, 3]

Referred pain is a commonly encountered clinical phenomenon, although its mechanism is not fully understood. **The trigeminal nerve is probably the most common pathway of origin of referred pain to the ear.** The mandibular division of the trigeminal nerve carries sensation from the anterior two-thirds of the tongue, floor of the mouth, palate, lower teeth, major salivary glands, temporomandibular joint (TMJ) and mandible. Referred pain arising from structures in these areas tends to be perceived in the ear canal. Although the facial nerve is mainly motor, it has sensory divisions including the nervus intermedius of Wrisberg and the greater superficial petrosal nerve, which conveys sensation from the posterior nasal cavity and sphenoid sinus. The glossopharyngeal nerve receives sensory input from the posterior third of the tongue, palatine tonsils, nasopharynx, hypopharynx and parapharyngeal and retropharyngeal spaces. Pain referred from these structures tends to be perceived as a deep intense otalgia. The vagus nerve supplies the valleculae, supraglottis, thyroid gland and more distant sites within the thorax including the tracheobronchial tree and oesophagus. The upper cervical nerves (C2 and C3) innervate the muscles and facet joints of the cervical spine.[4, 5]

The fact that sensory innervation of the ear is so diverse means that the potential origin of referred otalgia is widely distributed through the head and neck, and even beyond.

PRIMARY OTALGIA

External and middle ear diseases can lead to otalgia, and most otolaryngologists and primary care physicians are trained to recognize an abnormality in these areas. Conditions of the ear resulting in localized pain are discussed elsewhere in this book and further discussion will not be duplicated in this chapter. Table 92.1 summarizes the causes of primary otalgia.

REFERRED OTALGIA

In a patient presenting with otalgia with no identifiable primary cause, an origin for the referred pain must be sought. In some cases, for example a patient with acute follicular tonsillitis associated with earache, the diagnosis is obvious and therefore requires no further discussion here. However, in many cases referred otalgia can represent a diagnostic challenge and it is the aim of this chapter to highlight the possible causes.

TABLE 92.1 Causes of primary otalgia

Site	Possible cause(s)
Pinna	Chondrodermatitis nodularis helicis Chronic relapsing perichondritis Trauma/haematoma Cellulitis Herpes zoster oticus Malignancy
External canal	Otitis externa: • acute • chronic • benign necrotizing • 'malignant' Furuncle Bullous myringitis Keratosis obturans/canal cholesteatoma Trauma Herpes zoster oticus Malignancy
Middle ear	Otitis media +/- complications Malignancy
Inner ear	Noise discomfort

MALIGNANCY

Although malignancy is not the commonest cause of referred otalgia, its importance as a potential cause warrants this differential being high on the assessing clinician's list. Malignant tumours of the upper aerodigestive tract can present with various symptoms depending on their site of origin. It is important to remember that referred otalgia may be part of a symptom complex, or perhaps more importantly, can be the sole presenting symptom. A full examination of the oral cavity and flexible nasendoscopy to examine the pharynx and larynx are therefore an essential part of the assessment of a patient with otalgia in the absence of local pathology within the ear. The presence of otalgia, dysphagia, nodal metastasis and weight loss have all been shown to be independent predictors of duration of survival of patients with head and neck cancer.[6]

The majority of oropharyngeal carcinomas arise within the lateral wall, commonly involving the tonsil or the tongue base. Unlike carcinomas of the oral cavity, oropharyngeal tumours may not be visible until they are at an advanced stage and therefore imaging may be required to identify a primary in this area. Lymph node metastases are common at presentation. Like other aerodigestive tract malignancies, the most significant aetiological factor is smoking and to a lesser extent alcohol, but with a significant synergistic effect. However, HPV infection has had a dramatic effect on oropharyngeal malignancy rates and has been responsible for a significant increase in incidence over the last decade or more. This increase has been seen in younger patients (40–60 years) and non-smokers.[7]

Otalgia and odynophagia are often presenting symptoms of hypopharyngeal malignancy. On occasions, a supraglottic malignancy may lead to otalgia before involving the glottis and presenting with hoarseness, which is the cardinal symptom of laryngeal malignancy. The nasopharynx is not usually a subsite referring pain to the ear, but otalgia has been reported as being the presenting symptom in up to 14% of patients with nasopharyngeal carcinoma.[8]

Neoplasms arising in the infratemporal fossa can cause referred otalgia via the trigeminal nerve, Arnold's nerve or Jacobson's nerve. In a retrospective review of 18 cases presenting over a period of 8 years, all cases had otalgia with normal otological findings and a minority had subtle cranial nerve signs such as reduced corneal reflex. Adenoid cystic carcinoma was the most common pathological diagnosis, followed by adenocarcinoma, squamous cell carcinoma and osteogenic sarcoma.[9] If more common causes of otalgia cannot be identified by physical examination and appropriate investigation, an MRI scan with gadolinium enhancement should be considered to diagnose this rare finding.

While still rare, temporal bone metastases are seen more frequently due to the increasing incidence of cancer and to increase in life expectancy.[10] Haematogenous spread is the commonest route of spread and the commonest sites for the primary tumour are breast, lung, kidney, stomach and prostate. Although temporal bone metastases are often asymptomatic, they may present with otalgia, hearing loss (conductive, sensorineural or mixed), facial nerve paralysis and balance disturbance. The triad of symptoms of otalgia, periauricular swelling and facial nerve weakness should raise the suspicion of temporal bone malignancy. CT scanning will usually be diagnostic. Treatment is almost always palliative.[11]

DENTAL

Dental disorders are the most common cause of referred otalgia and were traditionally thought to account for up to 5.75% of all cases seen in an ENT clinic, but recent work by Fenton et al. suggests they may be considerably less frequent.[12–14] Dental otalgia may arise from the teeth, periodontal tissues or the TMJ.

Teeth/periodontal tissues

Dental pain arising from the teeth and periodontal tissues poses a diagnostic problem to a trained dentist, so it is understandable that referred otalgia from dental pathology may present more of a challenge when presenting to an ENT clinician. The commonest cause of inflammation of the dental pulp (pulpitis) is dental caries. The pain of pulpitis is often poorly localized as the sensory innervation is mainly via non-myelinated type C pain fibres. Chronic pulpitis may fluctuate over a period of weeks or months and, with poor localization of pain and lack of physical signs, is difficult to recognize. Pain associated with acute apical periodontitis and acute apical abscess tends to be severe, throbbing and localized to the affected tooth but, if the inflammation is mild and chronic, localization

may be poor. Partially erupted or impacted wisdom teeth can lead to inflammation of the surrounding soft tissue (pericoronitis). Chronic pericoronitis can present as poorly localized facial/jaw pain with referred otalgia.[15]

Temporomandibular joint dysfunction syndrome

The cardinal features of TMJ dysfunction are diffuse pain felt in or around the joint, crepitus and trismus. Pain is the most common and prevalent symptom. The true prevalence of TMJ dysfunction is not certain but it is estimated that between 20% and 40% of the population suffer from symptoms at some time.[15] Pain from the TMJ, or from related tissues, is common but there is often no definable organic disease. Sufferers of referred otalgia from TMJ dysfunction are more likely to be female, with statistically significant elevated levels of physical comorbidity and psychological stress.[16] Otalgia has been reported to be a symptom of TMJ dysfunction in 64% of patients.[17] Bruxism is a major aetiological factor and has been reported to be present in more than 50% of cases.[18] Patients who have a tendency to bruxism at night often awake with pain that settles during the day. Those who clench or grind their teeth through the day, perhaps secondary to stress, are prone to symptoms in the evening.[15]

The most reliable diagnostic clinical finding in TMJ dysfunction is tenderness of the masticatory muscles. In a large study of patients with TMJ dysfunction, muscle tenderness was seen in the majority of patients, with tenderness of the lateral pterygoid reported in 85%. Tenderness of the joint itself was reported in 67% of patients and 38% had crepitus on auscultation.[18] Intraoral palpation of the lateral and medial pterygoids frequently reveals tenderness, and this finding is more commonly seen in patients with referred otalgia.[19] Patients who have bruxism will often have flattening of the occlusal surfaces of the molar teeth, worn incisors and linear scarring of the buccal mucosa and lateral border of the tongue. Patients should also be assessed for malocclusion as this may cause stress on the TMJ, predisposing to TMJ dysfunction. Radiology rarely contributes to the diagnosis but MRI can demonstrate joint effusion or internal derangement of the joint.[5]

The mainstay of treatment for TMJ dysfunction is rest, a soft diet and simple analgesia, particularly nonsteroidal anti-inflammatory drugs. Application of local heat can be of benefit. Benzodiazepines or low-dose tricyclic antidepressants can help symptoms for more refractory symptoms, but there is risk of dependence. A small proportion of patients may require further investigation and treatment by maxillofacial surgeons, using occlusal splints in the first instance. TMJ surgery is generally considered only as a last resort.

Costen's syndrome[20] includes a variety of ear symptoms thought to originate from the TMJ. The original description was a constellation of symptoms including otalgia, tinnitus, impaired hearing, dizziness and aural congestion. Active treatment of TMJ dysfunction has been shown to relieve otological symptoms.[21] However, Bush et al.[22] found no association of TMJ dysfunction with tinnitus or dizziness, concluding that these symptoms may be more related to psychological distress.

CERVICAL

With the increasing age of the general population, cervical spine degenerative disease (CSDD) must be considered as an increasingly common cause of referred otalgia. Pain referred from the cervical spine is usually persistent retroauricular or infra-auricular and is frequently related to neck movement. In a retrospective study, Jaber et al.[23] found that 42% of referred otalgia was secondary to cervical disorders and the majority of these (37/51) were secondary to CSDD. The condition was also found to be much more common in females (4:1, female:male). This makes referred pain from the upper cervical plexus (greater and lesser auricular nerve) second only to pain referred from the region of the trigeminal nerve.

If cervical otalgia is suspected, clinical examination combined with imaging of the cervical spine is indicated. Imaging studies of the cervical spine have a high false-positive and false-negative rate. MRI of the cervical spine has been shown to be abnormal in nearly 20% of asymptomatic patients,[24] and therefore results should only be interpreted alongside the clinical findings.

First-line treatment of CSDD should be conservative with treatments such as analgesia and physiotherapy.[23]

NEURALGIA

Otalgia can present as one of the features of various cranial neuralgias. Trigeminal neuralgia and post-herpetic neuralgia are the commonest forms of craniofacial neuralgia, both of which have a similar incidence.[25] Trigeminal neuralgia has an incidence ranging from 4–5/100 000 per year up to 20/100 000 per year after the age of 60, and is more common in females than males.[25] It is defined as a sudden, usually unilateral, brief stabbing recurrent pain in the distribution of one or more of the branches of the fifth cranial nerve. Because of this classic mode of presentation and the fact that otalgia is only infrequently reported as a symptom of trigeminal neuralgia, it is not discussed further here. Herpes zoster oticus is often associated with severe acute otalgia, which can persist in the form of a post-herpetic neuralgia. Although the origin of the pain at presentation may initially not be obvious, the diagnosis becomes clear once the typical herpetic vesicles erupt.

Primary neuralgias should be considered as a diagnosis of exclusion and in most cases an MRI scan of the affected cranial nerve is indicated.

Glossopharyngeal neuralgia

The International Headache Society defines glossopharyngeal neuralgia as a severe transient stabbing pain experienced in the ear, base of tongue, tonsillar fossa, or beneath the angle of the jaw.[26] It is much less common than trigeminal neuralgia, the incidence being between 0.2 and 0.7 per 100 000 per year.[27, 28] Glossopharyngeal

neuralgia has been described as two clinical types based on the distribution of the pain: a tympanic type which mainly affects the ear, and an oropharyngeal type which affects the throat.[29] The onset of pain is commonly provoked by swallowing and on occasion by coughing, yawning or talking. A trigger zone may be present within the preauricular or postauricular area, the neck or external auditory canal. Symptoms are paroxysmal and last for seconds to minutes and remission periods occur. Because it is rare, glossopharyngeal neuralgia is often misdiagnosed.[30]

Glossopharyngeal neuralgia usually occurs without any evident lesion affecting the glossopharyngeal nerve. However, most authors implicate vascular compression of the nerve at the root entry zone as the main cause of 'idiopathic' glossopharyngeal neuralgia.[31] From MRI findings and observations during posterior fossa surgery, the posterior inferior cerebellar artery is the most frequent vessel responsible for compressing the glossopharyngeal nerve.[32] Secondary causes of glossopharyngeal neuralgia include stylohyoid syndrome, cerebellopontine angle tumours, parapharyngeal space lesions, pharyngeal malignancy, posterior fossa arteriovenous malformations and multiple sclerosis.[29, 33]

Patients with neuralgia do not respond to conventional analgesic drugs. Since the mechanism of pain begins in demyelinated fibres which become hyper excitable and generate high-frequency discharge, the ideal drugs are those which are able to limit the discharge frequency. Currently, the first-line medical treatment of neuralgia is with carbamazepine.[31] Although about two-thirds of patients who take carbamazepine for neuropathic pain can expect to achieve good pain relief in the short term, two-thirds can expect to experience at least one adverse event.[34] Surgery for glossopharyngeal neuralgia most commonly involves microvascular decompression.[35] This procedure has demonstrated complete pain relief in 64–75% of patients and substantial improvement in a further 16–25%.[36, 37] Nerve section can also be performed, either through a posterior fossa approach, through the neck or with a transtonsillar approach.

Stylohyoid (Eagle's) syndrome

The stylohyoid syndrome results in neuralgia secondary to an elongated styloid process or mineralization of the stylohyoid ligament. The condition was first reported by Eagle[38] in 1937 and subsequently came to bear his name. The normal styloid process is approximately 2.5 cm long and is generally accepted to be elongated if its length exceeds 4 cm. An elongated styloid process is said to be present in 4% of the population, but it has been reported that only 4% of these people present with symptoms.[39] Although Eagle originally described the syndrome as arising following tonsillectomy, later studies have concluded that tonsillectomy is not always an aetiological factor.[40, 41] Symptoms are postulated to occur as a result of compression of the hypoglossal nerve, impingement of the carotid vessels or inflammatory changes at the insertion of the stylohyoid ligament.[41] In fact, the existence of this syndrome is controversial and the Headache Classification of the International Headache Society dismissed it as 'not sufficiently demonstrated'.[26] The symptoms are classically a dull pharyngeal pain, often located within the tonsillar fossa, with radiation to the ipsilateral ear, odynophagia and a foreign body sensation. Although there may not be any specific findings on examination, the styloid process may be palpable in the tonsillar fossa and this can aggravate symptoms. Local injection of local anaesthetic can temporarily relieve symptoms. Radiological diagnosis of an elongated styloid process can be made either by orthopantomography or CT scan. Conservative management with steroids and local anaesthetic along with carbamazepine have been suggested but surgical reduction of the styloid process is considered the preferred treatment.[41, 42] Excision can be performed either transorally through the tonsillar fossa or via an external transcervical approach.

Geniculate neuralgia

Geniculate neuralgia, also known as intermediate nerve neuralgia or tic douloureux of the nervus intermedius, is a rare disorder characterized by brief paroxysms of neuralgic pain felt deeply in the ear. The intermediate nerve (of Wrisberg) is a root of the facial nerve containing sensory and parasympathetic fibres. It is considered to be responsible for the sense of taste in the anterior two-thirds of the tongue, floor of the mouth, palate and sensory information from the skin of the external auditory canal as well as the mucous membranes of the nasopharynx and nose. Its cell bodies are located within the geniculate ganglion. The cutaneous field of the nervus intermedius has been described as the zone of Ramsay Hunt (or zoster zone) and consists of the tympanic membrane, auditory meatus, tragus, concha and the groove between the pinna and scalp.[43] Although the aetiology is often not clear, symptoms have been ascribed to vascular loops[44, 45] and previous herpes zoster infection.

The literature on this condition stresses surgical management, concentrated on the nervus intermedius and geniculate ganglion, and vascular decompression.[44–47] Histological examination of the geniculate ganglion has concluded that geniculate ganglionectomy alone is inadequate, and that nervus intermedius section is also required.[47] Pulec[46, 48] has reported a 30-year experience excision of the nervus intermedius and geniculate ganglion via a middle fossa approach in 64 patients. All patients bar one (who had Lyme disease) had excellent results with respect to relief of ear pain. Other case series describe a combination of microvascular decompression of various cranial nerves combined with section of the nervus intermedius.[44, 47]

MISCELLANEOUS

inflammatory conditions affecting the pharynx and parapharyngeal spaces, larynx, major salivary glands cervical lymph nodes and the thyroid can all cause referred otalgia. Cardiac pain can also present as otalgia via vagal pathways.

Vestibular schwannoma (VS)

Although the commonest presenting symptoms of a vestibular schwannoma are progressive unilateral hearing, tinnitus and disequilibrium, otalgia can be a presenting feature. Studies reporting the incidence of otalgia in this condition suggest it is present 4–5% of the time,[49, 50] although in one study a further 25% complained of mastoid ache on direct questioning.[50] It is hypothesized that otalgia/mastoid ache is due to either compression of the nervus intermedius or dural stretching. The cranial dura mater is innervated by the upper three spinal nerves (C1–C3) and by the three divisions of the trigeminal nerve. As a result of this, pain arising in the dura can be referred to the ear. Indeed, a case of a non-traumatic subdural heamatoma presenting with otalgia as the sole feature has been reported.[51]

Cholesterol granuloma

As discussed above, malignancy within the petrous temporal bone can present with otalgia. Equally, benign processes in this area can cause otalgia. Cholesterol granulomas are expansile lesions of the temporal bone and can present with various symptoms including otalgia, pressure, hearing loss, vertigo and tinnitus.[52]

Nasal/sinus disease

The vidian nerve and greater superficial petrosal nerve supply the posterior ethmoids, sphenoids and nasal mucosa. Inflammation of the posterior ethmoids or sphenoid sinus can therefore cause referred otalgia although this is not a common pathway.[4]

Laryngopharyngeal reflux

As with many medically unexplained symptoms of the aerodigestive tract, laryngopharyngeal reflux (LPR) has been implicated as a cause of otalgia in both children and adults.[53, 54] It is hypothesized that the upper airway mucosa is more sensitive to tissue damage from acid exposure than oesophageal epithelium, therefore otalgia can occur in the absence of other symptoms more typical of gastro-oesophageal reflux.[55]

BEST CLINICAL PRACTICE

- ✓ Otalgia in the absence of discharge, hearing loss or otoscopic abnormality while the patient is symptomatic should raise suspicion of secondary otalgia.
- ✓ Expert dental examination may reveal the primary source of the pain to be the teeth/periodontal tissues or TMJ.
- ✓ Careful examination of the upper aerodigestive tract should be part of the routine clinical examination of a patient with unexplained otalgia.
- ✓ Further investigation/imaging should be guided by clinical suspicion.
- ✓ If a neuralgia is suspected, the opinion of a neurologist should be sought to guide medical management.

KEY POINTS

- Isolated unilateral otalgia may be an indicator of an otherwise asymptomatic malignancy in the aerodigestive tract.
- Dental and cervical disorders are relatively common causes of referred otalgia.
- Numerous neuralgias have been implicated as causes of referred otalgia, but all are rare.

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CHAPTER 93

BONE-CONDUCTION HEARING DEVICES

James Ramsden and Chris H. Raine

SEARCH STRATEGY

Data in this chapter may be updated by a search on Medline, Embase, Cochrane, TRIP and NICE Evidence Search for systematic reviews, meta-analyses, randomized controlled trials, prospective non-randomized clinical studies and health economics studies looking at the following devices: Sophono, Bonebridge, Baha systems and Ponto.

INTRODUCTION

Hearing impairment varies in severity and can affect patients of all ages. Hearing loss in infancy and during childhood can significantly impact on communication, language development and education. For adults it can lead to reduced quality of life, depression, social isolation and impact on employment.

Hearing loss may be unilateral or bilateral. In most situations, acoustic hearing devices (ACHDs) will provide benefit (see Chapter 54, Hearing aids). Patients who for various reasons are unable to use ACHDs now have access to a wide variety of audiological implants; each has different indications, benefits and drawbacks. Broadly speaking, bone-conduction hearing aids (BCHAs) can be helpful for purely conductive hearing loss, for mixed or mild to moderate sensorineural hearing loss (SNHL), and for single-sided deafness (SSD).

Related devices include middle ear implants (MEIs) (see Chapter 95, Middle ear implants), cochlear implants (CIs) (see Chapter 94, Cochlear implants) and auditory brainstem implants (see Chapter 96, Auditory brainstem implants). This chapter focuses on bone-conduction hearing devices (BCHDs) that aid conductive, mixed or mild to moderate SNHL and SSD.

HISTORY

The principles of hearing by conducting sound through bone have been known about for centuries. Following the development of the carbon microphone, transcutaneous 'oscillators' emerged in the early 1920s. It was in 1977 that Anders Tjellström first implanted patients with percutaneous bone-anchored hearing aids, ushering in the modern era of bone-conduction hearing.[1] This followed Per-Ingvar Brånemark's well-known work with titanium implant osseointegration.[2] Tjellström's implants allowed direct sound transmission to bone, avoiding the attenuation of the soft tissue over the mastoid. Nobel Pharma commenced initial production, with the Entific company subsequently created to take things forward. For additional background information, Mudry and Tjellström's paper is recommended.[3]

PHYSIOLOGY

Bone-conduction hearing devices (BCHDs) deliver sound energy to both inner ears.[4] The overall principle is to establish pressure differences between the scala tympani and the scala vestibuli such that there is movement of the

basilar membrane and hence neural stimulation. There are multiple complex sound pathways[5] (Figure 93.1):

- **Outer ear:** In addition to normal air conduction, bone-conduction (BC) sound vibrations enter the external auditory canal (EAC) via soft tissue and bone vibrations which are transmitted to the tympanic membrane (TM). The sound energy to the TM can change notably if the EAC is occluded.[6, 7]
- **Middle ear:** With a normal ossicular chain connected between the TM and stapes footplate, the ossicles have been shown to vibrate in phase with low frequencies but become decoupled at higher frequencies.[8]
- **Inner ear:** Sound and vibration transmission relies on fluid pressure changes and inertia/fluid inertia. Sound is therefore acting both by direct inertial forces through bone but also from the outer and middle ear.

Transcranial transmission is recognized to be quite efficient and hence the contralateral ear requires masking when BC audiometry is performed. Transcranial transmissions are close to 0 dB for frequencies up to 700 Hz and decrease with higher frequencies.[9]

This has clinical implications because BC sensitivity is fairly similar between percutaneous and transcutaneous modes of transmission for frequencies below 1 kHz.[10] There would be an expected 5–15 dB improvement in efficiency with percutaneous systems when a BC transducer is directly attached to the skull at higher frequencies. Transmission increases through the skin in line with the area of skin transducer interface.[11]

In cases of bilateral stimulation a low transcranial transmission is better for binaural cues; for single-sided deafness a high transcranial transmission is better. Looking into the benefit of bilateral implants, an improvement in terms of hearing thresholds, sound localization and speech perception has been reported.[12] Binaural fitting is preferred for bilateral conductive loss when the BC thresholds do not vary by more than 20 dB in the higher frequencies of 3 kHz and 4 kHz. In cases of unilateral hearing loss the contralateral ear should have a BC average of ≤20 dB HL to reduce the head shadow effect.[13]

CLASSIFICATION

BCHDs should be considered in context with other implantable devices such as middle ear, cochlear and brainstem implants. All these have a role in helping with hearing rehabilitation when acoustic aids are unable to give benefit.

BCHDs are broadly categorized as either **percutaneous**, i.e. where the device is in direct contact with the skull, or **transcutaneous,** where the skin and soft tissue are interposed. Percutaneous systems are well established, with a titanium abutment passing through the skin to allow a hearing aid to pass the sound directly into the bone. The transmission across the skin is 'passive' as there is no active component apart from the external hearing aid.

Transcutaneous systems are those with intact skin. These can pass the sound passively across the skin, or can be active with an internal vibrating actuator or amplification device (Table 93.1).

CLINICAL INDICATIONS

BCHDs are generally used for the rehabilitation of hearing loss only when conventional acoustic aids cannot be fitted, or have been trialled and have failed to improve the hearing.

Common current indications include the following:

- **Conductive and mixed losses**
  - congenital causes such as atresia or microtia (see Chapter 12)
  - acquired causes such as chronic otitis media or ossicular pathology (see Chapter 83)
  - chronic discharging ear (such as chronic suppurative otitis media (CSOM) or recurrent otitis externa) (see Chapter 78 and Chapter 83)
  - inability to wear a hearing aid following radical mastoid surgery
  - unilateral mixed hearing loss.
- **Single-sided deafness – sensorineural or conductive**
  - trauma resulting in hearing loss.

TABLE 93.1 Surgical classification of BCHDs

Type of device	Skin relationship
Percutaneous	Passive
Transcutaneous	Passive (skin drive)
	Active (direct drive)

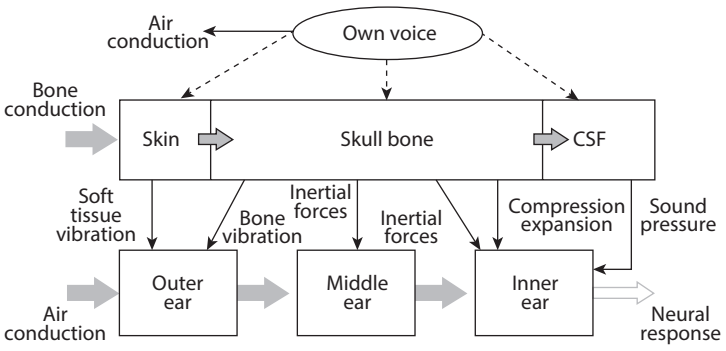

Figure 93.1 A model of the pathways involving sound conduction (reproduced courtesy of Stefan Stenfelt Karger publications).[9]

- unsuitable ear canal for a conventional hearing aid, e.g.
  - in a radical mastoid cavity
  - an extremely narrow ear canal
  - 'blind sac' ear canal closure
  - lateral temporal bone resection
  - extensive cranial base surgery.

ASSSESSMENT

The assessment of patients must be within a multidisciplinary team (MDT) framework, to ensure that the most appropriate system is used, as alternative devices such as MEIs and CIs complement the whole process.[14]

The devices are in continuous development. New systems will emerge in the future so it is recommended to follow the manufacturer's fitting criteria, but not to implant at the upper end of such fitting criteria, as a small additional drop in hearing will mean that the device is no longer suitable.

In 2016 NHS England published commissioning guidelines.[15] Funding would be considered for the following:

1a Patients with unilateral or bilateral conductive or mixed hearing loss within the manufacturer's fitting criteria
AND
Stable BC thresholds (≤15 dB deterioration in >2 frequencies in a 2-year period)
OR
1b Unilateral sensorineural hearing impairment (including SSD) where the better ear has BC hearing thresholds within the manufacturer's fitting criteria including SSD
AND
2 The patient has trialled an ACHA or wireless CROS/BiCROS hearing aid for a minimum of 4 weeks, or is anatomically or physiologically unable to undertake a trial of an ACHA
AND
3 Has trialled a BCHD on a softband or headband for a minimum of 14 days and shown benefit in speech tests.[10]

Systems are available to trial processors in a passive transcutaneous format. These are supplied as headbands and elasticated softbands and the recently introduced Sound Arc (manufactured by Cochlear) and the adhesive skin attachment ADHEAR (manufactured by MED-EL) prior to any surgical intervention (**Figure 93.2**).

Figure 93.2 Sound Arc.

For the child with congenital meatal atresia/microtia, consider carefully the management of the pinna, be it with prosthetics or reconstruction so that surgical approaches used for BCHDs do not compromise future reconstruction. Surgical correction of meatal atresia is now rarely performed in the UK (see also Chapter 16, Microtia and external ear abnormalities).

BCHDs will not be commissioned for:

- patients with a bone disease that is unable to support an implant
- patients who have a sensitivity or allergy to the materials used
- patients with physical, emotional or psychological disorders that, despite suitable treatment and support, would interfere with surgery or the ability to allow suitable rehabilitation such that significant benefit would be unlikely.

SURGICAL OPTIONS

Percutaneous (bone-anchored) devices

Two devices are currently available in the UK – the Baha® (Cochlear™ Bone Anchored Solutions) and the Ponto bone-anchored hearing system (Oticon Medical). The Cochlear Baha system was initially commercially available from 1984 (manufactured by Entific), and the Oticon from 2009.

Both are semi implantable, with a titanium osseointegrated fixation into the skull and a skin-penetrating abutment to facilitate attachment for the sound processor aid. This abutment allows for direct and effective transmission of sound vibrations to the skull and hence to the inner ear (**Figure 93.3**).

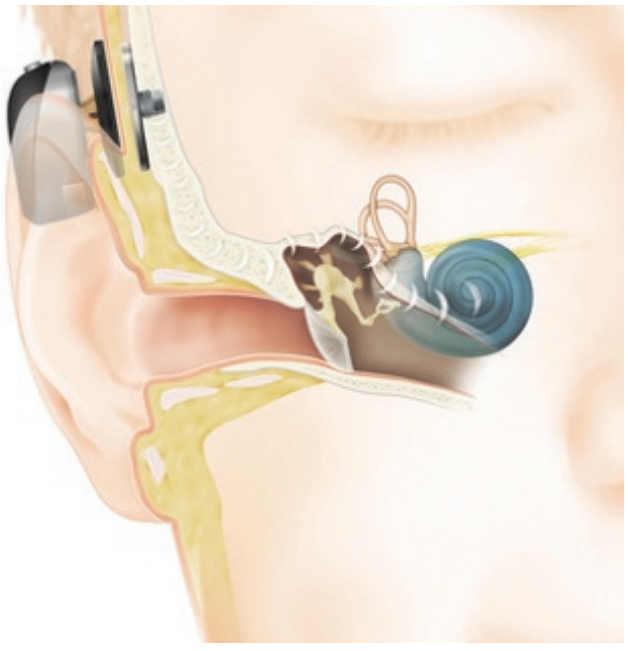

Figure 93.3 The Cochlear BAHA system (courtesy of Cochlear Limited).

Figure 93.4 Cochlear connect based on the BA400 abutment and BI300 implant (courtesy of Cochlear Limited).

In 2010 Cochlear introduced changes to the osseointegrated titanium fixture which included a wider base (4.5 mm versus 3.75 mm) for increased stability, smaller treads at the implant neck to improve load distribution and a tioblast™ coating for faster osseointegration to the BI300 system. In 2012 it further modified the abutment with a hydroxyapatite coating (BA400) (Figure 93.4).

Oticon Medical's system similarly comprises an implant and options of various lengths of percutaneous abutments to cater for various skin thicknesses which enable tissue preservation surgery. The dermatome to take split skin is no longer used.

Audiological criteria

The results of presurgical assessment with a transcutaneous processor give a good indication of outcome as skin attenuation can account for 10–15 dB. The power of processors has increased, with BC levels of about 65 dB over 1, 2 and 3 kHz using the most powerful processor currently available.

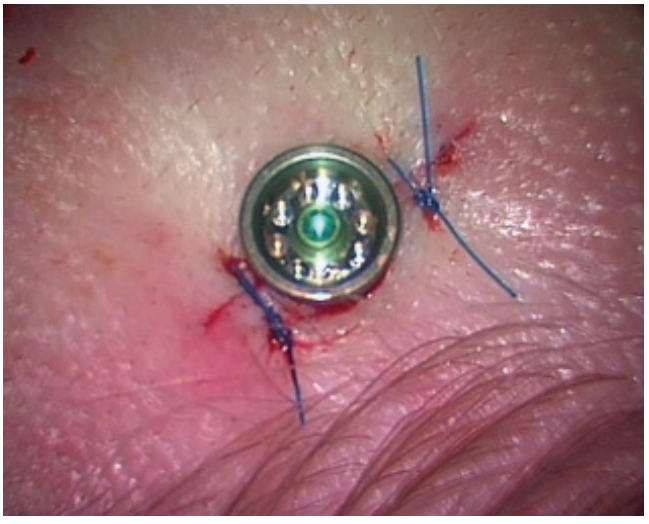

Figure 93.5 Oticon abutment inserted using minimal extended incision.

Surgical considerations

The Food and Drug Administration have set a minimum age for paediatric use at 5 years. However, the minimum age for implantation is debated and there is no fixed worldwide guideline. In 2005 an international consensus was issued regarding BCHAs, which recommended that surgery not be undertaken prior to age 2–3 years. This was to allow the skull to reach a minimum thickness and conditions to be suitable to fit the fixture and allow osseointegration.[16]

Though successful implantation has been reported in patients as young as 14 months, the complication rate is inversely proportional to the age at implantation.[17] It is important to stimulate hearing as early as possible, and therefore in children too young for implantation the use of a BCHA via a softband, which holds the hearing aid to the skin of the scalp via a metal or elastic headband, is advocated from about the age of 3 months.

In the past, bone-anchored hearing aid (BAHA) surgery on children was staged, but the newer tissue-preserving single-stage implants mean this is not always necessary. A simple linear incision eliminates the need for a skin flap (Figure 93.5).

However, in children a longer time to osseointegrate is recommended to compensate for the thinner bone, although this is subject to further evaluation at present.[18]

The implantation is usually performed under local anaesthetic and is well tolerated, although anxious patients and children may require sedation or general anaesthetic.

MRI compatibility

With the external processor removed, the remaining titanium implant and abutment are non-magnetic and pose no issue with MRI compatibility. A small area of artefact will, however, be caused adjacent to the implant.

Outcomes

The main post-operative difficulties from transcutaneous BAHAs relate to the protrusion of the abutment through the skin. There are cosmetic issues, although these vary in importance in different cultures. A practical and quite

TABLE 93.2 Classification of cutaneous complications of transcutaneous abutments in BAHAs (after Holgers et al.)[19]

Severity	Complication(s)
Grade 0	No skin reaction
Grade 1	Redness with slight swelling
Grade 2	Redness, moistness and moderate swelling
Grade 3	Redness, moistness and moderate swelling with tissue granulation
Grade 4	Profound signs of infection, resulting in removal of the implant

frequent (up to 10% of patients) difficulty with percutaneous BAHAs is that the skin requires daily hygienic care and there can be skin overgrowth around the abutment, skin infection and low-grade inflammation. This requires medical attention and can occasionally lead to loss of the fixture/abutment.

The most useful classification of cutaneous complications of transcutaneous abutments in BAHAs was suggested by Holgers et al. (**Table 93.2**).[19] This scale, which ranges from 0 to 4, with 0 being reaction-free skin around the implant and 4 being overt infection requiring implant removal, is usually used to report skin complications.

These complications seem to affect children more than adults. There is a higher rate of fixture loss (up to 14% over 15 years) in the paediatric population.[20] A much higher rate of fixture loss occurs with the shorter 3 mm fixture, so a 4 mm fixture should always be used where practical.

Challenges in a paediatric setting include accommodating for growth and increases in soft-tissue thickness, especially during puberty. The abutment is available in various lengths and may be changed to adapt to the child's growing needs.

Passive transcutaneous devices

Two passive systems are available for use with adults and children: the Sophono™ (Medtronic, Boulder, CO) and the Cochlear™ Baha® Attract (Cochlear™ Bone Anchored Solutions). Both depend on the fixation of an internal magnet to the skull, which is passive. An external hearing aid with oscillator can then be attached to an external magnetic pad, made soft with padding, to allow the firm attachment of the device to the skin. This then transmits the sound in a similar way to a softband, although there is additional transmission of sound through the firm connection of the internal magnet to the bone. One of the benefits of such systems is a reduction in the risk of inflammation, injury and the psychological problems that are associated with percutaneous devices.[21]

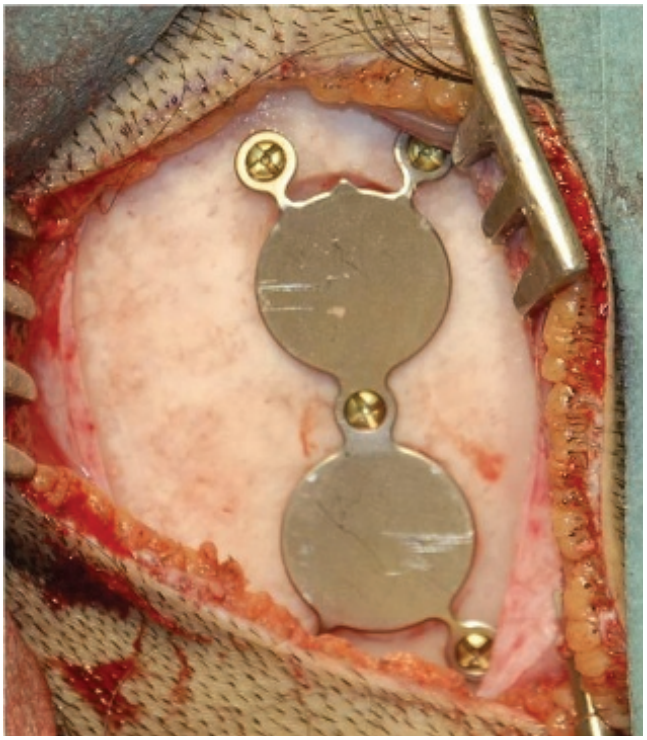

Figure 93.6 The Sophono plate *in situ*.

SOPHONO™

Professor Siegert initially published his results of the 'Otomag' system, a partially implantable bone-conduction device, in 2011.[22] The Sophono Alpha 2 MPO™ system comprises a surgically implanted internal plate containing twin hermetically sealed magnets (**Figure 93.6**) and the external digital sound processor is coupled to a base plate housing twin magnets corresponding to the internal ones. The processor transmits vibrations through the skin into the bone and then to the cochlea. The device is intended for people with conductive hearing loss, SSD and mixed hearing loss.

Audiological criteria

As processors have developed, so has candidacy. BC hearing thresholds should be ≤45 dB or in the case of SSD, ≤20 dB in the contralateral ('good') hearing ear. However, care should be taken to stay well within these limits as there is high-frequency attenuation in all passive transcutaneous devices which limits amplification significantly.

Surgical considerations

Magnets are implanted into shallow 2 mm bone beds in a one-stage procedure. They are secured with five titanium screws (**Figure 93.6**). The skin above the magnets should be reduced to a thickness of 4–5 mm, which reduces the attenuation to less than 10 dB compared to direct bone stimulation. Programming typically commences 4–6 weeks after surgery.

MRI compatibility

The Sophono™ is MRI conditional up to 3 Tesla.[23] It is reported that the magnets create a 5 cm shadow/artefact.

BAHA® ATTRACT SYSTEM

A new transcutaneous system, the Baha® Attract, uses a magnet to secure the BAHA. While a major advantage in a paediatric setting is eliminating the soft-tissue complications of a BAHA, disadvantages include artefact on subsequent MRI scans and possible dampening of the high-frequency signal through the skin.

Audiological criteria

These are essentially the same as the Sophono, and caution should be exercised if there is significant SNHL at the high frequencies.

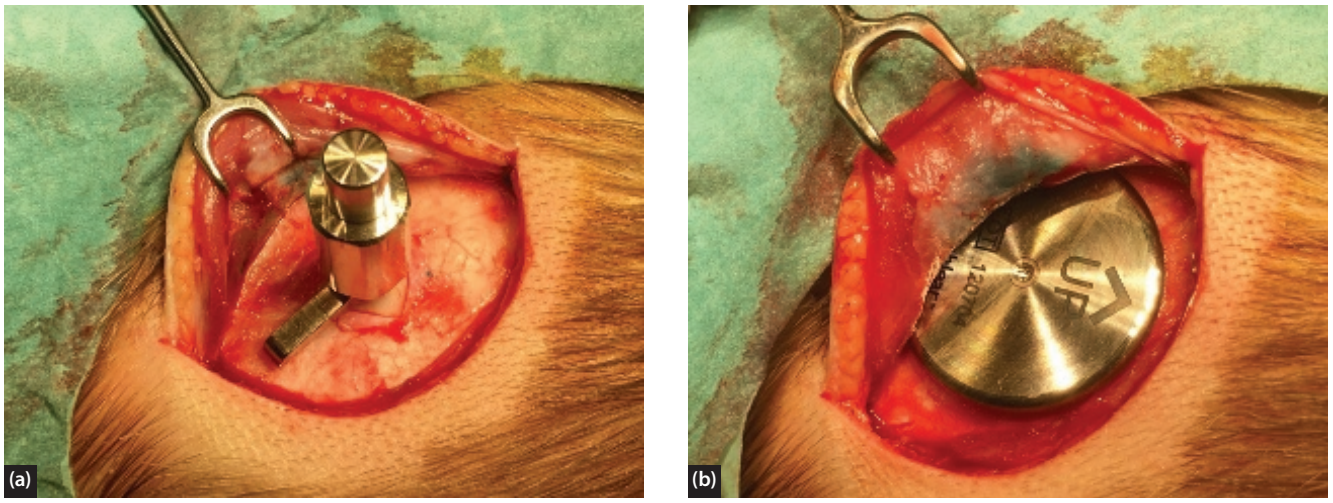

Figure 93.7 The BAHA® Attract. (a) A rotating sizer is used to make sure the bony bed is flat with no secondary points of contact with the magnet. **(b)** The BAHA Attract magnet *in situ*.

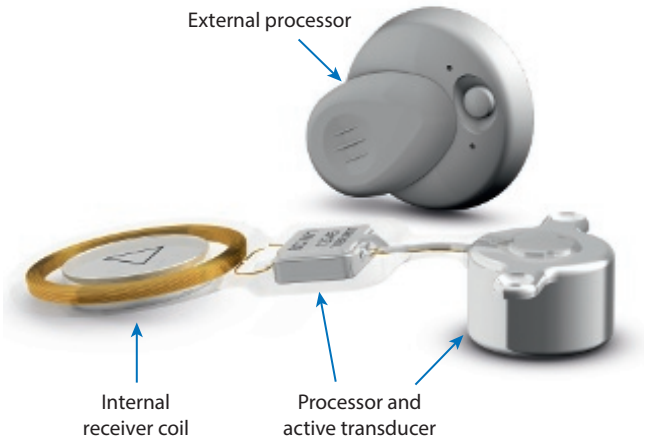

Figure 93.8 The Bonebridge components.

Surgical considerations

The system is based on the established osseointegrated BI300 implant secured to the skull behind the pinna and a BIM400 implant magnet that are implanted beneath the skin. Surgery is usually performed under local anaesthetic as a one-stage procedure. Surgically the magnet has to be correctly aligned and must not be in contact with the bone. A special bone bed indicator is used to ensure compliance (**Figure 93.7**). Prior to closure the optimal skin thickness is 3–6 mm. If the skin is too thick, the processor may be less efficient or fall off.

MRI compatibility

Non-clinical testing has demonstrated that the BIM400 implant magnet, in combination with the BI300 implant, is MRI conditional in a static field of 1.5 Tesla. An image artefact is approximately 11.5 cm.[24]

Active transcutaneous devices

There is currently one commercially available active transcutaneous system. This is the Bonebridge, an active semi-implantable internal device produced by MED-EL (Vibrant MED-EL Hearing Technology GmbH). Other devices are in clinical trials.

Introduced in September 2012 following on from the principles of the successful development of the Vibrant Soundbridge middle ear implant (see Chapter 95, Middle ear implants), the Bonebridge consists of an external audio processor and an internal BC implant (**Figure 93.8**). The internal component has a receiver coil, a magnet, a demodulator and a bone-conduction floating mass transducer (BC-FMT) secured to the bone by two titanium screws. The power to drive the FMT is transmitted transcutaneously via an inductive link to the internal coil, processed by the demodulator and then relayed to the BC-FMT, which then transduces the signals into mechanical energy. Osseointegration of the titanium screws is not thought to be crucial.

Audiological criteria

The Bonebridge is designed for patients with conductive and mixed hearing losses as well as SSD. The BC level should be better than 45 dB between 500 Hz and 4 kHz and 20 dB or better in the contralateral ear for SSD. There should be stable thresholds and no evidence of auditory neuropathy, retrocochlear or central hearing impairment.[25, 26]

Surgical considerations

The principle of surgery is the placement of the BC-FMT either within the mastoid or in the retrosigmoid position. The BC-FMT should not be placed in an unhealthy mastoid. Surgery is typically performed under general anaesthesia but local anaesthesia is a practical option.[27] Because of the size of the device, surgery is reserved until there has been sufficient skull growth to accommodate it.

It is recommended that radiological planning using 3D reconstruction be performed prior to surgical intervention (**Figure 93.9**).

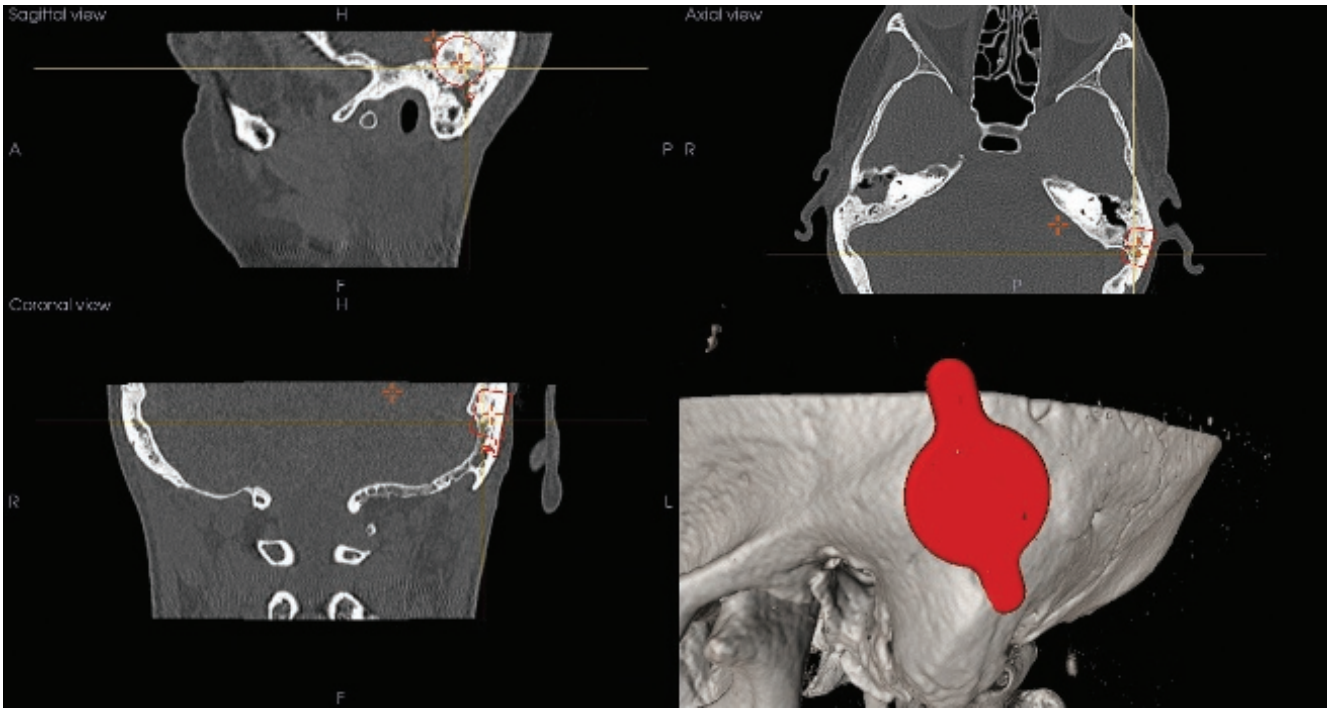

Figure 93.9 3D planning using radiological images.

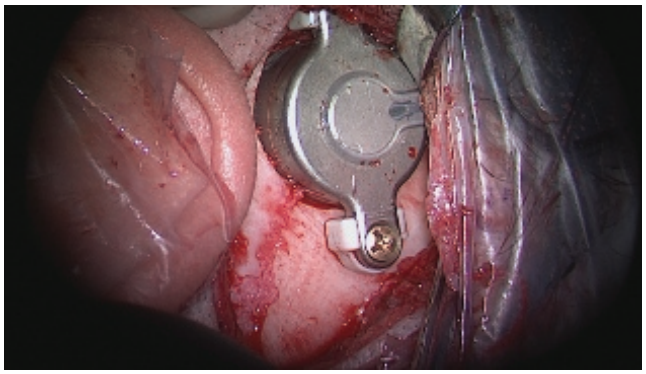

Figure 93.10 The Bonebridge *in situ* with 'lifts'.

Compression of the sigmoid sinus and/or dura may be necessary but 'lifts' of up to 4 mm can be used and are often required. The device is held in place by titanium screws (Figure 93.10). The system was found to be safe and effective.[28]

MRI compatibility

The device has a non-removable magnet. Following testing, the manufacturers report the device is conditional to 1.5 Tesla. As with the presence of a magnet, image artefacts will occur.

CONCLUSION

New devices continue to be introduced and current technology continues to evolve. With time, new indications continue to arise in the treatment of paediatric deafness. Despite the rapidity of introduction of new technology, it is important that the introduction and application of this into patient care be conducted in a rigorous evidence manner. In achieving this, it is essential that good collaboration continues between the clinicians and industry and, most importantly, that regular and thorough feedback from patients and caregivers about the influence on these on their quality of life is sought.

BEST CLINICAL PRACTICE

- ✓ A multidisciplinary team should oversee all children considered for BCHDs.
- ✓ Implanting children with percutaneous devices at too young an age risks an increase in complications. Children should be aged at least 2 years to permit sufficient growth in the skull. The FDA has set a minimum age of 5 years.
- ✓ Careful planning is especially important for children with microtia so that later reconstruction or cosmesis is not compromised.
- ✓ A simple linear incision with no elaborate skin flaps is usually sufficient for BAHA surgery.
- ✓ Some devices and device components cause difficulty with MRI scanning. Devices may also cause issues with airport security systems. Make sure clinicians, patients and parents are aware by consulting individual manufacturer's guidelines.

KEY POINTS

- A range of devices to transmit sound energy to the inner ear via the bones of the skull (BCHDs) is now available.
- BCHDs are used for the rehabilitation of hearing loss when conventional acoustic aids cannot be fitted or have been trialled and have failed to improve the hearing.
- Indications for use are increasing.
- Very good results are now reported in children with single-sided deafness.

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CHAPTER 94

COCHLEAR IMPLANTS

Andrew Marshall and Stephen Broomfield

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: cochlear implants, cochlear implantation AND hearing implants, surgery, candidacy, criteria, standards, adults, paediatric, children, elderly, quality of life, outcomes, complications and future.

INTRODUCTION

Cochlear implants have transformed the management of severe to profound hearing loss, particularly in both the very young and the elderly. Cochlear implant surgery and the subsequent rehabilitation are normally straightforward for implant centres within the UK and across the developed world. The technology has had greatest impact in transforming the education of children born with a profound hearing loss who are implanted early. The majority of these children attend mainstream education, using spoken language to communicate.

At the other end of the age spectrum, it is recognized that there is significant unmet need in the treatment of severe to profound hearing loss in the adult population, particularly the elderly.[1] The impact of this unmet need can have a significant effect on the individual's health and impose a financial burden on society as a result.[2]

BASIC PRINCIPLES

Cochlear implantation (CI) is considered in patients with severe to profound hearing loss who are failing to gain sufficient benefit from appropriate and well-fitting hearing aids. Audiological and other criteria for implantation are different for adults and children and are discussed further below. The external part of the cochlear implant detects the sound signal and converts it to an electrical signal which is transmitted to the internal processor. The way in which the signal is passed into the electrode array depends on the speech processing strategy utilized by that device. Each implant manufacturer has developed strategies that they believe have advantages over the others.

All cochlear implants make use of the tonotopic arrangement of the auditory system, whereby high-pitched sounds are transmitted through spiral ganglion cells corresponding to the basal turn of the cochlea, and low-pitched sounds by those at the apex of the cochlea. In normal young adults, there are approximately 35 000 auditory nerve fibres; it is estimated that at least 10 000 are required for speech recognition using a cochlear implant.[3] The success of an implant depends upon the transmission of the signal to the auditory cortex via the auditory pathways from the ear, followed by appropriate central processing to ensure understanding of the signal. Consideration of these central functions therefore forms part of the assessment of the cochlear implant candidate.

Performance with a cochlear implant is optimized postoperatively through a process of programming known as 'mapping', combined with intensive rehabilitation. The cochlear implant team is therefore multidisciplinary and includes teachers of the deaf, speech and language therapists, psychologists, audiologists, audiological scientists, radiologists and surgeons. Widely accepted standards exist for the assessment and management of patients being considered for CI.[4–6]

CANDIDACY

In the earliest years of cochlear implants, the technology was considered to be experimental and was offered only to the most profoundly deaf adults. In modern practice, the reliability and outcomes of CI have improved and criteria for candidacy have evolved to include both adults and children with some residual hearing as well as congenitally deaf infants. Criteria differ according to the healthcare systems and funding arrangements of individual countries. In England and Wales, the National Institute for Health and Care Excellence (NICE) have stipulated the following criteria for CI, based on clinical and cost-effectiveness assessments:[7]

- A cochlear implant should be considered for any person with a severe to profound hearing loss who does not gain adequate benefit from acoustic hearing aids.
- Severe to profound deafness is defined as the ability to hear only sounds louder than 90 dB HL at 2 kHz and 4 kHz without hearing aids.
- Hearing aids should be used for at least 3 months unless inappropriate or contraindicated.
- Adequate benefit with hearing aids is defined as:
  - For adults, a score of 50% or greater on Bamford–Kowal–Bench sentence testing at a sound level of 70 dB SPL.
  - For children, speech, language and listening skills appropriate to age, developmental stage and cognitive ability.
- Assessment should be by a multidisciplinary team and the tests used should be adapted to take into account the candidate's disabilities as well as their language and communication ability.
- Simultaneous bilateral CI is recommended for children and for adults who are blind or who have other disabilities that increase their reliance on auditory stimuli as a primary sensory mechanism for spatial awareness.

The audiological assessment of potential cochlear implant recipients usually also includes an auditory brainstem response (ABR) test. This aids in: validating the accuracy of the behavioural responses; detecting a central problem or absent cochlear nerve; and (in older patients) ruling out non-organic hearing loss.

Special cases

In many cases, a candidate clearly meets the above criteria and, following a full assessment (described in 'Assessment' below), decision-making is straightforward. Often, however, there are additional factors that must be taken into account. These factors are likely to lead to a further evolution of cochlear implant candidacy criteria in future.

Adults

RESIDUAL HEARING

Traditionally, any residual hearing in an ear receiving a cochlear implant would be lost. With current surgical techniques (described in 'Surgical technique' below), it is possible to preserve hearing in some cases. This allows for combining a hearing aid with a cochlear implant in the same ear, known as electric–acoustic stimulation (EAS). Typically, this applies to the patient with a 'ski-slope' hearing loss, i.e. some hearing in low frequencies, dropping abruptly to a severe to profound loss in the higher frequencies such that the criteria for CI are still met. Specially designed electrode arrays are available for this situation, for example the 'Hybrid' electrode (Cochlear Ltd) that is shorter than other electrodes, entering only the basal turn of the cochlea and therefore covering just the higher frequencies. Many surgeons prefer, however, to use a medium or standard-length atraumatic electrode with which residual hearing can often still be preserved; but should hearing be lost, the full range of frequencies is covered by the electrode, ensuring optimal performance.

THE ELDERLY

With the rising average age of the population of developed countries, cochlear implant candidates increasingly present in their seventies and eighties. There is good evidence that this group perform well with cochlear implants, with similar speech perception and improvement in quality of life when compared to younger recipients.[8, 9] Recently, a link between hearing impairment and cognitive decline in older adults has been shown,[10] and CI may have a role to play in improving social interaction and preventing cognitive decline in profoundly deaf elderly patients.[11]

FAR-ADVANCED OTOSCLEROSIS

The term 'far-advanced otosclerosis (FAO)', first used by House and Sheehy in 1961, is applied to the patient with otosclerosis and a profound hearing loss. Such patients may undergo stapedectomy in an attempt to restore their ability to wear hearing aids. However, results from CI are also good, with some series finding patients with FAO to be among the best performers, possibly due to the fact that the otosclerosis process generally spares the sensory elements of the cochlea.[12] Studies suggest that the outcomes of CI in FAO are equivalent to those in other aetiologies of deafness, with an improved quality of life.[13, 14] Patients with FAO are more prone to non-auditory stimulation (e.g. facial nerve stimulation), though in most cases this can be easily resolved by switching off the electrodes that are responsible, albeit with some potential reduction in performance.[13, 15, 16]

NEUROFIBROMATOSIS TYPE 2

Hearing loss in patients with neurofibromatosis type 2 (NF2) may be secondary to bilateral vestibular schwannomas or their treatment. Using modern surgical techniques, it is sometimes possible to excise tumours with preservation of the cochlear nerve. This allows for consideration of CI rather than auditory brainstem implantation, with more reliable outcomes. Intra-operative testing using electrically evoked auditory brainstem responses or cochlear nerve action potentials may be used to determine whether

a cochlear implant is appropriate. In England, the four specialist NF2 centres have agreed a protocol for the management of hearing loss in this challenging group.[17]

SINGLE-SIDED DEAFNESS

Following CI in a group of patients with single-sided deafness (SSD) who underwent surgery as a primary treatment for troublesome tinnitus, it was discovered that not only did the tinnitus improve but, in addition, the patients experienced significant audiological benefit.[18] It became apparent that previous concerns regarding the brain's ability to integrate electrical and acoustic signals from the two ears were unfounded. For patients with SSD, CI provides particular improvement in speech recognition in noise.[19] Criteria in the UK do not yet allow for CI for SSD, as cost-effectiveness is yet to be established.

PATIENTS OUTSIDE CURRENT CRITERIA

Whatever audiological criteria are applied, all cochlear implant centres frequently encounter patients who are struggling to hear using standard hearing aids but whose speech recognition scores are outside those criteria. Despite this, such patients often benefit significantly from CI.[20] Similar findings have been reported in children.[21] This highlights the need continually to review selection criteria and to reassess the measures used for assessment.

Children

ADDITIONAL DISABILITIES

In the early days of CI, children with significant additional disabilities (including cognitive impairment, developmental delay, visual impairment and communication disorders) were considered unsuitable candidates. As candidacy criteria have expanded, such children have been increasingly assessed for CI. In addition, with infants receiving CI before the age of 12 months, a number of children are diagnosed with additional disabilities (e.g. autistic spectrum disorder) only after their cochlear implant. Traditional assessment tools and post-operative speech perception measures may be unsuitable for children with additional disabilities, many of whom will never develop oral communication; decision-making and post-operative rehabilitation therefore often rely upon the experience of the cochlear implant multidisciplinary team.[22] Careful counselling of parents is crucial to decision-making and to ensure realistic expectations of outcome.

AUDITORY NEUROPATHY SPECTRUM DISORDER

Auditory neuropathy spectrum disorder (ANSD) is characterized by absent auditory brainstem responses with normal otoacoustic emissions. The prevalence of ANSD may be as high as 10% in children with permanent hearing loss.[23] There is a range of functional hearing impairment in ANSD, and in cases with severe to profound hearing loss CI can be an effective means of rehabilitation.[24] However, as the hearing in ANSD may improve over time, a period of observation is recommended before proceeding to surgery. This explains why the majority of children with congenital sensorineural hearing loss (SNHL) are observed until at least the age of 6 months, when behavioural hearing assessments are possible and the decision to proceed to surgery can be made with increased confidence. Longer periods of observation may be appropriate in some cases, though timely intervention is crucial to ensure optimal cochlear implant outcomes.[25]

ANATOMICAL ABNORMALITIES

Congenital profound SNHL is associated with inner ear anatomical abnormalities in approximately 20% of cases.[26] The cochlear nerve itself may be absent or hypoplastic; such cases require careful clinical and electrophysiological assessment to determine whether cochlear or auditory brainstem implantation is appropriate.[27] In some cases such abnormalities are isolated findings, but they may be associated with other anatomical variations (e.g. facial nerve position) or particular syndromes (e.g. CHARGE syndrome). Pre-operative assessment and surgical planning must be undertaken with additional care to ensure appropriate management of these complicated cases.[28]

ASSESSMENT

Medical

When considering cochlear implantation, patients who are found to meet the audiological criteria must undergo additional medical, otological, imaging and psychological assessments. Modern surgical and anaesthetic techniques mean that CI surgery is straightforward in uncomplicated cases. The pre-operative assessment of the patient considering CI focuses on ensuring fitness for general anaesthesia. This particularly applies to the very young and very elderly. CI is possible under local anaesthesia in adult patients who may not be fit for surgery otherwise.[29]

Otological

CI is contraindicated in patients with active middle ear infection or cholesteatoma, as infection around an implant may be associated with an increased risk of meningitis.[30] In addition, chronic infection is extremely difficult to eradicate and may necessitate device removal or lead to the device extruding. In such cases, any infection or disease in the middle ear or mastoid must be fully eradicated prior to implantation, with surgical treatment being required in many cases. Perforations of the tympanic membrane should be closed to provide a barrier against infection. In patients who have had canal wall-down mastoid surgery previously, or who require it to treat their disease in preparation for implantation, the usual recommendation would be to obliterate the middle ear and mastoid cavity and close the ear canal with a blind sac procedure. This must be done with meticulous surgical technique to

reduce the risk of development of cholesteatoma, which may remain asymptomatic for many years.[31] In cases that require surgical treatment for middle ear or mastoid disease, CI can be performed simultaneously or as a staged second operation, usually 3–6 months later.[32,33] The management of otitis media with effusion (glue ear) in children requiring CI, or who develop it following implantation, remains controversial. However, significant complications related to ventilation tube insertion either prior to, or following, CI are rare.[34]

Imaging

Cross-sectional imaging is a key part of pre-operative planning prior to CI. Identification of cochlear or cochlear nerve aplasia, which would make implantation impossible, is particularly important in prelingually deafened infants. Magnetic resonance imaging (MRI) is therefore the preferred initial imaging modality in this group.[35] Other abnormalities, including inner ear anomalies, cochlear lumen obliteration (e.g. following meningitis or in cochlear otosclerosis), middle ear pathology and anatomical variations (e.g. low-lying dura or anterior position of the sigmoid sinus) should also be identified pre-operatively. Computerized tomography (CT) scanning may improve the identification of such anomalies, and is routine practice in some centres. It is the authors' practice to use CT scanning selectively in infants, to avoid exposure of the developing brain and orbits to ionizing radiation. In adult patients, previously undiagnosed coexisting pathologies (e.g. acoustic neuroma) may be identified using MRI scanning, which is again the modality of choice.[36]

Psychological

The clinical psychologist is an important member of the cochlear implant team. Every patient and parent considering CI must be carefully counselled, to ensure that they are prepared for the surgery and post-operative rehabilitation, to ensure realistic expectation of outcome, and to discuss potential concerns regarding the process. While in some cases this work can be done by the other members of the multidisciplinary team, the psychologist is best placed to explore the complex social, family, cultural and peer-related issues that are not uncommon in this population.[37] Some groups, including adolescents, patients with a long duration of deafness and patients with a history of psychiatric problems, may have a particular need for psychological input prior to CI.

DEVICES

There are four manufacturers providing cochlear implants for use in the UK (Advanced Bionics, Cochlear, MED-EL and Oticon Medical (previously Neurelec)). A full discussion of the differences between the available devices is outside the scope of this chapter. Outcomes are generally similar with all devices (see 'Outcomes' below), and all have similar reliability according to internationally agreed reporting guidelines.[38] All of the devices share a similar basic design:

- the external part: the microphone, sound processor and transmitter coil
- the internal receiver–stimulator package
- the intracochlear electrode.

These components are summarized below.

The external part: the microphone, sound processor and transmitter coil

This part of the cochlear implant detects the acoustic signal and converts it to an electrical signal with both temporal and spatial components. The encoded signal is transmitted to the internal device using radiofrequency via the external coil. New developments in the external components include: the position of the microphone (including devices that are a single magnetic unit, with no behind-the-ear processor); improved functionality drawing on advances in hearing aid technology (for example the Advanced Bionics Naida system that allows direct communication between the cochlear implant and a hearing aid in the contra-lateral ear to provide bimodal hearing); wireless connectivity to external devices; improved waterproof capability.

The internal receiver–stimulator package

This contains the internal magnet, telemetry coil and hermetically sealed electronics system. There is also a ground electrode for current return, either incorporated within the package or as a separate electrode placed under the temporalis muscle. Once received, the decoded signal is sent to the electrodes within the cochlea according to the processing strategy being used. New developments in the receiver–stimulator package include new processing strategies and smaller size. In addition, the latest generation of cochlear implant devices are all compatible with MRI scanning to 1.5 Tesla without magnet removal. Special precautions may be required to reduce potential complications.[39] Stronger MRI fields may necessitate magnet removal, though new designs such as MED-EL's rotating magnet that self-aligns when in the MRI field allows MRI scans up to 3 Tesla with the magnet *in situ*.

The intracochlear electrode

The electrode that is placed into the cochlea is in fact a group of individual wires, each ending at a contact point along the silicone casing. The number of individual wires varies depending on the manufacturer and type of electrode. Electrodes have become generally smaller in an attempt to reduce the trauma of insertion and allow for hearing preservation as well as the potential use of future technologies that might require preservation of cochlear function. Modern electrodes can be inserted via the round window or through small cochleostomies with a diameter of 0.5–0.8 mm.

The optimal resting position of the electrode within the scala tympani is debated; various manufacturers advocate lateral wall, mid-scala or modiolar-hugging designs. There is also much debate as to the optimal length of electrode; longer electrodes may allow for stimulation of the full length of the spiral ganglion cells but are also more likely to cause trauma to the apical basilar membrane. New imaging techniques to calculate the cochlear duct length may allow for an electrode of optimal length to be selected for individual patients.[40] Some electrode designs are available for specific situations: examples include the short electrode for EAS (see above), the compressed array or split/double electrode for cochlear ossification, and the electrode with a stopper incorporated into the silicone casing for plugging the cochleosotomy in case of a perilymph gusher.

OUTCOMES

Advances in technology in recent years, in particular the improvement in speech-processing strategies, have led to improved speech perception with CI. In infants, speech perception is of paramount importance for the development of spoken language. Other outcomes in children and adults, such as effect on educational achievement, social interaction, employment and quality of life, are also important. Key evidence regarding outcomes can be summarized as follows.

Outcomes in children

- Earlier age at CI is associated with better language development. This is now well accepted and has been shown in many studies. Many children implanted before 18 months of age show a similar rate of language development as normal hearing peers. Those implanted after 3 years of age may struggle to catch up, and it is recognized that a proportion of children will remain language-delayed when compared to normal hearing peers.[41,42] It is important to note, however, that children with cochlear implants consistently show a higher level of language attainment than profoundly deaf children using hearing aids.
- The importance of early age at implantation is due to the fact that there is a 'sensitive period' of around 2–3 years during which development of the central auditory system shows greatest neural plasticity.[43] The introduction of universal newborn hearing screening has allowed for the early identification of children with profound hearing loss.
- The preferred age of implantation of profoundly deaf infants in the UK is currently considered to be around 12 months. There is emerging evidence that even earlier implantation (between 6 and 12 months) may be optimal, and this has been shown to be safe in experienced centres.[44]
- Cognitive impairment is an important factor in outcome following CI. Children with additional disabilities that include cognitive impairment may never acquire spoken language. Nonetheless, CI may still be an important method of improving quality of life in this group.[22]
- Other factors associated with improved language outcomes in children include the fitting of up-to-date processors, greater residual hearing prior to implantation, better interaction between parent and child, and higher socioeconomic status.[45]

Outcomes in adults

- Duration of severe or profound deafness (and not age at implantation) is the most important factor in predicting speech perception outcomes in adult patients. As with neural plasticity in infants, this is due to a deterioration in the spiral ganglion cell population and the central auditory pathways with a long period of auditory deprivation (e.g. 20–30 years).[46]
- Duration of deafness is often a key consideration in deciding which ear to implant. A common scenario is the patient presenting with one ear that has been unaided for more than 20 years and a small amount of residual hearing on the other side; such a patient is advised to undergo implantation in the better ear, putting the residual hearing at risk to ensure optimal outcome with the cochlear implant (compare this to the more usual situation where the preference is to implant the worse-hearing ear to optimze hearing aid use on the contra-lateral side).

Special considerations

When considering outcomes, some situations warrant special attention.

BINAURAL HEARING

Patients with binaural hearing, bilateral cochlear implants or bimodal hearing (a cochlear implant in one ear and a hearing aid in the other) have improved outcomes when compared to those using a unilateral implant. Advantages include sound localization, spatial acuity and improved speech understanding in challenging listening environments, such as in the presence of background noise (see Wanna et al.[47] for a review of this topic). Some of these advantages improve over time, often years, following implantation. Quality of life is improved in bilateral cochlear implant recipients compared to unilateral recipients, though in sequentially implanted cases the relative increase is higher following the first implant.[48] Due to the advantages offered, there is increasing interest in CI in SSD (see 'Candidacy' above).

For similar reasons, cochlear implant manufacturers are increasingly working closely with hearing aid companies to improve the compatibility of the two devices and thereby provide optimal binaural hearing when only one cochlear implant is inserted.

MUSIC PERCEPTION

Despite recent advances in cochlear implant technology, music perception in implant recipients remains generally poor.[49] Recently developed music test batteries have shown limited ability among postlingually deafened

adults in melody, pitch and timbre identification, albeit with some notable exceptional cases. Rhythmic identification remains normal in implant users when compared to the normal population. Some prelingually deafened infants are able to enjoy music, and there is much current interest in the use of musical training in postimplantation rehabilitation.

SURGICAL TECHNIQUE

The majority of cochlear implant surgeries undertaken in the UK are via the transmastoid approach, accessing the cochlea via the facial recess. Other surgical techniques have been described including the suprameatal[50–52] or the transcanal approaches (with or without use of an endoscope).[53–55] The transmastoid approach will be discussed here.

Most surgeons use a postaural incision, sufficient in length to allow the implant to be introduced. The surgeon should avoid placing the incision line directly over the receiver–stimulator package to minimize post-operative wound complications.

The soft tissue is dissected down to the periosteum, which is incised to create an anteriorly or posteriorly based flap. A cortical mastoidectomy is then performed. A subperiosteal pocket is created to house the receiver–stimulator. Some surgeons may drill a well in the bone to secure the implant and/or tie the implant down to secure it in position. However, with the evolution of thinner implants without a 'footprint', more surgeons are choosing simply to create a subperiosteal pocket. Often, a gutter is drilled for the electrode as it passes into the mastoid cavity.

A posterior tympanotomy is created to give access to the round window niche, taking care to preserve the chorda tympani. Depending on the surgeon's preference and the access achieved, the entry into the cochlea may be via a cochleostomy, via the round window membrane (once the niche has been drilled away), or by opening the round window in an anterior and inferior direction. Optimal placement of the electrode is within the scala tympani.

Once inserted, a soft-tissue seal is placed around the electrode as it enters the cochlea, to prevent the leak of perilymph. The residual electrode wire is coiled within the mastoid cavity, and the wound is closed in layers.

Hearing preservation

Increasingly surgeons are adopting less traumatic approaches to entering, and introducing the electrode, into the cochlea. This has come about due to the development of less traumatic electrodes, a recognition that atraumatic insertion leads to the electrode remaining within the scala tympani with better outcomes,[56] an understanding that paediatric recipients are likely to undergo multiple implant surgeries in the same ear over the course of their lifetime, and the need to preserve residual low-frequency hearing in individuals who are going to use combined electro-acoustic stimulation (EAS).

Hearing preservation surgery is undertaken in individuals with good or aidable low-frequency hearing as described earlier. The surgeon may opt for a shortened or full-length electrode. Electrode insertion can be via a separate cochleostomy, or via the round window membrane.[57–59] Most surgeons advocate a slow electrode insertion, to minimize intra-cochlear pressure change, when attempting to preserve hearing. Various steroid regimes are employed, including a systemic dose on induction of anaesthesia (e.g. dexamethasone), steroid solutions placed into the middle ear or soaked onto spongistan placed directly onto the round window membrane (e.g. triamcinolone), and varying regimes of post-operative steroid administration. All of these options are an attempt to protect cochlear function thus preserving residual hearing to facilitate EAS.

Challenging cases

Although the majority of cochlear implant surgeries are straightforward, there are some scenarios that can prove more challenging. These include cochlear ossification, perilymph gushers and abnormally formed cochleas.

Cochlear ossification is most frequently encountered if the patient has had meningitis. The degree of ossification can range from a small amount of immature bone in the proximal end of the basal turn to complete ossification and obliteration of the cochlea. It may be possible to predict the degree of ossification with pre-operative imaging and in this circumstance performing both MRI and CT scanning can be helpful. However, sometimes the surgeon may come upon ossification without prior notification from imaging, in particular if there has been a delay between imaging and surgery or if there is early scarring or bone formation in the proximal basal turn.

In early ossification, it is usually possible to drill through the immature bone and identify the cochlear duct in the more distal basal turn. If this is not the case and the cochlear duct cannot be identified, the surgeon may opt to insert the electrode into the drilled-out channel (partial insertion), or to consider a dual-array electrode, drilling a further channel anterior to the oval window to access the middle turn of the cochlea. In the significantly ossified cochlea the results can be difficult to predict.[60] In completely ossified cochleas, it may be necessary to consider an auditory brainstem implant (ABI) in place of CI.

A cerebrospinal fluid (CSF) gusher may occur in an abnormal inner ear, most commonly in patients with abnormal cochleas such as in X-linked deafness. Lesser degrees of perilymph leakage are most commonly seen in large vestibular aqueduct syndrome (LVAS) (**Figures 94.1** and **94.2**). In a true gusher, when the cochlea is entered, there is a rapid and significant filling of the mastoid cavity with CSF. The head of the patient should be raised and, when the flow of CSF slows, the electrode should be inserted in the usual manner. Following insertion, care should be taken to pack muscle or soft tissue tightly around the insertion of the electrode into the cochlea to stop any further leak. If a leak persists, despite all of the above, then a lumbar drain should be considered in the immediate post-operative period to reduce the pressure of the CSF and allow the leak to settle.

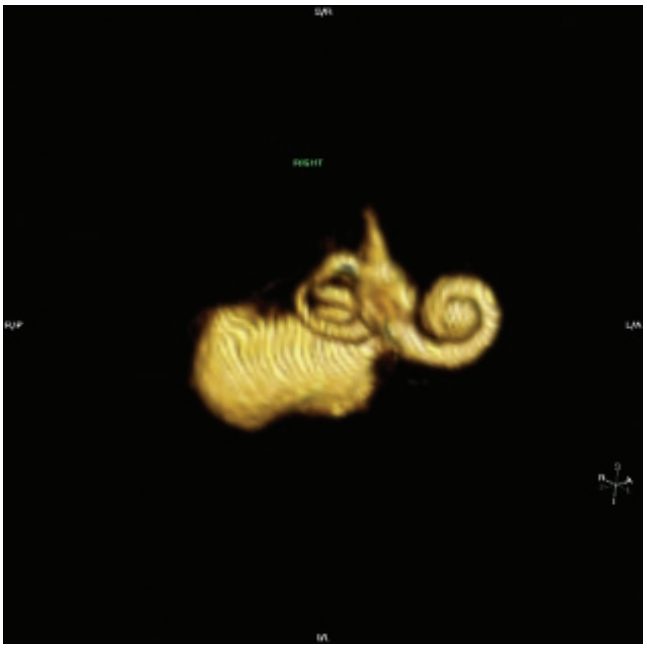

Figure 94.1 3-D reconstruction of the inner ear showing large vestibular aqueduct.

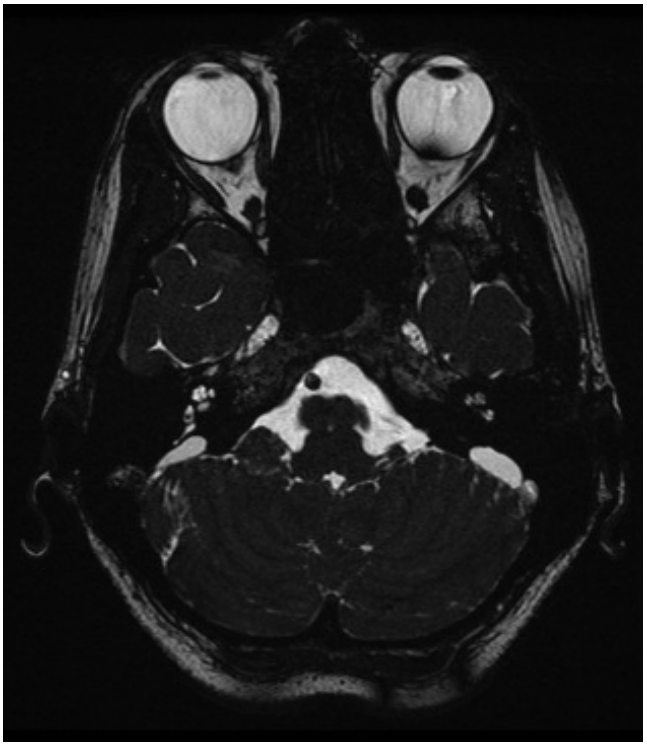

Figure 94.2 Axial T2-weighted MRI scan showing bilaterally enlarged vestibular aqueducts.

Due to the high quality of pre-operative imaging, it is possible to understand the anatomy of each cochlea to be implanted and the challenges they present. The surgeon may choose to use a shortened electrode in a malformed cochlea, or may request a custom electrode from one of the manufacturers in special cases such as a common cavity.

COMPLICATIONS

Complications in cochlear implant surgery can be classified by severity and timing:

- A major complication is one occurring during or after surgery that requires a major surgical intervention or results in a permanent disability (e.g. facial weakness).
- A minor complication is one that can be managed by medical measures or a minor surgical procedure (e.g. wound aspiration).

There are many published series quoting overall major and minor complication rates. Bhatia et al. looked at rates in 300 consecutive paediatric implants. They found major complications to occur in 2.3% of cases and minor complications in 16% of cases.[61] A recent prospective audit of 1397 paediatric bilateral cochlear implants in the UK reported a major surgical complication rate of 0.9%, with a minor complication rate of 6.5%, excluding device failure.[62]

Vertigo

Vertigo after CI is not uncommon.Most series report subjective and/or objective symptoms of dizziness or vertigo, usually transient, in approximately 30% of adult implant recipients.[63–65] In their series of 146 implanted adults, Enticott et al. noted that one-third of patients had vestibular disturbance and patients over the age of 70 were more prone to permanent injury.[65]

In a retrospective case review by Steenerson et al. almost three-quarters of adults with implants experienced vestibular symptoms, relieved by vestibular therapy. Of the 47 patients they studied, 74% experienced post-operative vertigo or imbalance; 19 of these 35 patients had experienced some imbalance sensations pre-operatively.[66] Forty-eight per cent demonstrated benign paroxysmal positional vertigo (BPPV) with positive Dix–Hallpike responses, arising from the implanted ear.

Limb et al. noted that BPPV occurs more frequently after CI than in the general population, and that routine BPPV treatment is effective in this group.[67]

With the advent of routine bilateral implantation, there is the potential risk of causing bilateral vestibular hypofunction. In patients with a pre-operative balance problem, vestibular assessment may be a useful adjunct enabling the team to select which ear to implant if unilateral implantation is proposed (i.e. opting for implanting the ear with poorer vestibular function).

The reported incidence of dizziness is less in the paediatric population.[68]

Device failure

With successive generations of implants, each manufacturer has pushed the agenda of device reliability. This is significant, as a large proportion of implant recipients are infants who will require an implant for the duration of their lifetime. Increasingly, a significant proportion of an implant programme's workload is replacing failed devices in their existing patients.

Device failure after CI surgery is one of the more common problems, although it should not be considered as a surgical complication, the cause rarely being surgical mismanagement. Trauma is linked to failure despite the device being built to withstand significant impact. Similarly, the device may fail suddenly or insidiously over time, sometimes referred to as 'soft' failures.

An implant is classed as failed if 50% of the electrodes are non-functioning. In a series of more than 900 implants from 1985 to 2003, Lassig et al. noted a device failure rate of 3.7%.[69] Battmer et al. looked at the European experience of 12 856 implants and found a similar device failure rate of 3.8%.[70]

Experience has shown that reimplantation is safe and effective (e.g. Woolford et al.).[71] Other studies, however, have shown variable post-reimplantation performance (e.g. Henson et al.)[72] and have also noted that patients need careful counselling regarding the possibility of differences in sound quality and speech recognition performance with the replacement device.

The facial nerve

Immediate post-operative facial palsy is due to damage to the nerve from direct trauma or by thermal injury. Facial nerve monitoring is commonly used and may help reduce problems. Gibbin et al. reviewed 1524 patients.[73] Four had an immediate partial facial nerve palsy, two of whom made a complete recovery. One immediate complete palsy occurred and partially recovered, leaving a permanent disability rate of 0.2%.

In the UK paediatric bilateral audit there were two (0.2%) temporary, partial facial nerve palsies in the post-operative period and no permanent facial palsies.[62]

Facial nerve stimulation has been reported to occur in between 7%[74] and 25%.[12] It occurs more frequently in patients with otosclerosis, particularly with the use of non-modiolar hugging electrodes in severe disease.[13] Facial nerve stimulation can be controlled by device reprogramming in nearly all cases.

Rare complications

MAGNET DISPLACEMENT

Many of the cochlear implant designs feature removable magnets. This facilitates temporary magnet removal, when an MRI is required of an implant recipient's brain, to minimize artefact on the scan. If an implant recipient experiences a degree of trauma over the implant, it is possible for the magnet to become displaced from its silicone pocket. The external component may then not connect to the internal device, as the coils are not aligned, or the displaced magnet may be palpable through the skin in an abnormal position. An X-ray confirms the diagnosis (**Figure 94.3**). A revision procedure is required to remove the displaced magnet and replace it within the implant or if the electrode is not fully functional following removal (this can be determined using intra-operative telemetry testing).

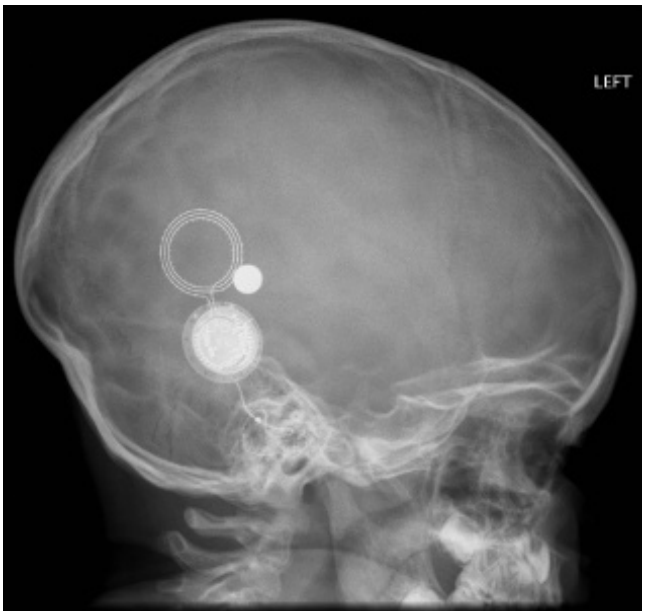

Figure 94.3 Plain lateral skull X-ray showing magnet displaced outside of the receiver-stimulator package.

TIP FOLD-OVER

Depending on the electrode design and insertion technique used, it is possible for the electrode tip to fold over upon itself. This may only involve a few electrodes, or a more significant portion of the array (**Figure 94.4**). This may not be recognized at the time of surgery, and is usually detected on post-operative imaging. The surgeon may choose to leave the implant if there is a minor degree of fold-over, or they may choose to revise the procedure. At revision, it may be possible to salvage the existing electrode by removing and reinserting (on-table imaging for confirmation of correct positioning is recommended), but the team should be prepared to use a second device if this is not possible or if the electrode is not fully functional following removal (this can be determined using intra-operative telemetry testing).

LOOKING TO THE FUTURE

Despite recent advances in CI, there is clearly still a great deal of work to be done to maximize the potential benefit to patients receiving this life-changing intervention. Some areas for potential developments include the following.

Unmet need

Despite the fact that many healthcare systems in the developed world already offer CI to appropriate patients, there are a large number of eligible patients, particularly adults, who are missing out on the potential benefits of this technology. For example, a recent study in the UK found that while 74% of eligible children between the ages of 0 and 3 years received an implant (increasing to 94% by age 17 years), only 5% of eligible adults underwent surgery.[1] This perhaps reflects a lack of awareness of the criteria for and benefits of CI in the wider medical and audiological

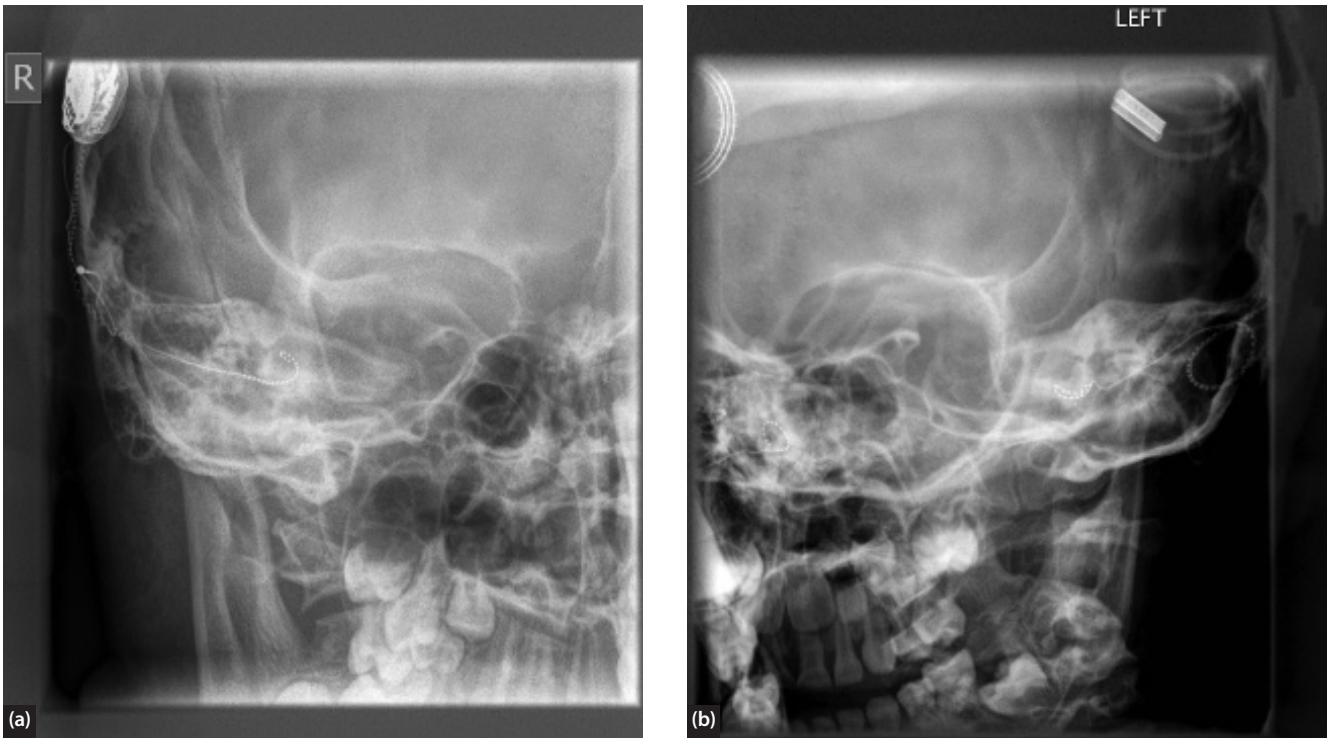

Figure 94.4 Plain skull X-rays showing **(a)** tip rollover of the distal electrode (note also incomplete electrode) and **(b)** more significant fold-over of the electrode.

communities as well as the general public. The unmet need in developed countries also highlights the huge burden of undertreated (or untreated) profound deafness in the developing world. While CI has been performed in many developing nations in isolated cases on a humanitarian basis,[75] wider implementation of CI is likely to require a change in the political and financial structures surrounding health care in such countries. Interestingly, uptake of CI in large numbers in emerging economies such as India and China has led to new avenues for research (e.g. the performance of cochlear implants in patients using tonal languages) and cochlear implant manufacturing, with global implications.

New technology applied to current devices

With the increasing uptake of CI, the cumulative number of adults being looked after by an individual centre rises rapidly, placing a significant burden on the professionals within that team. To reduce this demand, and to better serve patients who may be geographically remote from their cochlear implant centre, new methods of programming individual implants remotely have been explored. The majority use web-based connections between the implant audiologist and the patient. In future, software may allow the computer-literate patient to alter his or her own map without any external input.

Developing technologies

While the current design of the cochlear implant is continually being improved and updated, and new processing strategies developed, there are other potential developments that could change the nature of cochlear implants altogether.

- **The totally implantable cochlear implant (TICI).** Early prototypes of completely implanted cochlear implants have shown that such a device can be safe and effective.[76] Challenges remain in designing a microphone that can detect external signals without picking up unwanted noises related to movement, breathing, etc.
- **Drug-eluting electrodes.** These could be used to introduce anti-inflammatory or neurotrophic agents directly into the inner ear to prevent postimplantation neural degeneration, to prevent progression of deafness, or to improve the interface between the electrode and the neural elements.[77]
- **New insertion techniques.** As CI evolves, the need for atraumatic insertion is becoming increasingly important. This is reflected in the design of new implant electrodes. There has also been much interest in the use of robots to ensure a smooth and atraumatic electrode insertion (Zhang et al.)[78] and for minimally invasive and atraumatic drilling of the temporal bone and cochlea (Assadi et al.).[79] Such an instrument could potentially allow CI in remote settings using telesurgery.
- **New methods of neural stimulation.** At present, cochlear implants transmit an electrical signal through multiple electrodes and are therefore prone to current spread, meaning that the neural stimulation is not as specific as required for optimal performance. This has led to research into different ways to stimulate the auditory pathway (e.g. using optical stimulation).[80] To date, these techniques have not been applied in clinical

practice, but they may be important for future devices, particularly when used in combination with biological nanotechnology.

Inner ear treatment

Perhaps the ultimate measure in the management of profound sensory hearing loss will be treatment of the underlying aetiology and restoration of natural hearing. Such treatments would potentially have huge implications for patients with presbyacusis, the leading cause of deafness worldwide. Current research is examining the role of stem-cell and gene therapy in treating deafness (e.g. Kanzaki);[81] cochlear implants in the future may be as much about delivering such therapies to the inner ear to restore natural hearing as providing artificial stimulation.

KEY POINTS

- Cochlear implants have transformed the management of severe to profound hearing loss.
- Criteria to identify potential cochlear implant candidates differ between countries. In England and Wales, the NICE guidelines state that a patient must have severe to profound hearing loss (audiogram worse than 90dBHL at 2 and 4KHz) as well as failure to benefit from hearing aids (in adults, worse than 50% score on BKB sentence test at 70dB SPL; in children, failure to gain speech and language skills appropriate to age and development).
- Newborn hearing screening programmes allow early identification of children with severe to profound deafness. Implantation at or before 12 months of age gives optimal outcomes.
- Criteria are constantly evolving and cochlear implants may be appropriate for some patients with residual hearing, single-sided deafness, complex needs or anatomical abnormalities.
- Surgery is usually via a cortical mastoidectomy and posterior tympanotomy. Modern techniques allow for preservation of hearing in some patients. Serious complications are rare.
- One of the greatest challenges in cochlear implantation is to overcome the unmet need in both developed and developing countries.
- In addition to the continually improving electrode design, processing strategies and surgical techniques, future advances in cochlear implantation may include a totally implantable device, improved neural stimulation, routine use of drug-eluting electrodes and inner ear treatment with gene or stem-cell therapies.

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CHAPTER 95

MIDDLE EAR IMPLANTS

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the phrases 'middle ear implants', 'implantable hearing devices', 'middle ear implantable hearing devices' and 'vibratory ossicular prostheses', searched as keywords and also by combining the sets 'hearing aids' (all references) with 'middle ear' (all references).

INTRODUCTION

The primary impetus for active middle ear implant (AMEI) development is the desire to overcome many of conventional hearing aid shortcomings such as distortion, feedback, occlusion effect, discomfort and ear canal irritation. Next to that, AMEIs offer the potential for improved sound clarity, because most AMEIs bypass the external auditory canal (EAC) and do not use a speaker for signal amplification. A common characteristic of all implantable hearing aids is that the transducer is coupled to the ossicular chain or directly to the inner ear fluid. These implantable devices were initially designed for the treatment of sensorineural hearing loss (SNHL) in patients with healthy middle ears. Indications have expanded to patients with mixed hearing loss and middle ear malformations.[1] With the application of prostheses and coupling elements, the systems now cover all types of middle ear reconstructions for patients with moderate to severe mixed hearing loss.[2,3] This chapter addresses the application as well as the results of AMEIs for these indications.

HISTORY AND DEVICE DEVELOPMENT

Wilska[4] is credited with being the first to use electromagnetic induction to stimulate the middle ear, in the 1930s. Iron particles were placed on the tympanic membrane of a human subject and stimulated by an electromagnetic coil placed in the ear canal. Since then, and particularly over the past 30 years, much work has been done looking at different sites and methods of attachment of microphone, amplifier and transducer.

The majority of devices have utilized a postauricular microphone with resultant loss of the pinna effect. Overcoming this by placing the microphone in the EAC has been tried, but to date this has not been successful, largely due to problems with feedback.

Devices have predominantly used either a coil and magnet (electromagnetic) or a piezoelectric mode of transmission. The piezoelectric transducer works on the principle that, when a voltage is applied to a particular ceramic (piezoceramic or piezoelectric crystal), it causes a proportional deformation and hence displacement of that ceramic. This voltage-dependent displacement can then be coupled to the ossicles to drive them (used in the TICA and Envoy systems, see 'Devices no longer available' and 'Current devices' below). In the case of the electromagnetic transducer, the electrical signal is used to produce an electromagnetic field by means of a transduction coil. This then drives a magnet that can be attached to the ossicles in a variety of ways to transfer the vibrations.

The coupling mechanism of the device is the method by which the transducer is connected to one of the middle ear ossicles or cochlear windows. Most of the different devices are connected to one of the middle ear ossicles with or without need for disruption of the ossicular chain. The possibility of hydroacoustic transmission, via a

water-filled tube, either to the ossicles or directly to the round window membrane has been investigated.[5]

A major problem with these devices has been to produce a device that is small enough to fit within the confines of the middle ear and yet powerful enough to produce the required gain. Over recent years technological advances have resulted in a number of devices that have fulfilled these basic requirements. The translation from theory to a viable surgical and financial product has, however, proved extremely difficult and many projects have ultimately ended in failure.

CURRENT DEVICES

Vibrant Soundbridge (MED-EL, Innsbruck, Austria)

The Vibrant Soundbridge (VSB) developed by Symphonix and currently by MED-EL is an active semi-implantable hearing device. It consists of an internal, surgically implanted part – the vibrating ossicular prosthesis (VORP) – and an external audio processor. The VORP consists of a receiving coil, conductor link and transducer. The transducer employs a small electromagnetic coil and enclosed magnet to produce vibrations in this floating mass transducer (FMT), which can be coupled to the ossicles or round window. The VSB obtained the European certification mark for implantation in 1998 (Symphonix Devices Inc., 2000) and has also received Food and Drug Administration (FDA) approval.[6] In addition, the VSB received the European Union CE Marking for treatment of conductive and mixed hearing loss in adults (2008) and children (2009).[7]

Direct acoustic cochlear implant (DACI) (Cochlear Ltd, Sydney, Australia)

Initially called the direct acoustic cochlear stimulator (DACS, Phonak Acoustic Implants, Phonak AG, Stäfa, Switzerland) and later the Codacs™ Investigational Device, this device consists of an implantable electromagnetic transducer, which transfers acoustic energy directly to the inner ear via a conventional stapes prosthesis. An audio processor is worn externally behind the implanted ear. The stapes has to be removed in total. In order to restore the natural sound transmission of the ossicular chain, a second stapes prosthesis is placed in parallel to the first one into the oval window and attached to the patient's own incus.[3] This implant is indicated for profound mixed hearing loss. The device is CE approved but to date there has been no FDA approval.

Otologics semi-implantable middle ear transducer (MET) and fully implantable Carina (Otologics, Boulder, Colorado, USA, later Cochlear (Sydney, Australia)

This device is currently fully implantable, although the initial trials were done with a semi-implantable version, which has CE approval.[8] The technology was purchased by Cochlear (Sydney, Australia) in September 2012. The semi-implantable MET uses an external unit called the button external audio processor, containing a microphone, battery, signal processor and transmitter. The transducer drives an electromagnetic probe coupled to the body of the incus. The tip of the probe is made of aluminium oxide, which forms a fibrous connection with the incus body. The ossicular chain is left intact.

The fully implantable Carina uses the same electromagnetic transduction system, but consists of a subcutaneous microphone, battery and an electronic receiver connected to a transducer. The latter is used in patients with mixed hearing loss with a variety of implantation sites and aetiologies, including the round window and footplate.[9, 10] The device is CE marked for this purpose in Europe and South America.

Fully implantable Envoy Esteem Device

This device comprises a piezoelectric sensor placed on the incus body, acting as an internal microphone, and a driver cemented to the stapes head. Implantation of the device requires disarticulation of the ossicular chain with removal of the lenticular process of the sensor interface linked to the body of the incus, and the driver is cemented to the stapes head.[11] This device is indicated for patients with SNHL. CE marking was accomplished in 2006, and the FDA granted approval in 2010.[12]

EMERGING TECHNOLOGIES

Maxum Hearing Implant (Ototronix, LLC, Texas, USA)

The SOUNDTEC Direct Drive Hearing System (DDHS), initially designed by SOUNDTEC Direct, is another semi-implantable device containing an electromagnetic transducer. The implanted part consists of a magnet attached to the incudostapedial joint via a titanium alloy wire ring. Placement requires a transmeatal approach. The electromagnetic coil forms part of the external portion of the device and is placed deep in the ear canal.[13] The SOUNDTEC DDHS has had FDA approval,[6] but the results have been mixed.[14] The device was removed from the market in 2004 because of device-related adverse events. In 2009 Ototronix purchased the SOUNDTEC technology, and the device was rereleased as the Maxum Hearing Implant after incorporating several notable upgrades, including a self-crimping Nitinol wire that obviates incudostapedial joint separation. To date there are no clinical studies concerning this new upgraded system.

Semi-implantable middle ear electromagnetic hearing device

For this semi-implantable middle ear electromagnetic hearing device (SIMEHD), the magnet is cemented to the incus body and a titanium frame fixed to the temporal

bone supports an implanted electromagnetic coil. The gap between magnet and coil can be adjusted on the frame. Both magnet and coil are encased in titanium.[15] The SIMEHD has been implanted in cats and a human study has been proposed.[15]

Piezoelectric round window implant with infrared optical signal

This AMEI comprises a micro transducer, placed on the round window. It can receive power and signal transmission through an infrared optical transmitter located in an external unit. This also contains a microphone, sound processor and battery and is placed in the ear canal.[16] Notably, this AMEI can be implanted endaurally without mastoidectomy. The system has not yet been tested *in vivo*.

EarLens tympanic contact transducer

This device consists of a magnet placed in a silicone lens that sticks to the tympanic membrane by oil-induced surface tension. A small induction coil is placed in the ear canal.[17]

DEVICES NO LONGER AVAILABLE

Semicircular canal piezoelectric vibrator

This device stimulates inner ear fluids directly by means of a lateral canal fenestration, bypassing the middle ear. Welling and Barnes[18] used a piezoelectric biomorph material that could activate the auditory system via vibromechanical stimulation and thus showed the feasibility of this approach.

University of Bordeaux implantable piezoelectric transducer

The device consists of a piezoelectric biomorphic material with a short rod and platinum ball placed against the round window. However, since its initial publication in 1995,[19] no reports have been published regarding application of this technology to living individuals.

Rion partially implantable hearing aid

The Rion partially implantable hearing aid (PIHA) uses a piezoelectric transducer connected to the head of the stapes or footplate by a hydroxyapatite coupling. The transducer is held in place by a fixing plate screwed to the temporal bone.[20] This device has been implanted in patients in Japan under Japanese approval but is no longer in production.

Totally implantable cochlear amplifier

Developed by Implex, the totally implantable cochlear amplifier (TICA) was the first fully implantable middle ear device. Comprising an ear canal subcutaneous microphone and piezoelectric transducer, the device was revolutionary but problems with feedback necessitated disarticulation of the chain. The device is no longer in production.[21, 22] The technology was purchased by Cochlear to be implemented in cochlear implants.

PATIENT SELECTION

Candidates

Ideal candidates for middle ear implants are patients with high-frequency sensorineural or mixed hearing loss, in which amplification with conventional hearing aids – with or without stapedotomy – or bone-conduction implant (BCI) has failed. In most cases failure is caused by acoustic feedback, occlusion effect, insufficient high-frequency amplification or wearing discomfort. Although the VSB and the MET/Carina is cleared for use in patients under the age of 18,[7, 23] the majority of these devices have been placed in adults. Candidates should not have any skin conditions that may prevent attachment of any external component of the device and should be medically fit for surgery and the anaesthesia required. In addition, candidates should have been appropriately counselled by a surgeon and be judged to have realistic expectations. Further selection is made based upon audiological and otological conditions.

Audiological

Current devices are most suitable for mild to severe SNHL. In case of conductive or mixed hearing loss, the main objective of AMEI placement is to overcome the residual sensorineural component. Preferably, hearing loss should ideally be stable, while accepting very slowly progressive losses. The Codacs system is specifically designed for patients with a profound mixed hearing loss such as in advanced otosclerosis.[3] Aided thresholds for the candidates' present hearing aid should be taken into consideration. Tympanometry and acoustic reflexes may be required to assess middle ear function and speech audiometry to assess retrocochlear loss. The worse-hearing ear is usually selected for implantation.

Otological

In general, there should be an absence of retrocochlear or central involvement in the hearing loss. Middle ear inflammation must be controlled prior to implantation. In case the external processor is worn in the EAC, the ear canal must be assessed before surgery in order for it to be suitable. Beleites et al[1] suggested a classification of the different types of applications of AMEIs for specific pathological middle ear situations.

A Type A vibroplasty involves the coupling of an AMEI on an intact ossicular chain in patients with a mild to moderate SNHL (the classic indication). Different attachment points to the ossicular chain (e.g. umbo, incus or stapes) are used. The stapes head and footplate are the most favourable attachment points.[24] AMEIs that can be considered for this situation are the VSB, MHI and Carina.

Type B vibroplasty consists of aided hearing by means of an AMEI – mostly the VSB – coupled to a remnant of the ossicular chain, which is in most cases the stapes or its footplate. Although still experimental, solutions with the Carina and Esteem using additional couplers or passive prostheses are being researched.[25–29]

Type C vibroplasty involves the coupling of the actuator on one of the middle ear window membranes. The VSB is the only implantable actuator to suit this application on the round window. In recent years round window coupling has become an increasingly common alternative for the 'classic' coupling of the VSB on the long process of the incus.[1]

Type D vibroplasty is described as the direct coupling of an AMEI to the inner ear fluid. For this approach, the oval window is mostly used. The DACI system was designed for this application, but the VSB combined with a conventional stapes piston can also be used.

SURGICAL CONSIDERATIONS

For the AMEIs on the market today (VSB, MET/Carina, DACI and Envoy) the surgical approach is similar to that of a cochlear implant. It compromises retroauricular transmastoidal access to the middle ear via the facial recess (VSB) atticus (Carina) or a slightly different approach is needed to gain access to the round window niche (Codacs). Sometimes a combined approach is needed to gain sufficient access to the middle ear in case of a joined placement with a passive implant. An implant bed is drilled in the cortical temporal bone to accommodate the internal receiver and conductor link. For most implants (Carina, Esteem and Codacs) the transducer is fixed to the cortical bone in the mastoid cavity by means of cement or screws. Although the mastoid has more space available than the tympanic cavity, allowing stronger transducers, this procedure requires meticulous placement and is slightly more difficult than placement of other AMEI systems with separated coil and magnets (MHI and EarLens), which only require an transmeatal tympanotomy. The performance of the latter, however, depends heavily on the distance between the coil and magnets.

For VSB placement the posterior tympanotomy should be large enough to pass a 3 mm diamond burr in order to ensure sufficient space to site the FMT. For a classical placement its attachment clip is folded and crimped around the long process of the incus, although with the introduction of a short process clip this approach without a posterior tympanotomy is proving more popular and technically more straightforward. Also, placement of the FMT on the stapes head, footplate or round window can be performed.

The main advantages of these procedures are that they utilize an approach already familiar to otologists and do not require disruption of the ossicular chain, in case of an intact ossicular chain. However, bone work is required close to the facial nerve and there is also concern about crimping the clip to the long or short process of the incus. If the clip is crimped too tightly, there is a potential for necrosis of the long process of the incus; if it is too loose, the implant may fail. Placement of the FMT, other than the classical way, can be challenging. A consensus statement was published in 2014 to address this issue.[30]

For placement of the Codacs system a special 'retromeatal approach' is used to assess the facial recess at the level of the oval window. The device is electronically and mechanically tested during surgery.

For an MET/Carina device, the bone work is away from the facial nerve but perhaps less familiar to the otologist. An atticotomy is performed to expose the incus body and malleus head. A laser is used to make a hole in the body of the incus. The transducer is then inserted into the mounting system secured to the skull and the probe tip is aligned with the laser-made hole in the incus. Fine-positioning of the probe tip is made by screw adjustment.[8] For the Carina, a separate microphone connected to the implanted sound processor is placed in a postauricular subcutaneous pocket. For the Esteem system a large facial recess opening is needed so that resection of chorda tympani is often inevitable. Intraoperative testing by means of laser Doppler vibrometry is needed to assess the mobility of the incus and stapes. Hypomobility will require aborting the surgical procedure at this point. Meticulous cleaning of the stapes head and incus is needed for adequate placement of the sensor and driver.

RESULTS

Surgical results

In general, complications regarding AMEI implantation are poorly reported and may be subject to reporting bias.[31–33] Worldwide, the VSB has been implanted in the largest group of patients. Initial audiological and surgical results for this device came from a European multicentre trial including 47 patients.[34, 35] They showed no major complications in terms of permanent facial weakness or profound sensorineural loss. One delayed onset of temporary, partial facial weakness occurring 10 days post surgery was reported.[35] Clinical experience with this device has been described in a number of studies.[26, 34–41] Complications mainly consisted of damage to the chorda tympani[34, 42] and dislocation of the FMT, particularly in type C vibroplasty.[38, 41, 43] A consensus statement published in 2014 proposed a specific surgical technique to address the variable results due to the dislocation issue.[30] Also extrusion of the (sometimes) accompanied passive prosthesis has been reported.[26] Another frequently reported symptom following VSB implant surgery is aural fullness.

Initial studies on the Codacs system showed that most common post-surgical complaints were tinnitus, deterioration of bone conduction and vertigo. No major device-related adverse effects were noted.[3, 33, 44–46]

The most common event reported for the Carina device was device malfunction or failure, mostly related to charging. This occurred in 17.6% of patients in a pooled population of 68 patients. Device malfunction led to four explantations and three revision surgeries. Partial device extrusion occurred in four patients and resulted in two explantations.[10, 47–53]

After placement of the Esteem device, 8% of the patients in a pooled group of 87 patients reported facial weaknesses,

while 30% of the patients reported taste disturbance, mostly caused by a chorda tympani lesion, which was temporarily experienced in approximately 50% of the cases. Also, 13% of the patients underwent explantation or revision surgery because of insufficient benefit or device malfunction.[11,12,54–56]

Pooled data from a systematic review by Klein et al.[57] showed that, overall and in experienced hands, AMEIs are considered a safe alternative to amplification options such as conventional hearing aids (CHAs) or osseointegrated BCIs for patients with mixed hearing loss. Taking into account the challenging pathology of COM, advanced otosclerosis and congenital malformations,[33] Tysome et al.[31] concluded that AMEIs were safe to implant for SNHL, based on his systematic review.

With regard to long-term results, most studies show no initial decline of bone-conduction threshold after implantation. However, one study reported a mean threshold elevation of 8 dB in post-operative hearing thresholds in a series of 20 patients 2 years post implantation.[42] This might suggest overstimulation-induced cochlear trauma.

Patient-reported outcome measures

The Abbreviated Profile of Hearing Aid Benefit (APHAB) self-assessment questionnaire[58] was mostly used to evaluate patient satisfaction for all AMEIs. In general, patients experience a significant improvement of benefit for all current AMEIs in terms of ease of communication, reverberation and listening in background noise compared to the unaided situation. Regarding comparison with previous conventional hearing amplification, far less information is available. APHAB results suggest that patients experienced more benefit from the VSB over conventional amplification.[35,59,60] Kraus et al.[12] reported clinically significant greater benefit with the Esteem compared with CHAs in all subcategories. Jenkins et al.[10] found the Carina to be superior in all subcategories. However, the data are not statistically significant. The most convincing significant increase of benefit was seen for the Codacs system compared to the use of a conventional hearing aid and the unaided situation.[3,44,46] Overall, the reported benefits included improved quality of sound, elimination of occlusive effect, and an improved ability to lead an active lifestyle when compared with CHA use. With regard to subjective hearing improvements, patients generally prefer the sound quality of an AMEI to that of a CHA. Direct ossicular stimulation maximizes the ability to hear high-fidelity, naturally produced sound. Additionally, the proximity of the implant transducer to the cochlea reduces distortion.[32]

Audiology results

AMEIs in sensorineural hearing loss (type A vibroplasty)

Since open-fit hearing aids and AMEIs both service patients with high-frequency hearing loss, it seems logical to compare the benefit of these devices. However, since these patients are by definition dissatisfied with conventional aids, such a comparison is difficult, due to a patient bias.[61] AMEIs currently used in type A vibroplasty are the VSB on the long proces of the incus, Esteem and Carina. Functional gain between pre-operative non-aided and aided versus post-operative implanted conditions has been tested, both in quiet and noisy environments. Studies showed statistically significant post-operative AMEI-assisted hearing improvement in varying levels (ranging from 16 dB to 48 dB) compared to pre-operative unaided condition.[9–12,35,48,56,60–70] Compared to the best aided pre-operative condition, a positive – but not significant – functional gain was demonstrated in most studies. Some studies report a (clinically) statistically significant improvement with the VSB device[35] and Carina device[9,10,48,66] compared to optimally fitted conventional hearing aids, respectively. In general the functional gain was quite similar among the devices.[9–12,35,48,56,60–65,67–70]

In a quiet environment, these comparisons showed a statistically significant improvement in most studies.[11,12,48,71] However, word recognition scores declined in one study.[72] Finally, when comparing AMEI performance (VSB) to the best aided condition in a noisy environment, clinically statistically significant improvements were demonstrated too.[73] This suggests that AMEIs have a functional gain at least as good as, if not better than, conventional hearing aids. However, reports are contradicting and sparse.

AMEIs in mixed hearing loss (type B, C and D vibroplasty)

For the heterogeneous group of pathologies causing mixed hearing loss (otosclerosis, tympanosclerosis, cholesteatoma), different strategies for hearing rehabilitation have been proposed. AMEIs most commonly used for mixed hearing loss are VSB, MET/Carina and Codacs. In general, the status of the middle ear affects the performance of the AMEI. Reduced load impedance due to a partially missing ossicular chain is usually an advantage that improves performance.

Mostly, a VSB coupled on the round window (type C vibroplasty) is used to service mixed hearing loss. The results of the VSB with its actuator coupled to one of the cochlear windows shows statistical significant difference in terms of speech perception in quiet and in noise compared to conventional hearing aids.[38,39,74,75]

However, audiological results in round window placement (type C vibroplasty) of the VSB vary due to effectiveness of the coupling.[1,74,76,77] Recent publications report that adequate coupling might account for as much as 20 dB of the hearing benefit.[78,79] A type C vibroplasty with the MET/Carina has shown to provide an improvement of functional gain over the unaided situation, but there was no comparison with conventional hearing aids.[50,51,80] An interesting situation is the presence of a fixed stapes footplate.[23] Some authors perform a round window vibroplasty, others a clipping of the VSB on the fixed stapes. The results remain variable and some even with limited benefit.[78] Although it has been suggested that, with a VSB or Carina device placed on the round window, SNHL due to oval window fixation can be serviced, there was no comparison with conventional aiding.[51,81] Research has shown that the round window application of the VSB can be used in chronically diseased middle

ears, after subtotal petrousectomy with obliteration of the middle ear cavity, and in atretic ears.[82, 83]

As an alternative to round window placement, the VSB can be coupled to the stapes head by means of a partial ossicular replacement prosthesis (PORP) or on the footplate by means of a total ossicular replacement prosthesis (TORP) (type B vibroplasty). Although there is a risk of extrusion, the audiological results are promising and are comparable with placement on the ossicular chain or round window.[27–29, 84] Another solution to stapes fixation could be a type D vibroplasty, although opening the inner ear is not always possible. The DACI system or a VSB or Carina system in combination with a conventional stapes can be used. Significant improvement in terms of functional gain, speech perception in noise and word recognition scores was seen in favour of the Codacs compared to conventional hearing aids in several studies.[3, 44–46] Both the Carina and VSB–stapedotomy combination showed favourable results, but these were not compared to conventional hearing aids.[53, 85–87]

Recently, Zwartenkot et al.[88] compared the maximum output of both the Codacs and the VSB, mostly used in a vibroplasty type B, to bone-conduction devices and found that only with the Codacs is a patient capable of using his full dynamic hearing range. Nonetheless, only patients with advanced otosclerosis were included and long-term data are not yet available.

BEST CLINICAL PRACTICE

- ✓ Implantation of these devices using the classical indications of moderate to severe SNHL is now well established, although it should only be carried out in centres with considerable experience in implantation otology and after a proper trial with optimal fitted conventional aiding such as hearing aids or bone-conduction devices.
- ✓ The evaluation of middle ear implants for patients with mixed or conductive losses including otosclerosis should be undertaken only within the context of a clinical trial.

FUTURE RESEARCH

- ➤ The fundamental for the development of implantable hearing aids is based on the desire to provide an alternative hearing solution than conventional hearing aids for patients with moderate to severe hearing loss. Benefits for the patients would in theory include hearing improvement, as well as an increased potential for an active lifestyle.
- ➤ AMEIs have gained substantial improvements over the years in terms of sound quality and patient comfort. However, most theoretical advantages of an AMEI are still unaccomplished, as most studies do not reveal a statistically significant improvement compared to optimally fitted conventional hearing aids. Overall, the benefits of AMEI do not yet convincingly outweigh the drawbacks of this technique in all patients, especially since some patients experience unstable progressive hearing loss, which could exceed the output capabilities of their implanted device.
- ➤ The use of visible external components in semi-implantable devices still restricts patients from certain activities, while in the canal components may still result in an occlusion effect and canal irritation. Likewise, placement of one of the fully implantable devices requires ossicular resection, which could leave a patient with a more pronounced conductive hearing loss. There are also concerns of long-term device reliability and the need for revision surgery or battery replacement in totally implantable systems.
- ➤ Although use of AMEIs is expanding to patients with mixed hearing losses, the population benefiting is limited. On the one hand, the indications exclude patients with mild to moderate hearing loss. On the other hand, indications for cochlear implantation are steadily extended. Therefore, AMEI companies may suffer signicant financial obstacles. To be successful, their devices will need to be priced in such a way as to be competitive to other devices, especially the non-implantable alternatives and the more traditional bone-conduction devices.
- ➤ The level of evidence and the quality of the included studies were judged to be moderate to low. More comprehensive data comparing device performance with conventional hearing aids or alternatives for speech in noise is needed. More long-term follow-up data are also needed.

KEY POINTS

- Middle ear implants are classically indicated for patients with mild to severe SNHL as an alternative to a conventional amplification aid.
- The indications have expanded to moderate and severe mixed hearing loss by means of the round window membrane stimulation of direct inner ear fluid coupling.
- A middle ear implant service requires close collaboration between an experienced audiologist and otologist. To date these services have developed on the back of pre-existing cochlear implantation programmes. This trend is likely to continue.
- The current devices have established in being safe in terms of extrusion and maintaining residual hearing.
- Overall device performance is comparable to, and some are slightly better than, conventional hearing aids.
- Patients describe a higher satisfaction with AMEIs in terms of sound quality.
- More comprehensive data comparing device performance with conventional hearing aids or alternatives for speech in noise are needed.

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CHAPTER 96

AUDITORY BRAINSTEM IMPLANTATION

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SEARCH STRATEGY

Data in this chapter may be updated by a search using the keywords: 'auditory brainstem implantation in NF2' and 'auditory brainstem implantation in neurofibromatosis type 2'. The chapter is written without detailed explanation about neurofibromatosis type 2 or cochlear implantation, which are covered in separate chapters.

INTRODUCTION

The auditory brainstem implant (ABI) is indicated in severe to profound hearing loss when congenital or acquired abnormalities of the cochlea or auditory nerve (or sometimes both) preclude cochlear implantation (CI). The congenital group (invariably infants and children) includes those with dyplastic or aplastic cochleas and/or auditory nerves while the acquired group predominantly comprises neurofibromatosis type 2 (usually adults) and occasionally acquired cochlear diseases such as otosclerosis or post-meningitic cochlear ossification.

HISTORY

A single-channel ABI was first used to successfully stimulate the cochlear nucleus in 1979.[1] Prior attempts to elicit auditory sensations by stimulating the inferior colliculus had failed.[2] The House Institute developed their implant for patients with neurofibromatosis type 2 (NF2) who had no remaining hearing having undergone surgery for bilateral vestibular schwannoma (VS).[1, 3] Two ball electrodes were implanted near the surface of the cochlear nucleus.

The first multichannel device was implanted in 1991 and subsequently modified.[4, 5] Cochlear® Limited (Sydney, Australia) produced the device which had 21 electrode contacts and was based on their Nucleus™ cochlear implant (CI). In the UK, the use of the ABI was first introduced by Richard Ramsden in Manchester as part of a European multicentre clinical trial, paving the way for the utility of ABI in NF2 in the UK.[6] In 1997 the first MED-EL (Innsbruck, Austria) ABI was carried out. The device was based on their Combi 40+ CI. It has a paddle array of 12 electrode contacts on a 5.5 mm × 3.0 mmm soft silicone matrix and works with an external audio processor in the same manner as a CI. At the time of writing both the Cochlear® and MED-EL ABI are commercially available devices.

The aim of ABI is to rehabilitate patients with no hearing as a result of absence or damage to the auditory nerves and thereby no cochlea to brainstem connections.

ABI IN ACQUIRED HEARING LOSS – NF2 AND NON-NF2 DISORDERS

ABIs were initially designed for patients with NF2.[1, 3] Bilateral VSs are the pathological hallmark of NF2, occurring in 90–95% of patients.[7] NF2 patients may also have multiple central and peripheral nerve system tumours including meningiomas and gliomas. Less commonly, juvenile cataracts and skin lesions are a feature.

Hearing loss occurs as a result of tumour growth causing auditory nerve compression or cochlear damage from ischaemia, infarction or tumour involvement. The rate or extent of hearing loss does not correlate with tumour size or tumour growth.[8] Patients report hearing loss to be the most disabling symptom of the disease.[9] Auditory rehabilitation is therefore one of the key considerations in NF2 management and decision-making. Gold-standard care is delivered by MDTs.

AUDIOLOGICAL ASSESSMENT

The English consensus protocol for auditory rehabilitation in NF2[10] recommends annual audiological assessment as part of the regular review process for NF2. This involves pure-tone audiometry (PTA) and speech discrimination testing with the Arthur Boothroyd (AB) word test as well as hearing aid review to maintain optimum performance. If speech discrimination scores (SDS) fall below 50%, Bamford–Kowal–Bench (BKB) sentence testing is recommended. This should trigger assessment for auditory implantation if scores are below 50% in best-aided conditions at the optimum sound intensity (identified by the SDS), in accordance with the National Institute for Health and Care Excellence (NICE) guidelines.[11]

Auditory implant assessment involves free-field speech discrimination testing with and without lip-reading with hearing aids and potentially environmental noise discrimination tests as well. Sudden deterioration or noticeable progressive hearing loss requires interim review and reassessment.

The decision to operate/offer an auditory implant is complex and is underpinned by MDT decisions about patient tumour management.[7, 12] This involves consideration of patient factors, tumour factors (including size and growth rate), the contralateral ear/tumour and facial nerve function CI may be possible and assessment of auditory nerve function is therefore important to try to predict whether a functional auditory pathway still exists from the cochlea. Promontory electrical stimulation in an apparent dead ear involves electrical stimulation through a transtympanic needle placed on the promontory to attempt to elicit an auditory percept in a conscious patient. Auditory perception suggests a functioning cochlear nerve (CN) but does not predict outcome with a CI.[13] Transtympanic electrical auditory brainstem response (TTEABR) testing is useful in assessing the CN: it has been shown to correlate well with CI-evoked EABR and aids decision-making in patients with CN aplasia/hypoplasia.[14, 15] It may also aid decision-making pre-operatively in NF2 patients.

INTRA-OPERATIVE MONITORING

Intra-operative monitoring of the auditory nerve to aid hearing preservation has been used with varying degrees of success. Proponents use a combination of direct cochlear nerve action potential (CNAP) monitoring and fast auditory brainstem responses (ABR).[16] The ABR is elicited by a 104 dB sound pressure level click stimulus from an ear mould placed inside the ear canal pre-operatively. A combination of analogue and digital filters with specific software enables an interpretable trace and the surgeon is alerted if there is a change in latency of wave V of >0.5 milliseconds. To monitor the CNAP, a multistrand silver wire attached to a cotton pledget is placed proximal to the tumour adjacent to the CN. This acts as the positive electrode, and together with surface negative and ground electrodes enables monitoring of the CNAP. Any change in morphology of the wave is reported to the surgeon. CNAP is difficult to use in the middle fossa approach, as the brainstem proximal to the tumour is relatively inaccessible.

In a study of intra-operative monitoring in 75 patients with serviceable hearing undergoing VS surgery, it did not improve the rate of serviceable hearing preservation.[16] Absent or diminished fast-ABR or CNAP at the end of the procedure correlated with poor post-operative hearing in almost all cases. Sensitivity was poor; over 50% of those with a response after tumour resection did not have serviceable hearing preserved. Problems with these monitoring techniques include persistent presentation of a suprathreshold stimulus; difficulties with placement and maintenance of position of the positive electrode for CNAP; response to surgical manipulations; and interference or artefact from electrocautery.

The presence of post-tumour resection ABR, CNAP, EABR or CI-evoked EABR provides some prognostic information and is an indicator of residual auditory nerve transmission of electrical stimulation. In this situation CI may be worthwhile. In contrast, if these are negative and/or the auditory nerve has definitely been sacrificed, then ABI is the auditory rehabilitation choice.

MULTIDISCIPLINARY DECISION-MAKING

The English consensus of the options and numerous permutations for decision-making with regards to auditory rehabilitation in NF2 are shown in **Table 96.1**.[10] Surgery is usually only offered once hearing has deteriorated below 50% on BKB sentence testing. ABI may be indicated when planning VS excision where CN preservation is not likely to be possible or previous contralateral excision has taken place and there is no remaining hearing or a poorly performing/failed CI/ABI.

CN preservation surgery may be attempted for growing tumours up to 3 cm intracranial tumour diameter (ICTD), but the likelihood of success diminishes progressively over 1 cm ICTD. Hearing preservation is rarely possible for tumours >1.5 cm ICTD. For patients with no serviceable hearing and when intra-operative/post-resection evoked potentials are present, CI is the aim but there is still the possibility of a non-functioning CI.

TABLE 96.1 Indications for cochlear implantation and auditory brainstem implantation in neurofibromatosis type 2

	Cochlear implantation	Auditory brainstem implantation
VS excision planned	CN preservation thought possible	VS in contralateral ear and • CN preservation not thought possible **OR** • CN preserved but intra-operative ECAP and EBAR poor
		Contralateral VS excised and • no contralateral hearing **OR** • contralateral CI/ABI providing poor hearing rehabilitation
Bilateral profound hearing loss and no VS excision planned	Bilateral small to medium-sized stable tumours Stable unilateral tumour where previous contralateral VS excised and CN lost Hearing preserved at previous VS surgery	

CN, cochlear nerve; EABR, electrically evoked brainstem response; VS, vestibular schwannoma.

Counselling of patients requires comprehensive explanation and may take multiple sessions. As well as an introduction to the implants and an explanation of the risks of surgery and alternatives as part of formal consent, there are a number of key areas that must be emphasized:

- Pictorial explanation of the site/positioning of the implants is advised.
- The possibility of the implant being a 'sleeper' device while serviceable hearing is present in the contralateral ear is important to address in specific cases.
- The range of possible outcomes and the difficulties with predicting prognosis/benefit should be explained.
- Managing patient expectations is crucial.[10]
- It is important to stress the immense workload and commitment required by the patient and team for rehabilitation.

Introducing the patient to one who has previously been through surgery and the process of auditory habilitation with a CI/ABI is beneficial.

SURGICAL CONSIDERATIONS

There are a number of surgical approaches. The middle fossa, retrosigmoid and retrosigmoid–retrolabyrinthine approaches are options when aiming for hearing preservation in small tumours, the middle fossa approach being favoured when there is more tumour in the fundus of the internal auditory canal. However, hearing preservation is not often attempted in NF2 patients in England since common practice is to wait until the hearing has deteriorated. Translabyrinthine and retrosigmoid approaches are the two commonest approaches for larger tumours. A modified translabyrinthine approach has been described to enhance access for large tumours.[17] The extent of tumour resection has been classified as total (complete excision), near-total (<1% of tumour volume remaining), subtotal (1–5% of tumour remaining) and partial (>5% of tumour remaining).[7]

The aim of surgery in NF2 is total tumour removal with preservation of the facial nerve and CN. Surgical approach should be chosen based on experience and selecting the one most likely to enable optimal access to achieve the above. For unknown reasons, VSs in NF2 are 'more aggressive' than sporadic VS, which makes preservation of the cochlear and facial nerves more surgically challenging.[7] The tumour biology in NF2 is thought to be different and it is postulated that NF2 schwannomas may encapsulate the fibres of the CN rather than the stretching and spreading that is associated with sporadic VS.[18] Preservation of function is vital[19] hence more commonly nowadays, when there is severe adherence to critical structures (particularly in sporadic VS surgery), a small cuff of tumour may be left to avoid major complications.[12] However, this has implications of future growth, ongoing long-term surveillance and possible further treatment requirements that are not taken lightly, especially in NF2.

Total tumour excision is achievable in 78–92% of patients.[7, 12, 20] The cohorts undergoing surgery vary between centres; some units only offer surgery for patients when tumour growth is observed, others advocate early surgical intervention, as they believe this affords better functional outcomes. As expected, the centres with lower total tumour excision rates generally have better functional outcomes. The English consensus is for hearing deterioration or tumour growth to trigger reassessment, MDT discussion and consideration of the options with the patient and family.[10]

Auditory implantation usually takes place after tumour resection at the same operation. If a retrosigmoid approach has been used, a cortical mastoidectomy and posterior tympanotomy to enable EABR testing and potential subsequent CI are necessary. There are important considerations for all VS surgery that have specific implications for outcomes of auditory rehabilitation.[21]

Meticulous surgical technique is essential to minimize brainstem trauma from direct physical damage or collateral effects of electrocautery. A secondary effect of electrocautery is neural damage from repeated stimulation and excitotoxicity. There is therefore an argument for early division of the vestibulocochlear nerve at the brainstem. This decision may be made early with a large tumour, or cases where it is deemed unlikely to be able to preserve the CN. ABI would then be performed. To prevent migration of the receiver–stimulator, a well or anterior lip is usually drilled on the skull to recess the CI or ABI that is placed in a tight periosteal pocket. A channel for the array can also be drilled from the well to the edge of the craniotomy/mastoidectomy.

Particular challenges for ABI in NF2 include distortion of the brainstem anatomy making placement more difficult than in non-tumour cases. Subsequent remodelling/moulding of the brainstem to fill the tumour void may lead to movement or displacement of the array.

Intra-operative implant evoked ABR testing is a critical step in ABI surgery to optimize paddle position. Usually the four corners of the array are activated in succession, followed by other electrodes as necessary. Based on the presence or absence of ABR, the merits of adjustment of the paddle are discussed with the surgeons. Subsequent repositioning with further testing occurs until placement is optimal. Simultaneous facial and glossopharyngeal nerve monitoring take place to pick up any non-auditory stimulation and anaesthetic vigilance and close attention to the electrocardiogram is also warranted. The silicone mesh on the ABI paddle can be trimmed prior to placement. The advantage of the mesh is that it aids adherence to the brainstem, although, conversely, this may be a disadvantage when repositioning. Maintenance of the optimum position is crucial but challenging. If the implant is placed deep in the lateral recess, the brainstem itself may hug the implant and help keep the paddle stable, but this depends on the amount of distortion left by the tumour and the optimum position dictated by the EABR. Fibrin and dural sealants can be used to help prevent displacement as retraction is relaxed and closure takes place. Anchoring the array in the cavity or at the craniotomy edge should also be considered.

POST-OPERATIVE CARE

Post-operative care and recovery is similar to that for non-implantation VS surgery. Antibiotic prophylaxis for intracranial surgery is in keeping with antimicrobial guidelines, which vary from one unit to another. Meningitis risk should be explained as part of the consent, and pre-operative vaccinations 2 weeks or more before surgery are advised as per CI.

Device activation for CI patients follows the same procedures as for non-NF2 CI recipients. However, ABI activation is done with the patient nil by mouth in a setting (usually either an anaesthetic room or recovery) where there is cardiac monitoring and an anaesthetist present. This is due to the possibility of non-auditory stimulation and, in particular, the risk of vagal stimulation causing bradycardia, tachyarrhythmia or the need for a secure airway. Programming of the ABI involves stimulating each electrode in turn and then in groups across the array. Threshold and comfort levels are varied. Auditory perception with feedback on loudness and pitch enables programming, with the aim of access to a good range of frequencies while avoiding non-auditory stimulation. Numerous appointments over the first year enable adjustment of current levels according to progress and changes in perception. Speech and language therapists and habilitation specialists play a crucial role in helping the patient to learn to recognize sounds. Motivation, commitment and perseverance are important for the patients to be able to maximize their potential benefit from their implant. Assistive listening devices may also help to optimize performance in day-to-day situations.

TUMOUR SURVEILLANCE

Ongoing interval magnetic resonance imaging (MRI) is an important consideration in these patients who invariably require tumour surveillance, either of residual ipsilateral VS or contralateral VS. Previously with the Cochlear® device, temporary removal of the magnet reduced pain and discomfort during scanning and diminished the extent of the artefact/signal void from the implant body. There were, however, resultant problems with infection[22] and degradation of the magnet can occur with multiple removal and reinsertions over time.[10] The most recent MED-EL ABI implant is MRI conditional, enabling patients to be scanned in a 1.5 Tesla machine without the need for magnet removal so there is no pain/discomfort. This is due to an advance in magnet polarity technology where the magnet is self-aligning and rotates freely within its housing. Despite this innovation, artefact remains a problem, posing an issue for monitoring especially with ipsilateral residual VS, and hence magnet removal/replacement may still be necessary.

OUTCOMES

Outcomes of ABI are far more variable than outcomes of CI. CI placement in the scala tympani naturally guides the array around the cochlear turns close to the spiral ganglion neurons with presumed tonotopic organization. Comparatively uncertain positioning in the lateral recess of the fourth ventricle adjacent to the cochlear nucleus is then reliant on patient perception and feedback of auditory tones with pitch ranking for subsequent programming of the ABI. Patient factors, either NF2/tumour-related or from concurrent medical problems, may cause disabilities that interfere with programming and auditory habilitation. Intra-operative factors from mechanical or ischaemic damage to the cochlear nucleus or brainstem are also likely to influence outcomes.[21] Furthermore, habilitation and performance take longer with ABI and may not

plateau for several years[5] compared to several months for most CI users.

Initial hearing benefits with ABI ranged from sound awareness, identification of some environmental sounds and improved performance over lip-reading alone when communicating face-to-face.[6, 23–25] Better results were achieved with non-NF2 patients[26] and subsequently 'open-set' speech recognition (understanding without visual cues) has been reported in NF2.[27–31]

Collaborators from multiple centres have tried to identify reasons for better outcomes.[21] They looked at good performers, those with speech recognition scores >30%, totalling 26/84 patients in a series from June 1997 to September 2011 and found that short duration of deafness (<1 year) was associated with a mean increase in word recognition score of 20%. This suggests a possible degenerative process in the brainstem or higher auditory centres with time. Good results have, however, been reported with deafness durations of 15 years or more.[32] Two surgeons who operate with the patient in the semi-sitting position have achieved the best ABI outcomes. The effect of gravity on the cerebellum enables lower intracranial venous pressure, which in turn means less bleeding when compared to the supine position. This may, however, be a surgeon effect or in part due to less electrocautery use. The semi-sitting position does carry an increased risk of air embolism and tension pneumocephalus[33] and this approach is therefore only recommended for teams familiar with it. The maximum comfortable level (MCL) can be an indicator of distance/proximity to the cochlear nucleus[34] and a relationship between lower thresholds and better outcomes with higher stimulation rates was observed, the inference being (as one would expect) that proximity of the paddle to stimulable tissue is important. Increasing number of distinct pitch electrodes also had a positive correlation with performance such that number alone has less of an influence than the spectrum of pitch perceptions achieved with those in use. Good results where ABI provides more than an aid to lip-reading are definitely achievable in NF2, even in large tumours, but outcomes remain variable and difficult to predict.

ABI IN CONGENITAL HEARING LOSS

The experience described above of ABI in NF2 provided an impetus for exploration of the utility of this technology in non-NF2 patients in whom a CI could not be utilized. A small but important group is those infants and children with bilateral congenital profound hearing loss who are identified through newborn hearing screening programmes and referred for CI and found to have inner ear or CN abnormalities that preclude CI. These include children with absent cochleas or absent CNs or a combination thereof. While the precise incidence or prevalence of such abnormalities is unknown, it is a reasonable estimate that for every 100 children referred for CI one or two will have the abnormalities described and therefore not be suitable for a CI (Saeed, personal observation). For the parents or care-givers of such children this proves to be a substantial additional burden as they are often still coming to terms with the realization that their child has bilateral profound hearing loss and are then advised that the highly successful CI intervention is not appropriate. This challenging situation draws heavily on the skills acquired by experienced CI/skullbase teams in terms of assessment, surgery, habilitation and, critically, the management of the expectations of the family in terms of commitment to the habilitation process and outcomes of ABI in such children.

Nevertheless, based on the outcomes of ABI in a substantial number of non-NF2 adults, Colletti and his team extended the indications for ABI to include such children.[35, 36] This pioneering work served as catalyst for other centres across the world to utilize ABI in selected congenitally deaf children. In the UK the first three children were implanted by Richard Ramsden and his team in Manchester in 2005 and this was followed by teams in the USA, Turkey, Korea and, subsequently, London and Cambridge in the UK.[37–39] The emergent literature emphasized the importance of careful case selection as well as the surgical and habilitative challenges in such children but also the variable outcomes, ranging from no auditory benefit, environmental auditory perception through to development of vocabulary and the slow trajectory in achieving these outcomes when compared with children undergoing CI.

In an attempt to standardize the assessment and indications for ABI in children internationally, Sennaroğlu convened a meeting of key stakeholders in Istanbul which resulted in the first consensus statement, published in 2011.[15] This was followed up by a second such meeting and a second consensus statement in 2016.[40] Such a collaborative exercise involving 20 centres from 11 countries explored the clinical and radiological indications and timing of surgery, habilitation and evaluation of outcomes and emphasized the importance of appropriate teams managing such complex children. Key points include:

- The importance of a comprehensive MDT drawing on extensive CI and lateral skullbase experience and the management of the expectations of the family was emphasized.
- It was agreed that, in order to balance the potential auditory benefit based on neural plasticity against the metabolic stress of intracranial surgery and anaesthesia, the optimal age for ABI in congenitally deaf children is 18–24 months.
- The children with cochlear and or CN aplasia should be considered for ABI while those children with hypoplastic CN should be offered a CI in the first instance with a view to fast-tracking for ABI if the CI does not confer any benefit.
- It was also recognized that the majority of ABI recipients do derive auditory perception but not necessarily speech acquisition, in contrast to children with a CI.
- Finally, it was clear from the accrued global experience that those children with additional physical or cognitive disabilities fared less well than the non-sydromic otherwise healthy children.

In one of the largest series examined to date, Sennaroğlu and his team have reported the longer-term outcomes (<1 year) in 35 children undergoing ABI.[41] The majority of the recipients achieved grade 5 on the Categories of Auditory Performance (CAP) scale, implying understanding common phrases without lip-reading. The outcomes, however, as expected, were not as good as a comparable age group that had undergone CI, and those children with additional disabilities fared less well than those who had no additional physical or cognitive problems. Nevertheless, as has been observed by all who work in this field, in appropriately selected infants and children and appropriately counselled families, the ABI is a viable option for the family to consider as part of the habilitative process for their congenitally profoundly deaf child.

In summary, the assessment, surgery and management of a child undergoing ABI for congenital profound deafness, as well as the counselling of the child's family, is a complex process that is continuing to evolve as experience among centres undertaking this work continues to accrue. CI programmes that identify a child who is not suitable for a CI should refer the child to an ABI centre so that the family can have the benefit of appropriate multidisciplinary evaluation.

FUTURE RESEARCH

- ABI design to optimize the placement of the electrode array paddle with reference to the tonotopicity of the cochlear nuclei.
- Electrophysiological evaluation of the cochlear nerve post-NF2 surgery or the hypoplastic cochlear nerve.
- Auditory habilitation and rehabilitation of ABI recipients to improve outcomes.

KEY POINTS

- A vast number of factors affect decision-making and outcomes for this complex patient group. The multidisciplinary teams for neurofibromatosis and auditory implantation must work cohesively. In particular, the roles of the audiological scientists for pre-operative investigation, peri-operative monitoring/testing and post-operative programming are crucial to guide patient-centred decisions. Surgical and peri-operative management by experienced teams with fastidious attention to every detail are paramount.
- Outcomes continue to be varied; but, with centralization of services, technological advances, increasing experience and ongoing International collaboration, improvement will be seen in patient pathways, shared decision-making, quality of care and patient benefit.

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Section 3
Skull Base

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CHAPTER 97

IMAGING OF THE TEMPORAL BONE

Steve Colley

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search from using the following keywords: temporal bone, imaging, CT and MRI.

INTRODUCTION

The temporal bone is a complex anatomical area that is made up of five osseous components: the squamous, mastoid, petrous, tympanic and styloid portions of the temporal bone. Anatomically, the temporal bone may be separated into five distinct regions that demonstrate some specific types of pathology, and can dictate the optimum imaging method depending on the area of concern and the pathology suspected. These anatomical sub divisions of the temporal bone are: the external ear; the middle ear and mastoid; the inner ear; the internal auditory canal (IAC); and the facial nerve canal.

The imaging modalities used in common practice include computed tomography (CT), magnetic resonance imaging (MRI), nuclear medicine and, more recently, cone beam computed tomography (CBCT). The main imaging methods utilized in temporal bone imaging are CT and MRI, and a brief overview of scanning techniques, benefits and disadvantages is summarized as follows.

SCANNING TECHNIQUES

Computed tomography (CT)

Multidetector CT scanning allows extremely quick acquisition of imaging of the temporal bones. The data acquired is a volume, which can then be reconstructed in a variety of imaging planes depending upon the anatomical area being scrutinized. Typical temporal bone CT images are acquired at a thickness of 0.5–0.6 mm, and they provide excellent bony detail of the external auditory canal (EAC), middle ear and mastoid, ossicular chain, inner ear, and the facial nerve canal. CT also allows accurate identification of masses or opacification within the anatomical areas of the temporal bone, but suffers from its ability to differentiate between different types of opacity (e.g. fluid versus cholesteatoma).

CT utilizes ionizing radiation. The dose employed in CT of the temporal bones is more of an issue in imaging of children, adolescents and young adults – especially where repeat imaging is employed. CBCT offers a reduced radiation dose in comparison to MDCT, and is certainly an effective alternative in these settings.

Magnetic resonance imaging (MRI)

MRI utilizes strong magnetic fields (30 000 to 60 000 times greater than the earth's magnetic field) in order to produce images based upon the mobility of nuclei, especially protons within water molecules.

Advantages include excellent soft tissue contrast, and the ability to visualize and resolve the cranial nerves as they traverse CSF and the IAC. MRI can also differentiate between differing types of soft tissue opacification in the middle ear and mastoid, helping discriminate cholesteatoma from inflammatory or post-surgical changes.

Disadvantages of MRI include longer scanning times (up to 45–60 minutes), artefact from movement, surgical implants and metal, and safety issues secondary to the strong magnetic fields employed.

ANATOMICAL VARIANTS

Before considering the different types of pathology encountered in the temporal bone, there are a number of anatomical variants that are highly relevant for radiologists to assess and cover in reports, in order to avoid prolonged procedures and operative complications in a surgical field where access is often rather limited.

Tegmen tympani

A low-lying tegmen may hinder access to the middle ear via a mastoid approach, and pre-operative recognition is important in order to avoid breach during surgery.

Sigmoid sinus

The sigmoid sinus passes along the posterior margin of the mastoid, and varies greatly in the degree of anterior indentation in to the mastoid cavity. An anteriorly located sinus may have a very thin slip of cortical bone between it and the mastoid cavity, and sinus injury could result in significant bleeding complication during surgery.

Jugular fossa

Wide variation exists in the size and height of the jugular fossa and jugular bulb, both between patients and on either side in the same patient. A high riding jugular bulb may project into the hypotympanum, it may have a thin bone covering that may be damaged at surgery or be completely dehiscent of bone covering, or a small diverticulum may protrude from the jugular bulb towards or into the hypotympanum (Figure 97.1).

Carotid canal

Whilst there may be very minor variations in the internal carotid artery (ICA) canal course, these are generally insignificant. A true aberrant ICA is rare, but it is vitally important to identify on pre-operative imaging studies. Failure of the normal cervical carotid artery development leads to anastomosis between inferior tympanic artery and an enlarged caroticotympanic artery. An aberrant ICA is formed, which traverses the middle ear cavity.

Typically, an aberrant ICA passes through the infero medial middle ear cavity, adjacent to the cochlear promontory (Figure 97.2). In addition to a significant intra operative surgical complication risk, it may present as a pulsatile retro tympanic mass, or cause CHL via mass effect on the incudostapedial joint.

Facial nerve canal

The normal VIIth nerve canal arises from the anterior lateral IAC, passing to the geniculate ganglion (anterior genu). The geniculate segment then passes posteriorly along the middle wall of the middle ear, lying below the lateral semi-circular canal, above the oval window niche and stapes superstructure. At the posterior genu, the canal turns another 90 degrees, forming the descending or mastoid segment, which exits the temporal bone at the stylomastoid foramen. Variation in VIIth canal anatomy is important to highlight pre-operatively, to avoid inadvertent injury and to plan potentially difficult middle/inner ear access. More common variations include a nerve that protrudes inferiorly into the oval window niche, a dehiscent tympanic segment with no discernable bone covering, or a truly aberrant VIIth nerve course.

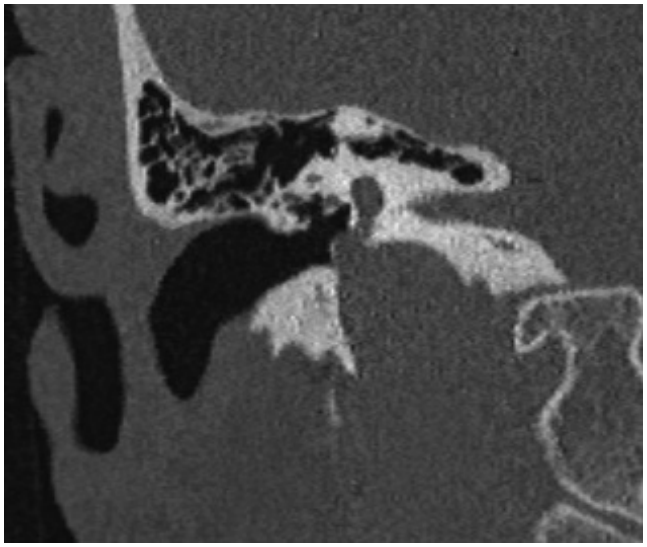


Figure 97.1 Coronal CT showing high riding right jugular bulb, protruding into hypotympanum.

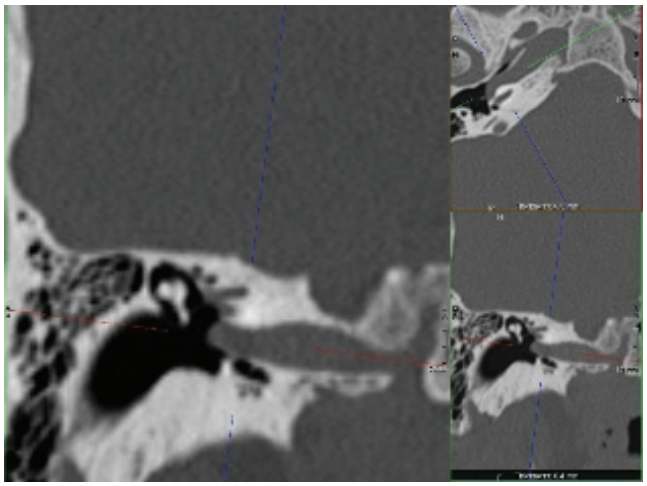


Figure 97.2 Coronal and axial CT with aberrant right ICA course, passing into middle ear cleft, just lateral to cochlear promontory.

IMAGING OF TEMPORAL BONE PATHOLOGY

Acute otitis media and mastoiditis

A mild degree of mastoiditis will generally been seen with acute otitis media. The more prevalent use of antibiotics in treatment of acute otitis media has reduced the number of significant cases of mastoiditis. The importance for radiologists is to identify the potentially serious coalescent mastoiditis, and any complications arising from mastoid infection.

Uncomplicated, or mild mastoiditis is seen as fluid within the mastoid air cells but, importantly, with preservation of the internal bony septations and peripheral bone margins. Destruction of the internal bony septations indicates the presence of acute coalescent mastoiditis, which requires prompt treatment to prevent complications such as soft tissue or intracranial extension and abscess formation.

When a more aggressive mastoiditis is present, the bony margins of the mastoid and surrounding soft tissue planes should be assessed. Infection can spread through the sutures to form a subperiosteal abscess, and extending into the upper neck, forming a Bezold abscess. Infection may spread posteriorly into the sigmoid sinus, or superiorly into the middle cranial fossa.

Chronic otitis media

Chronic otitis media (COM) is usually due to Eustachian tube dysfunction, and has a clinically different presentation to acute infection, being generally painless with chronic discharge with or without CHL often present. Negative middle ear pressure may cause tympanic membrane retractions, and subsequent acquired cholesteatoma formation. Imaging usually shows a middle ear and mastoid effusion, with increased sclerosis of the adjacent bony structures. Further complications from chronic otitis media include ossicular erosions (without cholesteatoma) due to chronic surrounding hyperaemia, and ossicular chain fixation. Fixation of the ossicles secondary to COM may be fibrous or calcific, the latter being termed tympanosclerosis. Calcifications with COM may affect the tympanic membrane, or surround and fix the ossicles in the epitympanum (Figure 97.4).

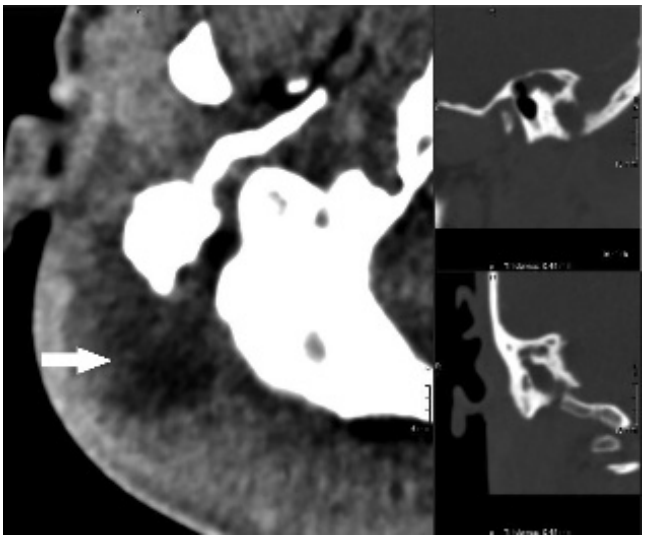


Figure 97.3 Axial, coronal and sagittal CT images showing right masoiditis, with loss of internal bony septation, and Bezold abscess below the mastoid tip (arrow).

Figure 97.4 Coronal CT showing diffuse ossification (tympanosclerosis) in the medial left epitympanum (arrow) with adjacent chronic effusion. Note the normal right epitympanum.

Necrotising (malignant) otitis externa

Necrotising otitis externa (NOE) usually presents in elderly patients with ear discharge and severe otalgia, generally with an underlying history of diabetes or chronic immune suppression. *Pseudomonas aeruginosa* are the most common causative organisms.

Imaging has a role to play in diagnosing presence and extent of disease, identifying complications, and in the long-term management and follow-up of this complicated and often difficult to manage condition. CT is normally the first imaging technique, and MRI can provide complimentary information when there is evidence of bone involvement and osteomyelitis.

Early disease is seen as subtle soft tissue thickening in the EAC. Disease can progress and invade the submucosa and spread beyond the bony or cartlagenous confines of the EAC. Early changes suggesting an aggressive or progressive form of NOE are the identification of subtle cortical bone erosions (osteomyelitis). Comparison with the normal contralateral side is often of benefit here (Figure 97.5).

Infection can then spread along a few different, but predictable, pathways: the petrotympanic fissure allows infection to spread from the middle ear to the temporomandibular joint (TMJ) and the soft tissues below the skull base. Disease extension medially to the carotid canal is often seen and, again, comparison with the contralateral side can help pick up early osteomyelitis and bone erosions in this region. Inferiorly, disease can spread through the soft tissue spaces below the skull base, and assessment of these regions is important on imaging (Figure 97.6).

Invasion of the central skull base (central skull base osteomyelitis) may occur from direct extension along the

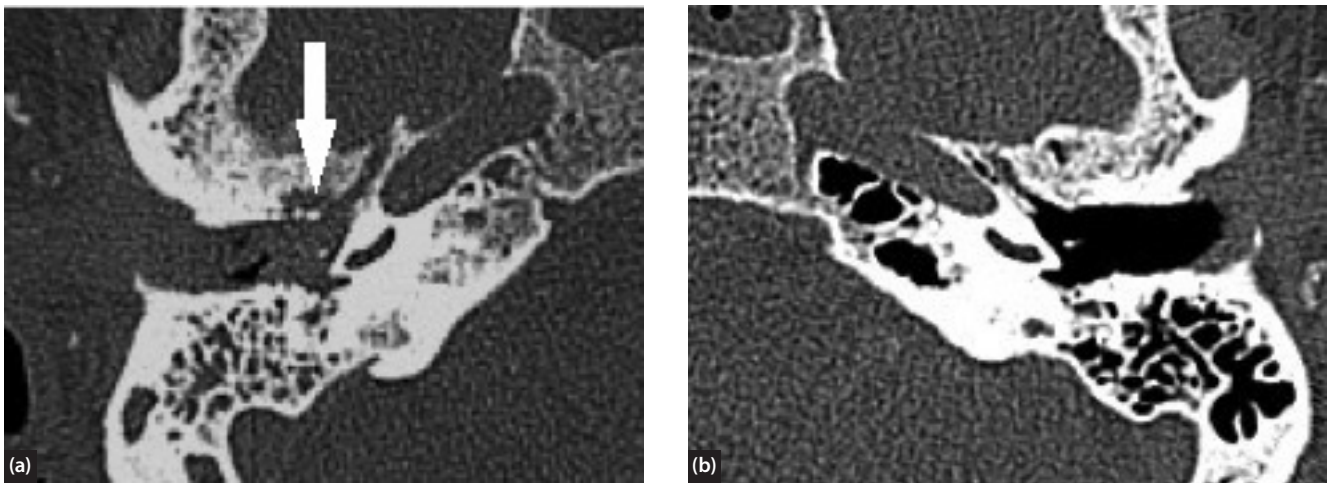


Figure 97.5 a and b Axial CT with thickened soft tissue in EAC, middle ear effusion and early subtle erosion of anterior epitympanum (arrow). Normal left middle ear for comparison.

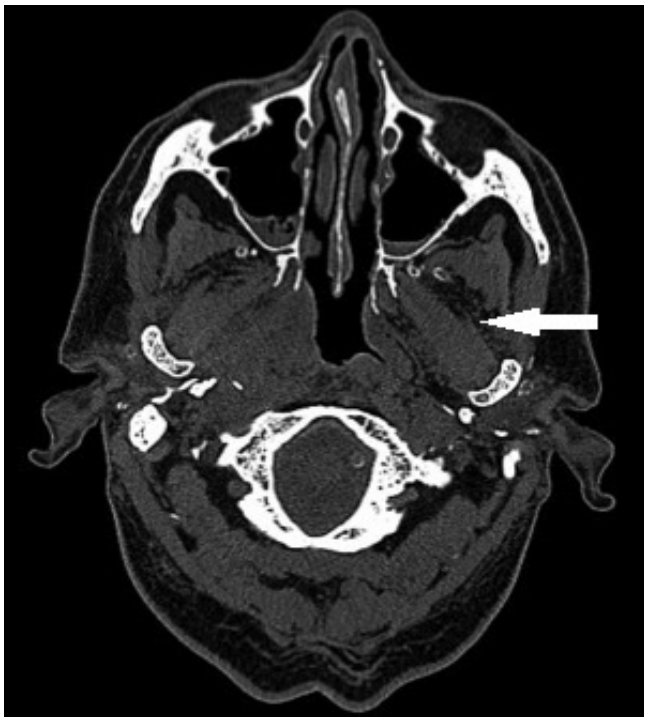


Figure 97.6 Axial CT in patient with NOE, with diffuse infiltration of soft tissue beneath the skull base, and loss of normal fat planes. Normal fat planes depicted by left sided arrow.

petrous apex and across the petroclival fissure, or from subtemporal disease directly invading the lower clivus. MRI is better at detecting early central skull base disease, with bone marrow changes being apparent on standard T1 weighted images before frank cortical destruction occurs. Intracranial extension of disease, either direct from the mastoid and middle ear, or via neural foramina, is best identified on MRI (Figure 97.7).

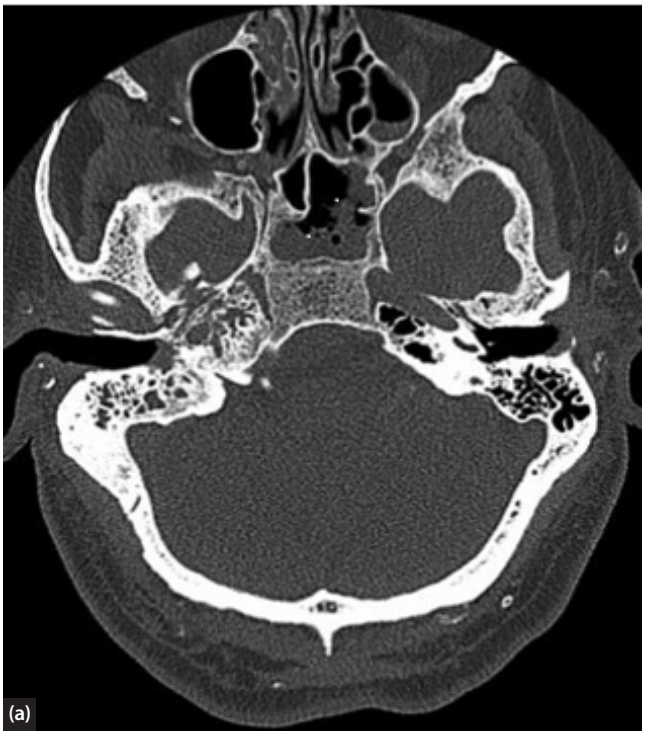
Imaging may be used to follow up patients and dictate appropriate antibiotic treatment duration. There remains confusion as to the best imaging strategy in follow-up of NOE. It is clear that both CT and MRI abnormality can persist after adequate disease treatment, and notably abnormality can remain in the bone marrow on MRI with imaging improvement lagging behind clinical improvement. Various nuclear medicine studies have been utilized in follow-up of NOE, with ^{99m}Tc or Gallium 67 bone scans potentially helping in follow-up; however, Gallium scans are thought better for follow-up, as imaging tends to return more rapidly to normal after infection has settled.[1]

Cholesteatoma

Cholesteatomas are a collection of keratinizing squamous cells in the middle ear cleft, which are associated with resorption or erosion of adjacent bony structures. Lesions may be congenital (occurring anywhere in the temporal bone) or acquired (middle ear location), the latter being far more common (around 98% of cholesteatomas)[2] as a complication of chronic otitis media.

Initially, CT is the imaging method of choice in depicting middle ear opacification and bone erosions of the scutum and adjacent ossicular. A normal CT has extremely high NPV for absence of cholesteatoma. The limitation of CT is that it cannot differentiate mucosal or inflammatory middle ear disease from the soft tissue mass of a cholesteatoma, cholesterol granuloma, granulation tissue or malignancy.[2] CT is also the best modality for detecting bone erosions that are seen with high frequency in both pars flaccida and pars tensa cholesteatomas.

Acquired cholesteatomas arise from invaginations of the tympanic membrane, or grow into the middle ear via perforations. The former type, derived from an apparently intact membrane, are more common, and typically arise from the pars flaccida region. Keratin accumulates in the lateral epitympanic (Prussak) space, and causes scutum erosion, medial displacement of the ossicular chain, and ossicular erosion (Figure 97.8). Cholesteatoma growing into the middle ear via a perforation usually arises from the pars tensa. These 'secondary acquired' cholesteatomas are often located medial to the ossicular chain, and cause



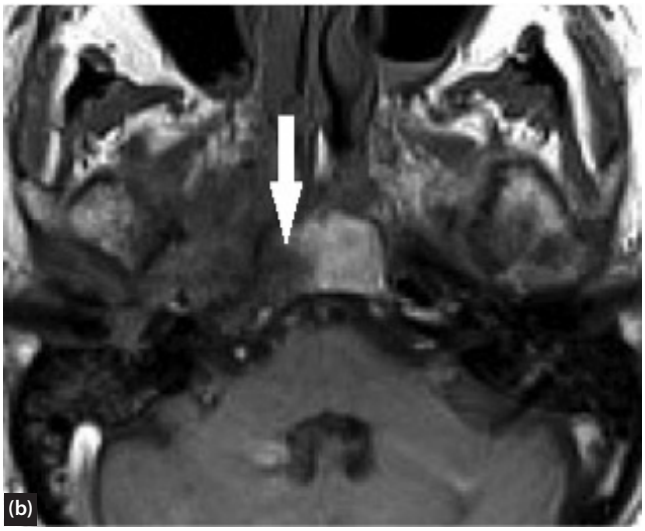


Figure 97.7 Axial CT (a) and T1 weighted MRI without fat suppression (b) in patient with right NOE. Normal bone cortex is preserved on CT, but T1 MRI shows early marrow infiltration and loss of normal fatty marrow signal (arrow) in keeping with early central skull base osteomyelitis.

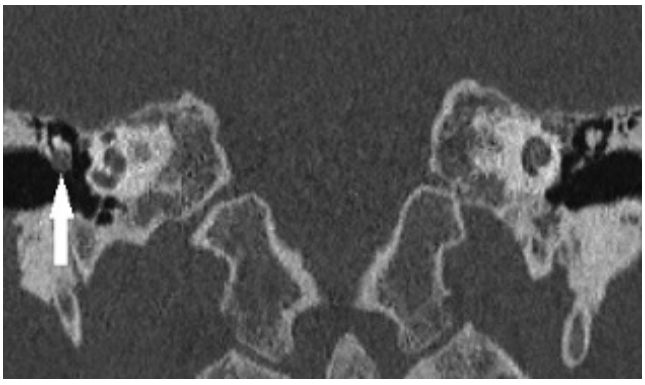


Figure 97.8 Coronal CT with 4 mm right lateral epitympanic pars flaccida cholesteatoma (arrow), with early ossicular erosion.

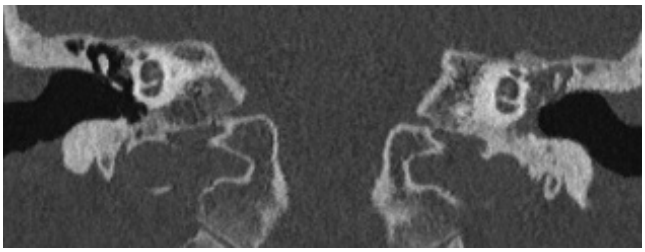


Figure 97.9 Coronal CT with left middle ear soft tissue opacification, with subtle lateral displacement and erosion of the ossicular chain compatible with pars tensa cholesteatoma.

early erosion of the long process of incus (LPI) and tend to more erosion of the inner ear structures (Figure 97.9).

Modern MRI techniques utilizing functional imaging sequences can assist in delineating extent of disease, but more importantly can now detect recurrence, replacing routine second-look surgery in many centres. Functional MRI utilizes diffusion weighted imaging (DWI), which characterizes tissues based upon the mobility of water molecules within them. Inflammatory disease will have good water mobility, whereas cholesteatoma, with tightly packed keratin and limited extracellular space, show reduced water diffusion. Early MRI techniques (echo-planar DWI – EPI) showed significant artefact at bone, soft tissue and air interfaces with both false positive and false negative results. Newer non-echo-planar (non-EPI) DWI does not suffer from such artefact, and allows imaging of sufficient resolution to detect cholesteatoma down to 2 or 3 mm diameter, without post-contrast sequences.[3] Positive scans typically show high signal on the b1000 sequence, with matched low signal on the Apparent Diffusion Coefficient Map (Figure 97.10).

A number of potential complications should be sought on imaging. Labyrinthine fistula due to lateral semicircular canal erosion (Figure 97.11) can result in vertigo, imbalance and sensorineural hearing loss. Less commonly, cochlear promontory erosion may occur. Importantly, the tegmen should be assessed for potential erosion or breach, as a meningocoele should be excluded in such cases pre-operatively.

Otosclerosis

Imaging is not always employed in the diagnosis of typical otosclerosis with CHL, but may be utilized in patients with sensorineural or mixed hearing loss, or an atypical history. CT is the imaging method of choice, as it depicts the early bone changes associated with otosclerosis in both fenestral and retrofenestral disease.

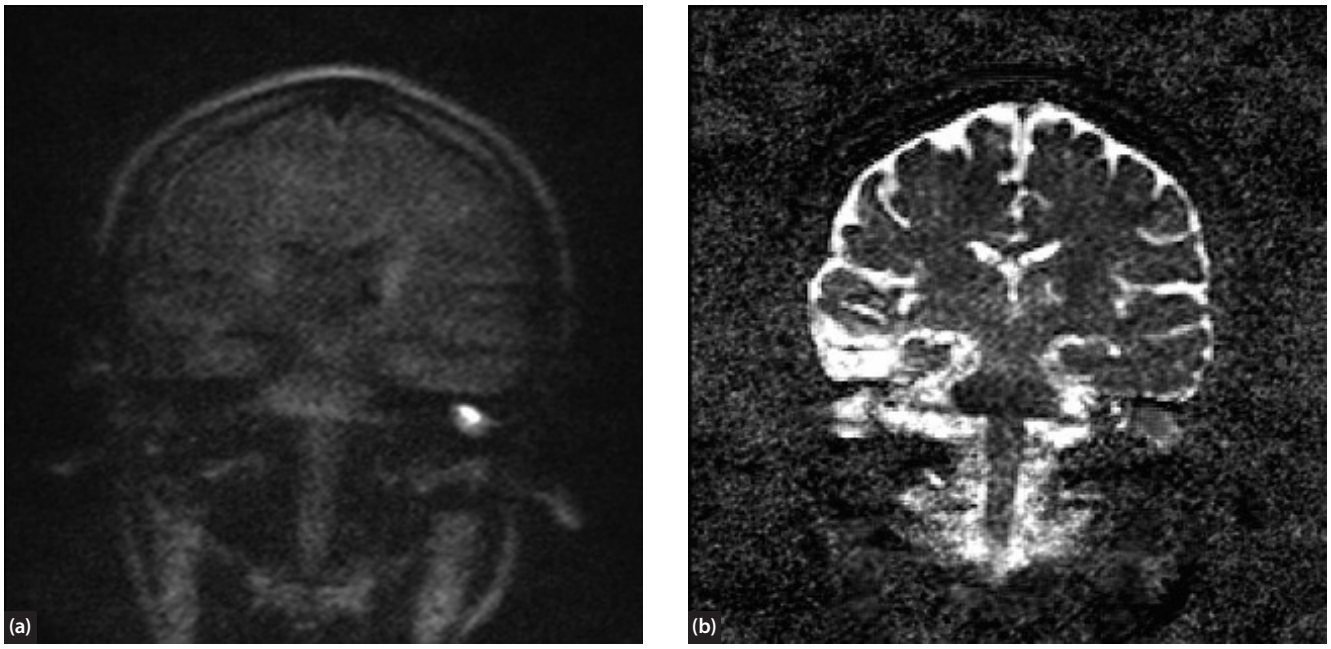


Figure 97.10 Coronal DWI MRI shows left sided high signal on the b1000 sequence (a) with matched low signal on the ADC map (b), compatible with left sided cholesteatoma.

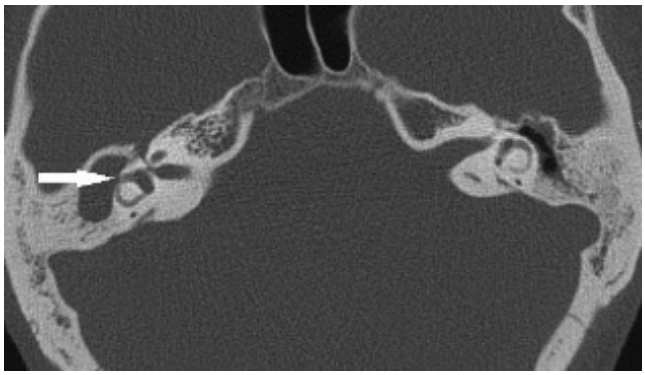


Figure 97.11 Axial CT shows right sided epitympanic cholesteatoma, with erosion of lateral semi-circular canal (arrow). Note normal bone covering of left lateral semicircular canal.

Thin section CT shows low-density (demineralized) plaques in early disease, which typically affects the fissula antefenestrum at the anterior border of the oval window. The otoscerotic plaque can extend to involve the stapes foot-plate, occlude the oval window and extend to the cochlear promontory and round window region. Disease is often bilateral (up to 85% of cases).[4]

Retrofenestral disease is the less common of the two types of otosclerosis – and often considered a continuation of fenestral disease. Low density is seen extending around the otic capsule, termed the fourth ring of Valvassori (Figure 97.12). Again, disease is usually bilateral.

CT for assessment of otosclerosis should also be used to evaluate alternative causes of conductive hearing loss (CHL). Anatomical temporal bone variants described at the beginning of the chapter should also be sought prior to considering surgical treatment – normally with stapedectomy and ossicular prosthesis in the setting of fenestral disease.

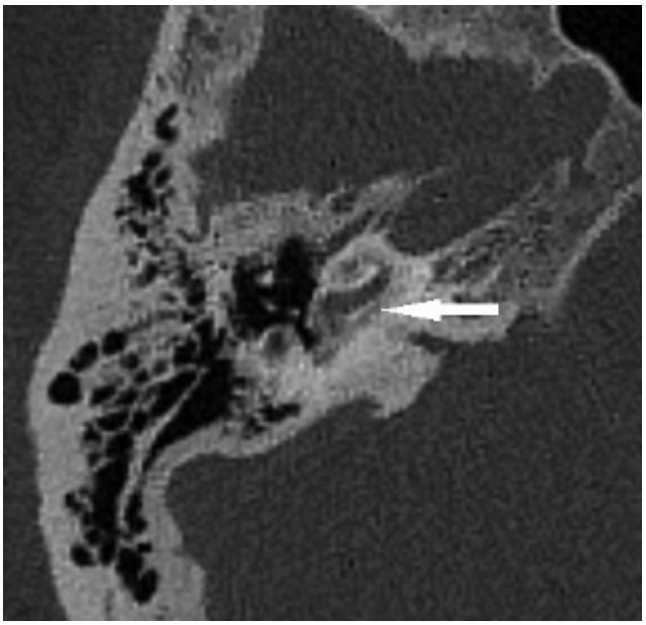


Figure 97.12 Axial CT at the level of the basal turn of cochlear shows low density surrounding the cochlea (arrow), indicating retrofenestral otosclerosis.

Superior semicircular canal dehiscence

Superior semicircular canal dehiscence (SSCD) has been increasingly recognized as a cause of a variety of vestibular and auditory symptoms. SSCD is thought to be due to a bony defect affecting the arcuate eminence of the superior canal, resulting in a mobile third window into the labyrinth. Absent bone over the SSC, however, is described in up to 13% of asymptomatic individuals.[5]

Thin section CT scans can demonstrate bone thinning and bone defects. Images should be reconstructed in

planes parallel (plane of Pöschl) and perpendicular (plane of Stenver) with respect to the superior canal to allow accurate demonstration of defects, the angle they subtend, and to help plan surgery if symptomatic.

Temporal bone trauma

Temporal bone fractures normally result from high-impact blunt trauma, such as road traffic accidents, falls from height or direct assault. High resolution CT is the imaging method of choice, and is normally undertaken as part of an initial trauma CT study. A dedicated temporal bone CT should be considered when there is suspicion of a temporal bone fracture but no obvious injury on initial trauma study. Traditional classification has described fractures as longitudinal or transverse, with respect to the long axis of the temporal bone (i.e. longitudinal fractures passing transversely through the temporal bone on an axial image, and transverse fractures running antero-posterior on axial images).[6]

Longitudinal fractures are by far the most common, accounting for up to 90% of temporal bone fractures. These fractures are more commonly associated with CHL, which may be due to tympanic membrane (TM) involvement, haemotympanum or ossicular chain disruption (fracture or dislocation, or both) and normally spare inner ear structures (**Figure 97.13**). Transverse fractures more commonly pass through the otic capsule and internal acoustic meatus (IAM), and are hence more commonly associated with sensorineural hearing loss, facial nerve paralysis and cerebrospinal fluid (CSF) leak.

Facial nerve paralysis is seen more commonly with transverse fractures (up to 50%) than longitudinal fractures (10–20%). Onset is usually more rapid with transverse fracture patterns due to nerve transaction in the labyrinthine segment, whereas longitudinal fractures may have delayed onset due to nerve contusion or compression from adjacent haematoma.

Further complications that should be considered are CSF leak, meningitis, meningocoele from tegmen involvement, and vascular injury to the carotid canal or jugular fossa. Delayed complications can include labyrinthine ossificans and post-traumatic cholesteatoma.[7]

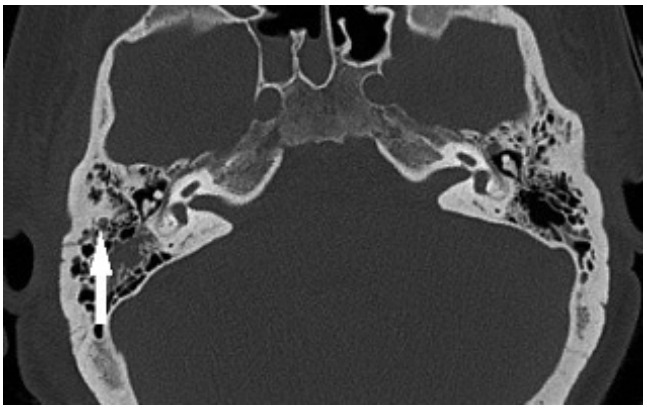


Figure 97.13 Axial CT showing right longitudinal temporal bone fracture (arrow), with incudostapedial joint disruption and widening. Note normal left incudostapedial joint.

TEMPORAL BONE TUMOURS

There are a number of benign and malignant tumours that may affect the temporal bone. Benign lesions include vestibular schwannoma, cholesterol granuloma, paragangliomas, facial nerve haemangioma, and osteomas. Malignant lesions include squamous cell carcinoma (SqCC) and other rarer EAC tumours, direct invasion (e.g. nasopharyngeal cancer or parotid malignancy) or perineural spread, or distant metastases.

Vestibular schwannoma

Vestibular schwannomas are the most common CPA and IAC tumour, accounting for 70–80% of lesions, with meningioma and metastases less common. MRI is preferred for detecting tumours and delineating extent. Thin section T2 weighted images (constructive interference in steady state, (CISS), Fast Imaging Employing Steady-state Acquisition (FIESTA)) (**Figures 97.14** and **97.15**) provide excellent CSF high signal and clear delineation of the cranial nerves traversing the IAC. Post-contrast thin section T1 weighted images can help pick up small or subtle lesions, and assist in follow-up.

Small lesions appear homogenous on T2 sequences, and show homogenous enhancement. Larger lesions may show heterogeneity on T2 and post contrast sequences due to areas of cystic change. Such cystic lesions often demonstrate more rapid growth patterns, but respond better to radiosurgical techniques than solid lesions.[8]

Lesions may be purely intra-cannalicular, extend through the IAC meatus to the cisternal compartment (producing a typical 'ice cream cone' appearance) or, less commonly, may be purely cisternal. Larger lesions may cause mass effect upon the brainstem and 4th ventricle. Occasionally, lesions may undergo acute internal

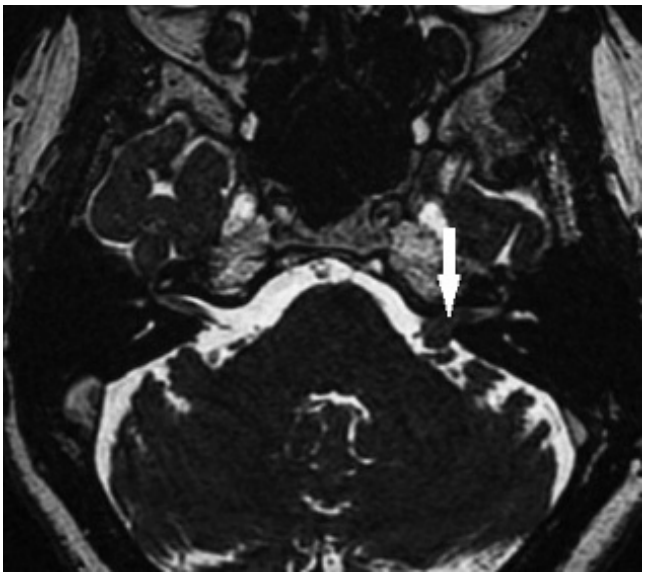


Figure 97.14 Axial CISS MRI showing left sided vestibular schwannoma (arrow), with intra cannalicular and cisternal component, but no brainstem compression.

haemorrhage with rapid expansion and development of cerebellar signs and vomiting.

Post-treatment scanning should assess volume reduction and, importantly, post-contrast T1 sequences may show nodular enhancement associated with tumour recurrence or regrowth.[9]

Cholesterol granuloma

Regardless of the aetiology of cholesterol granuloma, it is the repeated haemorrhage and accumulation of blood products that creates typical imaging appearances of high T1 and T2 signal intensity on MRI scan. There is no appreciable enhancement post-contrast, but T1 weighted scans pre-contrast should be performed in order to identify the characteristic high signal intensity. Diffusion weighted MRI does not show restriction. CT often shows a degree of smooth bone erosion.[2]

Paragangliomas

Temporal bone paragangliomas include glomus tympanicum, glomus jugulare and jugulotympanicum lesions, the latter being a combination of the former two.

Glomus tympanicum paragangliomas are the most common middle ear tumour.[10] On CT, tumours are seen as a nodular area of soft tissue located on the cochlear promontory. Lesions are often small but may extend to the TM and attic if larger, but do not normally cause erosion of the ossicular chain.

Glomus jugulare tumours are the most common lesions to arise in the jugular foramen, with schwannomas and meningiomas being less common. The glomus tumours arise from the jugular bulb, the Xth nerve ganglion, or from the Arnold or Jacobsen nerves.

CT of glomus jugulare shows a typical pattern of permeative bone destruction that involves the carotico-jugular spine early in the disease process. Large lesions may extend to the middle ear (jugulotympanicum tumours) or below the skull base. MRI scanning shows prominent post-contrast enhancement of lesions. Larger tumours may show a classical 'salt and pepper' appearance, which is a combination of flow voids from intratumoural vessels, and areas of microhaemorrhage.

Facial nerve haemangioma

These vascular lesions typically affect the geniculate ganglion, Fallopian canal and anterior aspect of the tympanic facial nerve canal. Low density change may surround an expanded geniculate ganglion on CT, progressing to permeative bone loss, and distinctive intralesional spicules of bone. Thin section MR imaging may show prominent enhancement of the tumour.

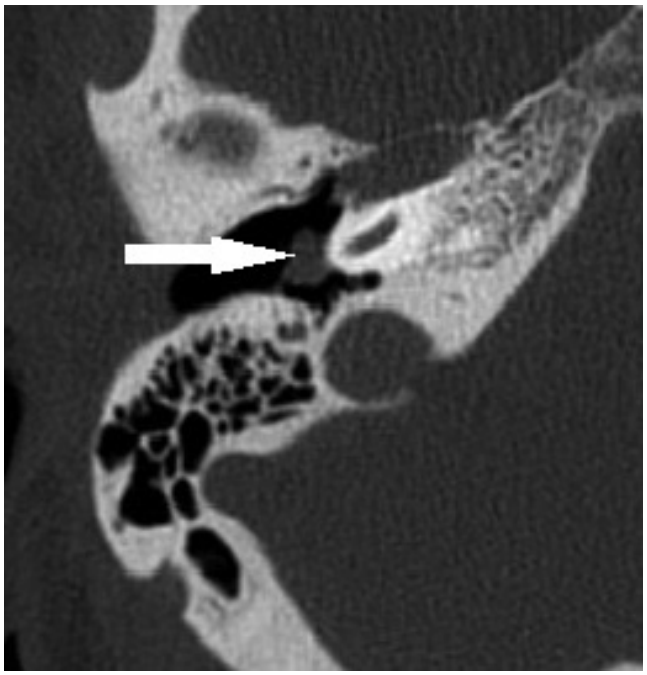


Figure 97.15 Axial CT shows a well demarcated soft tissue nodule behind the right TM, overlying the cochlear promontory – typical of a glomus tympanicum tumour.

Malignant tumours

Malignant lesions in the EAC are most commonly SqCC, with other histopathological types being numerous but much less common. CT and MRI imaging are complementary in assessment of such tumours. The aim of imaging is to assess the degree of aggressive tumour invasion into the various temporal bone anatomical sites, and involvement of critical neural and vascular structures, which would affect surgical planning (e.g. facial nerve or dural invasion). Where biopsy has proven a malignant lesion, appropriate staging should be obtained, which should include a CT of the neck and chest for SqCC, and sometimes systemic whole-body CT, or PET CT where metastasis is a diagnostic possibility.

KEY POINTS

- CT and MRI are the main imaging modalities used for temporal bone imaging.
- There are a number of important anatomical variants that should be sought by radiologists interpreting temporal bone imaging studies.
- Identification of anatomical variants can assist surgical planning and reduce potential complications.
- A variety of inflammatory, non-tumoral and tumour pathologies may affect the temporal bone.

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CHAPTER
98

ANATOMY OF THE SKULL BASE AND INFRATEMPORAL FOSSA

Charlie Huins

SEARCH STRATEGY

Data may be updated by a search using the following keywords: anatomy, temporal bone, skull base, anterior and lateral.

OVERALL TOPOGRAPHY OF THE SKULL BASE

In this chapter, the surgical anatomy of the skull base with reference to otolaryngology will be covered. In depth detail of the ear and nose are covered in separate chapters; details regarding the surgery of all aspects of the skull base are dealt with in the relevant chapters.

Anatomically, the skull base can be considered from both superiorly – within the cranial cavity – and inferiorly, and both aspects will be described here. The boundaries of the skull base are:

- *anteriorly* - by the upper incisor teeth
- *posteriorly* - by the superior nuchal line of the occipital bone
- *laterally* - by the remaining upper teeth, the zygomatic arch & its posterior root, and the mastoid process.

The three main areas of the skull base will therefore be described:

1. anterior
2. posterior
3. lateral.

ANTERIOR SKULL BASE

The anterior skull base forms the floor of the anterior cranial fossa, and a 'roof' over the orbits and ethmoid air cell system (sinuses). It is formed by the frontal bone, the cribriform plate of the ethmoid, the lesser wings and the body of the sphenoid.

The orbital part of the frontal bone forms the roof of the orbital cavity from its superomedial articulation with the nasal bones (the conjoint of these three being the Nasion), to its fusion with the zygomatic bone superolaterally, the anterior aspect being the supraorbital rim; medially, to form the medial orbital wall, it articulates from front to back with the nasal bone, the frontal process of the maxilla, the lacrimal bone, and the paper-thin orbital plate of the ethmoid bone (lamina papyracea) to its posterior articulation with the lesser wing and anterior part of the body of the sphenoid.

The ethmoid bone consists of:

- the central perpendicular plate
- the cribriform plate
- the paired labyrinths.

The midline perpendicular plate forms the central superior aspect of the nasal septum, articulating anteroinferiorly with the quadrilateral cartilage and posteroinferiorly with the vomer. It extends superiorly as the crista galli; either side of the crista lie the cribriform plates, through which pass 20 or so olfactory nerve filaments on each side. The labyrinths, containing numerous air cells, lie medial to the orbit and form part of the lateral wall of the nose, being anterior to the body of the sphenoid. They occupy much of the upper part of the maxillary hiatus, a large defect in the medial aspect of the maxilla, itself closed by several

bones, and the medial aspect of these is surgically important in endoscopic sinus surgery. The superior and middle conchae ('turbinates') are part of the ethmoidal labyrinth, as is the bulla ethmoidalis anteriorly. The lamina papyracea, the paper-thin orbital plate of the ethmoid, separates the ethmoid sinuses from the orbital cavity, knowledge of which is important for endoscopic access to the medial aspect of the orbit, such as for (medial) periorbital abscess drainage, orbital decompression or access to infraorbital/intrazonal tumours.

Two important structures are in this region, providing the blood supply to part of the nasal cavity. The first, found 24 mm posterior to the anterior lacrimal crest on the frontal process of the maxilla, along the frontoethmoid suture on the medial wall of the orbit, is the anterior ethmoidal foramina, transmitting the anterior ethmoidal artery; 12 mm behind this is the posterior ethmoidal foramina and its corresponding artery; 6 mm behind that lies the optic nerve in its canal. The second, found at the top of the perpendicular plate of the palatine bone, posterior to the maxillary hiatus (and so the middle concha), is the sphenopalatine foramen. This transmits the corresponding neurovascular bundle, important in control of the main blood supply to the nasal cavity and also in treating juvenile nasopharyngeal angiofibroma. Of note is the fact that the sphenopalatine artery rarely presents as one arterial trunk, as it divides in two or more (up to 10 branches) just after exiting the sphenopalatine foramen.

The posterosuperior nasal cavity is formed by the sloping anterior aspect of the body of the sphenoid; on the anterior aspect of this, the sphenoethmoidal recess, lying above and behind the superior concha, contains the sphenoidal sinus ostium.

Posterior to the inferior concha, the Eustachian tube orifice marks the medial end of its cartilaginous portion, behind which is found the fossa of Rosenmüller. This lies just anterior to the anteromedial aspect of the foramen lacerum and hence the petrous apex (see below). A nasopharyngeal carcinoma involving this fossa of Rosenmüller may invade upwards through the foramen lacerum, sometimes producing a lateral rectus palsy by compressing the VIth cranial nerve as it crosses the apex of the petrous bone and enters the cavernous sinus.

The salpingopharyngeus muscle arises from the posterior aspect of the tubal orifice, running vertically downwards inside the pharynx to insert into the posterior border of the thyroid cartilage. Its contraction, stimulated via the pharyngeal branch of the vagus, opens the tube.

The pharyngobasilar fascia, a rigid membrane connecting the superior constrictors to the skull base, with two 'paratubal' muscles arising either side of it. Levator palati arises medially (within the pharynx) and tensor palati originates laterally (outside the pharynx). Collectively, they aid opening of the tube due to their attachment to its cartilaginous portion.

Endoscopic endonasal approaches to the central skull base gain access to the:

- frontal sinuses
- cribriform plate
- olfactory bulbs
- frontal lobe
- ethmoid roof
- sphenoid sinus
- pituitary gland
- suprasellar region
- cavernous sinuses
- mid-clival regions.

The latter are accessed trans-sphenoidally; the pair of sphenoid sinuses vary greatly in size, each side separated by a septum usually not in the midline. When small, the sinus lies in front of the pituitary fossa but, when large, may extend beneath the fossa posteriorly to the basiocciput. Tiny at birth, their main development is during puberty. Superior to the sinus lie the pituitary fossa and middle cranial fossa, laterally is found the cavernous sinus and internal carotid artery (ICA), and posteriorly the posterior cranial fossa and pons.

Traversing the superolateral wall of the sphenoid is the optic nerve in its canal on each side; laterally lie the internal carotid arteries and inferiorly the pterygoid canal with its nerve. Further detail of this region is covered in Volume 1, Chapter 87, Anatomy of the nose and paranasal sinuses.

POSTERIOR SKULL BASE

The posterior skull base forms the base of the posterior cranial fossa and is formed by the occipital bone. It houses the cerebellar hemispheres together with the pons and medulla oblongata, the latter of which extends through the foramen magnum, the largest foramen in the skull base and encased by the basilar part of the occipital bone (basiocciput). Either side of the anterior aspect of the foramen magnum are the convex occipital condyles which articulate, via hyaline cartilage, to the convex surface of the atlas, allowing a nodding motion and slight abduction only; rotation is achieved via the atlantoaxial joints. Behind each condyle is the shallow condylar fossa perforated by the condylar canal carrying an emissary vein from the sigmoid sinus to the suboccipital plexus. Above the occipital condyle is the hypoglossal canal carrying the XIIth cranial nerve, which emerges medial to the jugular foramen.

The foramen magnum is oval shaped with the fibrous dura mater attaching to its margins; below this, the latter projects down the spinal canal as the spinal dura mater (theca); above it sweeps up into the posterior cranial fossa. Passing through the foramen, within the dural sheath in the subarachnoid space, lie the lower medulla with the cervical roots of the spinal accessory nerves, the spinal arteries and veins and the vertebral arteries.

A number of ligaments arising from the axis attach to the anterior margin of the foramen magnum: the membrana tectorial, the vertical limb of the cruciform ligament, together with the apical and pair of alar ligaments of the odontoid peg. The anterior and posterior atlantooccipital membranes attach to their corresponding edges of the foramen magnum.

The basiocciput extends forward from the foramen magnum to fuse with the basisphenoid. Along its midline, one third of the way from the foramen magnum to the posterior edge of the nasal septum, lies the pharyngeal tubercle, marking the midline attachment of the pharyngobasilar fascia and the highest fibres of the superior constrictor. Anterior to the tubercle, the bone forms the roof of the nasopharynx. Posterior to it attach the uppermost prevertebral muscles, longus capitis in front of rectus capitis anterior. Separating the nasopharynx from the prevertebral region is the pharyngobasilar fascia, with the prevertebral fascia just behind it.

Posterior to the foramen magnum and hence the basiocciput, the squamous part of occipital bone continues up to fuse along the lambdoid suture with the parietal bones superiorly and mastoid regions of the temporal bones laterally. Externally, a midline crest, the external occipital crest, extends from the foramen magnum up to a projection of bone around 6cm below the lambda, the external occipital protuberance. This crest separates the two sides of the occipital area. Either side of the external occipital protuberance, a concentric ridge of bone extends around to the mastoid process - the superior nuchal line - providing the surface landmark for the attachment of the tentorium cerebelli the transverse sinus (**Figure 98.1**). Sternocleidomastoid attaches to the lateral half of this line, trapezius to the medial half.

The muscles of the back of the neck are attached below this line. Each half of the occipital area is further subdivided by another concentric line – the inferior nuchal line – thus dividing this area into four. The two areas adjacent to the foramen magnum receive the rectus muscles, acting to extend and rotate the head, generally innervated by C1. The two areas between the nuchal lines receive semispinalis medially and superior oblique muscles laterally, giving lateral flexion to the head and also innervated by C1.

Surgical approaches via the occipital bone and posterior skull base include the retrosigmoid and lesser used suboccipital approach to cerebellopontine angle tumours, together with access to:

- occipital bone
- sigmoid sinus
- posterior cranial fossa
- foramen magnum
- upper cervical spine.

LATERAL SKULL BASE

The lateral skull base covers the remaining base of the skull between the anterior and posterior regions described above. Most surgical approaches to this both this area and midline structures anterior to the foramen magnum are made from a lateral, antero- or anterolateral direction.

It is bordered anteriorly by the anterior border of the *sphenoid* body together with its greater wings, and the zygomatic arch; the posterior border is the occipital bone. Laterally it is made up of the squamous and petrous parts of the *temporal bone*. Various regions relate to the undersurface of the sphenoid and temporal bones, which will be expanded upon below.

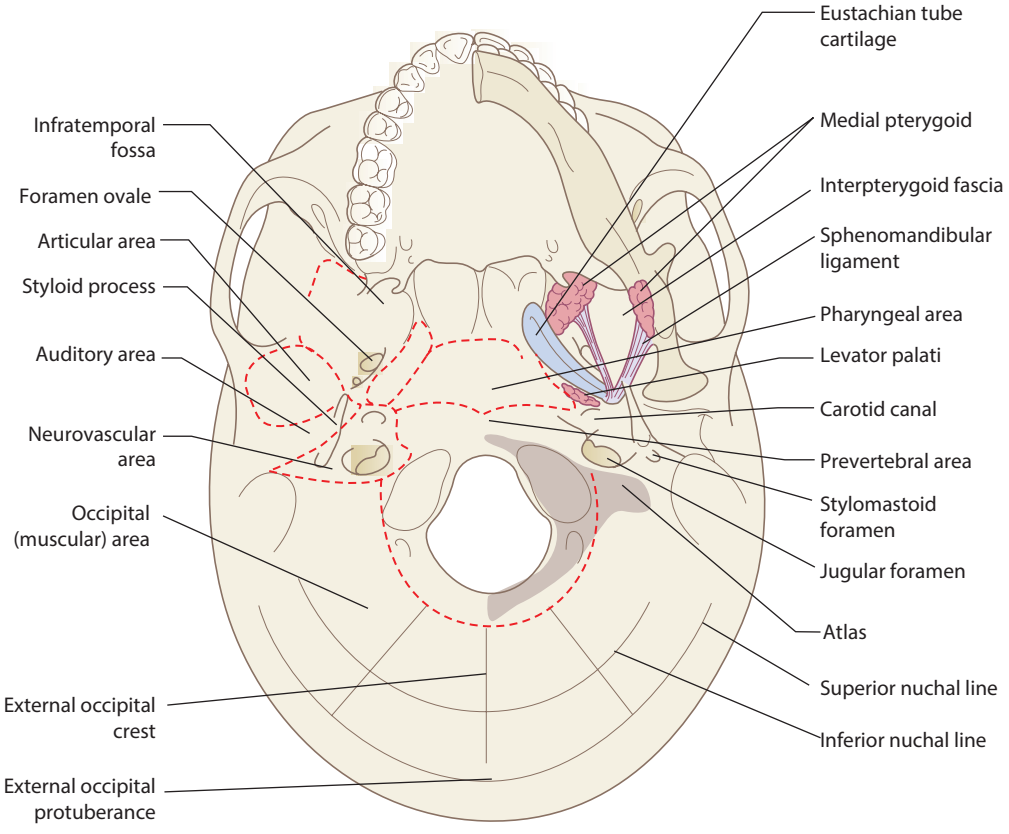

Figure 98.1 The skull base viewed from below. On the right half of the skull are indicated the regions of the central base.In the left half the mandible has been added in the occlusion, with the interpterygoid fascia and Eustachian tube in position. Redrawn from van Huijzen (1984), with permission of S. Karger.

Sphenoid bone

The anterior aspect of the lateral skull base is made up from the body, posterior border of the lesser wings, and the greater wings of the sphenoid superiorly, with the medial and lateral pterygoid plates inferiorly.

The central part of the sphenoid is the *body*, between the clinoid processes, its sloping inferior surface forming the roof of the postnasal space and containing the sphenoid sinus. Its superior surface is hollowed as the pituitary fossa, or sella turcica ('Turkish saddle'), itself roofed by a sheet of fibrous dura mater, the diaphragma sellae. This sheet is continuous laterally as the roof the cavernous sinus, this lying on and grooving each side of the sphenoid body.

Extending superolaterally from the body are the *lesser and greater wings* of the sphenoid, the former anterosuperior and the latter originating posteroinferior from the body, thereby encasing the obliquely slanting *superior orbital fissure*; the contents of this are the ophthalmic nerve and veins, together with the oculomotor, trochlear and abducent nerves.

Extending laterally, the greater wing articulates anteriorly with the frontal bone, laterally with the zygomatic bone and posteriorly with the petrous part of the temporal bone; it therefore forms part of the floor of the middle cranial fossa.

Medially, just in front of the petrous part of the temporal bone, the greater wing is perforated posteriorly by the small *foramen spinosum* (containing the middle meningeal vessels) and, anteromedial to this, by the much larger *foramen ovale* (transmitting the mandibular and lesser petrosal nerves). Occasionally, two smaller foramina also exist in proximity to the foramen ovale – the foramen of Vesalius medially and the innominate foramen posteriorly; anterior to the foramen ovale, the *foramen rotundum* extends forwards, transmitting the maxillary nerve to the pterygopalatine fossa.

Perforating through the base of the lesser wing is the *optic canal*, through which passes the optic nerve and ophthalmic artery.

Of note, the sharp posterior edge of the lesser wing of the sphenoid forms the posterior aspect of the anterior cranial fossa.

Dropping down, from the base of the greater wing of the sphenoid are the pterygoid plates. The *medial pterygoid plate* forms the posterior part of the lateral nasal cavity, articulating anteriorly with the vertical plate of the palatine bone. Inferiorly, it ends as the pterygoid hamulus, around which the tendon of tensor palati hooks. The cartilaginous Eustachian tube grooves the upper aspect of its posterior border, above which the border splits to pass posterolaterally to enclose the scaphoid fossa and give attachment to the tensor palati.

The *lateral pterygoid plate* extends backwards into the infratemporal fossa, giving attachments laterally to the lower head of the lateral pterygoid and medially to the deep head of the medial pterygoid; both involved in protruding the mandible and opening the mouth.

Temporal bone

The temporal bone consists of four parts, which each ossify independently and later fuse:

1. squamous
2. petromastoid
3. tympanic
4. styloid.

The *squamous* part is the largest, forming the convex lateral aspect of the temporal fossa. It articulates anteriorly with the greater wing of the sphenoid and posterosuperiorly with the parietal bone; where these three meet (together with the frontal bone) is an important landmark - the pterion, the weakest part of the skull under which passes the middle meningeal artery (MMA). A fracture here runs the risk of laceration of the MMA and thereby an extradural haematoma.

The *zygomatic* process of the temporal bone originates anteriorly, below which is the mandibular fossa housing the synovial temporomandibular joint. Behind this, the squamous part (together with part of the petrous bone) forms the anterior aspect of the external ear canal, the remainder formed by the curved c-shaped tympanic part of the temporal bone. Medially, the squamous part adjoins the petrous part which, together with the mastoid part (commonly collectively called the petromastoid), forms part of the medial bony external ear canal and thereon encases the middle and inner ear.

Anteriorly, the squamous part's inferior surface forms the posterolateral aspect of the infratemporal fossa, whilst on its lateral surface, the curved temporal line (suprameatal crest) delineates the lower aspect of the attachment of the temporalis fascia, limiting the origin of the temporalis muscle and, together with a small triangle of bone at the posterosuperior aspect of the external auditory meatus, the suprameatal (Macewen's) triangle, are important superficial landmarks for cortical mastoidectomy.

The petrous part is full adult size at birth. However, the *mastoid* process is absent, leaving the stylomastoid foramen near the lateral surface of the skull, covered only by thin fibres of sternocleidomastoid (SCM); the extracranial facial nerve is therefore very superficial and vulnerable in neonates. As the SCM grows, it draws down and thereby develops the mastoid tip, palpable in the second year of life, thereby protecting the emerging facial nerve on its medial surface. This mastoid process is filled to a varying degree by air cells, the *sigmoid sinus* deeply grooving its inner surface, itself receiving the superior petrosal sinus at its upper end, the latter draining part of the cavernous sinus. The deep surface of the mastoid is grooved by the digastric ridge for the origin of the posterior belly of the digastric muscle; just medial to this, the *facial nerve* exits the skull base through the stylomastoid foramen, the styloid process lying just anteromedial to this. Medial to the digastric notch, the occipital groove indents the mastoid bone along the temporo-occipital suture, in which lies the occipital artery.

Angled forwards and medially at 45 degrees, the anterior aspect, the apex, of the pyramidal shaped *petrous* part joins the clivus medially and greater wing of sphenoid anterolaterally; its tip forms the posterolateral boundary of the ragged-shaped foramen lacerum, the latter closed in life by dense fibrous tissue.

The superior surface of the petrous temporal bone contributes to part of the floor of the middle cranial fossa, a sharp ridge along its posterosuperior aspect, angled at 45 degrees, separating this from its near vertical posterior surface which borders the anterior aspect of the posterior cranial fossa. Several important landmarks can be found on this superior surface. Most laterally, just medial to its articulation with the squamous part of the temporal bone, the petrous part forms the roof of the epitympanum, the tegmen tympani. Running along the posterior aspect of the petrous ridge is found the groove for the superior petrosal sinus. Between the two, posteromedial to the tegmen tympani, a curved prominence - the arcuate eminence - is made by the underlying superior semicircular canal. Just anteromedial to this is found the hiatus and groove for the greater petrosal nerve, passing obliquely to the foramen lacerum; the groove for the lesser petrosal nerve lies just anterolateral to this en route to the foramen ovale. Towards the anteromedial aspect of the superior surface, the trigeminal impression houses the trigeminal ganglion.

The posterior aspect of the petrous bone is perforated by the internal auditory meatus (IAM), through which pass the VII and VIII cranial nerves, together with the superior and inferior vestibular nerves and the labyrinthine artery, an internal auditory branch of the basilar artery. Just behind the IAM, a small slit leads to the aquæductus vestibuli containing the endolymphatic duct.

Inferiorly, medial to the base of the styloid process, the petrous bone is hollowed to form the jugular fossa, itself the lateral aspect of the jugular foramen. Divided into three compartments by two transverse septa of fibrous dura, this transmits the jugular vein in the posterior compartment; the middle compartment is shared by the vagus nerve (X) and cranial root of the accessory (XI); the glossopharyngeal (IX) and inferior petrosal sinus occupy the anterior compartment.

Above this, the jugular bulb is the point at which the sigmoid sinus feeds into the upper end of the internal jugular vein. It usually lies inferior to the posterior part of the floor of the middle ear, divided from it by a thin bony covering that may be dehiscent, leaving only mucosa to separate it from the middle ear cavity. However, its position is extremely variable and it may intrude right up into the middle ear ('high jugular bulb').

The ICA enters the skull base through the carotid canal just anterior to the jugular foramen, separated from it by a wedge of bone; erosion of this 'keel' of bone is an early finding in patients with a glomus jugulare tumour. It traverses the petrous apex at an oblique direction, passing anteriorly, superiorly and medially. It gives off some small intrapetrous branches, including the caroticotympanic artery, which may enlarge as feeding vessels for a glomus tumour.

It emerges just lateral to the petrous apex to enter the cavernous sinus (see below). The carotid sheath in the neck will be discussed below in 'Inferior skull base'.

Superolateral to the emerging carotid artery at the apex, the bony Eustachian tube connects to its cartilaginous portion, itself lodged between the greater wing of sphenoid and the petrous apex (see **Figure 98.1**). It is in reverse proportions to the external auditory canal: the lateral third (around 1 cm long) is bony within the petrous bone, originating from the anterior mesotympanum (middle ear); the medial two-thirds is cartilagenous. This transition from bone to cartilage – the isthmus – marks the Eustachian tube's narrowest point. Angled forwards, inferiorly and medially at around 30 degrees and 45 degrees respectively, the cartilaginous portion grooves the posterior border of the medial pterygoid plate before opening into the nasopharynx, as described above.

Posteromedial to the traversing carotid artery, within the dense 'otic capsule' of the petrous temporal bone, are the inner ear structures, practically full adult size at birth.

Housed within an osseous labyrinth, the membranous labyrinth contains endolymph, running throughout the inner ear structures; surrounding this membrane labyrinth is perilymph, which does not communicate with the endolymph. The most anterior structure of the osseous labyrinth is the cochlea, behind which lies the vestibule followed by the semicircular canals, in that order; the parts of the membranous labyrinth, in the same order from front to back, are the cochlear duct, saccule and utricle (within the vestible, concerned with vertical and horizontal movement detection respectively) and semicircular ducts (concerned with kinetic balance). The conical-shaped cochlea lies at an oblique angle; its base at the fundus of the internal acoustic meatus and its apex directed across the long axis of the petrous bone, pointing anterolaterally towards the middle ear. It curls two and three-quarter turns around the central modiolus containing the spiral ganglion.

Detailed anatomy of the middle and inner ear can be found in the Chapters 46, Anatomy and embryology of the external and middle ear and 47, Anatomy of the cochlear and vestibular system: Relating ultrastructure to function. However, brief mention of the innervation will be made here. The tympanic branch of the IXth nerve (Jacobson's nerve) leaves the glossopharyngeal nerve at the petrous ganglion and passes through a canaliculus in the keel of petrous bone between the jugular and carotid foramina to supply the middle ear (tympanic plexus).

The auricular branch of the Xth nerve (Arnold's nerve) passes behind the internal jugular vein and enters the mastoid canaliculus on the lateral wall of the jugular foramen, from which it emerges by way of the tympanomastoid fissure to supply the skin of part of the external auditory meatus.

The *tympanic* part of the temporal bone lies lateral to the petrous bone, its lateral border ending at the cartilagenous part of the external auditory canal. The posterosuperior surface is concave, forming the anterior, floor and part of the posterior wall of the bony ear canal. Where each extent of the c-shaped bone attaches, a suture line forms along the ear canal – anteriorly the tympanosquamous

and posteriorly the tympanomastoid sutures; the skin is particularly adherent along these. The inferior aspect of the tympanomastoid suture line is an important operative landmark for identifying the facial nerve as it exits the stylomastoid foramen.

Medially, the tympanic part houses the tympanic sulcus, in which lies the fibrous annulus for attachment of the tympanic membrane.

Anteroinferiorly, the tympanic part makes up part of the posterior boundary of the mandibular fossa.

Arising from the inferior aspect of the fusion of the tympanic and petrous bones, the *styloid* part of the temporal bone projects downwards and forwards, giving attachment to several ligaments and muscles bearing its name.

Three muscles attach to the styloid process, each having a different nerve supply but all involved in swallowing:

- stylopharyngeus
- stylohyoid
- styloglossus.

The stylopharyngeus arises from the medial aspect of the base of the styloid process and slopes down across the lateral aspect of the ICA before passing between the superior and middle pharyngeal constrictors alongside the pharynx, inserting into the posterior border of the thyroid cartilage. It is both innervated and traversed by the glossopharyngeal (IX) nerve, the sensory part crossing over the muscle to reach the tongue; its action is elevation of the pharynx and larynx.

The stylohyoid arises from the posterolateral aspect of the base of the styloid process, passing anterolaterally to the posterior belly of digastric with which it shares its innervation from the facial nerve (VII). It inserts onto the greater cornu of the hyoid, its attachment here perforated by the intermediate tendon of digastric, to give retraction to the hyoid.

The styloglossus is the shortest of the three, arising from the anterolateral aspect of the styloid process, passing downward and forwards between the internal and external carotid arteries to insert into the side of the tongue, innervated by the hypoglossal (XII) nerve, retracting the tongue.

The external carotid artery is intimately related to these muscles above. Running deep to the stylohyoid (and hence the posterior belly of digastric, it lies superficial to the stylopharyngeus and the styloglossus en route to the parotid gland. Conversely, the retromandibular vein runs superficially to all elements of the styloid apparatus.

Facial nerve

The VIIth cranial nerve emerges from the brainstem, between the pons and olive. The nervus intermedius emerges between the pons and inferior cerebellar peduncle. Joining the main facial nerve in its cisternal segment, it traverses the cerebellopontine angle to enter the porus of the IAM, together with the VIIIth cranial nerve, as mentioned above. Lying anterosuperiorly in the IAM, it is above the cochlear nerve, the superior and inferior vestibular nerves being posteriorly located. At the lateral extent of the IAM, the facial nerve passes through its narrowest portion via the labyrinthine segment, between the cochlea and vestibule. It exits this segment to form the geniculate ganglion before turning backwards at its first genu. Here, it gives off the greater superficial petrosal nerve which runs in its groove along the floor of the middle cranial fossa between two layers of dura mater; intra-operative traction on this nerve can result in a facial palsy secondary to haemorrhage or oedema.

From the first genu, VII runs in its horizontal tympanic segment in the medial wall of the middle ear, passing above the promontory. It curves over the oval window niche before reaching the second genu, just inferior to the lateral semicircular canal, at which point it curves downwards into its vertical mastoid segment behind the external auditory canal. The nerve to Stapedius branches off here, reaching the muscle via a tiny canaliculus. Just before it exits the skull base, VII gives off the fibres of the nervus intermedius as the chords tympani, thereafter passing through the stylomastoid foramen as a purely motor nerve.

The extracranial facial nerve gives off the posterior auricular nerve (supplying the occipital belly of occipitofrontalis) and a muscular branch (supplying the posterior belly of the digastric and stylohyoid), before swinging forward to enter the parotid gland and dividing into its upper and lower branches. Further divisions in the parotid result in the five branches supplying motor innervation to the muscles of facial expression.

NOTABLE REGIONS OF THE SKULL BASE

Cavernous sinus

The *cavernous sinus* extends from the apex of the orbit back to the apex of the petrous temporal bone, its medial and inferior walls being deep grooves into the body and base of the greater wing of the sphenoid respectively. The medial, upper and lateral walls are made up of a fold of the inner layer of dura, medially continuous with the diaphragma sellae; posterolaterally, the wall is medial to the anterior parts of the trigeminal (*Meckel's*) cave, itself containing the trigeminal ganglion.

Containing cranial nerves III, IV and V (ophthalmic and maxillary branches) embedded within its lateral wall and, inferolaterally, VI, the sinus' main content is the ICA as it emerges from the petrous apex through the superior aspect of the irregular foramen lacerum and projects upwards, forwards and medially to the anterior clinoid process, a small posterior extension of the lesser wing. Here, just posterior to the optic canals, the ICA perforates the dura mater to enter the middle cranial fossa, immediately dividing into its terminal branches.

Each sinus also receives blood from the orbit and cerebral hemispheres, and each drains via the superior and

inferior petrosal sinuses to the sigmoid sinus and internal jugular vein respectively.

INFRATEMPORAL FOSSA

As the greater wing articulates with the squamous temporal bone, just in front of the articular eminence, it forms the medial roof of the *infratemporal fossa*, a space beneath the skull between the pharynx and the ramus of the mandible. Anteriorly, this infratemporal surface ends in the inferior orbital fissure behind the maxilla, transmitting the maxillary nerve. Laterally, the superior extent of the fossa is the space deep to the zygomatic arch, its lateral extent limited by the ramus of the mandible. The medial pterygoid muscle, together with the interpterygoid fascia, mark the medial border. The posterior boundary is the styloid process, with the carotid sheath behind. It has no anatomical floor, being continuous down into the neck.

The contents include the deep lobe of the parotid, the lateral and medial pterygoid muscles, the insertion of the temporalis muscle into the coronoid process, the maxillary artery and its branches, the mandibular nerve and otic ganglion, chorda tympani, the pterygoid venous plexus and maxillary veins.

Lateral pterygoid muscle

This muscle arises from two heads: the upper from the infratemporal surface of the greater wing of the sphenoid, the lower from the lateral surface of the lateral pterygoid plate. Passing backwards, these two heads converge forming a tendon that inserts into the front of the neck of the mandible. Supplied by the mandibular division of the Vth nerve, it acts to open the mouth by pulling the condyle forwards, down the articular eminence.

Medial pterygoid muscle

Also arising from two heads, the larger of these arises from the deep (medial) surface of the lateral pterygoid plate; a small slip joins from the tuberosity of the maxilla and the pyramidal process of the maxilla, initially passing over the inferior free edge of the lateral pterygoid. Angled laterally, posteriorly and inferiorly, it inserts into the angle of the mandible (Figure 98.2), acting to close the mouth and move the mandible towards the opposite side in chewing. It is innervated by the mandibular nerve.

Maxillary artery

A terminal branch of the external carotid artery, the maxillary artery enters the infratemporal fossa as the other terminal branch, the superficial temporal artery, passes laterally up behind the temporomandibular joint (see Figure 98.3.) Passing deep to the neck of the mandible, between this and the sphenomandibular ligament, it runs a variable course around the lateral pterygoid muscle medially towards the pterygomaxillary fissure and hence into the pterygopalatine fossa.

Traditionally, the artery is described in three parts in relation to the lateral pterygoid muscle. Proximal, on and distal to this; five branches come from each part.

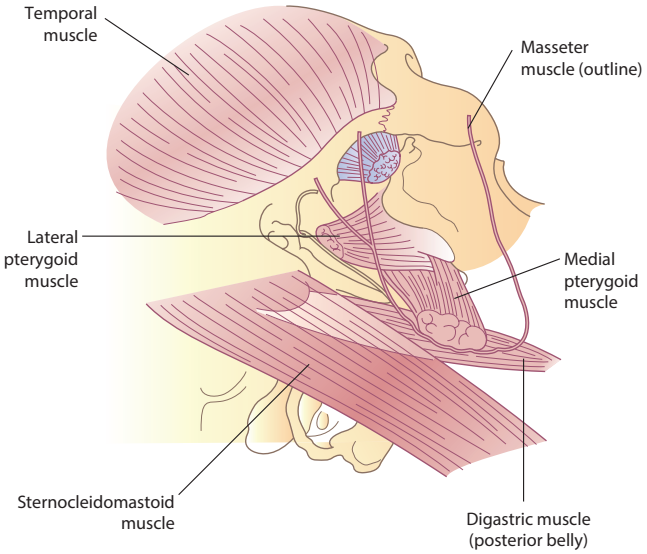

Figure 98.2 The superficial muscles of the central skull base. Redrawn from Goldenberg (1984), with permission.

The first part of the maxillary artery gives off the:

- inferior alveolar artery
- middle meningeal artery
- accessory meningeal artery
- deep auricular artery
- anterior tympanic artery.

The inferior alveolar artery passes down to join the inferior alveolar nerve and enter the mandibular foramen. The MMA passes straight up through the foramen spinosum, while the accessory meningeal artery passes through the foramen ovale. The deep auricular artery passes up to supply the external auditory canal and the anterior tympanic artery enters the petrotympanic fissure on its way to the middle ear.

The second part of the maxillary artery gives off five branches to the soft tissues:

- lateral and medial pterygoid muscles
- temporalis muscle
- lingual and long buccal nerves.

The third part of the artery divides in the pterygopalatine fossa, these five branches accompanying nerves including branches of the pterygopalatine ganglion, supplying the orbit, nose and palate. Of note, the *sphenopalatine artery* enters the nasal cavity through the sphenopalatine foramen to form the cavity's principal arterial supply. Endoscopic cautery or ligation of this artery is performed for persistent epistaxis; however, as mentioned previously, it rarely presents as one arterial trunk, as it divides in two or more (up to 10 branches) just after exiting the sphenopalatine foramen.

The pterygoid plexus and maxillary veins

The pterygoid plexus of veins lies within and on the lateral surface of the lateral pterygoid muscle, and receives tributaries corresponding to the branches of the maxillary artery.

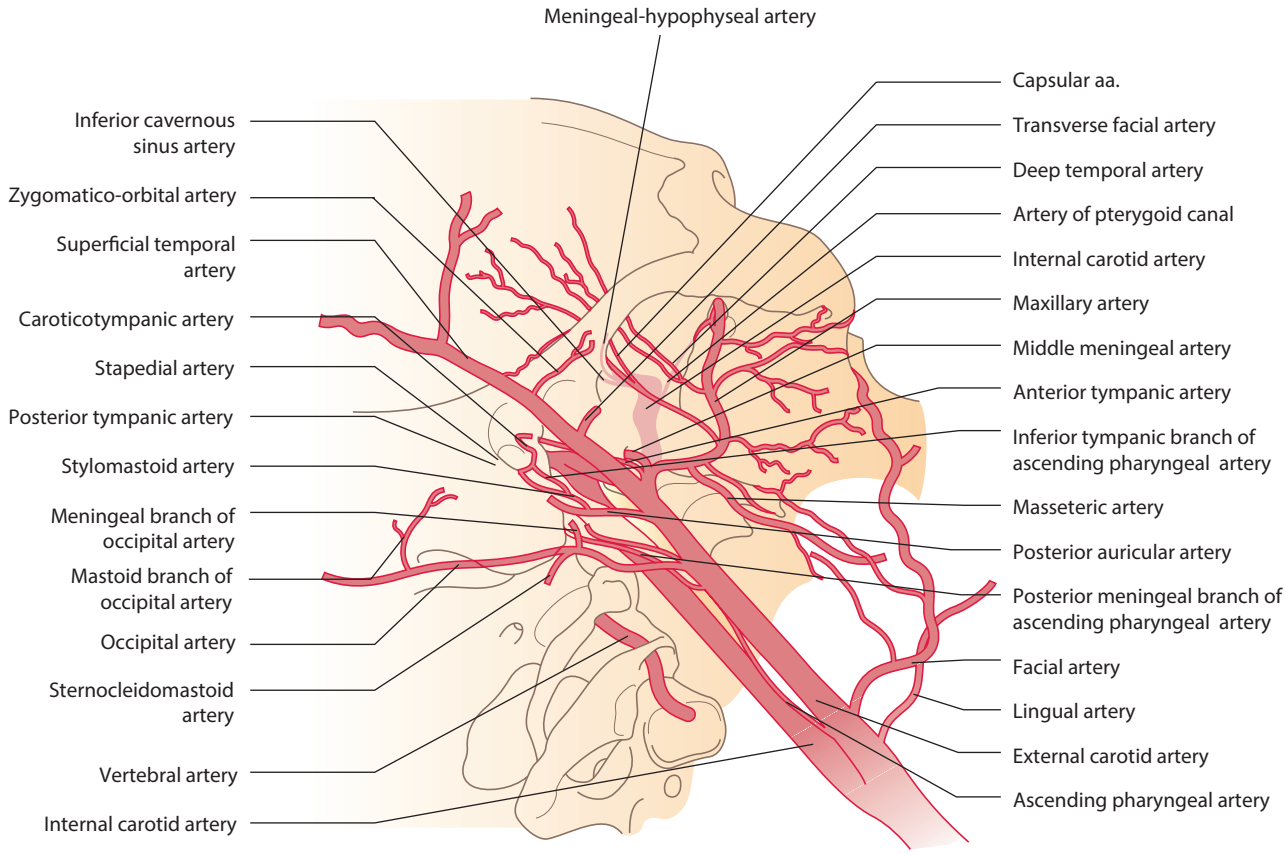

Figure 98.3 The arteries of the central skull base. Redrawn from Goldenberg (1984), with permission.

The plexus drains into two short, large maxillary veins which pass horizontally backwards deep to the neck of the mandible to join the superficial temporal vein and form the retromandibular vein (Figure 98.4).

The pterygoid plexus has three important communicating veins.

1. The inferior ophthalmic vein passes through the inferior orbital fissure to join the facial vein.
2. A connecting vein passes vertically down from the cavernous sinus via the foramen ovale or, when present, the foramen of Vesalius.
3. The deep facial vein runs forward beneath the zygoma to join the anterior facial vein.

These connections can allow infection from the face to spread by way of the pterygoid plexus to produce a cavernous sinus thrombosis.

The mandibular nerve

The mandibular nerve passes through the foramen ovale and, after a short course just deep to the upper head of the lateral pterygoid muscle, the main trunk divides into anterior and posterior divisions (Figure 98.5). Before it does so, the main trunk gives off the sensory nervus spinosus (which re-enters the middle fossa through the foramen spinosum) and the motor nerve to the medial pterygoid, which also supplies the tensor palati and tensor tympani.

The anterior division is motor except for the long buccal nerve. The latter passes between the heads of the lateral pterygoid to swing forwards and downwards on the deep surface of the temporalis muscle, and then pierces the buccinator to supply the mucous membrane of the cheek. The motor branches supply the temporalis, masseter (by a branch which emerges through the mandibular notch) and the lateral pterygoid.

The posterior division is sensory, except for the mylohyoid nerve. The auriculotemporal nerve springs from two roots, which pass either side of the MMA, and pass backwards between the sphenomandibular ligament and neck of the mandible. The inferior alveolar nerve swings downwards on the surface of the medial pterygoid muscle, passes between the sphenomandibular ligament and neck of the mandible, and gives off the mylohyoid nerve before entering the mandibular foramen. The lingual nerve is joined by the chorda tympani 2 cm below the base of the skull and passes downwards and forwards on the medial pterygoid, grooving the mandible before entering the mouth.

The otic ganglion lies close to the mandibular nerve just below the foramen ovale, between the nerve and the tensor palati muscle. It relays secretomotor fibres for the parotid gland, which it receives by way of the lesser superficial petrosal nerve and transmits to the auriculotemporal nerve. The lesser superficial petrosal nerve leaves the middle fossa through the foramen ovale, or sometimes through its own foramen, the foramen innominatum.

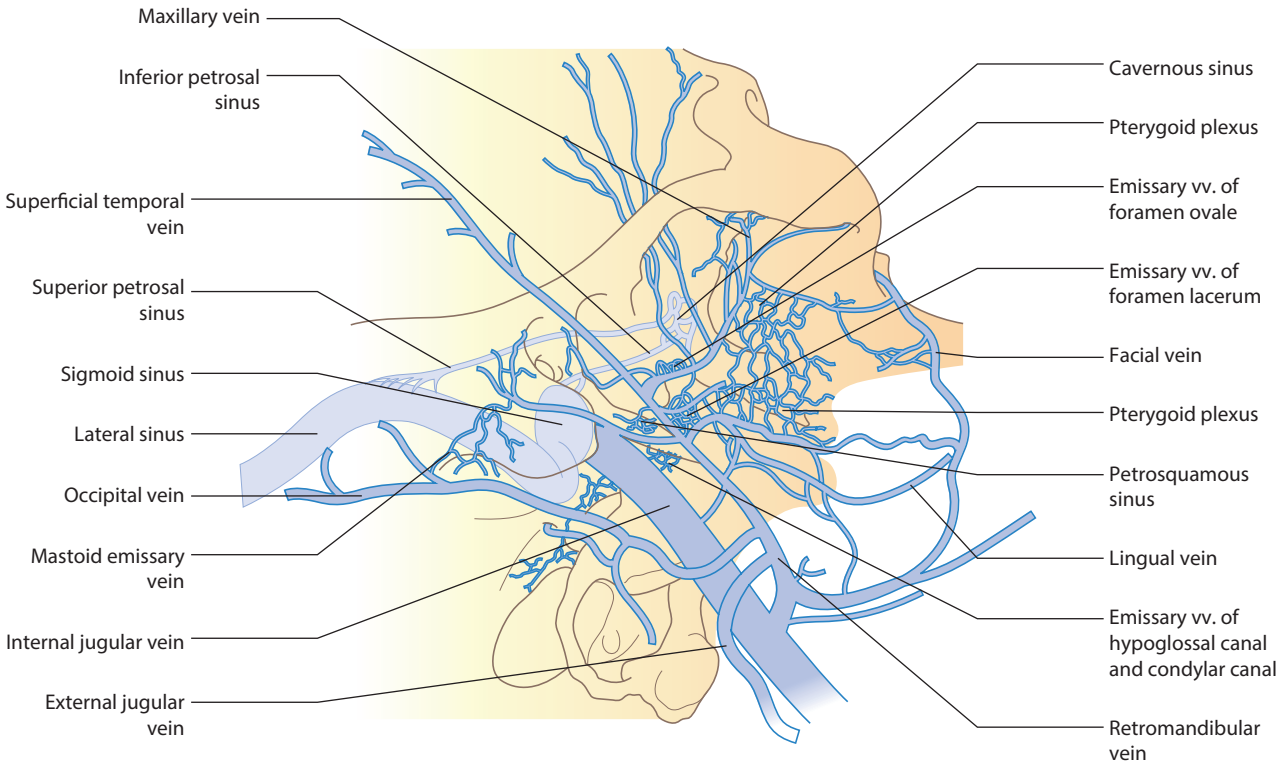

Figure 98.4 The veins of the central skull base. Redrawn from Goldenberg (1984), with permission.

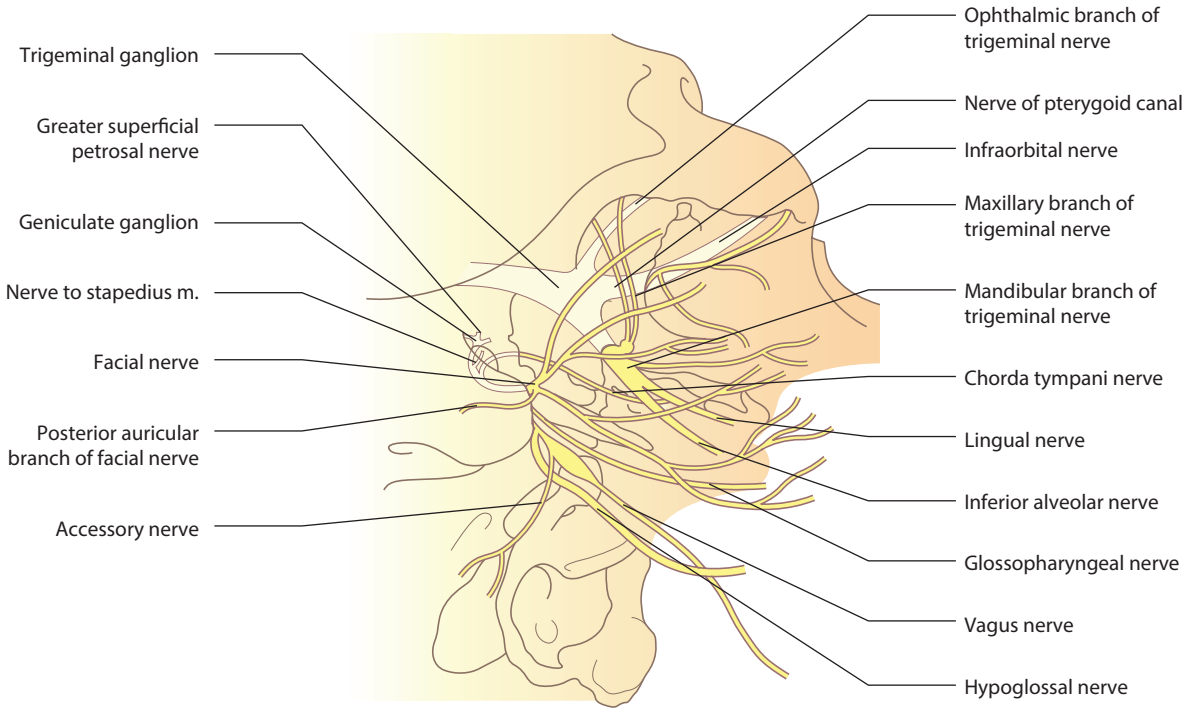

Figure 98.5 The nerves of the central skull base. Redrawn from Goldenberg (1984), with permission.

PTERYGOPALATINE FOSSA

A cone-shaped depression deep to the infratemporal fossa, posterior to the maxilla near the orbital apex, the small pterygopalatine fossa contains the terminal third of the maxillary artery, the maxillary nerve (V_2), the pterygopalatine ganglion just in front of the pterygoid canal (itself containing the Vivian nerve, a union of the greater and deep petrosal nerves, which then runs anteriorly to the sphenopalatine ganglion) and fat. Its roof is the body of the sphenoid and medially it abuts the

perpendicular plate of the palatine bone in the lateral nasal wall. It has several communications to other parts of the skull base, principally laterally via the pterygomaxillary fissure to the infratemporal fossa, medially via the sphenopalatine foramen to the nasal cavity and anteriorly via the inferior orbital fissure to the orbit; posteriorly, the pterygoid (Vidian) canal has been described, with the foramens rotundum and lacerum communicating to the middle cranial fossa.

MECKEL'S CAVE

As the trigeminal nerve leaves the pons in the posterior fossa, it runs forwards along the superior aspect of the petrous part of the temporal bone, grooving its surface. Passing under the superior petrosal sinus, an evagination of the tentorium cerebelli (inner layer of dura and the arachnoid) surrounds it to form the trigeminal cave of Meckel, lying in the trigeminal impression on the superior aspect of the petrous apex. Here lies the trigeminal ganglion, its posterior half therefore bathed in cerebrospinal fluid. The anterior half of the ganglion, together with the three divisions of the trigeminal nerve, lie in front of Meckel's cave, the dural and arachnoid layers having fused at the halfway point of the trigeminal ganglion. An extradural approach to the anterior half of the cave is therefore possible via the middle fossa.

The sphenomandibular ligament

The sphenomandibular ligament is a fibrous band joining the spine of the sphenoid to the lingula of the mandible. It is derived from the first branchial arch (Meckel's) cartilage. Anteriorly, it blends into the interpterygoid fascia, which separates the lateral and medial pterygoid muscles, stretching forward as a sheet to be attached to the posterior edge of the lateral pterygoid plate.

PAROTID SPACE

The space enclosed within the capsule of the parotid gland lies partly superficial to the mandible, and extends through the retromandibular space behind the infratemporal fossa to abut against the parapharyngeal space (Figures 98.6 and 98.7).

PARAPHARYNGEAL SPACE

The parapharyngeal space is described as having two compartments:

1. pre-styloid
2. retro- or post-styloid.

These compartments are separated anatomically by the styloid process of the temporal bone and its associated apparatus (see 'Temporal bone' above).

Pre-styloid compartment

This compartment contains the two palati muscles and two arteries, the ascending palatine and ascending pharyngeal (see Figures 98.8, 98.7 and 98.9 respectively).

The tensor palati muscle arises from the skull base between the pterygoid fossa and the spine of the sphenoid and is attached to the lateral side of the Eustachian tube. It tapers down to a tendon, which takes a right-angled

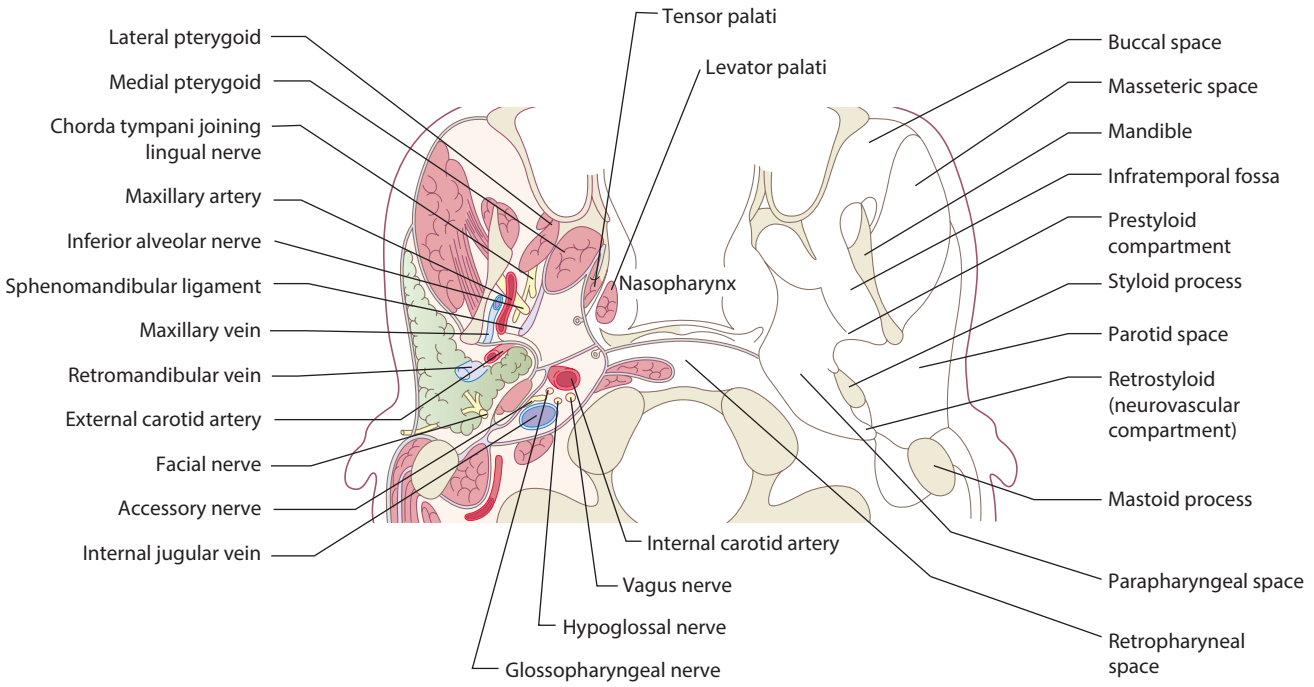

Figure 98.6 The central part of a horizontal section of the head passing through the foramen magnum, between the Eustachian tube and the palate. In the left half all relevant structures have been drawn; on the right, the different compartments are indicated as they appear at this level. Redrawn from van Huijzen (1984), with permission of S. Karger

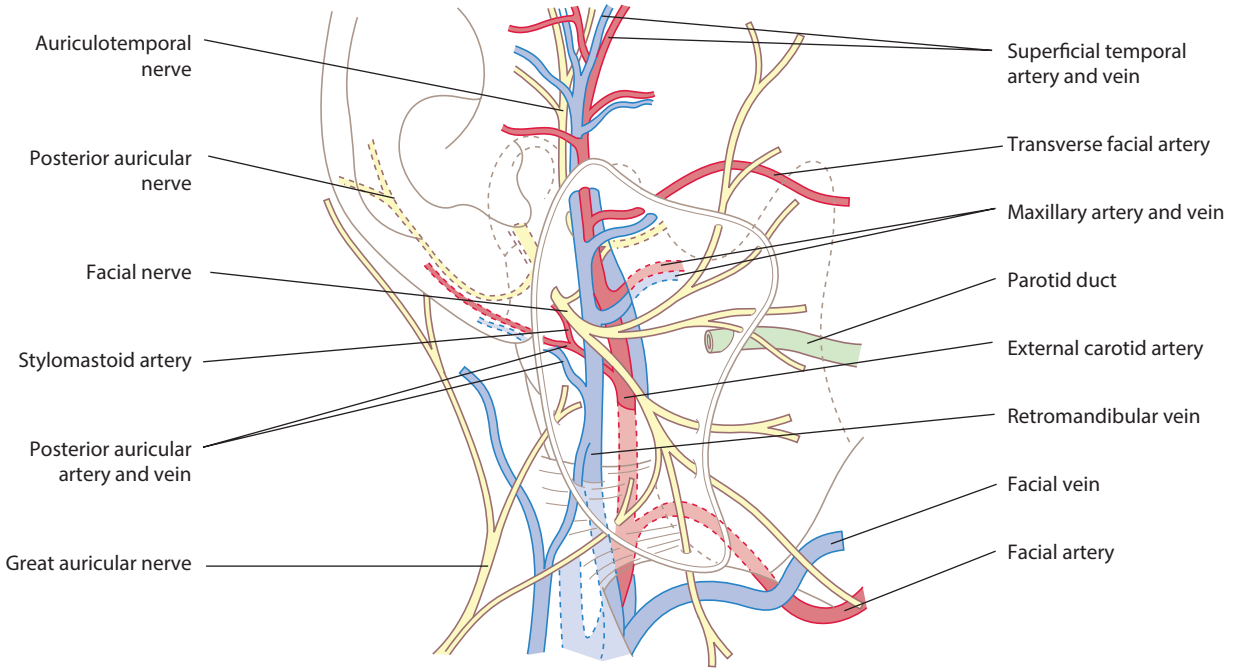

Figure 98.7 The structures of the parotid space, viewed from the lateral aspect. The parotid gland has been removed from its capsule, leaving the vessels and nerves intact. Redrawn from van Huijzen (1984), with permission of S. Karger.

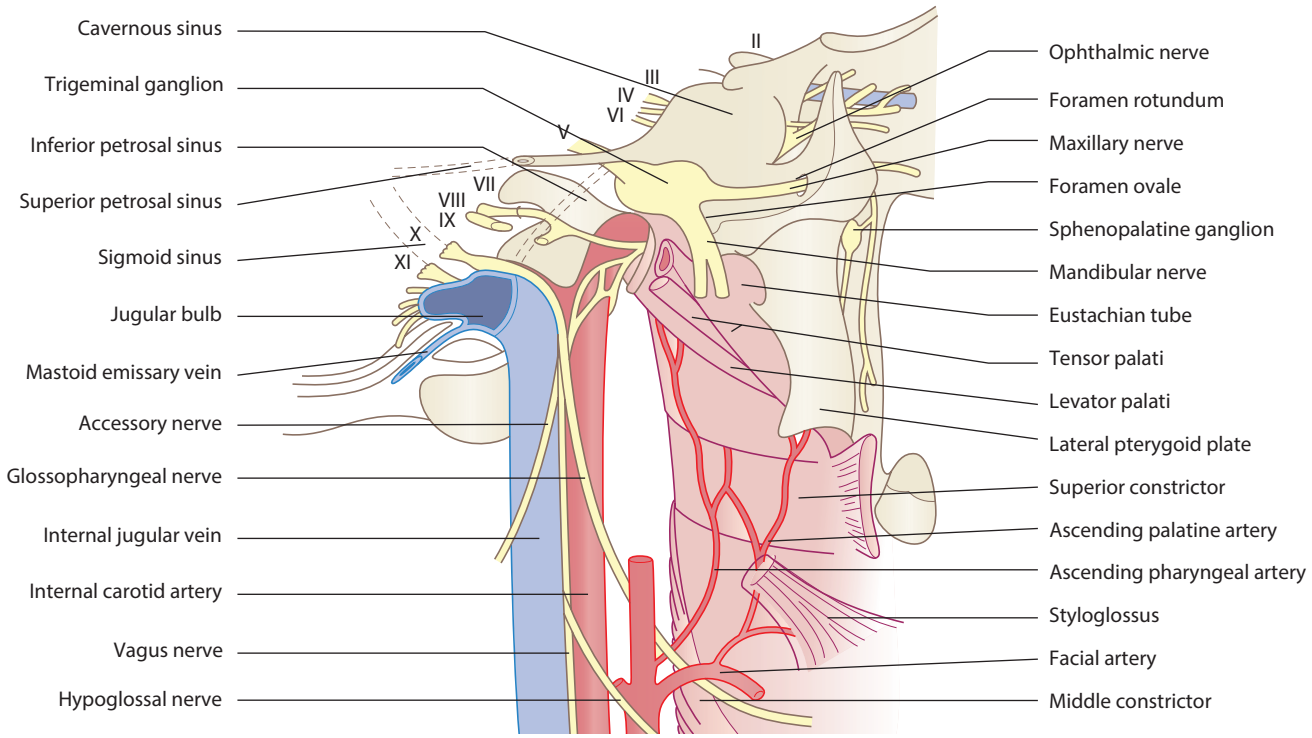

Figure 98.8 The structures of the parapharyngeal space and of the skull base above it, seen from the lateral aspect in a sagittal section passing through the foramen ovale. Redrawn from van Huijzen (1984), with permission of S. Karger.

turn around the hamulus to enter the pharynx, where it broadens into a flat aponeurosis; this triangular sheet blends with its counterparts on the opposite side and is attached to the posterior edge of the hard palate (the crest of the palatine bone). It is supplied by the nerve to the medial pterygoid, a branch of the trigeminal nerve. The action of this muscle is to tense the palate so that other muscles can raise and lower it.

The levator palatini muscle arises from the petrous apex anterolateral to the carotid foramen and from the

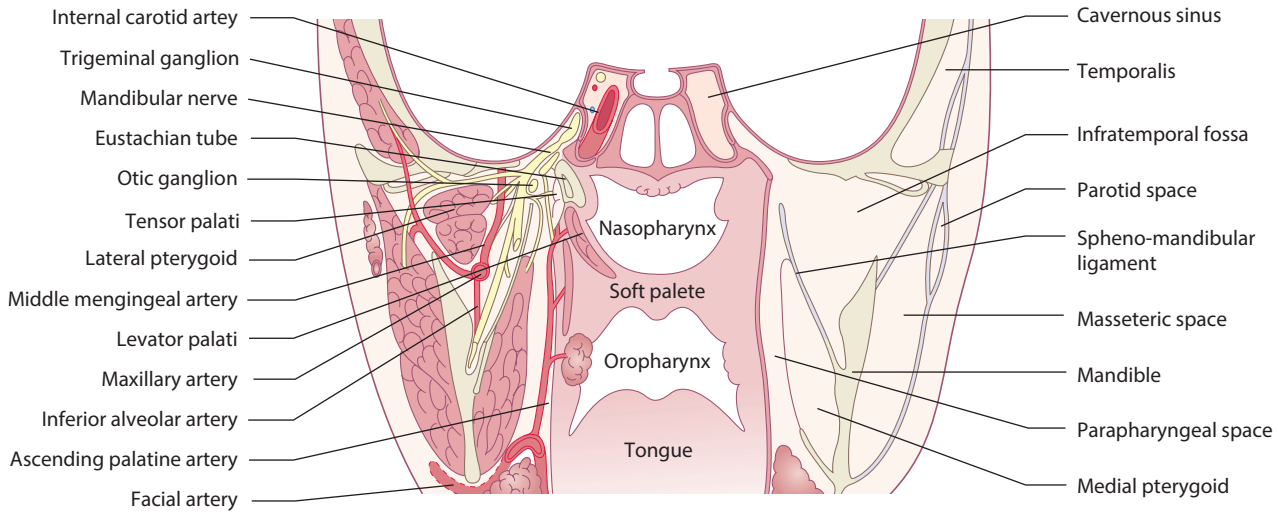

Figure 98.9 Coronal section of the head passing through the foramen ovale. On the left, all relevant structures are illustrated; on the right, the main compartments are shown. Redrawn from van Huijzen (1984), with permission of S. Karger.

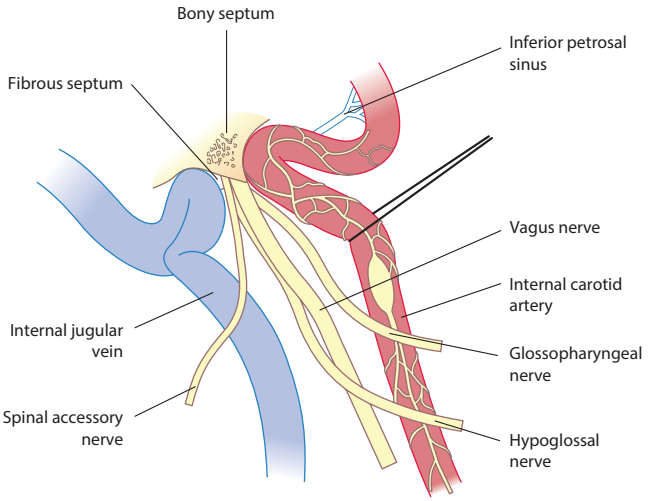

Figure 98.10 The structures in the jugular foramen. Redrawn from Goldenberg (1984), with permission.

medial end of the tubal cartilage and is inserted into the upper surface of the palatal aponeurosis. Supplied by the Xth nerve by way of the pharyngeal plexus, it acts to raise the soft palate and close off the nasopharynx.

The ascending palatine artery, a branch of the external carotid artery, ascends a little more posteriorly along the superior constrictor to supply the pharynx, the middle ear and the meninges. Often it is a major feeding vessel to a glomus tumour (see Figure 98.3).

Retrostyloid compartment

This corresponds to the neurovascular space and contains the carotid sheath.

INFERIOR SKULL BASE

Carotid sheath

The carotid sheath itself is not a membranous fascia, but a dense network of areolar tissue that surrounds the ICA and vagus nerve. It is virtually absent over the internal jugular vein, however, which is thus able to expand greatly during periods of increased blood flow. The carotid sheath is attached to the skull base around the carotid foramen and continues downwards as far as the aortic arch.

In the neck, the carotid sheath, together with the pretracheal fascia, is firmly attached anteriorly to the deep surface of the sternomastoid. Posteriorly, it is not attached to the prevertebral fascia, but is free to slide over it. This means that pus tracking laterally from a parapharyngeal abscess passes behind the sheath and behind the sternomastoid, to point in the posterior triangle.

The ICA passes vertically upwards from the carotid bifurcation in the neck to enter the carotid foramen (see Figure 98.3). It has no branches, but carries with it the carotid plexus of sympathetic nerves from the superior cervical ganglion.

The internal jugular vein descends from the jugular bulb to lie behind the ICA on the lateral mass of the atlas (see Figure 98.4). Just below the base of the skull, it receives the inferior petrosal sinus. As it descends, it passes across on to the lateral side of the ICA, receiving tributaries from the pharyngeal plexus of veins and is crossed on its lateral side by the accessory nerve. The deep cervical lymph nodes also lie on the lateral side of the vein.

The glossopharyngeal nerve (IX) lies lateral to the inferior petrosal sinus as it emerges from the anterior part of the jugular foramen (see Figure 98.5 and Figure 98.10). The nerve passes down on the lateral surface of the ICA and then gently curves forward around the lateral side of the stylopharyngeus, medial to the external carotid artery towards the tongue.

The vagus nerve (X) emerges from its superior ganglion in the middle compartment of the jugular foramen and runs straight down in the back of the carotid sheath between the carotid artery and jugular vein (see Figures 98.5 and 98.10). Just below the skull base, it is dilated into its inferior ganglion, where it receives a connection from the accessory nerve carrying fibres from the nucleus ambiguus.

The accessory nerve (XI) is just lateral to the vagus in the middle compartment of the jugular foramen and runs straight down in the back of the carotid sheath between the carotid artery and jugular vein (See **Figures 98.5** and **98.10**). It immediately begins to curve away posteriorly across the lateral surface of the internal jugular vein, medial to the styloid process and posterior belly of the digastric, giving a branch to the sternomastoid before piercing the muscle to gain the posterior triangle.

The hypoglossal nerve (XII) emerges from the anterior condylar foramen, medial to the carotid sheath and spirals in a lateral direction behind the vagus between the internal jugular vein and ICA (that is, through the carotid sheath) (see **Figures 98.5** and **98.10**). It then swings forwards lateral to the carotid arteries, deep to the styloid muscles and digastric, on its way to the tongue.

The cervical sympathetic trunk lies behind the carotid sheath in front of the prevertebral fascia, just medial to the vagus nerve. It ends superiorly at the superior cervical ganglion. The deep petrosal nerve arises from this ganglion and passes superiorly to join the greater superficial petrosal nerve to form the Vidian nerve.

MUSCLES SUPERFICIAL TO THE LATERAL SKULL BASE

Four muscles that lie lateral to the base of the skull are important in achieving surgical exposure of the area, namely:

1. masseter
2. temporalis
3. sternomastoid
4. digastric.

These are briefly described below (see also **Figure 98.2**).

The masseter muscle arises from the zygomatic arch and is inserted into a wide area on the lateral aspect of the mandible from the angle forwards along the lower border, and upwards over the lower part of the ascending ramus. It is supplied by the Vth nerve by way of the masseteric branch from the anterior division of the mandibular nerve and its action is to close the jaws.

The temporalis muscle arises from the temporal fossa on the side of the skull and from this large origin it converges in the shape of a fan to be inserted into the coronoid process of the mandible. It acts to close the jaws and its posterior fibres also retract the mandible.

The sternomastoid muscle arises by two heads from the manubrium and the clavicle. It is inserted into a curved line extending from the tip of the mastoid process to the superior nuchal line of the occiput. It is supplied by the XI nerve and its main action is to protract the head (moving it forwards while keeping it vertical with a horizontal gaze).

The digastric muscle arises from the digastric notch on the medial surface of the mastoid process. Two muscular bellies (anterior and posterior) separated by an intermediate tendon are described. The posterior belly narrows anteriorly into the intermediate tendon, which passes through a fibrous sling on the hyoid near the lesser cornu, and then expands into the anterior belly, which runs beneath the mylohyoid to its insertion into the digastric fossa on the lower edge of the mandible. The posterior belly is supplied by the VIIth nerve (nerve to digastric) and the anterior belly by the Vth nerve (mylohyoid nerve). Its action is to depress and retract the chin.

Surgical approaches to the following structures may be made via lateral skull base approach:

- middle ear, mastoid and associated structures
- sigmoid sinus and jugular bulb and uppermost part of the internal jugular vein
- middle cranial fossa
- parotid gland
- facial nerve
- inner ear, cochlear and vestibular nerves
- petrous apex
- infratemporal fossa
- carotid artery
- IX, X, XI and XII
- Eustachian tube
- clivus
- basiocciput
- basisphenoid
- nasopharynx.

KEY POINTS

- Intimate knowledge of the course of the facial nerve through the temporal bone and its relation to the lateral semicircular canal is essential for safe mastoid surgery.
- The relationship of the sigmoid sinus, jugular bulb, carotid artery and inner ear structures must be understood for extended mastoid exploration, such as towards the petrous apex.
- Identification of the bulbar nerves and their relationship to the carotid sheath and jugular foramen prevent morbidity in paraganglioma surgery.
- Detailed understanding of the course of the carotid arteries and optic nerves in the lateral walls of the sphenoid sinus are essential in extended endoscopic sinus surgery.

FURTHER READING

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CHAPTER 99

EVALUATION OF THE SKULL BASE PATIENT

Jeyanthi Kulasegarah and Richard M. Irving

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: otalgia, CSF otorrhoea, hearing loss, pulsatile tinnitus, vestibular schwannoma, cerebellopontine angle and skull base, with the use of wildcards.

INTRODUCTION

This chapter aims to provide a simple framework for the assessment of patients with skull base lesions. It is difficult for it to be all embracing and therefore the more common conditions have been covered discussing typical symptoms, signs and investigations in such patients. In writing the chapter, the major difficulty has been that most of the literature deals with skull base lesions in terms of aetiology (e.g. studies of vestibular schwannomas (VS)) rather than the incidence of specific symptomatology (e.g. deafness). It has been necessary to focus on the few studies that have looked at clinical manifestations and collate these with findings from other studies. Due to the relatively low incidence of skull base lesions, most studies are of low impact (i.e. level 3 or 4 evidence).

The skull base has an intricate, three-dimensional conformation that is closely associated with and penetrated by numerous vital neurovascular structures. In order to understand the complexity and clinical manifestations of specific lesions it is extremely important to have a thorough understanding of the anatomy of the skull base. The skull base can be broadly sub-classified into three distinct areas: anterior skull base, central skull base and posterior skull base.[1] The anterior skull base is formed by the posterior wall of the frontal sinus (anterior border); lesser wing of the sphenoid bone and anterior clinoid processes (posterior border); cribriform plate of the ethmoid bone (midline) and nasal cavity, ethmoid sinus and orbits (inferior border); and orbital plates of the frontal bone (lateral border). The central skull base is mainly formed by the sphenoid bone and the temporal bone anterior to the petrous ridge.[2] The central skull base is further divided into midline sagittal, off-midline parasagittal, and lateral compartments.[2] The midline sagittal compartment includes the body of the sphenoid and the portion of the clivus anterior to the basisphenoid. The sella turcica is a depression in the superior surface of the body of sphenoid bone for the pituitary gland. The parasagittal compartment contains important components, which include carvernous sinus, superior orbital fissure, foramen rotundum, vidian canal and foramen lacerum. The carvernous sinus forms the superior and medial boundary of the parasagittal compartment while the parapharyngeal and masticator spaces are along the inferior aspect.[2] The sphenoid triangle, squamous part of temporal bone, and temporomandibular joint forms the lateral compartment of the central skull base. The posterior skull base is formed anteriorly by the posterior surface of the clivus, laterally is formed by the posterior surface of the petrous temporal bone superiorly and the condylar part of the occipital bone inferiorly. The mastoid temporal bone and the squamous occipital bone form the posterior portion of the posterior skull base.

The skull base is composed of a vast number of different tissues and cell types, and consequently can be affected by many different disease processes that include inflammation, trauma, benign and malignant neoplasia, and congenital abnormalities. The more common skull base lesions are shown in **Table 99.1**.

The symptoms produced by any skull base lesion are determined by its anatomical location. Anterior skull base disease may produce hyposmia, diplopia, blindness and

TABLE 99.1 The more common lesions found in different areas of the skull base

Anterior skull base	Central skull base	Posterior skull base
Mucocoeles	Pituitary adenoma	Vestibular schwannoma
Inverted papilloma	Craniopharyngioma	Meningioma
Juvenile angiofibroma	Cavernous sinus meningioma	Cholesteatoma
Olfactory neuroblastoma	Chordoma	Paraganglioma
Nasopharyngeal carcinoma	Chondrosarcoma	Squamous cell carcinoma
Lymphoma	Plasmacytoma	Schwannoma
Encepholocele	Encepholocele	Fibrous dysplasia
Meningioma	Meningioma	Metastasis
Schwannoma	Schwannoma	Endolymphatic sac tumours
Fibrous dysplasia	Fibrous dysplasia	
Metastasis	Metastases	

Modified from Policeni & Smoker, 2015; Borges, 2009; and Raut et al., 2012.[1–3]

frontal headaches. Central skull base lesions may cause facial numbness, in addition to headaches and diplopia. If the greater wing of the sphenoid is also involved, central and vertex headaches, loss of the corneal reflex and trismus can develop. In general terms, posterior skull base lesions usually produce deafness and tinnitus at an early stage, associated in some cases with vertigo and disequilibrium. Facial palsy is a characteristic, though typically late, feature of posterior skull base lesions. It can also cause neck stiffness, difficulty swallowing and hoarseness.

Different disease processes may produce different symptoms at the same location; for example, irritation or invasion of the dura by a neoplastic process is more likely to produce pain than benign lesions such as cysts. So, the nature of a lesion is important in determining the symptoms and signs that it may produce, as well as the site and extent of the lesion concerned.

EPIDEMIOLOGY

Posterior skull base lesion, in particular, cerebellopontine angle (CPA) tumours, predominate in any typical skull base practice and the literature reflects this with little epidemiological information available on other conditions. Within the CPA, VSs are the most common lesions and therefore the management of these tumours forms a major part of any skull base surgeon's work. In a series of 1354 CPA lesions, VS accounted for 91.3%, meningiomas 3.1%, epidermoids (cholesteatomas) 2.4%, facial nerve tumours 1.2% and other cranial nerve tumours 0.2%.[4] Less common lesions included intrinsic brain tumours, metastatic tumours, dermoids and lipomas. In another study of 305 CPA tumours, VS comprised 80%.[5] Smaller studies have shown much greater incidences of rare CPA tumours. Kartush et al.[6] reported two patients with rhabdomyosarcoma and one patient with a chondrosarcoma out of a total of 82 cases. Bozorg Grayeli et al.[7] reported 18 patients with paragangliomas and 18 other patients with malignant lesions that included 8 epidermoid carcinomas and 3 chondrosarcomas in a series of only 81 patients. Undoubtedly, the disease spectra reported in the smaller series were skewed by the effects of local factors and personal practices of individual clinicians.

The incidence of VS based on the Danish data has shown a steady increase of VS from 7.8 VS per 1 million population per year in 1976[8] to a peak of 123 VS per 1 million population per year in 2004. From 2004, the incidence seems to have plateaued to 19 per 1 million population per year in 2008 and may reflect the approximate true incidence of VS.[9]

SYMPTOMS OF SKULL BASE DISEASE

Hearing loss

The hearing loss can be conductive, sensorineural or mixed, depending on the precise site of the abnormality. For example, otitis media with effusion may develop as a result of Eustachian tube obstruction or compression by a tumour. Deafness caused by VS is usually of a high frequency sensorineural type and develops in 80–90% of patients,[10] but low frequency sensorineural loss (500 Hz) is characteristic of larger tumours.[10] In the modern era, due to the wide availability of magnetic resonance imaging (MRI) and the heightened awareness of these lesions, VS are generally detected at an early stage when unilateral sensorineural deafness is the only clinical manifestation. The typical history is that of a gradual hearing loss over the course of years, perhaps even decades, as these tumours grow very slowly. A survey of 580 VS patients found 84% of respondents had hearing loss worse in one ear. Of these, 64.8% had progressive hearing loss, 14.7% had sudden hearing loss, and 13% had both progressive and sudden hearing loss.[11]

Sudden sensorineural deafness has been reported as the presenting feature in 6.5–10.2% of patients.[12] The presumed aetiology maybe labyrinthine artery vascular occlusion, a rapid expansion of the tumour due to haemorrhage, oedema or cyst formation, or alterations in inner ear biochemistry.[13] Typically, 30% of VS that present with sudden hearing loss have caused total loss of function in that ear by the time they are diagnosed compared with only 16% of VS with progressive deafness.[14, 15] Patients who present with sudden hearing loss may have symptoms of an upper respiratory tract infection and sometimes also with vertigo. Labyrinthine function tests in these patients often show reduced or absent caloric responses. When other neurological symptoms and signs are present, the true diagnosis is often considerably delayed as clinicians are misled by the plethora of abnormalities. Similarly, the screening of patients with idiopathic sudden sensorineural deafness by MRI, has found a large number of VS. In one series of 295 patients with sudden onset sensorineural hearing loss, VS was found in 4% of patients.[16] In another

series, there were 10 cases (1.85%) of VS diagnosed in 542 cases of sudden onset sensorineural hearing loss.[17]

Almost 90% of skull base paragangliomas present with a conductive hearing loss.[18] A glomus tympanicum may present early with conductive deafness; whereas an advanced glomus jugulare may present with a mixed deafness when the middle and inner ears are both involved. Fifty to 80% of CPA meningiomas produce auditory symptoms, a much lower incidence than in VS.[19] When confronted with a CPA lesion in a patient with normal hearing, pathology other than a VS should be suspected.

Otorrhoea

Infected otorrhoea is such a common symptom that its presence does not immediately suggest serious underlying pathology unless persistently tinged with blood. For this reason, a temporal bone tumour may be overlooked in these cases and delay in diagnosis is common. Extensive temporal bone cholesteatomas and paragangliomas can present with otorrhoea and is reported in 61% of external auditory canal cancers.[20]

Cerebrospinal fluid (CSF) otorrhoea can be caused by bony erosion or insufficiency as a result of trauma, prior surgery, chronic ear infection, or destructive processes such as cholesteatoma or tumour, leading to temporal bone encephaloceles and/or CSF fistula. However, over the last two decades, there has been a significant increase in the number of spontaneous cases, where no discernible cause can be found. Several studies have demonstrated a strong link between obesity, empty sella syndrome and elevated intracranial pressure among these patients. In one series of 89 cases, nearly 40% of the cases occurred without antecedent trauma, chronic ear disease or surgery, and were considered spontaneous.[21] The mean delay between symptom onset and diagnosis was nearly 3 years, and over 10% of patients had symptoms over a decade,[21] as the majority of these patients present with persistent otorrhoea and hearing loss, mimicking chronic otitis media.

Tinnitus

Tinnitus may be either subjective (only audible to the patient) or objective (the clinician can hear the sound). Subjective tinnitus commonly occurs secondary to hearing loss. Less than 10% of tinnitus is due to pulsatile tinnitus,[22] also known as pulse synchronous tinnitus, which is produced by (i) a hypervascular tumour, for example a paraganglioma; (ii) compression of a major vessel by a tumour, for example a jugular foramen schwannoma; or (iii) an arteriovenous malformation or fistula. It is often possible to identify the cause of pulsatile tinnitus with careful examination and imaging, but in up to 30% of cases no cause is found.[23] **Table 99.2** lists the causes of pulsatile tinnitus. Unilateral subjective tinnitus may be the only presenting symptom of VS and warrants further investigation similar to unilateral or asymmetric sensorineural deafness. The incidence of tinnitus with VS can vary from 11% to 63%.[24, 25] Glomus tumours usually present with pulsatile tinnitus (50%) and deafness (30%), but they can occasionally cause otalgia (7%), a feeling of fullness within the ear (4%) and persistent otorrhoea (3%).[26]

TABLE 99.2 Causes of pulsatile tinnitus reported in the literature

Type of lesion	Aetiology
Arterial lesion	Extracranial arteriovenous malformation
	Dural arteriovenous fistulae
	Carotid cavernous fistulae
	Aneurysm of internal carotid artery or vertebral artery
	Fibromuscular dysplasia of internal carotid artery
	Dissection of internal carotid artery
	Atherosclerosis
	Vascular anomalies of ear (persistent stapedial artery, carotid-cochlear dehiscence)
	Vascular compression of VIIIth nerve
	Migraine
Venous lesions	Jugular bulb anomalies (high riding jugular bulb, enlarged jugular bulb, jugular bulb diverticulum)
	Abnormal condylar/mastoid emissary veins
	Diverticulum of sigmoid or transverse sinus
	Stenosis, stricture of segmentation of transverse sinus
Skull base, temporal lesions	Paragangliomas
	Temporal bone tumours (metastasis, basal meningiomas, haemangiomas, Heffner tumours)
	Labyrinthine fistula
	Meningocele/meningoencephalocele
	Otosclerosis
	Superior canal dehiscence
	Cholesterol granuloma
	Paget's disease
	Histiocytosis X
Miscellaneous	Anaemia
	High cardiac output
	Hyperthyroidism
	Benign intracranial hypertension

Data from Hofmann et al., 2013 and Callander, 1920.[22, 27]

Vertigo and dysequilibrium

True vertigo and dysequilibrium affect between 11% and 50% of patients with VS.[24, 25] The character of the vertigo or dysequilibrium produced by VS is extremely variable and tends to differ from those caused by more common vertigo-inducing syndromes in that nausea is absent in up to 63% and described as mild in 18%.[10] However, vertigo or dysequilibrium is the presenting symptom in 32% of intratemporal lesions.[7] A worryingly large number of patients with VS, as many as 10%, may be labelled as having Menière's disease because of the presence of sensorineural deafness, unilateral tinnitus, episodic vertigo

and pressure sensations within the ear.[14] In order to avoid diagnostic delay, all patients with such symptoms require further investigation in the form of MRI.

There have been a number of reports in the literature of patients with skull base and intracranial tumours who have presented with symptoms and signs of benign positional paroxysmal vertigo (BPPV) (e.g. meningiomas, VS, gliomas, lipomas and CPA cholesteatomas).[28] Non-benign positional vertigo should be suspected in patients with: (i) the presence of other signs or symptoms of neurological disorders (e.g. headaches, double vision); (ii) appearance of nystagmus without dizziness in positional testing; (iii) atypical nystagmus, especially downward-beating vertical nystagmus; (iv) poor response to therapeutic manoeuvres; and (v) recurrence of symptoms on at least three occasions.[29] It is therefore recommended that these patients should be investigated by MRI scan.

Tullio phenomenon is sound-induced episodic vertigo and dysequilibrium and has been associated with a number of conditions, including superior semicircular canal dehiscence (SSCD),[30] perilymph fistula[31] and middle ear osteoma.[32] In a series of 65 patients with SSCD, 60 patients had vestibular manifestations and Tullio phenomenon was noted in 90% of patients.[30] Oscillopsia is an unpleasant blurring and jumping of the external world during active and/or passive head movements. If oscillopsia is only present during head movement, the likely underlying cause is bilateral defect in the vestibulo-ocular-reflex (VOR). The more common causes are post-meningitic vestibular failure, gentamicin toxicity or bilateral idiopathic vestibular failure. If oscillopsia comes in brief attacks and is unrelated to head movements, it is usually due to irritative VIIIth nerve and brainstem lesions.[33]

Headache, otalgia and facial pain

The presence of localized cranial or facial pain and neurological symptoms should alert the clinician to the possibility of a skull base lesion. These symptoms may also suggest more advanced disease. Lesions with an intracranial, inflammatory component are more likely to cause intense headache (e.g. giant cholesterol cysts and tumours that obstruct sinuses). In one series of skull base lesions, the incidence of headache was 18%.[10]

Otalgia can be classified into otogenic otalgia, which originates from external, middle and inner ear, and referred otalgia, which arises from pathology outside the ear. Referred otalgia is associated with: (i) auriculotemporal nerve (cranial nerve V3); (ii) posterior auricular nerve (cranial nerve VII); (iii) Jacobson's nerve (cranial nerve IX); (iv) Arnold's nerve (cranial nerve X); (v) greater auricular nerve (C2); and (vi) lesser occipital nerve (C3). Severe otalgia is a cardinal symptom of intratemporal malignancy, particularly carcinoma of the external auditory canal or middle ear.[7]

Trigeminal schwannomas may present with facial pain that can be either episodic, like trigeminal neuralgia, or persistent. However, in a series of 120 trigeminal nerve lesions, the presenting symptom, in decreasing order of incidence, was facial hypoaesthesia or paraesthesia, weak mastication, tics and deafness.[34] More than 75% of these lesions also had other neurological symptoms, particularly other cranial nerve deficits, most notably diplopia caused by a lateral rectus muscle weakness. As many as 11% of VS may have an atypical presentation with other cranial nerve symptoms, pain over the mastoid or headache. On the whole, these tend to be larger tumours.[24] In a series of 55 large VS, over 50% of patients had trigeminal hypoaesthesia, while trigeminal neuralgia occurred in about 5% of patients.[35] Other tumours that may mimic trigeminal nerve tumour and present with facial pain include cavernous sinus meningioma, metastasis to skull base, haemangiopericytoma and chordomas spreading to the cavernous sinus.[36]

Ophthalmic symptoms

Diplopia on lateral gaze due to VIth nerve involvement is a characteristic feature of petrous apex pathology. At the tip of the petrous apex, the VIth nerve is within Dorello's canal, which makes it susceptible to various pathologic processes. Blurred vision can result from involvement of the optic tracts, raised intracranial pressure or lesions of the anterior skull base.

Facial palsy

Facial palsy is a very important presenting feature of intratemporal lesions and is established in 30% of patients before diagnosis.[7] The possible underlying pathologies include VS, meningioma, cholesteatoma, facial nerve tumours (schwannoma, haemangioma, neurofibroma), carcinomas (squamous cell carcinoma, adenoid cystic carcinoma) and paragangliomas. Facial nerve schwannoma is the most common neoplasm to cause facial nerve palsy, but it is responsible for less than 5% of all facial nerve palsies,[37] with geniculate ganglion involvement being the most common. Facial nerve haemangiomas, on the other hand, which were previously considered rare tumours, are now as frequent as facial schwannomas.[38] Clinically, haemangiomas present with facial nerve palsy and hemifacial spasm at an earlier stage than schwannomas.[39] Within the CPA, abnormal facial nerve function is found in 10–50% of patients with meningiomas, compared with less than 5% in patients with VS.[19] Among patients with jugular paragangliomas, facial nerve weakness or paralysis is present in 11–17% of patients.[40, 41] Glomus faciale are an exceedingly rare cause of facial nerve paralysis but should be considered in the differential diagnosis. Malignant involvement of the intratemporal portion of the facial nerve from head and neck malignancies may occur. The prognosis of patients with squamous cell carcinoma of the temporal bone who present with facial nerve paralysis is poor and comparable to that of T4 disease, leading to the modification of the University of Pittsburgh staging system in 2000.[42] Unexplained cases of facial palsy or those that fail to show any sign of recovery always require radiological investigation.

Lower cranial nerve symptoms

Jugular foramen tumours that extend medially and anteriorly can present with loss of bulbar function, hoarseness, dysphagia, dysarthria or shoulder weakness. They often cause these deficits long before the development of auditory or vestibular symptoms. Any isolated or combination of lower cranial nerve palsies should be investigated by imaging the skull base. The sequence of images must be extended to include the full length of the relevant nerve(s). Neuralgias of the lower cranial nerve include the uncommon glossopharyngeal neuralgia and the even more rare laryngeal nerve neuralgia. Glossopharyngeal neuralgia is characterized by attacks of excruciating unilateral pain of short duration of the ear, throat or neck. Pain can be triggered by swallowing, chewing, coughing, yawning or head movements and in about 10% of patients it is also associated with syncope due to reflex bradycardia.[43] There are seven reported cases of schwannoma of tympanic branch of glossopharyngeal nerve (Jacobson's nerve).[44]

RELEVANT MEDICAL HISTORY

The acquisition of a past medical history is essential for all patients. For those in whom a glomus tumour is suspected, symptoms or conditions that may be caused by catecholamine excess must be sought, for example, palpitations, labile hypertension, and so on. It is also important to ascertain the general fitness of the patient, with particular emphasis on their medical fitness to tolerate future management.

FAMILY HISTORY

Familial predisposition to some skull base tumours can happen in the hereditary cancer syndromes. Neurofibromatosis type 1 (plexiform neurofibroma), neurofibromatosis type 2 (VS and meningioma), paragangliomas and von Hippel–Lindau syndrome can all have implications for the patient's family. The genetic basis for these diseases is well established now and while some may arise as a result of spontaneous mutations, a large proportion do not.

EXAMINATION

Otoscopy

Otoscopy of both ears may provide valuable information regarding the underlying aetiology. Examination of the ear canal may demonstrate the presence of a mass or ulcer, indicative of a squamous cell carcinoma (SCC), the most common primary malignancy of the external auditory meatus. SCCs make up 82% of all ear canal cancers; others include basal cell carcinoma, adenoid cystic carcinoma, melanoma, adenocarcinoma, lymphoma and metastases.[10] Glomus jugulare tumours often infiltrate the floor of the external auditory canal and can be detected clinically as an area of hypervascularity and, sometimes, obvious, frank tumour.

A red pulsatile mass behind the tympanic membrane may be a glomus tympanicum tumour, but could also be a meningioma or adenoma. If arising from the hypotympanum with the classical appearance of the 'setting sun', a glomus jugulare tumour is the most likely diagnosis. Overall, paragangliomas are by far the most common tumours affecting the middle ear cleft and they can sometimes be made to blanch by pneumatic otoscopy. It is important to perform this examination with a microscope in order to enable the clinician to determine whether or not the tumour extends below the lower margin of the annulus. If it does not, the lesion is probably restricted to the middle ear or mastoid; if it does, significant skull base infiltration is possible and more detailed imaging is required.

Head and neck examination

In suspected malignant disease of the temporal bone, it is important to rule out a mass over the mastoid, squamous temporal bone, the parotid or the neck, as these may signify either direct spread or metastases.[17] Examination of the neck is also important in patients with glomus tumours to identify synchronous paragangliomas or detect direct extension of a large tumour into the neck (e.g. glomus jugulare or vagale). Auscultation should be carried out over the upper neck and mastoid and an audible bruit should be taken as being indicative of underlying pathology.

Neurological examination

A thorough neurological examination is essential as it may demonstrate subtle signs that are indicative of the underlying pathology and its probable extent. The minimum assessment must detail the function of the cranial nerves and the state of the optic discs, and test cerebellar function. A more complete examination, including the peripheral nervous system, may be indicated in some cases with extensive intracranial or coexistent spinal disease (e.g. NF1 and NF2). Similarly, the skin must be scrutinized for signs of freckling or pigmented patches in those suspected of having NF2.

The most useful screening tests for optic nerve disorders are visual acuity, visual fields, pupillary reflexes and fundoscopy. Fundoscopy may indicate the presence of incipient or established hydrocephalus. A careful examination of eye movements will reveal any involvement of the nerves supplying the extraocular muscles.

It is essential to appreciate that asymmetry of corneal sensation may be the only sign of trigeminal involvement. Reduced corneal reflexes, facial hypoaesthesia and weakness in the muscles of mastication are more obvious signs of trigeminal dysfunction. Trigeminal deficits can result from primary trigeminal lesions, petrous apex lesions, extensive infralabyrinthine lesions and CPA tumours. Facial hypoaesthesia is present in up to 4% of patients with skull base lesions[6] and loss of the corneal reflex is an important sign in patients with VS, indicating that the tumour may be more than 2 cm in diameter.

Facial weakness is present in up to 30% of all skull base lesions and clinicians should grade the degree of

weakness according to a recognized scale such as the House–Brackmann (HB) system.[18] The majority of skull base tumours do not present with a complete paresis but an asymmetry, particularly at rest. In fact, only 15% of patients present with a HB grade IV weakness or worse.[6] In VS, only about 7% of patients have abnormal facial nerve function at the time of presentation.[5] A diagnosis of VS in the presence of facial weakness should be made with caution.

Asymmetric palatal elevation or an abnormal gag reflex suggests IXth and Xth cranial nerve palsies. Laryngeal examination must be carried out to assess vocal cord function and laryngeal competence. The tongue should be examined for deviation on protrusion, wasting and fasciculation, all of which are signs of a XIIth nerve lesion. Palsies of the IXth, Xth, XIth and XIIth nerves are usually caused by infralabyrinthine disease, though occasional translabyrinthine lesions can involve the jugular foramen, its contents and the surrounding areas. Parapharyngeal tumours, particularly paragangliomas, may involve the sympathetic plexus around the internal carotid artery and cause a Horner syndrome (ptosis, meiosis, anhydrosis and enopthalmus). In a series of 36 patients with glomus tumours, 30 had deafness and tinnitus, 13 had facial weakness, 13 had dysphagia and hoarseness (IXth and Xth), 12 had shoulder weakness (XIth) and 14 had tongue weakness and fasciculation (XIIth).[45] Lower cranial nerve weakness with associated skull base lesions may occur in particular distributions giving rise to various syndromes, such as Horner syndrome, Collet-Sicard syndrome, Vernet syndrome or Villaret's syndrome (**Table 99.3**).[43]

TABLE 99.3 Syndromes of lower cranial nerves associated with skull base lesions

Syndrome	Definition	Aetiology
Collect-Sicard syndrome	Palsy of the IX, X, XI and XII cranial nerves	Glomus jugulare
		Skull base metastasis (breast, prostate, renal, lung)
		Hypoglossal schwannoma
		Neck fibrosarcoma
		Jugular foramen neuroma
		Skull base osteomyelitis
		Haemangiopericytoma of skull base
		Thrombosis of sigmoid-jugular complex
		Carotid artery dissection
		Head/C1 injury
Vernet syndrome	Palsy of the IX, X and XI cranial nerves	Osteolytic metastatis of petrous pyramid
		Skull base fracture
Villaret's syndrome	Palsy of the IX, X, XI, XII and ipsilateral Horner's syndrome	Paragangliomas
		Carotid artery dissection
		Skull base metastasis

Data from Finsterer and Grisold 2015.[43]

Vestibular examination

Spontaneous and induce nystagmus are common findings in neurotologic disorders. Examination of the eyes demonstrates spontaneous nystagmus in up to 46% of patients with VS.[10] The examination for induced nystagmus includes positional testing (Dix–Hallpike), head shaking and looking for either sound- or pressure-induced nystagmus (Fistula sign). Elimination of optic fixation by using Frenzel's glasses may improve the sensitivity of these tests. Balance and coordination can be tested in the clinic using a variety of tests. Romberg and Unterberger testing can indicate an uncompensated peripheral vestibular lesion. A positive Romberg's test can indicate abnormalities with the dorsal columns, whereas Unterberger's will induce turning towards a paretic and away from an irritative lesion of the labyrinth. Tandem gait may be instructive and any patient who can tandem walk backwards has excellent balance. Cerebellar testing includes coordination tasks, such as finger-nose-finger, heel-shin and rapid alternating motion and the patient is observed for dysmetria or dysrhythmia. The presence of limb dysmetria or dysdiadochokinesia is a useful indicator of cerebellar disease.

INVESTIGATIONS

Audiology

All patients with lateral skull base tumours should have an assessment of their hearing. Air- and bone-conduction pure-tone audiometry is the minimum requirement. The addition of speech audiometry to this protocol is preferable and mandatory whenever hearing preservation surgery is contemplated. It is worth noting that about half (49%) of all skull base patients have severe to profound deafness at the time of presentation and a third (33%) mild to moderate hearing loss.[7] Auditory brainstem responses (ABR) are no longer documented routinely. In the past it was used in a diagnostic role to determine which patients required more detailed investigation. MRI has now superseded that role.

Vestibular function tests

Caloric testing is by far the most common vestibular function test described in relation to skull base lesions and in particular with reference to VS. In general terms, they are non-specific and, like evoked response audiometry, cannot be utilized usefully in the diagnosis or screening for VS. Caloric asymmetry (>25%) may be present in up to 66% of patients with CPA tumours and this can further increase with tumour size.[10] Similarly, electronystagmography (ENG) and videonystagmography (VNG) can demonstrate abnormal function in up to 50% of all skull base lesions,[7] but these tests are seldom employed routinely.

Tests of facial function

Electroneurography (ENoG) has been used both pre- and post-operatively as a predictive test in patients with

skull base lesions. Kartush et al.[6] subjected a series of patients with tumours to ENoG and found that a significant reduction in response did not correlate with post-operative facial nerve function. However, in patients with VS, a correlation was found between pre-operative ENoG amplitude and tumour size. In other situations, a 20% or greater reduction in the amplitude of the pre-operative ENoG correlated well with facial nerve involvement by cholesteatoma or non-VS tumours.[6] Electromyography, maximal stimulation testing and electrogustometry have also been described and used to assess the degree of facial function prior to surgery, but have been shown to be of little clinical relevance.

Radiology

The advent of high resolution imaging modalities has totally revolutionized the investigation and management of patients with skull base lesions. There are four principal reasons for imaging: (i) screening; (ii) investigation of suspicious symptoms or signs; (iii) surgical planning and navigation; and (iv) for monitoring size, extent or recurrence of lesions.

The investigation and targeted screening tool of choice for VS is MRI. At first, gadolinium-enhanced MRI was employed, but this has now been superseded by fast spin echo T2-weighted images. Daniels et al.[46] reported the diagnostic outcome of screening 1070 patients with unilateral sensorineural deafness with MRI. From this group of patients they found 56 VS, 27 other CPA lesions, 29 inner ear lesions and 15 lesions affecting the brain parenchyma. Data from Iceland has shown that, about 10% of VS diagnosed were an incidental finding on imaging.[47] Diffusion-weighted imaging (DWI) can increase the conspicuity of skull base lesion and can be used to differentiate between malignant from benign lesions. DWI has also proven to be useful for identifying recurrent tumours, and differentiating these from post-treatment changes.[48] Non-echo-planar imaging DWI can be used to detect recurrent cholesteatoma and confers a positive predict value of 93 to 100%.[49, 50]

The purposes of imaging are not simply to confirm the presence of an abnormality but also to discern characteristics that might indicate the nature of the problem. Equally important are the assessment of size, relationship to other structures and detection of imminent complications, for example, hydrocephalus. In some conditions, NF2 being the best example, additional scans of the entire neuraxis are required to detect other tumours.

In several instances, both computed tomography (CT) and MRI are complementary and essential. There are a number of good examples to illustrate this point. In the assessment of facial nerve tumours, CT portrays the extent of bone destruction and gives an indication of the speed of the destructive process, while MRI can suggest whether the lesion is a schwannoma or an angioma. Similarly, the assessment of SCC of the temporal bone would be incomplete without both CT and MRI as the combination is highly predictive of the actual operative findings.[46]

MRI and CT are adequate for the evaluation of most patients with skull base lesions, but some may also require carotid and vertebral artery angiography as well. Presently, selective angiography can be undertaken by intra-arterial catheterization and injection with contrast into every feeding artery but, if far less detail is required, magnetic resonance angiography (MRA) gives considerable information in a non-invasive way. The assessment of patients with glomus tumours almost always needs a combination of CT, MRI and angiography. CT demonstrates the extent of temporal bone destruction. Gadolinium-enhanced MRI is exquisitely sensitive and will detect even very small glomus tympanicum tumours, while in larger parapharyngeal tumours flow voids give the characteristic 'salt and pepper ground' appearance that is so suggestive of paragangliomas. Subsequent carotid angiography then confirms the diagnosis, defines the blood supply and determines the integrity of the circle of Willis and potential for cross-flow should the carotid have to be sacrificed. It may also demonstrate the target vessels for pre-operative embolization to minimize intra-operative blood loss.

Cone-beam CT (CBCT) is being increasingly used in anterior and lateral skull base imaging. It is an advancement in CT imaging that provides relatively high isotropic spatial resolution of bony structures with a reduced radiation dose reported to be 60% of conventional CT scans.[51] CBCT provides much better images of the ossicular chain within the middle ear, and inner ear imaging is sufficient to diagnose most malformations and dysplasia, traumatic lesions, labyrinthine wall erosion or dehiscence.[52, 53] A low sensitivity to metallic artefacts makes it the imaging of choice in the follow up of cochlear implants. However, its lacks soft tissue contrast and therefore in cases of tumoral, septic or hematic soft tissue infiltration, HRCT and MRI are mandatory.

Positron emission tomography (PET) and single photon emission computerized tomography (SPECT) can be extremely helpful in certain circumstances where biopsy is difficult or potentially dangerous. PET is useful in identifying metabolically active tissues and can differentiate between post-therapeutic changes, for example, granulations and scars from recurrent and residual disease. By contrast, SPECT is 50% more effective at detecting skull base destruction than CT and also shows specific uptake in glomus tumours followed by rapid 'wash-out' of the radiotracer that suggests a benign vascular tumour.[22] This form of dynamic imaging is not possible with MRI. However, both PET and SPECT have limited resolution and can fail to detect small lesions.[23]

In some circumstances isotope scans can be helpful. The detection of multiple paragangliomas or metastatic disease has been facilitated by radionucleotide scintigraphy with metaiodobenzylguanidine (MIBG) or indium-11-octreotide.

General investigations

For the most part, other investigations are limited to those required to assess suitability or fitness for surgery. However, 24-hour urine collection for excreted catecholamines (vanillylmandelic acid (VMA)) is a wise precaution

in patients with paraganglioma, as it can detect a secreting tumour that could cause problems during surgery. The initial screening for paraganglioma should also include measurements of plasma-free metanephrines and urinary fractionated metanephrines.[54]

BEST CLINICAL PRACTICE

- ✓ The cornerstone of diagnosis remains imaging, which can provide an accurate 'tissue' diagnosis in many instances.
- ✓ Subsequent management, undertaken by a multidisciplinary team in a tertiary referral unit, depends on characteristics of the lesion (aetiology, site and extent) together with patient factors (age, general fitness, severity of symptoms).
- ✓ Management consists of simple surveillance, surgery and/or other therapeutic modalities, such as radiotherapy.

FUTURE RESEARCH

- ➤ Due to the rarity of skull base lesions, most of the literature is level 3–4 evidence. There is a place for larger, multicentre trials, in order to provide level 1 and 2 evidence for the investigation and management of these challenging conditions.

KEY POINTS

- Skull base lesions are infrequently encountered by general otorhinolaryngologists and require a high index of suspicion in order to avoid diagnostic delay.
- They may present with symptoms that could be mistaken for a more common otological pathology.

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CHAPTER 100

VASCULAR ASSESSMENT AND MANAGEMENT

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords: skull base surgery, embolization and interventional neuroradiology. The evidence is generally at level 3 or 4, with some animal studies at level 1 evidence. However, there is always the possibility that the results and conclusions drawn from these animal studies may not be reproducible in humans.

INTRODUCTION

The skull base is anatomically complex, particularly with respect to its blood supply. Many skull base tumours are either intrinsically hypervascular or secondarily involve the arteries and veins of the brain that enter and exit the cranium through the skull base. Angiography and interventional techniques have a pivotal role in the investigation and treatment of these conditions. Pre-operative embolization aims to devascularize hypervascular tumours selectively in order to improve intra-operative conditions while preserving blood supply to surrounding normal tissues. Permanent occlusion of the internal carotid artery (ICA) when possible enables the safe removal of those tumours that have an intimate relationship with the ICA.

It must be appreciated that angiography and intervention carry risks. The potential benefits that they offer must outweigh the risks of their possible complications. These risks differ from operator to operator and can be minimized by the combination of experience and detailed knowledge of relevant anatomy, pathology and procedural techniques. These techniques are certainly not for the occasional operator.

CATHETER ANGIOGRAPHY

Indications and technical considerations

Diagnostic angiography is an essential part of the pre-operative evaluation of skull base tumours, particularly if neurointerventional endovascular treatment is being considered. As well as evaluating the suitability of a tumour for embolization, it also provides the surgeon with information regarding the anatomy of the Circle of Willis and the likely tolerance to potential carotid sacrifice.

Primary assessment is made by computed tomography (CT) and magnetic resonance imaging (MRI) in order to determine the following features:

- exact tumour location
- relationship to surrounding bone, nerves, major blood vessels, brain and dura
- pattern of tumour extension
- degree of vascularity
- presence of intratumoural vessels (MRI)
- vascular territories involved by the tumour.

Diagnostic angiography and subsequent intervention can be performed in one session under general anaesthesia. Owing to the complex nature of these lesions, it is not uncommon to perform diagnostic angiography under local anaesthetic as a separate procedure prior to intervention. A size '4' French sheath and catheter is used and is introduced by the trans-femoral route. Subtraction images, fluoroscopy and a map of the vascular structures – the 'road map' – are acquired. The road map superimposes fluoroscopic images onto a previously acquired image of the vessels. This enables the guidewire and catheter to be imaged in relation to the vessels and facilitates safe navigation.

The angiographic protocol is tailored according to the vascular territory in which the tumour is located. At the very least, both ICAs and external carotid arteries (ECAs) are examined. Vertebral artery injection and selective ascending pharyngeal artery injection may be considered, the latter in view of its extensive supply to the skull base, temporal bone and dura. For any skull base tumour that is related topographically to a segment of the ICA, determination of the intracranial collateral circulation at the level of the Circle of Willis is absolutely mandatory. A comment is always made on the anatomy of the anterior and posterior communicating arteries, which may be best visualized by cross compression. This is achieved by compressing the carotid artery on the contralateral side to the vessel catheterized to visualize the anterior communicating artery, and compressing the ipsilateral carotid artery during a vertebral artery injection to visualize the posterior communicating artery. Temporary impediment to flow encourages flow of contrast across these communicating arteries.

A more detailed angiographic assessment is required for tumours in which embolization is being considered. This includes identification and characterization of all feeding pedicles, a search for collateral supply to the tumour, dangerous arterioarterial anatomoses or any arterial supply to cranial nerves, skin or pinna. In addition, it is also important to assess the vascular composition and angioarchitecture of the tumour as well as its venous drainage or any dural venous sinus involvement. Features of tumour angioarchitecture include compartmentalization, flow characteristics and arteriovenous shunts (**Figure 100.1**).[1]

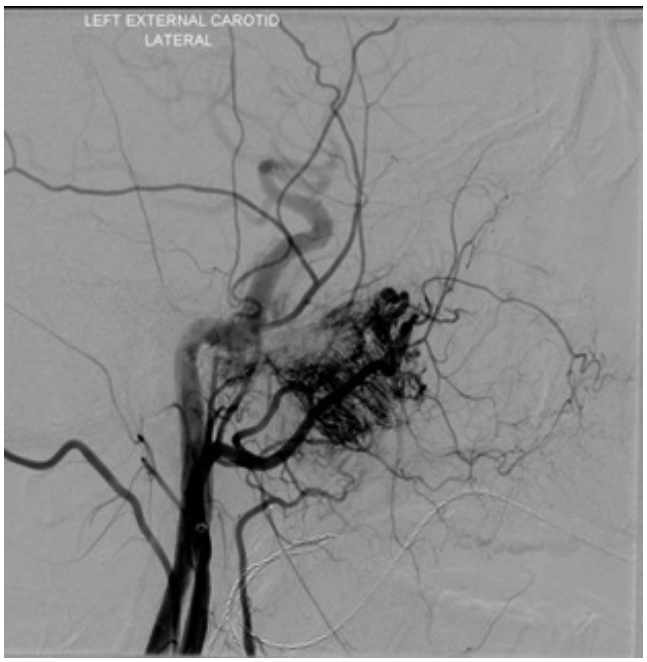

Figure 100.1 External carotid angiogram of an extensive glomus jugulare tumour; superselective angiogram of one compartment of the tumour demonstrating compartmentalization of arterial supply, typical of glomus tumours.

Risks

Carotid angiography carries a risk of permanent neurological deficit of less than 1%.[2] Other complications include arterial dissection, haematoma of the groin and reactions to contrast media that can range from a relatively minor itch to anaphylactic shock. The risk of contrast-induced nephropathy has been shown to be low even in patients undergoing emergency endovascular treatment for stroke.[3] Patients should be warned that it is normal to experience transitory unpleasant sensations or pain during the procedure, particularly following more selective catheterization and contrast injection of ECA branches.

INTERNAL CAROTID ARTERY TEST AND PERMANENT OCCLUSION

Tumours of the skull base may be intimately related to the ICA or may receive significant arterial supply from extradural ICA branches. These features can limit the surgeon's ability to obtain a complete resection. It is in precisely these cases that assessment of the cerebral circulation to tolerate permanent sacrifice of a major vessel is warranted. Given that this is a high-risk procedure, it should only be undertaken if occlusion is intended or likely.

The balloon test occlusion (BTO) is performed under local anaesthetic as this enables assessment of both motor and sensory function, speech and visual fields. Following femoral arterial puncture, a guiding catheter is placed in the ICA. The patient is fully heparinized. A soft micro-balloon is inserted through the guiding catheter into the ICA to the point of anticipated permanent occlusion and then inflated. The occlusion test lasts approximately 30 minutes, during which both clinical and angiographic evaluation is performed, the latter via a second catheter into the contralateral ICA via the contralateral femoral artery. Clinical tolerance of BTO would imply a reduced risk with parent vessel sacrifice, but does not eliminate the risk of stroke, which can happen due to haemodynamic and thromboembolic causes. When crossflow through the Circle of Willis is evaluated, any delay in transit of contrast medium on the side of the occlusion is also assessed. This is best achieved by comparing the appearance of the cerebral veins in the cerebral hemispheres. Adequacy of collateral blood flow can also be assessed by a number of methods such as transcranial Doppler ultrasound, single photon emission CT, xenon CT, pharmacologically induced hypotension, CT or MR perfusion techniques, measurement of arterial sump pressure, EEG and transcranial Doppler ultrasonography.[4, 5] A recently published study in 150 subjects utilizing BTO to assess adequacy of collateral circulation reported a stroke risk of 16% and TIA risk of 8% with parent vessel sacrifice; however, another smaller study in 31 patients reported no neurologic sequelae with parent vessel occlusion in patients who passed both BTO and single photon emission computed tomography (SPECT).[6, 7]

Permanent balloon occlusion of the ICA can be achieved by replacing the non-detachable balloon with a detachable balloon, which is positioned in precisely the same location as the temporary balloon. There are also other devices which can be used to occlude major vessels such as coils, Amplatzer vascular plug (AVP) and the microvascular plug. The AVP can be delivered through the guiding catheter to occlude vessels such as the common carotid artery, the ICA or the vertebral artery while the microvascular plug can be delivered through a microcatheter to occlude intradural vessels.[8, 9]

An external–internal carotid bypass should be considered for those patients who fail the test procedure yet need carotid occlusion. In this way the risk of stroke is reduced after permanent balloon occlusion.[10] In the event that there is doubt about the need to sacrifice the carotid, a balloon occlusion test should be performed prior to surgery and intra-operative permanent ICA occlusion can precede tumour resection if carotid involvement is found during the operation.[11]

EMBOLIZATION OF SKULL BASE TUMOURS

Indications

The main indication for pre-operative embolization of skull base tumours is to reduce intra-operative blood loss and improve visualization of the operative field during surgery. This may translate into shorter operative times and lead to a safer, easier and more successful surgical procedure. Embolization is rarely curative but improves the rate of radical tumour removal and reduces the surgical complication rate and the incidence of recurrence. Other indications for embolization include palliation of symptoms by inducing a reduction in size of the tumour and control of haemorrhage that has been caused by tumour erosion of a vessel wall.

The aim of tumour embolization is complete obliteration of the vascular bed within the tumour. Simply occluding the feeding arteries with emboli may result in the recruitment of a new collateral blood supply and make removal of the tumour even more difficult. Tumours with a rich vascular bed are most suitable, a feature that is usually indicated by the degree of contrast enhancement seen on CT or MRI. This is not always the case as increased contrast enhancement can be produced by accumulation in extravascular intercellular spaces. It does not necessarily indicate high vascularity but certainly cannot be ignored.

Skull base tumours that may benefit from pre-operative embolization include meningiomas, glomus tumours, chordomas, sarcomas, oestrogenic tumours, metastases, olfactory neuroblastomas and juvenile angiofibromas.

Catheters and embolic materials

Microcatheters enable superselective catheterization and embolization of individual feeding arteries and are generally less than 0.02 inches in diameter. Two basic types of microcatheter are used: flow-directed catheters and over-the-wire catheters. Flow-directed catheters take advantage of antegrade blood flow and are therefore more suitable for tumours that have high flow arteriovenous shunts, whereas over-the-wire catheters require the use of a guidewire and are employed in tumours with slower blood flows. While smaller microcatheters can access smaller vessels, their luminal diameter limits the size of the embolic agent that can be injected.[12] Embolic agents can be classified into mechanical agents, particulates and liquids.

Mechanical agents include coils and Gelfoam and are used in vessel occlusion proximal to the tumour. Gelfoam powder is derived from pork-skin gelatin. It is a pliable material that can be cut to appropriately sized particles and is used for more proximal vessel occlusion, often following embolization of distal vessels with particulate material.

Particulate agents achieve penetration into the tumour and can further be classified into non-spherical agents such as polyvinyl alcohol (PVA) particles and spherical particles such as Embosphere® and Embozene®. Spherical particles are the most widely used particulate embolic agents for embolization of skull base tumours and are available in a range of sizes from 40 µm to 1300 µm. Spherical particles offer more predictable embolic penetration compared to PVA.[13] Smaller particles have the ability to penetrate into vessels with a diameter of 40–60 µm. However, the use of particles with sizes in the 40–140 µm range, although more effective in inducing tumour necrosis, is also more likely to cause ischaemia of normal tissue.[14] Evidence also shows that they have a longer occlusive effect.[15–17] Particles smaller than 80 µm may risk cranial nerve palsy, likely due to occlusion of vasa nervorum, while angiographically non-visualized arterial anastomoses would be in the 50–80 µm size range. It is therefore recommended to use particles more than 150 µm.[18]

Liquid embolic agents include dehydrated alcohol, acrylate glues such as N-butyl-cyanoacrylate (NBCA), Onyx® Liquid Embolic System (ev3 Neurovascular, Irvine, CA) and Precipitating Hydrophobic Injectable Liquid (Microvention, Inc, CA). The main application of dehydrated alcohol is the percutaneous treatment of haemangiomatous malformations of the head and neck while other agents are used in embolization of cerebral arteriovenous malformations and dural fistulae. NBCA is also sometimes useful for embolization of tumours exhibiting rapid arteriovenous shunting, in which particles may pass directly though the tumour to the lungs. Liquid embolic agents can also be injected into the tumour upon direct puncture and have been suggested to decrease intra-operative blood loss.[19]

Technical considerations and complications

Embolization is preferably performed under general anaesthesia. This guarantees optimal working conditions by reducing unwanted patient movement, caused by pain,

and enabling haemodynamic monitoring. Local anaesthetic may be adequate for short, relatively painless procedures but requires a cooperative patient.

The vascular anatomy of the skull base is complex. It is important that the likely sources of arterial supply are considered thoroughly, together with any common anatomical variants and potential pathways of communication between the intra- and extracranial arteries, before embolization is attempted. As a general statement, any foramen, especially those carrying a cranial nerve, can be expected to contain a potential site of communication between these circulations. In addition, at each segmental level, residual metameric communications can be expected, particularly between the vertebral arteries and the ascending cervical, deep cervical, ascending pharyngeal and occipital arteries. Unless actively sought, these small vessels are easily overlooked, even on high-quality angiography. Even a small volume of embolic material in these vessels can lead to cranial nerve palsies or stroke. The operator should also be aware that in the course of embolization, as blood flow towards the target decreases, the direction of flow in collateral pathways may reverse and result in flow through extra- to intracranial anastomoses that were not evident on the initial angiogram. Repeated angiograms may have to be performed in the course of the procedure to exclude this possibility.

Other serious complications include blindness and skin necrosis. Blindness can usually be attributed to inadvertent injection of embolic material into the ophthalmic artery through anastomoses with the middle meningeal artery, other arterioarterial anastomoses or unrecognized variant origins. Skin necrosis is caused by embolic occlusion of cutaneous branches of the ECA. The pinna is particularly susceptible, and embolization in the anterior and posterior auricular arteries should be conducted with extreme care.

Three commonly treated tumour types – paragangliomas, juvenile nasopharyngeal angiofibromas and meningiomas – are now discussed in more detail.

PARAGANGLIOMAS

Angiography has several potential roles in the management of paragangliomas. They are:

- identification of the blood supply and flow dynamics to the tumour
- delineation of the venous drainage and demonstration of intraluminal tumour in the internal jugular vein
- assessment of the Circle of Willis for possible carotid occlusion
- detection of synchronous tumours.

Carotid occlusion should be considered when:

- imaging shows extensive destruction of the horizontal portion of the carotid canal (Fisch class C3)
- tumour is present within the foramen lacerum and cavernous sinus (Fisch class C4)
- there is the presence of large caroticotympanic and/or cavernous branches from the ICA.

A number of studies have shown that pre-operative embolization of paragangliomas provides significant benefit. Comparison of surgical data for embolized and non-embolized tumours indicates that pre-operative embolization of paragangliomas of 3 cm or more with PVA is safe, facilitates surgery and results in significantly reduced operative bleeding, shorter operative times and decreased surgical risk.[20–22] Liquid embolic agents such as Onyx or PHIL™ can also be used for transarterial embolization; they can also be injected with direct tumoural pucture.[23, 24] In a study comparing transarterial particulate embolization with direct puncture and percutaneous embolization of carotid body tumours with Onyx, a significant reduction in intra-operative blood loss was observed. Blood transfusion requirement, operative time, and complications were also less in the direct puncture group. Despite the evidence, it is not a universally accepted view and, ultimately, the decision whether to embolize depends on the location and extent of tumour as well as local practice and experience of the surgeon and interventional neuroradiologist.[25–29]

Knowledge of the angioarchitecture of these tumour types is required before embolization. The typical angiographic appearance is that of a tumour with enlarged feeding arteries, an early and intense, slightly inhomogeneous tumour blush, and early appearing draining veins. Histological studies have shown that there is a centripetally orientated system of intratumoural arterioles with a diameter of approximately 90 µm at the tumour periphery and of 300–600 µm in the centre. There are intratumoural arteriolo-arteriolar anastomoses as well as arteriolar-venous shunts.[30] This arrangement of vessels may prohibit the use of smaller particles due to the potential risk of distal migration of emboli into the systemic circulation. NBCA, a polymerizing glue, is indicated in certain cases. The majority of paragangliomas exhibit a multi-compartmental blood supply, with an arterial supply and venous drainage confined to a single area. Separate injections of embolic agent have to be made into each feeding artery to achieve complete transarterial embolization (**Figure 100.2**). Encapsulation of the tumour restricts recruitment of feeders from adjacent territories.[31]

All paragangliomas are supplied by branches of the ascending pharyngeal artery. Its inferior tympanic branch supplies glomus tympanicum tumours, the neuromeningeal branch supplies glomus jugulare tumours and the musculospinal branch supplies glomus vagale and carotid body tumours. The latter acquire an additional blood supply from the carotid body artery that arises directly from the carotid bifurcation. These tumours splay the ICA and ECA. Glomus vagale tumours, on the other hand, displace both ICA and ECA anteriorly and receive additional blood supply from muscular branches of the occipital artery. Contributions from meningeal arteries such as the mastoid artery, a meningeal branch of the occipital artery, indicate intracranial

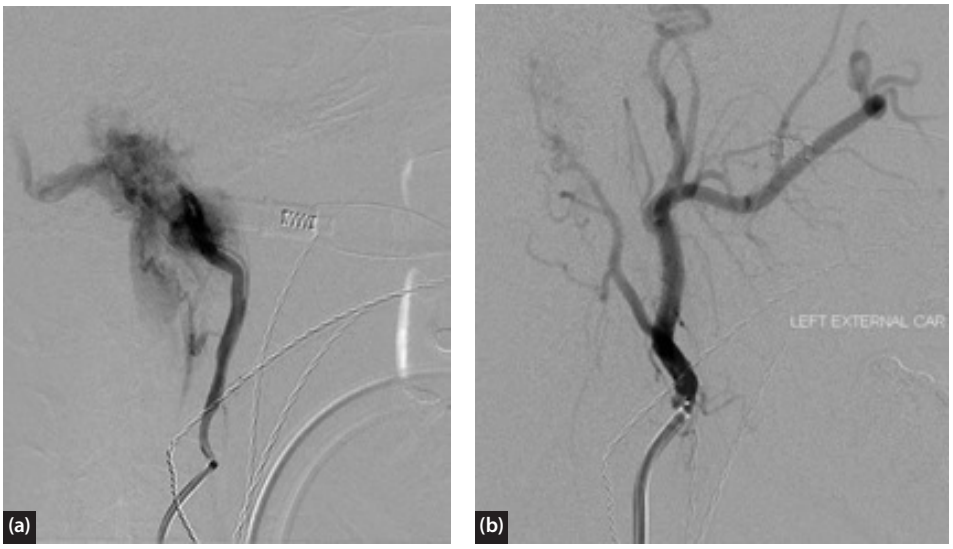

Figure 100.2 Complete particle embolization of extensive glomus jugulare tumour. **(a)** Pre-embolization; **(b)** post-embolization.

extradural extension. Supply from the anterior inferior or posterior inferior cerebellar arteries indicates intradural spread, and in these cases the risk of posterior fossa stroke precludes embolization.

JUVENILE NASOPHARYNGEAL ANGIOFIBROMAS

Angiofibromas are non-encapsulated fibrovascular tumours that arise in the region of the sphenopalatine foramen. Although benign, they show an aggressive growth pattern and spread through foraminae or fissures. Their vascular components consist of endothelial-lined vascular spaces that are without muscular layers. As a result, these tumours tend to bleed profusely and patients may present with epistaxis.

Pre-operative embolization is an important tool for reducing intra-operative blood loss and is considered by many to be essential. Several retrospective studies, albeit small, have illustrated the effectiveness of pre-operative embolization of these tumours. Prior to the use of endovascular techniques, average intra-operative blood loss was reported to be approximately 2000 mL; this has now been reduced to less than 1000 mL by the routine use of embolization.[32, 33]

Angiographic assessment of juvenile angiofibromas prior to embolization aims to define the blood supply, vascular composition and venous drainage of the tumour as well as any dangerous anastomoses. The distal internal maxillary artery, together with its sphenopalatine and pterygovaginal branches, supplies the tumour at the site of origin in the anterior nasopharynx and posterior nasal cavity. Larger tumours that extend into the sphenoid sinus, infratemporal fossa or parapharyngeal space receive additional supply from further ECA branches, namely the accessory meningeal, ascending pharyngeal and ascending palatine arteries. Further supply from branches of the internal carotid and vertebral arteries are features of advanced tumours and, in some, there may be bilateral blood supply. Other angiographic features of these tumours include an early vascular blush that is intense but inhomogeneous and persists until the late venous phase. Once the feeding vessels have been identified, embolization of the tumour compartments can be performed. Permanent balloon occlusion of the ICA may be indicated in those rare tumours that extend into the cavernous sinus (**Figure 100.3**).[34, 35]

Direct percutaneous punctures may again be done in juvenile angiofibromas for embolization with Onyx prior to surgery. A study comparing transarterial embolization to direct percutaneous embolization with Onyx found significantly lower intra-operative blood loss and red blood cell transfusion requirements.[36]

MENINGIOMAS

Meningiomas are often hypervascular although this feature is somewhat dependent on histological subtype, the angioblastic and transitional types tending to be more vascular than fibroblastic or syncytial types (**Figure 100.4**). Psammomatous subtypes are sometimes almost avascular. Tumoural calcification is more common in histological subtypes associated with less vascularity.

There is usually a dual blood supply to meningiomas. A radial pattern of vessels derived from meningeal arteries penetrate the tumour from its base while an additional supply may be derived from its cerebral surface through pial cortical arteries arising from the ICA. The relative contribution of meningeal and pial arterial supply is variable, ranging from an exclusive meningeal supply to a dominant pial supply. Embolization is most effective when an exclusive meningeal supply is present.

The location of the meningioma determines its blood supply and may also be a good predictor of suitability for devascularization. Some of these tumours present to otolaryngologists or require their input for removal, for example frontobasal meningiomas that arise in the

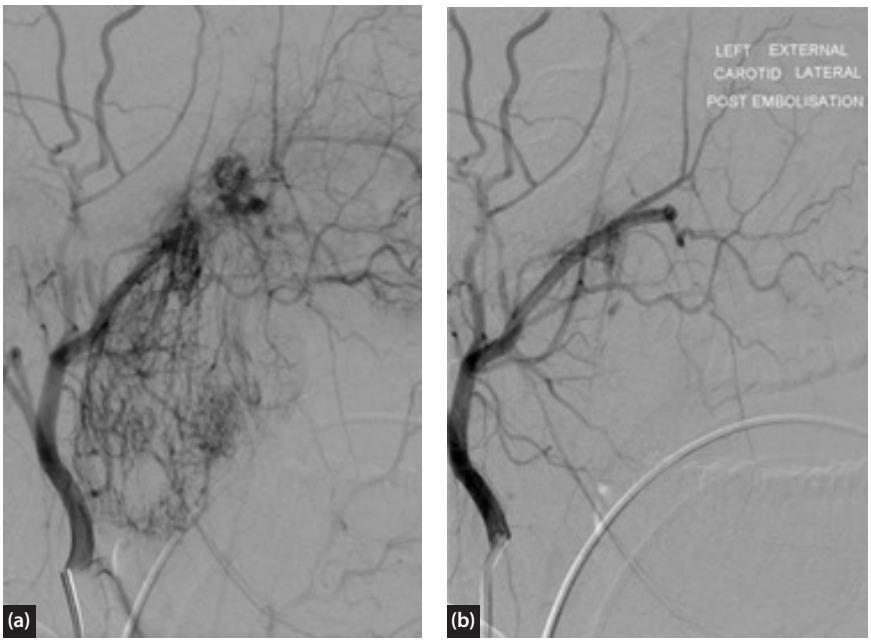

Figure 100.3 (a) Selective angiogram of angiofibroma; (b)post-embolization.

orbital roof, olfactory groove and planum sphenoidale. Orbital roof meningiomas are supplied by the anterior frontal meningeal artery, which arises from the recurrent meningeal branch of the second portion of the ophthalmic artery and from anterior branches of the middle meningeal artery. Meningiomas of the olfactory groove and of the planum sphenoidale receive their dural supply from the anterior and posterior ethmoidal arterial branches of the ophthalmic artery. The small size of these dural branches, the unfavourable vessel geometry and the dangers associated with the ophthalmic artery territory are all factors that limit the role of, although do not preclude, embolization of frontobasal meningiomas.

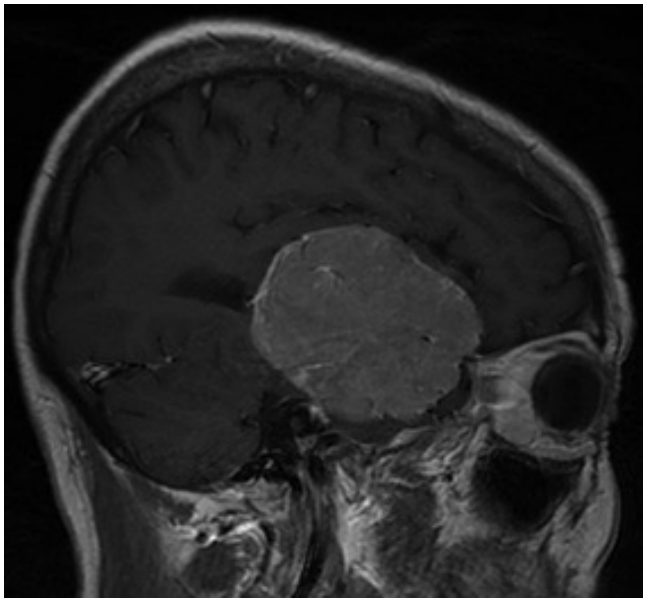

Figure 100.4 Post contrast T1 Sagittal image showing the large vascular skull base meningioma.

The efficacy of embolization can be assessed with gadolinium-enhanced MRI, which may show loss of flow signal void, decrease in contrast enhancement and new areas of non-enhancement indicating tumour necrosis.[37–39] The optimum timing of surgery following embolization is a matter of some debate. Some surgeons prefer to perform surgery within hours of embolization to avoid the effects of acute peritumoural oedema developing, while others prefer to let tumoural necrosis take place, a process that usually takes about four days.[40, 41] It is thought that corticosteroids given immediately before embolization limit tumour swelling.

Many studies have now reported the efficacy of embolization in meningiomas showing effective embolization, reduction in blood loss to tumour volume and improved surgical and functional outcomes (**Figure 100.5**).[42–49]

Complications

In addition to the technical complications already described, there have been reports of tumoural haemorrhage and hemiparesis secondary to tumour oedema.[45, 50] Risk factors include large tumour size and the presence of cysts. Vessel damage and subsequent arteriovenous shunting due to catheter and guidewire manipulation at a sharp bend of a feeding artery has also been reported.[51, 52] A review of 36 studies involving 459 patients reported two mortalities, once again highlighting that these procedures should only be done by experienced interventionalists.[53] It is worth nothing that reported complication rates in meningioma embolization have fallen from as high as 21% to 6% in the more recent literature.[54]

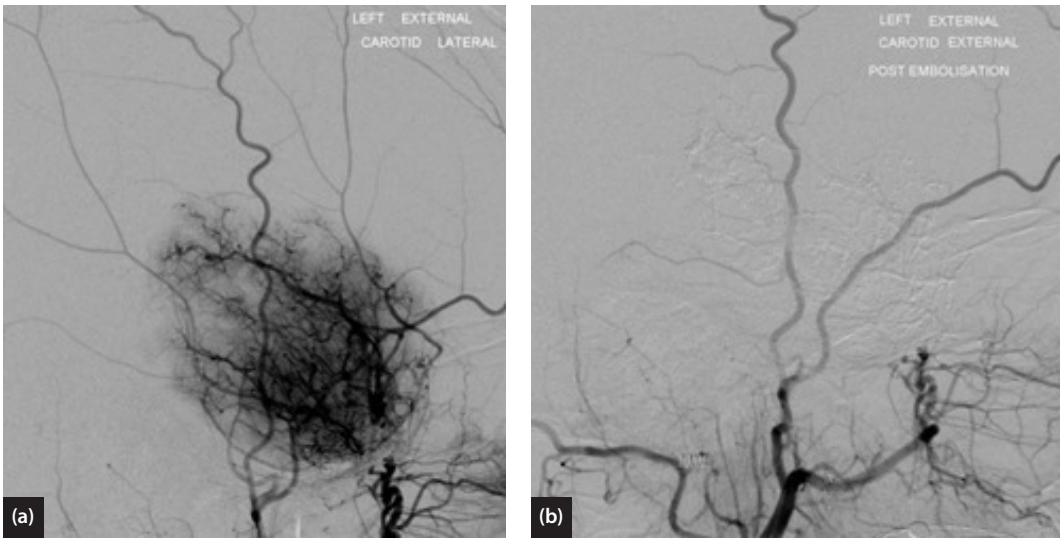

Figure 100.5 Complete particle embolization of extensive skull base meningioma. **(a)** Pre-embolization; **(b)** post-embolization.

BEST CLINICAL PRACTICE

- ✓ Angiography should be undertaken whenever a skull base tumour surrounds or is closely adherent to the ICA.
- ✓ Angiography is mandatory for vascular skull base tumours.
- ✓ Trial balloon occlusion or crossflow studies should be undertaken before any surgery in which the carotid artery might be lost.

KEY POINTS

- Both carotid angiography and embolization carry risks and the patient should be made aware of them.
- The angiographic protocol is tailored to the particular needs of the patient and their tumour type.
- Interventional techniques can make some tumours operable and decrease morbidity.

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CHAPTER 101

NATURAL HISTORY OF VESTIBULAR SCHWANNOMAS

Mirko Tos†, Sven-Eric Stangerup and Per Caye-Thomasen

SEARCH STRATEGY

Data in this chapter may be updated by a prospective and continuous data collection of data from all patients in Denmark, diagnosed with a unilateral sporadic vestibular schwannoma since January 1976, and supported by a Medline search using the keywords: acoustic neurinoma and vestibular schwannoma (VS): anatomy, pathology, histopathology, epidemiology, incidence, growth and natural history.

INTRODUCTION

Unilateral vestibular schwannoma (VS) (**Figure 101.1**) is a benign tumour arising from abnormally proliferative schwann cells, which envelope the lateral portion of the vestibular nerve in the internal acoustic meatus. At a consensus conference[1] it was determined that the term 'acoustic neuroma', often used in the past to describe this entity, should be replaced by the more accurate term 'vestibular schwannoma'.

The aetiology of VS is not known. Recent advances in molecular biology indicate that a defect of chromosome 22q may be responsible for the development of both the unilateral sporadic VS and the bilateral VS in neurofibromatosis type 2.

Because the tumour develops in the nerve sheath, it compresses rather than invades the nerve on which it arose, thereby leaving a plane between the nerve fibres and the tumour. This feature facilitates dissection of the meatal portions of most tumours at surgery. As the VS grows, it gradually fills all the internal acoustic meatus (**Figure 101.2a, b**) and eventually protrudes out of the porus (**Figure 101.2c**).

Bone resorption is an active, slowly progressive process, caused presumably by increased vascularization, fibrosis and adhesions in the tumour area, where the pressure from the tumour, due to its growth, plays an important role. The degree of bone resorption of the internal acoustic meatus varies in VS. Some large and giant tumours have minor or modest bone resorption, some small- and medium-sized tumours have extensive resorption extending inferiorly as far as the cochlear aqueduct and superiorly to the middle fossa dura. Extra-meatal expansion of the tumour into the relatively large and empty pontine cistern initially develops silently (**Figure 101.3**). Growth and extension in this direction causes some displacement and stretching of the VIIth and VIIIth cranial nerves on the anterior aspect of the tumour and of the anterior inferior cerebellar artery (AICA) on the inferior aspect. Angioneogenesis is visible at surgery, with new small vessels running from the porus to the extrameatal portion of the tumour. After further growth, the tumour expands sufficiently to touch and compress the cerebellum and trigeminal nerve. During this process, the VIIth and VIIIth nerves are thinned or ribboned, become compressed and even more stretched. At the same time, the internal acoustic meatus continues to become more and more widened. Further growth and expansion causes compression and displacement of the brainstem and the fourth ventricle, which leads gradually to hydrocephalus.

CLASSIFICATION OF SIZE

Reporting the size of VS has always been a great problem. The main problem has been the inclusion and addition of the intrameatal element to the overall size of the tumour.

† deceased.

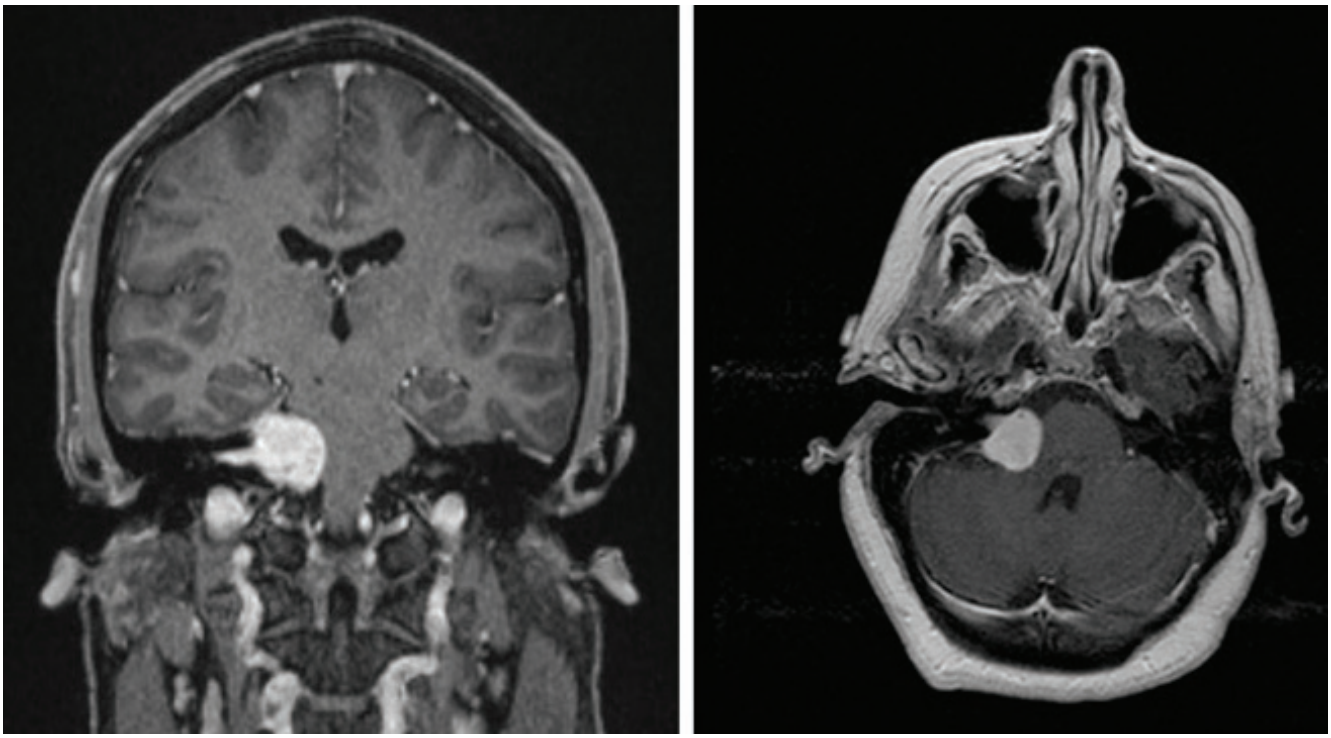

Figure 101.1 MRI scan showing a 3 cm right intra- and extrameatal vestibular schwannoma, touching the brainstem.

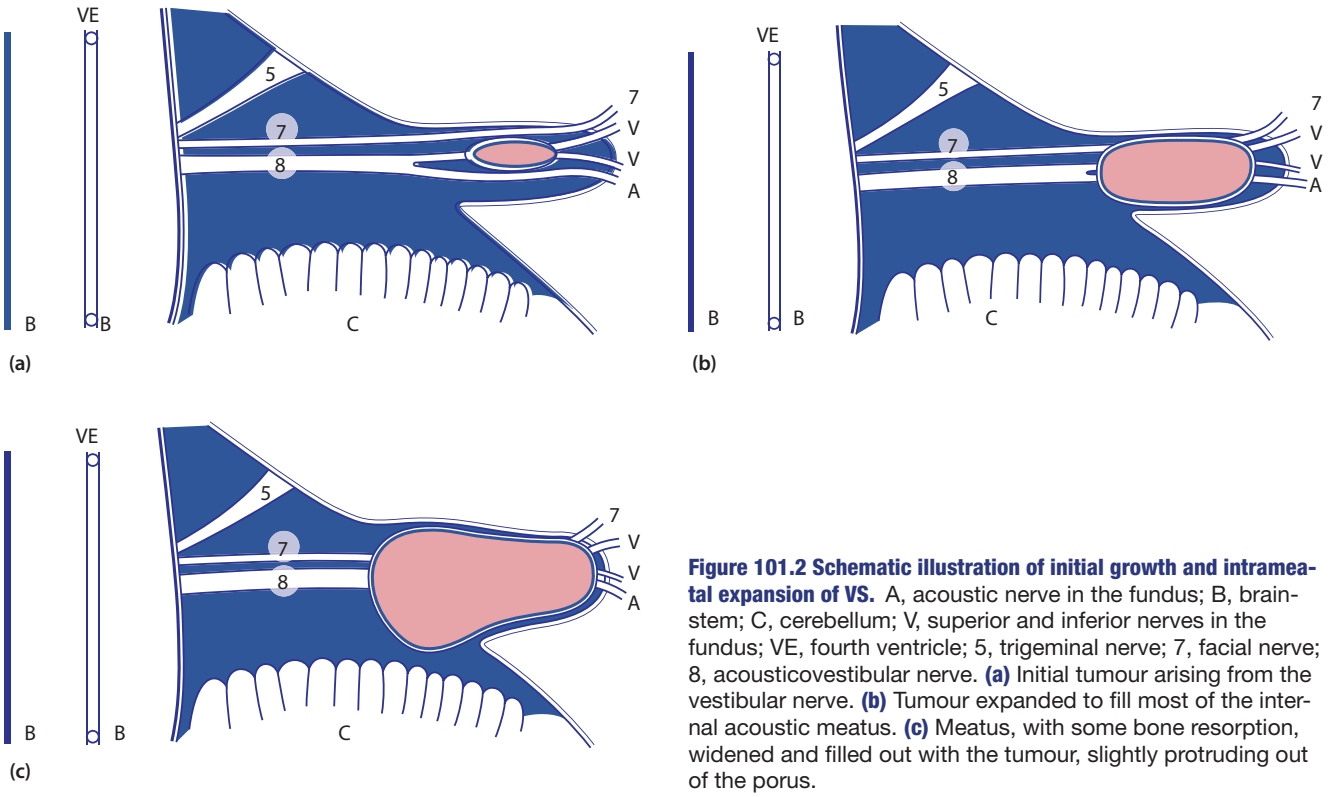

Figure 101.2 Schematic illustration of initial growth and intrameatal expansion of VS. A, acoustic nerve in the fundus; B, brainstem; C, cerebellum; V, superior and inferior nerves in the fundus; VE, fourth ventricle; 5, trigeminal nerve; 7, facial nerve; 8, acousticovestibular nerve. **(a)** Initial tumour arising from the vestibular nerve. **(b)** Tumour expanded to fill most of the internal acoustic meatus. **(c)** Meatus, with some bone resorption, widened and filled out with the tumour, slightly protruding out of the porus.

At the Consensus Meeting on Reporting Systems on Vestibular Schwannoma in 2003,[2] the classification scheme shown in Table 101.1 was proposed and recommended for adoption. It is based on the size of the largest extrameatal diameter and it was further recommended that a note should be made if the fundus is empty or filled by tumour and whether the VS is cystic. If the tumour is entirely within the meatus without any extension out of the porus, the term 'intrameatal' should be used. The extrameatal size of such a tumour is zero.

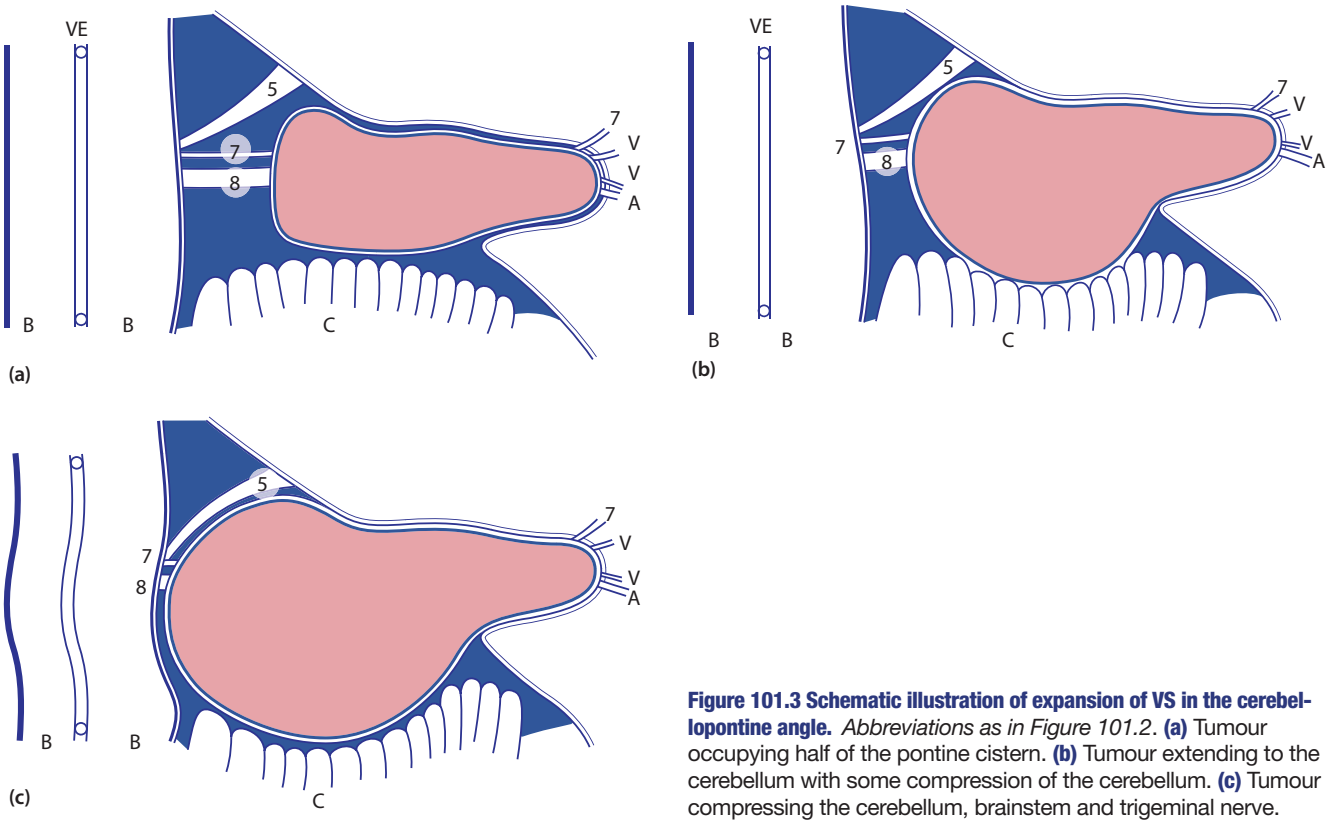

Figure 101.3 Schematic illustration of expansion of VS in the cerebellopontine angle. *Abbreviations as in Figure 101.2*. **(a)** Tumour occupying half of the pontine cistern. **(b)** Tumour extending to the cerebellum with some compression of the cerebellum. **(c)** Tumour compressing the cerebellum, brainstem and trigeminal nerve.

TABLE 101.1 Classification of VS according to size

Classification	Grade	Size (mm)
Grade 0	Intrameatal	0
Grade 1	Small	1–10
Grade 2	Medium	11–20
Grade 3	Moderately large	21–30
Grade 4	Large	31–40
Grade 5	Giant	>40

SYMPTOMS

In more than 90% of patients, the first symptom is unilateral progressive hearing loss with or without tinnitus. In 5–10% of cases, hearing loss is sudden and may be profound. Classically, there is a slowly progressing retrocochlear hearing loss, which is more pronounced in the higher end of the auditory range and is often accompanied by poor speech discrimination. However, it is salutary to note that the hearing was good with normal speech discrimination in 17% of our patients. The caloric test was normal in 8% of our patients, significantly more often (14%) in medium-sized than large tumours. Except for the hearing, symptoms caused by a VS, depend largely on its size. Seventeen per cent had nonacoustic first symptoms[3] such as vertigo, trigeminal or cerebellar symptoms.

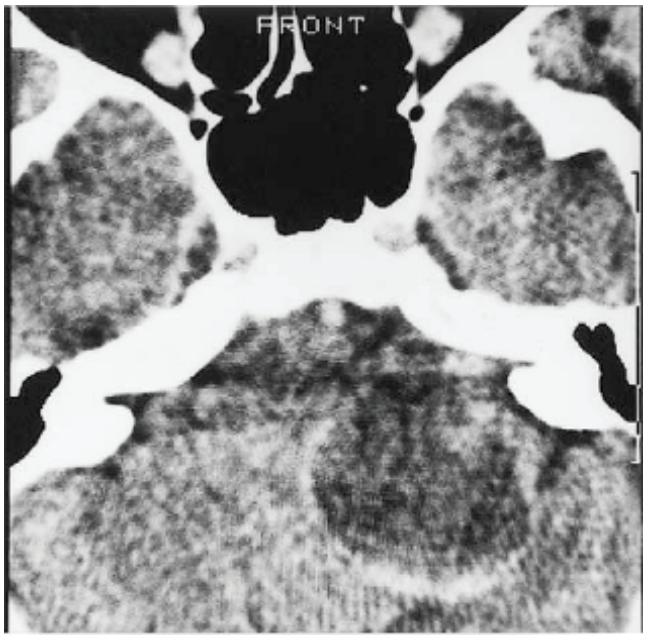

Figure 101.4 A large cystic tumour with a large hypodense area on CT scan.

CYSTIC VESTIBULAR SCHWANNOMA

Cyst formation within VS (Figure 101.4) is seen regularly and is easily detected by MR. This has been thought to represent degenerative change or coalescence

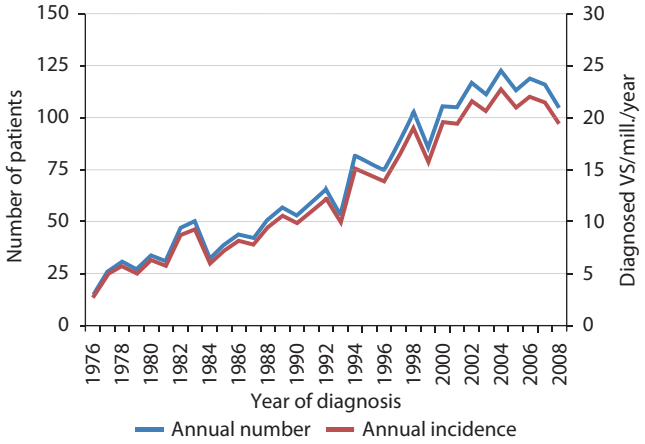

Figure 101.5 Annual number of diagnosed VS and corresponding annual incidence/million/year.

of microcysts in Antoni A tissue. More recently, it has been shown that cystic tumours contain an increased amount of Antoni B tissue that is surrounded by a membrane-like structure composed of Antoni A type cells.[4] Therefore, three criteria are required to be present before a tumour can be termed 'cystic'. First, there must be a hypodense/hypointense area on CT/MR. Second, perioperative identification of the cystic elements must be achieved and, third, there must be histological verification of S-100 positive membrane. Using these criteria, in our series of 773 resected VS, in the period 1976–96, 5.7% were cystic, making an incidence of 0.4 cystic VS per million population per year.

Several studies have shown that the surgical outcome of cystic VS is less favourable than that of solid tumours of comparable size. Furthermore, the cystic elements expand, causing displacement of the brainstem and compression of the fourth ventricle and hydrocephalus. The large size of these tumours at diagnosis, and their cysts, which can increase in size dramatically, have been considered by some to represent a contraindication for treatment by either radiotherapy or a 'wait and scan' policy.

DIAGNOSIS

Until the mid 1980s, diagnosis of VS was based on X-ray, X-ray tomography and computerized tomography. The first magnetic resonance imaging (MRI) scanner became available in most countries from 1980 and over the following years more MRI scanners were introduced. Today, VSs are diagnosed by MRI, except in a few patients with metallic implants, extreme obesity or claustrophobia. At diagnosis, 20% of the patients had a purely intrameatal tumour and in 80% the tumour extended into the cerebello-pontine angle. Nowadays, all patients with unilateral audiovestibular symptoms that cannot be readily explained should proceed to MR imaging with gadolinium enhancement.

Incidence

Several centres have reported an increasing number of diagnosed VS during the last several years.[5,6] In the period from January 1957 to July 1976 the incidence of VS in Denmark was estimated to be 5.4 VS per million per year. This estimate was based on publications from Danish neurosurgical departments.[7,8] Since 1976, the number of diagnosed VS has been constantly increasing from 3 VS per million per year in 1976[9] until an apparent peak in 2004, with 123 diagnosed tumours (23 VS per million per year, **Figure 101.5**).

The increase in the number of diagnosed VS has plausibly been caused by several factors, the most important being continuously improving access to diagnostic equipment (i.e. MRI). Another cause may be heightened symptom awareness amongst the general population and especially among the elderly, as a longer and healthier lifetime may be expected in the developed countries. Better and more widespread audiological testing equipment, as well as easier access to diagnostic imaging, may in addition have heightened the awareness of a possible VS amongst general practitioners and otolaryngologists.

Tumour size at diagnosis

From a mean extrameatal size of about 30 mm in the mid-1970s, the tumour size at diagnosis has decreased continuously over the decades to a mean size of 10 mm in the most recent period from 2003–08. In the 1970s, no purely intrameatal tumours were diagnosed, whereas the large and giant tumours constituted about 40% of all the tumours. Now, the intrameatal tumours constitute 33%, whereas the large and giant tumours constitute about 6% of the diagnosed tumours (**Figure 101.6**).

Age at diagnosis

The age of the patient at the time of diagnosis of the VS has been slowly increasing from 49 years in 1976 to 58 years in 2008 (**Figure 101.7**).

Analyzing the diagnostic age distribution throughout the 33-year period, the number of patients aged 40 years or younger has remained almost unchanged. Thus, the increasing number of diagnosed VS is primarily constituted by patients belonging to the age group older than 50 years.

In the beginning of the period covered, 81% of the patients were 60 years or younger and only 4% older than 70 years. At the end of the period, 59% of the patients were younger than 60 years and 12% older than 70 years.

In the age group of 40 years or younger, the mean tumour size at diagnosis was 23 mm. The size decreased with increasing age, and was 13 mm in the group of patients 70 years or older, even though the mean tumour size decreased throughout the period.

GROWTH PATTERN AND HEARING

The natural history of VS growth is enigmatic. The tumour may grow continuously or only to a certain size,

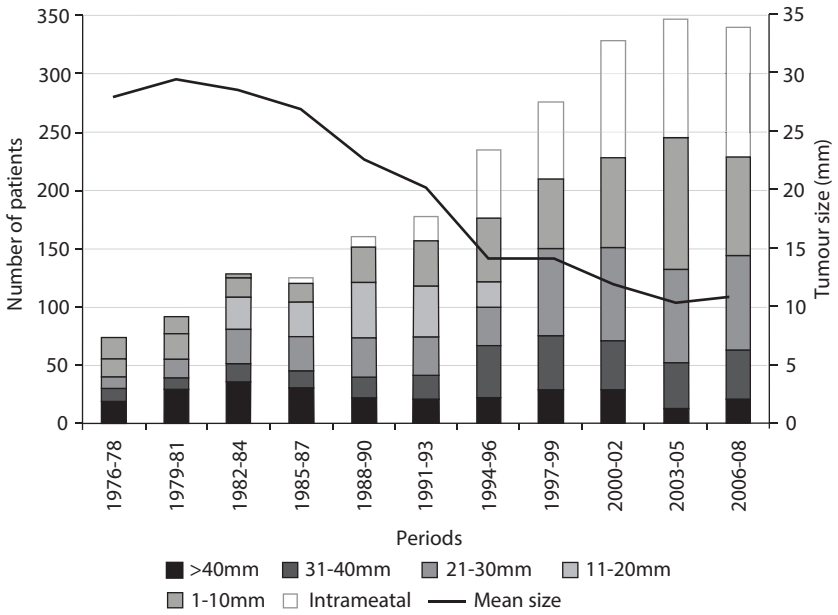

Figure 101.6 Mean size (mm) of diagnosed VS through the period 1976 to 2009.

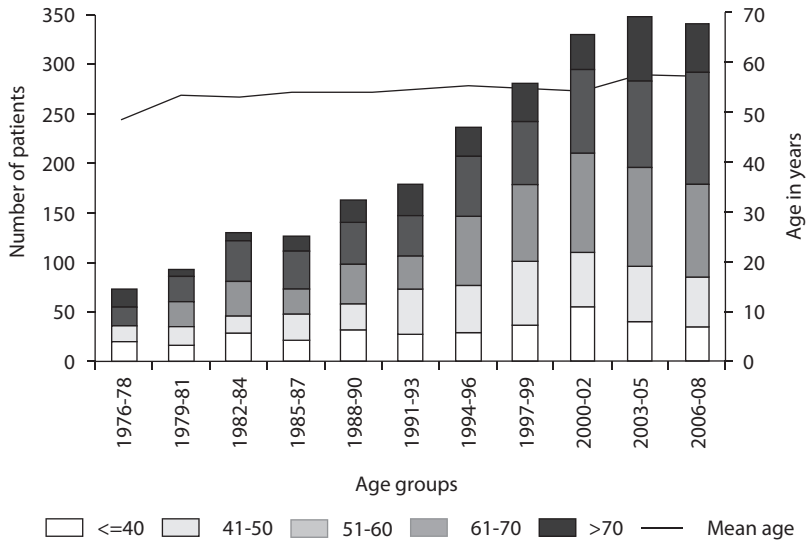

Figure 101.7 Mean age at diagnosis of VS through the period from 1976 to 2009.

followed by stagnation or even shrinkage. Progressive growth in the cerebello-pontine angle will eventually lead to compression of the brain stem and/or the cerebellum, occlusion of the fourth ventricle and subsequently incarceration.

The percentage of growing tumours has been reported to vary from 30% to 90%,[10–27] depending at least in part on the length of the observation period. Most growth observation studies have, however, surveyed a relatively small number of patients and have further been subject to considerable referral bias and patient selection bias, by only including very old patients, patients unwilling to undergo surgery or patients not eligible for surgery due to significant concurrent disease.

Tumour growth

Determined tumour growth rate may depend on the diagnostic tool (CT versus MRI),[13] the method of measurement (number or plane of dimensions assessed)[28] and criteria for the determination for growth (number of millimeters).

The present criterion for growth of a purely intrameatal tumour was growth to extrameatal extension.

For intra- and extrameatal tumours, growth was defined as an increase of at least 3 mm in the largest extrameatal diameter, in order to rule out inter-individual measuring variability and error due, for example, to unaligned scanning images. Largest diameter measurement is adequate when merely questioning absolute growth,[18] which is the

parameter relevant for a clinical assessment and decision-taking, as it is the absolute size that determines the risk of brain stem or adjacent cranial nerve compression. The adequacy of largest diameter measurement has, however, been questioned by one group of investigators, advocating Bayesian tissue classification and partial tumour volume segmentation on MR images for control of tumour growth.[26] Volumetric determination of relative growth rate is definitely mandatory when addressing basic science issues, as a tumour may grow in only one or two dimensions and as, for example, 2 mm growth in a 6 mm tumour is dramatically different from 2 mm growth in a 26 mm tumour, considering, for example, the rate of cellular proliferation.

Growth of intrameatal tumours

Of the intrameatal tumours, 83% remained purely intrameatal during the observation. In 17%, the intrameatal tumour increased in size to extrameatal extension. Of the tumours that grew, 64% grew during the first year, 23% during the second year, 5% during the third year and 8% during the fourth year of observation. No tumour growth occurred after the fifth year of observation (**Figure 101.8**). There were no significant differences in growth between male and female patients or between different age groups.

Growth of extrameatal tumours

Of the extrameatal tumours, 1% decreased in size, 70% remained unchanged and 29% increased in size during observation. Growth was determined during the first year of observation in 62%, during the second year in 26 %, during the third year in 10 % and during the fourth year of observation in 2%. No tumour growth occurred after the fifth year of observation (**Figure 101.8**).

There was no significant difference in the proportion of patients with growth between male and female patients, age groups or diagnostic tumour size. Importantly, the growth occurrence or rate is not related to gender or age, which is in agreement with a recent publication addressing potentially predictive parameters for tumour growth.[29]

Spontaneous change of hearing level

The hearing quality may be evaluated by the pure tone hearing and by speech discrimination.

In order to classify the pure tone hearing, the pure tone average (PTA) is most frequently used. The PTA is calculated as the mean sum of the hearing level (dB) at the frequencies 500 Hz, 1000 Hz and 3000 Hz, or 500 Hz, 1000 Hz, 2000 Hz and 4000 Hz.

The speech discrimination (SD) test is performed in a quiet environment, using word list scoring by phonemes correctly repeated at the most comfortable hearing level.

Over the period 1976–2008, the PTA at diagnosis has improved from 60 dB in 1976 to 50 dB in 2008 (**Figure 101.9**). In the same period the SD at diagnosis has improved from 30% in 1976 to 60% in 2008 (**Figure 101.10**).

Different hearing classifications systems may be used to evaluate the overall hearing acuity.

The AAO-HNS classification

The American Academy of Otolaryngology – Head and Neck Surgery (AAO-HNS) classification of the hearing level is as follows: class A: PTA < 30 dB and SD >= 70%; class B: PTA < 50 dB and SD >= 50%; class C: PTA > 50 dB and SD >= 50%; and class D: SD < 50% (**Figure 101.11a**).[30] Most authors consider AAO class A as good and preservable hearing.

At diagnosis, 19% of the patients had AAO class A hearing on the tumour ear. The hearing deterioration during observation is seen in **Figure 101.12**. After one year, 26% had lost class A hearing, whereas this was the case for 45% after 5 years and 54% after 10 years.

The word recognition scoring (WRS) classification

The word recognition scoring (WRS) classification[31] has: class 0: designates patients with 100% speech discrimination; class I: SD = 99% to 70%; class II: SD = 69% to 50%;

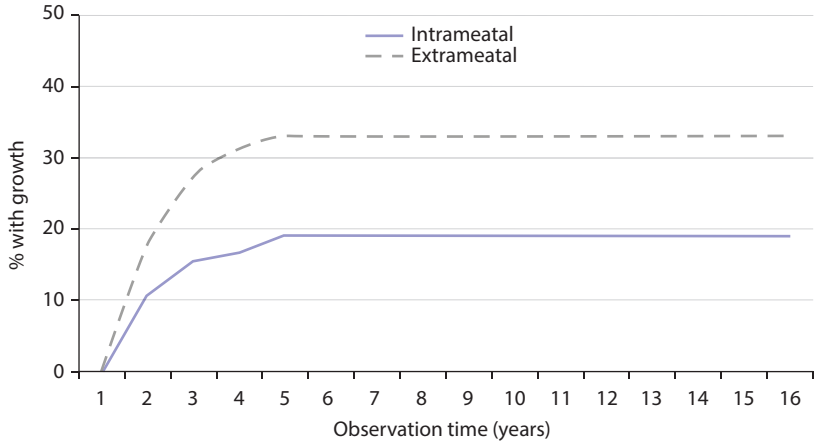

Figure 101.8 Nelson-Aalen curve of growth of intrameatal and extrameatal VS.

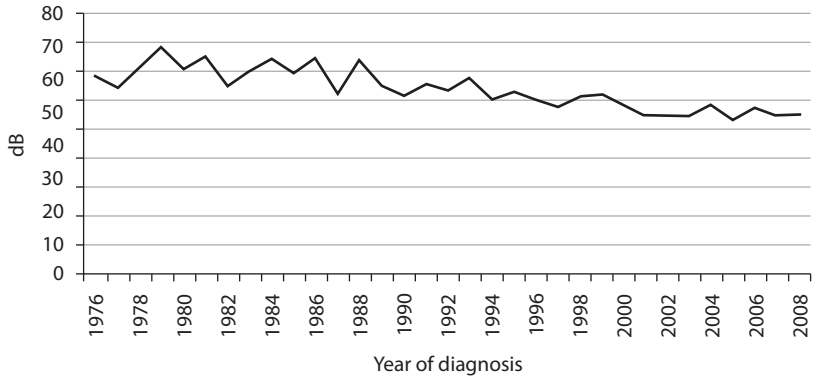

Figure 101.9 Mean PTA (dB) at diagnosis through the period from 1976 to 2008.

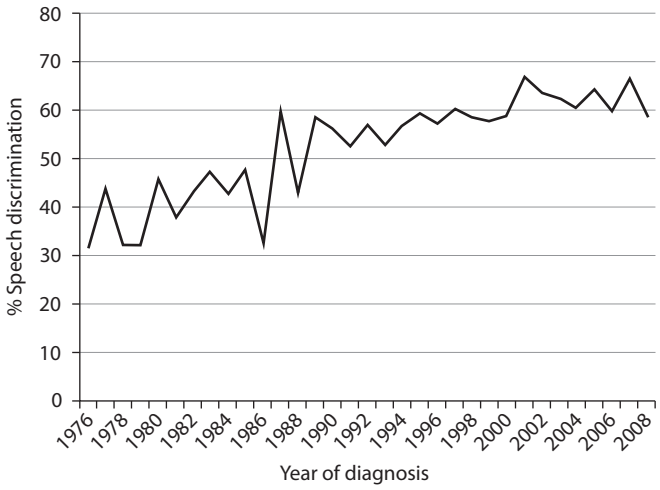

Figure 101.10 Mean speech discrimination at diagnosis through the period from 1976 to 2008.

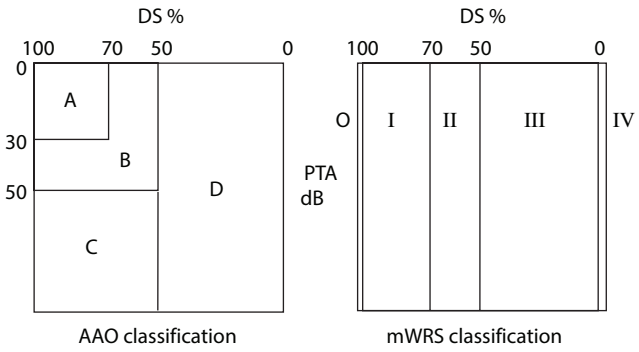

Figure 101.11 AAO and WRS classification of hearing quality.

class III: SD=49% to 1%; and class IV: SD=0% (Figure 101.11b). The hearing is considered good if the SD score is 70% or better (WRS class 0 or I).

At diagnosis, 17% had good hearing (WRS class 0) on the tumour ear, and 36% had WRS class I.[32] In the group with 100% SD at diagnosis (WRS class 0), 3% had lost good hearing after the first year. After 5 years, 12% had lost good hearing and after 10 years 31% had lost good hearing. In patients with even a minor loss of speech

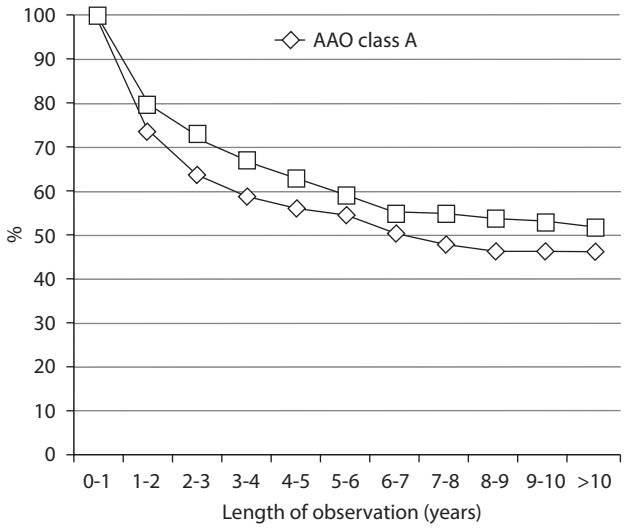

Figure 101.12 Preservation of good hearing (AAO class A or WRS class 0/1) during observation, for patients with good hearing (AAO class A or WRS class 0/1) at diagnosis (*n*=932).

discrimination at diagnosis (WRS class I), 18% had lost good hearing after 1 year, 60% after 5 years and only 38% of the patients with a speech discrimination loss between 1% and 10% maintained good hearing (Figure 101.13).

SPONTANEOUS COURSE OF HEARING AND ACTIVE TREATMENT

Hearing preservation after surgery is usually reported as the results after 1 year, and is reported to vary between 24% and 83%.[33–35] In a study from House Ear Clinic from 2003,[36] the long-term hearing preservation after surgery was evaluated over a five-year period in 38 patients. Of these 38 patients, 61% had AAO-HNS class A-B hearing after surgery. Over the subsequent five-year period, 30% lost class A-B hearing. The great variability in the success rate of hearing preservation after surgery may be explained by difficulties in comparing data, due to variable definitions of good or serviceable hearing and different reporting of the size of the operated tumour. Some surgeons include the intrameatal

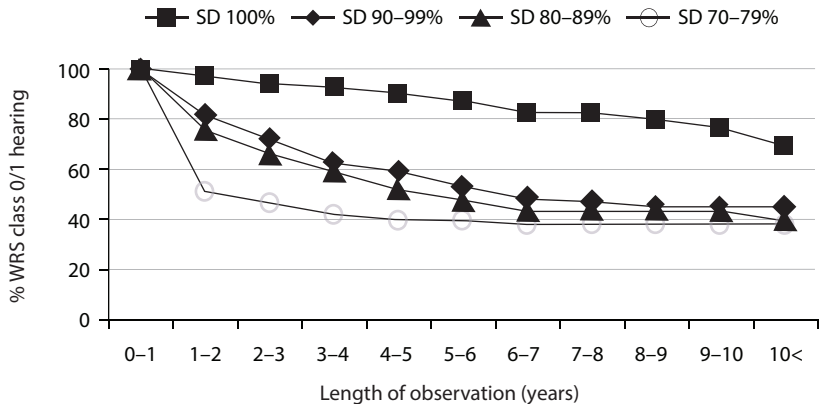

Figure 101.13 Preservation of good hearing (WRS class 1) during observation related to the different SD groups at diagnosis (*n* = 932).

part of the tumour in size measurement, while others measure the extrameatal part only. Most authors agree that the chance of hearing preservation is significantly reduced for tumours with an extrameatal diameter of more than 15 mm, while others have good results of hearing preservation in large tumours.[37] Hearing preservation surgery may be performed by the middle fossa approach, the retrolabyrinthine approach or by the retrosigmoidal approach. Comparing the approaches, it seems that the results are better by the middle fossa approach in small and intrameatal tumours.

The hearing preservation results after radiotherapy is reported to vary between 33% and 79%.[38–40]

During 'wait & scan', 73% of patients with AAO-HNS class A hearing at diagnosis preserve good hearing after one year of observation. According to the WRS classification, 87% of patients with WRS class 1 hearing at diagnosis maintain good hearing. The spontaneous outcome is emphasized further by patients with 100% SD at diagnosis (WRS class 0), in which 99% of tumour ears preserve good hearing after 1 year, whereas 91% of patients preserve good hearing after 5 years of observation, and 68% after 10 years.[32]

The main clinical implication of the hearing results is that the results indicate that it may be possible to identify patients who have a good chance of maintaining good long-term hearing spontaneously, by focusing on the speech discrimination at the time of diagnosis. Thus, a small non-growing tumour with 100% discrimination should be allocated to 'wait and scan', since it is highly likely that the tumour will not grow, and the patient will preserve good long-term hearing spontaneously and thus have an outcome superior to radiotherapy or hearing preservation surgery.

A TREATMENT STRATEGY BASED ON THE NATURAL HISTORY OF TUMOUR GROWTH AND HEARING

As more, primarily small and medium-sized VSs are diagnosed and need to be treated, the medical community is in need of a treatment strategy based on hard data on the spontaneous course of hearing and the growth pattern of these tumours.

Based on the data presented above, our centre has adapted and proposed the following strategy for all sporadic, unilateral VSs smaller than 15–20 mm extrameatal: yearly MRI for 5 years, followed by MRI every other year for 4 years, followed by MRI after 5 years, after which the observation is terminated, if no growth occurs. A rigid data interpretation indicates no reason to follow patients for more than 5 years, as tumour growth only occurred within the first 5 years after diagnosis. We have, however, chosen the above treatment policy as only a limited number of tumours have been followed for more than a decade, and to be on the safe side. If significant growth occurs, active treatment (surgery or radiotherapy) is recommended. Naturally, special considerations may indicate an aberration from this management policy (e.g. observation of old patients with large tumours or surgery for small tumour in patients insisting on a primary operation). However, unless realistic hearing preservation is intended[41] or special reasons (e.g. patient psychology) prevail, there are no available data indicating or substantiating a reason for active treatment of a non-cystic, non-growing VS smaller than 15 mm. Although reasonably surmounted, both surgery and radiotherapy are associated with risks, and the quality of life of our patients appears to be significantly better when their disease is observed.

Primary treatment of tumours larger than 15–20 mm is recommended, as further growth extends the tumour diameter into the range associated with a considerable increase in treatment comorbidity (e.g. damage to the facial nerve function). Cystic tumours are not eligible for radiotherapy and primary surgery is recommended, as these tumours may display sudden and dramatic growth, which implicates a poorer surgical outcome. NF-2 associated VSs are treated individually, as these tumours often display a distinct growth pattern and often are subjects of special consideration.

BEST CLINICAL PRACTICE

- ✓ The size of a VS should be recorded according to the International Consensus Guidelines.
- ✓ Patients allocated to a 'wait and scan' management policy should be observed with annual MRI for at least 5 years.
- ✓ Patients with small non-growing tumours and 100% speech discrimination should be managed conservatively.

KEY POINTS

- The term 'acoustic neuroma' should be replaced by the more accurate term 'vestibular schwannoma'.
- When reporting the size of vestibular schwannomas, the largest extrameatal diameter should be recorded and a note made of whether the VS is cystic.
- Symptoms caused by VS depend largely on its size, but good hearing may be found even in large tumours.
- Trigeminal symptoms and signs together with ataxia indicate a large tumour with significant brainstem compression.
- The precise incidence of VS in the population is not known, but the number of diagnosed tumours is increasing, probably due to easier access to diagnostic tools. The incidence is not less than 25 tumours per million per year.
- Only one fifth of the intrameatal and one third of the extrameatal tumours grow, and in almost all cases within the first 5 years after diagnosis.
- In patients with 100% speech discrimination at diagnosis, most maintain good hearing, in contrast to patients with even a minor impaired discrimination, where about 60% lose good hearing after 5 years observation.

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CHAPTER 102

SURGICAL MANAGEMENT OF VESTIBULAR SCHWANNOMA

Shakeel R. Saeed and Christopher J. Skilbeck

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the following keywords: vestibular schwannoma, acoustic neuroma and acoustic neurinoma.

INTRODUCTION

This chapter introduces the indications for surgical management of vestibular schwannoma (VS), explaining the current management philosophy. The common approaches to the cerebellopontine angle (CPA) are described with explanation of the advantages and disadvantages of each. A review of the current literature with particular focus on developments of adjunctive surgical techniques has been undertaken.

With the advent of high quality imaging and the increased level of awareness amongst clinicians seeing patients with otological complaints, the diagnosis of VS is frequently made earlier.[1] As a result, the tumours are detected at a smaller size and the incidence appears to have increased from the previously quoted 1:100 000 per year to 1:80 000 per year.[1–3] In addition, the epidemiological work of many has shown that a high proportion of patients with VS have static tumours.[4] Although surgery has a role for those with large tumours (>30 mm maximal intracranial diameter), beyond which the role of stereotactic radiotherapy is considered minimal, for smaller tumours, a conservative approach is commonly advised.[5, 6] There is no way of predicting which tumours will grow at the time of initial diagnosis and the majority of patients are offered active monitoring.[7] This active monitoring involves serial scanning to detect any evidence of growth, after which an intervention is offered. Despite this commonly held belief, some growth in small and intracanalicular tumours is tolerated without the need for urgent intervention.[8] Many series have shown 60–70% remain stable with no growth for many years.[9]

Historically the intervention offered was surgery. However, the skull base multidisciplinary team is increasingly offering patients the choice of surgery or radiotherapy, delivered as a single fraction (Gamma Knife) or multiple fractions. This is beyond the scope of this chapter as it is covered elsewhere.

Nevertheless, surgery remains the mainstay of treatment and this chapter deals with the commonly favoured approaches to the CPA. Certain generalizations apply to surgery, whichever approach is employed. Each of the three approaches described has its own advantages and disadvantages and these will be highlighted. The surgical outcomes will be discussed and the complications of surgery mentioned.

HISTORY

It is interesting to look at the history of the two main surgical approaches now in common use, the suboccipital (retrosigmoid) approach and the translabyrinthine approach, and to look at the vitriolic arguments that characterized the debate between the neurosurgeons and the emerging genre of neurotologists in the middle of the 20th century. Going back to the end of the 19th century, it remains unclear whether it was Ballance[10] in London or Annandale in Edinburgh who performed the first successful VS removal. Although Ballance's case was earlier,

Cushing was of the opinion that his case was a meningioma, and said of Annandale's case: 'a brilliant result, the first recorded'.[11] Be that as it may, these operations were carried out though the suboccipital approach by multi-tasking general surgeons before the emergence of neurosurgery as a separate specialty after the First World War. Undeterred by peri-operative mortality of apocalyptic magnitude (Krause in 1903 reported an 84% death rate),[12] surgery of the CPA developed in the hands of the new breed of neurosurgeon, of whom the leaders were the two great Americans Harvey Cushing and Walter E Dandy. Cushing[13] proposed intracapsular debulking of the tumour whereas Dandy[14] was a strong advocate of total removal. Despite their advances it is significant that as recently as the 1950s there still prevailed an attitude amongst many neurosurgeons that surgery should be deferred until the tumour was in fact a threat to life. An article by Pennybacker and Cairns in 1950[15] is worth reading in that it encapsulated much of the thinking of the time.

It was this situation that William House found so unacceptable in the 1960s. He could not see the logic of letting a small or medium-sized tumour become a large or giant tumour before performing an operation that was almost inevitably bound to be associated with a poor outcome or even death. He therefore proposed surgery as soon as the diagnosis could be made and suggested the translabyrinthine approach to the CPA.[16] This approach was first suggested by Panse as long ago as 1904[17] but was dismissed as inappropriate and remained in obscurity for half a century. House endured many hostile confrontations with the neurosurgical community, whose objections were as much due to the fact that otologists were becoming involved with this type of surgery as with the approach itself. Battles raged at international meetings as to which approach was better. It now seems quite clear that the 'best' approach is the approach that gives the best results in the hands of the individual surgeon. Beyond that the argument is sterile. Many developments occurred in the second half of the 20th century that led to improvements in surgical outcomes regardless of approach. There is no doubt that the advent of microsurgical technique was a major breakthrough. So too was the understanding of the importance of the blood supply of the brainstem from the work of Atkinson.[18] Neuroanaesthesia made important strides and enabled surgeons to take many painstaking hours over the surgery (an offer they were happy to accept!). Also, of course, early diagnosis enabled House's vision of early diagnosis and treatment to come a long way to fruition.

SURGICAL APPROACHES TO THE CEREBELLOPONTINE ANGLE

Translabyrinthine approach

This is now the favoured approach for the removal of VS for the majority of neurotologists. Its advantages are the avoidance of cerebellar retraction or resection, and the early identification of the facial nerve at the lateral end of the internal auditory meatus (IAM). Its disadvantages are that it involves destruction of the inner ear and so is not an option for hearing preservation surgery. It has a higher incidence of cerebrospinal fluid (CSF) fistula than other approaches and it is said by its detractors to provide only limited access to the posterior fossa. This criticism is in fact unfounded, and a well performed translabyrinthine approach will allow removal of a VS of any size.[19] It can be extended posteriorly to allow further access to the posterior fossa, jugular foramen, hypoglossal canal and foramen magnum. It can be extended anteriorly to allow access to the petrous apex and clivus (transcochlear approach). It can be extended superiorly to allow access to the middle fossa, and inferiorly to allow access to the jugular foramen and upper neck. Morrison combined the translabyrinthine approach with the middle fossa approach as the translabyrinthine transtentorial approach for large or giant tumours.[20] The technique gives excellent exposure of the tumour and of the brainstem but there is an unacceptable incidence of post-operative epilepsy and occasional temporary dysphasia if the dominant temporal lobe is retracted. The basic translabyrinthine operation is the essential starting point for many lateral skull base operations and must be a routine exercise for all aspiring neurotologists and skull base surgeons.

The key stages in the operation are:

1. Skin and periosteal flaps
2. Extended cortical mastoidectomy
3. Bony labyrinthectomy
4. Skeletonization of the jugular bulb and vertical portion of the facial nerve
5. Skeletonization of the IAM
6. Identification of the facial nerve at the lateral end of the internal meatus
7. Opening of the posterior fossa through the dura of the posterior surface of the petrous bone
8. Removal of tumour using standard neurosurgical techniques
9. Closure with obliteration of the middle ear and petrosectomy defect, usually with abdominal fat.

DETAILS OF THE TRANSLABYRINTHINE APPROACH

Position

The patient is placed on the operating table in the supine position with the head turned 30 degrees away from the surgeon and supported either in a soft head ring or fixed in the Mayfield clamp. Two-channel neuromonitoring for the facial nerve is usually sufficient, but with very large tumours it may be necessary to monitor the lower cranial nerves as well. The anaesthetist should be reminded that neuromuscular blocking agents must not be used after intubation.

Skin incision

A curved incision above and behind the pinna is planned, to allow adequate access for bone removal behind the

lateral sinus and anterior access to the labyrinthine part of the facial nerve. For tumours up to about 2.5 cm intracranial diameter the incision can be about 3 cm behind the postauricular sulcus but for larger tumours the incision should be sited further back to allow exposure of the dura behind the lateral sinus. The anterior limb should extend to a line tangential to the anterior wall of the external auditory canal.

Musculoperiostial flap

It is desirable to create a separate flap that can be used during closure to secure the abdominal fat plug. The flap can be pedicled superiorly or anteriorly. The superiorly based flap has the advantage that, if necessary, it can easily be extended upwards to allow access to the middle cranial fossa.

Cortical mastoidectomy

The secret of the operation is the extent of the bone removal (Figure 103.1). Using cutting and coarse diamond paste burrs, bone is removed up to the middle fossa dura, exposing it widely, both over the floor of the middle fossa and some 3–4 cm up the squamous portion of the temporal bone. If needed, this allows easy retraction of the dura with the instruments during tumour removal. In a similar manner, bone is removed from the sigmoid sinus and from the bone overlying the posterior fossa dura for 2–3 cm behind the sinus. Some surgeons like to leave an island of thin bone over the sinus that can be retracted with the sinus and provides some protection for the sinus. The sinus can thus be compressed backwards to increase access. During preparation of the sigmoid sinus, troublesome bleeding may be encountered from a large emissary vein. If possible it is better to anticipate trouble and identify and control the vein before making it bleed. Its bony canal can be skeletonized and obliterated with bone wax or, alternatively, the vein can be coagulated with bipolar diathermy. Coagulation should not be too close to the main sinus otherwise the manoeuvre may simply convert a small bleed from the emissary vein into a large bleed from the sinus. Care must be taken to avoid damage to the superior petrosal sinus, which runs along the posterior petrous ridge and therefore in the angle created by the bone removal between the middle and posterior fossa dura. The bipolar diathermy, if applied lightly over the dura or the surface of the sigmoid sinus, will make it retract and increase access. Bleeding from the superior petrosal sinus and, indeed, even from the lateral sinus, is easily controlled with pressure and the application of haemostatic mesh (Surgicel). Should more dramatic bleeding occur, it is still possible to apply a tie-over mesh, possibly with the addition of muscle, to avoid tying off the sinus, which is a last resort. Air embolus is only a theoretical risk in our experience.

Attention can now be turned to further bone removal medially. Ensuring the mastoid tip is removed with exposure of the digastric ridge, which aids in identification of the descending facial nerve.

Bony labyrinthectomy

A standard total bony labyrinthectomy is performed (Figure 103.2). Care must be taken in drilling out the ampulla of the posterior canal, which lies medial to the second genu of the facial nerve. The ampulla of the superior semi-circular canal should be retained as it is a landmark for the superior vestibular nerve (SVN). In drilling out the superior canal the surgeon will encounter the subarcuate artery, which runs under the canal and leads to the posterior fossa dura just behind the porus of the internal meatus. The endolymphatic duct can be traced from the vestibule along the line of the common crus where it turns through 90 degrees towards the posterior fossa dura and widens out to become the sac. The bone over the posterior fossa dura between the labyrinth and the anterior margin of the sigmoid sinus should be removed and access is further enhanced, especially in small temporal bone, if bone is

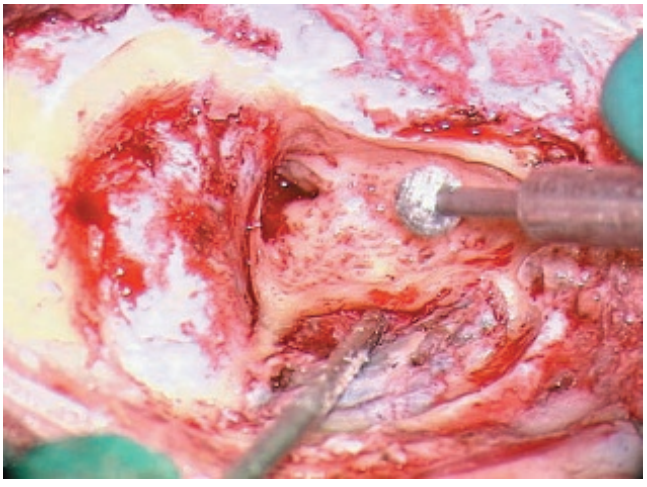

Figure 103.1 Translabyrinthine approach, right ear. Extended cortical mastoidectomy has been performed. Note the wide bone removal over the middle fossa dura and the sigmoid sinus, allowing the dura and the sinus to be retracted and the access improved.

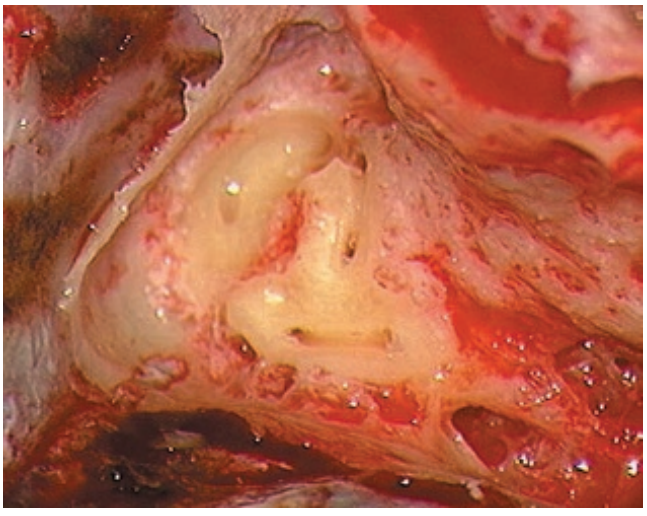

Figure 103.2 Translabyrinthine approach, right ear. Bony labyrinthectomy.

progressively removed from the dura of the middle fossa. It is by removing these bony boundaries of the petrous bone so that the limits of the resection are the soft and compressible dural surfaces that the surgeon gets maximum access to the posterior fossa. This is one of the secrets of success in the translabyrinthine operation. Although opening of the labyrinth almost inevitably leads to total hearing loss there have been attempts to perform a conservative labyrinthectomy with sealing of the vestibule and thus isolation of the cochlea from the labyrinth with preservation of the hearing. This technique was first described by McElveen et al.[21] with a further updates by Magliulo et al.[22, 23] These authors conserved class 1 or class 2 hearing in 7 out of 12 patients treated in this manner.

Others have shown that preservation of the cochlear nerve in the CPA and IAM allows subsequent cochlear implantation.[24, 25] Currently in attempting cochlear nerve preservation, a three-channel intracochlear electrode is inserted during the latter stages of the approach and tumour dissection to allow monitoring of the cochlear nerve function.[26]

Skeletonization of the jugular bulb and the vertical portion of the facial nerve

The jugular bulb is the lower limit of bone removal and in nearly all cases bone should be removed down to its level. The height of the bulb does vary enormously. In some very large, well pneumatized temporal bones with a low bulb and a small tumour it may not be absolutely necessary to expose the bulb. On the other hand it is not at all uncommon for the dome of the bulb to rise up to, and beyond, the level of the floor of the internal meatus, even as high as the middle fossa dura, and in these cases the surgeon must be prepared to mobilize and depress it. This is done by gently freeing the bulb from its bony bed and packing it downwards using haemostatic mesh (Surgicel) and bone wax. Bleeding, sometimes quite brisk, may occur but it is usually easy to control. Bone wax provides excellent protection for the mobilized bulb from the rotating shaft of the drill during the subsequent creation of the inframeatal gutter. The retrofacial air cells are exenterated and bone may be removed over the vertical portion of the facial nerve until the sheath is visible through the bone. The exact extent of bone removal over the nerve depends on the access in the individual temporal bone and the size of the tumour.

Skeletonization of the internal meatus

A U-shaped gutter is drilled below, behind and above the internal meatus (**Figure 103.3**). The extent of bone removal should be approximately 270 degrees round the meatus, and is much faster if the temporal bone is well pneumatized. An extended translabyrinthine approach has been described with removal of bone around the internal meatus to a full 360 degrees by retracting the contents of the meatus inferiorly and carefully continuing drilling towards the petrous apex.[27] This modification is helpful in dealing with lesions of the petrous apex, but is not necessary for the great majority of VSs. It is important to check the degree of meatal expansion on the pre-operative scan. Superiorly bone is removed between the meatus and the dura of the middle cranial fossa, from which the bone should be removed to allow superior elevation of the temporal lobe and easier access. One should constantly keep in mind the position of the facial nerve in the anterosuperior quadrant of the meatus, and remember that in an expanded meatus it may in fact be very close to middle fossa. To guard against inadvertent facial nerve trauma, the inferior meatal gutter is drilled first, allowing the meatal contents to displace inferiorly when the drilling turns to the superior side, where the nerve is immediately under the dura. One should be on the lookout in a pneumatized temporal bone for tumour that has eroded out of the meatus and into the air cell system. In such a situation the facial nerve may be engulfed by tumour and appear to be running through the tumour. Inferiorly one frequently encounters the cochlear aqueduct in a position superomedial to the jugular bulb. It is heartening if a brisk flow of CSF results as this allows the intracranial contents to slacken off and ease the subsequent opening of the posterior fossa. The cochlear aqueduct is a useful guide to the position of the lower cranial nerves, which are just anteroinferior to the duct. Subsequent bone removal round the meatus should be above the level of the aqueduct. When drilling round the porus, especially behind it, one must be aware of the possibility of an arterial loop lurking just under the dura, especially with a large tumour or if CSF has not been run off. There should now be an eggshell of bone over the dura of the internal meatus and the posterior fossa dura adjacent to the porus. At the lateral end of the meatus the transverse crest and the canal for the SVN should be sought. The latter runs from the lateral end of the meatus towards the retained ampulla of the superior semi-circular canal, and is a constant and reliable landmark. As the surgeon looks through the microscope it runs from 12 o'clock to 6 o'clock in the surgical field. Bone should now be picked off the dura of the internal meatus and the posterior cranial fossa if any remains.

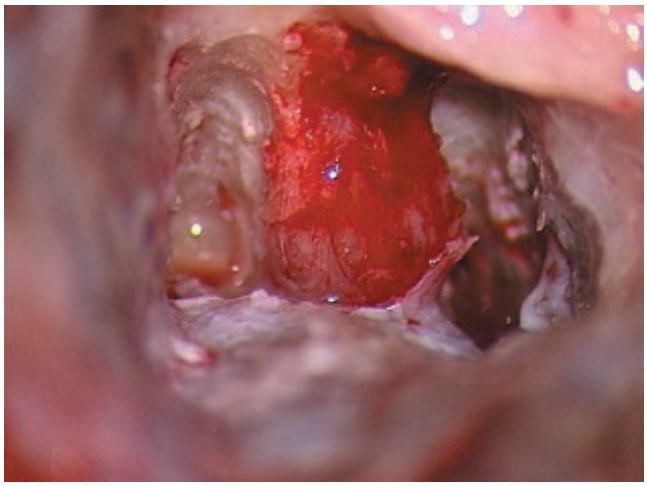

Figure 103.3 Translabyrinthine approach, right ear. The internal meatus has been skeletonized and the intrameatal portion of the tumour exposed.

Opening the posterior cranial fossa and internal auditory canal

The dura is opened to make full use of the exposure. The upper limit is close to the superior petrosal sinus, the lower limb close to the jugular bulb. The medial limb is at the level of the porus. The dura is usually thin superiorly but can be very tough inferiorly where it is bilaminar. If CSF has already escaped though the cochlear aqueduct, this step of the operation is easy, because the cerebellum and any important blood vessels have dropped away from the dura. If the intracranial pressure is high, however, this can be a surprisingly difficult exercise, as the cerebellum tries to force its way out, often accompanied by arterial loops. Careful use of neurosurgical patties provides protection until CSF can be released. This is usually done by carefully opening the subarachnoid space at the lower pole of the tumour with a dissector. Alternatively, if a lumbar drain has been inserted the anaesthetist can be asked to run off some CSF. The dura of the internal meatus should be cut from lateral to medial at the level of the transverse crest, with the superior and inferior dural flaps reflected off the tumour, which is usually arising from the inferior vestibular nerve, and the other internal auditory canal (IAC) nerves.

Identification of the facial nerve

The facial nerve is displaced from its normal position by the tumour, but in the majority of cases it is displaced in a fairly predictable way. It runs along the anterosuperior quadrant of the meatus as far as the porus where it is displaced to a variable extent anteriorly and/or superiorly before turning down over the front of the tumour to the brainstem, which it joins just above the pontomedullary junction. Thus in the translabyrinthine approach the tumour is usually between the surgeon and the facial nerve. However, this is not always the case. There are occasions when the facial nerve is rotated backwards in the meatus and comes to lie on the posterior surface of the tumour. This may occur if the tumour arises on the cochlear nerve. It may on occasion be displaced down to the floor of the meatus and run in a more inferior position to the brainstem. If the tumour turns out to be a meningioma, the relationship of the nerve to the tumour may be variable, and it commonly runs over the posterior surface of the tumour. It is therefore essential to establish the relationship of the nerve to the tumour before any tumour is removed. At the lateral end of the meatus the SVN has already been identified. The exposed intrameatal portion of the tumour should be closely examined, both visually and using the facial nerve monitor, to be sure that the nerve has not been displaced on to the posterior surface. Assuming this is negative the nerve should then be sought in front of the SVN both visually and with the monitor. The routine identification of Bill's bar, the vertical crest separating the SVN from the facial nerve, has been abandoned by many surgeons now that reliable monitoring is in use in every case, but it may be useful to do so in cases of doubt. Access to the anterosuperior part of the meatus may be helped by careful debulking of the tumour in the lower half of the meatus.

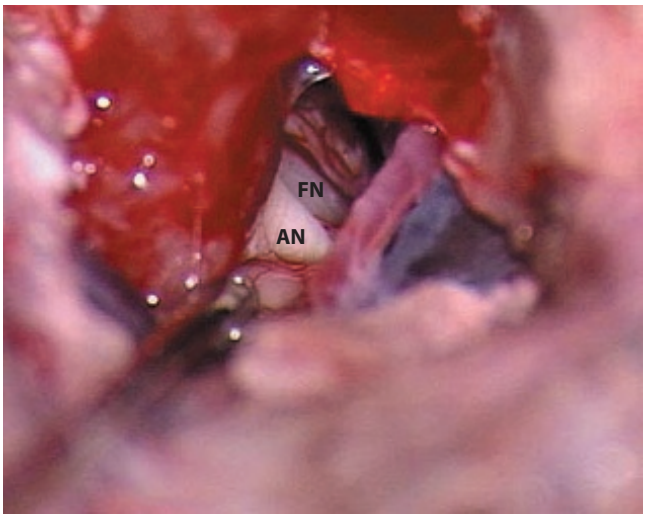

Figure 103.4 Translabyrinthine approach, right ear. The posterior fossa has been opened. The medial pole of the tumour is seen and below it the audiovestibular nerve (AN) and (deeper) the facial nerve (FN) on the brainstem.

It is also useful to try to identify the facial nerve on the brainstem at the earliest opportunity (Figure 103.4). With a small tumour it may be immediately obvious in front of the audiovestibular nerve and usually separated from it by a loop of the anterior inferior cerebellar artery (AICA). With a larger tumour it may not be possible to see it until some intracapsular debulking of the tumour mass has taken place. Once both proximal and distal ends of the nerve have been identified the surgeon starts to form a mental image of the likely course of the nerve in relation to the tumour. This three-dimensional conceptualization of the relationship between tumour and nerve is only acquired with considerable experience and makes tumour removal much more predictable and rapid.

Tumour removal

With tumours confined to the internal meatus or with little intracranial extension, dissection can start at the fundus and proceed medially, keeping to the arachnoid plane, and little difficulty should be encountered, although even small tumours may be surprisingly adherent to the facial nerve just at and medial to the porus, and sharp dissection may be needed (Figures 103.5 and 103.6). With larger tumours, debulking of the inside of the tumour is carried out so that the tumour is converted from a solid ball to a hollow ball. This technique is based on the fact that as the tumour expands all important structures such as the facial nerve and AICA are pushed before the tumour and are to be found in the arachnoid sheath on the outside of the tumour capsule. Dissection that is confined to the inside of the tumour should be safe. A number of techniques and instruments can be used for debulking. If the inside tumour is very soft it is possible to reduce the volume quite rapidly with suction alone. More solid tumours may require the use of the cavitational ultrasonic surgical aspirator (CUSA). The CUSA is certainly effective but one must be sure to use it with great care because it is

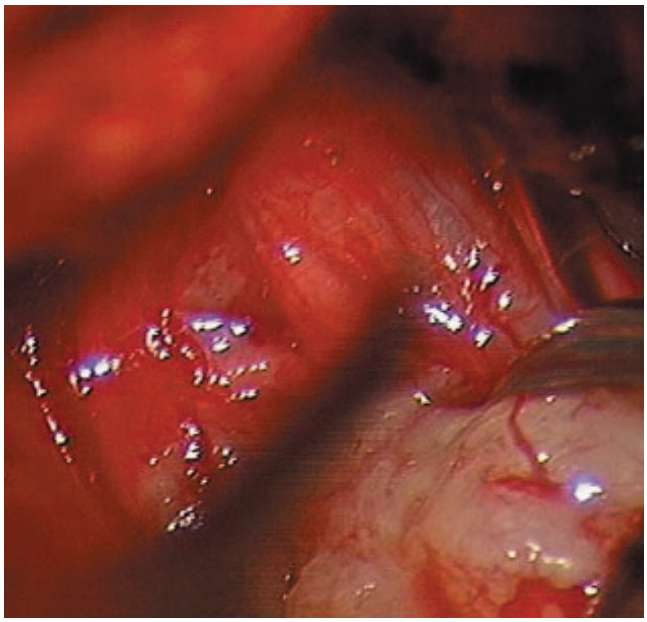

Figure 103.5 Translabyrinthine approach, right ear. The tumour is dissected off the facial nerve (FN) in a lateral to medial direction.

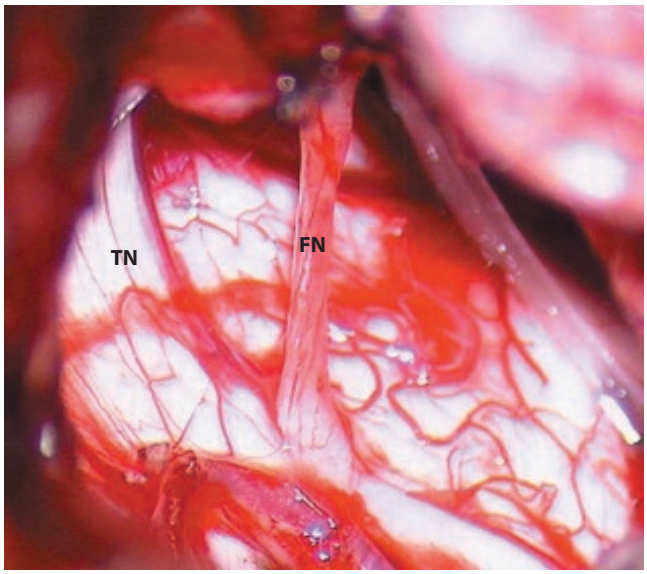

Figure 103.6 Translabyrinthine approach, right ear. Tumour has been removed completely. The facial nerve (FN) can be seen crossing the CPA to the meatus. The trigeminal nerve (TN) is seen more cranially and a loop of AICA inferiorly.

not difficult to penetrate the capsule on the far side of the tumour and risk causing damage to the facial nerve, AICA or the brainstem. It also tends to produce quite a bit of bleeding from the tumour, necessitating frequent coagulation using bipolar forceps. As the tumour bulk reduces it becomes progressively easier to manipulate the tumour capsule, and careful retrograde dissection of the capsule off the brainstem end of the facial nerve may allow the surgeon an increasingly confident image of the path that the nerve is taking. When dissecting at the lower pole one must be careful to protect the lower cranial nerves and AICA, although it must be said that it is not usually difficult to dissect them off the tumour and damage to these structures is rare. With a combination of lateral to medial and medial to lateral dissection the tumour is removed from the facial nerve. The extent to which one can follow the traditional advice to stay in the arachnoid plane varies from tumour to tumour and it is very important that the surgeon knows just where he is in relation to that plane at any moment in the operation. When dissecting the tumour off the facial nerve in the internal meatus he is within the arachnoid plane. When dissecting in a retrograde manner from the stem he is outside the arachnoid plane. Failure to appreciate this subtle difference in location carries the risk of dividing the nerve. In the internal meatus and close to the brainstem the plane between the facial nerve and the tumour is usually quite easy, but at a point at or just medial to the porus it may be almost impossible to identify and sharp dissection may be necessary to get the tumour off the nerve. This is the point where the facial nerve is most likely to be lost. In addition to difficulties with the plane, it is here that the nerve becomes very thin and may be impossible to differentiate visually from the surrounding arachnoid, although the monitor does certainly help. The facial nerve is placed at further risk if the tumour extends far forwards towards the petrous apex carrying the facial nerve with it. The surgeon may in fact decide to leave a small nubbin of tumour on the nerve at this point to reduce the risk to the facial nerve. There is good evidence that these small fragments become devitalized and either disappear on follow-up scanning or at least seem to remain biologically inert.[28,29] Dissection of the capsule off the trigeminal nerve and the brainstem is usually not difficult but some tumours bury their way into the stem and very gentle technique is required to separate one from the other. There may be occasions when the surgeon chooses to leave a fragment of tumour behind, especially if the anaesthetist reports repeated or sustained changes in the pulse or blood pressure during manipulation on the stem. The VIth nerve can usually be seen running up the length of the stem. Large tumours may make contact with this nerve and it must be handled carefully. Even quite gentle dissection can cause a temporary dysfunction of the nerve with transient post-operative diplopia. All blood vessels apart from obvious tumour vessels should be treated with the greatest respect. It is not possible to tell which branches of AICA are essential and it is wise to assume that they all are.

Special attention should be drawn to the unique surgical problems with the so-called medial tumour that arises in the CPA without involving the internal meatus and is usually large at presentation.[30,31] Because they have little attachment to the internal meatus these tumours tend during surgery to be suspended on the VIIth/VIIIth nerve pedicle or even on the facial nerve alone. The surgeon has to be particularly careful to avoid traction on this pedicle if avulsion of the facial nerve is to be avoided.

After tumour removal, haemostasis must be secured. Care must be taken with the use of the bipolar diathermy in the vicinity of the facial nerve. Rather than risk thermal damage to the nerve, one should allow bleeders close to

the nerve to stop spontaneously or use a small fragment of Surgicel to assist haemostasis.

Closure

This is one of the most important steps in the translabyrinthine operation. CSF fistula remains one of the most common post-operative problems, even in large series from experienced centres. To minimize the risk, careful obliteration of the middle ear and the temporal bone defect is essential. Harvest of free autologous fat (and fascia) from the abdominal wall or thigh is performed and prepared for use. The incus is removed and a posterior tympanotomy created. The middle ear, Eustachian tube and vestibule are obliterated with muscle or fascia and bone wax. The supra and inframeatal gutters are obliterated with fat and obvious air cell tracts sealed with bone wax. The temporal bone defect is obliterated with abdominal fat either in strips or in one large piece. Some surgeons first seal off the posterior fossa and drilled anterior surface of the petrous bone with fascia lata from the thigh or fascia from the superficial layer of the external oblique from the anterior abdominal wall. The repair is secured with fibrin glue, although excessive reliance on biological glues is to be regarded with caution. It is possible that they may interfere with the body's natural healing response and, when they are absorbed, actually predispose to CSF fistula.[32] Although predominantly remaining in the surgical bed, post-operative imaging has shown embolic distribution of fat throughout the CSF with no clinical significance.[33] The periosteal flap is then sutured back over the fat and the skin closed in two layers. A firm pressure dressing is applied and kept in place for a week. It should not, however, be so tight that it causes pressure changes in the skin of the forehead. The use of a peri-operative lumbar drain is not routine but is employed in some centres.

Middle fossa approach

The middle fossa approach is one of the possible routes of access for hearing preservation surgery. The internal meatus is approached extradurally from above through a small craniectomy. It has the advantage of allowing good visualization of the lateral extent of the internal meatus. The approach is somewhat cramped, however, and access to the posterior fossa limited, certainly through the standard middle fossa approach. The maximum size of tumour that can comfortably be removed is about 1–1.5 cm in intracranial diameter, which is in fact about the limit beyond which the possibility of hearing preservation recedes. Furthermore there is a small but real risk of epilepsy following extradural retraction of the temporal lobe. Aggarwal et al.[34] described two cases of single ictal events that had the effect of prohibiting the patients from driving for a period of one year. In the extended middle fossa approach (EMFA), more bone is removed in front of and behind the meatus and access to the posterior fossa increased. This approach is more suited to removal of petrous apex lesions such as congenital cholesteatomas or meningiomas, and Wigand et al., who did much to develop this technique, are able to remove VSs with an intracranial diameter of as much 3 cm by this approach.[35, 36]

The key stages in the middle fossa approach are:

1. Skin and soft tissue incisions
2. Middle fossa craniectomy
3. Extradural approach to upper surface of temporal bone and to posterior fossa
4. Skeletonization of internal meatus
5. Identification of facial and vestibular nerves
6. Removal of tumour
7. Closure

DETAILS OF THE MIDDLE FOSSA APPROACH

Position

The patient is supine with the head on a head ring or in a neurosurgical clamp. The essential point is that the intermeatal line should be perpendicular to the floor. This ensures that the internal meatus is in the same plane as the external meatus and assists the surgeon's orientation in identifying the internal meatus. Facial nerve monitoring is routine with auditory monitoring added in cases of attempted hearing preservation.

Incision

A 6–7 cm vertical or gently backward curving incision starts at the level of the zygomatic arch just in front of the pinna. The temporalis muscle is exposed and an inverted T-shaped incision is made though the muscle down to the skull.

Craniectomy

A 5 cm × 5 cm square bone flap is cut with about two-thirds in front of the intermeatal line and one third behind it. The dura over the temporal lobe is exposed. The lower edge of the craniectomy should be at the level of the floor of the middle fossa – it may be necessary to remove further bone down to the floor of the fossa with bone nibblers. Air cells are frequently opened and should be sealed off with bone wax or muscle.

Exposure of upper surface of petrous bone

The dura is elevated off the surface of the petrous pyramid. This is facilitated considerably by the administration of intravenous mannitol at this stage and the dura can be elevated as far medially as the petrous ridge and the superior petrosal sinus. A middle fossa retractor is introduced. As the dura is elevated troublesome bleeding is often encountered from the venous plexus that surrounds the middle meningeal artery in the region of the foramen spinosum. This is controlled with Surgicel packing. As the dura is elevated the greater superficial petrosal nerve is identified running up from the region of the middle meningeal artery to the geniculate ganglion. It is frequently adherent to the dura and may have to be separated from it by sharp dissection. One should also be aware that the geniculate ganglion may be dehiscent in up to 5% of individuals and

at risk of damage as the dura is elevated.[37, 38] The arcuate eminence is the other important landmark to be identified. It corresponds approximately to the superior semi-circular canal.

Location of the internal auditory meatus

There are two favoured approaches to the internal meatus. In the method originally proposed by House, the geniculate ganglion is identified and the facial nerve is followed medially along its labyrinthine segment until the meatus is reached. This method involves drilling between the cochlea anteriorly and the superior semi-circular canal posteriorly. If either of these structures is breached the hearing will be lost. The other approach was suggested by Fisch and others. The angle between the line of the greater superficial petrosal nerve and the plane of the superior semi-circular canal is bisected and that gives the line of the internal meatus. If necessary the superior canal may be blue-lined to establish the exact anatomy of the area, and good quality CT images of the temporal bone will provide the surgeon with important information on the degree of pneumatization that will be encountered as the internal meatus is approached. The internal meatus is skeletonized anteriorly, superiorly and posteriorly. At the lateral end Bill's bar is identified and the ampulla of the superior canal blue-lined. Medially the porus is skeletonized and the dura of the posterior fossa increasingly exposed. Initial drilling of the medial end of the internal meatus is advised, where there is usually more bone overlying the canal, whereas laterally the nerves become more superficial to the middle fossa.[39]

Identification of the facial, cochlear and vestibular nerves

The dura of the meatus is opened longitudinally with scissors as far as the porus and access to the posterior fossa can be gained by opening the dura in front of and behind the porus. The facial nerve is identified in the anterosuperior quadrant of the meatus and is protected under the cut dural edge. The SVN may be seen to be running into the tumour, or alternatively may be seen to be running over the surface of the tumour depending from which branch of the vestibular nerve the tumour arises. The cochlear nerve is concealed under the facial nerve and cannot be seen at this stage. If the tumour does reach right to the fundus, identification of the neural structures lateral to the tumour is easier. Careful positioning of the retractor under the superior petrosal sinus usually provides adequate access into the posterior fossa where the medial pole of the tumour and the facial and vestibulocochlear nerves are identified. It is rarely necessary to divide the sinus. As mentioned previously it takes the surgeon considerable experience to picture these three-dimensional relationships in his or her mind.

Tumour removal

The principles of tumour removal are no different from those outlined in the description of the translabyrinthine approach. The surgeon must recognize that the facial and cochlear nerves lie in the arachnoid plane. Debulking of the inside of the tumour can proceed safely, both inside the meatus and in the posterior fossa. One major difference from the translabyrinthine approach is that the facial nerve lies between the surgeon and the tumour and is thus more vulnerable to damage from instrumentation. When the stage of dissection of the capsule of the facial and cochlea nerves is reached, it is important to remember that the forces applied to the tumour should be in a medial to lateral direction in order to minimize stretching effects on the fibres of the cochlear nerve as they pass through the basilar membrane at the *habenula perforata*.

Closure

The internal meatus is closed with a free muscle plug. A couple of dural hitch stitches are inserted to minimize the risk of an extradural collection, the free bone flap is replaced and secured with non-absorbable ties and the muscle and skin closed in layers.

Retrosigmoid approach

This approach has evolved from the classic suboccipital operation that was favoured by neurosurgeons for the removal of all posterior fossa tumours but particularly for large ones. A very large portion of the occipital bone was removed, from the transverse sinus above to the foramen magnum below and from the sigmoid sinus laterally to the midline. Such a large craniectomy is now rarely necessary and a much smaller retrosigmoid craniectomy of around 5 cm × 5 cm allows good access to the posterior fossa, although the exact amount of bone removal will depend upon the preference of the surgeon and the size of tumour to be removed. The advantage of the retrosigmoid/suboccipital approach is that it allows the possibility of hearing preservation in small tumours. The disadvantage is that, especially for large tumours, considerable cerebellar retraction may be necessary, and even on occasion resection of part of the cerebellar hemisphere. Kim et al.[40] report, however, that the significantly greater cerebellar retraction that is necessary for retrosigmoid surgery does not result in greater long-term balance and disability as compared with those patients who have undergone the translabyrinthine approach.

Post-operative headache is more common with this approach than with the translabyrinthine operation.[41, 42] The mechanism is unclear, although several have been proposed including dural irritation around the IAM, adherence of scalp flap to the dura, extent of dissection of the neck muscles and occipital nerve injury.[43–45] If the facial nerve is lost near the fundus of the internal meatus, it is virtually impossible to perform a primary nerve grafting procedure.

DETAILS OF THE RETROSIGMOID APPROACH

Positioning

The operating position depends on preference. Neurosurgeons will favour the lateral position or park-bench position with or without the use of a clamp.

The sitting position has largely been abandoned in the UK because of the risk of air embolus if the venous sinuses are opened. It does have the considerable merit of enhanced visibility for the surgeon as gravity keeps the field clear of CSF and blood. Neurotologists may find that the supine position with the head turned to the opposite side provides access just as easily. Facial nerve monitoring electrodes will be in place, as will electrodes for intra-operative recording of auditory evoked potentials in cases where hearing preservation is the aim.

Incision

A vertical or slightly curving incision is made about 3 cm behind the mastoid process, from above the level of the transverse sinus to the level of the tip of the mastoid. The soft tissues may be incised down to the bone, but the authors prefer to maintain a superiorly based musculoperiostial flap to assist in the closure.

Craniotomy and exposure of the tumour

A 5 cm × 5 cm craniotomy is made using the drill, taking the mastoid emissary vein as the starting point, and the bone dust is retained for closure. The anterior and superior limits of bone removal are the sigmoid and the transverse sinuses respectively. It is essential to get as close to the sigmoid sinus as possible so that the surgeon's line of sight is along the posterior surface of the petrous pyramid. As the drilling progresses, any mastoid air cells encountered must be closed using bone wax or muscle, to minimize the risk of post-operative CSF leakage. The extent of bone removal required is to some extent determined by the size of the tumour; some advocate completing the craniotomy to the level of the foramen magnum, allowing wider exposure and enabling access to drain CSF. The dura is opened through a U-shaped flap based anteriorly on the posterior edge of the sigmoid sinus and the cerebellar hemisphere is exposed. In order to get good exposure of the tumour, CSF must be run off from the CPA, usually initially by accessing the cisterna magna. This is not always easy as the cerebellum is in the way, but with gentle retraction and reduction of the intracranial pressure by the anaesthetist, this is achievable and an instrument can be passed into the subarachnoid space. Now the cerebellum falls away under its own weight and if the surgery is for a small tumour, as in a hearing preservation operation, little retraction is needed (**Figures 103.7** and **103.8**).

Tumour removal

The previously outlined principles apply. Intracapsular debulking is safe and allows one progressively to handle the capsule of the tumour. It is desirable to identify the facial and audiovestibular nerves on the brainstem as soon as possible, and to note the position of AICA. The intracranial part of the tumour can be dissected off the facial and audiovestibular nerves back to the porus of the internal meatus, but for complete tumour removal the IAM must be drilled out. One of the principles of tumour removal for hearing preservation is that dissection should be in a medial to lateral direction in order to avoid traction on the fibres of the cochlear nerve as they pass from the cochlea through the habenula perforata into the internal meatus.

Drilling of IAM

A dural flap should be elevated over the IAM. This may be based either laterally or medially. The medially based flap has the advantage that it may be turned in over the facial and auditory nerves for protection during the drilling. The internal meatus should be skeletonized above, behind and below, though at least 180 degrees and as far laterally to the fundus as possible. The obstacles to this are the jugular bulb if it is high, and the posterior semi-circular canal.

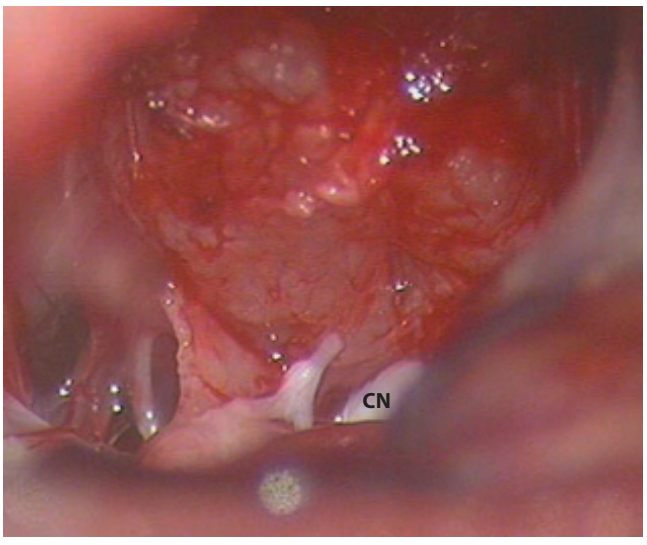

Figure 103.7 Retrosigmoid approach, left ear. Small tumour with cochlear nerve (CN) seen at medial pole.

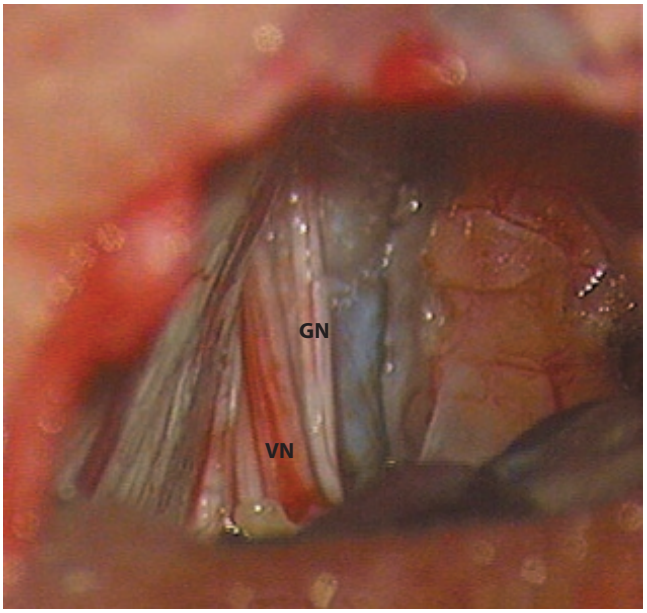

Figure 103.8 Retrosigmoid, left ear. Lower cranial nerves seen below lower pole of tumour. GN, glossopharyngeal nerve; VN, vagus nerve.

A high bulb is more difficult to depress through the retrosigmoid approach than in the translabyrinthine operation. Opening the posterior semi-circular canal is not important unless hearing preservation is intended. The surgeon must look out for the blue line of the canal and avoid it. The combination of a high bulb and an unfavourably placed posterior canal can make the surgical view to the fundus almost impossible. When the bony removal is complete the dura of the internal meatus is opened and tumour removal continues in a medial to lateral direction. If there is a decrease in the magnitude of the auditory brainstem response (ABR), dissection should be halted and local vasodilating agents such as papaverine applied to the vessels in the IAM. As stated above, despite one's best efforts, it may be impossible to see right to the fundus and the last fragment of tumour may have to be removed 'blind'. This manoeuvre clearly carries a risk of damage to the facial and cochlear nerves, and of course there is the risk that tumour may be left behind at the fundus. Some surgeons find it useful to inspect the fundus with a 30 degree fibre-optic rigid endoscope to ensure completeness of removal.[46] Complete endoscopic tumour dissection through a 'key-hole' retrosigmoid craniotomy has also been described.[47]

Closure

After haemostasis is achieved, any remaining air cells are obliterated with bone wax. The dural flap is repaired as far as possible. The repair may be strengthened with fascia or with artificial dura. Steps should be taken to ensure, as far as is possible, that the subcutaneous soft tissues do heal directly on to the dural repair. The authors mix up a pâte of bone dust and tissue glue, which sits on the dural repair and fills the bony defect. A separate periostial flap is then used to cover the pâte repair and the skin and subcutaneous tissues are closed in layers. Hydroxyapatite cement has been used successfully to repair the drilled bony defect in the porus acousticus as a method of preventing CSF rhinorrhoea.[48]

EXTENDED OR COMBINED APPROACHES

There are occasions when extended approaches are applicable, whether via a translabyrinthine approach with transtentorial extension or by utilizing a retrolabyrinthine approach combined with a retrosigmoid and middle fossa bone removal. Occasionally it may be advisable to stage the surgery for very large tumours, with a primary debulking operation and subsequent 'completion'.[49] However, it is quite possible that the 'second stage' may be delivered as single fraction radiotherapy, should the remnant grow.

NOTE ON THE AUDITORY BRAINSTEM IMPLANT

The auditory brainstem implant is increasingly used to rehabilitate patients with neurofibromatosis type 2 (NF2) who are totally deaf and have no functioning cochlear nerves as a result of their bilateral VS or the surgery to remove them. The auditory brainstem implant electrode array comprises 21 small disc electrodes mounted on a Silastic paddle, which is placed onto the surface of the cochlear nucleus. This is found in the floor of the lateral recess of the fourth ventricle, which is entered through the foramen of Luschka. The procedure is usually performed as a combined operation following tumour removal, via either a translabyrinthine or a retrosigmoid approach. The foramen is located by following the glossopharyngeal nerve upwards and the stump of the VIIIth nerve if present downwards. The choroid plexus is seen emerging from the foramen. The taeniae of the fourth ventricle may have to be divided and there is often an arterial loop that has to be moved to one side. The cochlear nucleus is identified by its very white colour and by a fairly constant thin vein that runs over its surface. Intra-operative neural responses using electronically evoked auditory brainstem responses (eABR) are performed to ensure optimal placement of the whole paddle.

OUTCOMES AND COMPLICATIONS

The two key determinants of outcome and complications in VS surgery are the size of the tumour being removed and the experience and surgical skills of the team removing it. Not surprisingly the bulk of the literature on this subject emanates from experienced centres reporting their results: this in effect represents the benchmark for outcomes and complications. Evidence of surgical outcomes from teams undertaking occasional VS surgery are limited. However, the evidence as it exists shows adverse outcomes and higher complication rates when parameters such as death, facial nerve function and CSF leak rates are examined.[50, 51] The evidence for centralisation in NF2 care is certainly strong.[52]

Following enthusiasm from many quarters and the agreement of the British Skull Base Society and the Society of British Neurosurgeons, mandatory data collection for a national audit in VS management is now ongoing in the UK (https://orioncloud.org).[53]

The single most important factor in all studies quoting facial nerve and hearing preservation and extent of resection is the tumour size.[54] Many feel that there is a difference in outcomes between solid and cystic tumours, with cystic ones faring less well with surgery.[55–57] This is by no means universal.[58] It is commonly believed that they are also less successfully treated with radiotherapy.

Facial nerve outcomes are of the utmost importance to the patients, and multiple attempts to improve prognostic information for pre-operative counselling as well as post-operative prediction have been made. Reviewing the pre-operative imaging, the size of the tumour, the anterior extent and the shape have all been correlated with poorer facial function.[59] Intra-operative neurophysiological stimulation has been used with some success to try and predict the degree of facial dysfunction post-operatively.[54, 60–66]

Complications after VS surgery are quite frequent but the vast majority of patients undergoing tumour removal do not suffer any significant long-term sequelae. As complications and outcome are inextricably linked, the two are considered together.

Death, stroke, haemorrhage, brain injury

As indicated earlier in this chapter, the early results of VS surgery were not encouraging, with peri-operative mortality of over 80%.[12] The efforts of Cushing,[13] Dandy[14] and Pennybacker and Cairns[15] brought the death rate down to more acceptable levels, but it was not until the era of microsurgery in the 1960s that it really came down the levels we see today, at around 1% or less in specialist centres.

The actual causes of death have not changed much over the years: vascular events and their effects on the brain and general medical complications associated with major surgery such as myocardial infarction, pulmonary embolus and pneumonia. A meta-analysis including over 30 000 operations for VS focusing on non-audiofacial outcomes showed an overall mortality rate of 0.2%. Approximately 20% of patients experienced one surgically attributable complication.[67] The likelihood of serious vascular events is for the most part related to tumour size and is considered in more detail below.

ARTERIAL BLEEDING

Vigorous arterial bleeding is not a common occurrence during VS surgery. The surgeon must of course take great care to identify and protect the major arterial systems in the posterior fossa, notable the anterior and posterior inferior cerebellar arteries (AICA and PICA) and the superior cerebellar artery (SCA). Gentle handling of tissue, adherence to correct tissue planes and the avoidance of traction are essential. If serious bleeding does occur it must, of course, be controlled with the minimum of damage to the arterial tree, and precise identification of the bleeding point. A small side hole in even a large vessel can often be controlled with skilful and accurate use of the bipolar diathermy. Alternatively, minor degrees of arterial bleeding may be controlled by application of a piece of muscle to the affected site. Serious injury to the main trunk of AICA requiring clamping is of grave significance and carries a high risk of death. It is fortunately excessively rare. Less uncommon is damage to more distal branches of AICA. The extent of brainstem damage in the event of loss of these vessels is variable and depends on the degree of anastomosis from PICA and SCA. It may give rise to fatal infarction of the lateral tegmental pons or the damage may be confined to the cerebellar peduncle, as pointed out by Hegarty et al. (**Figure 103.9**).[68] This may result in serious gait, balance and co-ordination problems. The distal branch in question may loop into and out of the IAM. The vessel must therefore be identified, separated from the tumour and preserved in order to avoid these potential problems. Feeding vessels from branches of AICA to the tumour may be cauterized close to the tumour but, as a rule, every attempt is made to preserve all arterial vessels encountered by remaining in the arachnoid sheath between the tumour and the neurovascular structures of the posterior fossa.

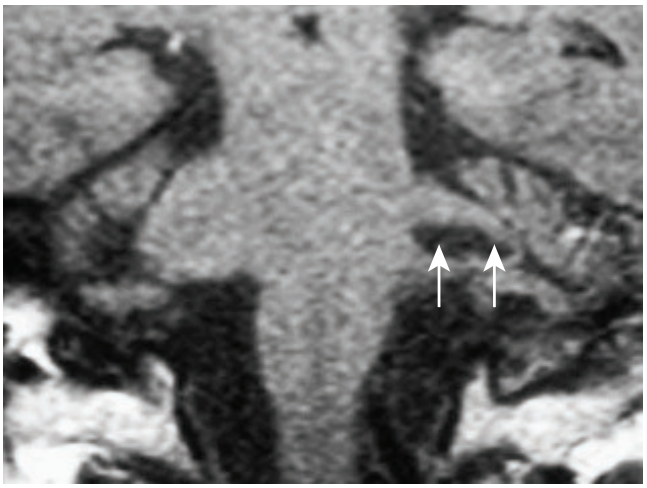

Figure 103.9 Peduncular infarct (arrowed).

VENOUS BLEEDING

Troublesome venous bleeding may occur during the petrosectomy in the translabyrinthine approach and during tumour removal itself. Bleeding from the mastoid emissary veins is readily controlled by a combination of bipolar cautery and the use of bone wax. During the skeletonization of the lateral, sigmoid and superior petrosal sinuses and the jugular bulb, inadvertent injury to the dura of these structures gives rise to dramatic venous haemorrhage. Despite this, careful use of haemostatic mesh (Surgicel) over the tear with compression using bone wax and a neurosurgical cottonoid usually solves the problem and allows the procedure to continue, as the dural sinus veins are a low-pressure system. Care must be taken to prevent air embolism but it should be emphasized that this is an exceptionally rare occurrence, especially since the sitting position for surgery has been abandoned in the UK. Excessive compression of the jugular bulb should be avoided as it may give rise to lower cranial neuropathies. In the experience of the authors it has never been necessary to ligate the lateral venous sinus or the internal jugular vein in the neck to control bleeding from the venous sinuses encountered during the petrosectomy.

During tumour removal itself, the petrosal vein (Dandy's vein) is invariably encountered. This fragile vein drains the brainstem and cerebellar hemisphere and is a tributary of the superior petrosal sinus. It is easily torn during tumour dissection and it is mostly safe to clip or cauterize and divide the vein rather than have to deal with the troublesome back bleeding from the superior petrosal sinus.[69]

Finally, numerous often quite substantial veins are encountered between the arachnoid sheet and the brainstem. These are best dissected away from the tumour and then coagulated if necessary, but the surgeon must be aware of the risk of venous infarction of the brainstem from the indiscriminate sacrifice of these vessels. Overall, while venous bleeding can be troublesome and occasionally dramatic, it is rare for it to lead to hypovolaemia and it is very uncommon to have to transfuse a patient during a VS resection. Finally, the incidence of air embolism during

VS surgery has declined significantly since the almost universal adoption of the supine or lateral position of the patient as opposed to the sitting position.

POST-OPERATIVE HAEMATOMA

The risk of a post-operative haematoma is greatest in the first 72 hours after the operation but continues for about a week. Failure to regain consciousness after surgery is the classic sign of a posterior fossa haematoma and necessitates immediate re-exploration of the operative site. Signs of a delayed haematoma in a patient who has already woken up from the anaesthetic include progressive hypertension, bradycardia, reduction in consciousness level and alterations in pupil size and reactivity. These signs should be recognized by assiduous post-operative neurological observation and recording of the Glasgow Coma Scale. If time permits, a CT scan will confirm the diagnosis but in the rapidly deteriorating patient immediate return to theatre and evacuation of the haematoma is required to save the patient's life. When the translabyrinthine approach has been employed, the wound can be reopened in the ward or the recovery room and the abdominal fat removed. This may bring about a rapid improvement in the patient's neurological status, and he may then be returned to theatre for more leisurely haemostasis.

Ventricular haemorrhage, whether intra-operatively or after surgery, is a rare but very serious complication. External ventricular drainage may help but the condition carries a high risk of death.[70]

In contrast, a small haematoma without neurological sequelae may be managed conservatively, and be left to reabsorb naturally. The incidence of serious post-operative haematoma is approximately 1% and contributes to the overall mortality risk of this type of surgery.[67]

BRAIN INJURY

Cerebellum

The cerebellum is at risk of injury during opening of the dura of the posterior fossa and during tumour removal itself. The mass effect of a large tumour will push parts of the cerebellum against the overlying dura, compressing the cerebellar surface vessels. Minor degrees of venous injury are tolerated without problems but more substantial injury is likely with prolonged cerebellar retraction during retrosigmoid surgery. A degree of encephalomalacia of the superficial lateral part of the cerebellar hemisphere is frequently noted on post-operative MR imaging, though this does not usually give rise to any clinical manifestations.[40] The surface of the cerebellum may become oedematous during removal of large tumours but the historic procedure of resecting the lateral one third of the cerebellum for access and creation of space for post-operative swelling is rarely required now with modern surgical and anaesthetic techniques. Less commonly, parenchymal injury or oedema extends into the deeper parts of the cerebellum. This may signify venous insufficiency of the cerebellum or a cerebellopontine haematoma. This type of injury may well leave the patient with prolonged or permanent ataxia.

Brainstem

Direct injury of the brainstem is avoided by maintaining the subarachnoid plane between the tumour and the brain. In small and medium-sized tumours the plane between the brain and the tumour is usually easily identified and adhesions between the two tend not to be particularly dense and are readily divided. As discussed above, vascular injury is avoided by careful dissection and preservation of arterial anatomy. With larger tumours, however, there is often a degree of malacia of the brainstem due to prolonged compression by the tumour. In these instances the brain is very soft and breach of the pial layer can occur easily. In addition, ischaemia of the brainstem due to traction during tumour removal may give rise to bradycardia or even asystole. Both respond to cessation of dissection of that particular part of the tumour and appropriate intra-operative resuscitative measures. Rarely, the procedure needs to be abandoned due to persistent changes in the vital signs. Direct injury of the brainstem parenchyma is uncommon and the more likely cause of serious or fatal injury is secondary ischaemia consequent to the tumour dissection or injury to vessels such as the AICA as described above.

Temporal lobe and seizures

Seizures after translabyrinthine or retrosigmoid surgery are extremely rare. This, however, is not the case for transtemporal (middle fossa) tumour removal. The middle fossa approach (invariably in an attempt to preserve hearing with a small tumour) involves extradural retraction of the temporal lobe. This carries a risk of seizures, as noted by the authors in two cases.[34] While the fits did not lead to a residual neurological deficit, in both instances the patients were legally obliged to refrain from driving until they were fit-free for a year. Long-standing electroencephalographic changes have been reported[71] in patients undergoing middle fossa VS surgery. In addition, injury to or occlusion of the vein or veins of Labbé, which drain the inferior and lateral temporal lobe, carries the risk of venous temporal lobe oedema and infarction leading to seizures, dysphasia or even loss of life. These veins drain into the distal transverse sinus so are potentially at risk from excessive packing of the proximal lateral venous sinus in order to control bleeding during translabyrinthine or retrosigmoid surgery.

Cranial neuropathies

FACIAL NERVE

Of all the potential sequelae of VS surgery, without doubt the one concern raised by patients above all others is that of post-operative facial function. Most patients expect to survive their operation, be free of disability and be tumour free. It is their facial function that is usually at the forefront of their minds. On this basis, a full and frank discussion with reference to one's own facial nerve outcomes is required in order to secure informed consent for the surgery. Facial nerve preservation refers to

anatomical preservation of the facial nerve, while facial function refers to the physiological function of the nerve at a defined time post-operatively. Both are determined largely by tumour size and experience of the surgical team and, to a lesser but important degree, by the nature of the tumour (solid or cystic)[55–58] and the surgical philosophy of the team. The latter is important. Those surgeons who attempt to remove every last bit of tumour may well find their facial nerve outcomes are less favourable than those who have a low threshold for leaving tumour remnants in order to maintain the anatomical and functional integrity of the nerve.[72–75] It is vital, therefore, when examining facial nerve outcomes, to put the results in context: what is the rate of residual or recurrent tumour in the series that is being studied? In the experience of the authors, if a small nubbin of tumour is particularly adherent to an attenuated facial nerve (often just medial to the porus of the internal meatus) then it reasonable to leave this remnant in order to preserve the facial nerve. Usually, imaging a year later shows the nubbin to have disappeared. If it has not disappeared, serial imaging almost invariably shows the size of the residuum to have remained static.[29]

Facial function is assessed using a grading system, of which the House-Brackmann (HB) system is the most common in general use and relatively easy to use. Nevertheless it is far from perfect and suffers the same criticism that is applicable to any system that tries to fit a dynamic spectrum of movement into a finite number of categories (in the case of the HB system, six categories).

Stratifying the patients by tumour size is helpful in presenting facial nerve results. For intracanalicular tumours and tumours with a maximum intracranial diameter on imaging of less than 1.5 cm, most large series publish facial nerve anatomical preservation rates approaching 100%.[76–78] This is in keeping with the authors' series in which loss of the facial nerve is rare when removing such small tumours. Facial function outcomes for this group is between 80% and 95% HB grade I or II. At this juncture a comment about what constitutes a good facial outcome is required. From the patient's perspective, anything less than normal facial function post-operatively represents a less than ideal outcome. However, the patient will invariably take into account the size of the tumour that he or she presents with (as will the surgeon when counselling the patient) and with larger tumours, HB grade II or even III may be considered satisfactory. When reporting results, therefore, by convention most surgeons consider HB grade I or II as a satisfactory outcome. HB grade III is not a satisfactory outcome for small or medium-sized tumours, though some surgeons fail to appreciate this point when presenting their results.

For medium-sized tumours (maximum intracranial diameter 1.6–2.5 cm), anatomical facial nerve preservation rates fall to around 90% with HB grade I or II outcomes between 80% and 90%.[78, 79] An interesting observation occurs for tumours greater than 2.5 cm intracranial diameter: the facial nerve outcomes decline in an almost inverse linear proportion to the size of the tumour.[80–82] However, this threshold may change with increasing experience of the surgeon. A meta-analysis of more than 10 000 patient outcomes showed a cut-off of 20 mm.[54] Overall, for large and giant (more than 4 cm) tumours, anatomical preservation of the nerve occurs in between 65% and 80% with normal or good facial function (HB I or II) in 50–70%.[83–85]

In assessing facial function, consideration must be given to synkinesis, either the involuntary closure of the eye when the patient smiles or eats or, less commonly, unwanted movement of the corner of the mouth in time with blinking. The phenomenon may detract from an otherwise good facial nerve outcome and cause the patient considerable distress. The judicious use of botulinum toxin may be necessary to minimize this phenomenon. The development of a multidisciplinary facial palsy service in centres offering skull base surgery has allowed improvements in the rehabilitation of patients with facial palsy.[86]

NERVUS INTERMEDIUS

The importance of the function of the nervus intermedius (NI) is perhaps overlooked when reporting the results of VS surgery. Understandably, the nerve is not in the forefront of the surgeon's mind when trying to remove a large tumour and preserve the facial nerve itself. Nevertheless, the morbidity of loss of NI function should not be underestimated. Difficulties with a dry eye (even with normal facial and trigeminal function), altered taste and dryness of the nose and mouth can be very troublesome for the patient.[87] Aberrant re-innervation leading to gustatory tearing can also be troublesome. Attempts should be made to preserve the nerve, though with larger tumours it is often impossible to identify it as a separate entity.

TRIGEMINAL NERVE

Tumours of less than about 2 cm intracranial diameter do not usually come into contact with the trigeminal nerve, which lies antero-superiorly and medial to the tumour. Smaller tumours may stretch the trigeminal nerve as the brainstem is displaced to the opposite side of the posterior fossa. Inadvertent injury to the trigeminal nerve during the removal of small and most medium-sized tumours is rare. For larger tumours, however, there is invariably indentation, stretching and compression of the trigeminal nerve to some degree. This may or may not be associated with trigeminal symptoms pre-operatively. Even large tumours do dissect off the nerve fairly easily in most instances, however, particularly if the surgeon remains within the arachnoid plane between the tumour and the nerve and therefore the incidence of trigeminal symptoms post-operatively lies between 3% and 15%.[88] Such damage can have grave consequences for the eye if there is a concomitant facial weakness, as the loss of corneal sensation with a dry eye (nervus intermedius) and incomplete eye closure puts the unprotected cornea at risk of ulceration leading to loss of vision.

ABDUCENS AND TROCHLEAR NERVES

Palsies of these two oculomotor nerves are uncommon.[84] The abducens nerve may be inadvertently injured during packing of the superior petrosal sinus for control of

haemorrhage from the sinus or from anterior tumour dissection. The resultant paresis invariably recovers over a period of several weeks to a few months. Damage to the trochlear nerve is extremely uncommon although in theory it may be at some risk of injury during anterosuperior tumour dissection towards the free edge of the tentorium cerebelli.

LOWER CRANIAL NERVES

Injury to the lower cranial nerves may cause significant morbidity and a protracted hospital stay, due to the effects on swallowing and the competency of the upper airway. The glossopharyngeal, vagus and accessory nerves are at risk during two stages of surgery: the petrosectomy during translabyrinthine surgery; and during the removal of the inferior pole of the tumour. The relationship of the internal meatus, the cochlear aqueduct, the jugular bulb and the lower nerves has been described above. By keeping above the cochlear acqueduct during skeletonization of the IAM, and by avoiding over-compression of the jugular bulb, damage to these nerves should be avoided.

In small and medium-sized tumours, the intracranial tumour resection puts the lower cranial nerves at almost no risk as long as the nerves are identified early in the procedure. With larger tumours the multiple nerve rootlets of the glossopharyngeal and vagus nerves are stretched and splayed over the inferior pole. Dissection of the tumour off these nerves is usually straightforward and their function is therefore almost invariably preserved. Post-operative lower cranial nerve palsies are uncommon (less than 1%) except in revision cases when fibrosis and distortion of the anatomy can make the dissection more difficult. In such instances, and in larger tumours, electrophysiological monitoring of the vagus using electrodes on the endotracheal tube (NIM TriVantage® EMG Tube) as well as the XIth and XIIth nerves should be considered. Finally, during surgery, manipulation of the IXth and Xth nerves can cause profound but temporary bradychardia and even asystole, and the anaesthetist needs to be warned when dissection of the lower pole of the tumour is taking place.

CSF leakage

Leakage of CSF after VS surgery is the commonest significant post-operative complication. CSF leak rates reported in the literature vary depending on the approach, the size of tumour, the extent of petrous bone pneumatization and primary versus revision surgery.[89–91] The literature is conflicting when comparing the incidence of CSF leakage after translabyrinthine, retrosigmoid and transtemporal approaches – several studies cite no difference and others cite a higher incidence after translabyrinthine surgery, while others cite a higher incidence after the retrosigmoid approach.[42, 67, 90–92] The leak may be classified as minor (requiring no additional surgical procedure to deal with it) or major, necessitating a return to theatre. A subcutaneous scalp collection of CSF with or without leakage through the wound is considered a minor leak, as it is usually remedied with reapplication of a firm pressure dressing and an additional full-thickness scalp suture at the site of leakage, which is often at the bottom end of the wound. Such collections and leaks tend to occur within the first week of surgery and can be dealt with at the bedside, without a need to return the patient to theatre. In addition, continuous lumbar CSF drainage for 3–5 days usually solves this problem. The latter may be used electively after all VS surgery or in response to scalp collections or leaks that persist despite the conservative measures described above. Lumbar drains, however, are not without their own problems. They inherently incur a degree of immobility in the patient at a time when one would wish to encourage mobilization to enhance vestibular rehabilitation and reduce the risk of venous thrombo-embolism. In addition, the drain represents a portal for sub-arachnoid infection and may lead to pneumocephalus if there is entry of air from the nasopharynx through the temporal bone into the posterior fossa as the CSF is siphoned off.[93] Pneumocephalus may lead to a significant neurological deterioration, particularly if the air collects in the ventricles or is under tension. The use of lumbar drains after VS surgery is therefore not universal and evokes debate amongst surgeons who undertake this type of surgery.

It has also been postulated that the inflammation associated with meningeal irritation may result in a spontaneous resolution of CSF rhinorrhoea post-operatively. This has not been our experience and we would advocate early intervention with reoperation and blind sac closure, combined with lumbar CSF drainage if necessary.[94]

Revision surgery and surgery following failed radiotherapy is considered more risky and results in poorer outcomes.[95]

CSF otorrhoea

An intact tympanic membrane at the time of surgery should guard against any leakage of CSF via the external meatus. Any injury to the tympanic membrane or external ear canal skin during VS surgery is rare. CSF otorrhoea has, however, been described in relation to the use of bioglue to seal the Eustachian tube opening and the middle ear.[32] The glue had led to an acute myringitis with perforation of the tympanic membrane and additionally failed to prevent CSF entering the middle ear.

CSF rhinorrhoea

Leakage of CSF through the temporal bone air cells via the Eustachian tube into the nasopharynx remains a troublesome complication that invariably prolongs the patient's hospital stay and often necessitates a return to theatre. Ultimately the leak has to be stopped lest the patient develops intracranial infection. In the retrosigmoid approach the air cell system is most commonly opened posterior to the lateral venous sinus and around the IAM. In both instances most surgeons utilize bone wax to obliterate these cells in an attempt to seal communications between the CPA and the temporal bone. During translabyrinthine surgery the temporal bone surgery is much more extensive

and air cell tracks anterior to the IAM and around the jugular bulb are potential conduits for CSF to enter the middle ear or Eustachian tube directly. In addition, subluxation of the stapes may have the same effect. On this basis several methods to reduce the risk of CSF rhinorrhoea have been described by various surgeons, illustrating that no single method is universally successful. These include using pieces of muscle, fat, fascia, bone wax and tissue glue to seal the areas described. In addition, some surgeons advocate routine lumbar drainage for a few days post-operatively.

Interestingly, there is evidence that despite packing the Eustachian tube at the time of surgery, the middle ear regains ventilation via the tube and, in addition, packing of the tube or waxing opened mastoid air cells didn't result in a reduction of CSF rhinorrhoea.[89, 96] However, like others, it is our practice to ensure the Eustachian tube is tightly packed and the middle ear cleft filled with fat.

Finally, there is the occasional patient who, despite all measures at primary and subsequent surgery, continues to suffer CSF rhinorrhoea. In these instances (less than 1%) the only remaining option is to undertake permanent CSF diversion such as a lumbo-peritoneal or ventriculoperitoneal shunt. It is postulated that in these patients there is a subclinical post-operative hydrocephalus that drives the persistent leak.

Intracranial infection

MENINGITIS, ENCEPHALITIS, CEREBRITIS

Meningitis after VS surgery is one of the more common serious complications occurring in 1% to 5% in the reported larger series.[79, 97] It is invariably associated with CSF leakage (usually rhinorrhoea) and may occur within the first week of surgery or as a delayed event weeks or even months later. In the latter situation the CSF leakage may have passed unnoticed by the patient and the surgeon. Most VS surgeons give prophylactic peri-operative antibiotics empirically as there is no formal evidence that this measure reduces the incidence of post-operative infections. The diagnosis requires clinical vigilance as headache and neck stiffness are not uncommon after VS surgery.[41] In addition, many patients develop low-grade pyrexia within the first week after surgery, which in part may be due to an aseptic meningeal irritation due to blood, air and bone dust in the subarachnoid space. If any doubts exist, a lumbar puncture will confirm the presence of a leucocytosis, though the causative organisms are often not isolated or cultured. The treatment regimen will vary from institution to institution but parenteral Vancomycin and Ceftriaxone are the current first-choice empirical treatment. CSF culture will guide ongoing management and, if sterile after 3–7 days, a diagnosis of aseptic meningitis can be made and the antibiotics stopped. This treatment schedule almost invariably resolves the problem, although rarely the infection may progress to a fulminant encephalitis or cerebritis, both of which carry a high mortality.

OUTCOMES

Tumour extirpation: Residual/recurrence

In the majority of cases undergoing VS surgery, the aim is to remove the tumour completely while maintaining perfect facial nerve function. It was previously thought unacceptable to subject the patient to the inherent risks of this type of surgery and then not remove the tumour in its entirety. However, it is fair to say that this philosophy has changed. While total removal has the obvious benefit of reassuring the patient that their tumour has gone and there is very little chance of recurrence, the evidence is very clear that the facial nerve outcomes are worse when comparing near-total to subtotal, and again in total versus near-total.[75]

There are instances where a planned subtotal removal procedure is reasonable: in patients with large tumours giving rise to hydrocephalus in the elderly; or in those who have concomitant medical problems that necessitate as short a procedure as possible. The residual tumour in these instances can then be monitored with serial imaging and the residuum dealt with by way of further surgery or stereotactic radiotherapy if it grows to a size that once again requires intervention.

The impression of the operating surgeon as to the extent of resection when a 'subtotal resection' has been performed is open to interpretation. It is considered important to document the size of the residual tumour with early post-operative contrast-enhanced MRI.[81] In addition, the post-operative imaging in patients who have undergone incomplete removal often shows no enhancing tissue at all.[28]

Following presumed gross total excision there is a documented rate of recurrence. Despite expecting it to be zero, it has been shown to be in the order of 1–3%. However, it goes without saying that a higher rate of recurrence is expected in situations where a visible quantity of tumour remains, either in subtotal removal or near-total removal, where in both there is lack of clarity as to what exactly is meant. Subtotal removal suggests a solid mass of tumour is left, whereas in near-total removal a linear remnant adherent to the facial nerve is all that remains. One series reporting rates of regrowth showed 3% of patients subjected to gross total excision had regrown, compared to 21% and 22% regrowth rates for near-total and subtotal resections respectively.[72] Choosing to stop tumour dissection short of obtaining a complete resection is usually a consequence of maintaining good facial nerve function. However, in addition to the facial nerve, attempting to preserve integrity of the cochlear nerve and functional hearing may impair a complete resection. This is more often the case in the middle fossa approach because the bone drilling required to visualize this area directly puts the inner ear structures (and therefore the hearing) at risk and tumour removal at the fundus is almost a blind procedure.[98] Intra-operative endoscopy may help in this situation.[46, 99] Finally, there is some debate about the frequency and length of imaging follow-up needed after surgery

before declaring the patient tumour-free. Practice varies from a single scan 1 year post-operatively (as advocated by the authors) to imaging 2, 5 or even 10 years after the surgery.

Hospital stay

The median hospital stay for patients undergoing VS surgery under the care of the authors is 7 days. The literature varies citing a hospital stay of between 5 and 10 days if the immediate convalescence is uncomplicated.[19] The commonest cause of delay in discharge from hospital is CSF leakage, particularly CSF rhinorrhoea. Management of this complication invariably prolongs the hospital stay, particularly if further surgery is required to rectify the leak. One study calculated an additional 13.3 days in hospital in patients who developed post-operative CSF leak.[32] The two causes of a more prolonged hospital stay (several weeks or more) are bulbar symptoms due to brainstem injury or lower cranial neuropathies and the development of meningitis.

Vertigo/balance/return to work or previous physical activity

Many patients with a VS describe a period of vertigo, dysequilibrium or imbalance when questioned directly about pre-operative symptoms. The gradual reduction in vestibular function on the affected side due to the tumour is compensated for by the opposite vestibular end organ, vision, proprioception and the central nervous system such that day-to-day balance is rarely a problem for most individuals before surgery.

Post-operative balance problems depend on the degree of pre-operative impairment, with those with a complete canal paresis on caloric testing seemingly unfazed by the loss of vestibular function. However, those with a functioning labyrinthine system pre-operatively have acute vestibular failure with a paralytic nystagmus and are functionally much worse for a few days until compensation can occur.[100] Other than for initial symptomatic relief, vestibular sedatives should therefore be avoided to allow for this process to occur. In addition, the implementation of vestibular-ocular reflex exercises further accelerates the rate of compensation.[101]

In an attempt to mitigate the impact of acute vestibular failure in patients undergoing translabyrinthine surgery for VS, a chemical labyrinthectomy with intratympanic gentamicin and focused vestibular exercises (prehab) have been shown to reduce vestibular dysfunction immediately after surgery, but also longer term.[102, 103]

In those individuals who have already slowly lost much of their vestibular function due to the tumour, the post-operative vertigo may be minimal. Over the ensuing weeks and months the majority of patients find that their balance recovery is such that they can resume their pre-operative occupation or return to a comparative level of physical activity.[104] However, as expected, an individual with a complete unilateral vestibular deficit cannot be expected to have perfect balance and this may be more noticeable in the dark or with sudden movements. The patient's perception of their balance dysfunction is important, with over 10% perceiving disequilibrium as disabling.[100] Patients with occupations that rely on fine balance therefore need to be counselled in this respect.

Tinnitus

Unilateral tinnitus is one of the cardinal symptoms of a VS. Occasionally it represents the sole presenting symptom.[105] Tinnitus probably remains the most troublesome symptom following surgery for VS. Most clinicians advise that patients presenting with tinnitus are very likely to have persistence of their tinnitus post-operatively and studies support this viewpoint.[106–108] An interesting observation described is that of gaze-evoked or enhanced tinnitus after VS surgery. This is probably a rewiring phenomenon in the brainstem.[107, 109]

Hearing preservation

In discussing the possibility of hearing preservation, a number of issues need to be considered. The commonest presenting symptom of VS is unilateral hearing impairment. As in any hearing impairment, the degree of resultant disability needs to be taken into account with respect to the better, often normal contralateral ear. This is well recognized in reconstructive middle ear surgery such as ossiculoplasty and stapedotomy, where the patient's perception of benefit will only be realised if the middle ear surgery brings the hearing within a defined level of the opposite ear (Belfast rule of thumb, Glasgow benefit plot).[110, 111] On this basis the audiometric criteria for considering hearing preservation surgery advocated by the authors is a pure tone average of 30 dB or better and a speech discrimination score of 70% or better in the affected ear, if the opposite ear is normal (Gardner Robertson class A).[112] This in itself significantly reduces the number of potential hearing preservation candidates. In addition, the tumour should be less than 1 cm diameter intracranially and be well away from the fundus of the internal meatus in order to have a realistic chance of preserving not just a functioning cochlear nerve but also the fine vasculature in the internal meatus that supplies the cochlea. In reality, few patients meet these requirements and in our experience of those that do, the hearing is preserved at the pre-operative level in one in three. In our experience, perhaps the best way to preserve good hearing in a patient with a small tumour is to leave the tumour alone and only intervene of there is evidence of growth on serial imaging.[6, 113] This philosophy of the place of hearing preservation surgery is not uniform by any means.[114] The literature is replete with difficulties when it comes to evaluating this aspect of VS surgery. First, much of the earlier literature fails to define what is meant by good hearing, useful hearing or serviceable hearing in the affected ear. This makes evaluation of hearing outcomes very difficult.[115] Second, many surgeons advocate attempts to preserve hearing at 50 db pure tone and 50%

discrimination scores in the presence of normal contralateral hearing. Some surgeons will even attempt to preserve any measurable hearing, although the utility of this is questionable. While such attempts are acceptable if no additional harm is done, the risk of a higher facial palsy rate (particularly in the transtemporal approach)[116] or a higher incidence of residual tumour in the retrosigmoid approach raises the issue as to whether such hearing preservation attempts are justified.

In attempting to preserve functional hearing, the proponents of both middle fossa and retrosigmoid approaches report good results, even in larger tumours.[117] Vast amounts of evidence exist arguing for one approach over another, although it seems that no one approach confers all the benefits and none of the complications.[118, 119]

Hearing preservation rates vary depending on the size of the tumour, the resultant tumour—nerve interface and the level of hearing pre-operatively.[120, 121] Continuous monitoring of the cochlear nerve during tumour dissection has been shown to improve the preservation of hearing.[122–124] In addition to the actual size of the tumour, the amount of tumour filling of the IAC also has an effect. In cases where there is some CSF lateral to the tumour the rate of preservation is also higher.[125]

Finally, more recent quality of life assessments of patients undergoing VS surgery suggest that the loss of the impaired hearing is not as significant a handicap as one might imagine[126] and, indeed, it is the experience of the authors that the loss of impaired distorted hearing actually allows the patient to gain better overall hearing using the normal contralateral ear alone. This observation is in part responsible for the more recent development in auditory rehabilitation described below.

HEARING REHABILITATION

Complete unilateral hearing loss is an inevitable consequence of translabyrinthine VS surgery and occurs in a large proportion of those undergoing other approaches, including those in which hearing preservation is attempted. Therefore the hearing handicap of single-sided deafness (poor sound localization, reduced intelligibility of speech in noise and overall ease of listening) should be minimized as much as is possible. Advances in hearing aid technology in the form of behind-the-ear aids utilizing wireless contralateral routing of signal have enabled excellent rehabilitation of VS patients at presentation, as well as following intervention.[127] Bone-anchored hearing aid (BAHA) technology has also developed and allows an alternative method of hearing rehabilitation.[128, 129]

As well as accessing the hearing in the contralateral ear, simultaneous or sequential cochlear implantation and translabyrinthine surgery has been performed with good results, both in patients with sporadic tumours and those with NF2.[25]

Quality of life

The patient's perception of their facial appearance, their hearing handicap, their ability to perform routine daily tasks of living and their overall quality of life is of greater importance to them than the surgeons' perspective of success in managing their condition. The emphasis on patient reported outcome measures (PROMs) is reflected across the whole medical literature and VS management is no exception. The development of the first disease-specific quality of life instrument, the Penn Acoustic Neuroma Quality of Life (PANQOL) scale has given the ability for all professionals managing patients with VS to report their outcomes in a similar manner.[130] The UK Skull Base community has adopted this measure as part of the compulsory prospective VS audit that is ongoing[131] (https://orioncloud.org).

At different stages of each individual patient's journey, a change in their perception of quality of life may be anticipated. Diagnosis is a time associated with significant uncertainty and stress and a subsequent reduction in quality of life.[132] Conservative management, where appropriate, provides the highest chance of maintaining a good quality of life. However, there remains an ongoing health and psychological burden in the requirement for regular imaging. Dizziness has the most significant impact on quality of life, with tinnitus also rated as having an impact. Hearing, interestingly, doesn't seem to influence quality of life.[133]

At the stage of intervention, and in particular surgery, the patient is most likely to experience a reduction in quality of life.[134] The potential impact on mobility, balance and facial function is condensed into a short period. This is reflected in the scores in the assessment tool up to 5 years. Longer-term follow-up has shown no significant difference between any of the three groups.[134]

Ongoing collection of quality of life and other surgical outcome data will provide guidance to those professionals involved in the management of VS; with this it is hoped that the standards can be further raised.

KEY POINTS

- The management of a patient with a vestibular schwannoma has evolved over the last 20 years such that many small tumours are managed conservatively.
- Surgery remains the treatment of choice for large tumours and continues to be a viable option for growing small- and medium-sized tumours.
- The outcomes of surgery are largely dictated by the size of the tumour and the experience of the team managing the patient.
- All patients with a diagnosis of vestibular schwannoma must be given the benefit of a multidisciplinary evaluation which includes neuro-otology, neurosurgery, radiation oncology and radiology.

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CHAPTER 103

STEREOTACTIC RADIOSURGERY

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SEARCH STRATEGY

Data may be updated using a PubMed or MedLine search using the following keywords: stereotactic radiosurgery, stereotactic radiotherapy, meningioma, pituitary adenoma and vestibular schwannoma.

OVERVIEW OF STEREOTACTIC RADIOSURGERY DELIVERY TECHNIQUES

Principles of stereotactic radiosurgery

The term 'stereotactic radiosurgery' is applied to techniques involving a well-defined co-ordinate base that enables the precise localization of a tumour and targeting of radiotherapy treatment. Localization may be achieved through the use of a fixed or removable headframe, or using the patient's own anatomy to determine a Cartesian based co-ordinate system. Using this with magnetic resonance imaging (MRI), it can be used to target pathological lesions including skull base tumours. Stereotactic radiosurgery uses ionizing radiation to ablate a volume of tissue, or to alter its biological activity, thus preventing further growth. The dose of radiation can be either delivered in a single treatment (stereotactic radiosurgery (SRS)) or in several fractions (stereotactic radiotherapy (SRT)). The decision of whether to deliver the dose in a single or multiple fractions will be based on the type of delivery equipment, and the requirement to allow nearby healthy tissue to recover in the intervals between each radiotherapy dose fraction. SRS is generally restricted to targets less than 3 cm in diameter and steep dose gradients are essential due to the risk of damaging adjacent normal tissue.

The delivery equipment for SRS can be broadly divided into two categories: modified conventional linear accelerators; and dedicated stereotactic devices. Both categories utilize enhanced imaging to determine tumour location and targeting, and a high-resolution collimation system to achieve sharp dose gradients.

MODIFIED CONVENTIONAL LINEAR ACCELERATORS

Modified conventional linear accelerators have the advantage that they offer flexibility for the workflow of a radiotherapy department, since they can be used to treat a wide range of indications. The equipment is readily available; however, a modification is often required to the machine to enable it for stereotactic use, such as a secondary high-resolution small field multi-leaf collimator (MLC). In order to correctly position the patient, additional stereoscopic X-ray images are often acquired, which, in conjunction with a modified treatment couch and patient fixation system, can achieve sub-mm delivery precision.

DEDICATED STEREOTACTIC MACHINES

Dedicated machines, such as the CyberKnife linear accelerator (Accuray) and the Gamma Knife unit (Elekta), utilize high-precision patient localization and high-resolution radiation beam collimation to deliver dose with sub-mm precision without need for modification.

The high collimation means the units are restricted to treating small volumes. The ability to deliver beams from multiple (several hundred) angles provides the steep dose gradient required to protect against normal tissue damage when using SRS.

The Gamma Knife unit uses a fixed array of 192–201 radioactive cobalt sources to deliver the dose to a patient wearing a rigid stereotactic frame to achieve precise targeting. The Gamma Knife was developed for intracranial SRS several decades ago and the current version has been subject to significant refinement. A CyberKnife unit uses stereoscopic imaging of the patient for precise localization without the need of a headframe (**Figure 103.1**). Since the linear accelerator on the CyberKnife unit is mounted on a robotic treatment arm it is not restricted to any angular position, unlike gantry mounted modified conventional accelerators. The size of the beams can be varied by changing the collimators, and complex dose distributions can be achieved by moving the patient and by blocking sources (Gamma Knife) or by changing the beam angles (CyberKnife). These variables allow treatment plans to be formulated that precisely match even irregular tumour volumes.

The Gamma Knife system uses a surgically attached headframe to enable localization to the machine. The Gamma Knife is dedicated to intracranial or skull base pathology and it is not possible to target disease extending into the neck. A CyberKnife unit uses digitally reconstructed radiographs of the skull from a planning CT scan to produce sub-mm localization. The system is also able to use the spine or fiducial markers to enable extracranial treatment delivery. Intracranial targeting accuracy of a CyberKnife machine is <0.5 mm, and <1 mm extracranially. Intrafractional patient movement during delivery is detected via the stereoscopic X-ray system and corrected by changes to the robotic delivery path, rather than repositioning the patient. Since the system does not require a headframe for positioning, there is no loss in delivery precision if the dose is delivered in one (radiosurgery) or over several (radiotherapy) fractions.

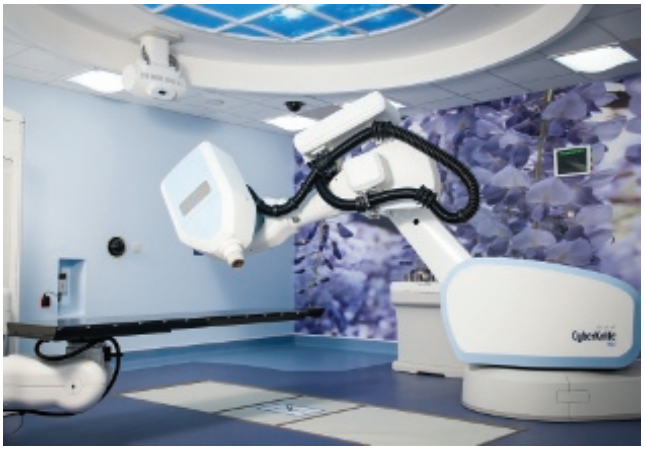

Figure 103.1 CyberKnife unit.

Patient treatment

Prior to any treatment being carried out, several preparation stages are required as well as offering the patient appropriate counselling and support.

Pre-treatment imaging is required for target definition; usually this is MRI but other modalities may be appropriate depending on the pathology of the target. Imaging (often computed tomography (CT)) is also required for localization and this needs to be performed using the treatment immobilization device. For stereotactic frame-based systems (e.g. Gamma Knife) this imaging is performed after application of the frame on the day of treatment. For stereoscopic imaging-based systems (e.g. CyberKnife) this can be done in advance. These images need to be transferred to the planning software. A multistage and multidisciplinary process then ensues, with the images from the various modalities being fused and the target and critical structures defined. A plan is subsequently produced that aims to highly conform the prescribed dose to the target and minimize the dose to the adjacent structures and organs at risk. This plan is subject to a rigorous schedule of checks before treatment can be delivered. The planning process often involves several specialist disciplines dependent upon local set-up and can include radiation oncology, neurosurgery, neuro-radiology and medical physics.

Treatment time depends on the system used and complexity of the target and plan. Typical delivery times are in the order of 1 hour. The patient is positioned on the couch using the system-appropriate immobilization device and localized by use of either a stereotactic headframe or imaging. Once this step is complete, treatment delivery can begin. If the patient moves, this step will need repeating. As with all photon treatments, the patient does not feel anything but can see and hear the machine moving. Treatment is generally delivered as an outpatient and general anaesthesia is not required, but it can be considered for young children.

Further information

For an extensive introduction to skull base and intracranial radiosurgery using all platforms, readers are referred to *Principles and practice of stereotactic radiosurgery*, edited by Chin.[1]

MENINGIOMAS

Role of radiosurgery in meningioma management

The majority of skull base meningiomas are benign and classified as WHO Grade 1.[2] Many are well demarcated; however, they can be difficult to excise completely due to risks of damaging adjacent neurovascular structures such as those within the cavernous sinus. They therefore represent an ideal target for consideration of SRS. Treatment may be considered following partial

resection, either to prevent regrowth or to improve symptoms. As a primary treatment, SRS can be used providing there is a high degree of confidence in the radiological diagnosis and early intervention is warranted. One of the main limitations of SRS for skull base meningiomas are dose constraints to the optic pathway, which is sensitive to the high doses per fraction delivered with this technique. Radiation induced optic neuropathy (RION) is rare if the dose is limited to < 8 Gray in a single fraction.[3] Where it is not possible to achieve safe optic pathway constraints (typically for lesions within 2 mm of the optic nerves/chiasm), fractionated radiotherapy treatment offers similar local control rates without significant risk of RION.

The timing of intervention with SRS or fractionated radiotherapy for skull base meningioma remains controversial. Contrary to surgery, the philosophy with radiotherapy is to treat while the tumour volume is low and prior to clinical deterioration. However, growth kinetics for benign meningiomas can be complex and difficult to predict. Some remain relatively indolent for many years and many small (sub-2 cm) skull base meningiomas do not cause any symptoms within 5 years, supporting an initial period of observation.[4] Given that observation carries a risk of increasing tumour volume, associated with a greater risk of toxicity with SRS, serial MRI scans and clinical examination are essential for active monitoring.

Clinical outcomes

Both SRS and fractionated radiotherapy offer effective treatment for skull base meningiomas with 10-year local control rates typically exceeding 85% (**Table 103.1**).[5–11] However, evidence is confined to retrospective studies and many fail to clearly distinguish outcomes between primary treatment at presentation, treatment immediately following surgery and treatment at progression with or without earlier surgery. In a retrospective multicentre analysis of 3768 patients with benign meningiomas, 5- and 10-year progression free survival (PFS) were 95.2% and 88.6% respectively with a permanent morbidity incidence of 6.6%.[6] Prescribed doses for benign meningiomas are typically in the range of 12–15 Gy with single fraction SRS.[12] Due to increased risk of morbidity SRS is typically used for tumours with volumes less than 8 cubic centimetres (generally < 3 cm). Multisession SRT (up to 5 fractions) using a platform such as CyberKnife is now being successfully used for larger volume tumours although more mature data are awaited.[13] Cranial nerve deficits have been reported following SRS for anterior skull base meningiomas. In one series of 763 patients with sellar/para-sellar meningiomas with mature follow-up, new or worsening deficits were seen in 9.6% of patients, with the trigeminal nerve being most adversely affected.[8]

TABLE 103.1 Selected published long-term local control rates using radiosurgery and fractionated radiotherapy for meningioma

Reference	Patients (n)	Technique	Median dose	Local control
Debus 2001[7]	189	FSRT	56.8 Gy	96% (10 years)
Milker-Zabel 2005[9]	317	FSRT	57.6 Gy	89% (10 years)
Kondziolka 2008[5]	972	GK	13 Gy	87% (10 years)
dos Santos 2011[10]	88	Linac SRS	14 Gy	83% (10 years)
Tanzler 2011[11]	146	CFRT IMRT FSRT	52.7 Gy	96% (10 years)
Sheehan 2014[8]	763	GK	13 Gy	82% (10 years)
Santacroce 2012[6]	4565	GK	14 Gy	87% (10 years)

FSRT, fractionated stereotactic radiotherapy; GK, Gamma Knife; CFRT, conformal radiotherapy; IMRT, intensity modulated radiotherapy; SRS, stereotactic radiosurgery; Gy, Gray.

Optic nerve sheath meningiomas

Optic nerve sheath meningiomas (ONSM) have an intimate circumferential relationship with the optic nerve and can interfere with its vasculature. The natural history of most ONSMs is variable but symptoms of optic pathway compression can occur including painless loss of visual acuity, visual field deficiencies, relative afferent pupillary deficits or proptosis.[14] Observation with serial neuro-ophthalmological assessment to determine rate of symptomatic progression is often considered initially. Presentation with significant optic pathway symptoms and progressive decline in function are considered indications for intervention. Surgical intervention including biopsy is associated with high risk of damage to vision, therefore primary radiation is often considered the treatment of choice. Due to the sensitivity of the optic pathways to high doses per fraction, fractionated radiotherapy is safer than SRS. With the use of highly conformal fractionated radiotherapy, vision commonly stabilizes, and improves in approximately one-third of patients.[15, 16]

Atypical and anaplastic meningiomas

A small proportion of meningiomas are WHO grade 2 or 3 due to atypical or anaplastic pathological features. These tumours have a high propensity for recurrence and can invade surrounding tissue. There remains a paucity of high quality data to guide management. In principle, SRS is generally not suited to tumours with an infiltrating margin. One combined analysis of series using SRS estimated a median 5-year PFS or 59% for Grade 2 and 13% for Grade 3 meningiomas.[17] The definitive role of SRS is unclear although in the authors' experience it has been helpful in selected cases including palliation.

KEY POINTS

- Five-year control rates in excess of 90% with acceptable neurological morbidity may be achieved with SRS for grade 1 meningiomas.
- The timing of intervention with SRS remains debated, given that many grade 1 tumours grow slowly.
- Fractionated radiotherapy is preferable to SRS for tumours in close proximity to the optic pathways or of larger volume unsuitable for resection.

PITUITARY ADENOMAS

Pituitary adenomas are classified by size and ability to hypersecrete hormones (functional versus non-functional adenoma (NFA)). Functional adenomas are typically microadenomas (i.e. <1 cm in size) presenting with clinical seqeulae of hormone hypersecretion while NFAs may be diagnosed incidentally or present with symptoms from local pressure such as visual disturbance.

Therapeutic goals include the reversal of symptoms from pressure or hormone hypersecretion, maintain normal hormone function and ideally prevent regrowth in the future through definitive treatment providing the risks are acceptable. Options available include surgical resection, medical therapy, fractionated radiotherapy, SRS and observation. A multidisciplinary approach is essential.

Non-functional adenomas

Symptomatic non-functional adenomas (NFAs) often require surgery to reverse clinical problems such as visual disturbance caused by optic pathway compression. However, complete resection may not be feasible, particularly if the tumour extends into the cavernous sinus. Furthermore, high late recurrence rates are seen, even in patients thought to have had a complete resection.[18] Despite potential high rates of recurrence, observation following initial surgery is still appropriate in the absence of adverse features, given that most tumours grow slowly and progression can be detected through serial imaging. SRS or fractionated radiotherapy are commonly reserved for recurrence or progression.

Although there is a lack of randomized data, a matched cohort comparison clearly confirmed that early adjuvant radiotherapy improves PFS over surgery alone.[19] A UK series with a median follow-up of 9.1 years reported actuarial PFS of 97% and 96%, at 10 and 20 years respectively, following radiotherapy.[20] However, concerns exist over the use of routine adjuvant radiotherapy, due to the risks of long-term consequences including hypopituitarism, potential increased of stroke and radiation induced cancers.

SRS offers an attractive alternative for low volume inoperable tumours (of an adequate distance from the optic apparatus) and is increasingly used in preference over fractionated radiotherapy (**Figure 103.2**). A retrospective combined analysis of 512 patients treated with SRS reported actuarial PFS of 95%, 91% and 85% at 5, 8, and 10 years respectively.[21] All patients were treated with Gamma Knife and the median follow-up was 36 months with 37.3% of patients completing 5 or more years of follow-up. Tumour volume was the strongest predictor of progression. New or worsened hypopituitarism was seen in 21% of patients. Similar local control rates have been shown with other SRS platforms.[22] The authors are not aware of any data confirming an increased incidence of stroke following SRS; however, dose to the adjacent carotid is often high and carotid stenosis has been documented as a rare event.[23] Steep dose gradients make it possible to reduce the dose to the hypothalamic-pituitary axis with some investigators suggesting safe limits to preserve function; however, mature data are lacking and tumour coverage should take priority.[24] Case reports of second malignancy following SRS do exist; however, one population-based study failed to show any increased risk.[25]

Functional pituitary adenomas

Excluding prolactinomas, where medical therapy is the primary treatment of choice, complete microsurgical resection is often considered the optimum treatment. However, cure through surgical resection may not always be possible due to local invasion and risks of injury to neurovascular structures. SRS is considered a useful adjunct for functional tumours, and may remove the need for ongoing medical therapy.

A review of retrospective data was recently published by Sheehan et al.[21] Although radiological control rates were high, endocrine remission rates varied considerably between series and did not reflect the high rates of local control. The review suggested that SRS was most effective for Cushing's disease where biochemical remission rates were typically in the region of 50% (range 0–100%). This was followed by acromegaly with an overall average endocrine remission rate of 43.6% (range 0–82%). The overall remission rate for prolactinomas was only 30% (range 23.3–41%).

Compared to surgery, there is a latent period of at least a year post-SRS prior to biochemical remission, during which medical therapy needs to continue. Higher doses are required to treat functional tumours; however, morbidity is generally low providing adequate clearance is achieved from the optic pathways.

KEY POINTS

- SRS can be used for low volume (typically <5 cc) recurrent or progressive non-functioning adenomas that are unsuitable for surgical resection.
- SRS is a useful adjunctive treatment in functional pituitary tumours; however, biochemical response rates are variable despite high rates of local control.
- Long-term follow-up is required to monitor for pituitary insufficiency following any radiation to the hypothalamic pituitary axis.

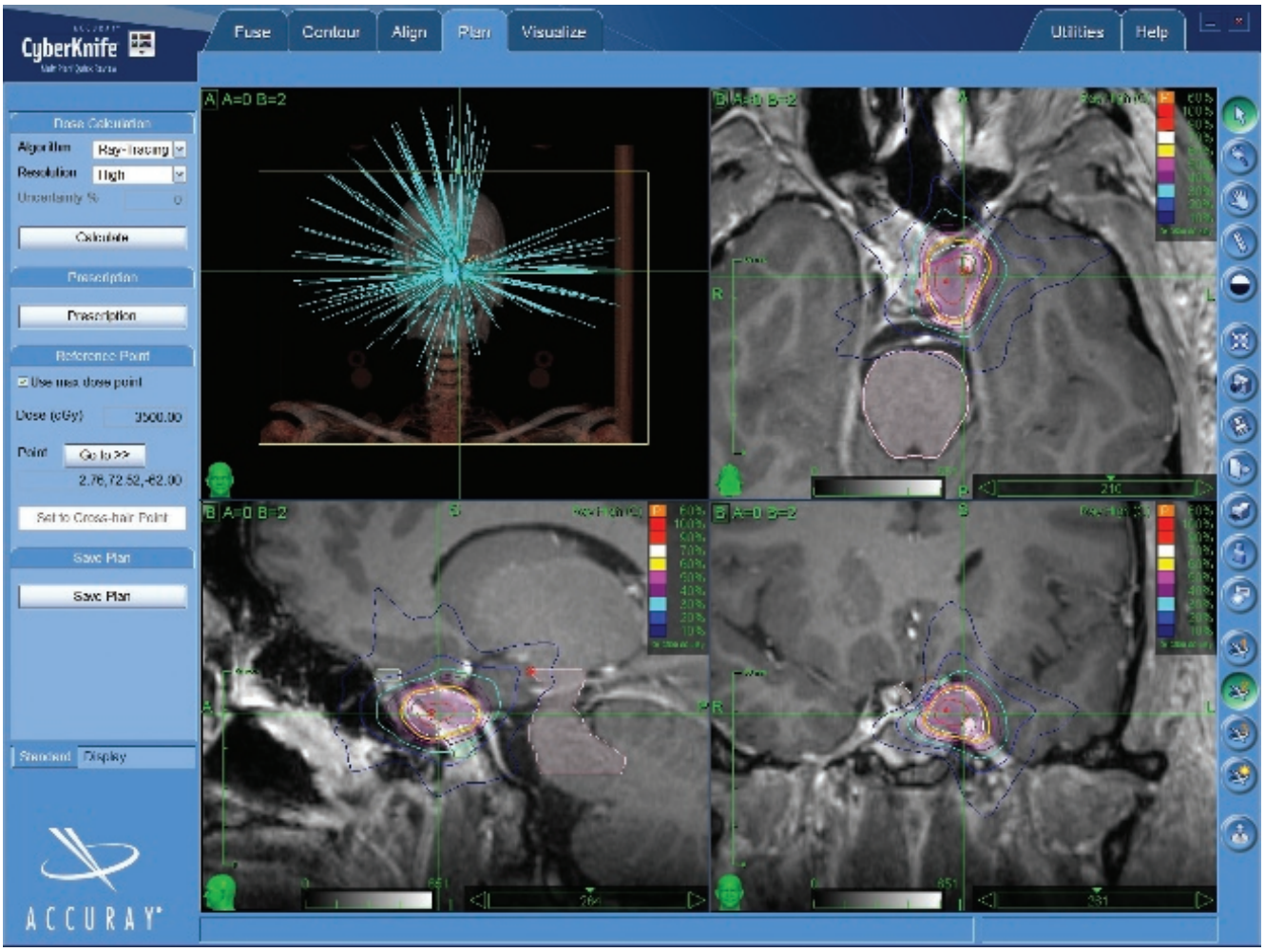

Figure 103.2 Example of pituitary tumour SRS plan (MultiPlan, CyberKnife, Accuray), showing high conformality and steep dose fall off to chiasm and carotids.

VESTIBULAR SCHWANNOMA

Although vestibular schwannomas (VS) are slow-growing, benign tumours, progressive enlargement can cause morbidity. Management strategies for VS include observation with serial MRI (usually indicated for small, newly diagnosed tumours), surgical resection and radiotherapy (both SRS and fractionated). Radiotherapy is used to stop growth (and hence avoid surgery) but is also used in some centres to preserve auditory function. However, the benefits of early intervention with regards to hearing preservation with radiation versus observation remain unproven and this issue continues to be debated.

Numerous published reports of high local control rates (predominantly using Gamma Knife) with minimal toxicities have established SRS as an accepted alternative to surgical resection (**Table 103.2**). [26–28] Similar outcomes have also been reported for other SRS platforms.[29] However, observation with annual imaging and hearing evaluation is believed to have a role in the management of small minimally symptomatic tumours, as SRS or resection can potentially compromise function.[30] Growth can be unpredictable, however, and if significant may limit future therapeutic options. As a result, deciding between early definitive treatment and observation can be challenging.

Currently, most centres prescribe 12–13 Gy to the margin of the tumour (**Figure 103.3**). Over time, the recommended dose has reduced from 16 Gy, which has lowered the incidence of cranial nerve complications, without adversely affecting local control rates.[31]

SRS is generally recommended for tumours < 3 cm in extra canalicular diameter with no significant brainstem compression, as tumour swelling post-radiosurgery can lead to 4th ventricular distortion with resultant obstructive hydrocephalus.

Following SRS, transient enlargement of the tumour followed by stability or even regression (i.e. 'pseudoprogression') is known to occur. In one series, 23% of VS treated with SRS underwent pseudoprogression, most commonly regressing at 24 months post-treatment.[32] As a result, only tumours that begin or continue to enlarge after 24 months post-SRS should be considered as treatment failures, and further intervention (most commonly resection) should not be rushed. The length of clinical and

TABLE 103.2 Selected published outcomes using stereotactic radiosurgery for vestibular schwannoma

Reference	Median follow-up (years)	Patients (n)	Platform	Median marginal dose (Gray)	Local control	Definition of local control	Cranial nerve V preservation (%)	Cranial nerve VII preservation (%)
23	2.9	232	Gamma Knife	15 Gy	97%	No additional surgical intervention	98.5%	99%
24	5.6	216	Gamma Knife	13 Gy	98.3% (10 years)	No additional surgical intervention	94.9%	100%
25	8.1	75	Linac	14 Gy	92%	No change in tumour volume	100%	92%
26	5	103	Gamma Knife	13 Gy	91.1%	No additional surgical intervention	99%	95%

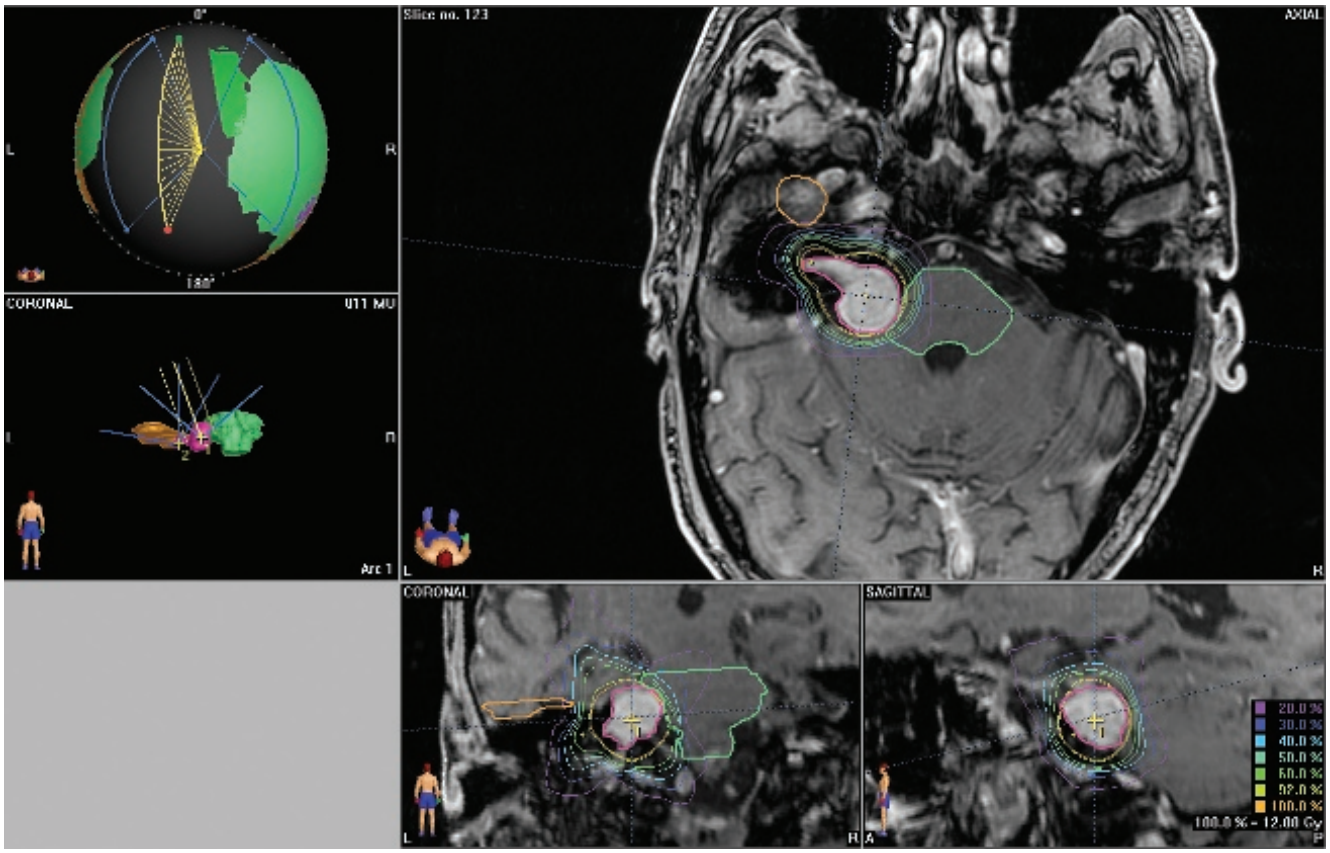

Figure 103.3 Typical dose distribution achieved using BrainLab generated SRS plan (linear accelerator platform).

radiological follow-up required post-SRS is controversial. In the authors' centre, patients are routinely imaged for 10 years post-radiosurgery.

Preservation of cranial nerve function

Following SRS with a marginal dose of 12–13 Gy, published trigeminal nerve preservation rates vary from 78.7% to 100%.[33, 34] The aetiology of trigeminal neuropathy post-SRS is complex and multifactorial. Factors associated with trigeminal dysfunction in published series include: tumour volume; maximum dose received by the trigeminal nerve and brainstem; and length of nerve irradiated.[33] The likelihood of trigeminal toxicity is no doubt higher for patients with tumour in contact with the nerve as a result of post-radiosurgery swelling.

The risk of a persisting facial nerve palsy post-SRS is low with contemporary radiosurgical doses and planning techniques (Table 103.2). Pre-existing facial nerve palsy and hemi-facial spasm is associated with an increased risk of worsening CNVII dysfunction after radiosurgery.[26]

The majority of patients with VS have unilateral sensorineural deafness at presentation. However, for patients with 'serviceable' hearing (Gardner-Robertson Grades I–II), some centres advocate early radiosurgery to preserve auditory function. To date there are no prospective, randomized data to inform practice, and large variations in hearing outcomes are reported between published series. Regis et al. reported prospective non-randomized hearing data for patients with intracanalicular VS managed with observation versus immediate Gamma Knife SRS with a marginal dose of 12 Gy. This series reported improved hearing preservation rates in patients who underwent early radiosurgery (77%, 70% and 64% at 3, 4 and 5 years, respectively) as compared to 75%, 52% and 41% in the observation group.[35] The authors of this chapter therefore support early intervention with SRS in patients with serviceable hearing.

There may be radiobiological advantages of fractionated radiotherapy over SRS in terms of reducing risk of cranial neuropathy and improving hearing preservation. Similar local control rates have also been reported.[36] No prospective comparison has been carried out with SRS to date, however.

Radiosurgery for NF2 vestibular schwannomas

Patients with neurofibromatosis type 2 (NF2) usually have bilateral VS and are therefore at risk of developing bilateral deafness, trigeminal and facial neuropathies at a young age. Results of surgery and radiotherapy for NF2-associated VS are worse than for sporadic unilateral tumours. Tumour control rates are lower and iatrogenic hearing loss is more common.[37, 38]

Plotkin et al. identified that vascular endothelial growth factor (VEGF) is expressed by VS and medical therapy with bevacizumab (an anti-VEGF monoclonal antibody) may improve hearing in some (but not all), as well as reducing tumour volume in the majority of patients with NF2-associated VS.[39] As a result, bevacizumab is increasingly being used as first line management in this patient group when intervention is required.

CHONDROSARCOMA AND CHORDOMA

Small, relatively well-demarcated residual tumours can represent an attractive target for SRS. There are some data reporting use of SRS for small chordomas or chondrosarcomas that are relapsing or remain visible targets after surgery.[40–42] However, series using fractionated radiotherapy with doses in excess of 70 Gy report the highest rates of local control.[43, 44] The local control rates for chondrosarcoma are more favourable than for chordoma. Fractionation permits treatment of a wider region including the presurgical bed. Delivering such high doses of radiotherapy in such close proximity to critical neural structures (in particular brainstem) demands maximum surgery and highly conformal techniques such as proton therapy, fractionated SRT or imaged guided intensity modulated photon radiotherapy. The role of SRS remains uncertain for those patients suitable for resection and high dose fractionated radiation.

GLOMUS TUMOURS

Glomus tumours (also known as paragangliomas or chemodectomas) are rare, benign tumours that can develop in a number of locations including in and around the ear (glomus tympanicum and glomus jugulare). If causing local mass effect on the brainstem, surgical resection is preferred. However, these tumours are often intimately involved with surrounding neurovascular structures and complete excision is usually impossible without significant morbidity. SRS and fractionated radiotherapy are both therapeutic options, given with the aim of tumour control rather than eradication. A meta-analysis, combining results from 276 patients, showed pooled local control following radiotherapy (both fractionated and SRS) as initial, combined and salvage treatment was good, ranging from 79% to 100%.[45] SRS is preferred for relatively small, well demarcated tumours that are in difficult surgical locations. Timing of intervention remains debated given that many tumours will remain relatively indolent for many years.

KEY POINTS

- SRS is an established therapeutic option for VS < 3 cm with no significant brainstem compression with local control rates in excess of 90% with marginal doses of 12–13 Gy.
- It is postulated that early radiosurgery preserves serviceable hearing, although prospective randomized data are lacking.
- Post-SRS cranial nerve preservation is high and treatment-associated complications are low.

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CHAPTER 104

NEUROFIBROMATOSIS 2

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SEARCH STRATEGY

Data in this chapter may be updated by a PubMed search using the keywords neurofibromatosis 2/NF2.

HISTORICAL OVERVIEW

The neurofibromatoses consist of at least three distinct autosomal dominantly inherited disorders: neurofibromatosis 1 (NF1), neurofibromatosis 2 (NF2) and schwannomatosis. Historically, these conditions were aggregated as generalized neurofibromatosis (von Recklinghausen disease). NF2 was first described by Wishart in 1822.[1] The heritable nature of NF2 was reported in 1920 by Feiling and Ward,[2] who described a three-generation family with vestibular schwannomas (VS). The autosomal dominant transmission (i.e. a 50% risk of transmission from an affected parent) was confirmed in a large family reported by Gardner and Frazier in 1930.[3] NF1 was delineated by von Recklinghausen in the late 19th century; Harvey Cushing aggregated NF1 and NF2 in 1916,[4] and his scientific stature was such that, despite reports that the conditions were different, many decades were to pass before the distinction between the two diseases was widely recognized. The neurofibromatosis literature prior to 1985 is scattered with cases of NF2 being described as part of von Recklinghausen disease, with cases of bilateral vestibular schwannomas being included in large series of NF1.[5] The conditions were recognized as separate entities only when the *NF1* and *NF2* genes were localized to chromosomes 17 and 22 in 1987 and NF2 was cloned in 1993, respectively. The two diseases were clinically delineated at a US National Institutes of Health (NIH) consensus meeting in 1987.[6] Subsequent studies have indicated that NF2 is a genetically homogeneous condition, with no evidence of exclusion of classical NF2 (bilateral VS) from the *NF2* locus on 22q. Indeed, genetic analysis in Manchester detects aberrations in the NF2 gene in 95% of familial cases. The initial studies on small numbers of families were confirmed in all studies of people with bilateral VS that have been undertaken since the identification of the *NF2* gene in 1993. However, it is possible that there is another closely linked gene that affects NF2 phenotype.

MOLECULAR GENETICS

The initial keys to identifying the *NF2* gene were studies of tumour material.

Chromosome studies of meningiomas highlighted chromosome 22 as the likely location of the *NF2* gene, since many tumours had loss of all or part of chromosome 22. Subsequent cytogenetic studies of schwannomas also confirmed that loss of chromosome 22 or its long arm was by far the most frequent event, which was later confirmed by DNA studies.[7] Seizinger et al. demonstrated loss of constitutional heterozygosity of chromosome 22, with DNA markers being lost in tumours from a person with NF2.[7] Linkage studies then confirmed that all affected members of a large family carried the same copy of chromosome 22.

The *NF2* gene was identified by the simultaneous discovery of constitutional and tumour deletions in a cell membrane-related gene, termed merlin or schwannomin.[8, 9]

Standard mutation techniques, such as single-strand conformational polymorphism analysis or denaturing gradient gel electrophoresis, detect 35–66% of pathogenic mutations. The majority of these mutations are protein-truncating mutations (frameshift or nonsense mutations) and lead to a smaller and probably non-functional protein product. C>T transitions causing nonsense mutations are the most common mutations in the *NF2* gene. Genotype-phenotype correlation studies have found that missense mutations (which result in a complete protein product) and large deletions (which result in no protein product) each cause predominantly mild phenotypes.[10–13] Patients with splice-site mutations have variable clinical manifestations. The more severe phenotype in patients with protein-truncating mutations may be due to a dominant negative effect, with mutant protein dimerizing with the normal product, leaving less wild type protein for tumour suppression. This is supported by a positional effect of mutations (particularly for meningiomas with more severe disease associated with mutations in exons 1–4 and mild disease in the last two exons with mutations).[13]

Some people with mild NF2 are somatic mosaics, in whom a smaller proportion of cells contain the mutated *NF2* gene. One of the clues to the existence of mosaicism in NF2 was that *NF2* mutations were harder to find in blood in sporadic cases than in people who had inherited the disease from an affected parent. In mosaicism, the initiating mutation happens after conception, leading to two separate cell lineages. The proportion of cells affected depends how early in development the mutation takes place. Evidence suggests that as much as 25–35% of NF2 cases without a family history of the disease are mosaic, carrying the mutation in too small a proportion of their cells to be detected from a blood sample.[14, 15] This accounts for the milder disease course in many individuals with unfound mutations, and since only a subset of germ cells will carry the mutation, there is less than a 50% risk of transmitting the disease to their offspring.[15, 16] However, if an offspring has inherited the mutation, they will be more severely affected than their parent, since the offspring will carry the mutation in all of their cells.[17] Mosaicism may be particularly likely in NF2 if the tumours are anatomically localized, for example, limited to one side.[16] The mosaic mutation can be detected by analyzing tumour material from an affected individual. If an identical mutation is found in two tumours from that individual, their offspring can be tested for the presence of the mutation. Other causes (apart from mosaicism) of the low detection rate for constitutional *NF2* mutations using standard techniques are large deletions and rearrangements at the *NF2* locus. The chances of mosaicism depending on age at onset and laterality and the risks to children can be found in recent publications.[15, 16]

NF2 PROTEIN

The NF2 protein (merlin or schwannomin) is a cell cytoskeleton-associating protein of 595 amino acids coded by the 17 exons of the *NF2* gene. The name 'merlin' derived from the sequence homology and shared overall domain structure with ERM (moesin, ezrin and radixin) superfamily of membrane-cytoskeleton linker molecules. Alternative splicing of exon 16 gives rise to two isoforms, which differ by the last C-terminal 11 amino acids. The NF2 protein is expressed in many tissues including neurons, Schwann cells and meningeal cells. Mutant NF2 protein impairs cell adhesion, motility and spreading properties, which are known to be essential for tumour formation. Loss of NF2 protein is the main and possibly the only rate-limiting step in the formation of all schwannomas and most meningiomas. Merlin is localized to the cell membrane/cytoskeletal interface and appears to have a number of different roles involving interactions including the Ras/Raf/MEK/ERK, FAK/Src, PI3K/AKT, Rac/PAK/JNK, mTORC1 and Wnt/β-catenin pathways.[18] NF2 links receptors at the plasma membrane to their cytoplasmic kinases to facilitate contact inhibition. However, NF2 can also interact with a large number of cytoplasmic and nuclear proteins that affect cell cycle progression. NF2 may also, through these pathways, reverse the functional inhibition of conventional tumour suppressor pathways.[19]

EPIDEMIOLOGY

An estimate of the birth incidence of NF2 (1 in 50 000) was made at the 1987 NIH Consensus Conference on the Neurofibromatoses, but this was not epidemiologically based. In the UK, population-based studies have estimated the birth incidence of NF2 as 1 in 33 000 people.[20, 21] A smaller study in southern Finland estimated the birth incidence as 1 in 87 000.[22] Both studies were based on hospital records and cancer registries, and the higher incidence in the UK study is likely more reliable as it is based on a larger area with longer follow-up. Initial estimates of prevalence suggested that as few as 1 per million were affected in the US.[6] The diagnostic prevalence in the UK population-based study is now 1 in 56 000.[21] This has probably increased due to early diagnosis and improved survival. The annual incidence rate for NF2 was estimated as 1 per 2 355 000, [20] equivalent to about 1 case per year for each health region in the UK or over 100 cases per year in the US. The birth incidence is significantly higher than the diagnostic prevalence because many people do not develop features of the condition until the third decade of life or later, and many other people die before this time. The diagnostic prevalence is likely to rise, as the median 15-year survival from diagnosis more than 20 years ago[23] will lengthen due to improvements in early diagnosis and tumour treatment.

Individuals who inherit a pathogenic mutation in the *NF2* gene will almost always develop symptoms by 60 years of age; [23] very occasionally, such people will have apparent non-penetrance (have no features of the disease even late in life). The transmission rate is 50% in the second generation and beyond, but the risk of transmission in apparently sporadic cases of NF2 is less than 50% due to mosaicism.[16, 17] Anecdotal evidence suggested that, in

many NF2 families, the disease course 'breeds true'. More recent research has established that the intra-familial correlation of clinical manifestations of NF2 (age at onset of symptoms, age at diagnosis and number of intracranial meningiomas) is greater than the inter-familial correlation. Stochastic events such as loss of the second *NF2* allele clearly play a role in the natural history of the disease, since the disease course is not identical even in monozygotic twins with NF2.

Initial indications of a maternal gene effect (earlier age at onset in individuals who inherited the *NF2* mutation from their mother) have not been borne out by further study,[20] nor is there evidence for anticipation (an increase in disease severity with successive generations). An apparent worsening of the disease course in affected females is due mainly to meningiomas, not on schwannoma growth and development, and there is no gender difference in risk of mortality.[23, 24]

CLINICAL MANIFESTATIONS, DIAGNOSTIC CRITERIA AND DIFFERENTIAL DIAGNOSIS

Bilateral VS are pathognomic for NF2. Schwannomas of the other cranial, spinal and peripheral nerves are very common. Meningiomas are present in about half of patients, primarily intracranially (including optic nerve sheath meningiomas) but also in the spine, and lifetime risk probably approaches 75%.[13] Less frequently, there are low-grade central nervous system (CNS) malignancies (ependymomas and very rarely gliomas) (**Table 104.1**).[23, 25–29] Individuals may present with cranial meningiomas or a spinal tumour long before the appearance of a VS.

Most individuals with NF2 present with hearing loss (often initially unilateral) that may be accompanied or preceded by tinnitus. Other vestibular presenting symptoms of VS are dizziness or imbalance. About 20–30% of cases present with an intracranial meningioma, spinal tumour or cutaneous tumour. When NF2 presents in early childhood, the first sign is often a non-VIIIth nerve tumour. Adult presentation is therefore quite different from paediatric presentation, in which VS causes only 15–30% of initial symptoms. There have been a number of recent reports of mononeuropathy in NF2, which is most common in people who present at young ages. Mononeuropathy affecting the facial nerve causes facial palsy similar to Bell's palsy, which does not fully recover. Some children present with wasting of muscle groups in a lower limb, similar to polio, which again does not fully recover. In adults, a more generalized polyneuropathy develops in about 3–5% of patients, often associated with an 'onion bulb' appearance on nerve biopsy.[7] This can progress, leading to severe muscle wasting and even death.

Ophthalmic abnormalities are very common in NF2. Between 60–80% of people have cataracts,[7, 10] which are usually presenile posterior subcapsular lenticular opacities that rarely require removal. Cortical wedge opacities are also common and may be present from near birth. Optic nerve sheath meningiomas and retinal hamartomas can cause visual impairment in the first years of life; misdiagnosis of each of these abnormalities as retinoblastoma has led to the eye being removed in the first few years of life.

Skin abnormalities are useful in diagnosis, but cutaneous features of NF2 are much more subtle than those seen in patients with NF1. About 70% of NF2 patients have skin tumours but only 10% have more than 10 skin tumours and there appear to be at least three different types. The most frequent type is a plaque-like lesion, which is intracutaneous, slightly raised and more pigmented than surrounding skin, often with excess hair (**Figure 104.1**). More deep-seated subcutaneous nodular

TABLE 104.1 Clinical characteristics of NF2 patients in four studies

Characteristic	Study			
	Kanter et al.[26]	Evans et al.[23]	Parry et al.[27]	Mautner et al.[28]
Number of cases	73	120	63	48
Number of families	17	75	32	44
Sporadic cases	0	45	17	44
Mean age at onset (years)	20 (of 59)	22	20	17
Intracranial meningiomas (%)	18	45	49	58
Spinal tumours (%)	N/A	26	67	90
Skin tumours (%)	32 (of 73)	68 (of 100)	67	64
>10 skin tumours (%)	N/A	10 (of 100)	N/A	N/A
Café-au-lait macules (%)	42 (of 31)	43 (of 100)	47	N/A
Cataract (%)	N/A	38 (of 90)	81	62
Intracranial astrocytoma (%)	N/A	4.1	1.6	N/A
Ependymoma (%)	N/A	2.5	3.2	6.0
Optic sheath meningioma (%)*	N/A	4.1	4.8	8.0

* In Mautner et al.[29] the frequency of optic nerve sheath tumours is for all histological types (i.e. schwannomas and meningiomas).

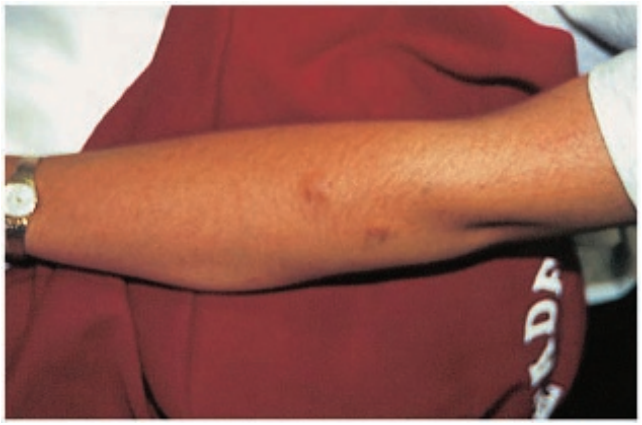

Figure 104.1 Plaque-like lesions on the arm of a patient with NF2. These are raised, often slightly pigmented lesions that are also frequently hairy.

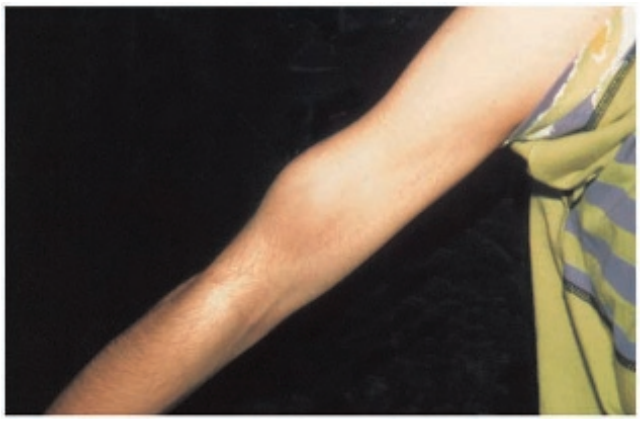

Figure 104.2 Subcutaneous schwannoma on a major nerve in the upper arm in a patient with NF2.

tumours can often be felt, sometimes on major peripheral nerves. These tumours are detected as a fusiform swelling of the nerve with thickened nerve palpable on either side (Figure 104.2). There are also occasional intracutaneous tumours similar to those in NF1. The great majority of these tumours are schwannomas, but occasional definite neurofibromas may be found.

The Manchester (modified NIH) diagnostic criteria for NF2 are shown in Box 104.1. The original NIH criteria have been expanded to include patients with no family history who have multiple schwannomas and or meningiomas but who have not yet developed bilateral VIIIth nerve tumours. Constitutional mutations in the *NF2* gene are found as frequently in patients who fulfil these modified criteria as in sporadic cases with bilateral VS (Box 104.1). This justifies future inclusion of these individuals as having 'definite' NF2, rather than having only one criterion (bilateral VS) for 'definite' NF2 in isolated cases. In addition, the inclusion of criteria for 'probable' NF2 (unilateral VS < 30 years plus other NF2 criteria, or two or more meningiomas plus other NF2 criteria) is a helpful addition. Since 50% of cases are new mutations, the modified criteria increase sensitivity but are unlikely to reduce

BOX 104.1 Diagnostic criteria for NF2 (these include the NIH criteria with additional criteria)

Bilateral vestibular schwannomas or family history of NF2 plus:

- unilateral VS *or*
- any two of: meningioma, glioma, neurofibroma, schwannoma, posterior subcapsular lenticular opacities.

Additional criteria:

- unilateral VS plus any two of: meningioma, glioma, neurofibroma, schwannoma, and posterior subcapsular opacities *or*
- multiple meningioma (two or more) plus unilateral VS *or* any two of: glioma, neurofibroma, schwannoma, and cataract.

Note: 'Any two of' refers to individual tumours or cataract, not to tumour types.

specificity because chance associations of typical NF2 disease features in people without NF2 are extremely rare. A new scoring-based system for diagnosis, the so-called 'Baser' criteria, has also been developed.[30]

The main possible differential diagnostic dilemmas are in people with multiple non-cranial schwannomas who do not have a family history of NF2. All require a cranial MRI scan. Some of these people develop NF2 and others are somatic mosaics. There are nonetheless a small group of people with tumours largely confined to the spine and subcutaneous nerves, with sparing of the VIIIth nerve, who do not have a constitutional *NF2* mutation detection using conventional techniques.[31, 32] These individuals may pass the condition on to their children, and in families where this happens there is still tight linkage to the *NF2* locus, although *NF2* mutations are found in only a minority of patients with this variant form of the disease.[32] Around 50% of familial cases and 10% of sporadic schwannomatosis cases have now been shown to be due to *SMARCB1* mutations.[32] Confusion with NF1 is unlikely since only 1–2% of NF2 patients have more than 6 café-au-lait macules and Lisch nodules are rare in NF2. Nonetheless, review of tumour histology is a wise precaution in equivocal cases. NF1 is extremely unlikely in a person with a schwannoma who does not meet the NIH criteria for NF1; conversely, NF2 is very unlikely in a person with multiple neurofibromas.

NEURORADIOLOGY

Several groups of individuals are at risk of having NF2 and should be investigated using MRI. These are people with a family history of NF2; people under 30 years old who present with a unilateral VS or meningioma; people with multiple spinal tumours (schwannomas or meningiomas); and people with cutaneous schwannomas.[16] The 'gold standard' in terms of diagnostic precision

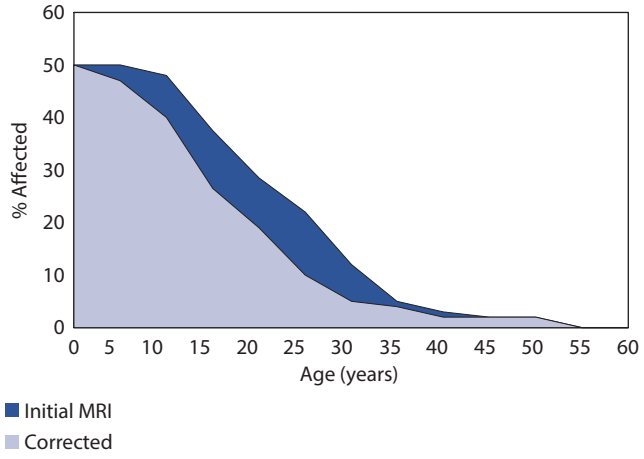

Figure 104.3 Decrease in risk from 50% by age of an individual with a normal cranial scan and an affected parent with NF2.

is magnetic resonance imaging (MRI) with gadolinium enhancement. Initial assessment should include full spinal imaging in addition to a cranial scan. MRI will now detect tumours as small as 1–2 mm in diameter on cranial and spinal nerve roots. Many of these small spinal tumours will never lead to symptoms. Using MRI of the full spine, there are tumours in 80–90% of NF2 patients[28] but only 30% of these patients have symptomatic spinal tumours.[23, 26, 27] Intramedullary tumours, often associated with a syrinx, are mainly found in the upper cervical spine and brainstem. On biopsy, these tumours are usually low-grade ependymomas and the great majority do not progress. Another common finding is schwannomas on other cranial nerves. The Vth nerve is most frequently affected. It is rare for non-VS cranial nerve schwannomas to grow to a size where surgical excision is required. Meningiomas are detected on MRI as enhanced areas on the meninges around the spinal cord, brain or optic nerves. They can form confluent areas on scan or 'meningioma en plaque'. The growth rates of VS are often slow but are extremely variable; on average, growth rates are higher in younger patients.[13] Meningiomas usually have faster growth rates than VS.

CT scans have been largely replaced by MRI due mainly to their poor sensitivity at detecting small VS (**Figure 104.3**). Some NF2 patients have intracranial calcification, but this sign is not useful enough in diagnosis to supplement MRI with CT. Without firm clinical justification, repeated CT scans should be avoided in NF2 due to the tumour-prone nature of the disease and the possibility of radiation-induced tumours.

PATHOLOGY

The main tumour sites, their frequency and pathology are presented in **Table 104.1**. As previously noted, schwannomas can develop at all locations in the body where there are nerves with Schwann cells. The reason for the predilection for the superior vestibular branch of the VIIIth cranial nerve is unknown. Schwannomas are encapsulated tumours of pure Schwann cells, growing around the nerve that may contain blood vessels and have areas of sheets in intertwining fascicles (Antoni A) and looser arrangements (Antoni B). The tumours stain for S-100 protein and vimentin. In NF2, schwannomas tend to be more multifocal and have a more lobular architecture than sporadic tumours.[33] Spontaneous malignant transformation of these tumours to malignant peripheral nerve sheath tumours is recognized, but is more than 10 times as likely to happen after radiation treatment.[34] The background rate of 0.5% for CNS malignancy in NF2 is also very much less than for NF1. A small proportion of nerve-related tumours in NF2 are pathologically delineated as neurofibroma. In these tumours, there is an admixture of cell types (Schwann cells, fibroblasts and mast cells) and the tumour usually has identifiable axons within it. Neurofibromas are mainly found in the skin (where they are still outnumbered by schwannomas by a factor of 5–10) but are also found on the spinal nerve roots. Neurofibromas in NF2 do not develop intracranially. There is currently no evidence of histological or molecular differences between neurofibromas in NF1 and those in NF2. Halliday et al.[35] showed that, in a series of spinal schwannomas and neurofibromas, all spinal tumours in patients with NF1 were neurofibromas, while, with one exception, all spinal tumours in patients with NF2 were schwannomas (one patient had a mixed tumour). In contradistinction to NF2, schwannomas and meningiomas are not found in excess in NF1.[36]

The second most characteristic tumour of NF2 is meningiomas, which usually develop supratentorially in the falx and around the frontal, temporal and parietal regions. Surgical excision of meningiomas around the spinal cord can be difficult. Although there are different histological types of meningioma (meningothelial, fibroblastic and transitional), there is no evidence for a clinical subdivision into NF2-related and non-NF2 related meningiomas. Collision tumours consisting of a schwannoma and meningioma are sometimes seen, particularly in the cerebello-pontine angle. Antinheimo et al.,[22] in a study of all meningiomas and schwannomas in an 11-year period in the Helsinki area, found that 3% of schwannoma patients and 1% of meningioma patients had NF2. A further 2% of schwannoma patients and 4% of meningioma patients had multiple tumours without fulfilling clinical diagnostic criteria for NF2. The great majority of NF2 patients do not present with an isolated tumour, and there is only a small risk of NF2 after a truly isolated VS (no other features of NF2 on clinical examination or scan).[37] However, it is important to recognize that as many as 10% of those presenting in childhood with an apparently isolated meningioma develop NF2.

Low-grade ependymomas and occasionally gliomas also develop; they are very indolent and rarely metastasize. The primary location for these tumours is in the cervical spine and brainstem.

Recently a new era in drug therapy was heralded by evidence that the VEGF antibody bevacizumab had efficacy in shrinking growing schwannomas in NF2.[38]

CLINICAL MANAGEMENT

NF2 presents complex management issues and patients should be managed by a multidisciplinary team consisting of a neurosurgeon, otolaryngologist, audiologist, ophthalmologist, neuroradiologist and geneticist. Surgical results are certainly far better when managed by an experienced team.[39, 40] Indeed there is now firm evidence of a statistically significant reduced risk of mortality for NF2 patients managed at speciality centres in the UK.[25] Radiation treatment can have a role for patients who have particularly aggressive tumours, who are poor surgical risks or who refuse surgery. Teams that are experienced in the positioning of brainstem implants can offer partial auditory rehabilitation to those who are deaf, although results are still behind those achievable for cochlear implants. Because detection of tumours at an early stage is effective in improving the clinical management of NF2, presymptomatic genetic testing is an integral part of the management of NF2 families.

Once a mutation has been identified in an affected individual, a 100% specific test is available for that family. Linkage analysis is still possible in rare families where no mutation is identified. In sporadic cases, testing of a tumour specimen usually identifies the underlying mutation and creates a test for offspring, especially in those with mosaic disease.[15, 16] Age at onset curves aid genetic counselling; for example, it can be seen that the risk of having inherited NF2 for an asymptomatic at-risk individual of 25 years of age, prior to screening, decreases to 25% (see **Figure 104.3**).[16, 41] At-risk individuals who have been shown not to have inherited the mutated *NF2* gene do not need further follow-up.

OUTCOMES

Even with improvements in microsurgery and use of radiation therapy, the great majority of individuals with NF2 become completely deaf. The tumours in NF2 are more difficult to treat than those of sporadic unilateral VS because NF2 VS are often multifocal, appearing like a 'bunch of grapes' around the vestibular nerve in particular. Histologically, NF2 VS are more lobular and less vascular than their sporadic counterpart,[33] which leads to a greater risk of facial nerve damage in NF2. Loss of facial nerve function and the resultant disfigurement is one of the most feared aspects of the condition for many people with NF2, although in good surgical hands this complication is now much less common.[39, 40] Patients may also be severely disabled by a combination of poor balance, visual problems and weakness due to spinal tumours. Indeed, many people with severe NF2 become wheelchair-bound in early adulthood, and many with severe, multi-tumour disease die in the second and third decades of life.

SCREENING PROTOCOL

Children of affected patients are at 50% risk of NF2 and screening for the disease can start at birth. Cataracts can affect vision in early life and other tumour implications are present in the first 10 years of life, particularly intracranial meningiomas. Screening for VS should start at 10 years of age because it is rare for VS to become symptomatic before then, even in severely affected families. Annual audiological tests, including auditory brainstem response, are still a useful adjunct to MRI.[41] Surgery is unlikely to be more successful for tumours <6 mm in diameter than for tumours 6–10 mm in diameter, but VS growth is higher in younger patients. Even in multiple affected patients of similar ages in NF2 families, however, there can be dramatic differences in VS growth rates. For these reasons, MRI screening every 2 years for those under 20 years old and every 3 years for those aged over 20 years should be sufficient for asymptomatic at-risk individuals without tumours. The initial MRI scan can be at about 10–12 years old, or earlier in severely affected families. Once tumours are present, MRI screening should be annual. Spinal tumours are found very frequently on MRI, as discussed previously. While only 30% of patients with spinal tumours have symptomatic tumours that may require operation, a full annual neurological examination is a wise precaution. In most families, it is now possible to develop a genetic test so that only those individuals who have inherited an *NF2* mutation need to be followed.

FUTURE PROSPECTS

Localization and cloning of the *NF2* gene has allowed precise diagnosis when a specific mutation is found in a family. Clinical factors that are closely related to mutation type, such as age at onset or age at diagnosis, predict the risk of mortality and VS growth rate more strongly than the type of constitutional *NF2* mutation. This may be particularly useful in patients with new mutations, in whom insight into the likely speed of tumour progression and risk of other tumours may not be apparent, but it should be noted that such aggregate correlations may be less useful in predictions for individual patients. DNA predictive testing for 70% of families is available with flanking markers or mutation testing, but there is currently little demand for prenatal NF2 diagnosis in the UK. A less controversial option may be pre-implantation diagnosis, which is being evaluated for other genetic diseases such as familial adenomatous polyposis and cystic fibrosis.

Replacement of the tumour suppressor product in the tumours through viral vectors or direct recombination of the *NF2* gene, although requiring great advances in our knowledge, could be very rewarding. Use of newer drugs, such as anti-angiogenesis and drugs targeted at the NF2 pathway, may also offer promise.[42]

KEY POINTS

- NF2 is an autosomal dominant condition caused by mutations in the NF2 gene on chromosome 22q.
- De novo cases have a high chance of having mosaic disease where the genetic mutation is present in only some of the cells and transmission risk is lower to children.
- Although treatment is primarily surgical, newer drug therapies particularly with bevacizumab are showing promise.

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CHAPTER 105

NON-VESTIBULAR SCHWANNOMA TUMOURS OF THE CEREBELLOPONTINE ANGLE

Simon K.W. Lloyd and Scott A. Rutherford

SEARCH STRATEGY

A Medline search the MESH headings Cerebellopontine Angle OR CPA was carried out. A further search was performed for the following MESH headings: neoplasm, tumour, meningioma, epidermoid cyst, CPA cholesteatoma, arachnoid cyst, glomus jugulare, lipoma, dermoid cyst, facial schwannoma, trigeminal schwannoma, vagal schwannoma, cranial nerve neoplasms, glossopharyngeal schwannoma, jugular schwannoma, chondrosarcoma, chordoma, endolymphatic sac, cochlear schwannoma and haemangioma. A search combining the first and second searches was then performed. Finally, the headings vestibular schwannoma and acoustic neuroma were excluded. Additional searches for other rarer pathologies were also performed.

INTRODUCTION

Lesions of the cerebellopontine angle (CPA) are uncommon, making up 6–10% of intracranial tumours; 80–90% are vestibular schwannomas (VS), with the remaining 10–20% a heterogenous mixture of predominantly benign pathologies, although malignant also occur.[1–9] Pathology may arise from any of the anatomical structures that are found within or adjacent to the CPA. **Table 105.1** summarizes the types of pathology that may occur. Meningiomas and epidermoid cysts are the commonest non-vestibular schwannoma tumours of the CPA, making up approximately 10% and 6% respectively in this location.

SYMPTOMS AND SIGNS OF NON-VS CPA TUMOURS

Lesions of the CPA cause damage to the neurological structures traversing the CPA and it is not usually possible to differentiate between different pathologies based on symptoms and signs. Most present with audiovestibular compromise in the form of sensorineural hearing loss, tinnitus or vertigo.[7, 10, 11] Other cranial nerves may also be affected resulting in altered facial sensation, facial weakness, twitching or spasm and lower cranial nerve weakness depending on the position and nature of the lesion.

Larger tumours also cause brainstem compression that may result in ataxia, headache, hydrocephalus and, in the extreme, may compromise brainstem reflexes, particularly respiratory drive. Onset of symptoms and signs is usually insidious.

It is important to note that the majority of patients with these clinical features have no tumour but have other non-neoplastic pathology such as ischaemic disease, migraine or other neurological conditions.

IMAGING OF NON-VS CPA TUMOURS

Where symptoms and signs are often unhelpful in differentiating between CPA pathologies, modern radiological techniques have, in contrast, revolutionized the diagnosis of CPA pathology. This paradigm shift in the ability to diagnose and differentiate between CPA pathologies has resulted in fundamental philosophical changes in the management of CPA pathology with conservative management and stereotactic radiosurgery becoming increasingly popular in the management of such lesions.

Magnetic resonance imaging (MRI) is the gold standard imaging modality. It provides excellent definition of soft

TABLE 105.1 Differential diagnosis of non-vestibular schwannoma lesions of the cerebellopontine angle

	Benign	Malignant
Lesions arising from the CPA	• Meningioma • Epidermoid cyst • Arachnoid cyst • Trigeminal schwannoma • Facial schwannoma • Lower cranial nerve schwannoma • Lipoma • Dermoid cyst • Tuberculoma • Sarcoid granuloma • Neurenteric/enterogenous cyst • Trigeminal ganglioneuroma • Solitary fibrous tumour • Melanocytoma • Lipomatous glioneurocytoma • Benign glandular peripheral nerve sheath tumour • Neurocytoma	• Metastases (breast, gall bladder, nasopharynx, parotid) • Malignant melanoma • Lymphoma • Neuroectodermal tumour • Malignant peripheral nerve sheath tumour • Haemangiopericytoma
Temporal bone lesions involving the CPA	• Cholesterol granuloma • Glomus jugulare • Haemangioma	• Squamous cell carcinoma • Chondrosarcoma • Chordoma • Endolymphatic sac tumours (Papillary adenoma/adenocarcinoma) • Plasmacytoma
Intra-axial lesions involving the CPA	• Low grade glioma (Ependymoma/Astrocytoma) • Choroid plexus papilloma • Glioependymal cyst • Lipomatous hamartoma • Cysticerosis • Haemangioblastoma • Plasma cell granuloma	• High grade glioma (Glioblastoma/Malignant astrocytoma) • Medulloblastoma • Meningosarcoma • Choroid plexus carcinoma

TABLE 105.2 Table showing the imaging characteristics of the common pathologies affecting the CPA

Lesion	CT	CT + contrast	MRI T1- weighted	MRI T2-weighted	MRI + Gadolinium	Special features
Vestibular schwannoma	→	+	↓	↓/↑	+	'Ice cream cone'; heterogeneous enhancement if cysts
Meningioma	↑	+	→/(↑)	→/↓/(↑)	+	'Dural tail' on post-contrast imaging; may be calcified
Epidermoid	↓	–	↓	↑	–	Bright on DWI b1000 trace; internal structure may be visible on T1-W and T2-W MRI; close to CSF on T1-W and T2-W MRI; not CSF signal on FLAIR MRI
Lipoma	↓/fat	–	↑/fat	↑/fat	–	Complete saturation on T1 fat saturation MRI; chemical shift artefact on T2-W MRI
Arachnoid cyst	↓/CSF	–	↓/CSF	↑/CSF	–	
Glomus tumour	→/↑	+	↓	↑	+	'Salt and pepper'; T1-W MRI, bright haemorrhagic foci; T2-W MRI, dark flow voids
Choroid plexus tumour	→/↑	+	→/↓	→/↑	+	May be calcified; MRI may not distinguish papilloma from carcinoma; children > adults

↓, hypodense (CT)/hypointense (MRI) to brain; →, isodense (CT)/isointense (MRI) to brain; ↑, hyperdense (CT)/hyperintense (MRI) to brain; +, enhancement; –, no enhancement; CSF, cerebrospinal fluid; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuation inversion recovery.

tissue structures. Axial and coronal T1-weighted imaging with gadolinium enhancement and T2-weighted imaging are widely used. Fat suppression in conjunction with gadolinium-enhanced imaging is also extremely helpful. Diffusion-weighted imaging (DWI) MRI has been introduced in the last decade and is also helpful, particularly in identifying epidermoid tumours.

High-resolution axial and coronal computed tomography (CT) is often a useful adjunct to MRI and provides excellent definition of bony structures.

Table 105.2 summarizes the radiological characteristics of the common CPA pathologies.

Other forms of imaging may also be helpful. This includes MR angiography and traditional angiographic imaging.

These are particularly helpful in delineating vascular lesions such as glomus tumours.

BENIGN LESIONS ARISING FROM THE CPA

Meningiomas

DEFINITION AND PATHOLOGY

Meningiomas arise from clusters of epithelial cells that are present at the tips of arachnoid villi that are concentrated in the walls of venous sinuses, in their tributary veins and at the cranial nerve exit foramina.[11, 12] They may be well circumscribed or, more rarely, *en plaque* when their growth pattern results in a flat lesion. Bony infiltration via Haversian canals can occur and may result in hyperostosis that is demonstrable radiographically. They displace or surround cranial nerves and blood vessels rather than invading them. Nevertheless, they can become strongly adherent to these structures.[10, 12]

Histologically, meningiomas may be graded from 1 to 3 according to the WHO grading system.[10–16] Grade 1 tumours make up 81% and are described as classical. Grade 2 tumours make up 15% and are described as atypical. Grade 3 tumours make up the remaining 4% and demonstrate malignant features including the ability to metastasize either haematogenously or via CSF.[17] Grade 1 and 2 tumours are regarded as benign. Meningiomas often contain 'psammoma bodies', spherical calcifications responsible for a sandy appearance of the tumour surface.

Most tumours are regarded as being idiopathic with the exception of those associated with neurofibromatosis type 1 and type 2. Twenty per cent of adolescents with meningiomas have some form of neurofibromatosis.[13] Some authors have suggested an endocrine aetiology based on high concentrations of progesterone receptors, moderate numbers of androgen receptors and a low level of oestrogren receptors within meningiomas. A recent meta-analysis of the influence of hormone replacement therapy on development of meningiomas in women suggests that there is an association.[18] There may also be an association with androgen use in males.[19] Irradiation to the head is also associated with an increased risk of meningiomas.

EPIDEMIOLOGY

Meningiomas account for approximately 10–20% of all intracranial neoplasms. The incidence increases with age, the average age at the time of diagnosis of posterior fossa meningiomas being approximately 43 years.[13] Between 5% and 10% of all meningiomas arise in the CPA and are more common in middle-aged females. Second to vestibular schwannomas, meningiomas are the most common neoplasm found in the CPA, constituting roughly 10% of lesions in this location.[10–12]

CLINICAL PRESENTATION

Meningiomas differ from vestibular schwannomas in their clinical presentation. Audiovestibular symptoms are common but are often less marked and of shorter duration in patients with meningiomas compared with vestibular schwannomas.[2, 4, 7, 10, 12, 14, 20–23] Hearing loss is present in 41–80% of patients. This is usually sensorineural in nature but may be conductive if the middle ear is involved.[24] Tinnitus is present in about 15–60% of patients and dysequilibrium is a presenting symptom in 20–60% of patients. Other cranial nerve symptoms and signs tend to be more common with meningiomas than with vestibular schwannomas, occurring in up to 30% of patients. Fifth and seventh nerve symptoms are present in up to 20–60% and 10–50% of patients respectively.[4, 7, 10, 12, 14, 22, 23] Cerebellar signs are reported in about 30–90% of patients.[7, 12, 14, 21–23]

DIAGNOSIS

CT scans usually reveal a durally based homogenous tumour that is either iso- or slightly hyperintense. They avidly take up contrast.[10, 11] Peri-tumoural oedema may also be demonstrated, as may bony erosion, hyperostosis and intra-tumoral calcification. CT is superior to MRI in evaluating bone involvement and calcification of the tumour and is also helpful in demonstrating extension into the middle ear.[11, 13]

The gold standard imaging modality for demonstrating meningiomas is, however, MRI. T1-weighted imaging shows a homogenous iso- or hypointense tumour relative to brain parenchyma that is durally based. They take up gadolinium although they often enhance less avidly than vestibular schwannomas (**Figure 105.1**). With gadolinium, a dural tail is seen in around 60% of tumours. It has not been established whether the changes are neoplastic or represent reactive changes in the meninges adjacent to the tumour.[11, 13, 14] They are very variable in intensity on

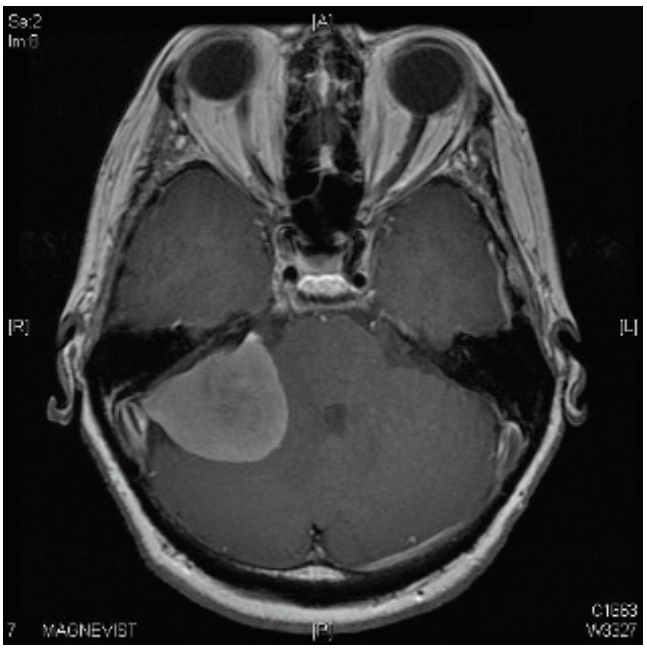

Figure 105.1 T1-weighted axial MRI scan with gadolinium enhancement showing a large right CPA meningioma.

T2-weighted imaging.[10, 11, 13, 14] Again, MRI may identify significant peri-tumoral brain oedema.

The natural history of untreated meningiomas is generally benign. A systematic review by Sughrue et al. have demonstrated that, over a 4 year period, 50% demonstrate growth. Half of these increase in size by less than 10% per annum.[25]

TREATMENT

For selected cases, particularly for those patients with severe co-morbidities, advanced age or small tumours, observation with serial MRI has become increasingly popular. This reflects the generally benign natural history of meningiomas. This type of management is, however, less effective for meningiomas compared to vestibular schwannomas that demonstrate growth in only 20–30% of cases.

For large or symptomatic tumours, the treatment of choice for meningiomas is surgical excision and the ideal is complete resection of tumour together with involved dura and affected underlying bone. Although complete macroscopic clearance has been described in up to 91% of CPA meningiomas,[26] complete resection is not always possible, particularly if there is extensive bony involvement or strong adherence to neurovascular structures or brain.[27] The extent of resection may be graded using the Simpson criteria.[28] This and the histological grade of the tumour determines recurrence rates. For example, for Simpson grade I tumours, the recurrence rates for WHO grades 1 and 2 respectively are 12% and 41%.[16] **Table 105.3** summarizes the Simpson criteria together with the 10-year recurrence risk for each grade.

Surgical approach is determined by hearing status and the size and location of the tumour, including involvement with neurovascular structures as well as local preferences. The retrosigmoid approach is the standard neurosurgical approach to the posterior fossa and offers the possibility of hearing preservation in appropriate cases.[20, 26, 29, 30] The translabyrinthine approach offers direct access to the CPA and may offer lower mortality and improved facial nerve outcome compared to the retrosigmoid approach, but sacrifices residual hearing.[3, 30–32] A combined translabyrinthine-retrosigmoid approach can be used for tumours greater than 3–4 cm. The transcochlear approach offers anterior exposure to facilitate resection of tumours extending into the region of the clivus, Meckel's cave and the petrous portion of the internal carotid artery, and may be used in combination with a trans-tentorial approach if required.[30, 32] The middle fossa approach may also be used for tumours within the internal auditory canal that have a small CPA component.

Several authors have investigated the potential role of radiotherapy as a primary treatment modality and for recurrent or residual tumours.[33, 34] A number of types of radiotherapy have been used. Historically, external beam radiotherapy was used but this achieved relatively poor control rates of around 85%.[35, 36] Latterly, fractionated stereotactic radiotherapy and stereotactic radiosurgery have been used. For WHO grade 1 tumours, these techniques produce growth control rates of 86–99% although control becomes less likely with increasing tumour volume.[34, 37, 38] Similarly, brachytherapy with iodine-125 seems to be of value in both recurrent and primary skull base meningiomas.[39]

Medical therapies including hormone therapies, temozolomide, hydroxyurea, alpha-interferon, mifepristone and COX-2 inhibitors are currently being investigated but results to date have generally been disappointing.[13, 40, 41] Targeted chemotherapy aimed at blocking specific growth factors or intracellular signalling pathways are currently under investigation.[42]

TABLE 105.3 Table summarizing the Simpson criteria for completeness of tumour removal

Simpson grade	Completeness of resection	10-year recurrence[28]
I	Complete removal including underlying bone and associated dura	5–9%
II	Complete removal and coagulation of dural attachment	15–19%
III	Complete removal without resection of dura or coagulation	12–29%
IV	Subtotal resection	19–40%

Epidermoid cysts

DEFINITION AND PATHOLOGY

Epidermoids or primary cholesteatomas are keratinous cysts that originate from inclusion epithelial cells trapped during neural tube closure between the third and fifth weeks of gestation. In the CPA, they are thought to originate from transplantation of epithelial cell rests by the laterally migrating optic and otic capsules or developing neurovasculature.[2, 11, 43] They are distinguished from dermoids by the absence of skin adnexal components. They increase in size slowly by the accumulation of keratin and cholesterol produced by the desquamation of the squamous epithelial lining of the cyst and their growth rate is similar to that of normal skin and not the exponential growth seen with most neoplasms.[2, 11, 43] They insinuate around neurovascular structures, irritating rather than displacing them, and they fill the cisterns from which they arise following the line of least resistance.[10, 43, 44] Thirty to 40% of epidermoids occur in the CPA but they can be found elsewhere in the brain.[2, 11, 43] Macroscopically, these tumours have a soft texture and a pearly white colour. Microscopically, they are avascular tumours lined by stratified squamous epithelium that surrounds a mass of keratinous debris and, frequently, cholesterol crystals.[10, 43]

EPIDEMIOLOGY AND AETIOLOGY

Epidermoids account for 0.2–1.8% of all intracranial neoplasms and constitute 5–9% of tumours in the CPA.[2, 11, 43, 45] They may be slightly more common in

males than in females. They are not associated with any other congenital abnormalities.[43]

CLINICAL PRESENTATION

Because of their slow growth, CPA epidermoids may be asymptomatic for years.[2, 7, 43] As with meningiomas, hearing loss is less common than with vestibular schwannomas, occurring in 50–80% of cases.[4, 7, 43, 46–48] Fifth and seventh nerve symptoms occur in 30–50% of cases. Cerebellar signs or signs of increased intracranial pressure may also occur.[4, 7, 43, 46–48] Lower cranial nerve symptoms and signs are more rare.[4, 7, 43, 46–48] Spontaneous meningitis without surgery has been reported and an intracranial epidermoid should be suspected in a patient with repeated episodes of aseptic meningitis.[49] Malignant transformation of epidermoids into squamous cell carcinoma has been reported and present with more severe and rapidly progressive symptoms.[50, 51]

DIAGNOSIS

As with other types of CPA pathology, MRI is the imaging modality of choice.[11] On T1-weighted imaging, the lesions are heterogenous and of low signal showing no enhancement with gadolinium, although granulations around the cyst may enhance. T2-weighted imaging is particularly helpful and shows a high signal homogenous lesion that is lobulated, conforming to the shape of the cistern in which it has developed (**Figure 105.2**).[11] Large epidermoids compress adjacent brain. In addition, FLAIR or DWI is usually diagnostic with the lesion having high signal. This is very helpful in differentiating epidermoid cysts from arachnoid cysts.[52]

CT may also be used and shows a lesion with similar signal to CSF. There are not usually any changes within the adjacent bone. CT is often, therefore, not particularly helpful. Atypical MRI and CT appearances have been reported.[53, 54]

TREATMENT

Microsurgery is the treatment of choice with the retrosigmoid approach being the standard approach, although the translabyrinthine and middle fossa approaches may be used if required.[4, 7, 46–48] The goal of surgery is decompression of the cyst and, if possible, removal of the capsule. The interior of the tumour can be easily removed using suction or curettage. The capsule can, however, be very difficult to remove because of the way that epidermoids engulf neurovascular structures, and total removal is associated with a significantly higher morbidity and mortality.[4, 7, 43, 46–48] A comparison of recent major series shows a rate of total removal of between 0% and 97%. Most authors advocate subtotal removal of the tumour rather than compromising neurovascular function. Surgery may be repeated but is often only required every decade or more.[4, 7, 43, 46–48] Post-operative aseptic meningitis may occur in up to 40% of cases and is almost unique to this condition. This complication may be avoided by the use of prophylactic steroid use and minimal intra-operative spillage of tumour. If it occurs, the patient should be treated with antibiotics and steroids.

Even in modern series, recurrence rates of up to 35% have been reported.[4, 7, 43, 46–48] Serial imaging of any recurrence should be performed and a conservative approach taken, given that tumours may not become symptomatic during the patient's normal life span.

Arachnoid cysts

DEFINITION AND PATHOLOGY

Arachnoid cysts are congenital malformations of the arachnoid and are histologically characterized by a cyst wall that resembles arachnoid[55] and a cystic space filled with CSF or xanthochromic fluid.

EPIDEMIOLOGY

Arachnoid cysts make up approximately 1% of all intracranial lesions and the CPA represents the second most

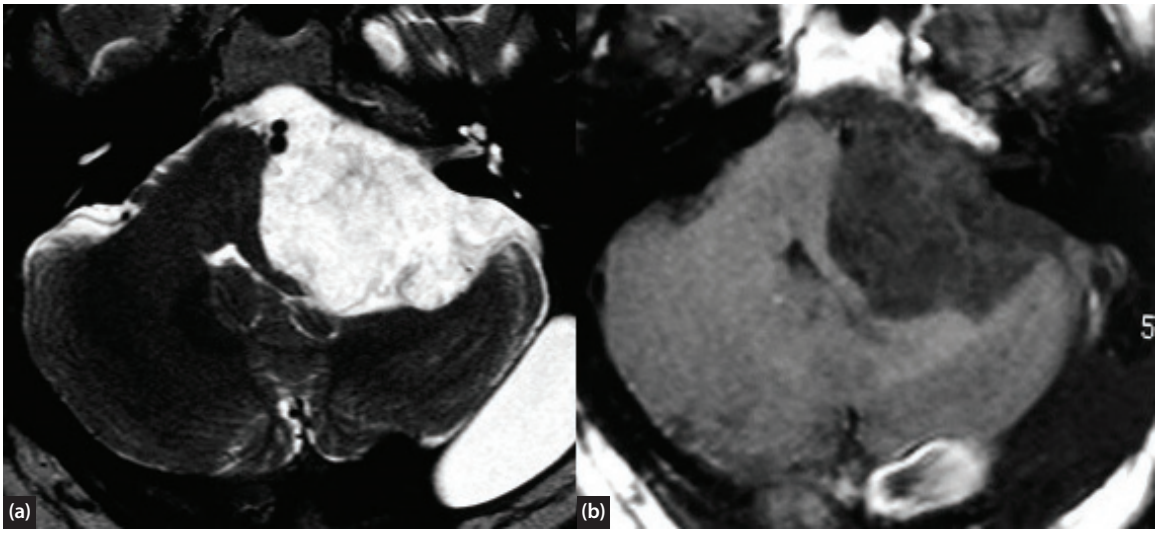

Figure 105.2 Axial MRI scans showing a large left CPA epidermoid. **(a)** T1-weighted scan without gadolinium enhancement. **(b)** T2-weighted scan.

common location after the Sylvian fissure. The aetiology remains unknown, but abnormal CSF flow, trauma or inflammation have been proposed.[56]

CLINICAL PRESENTATION

Eighty-five per cent of cysts are asymptomatic. Symptomatic cysts present with symptoms similar to other CPA lesions, with gradual onset of cranial nerve dysfunction especially of the VIIIth cranial nerve.[56–60] Sudden sensorineural hearing loss has been reported[61] and there have been a number of reports of hemifacial spasm.[62, 63] They may also present with symptoms of brainstem and cerebellar compression, and syringomyelia has been described.[64]

DIAGNOSIS

MRI is the primary diagnostic imaging modality. The cysts are heterogeneous in their appearance but they have the same signal as CSF, being hypointense on T1-weighted images and hyperintense on T2-weighted images (**Figure 105.3**). No enhancement is seen.[10, 56, 60] The cyst wall is smooth and round and the cysts compress or displace adjacent structures. Erosion of adjacent bone may also be seen.[44] They may be confused with epidermoid cysts and diffusion weighted imaging is helpful in differentiating these two pathologies. Only 2% of them demonstrate growth.

TREATMENT

Asymptomatic cysts require no treatment and should be followed by serial MRI scans. For symptomatic cysts, microsurgical decompression and fenestration via the retrosigmoid approach is the most commonly recommended procedure,[10, 11] although some authors have described an endoscopic approach.[65, 66] Sporadic reports of cyst recurrence after inadequate fenestration exist and some authors advocate complete cyst resection.[60] Others suggest cystoperitoneal shunts but these appear to be less effective than fenestration.[56, 60]

Lipomas

DEFINITION AND PATHOLOGY

CPA lipomas are likely to be congenital malformations and not actual neoplasms.[67–70] They may result from the failed dissolution and aberrant differentiation of the meninx primitiva, the mesenchymal derivative of neural crest,[67, 70, 71] which contains mature adipose cells accompanied by a varying degree of fibrovascular tissue. Blood vessels and nerves pass directly through them and are not displaced.

EPIDEMIOLOGY

These are rare tumours with an incidence of 0.08% in autopsy cases.[71, 72] They make up approximately 0.05–0.1% of CPA tumours,[11, 44, 67, 71, 73–78] although this may be an underestimate given that they may be mistaken for vestibular schwannomas.[71, 79] It is thought that only 9% of intracranial lipomas are found in the CPA, with interhemispheric lipomas being the most common.[70] A male preponderance has been reported by several authors.[73, 79, 80] Mean age at diagnosis is around 50 years.[80] Bilateral tumours have also been described.[71]

CLINICAL PRESENTATION

They present clinically with similar symptoms to other more frequent CPA tumours like vestibular schwannomas,[11, 67, 71, 73–75, 77, 79–81] although the onset of symptoms may be more insidious. Hearing loss is the most common presenting symptom followed by tinnitus and dizziness.[71–73, 76, 79, 80] Reports regarding their effect on the facial nerve vary in the literature, with some series showing no effect on facial nerve function and others suggesting that up to 9% of cases have facial nerve weakness.[73]

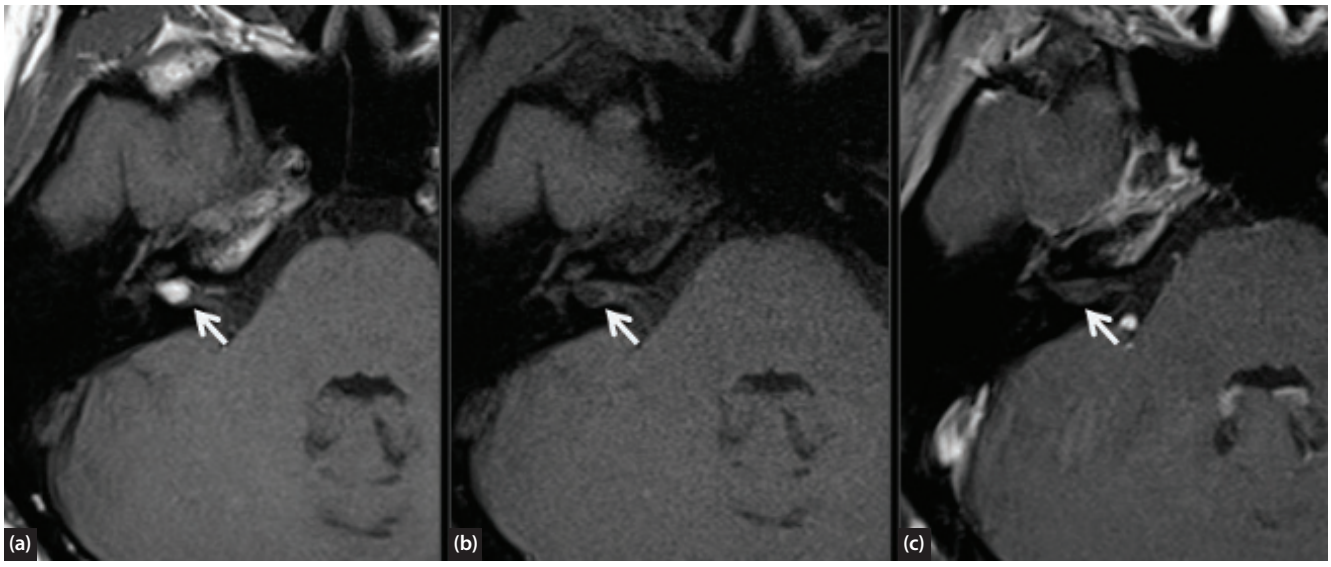

Figure 105.3 An intracanalicular right sided lipoma. (a) Very high signal intensity on axial non-contrast enhanced, T1-weighted imaging. **(b)** Hypointense on axial T1-weighted following fat suppression. **(c)** No enhancement following administration of gadolinium.

Other reported symptoms include hemifacial spasm[82, 83] and trigeminal neuralgia.[68, 84, 85] Weakness of other cranial nerves (with the exception of the vestibulocochlear nerve) has not been reported.

DIAGNOSIS

On MR imaging, lipomas have the same imaging characteristics as subcutaneous fat with high intensity on non-enhanced T1-weighted MRI studies, with progressive iso- to hypointensity with increasing T2 weighting. They produce no signal with fat suppression sequences.[75, 77, 80, 86, 87] The latter is extremely useful in differentiating lipomas from other CPA pathology (**Figure 105.4**). Furthermore, lipomas have also been said to display the MRI phenomenon of chemical shift and this may assist further in confirming the diagnosis. This phenomenon consists of a ring of low signal intensity at the posterior edge of the mass because of mis-registration of the fatty tissue at the interface with soft tissue and cerebrospinal fluid.[71]

Most of the literature suggests that CPA lipomas rarely grow,[11, 71–73, 78–80] with only one documented case of a CPA lipoma demonstrating growth in the current literature.[71] It has, however, been hypothesized that CPA lipomas might fluctuate in size, depending on the patient's weight.[71] This is not a consistent finding in the literature, however.[80]

TREATMENT

Because they are very unlikely to grow, conservative management has become the mainstay of management with some authors suggesting that long-term follow-up is not required.[80] Surgical removal has, however, been performed in cases with symptoms related to compression phenomena, mostly of the cranial nerves[67, 71–73, 79] or in cases of misdiagnosis.[78] In many of these cases, total removal of the lipoma has been very difficult and surgery has been associated with significant post-operative morbidity.[67, 71–73, 79] This is because CPA lipomas tend to be adherent to cranial nerves and the brainstem, making dissection challenging.[71, 73, 78] Most authorities therefore recommend subtotal removal if surgery is indicated. Both the translabyrinthine and retrosigmoid approaches have been described.[11, 67, 71]

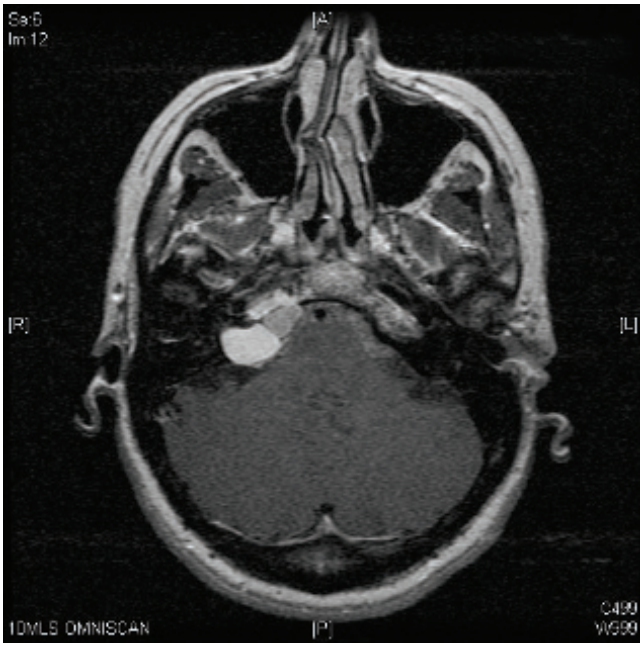

Figure 105.4 Axial T1-weighted MRI scan showing a right petrous apex cholesterol granuloma.

Non-vestibulocochlear cranial nerve schwannomas

Schwannomas are the commonest neoplasm of cranial nerves and may develop on the V, VII or lower nerves. Symptoms reflect the nerve involved. Overall, they constitute 2–3% of all CPA tumours. Microscopically, non-vestibular schwannomas cannot be distinguished from vestibular schwannomas.

Facial schwannomas

DEFINITION AND PATHOLOGY

Facial nerve schwannomas (FNS) are rare benign tumours of the Schwann cell sheath of the facial nerve. Tumour may develop at any point along the course of the nerve from the CPA to the muscular branches in the face. Single or multiple segments of the nerve can be involved although the latter is more common.[88] The CPA is involved in 22 to 46% of cases depending on the series reviewed.[88, 89]

EPIDEMIOLOGY

FNS tend to present in the fourth or fifth decades of life[88] and have a male preponderance.[90]

CLINICAL PRESENTATION

In a meta-analysis of 427 patients, the commonest presenting symptoms were facial weakness and hearing loss occurring in 63% and 51% of cases respectively.[91] Facial weakness tends to be more common with tumours involving the extracranial segments of the nerve, especially the geniculate and labyrinthine segments. It can be of variable severity and may be transient or progressive or recurrent.[92, 93] The proportion of patients showing deterioration of facial function following diagnosis ranges from 21% to 38% depending on the series.[88, 94] Audiovestibular symptoms are more common with tumours involving the CPA and internal auditory canal (IAC),[95] although conductive hearing loss may occur if the middle ear is involved.

DIAGNOSIS

The gold standard diagnostic tool for the identification of a FNS is T1-weighted MRI with gadolinium enhancement. This allows identification of multiple segments of the facial nerve, a feature that is highly suggestive of FNS. Nevertheless, it may be extremely difficult to differentiate FNS from other pathologies, particularly if the radiological changes are confined to the CPA or the IAC as the

appearance can be identical to that of a vestibular schwannoma. It may also be difficult to differentiate FNS from other rarer pathologies such as haemangiomas. All CPA tumours should therefore have at least one scan with gadolinium to ensure that there is no adjacent VII nerve enhancement to suggest an FNS rather than a VS.

Tumour growth (>2 mm) has been reported to occur in 14% to 31% of patients.[88, 94]

TREATMENT

In the absence of significant tumour growth, significant brainstem compression or deterioration of facial function to grade 4 or worse, most clinicians recommend conservative management. Over half of tumours are therefore managed conservatively, at least initially.[88, 94, 96]

In those patients not managed conservatively, most undergo surgical excision although stereotactic radiotherapy may also be considered.

For those having surgery, the approach depends on the segment of nerve involved but most often requires a translabyrinthine or transotic approach if the CPA is involved. If there is serviceable hearing a combined transmastoid/middle fossa/retrosigmoid approach may be considered. Facial nerve grafting with great auricular or sural nerves is carried out following tumour removal. The possibility that a CPA tumour could be an FNS rather than a VS should always be considered. Fascicle preservation surgery has also been described with successful preservation of facial function.[97] Bony decompression of the tumour may also be considered under certain circumstances and may avoid deterioration in facial function.

The indications for radiotherapy are, as yet, unclear. A single case report of treatment with stereotactic fractionated radiotherapy has shown that tumour growth can be controlled and facial function not worsened by this modality of treatment.[98]

Trigeminal schwannomas

Tumours tend to involve either the ganglion or the nerve root, or both. Fifth nerve symptoms tend to dominate over VIIIth nerve dysfunction and the patients present with facial pain or numbness.[10] Other symptoms of an expanding CPA tumour may also be present. CT scans demonstrate enlargement of Meckel's cave or foramen lacerum and the tumours tend to be hypo- or isodense and show contrast enhancement. On MRI, the tumours appear iso- or hypointense on T1-weighted images and isointense on T2-weighted images and show bright enhancement as with other schwannomas. Tumour removal is possible through combined posterior, middle fossa or infratemporal fossa approaches.[10, 99] Endoscopic transnasal removal of tumours involving the middle fossa and infratemporal and pterygopalatine fossae has also been described.[100] The use of stereotactic radiosurgery has also been reported.[101]

Lower cranial nerve schwannomas

Lower cranial nerve schwannomas account for less than 1% of all CPA lesions.[45] They develop within the jugular foramen and may extend intracranially or extracranially, often developing a dumbbell shape. Symptoms reflect the nerve involved but may also result in audiovestibular dysfunction or clinical features of brainstem compression if large. Their imaging characteristics are those of any cranial nerve schwannoma. Treatment is by conservative management unless there is significant brainstem compression, in which case surgical resection may be undertaken. The decision to proceed is easier if there has already been loss of lower cranial function. Approaches include retrosigmoid, transcochlear and infratemporal fossa approaches depending on the position of the tumour.[102, 103] Growing tumours with good lower cranial nerve function may be treated with stereotactic radiosurgery.

Miscellaneous tumours

Dermoids are midline cysts and rarely invade the CPA laterally. They contain skin adnexal components, contrary to epidermoids.[45]

Choroid plexus papillomas are rare tumours, representing less than 1% of intracranial neoplasms. They are derived from the epithelial cells of the choroid plexus and demonstrate the structure of the normal choroid plexus when benign. Most often affecting children, they typically arise in the lateral ventricles. In adults, the primary site is the fourth ventricle. Malignant forms are very rare. They may produce signs of a CPA tumour, and signs of raised intracranial pressure are almost always present. Evaluation of CPA choroid plexus papillomas is by CT, MRI and angiography. Their prognosis is excellent when total surgical extirpation is possible. When surgery is not possible, radiotherapy has been evaluated, but results are variable.[104, 105]

Enterogenous cysts[106] are midline cysts that have very rarely been reported within the CPA. They may mimic arachnoid cysts, lipoma, epidermoids or cystic vestibular schwannomas on MRI.[45] They are usually symptomatic and treatment is usually by complete excision.

Neurenteric cysts are cysts derived from notochordal gastrointestinal or respiratory cell rests. They are very rare in the CPA and are usually treated with surgical resection.[107]

Inflammatory disease such as autoimmune or idiopathic pachymeningitis can occur in the CPA and may produce symptoms of CPA pathology due to compression of CPA structures by hypertrophied dura. Similarly, granulomatous diseases, such as tuberculosis and sarcoidosis, may affect the CPA.

The vertebral and basilar arteries and some of their branches pass through the CPA and aneurysms of the vessels, although not true neoplasms, may cause a mass effect on adjacent neural structures.[10, 44, 45]

MALIGNANT LESIONS ARISING FROM THE CPA

Metastatic lesions from either intracranial or extracranial sources account for around 1% of CPA tumours. Sources of extracranial origin are breast, prostate, lung,

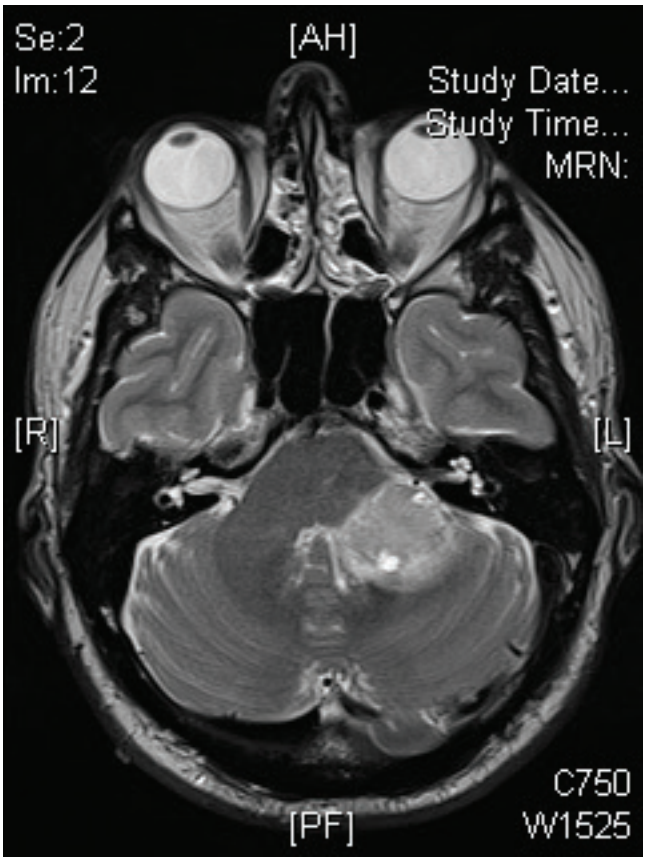

Figure 105.5 Axial T1- weighted MRI scan with gadolinium enhancement showing a left CPA metastasis.

melanoma, thyroid and gynaecological tumours.[45] They usually have similar signal characteristics to schwannomas on MRI (**Figure 105.5**). Diagnosis may be aided by lumbar puncture and CSF cytology. Solitary metastases may be treated with surgical resection or with stereotactic radiosurgery.

Melanomas of the CPA are very rare and may occur as either primary or metastatic tumours, the latter being the most common. Again, they often have similar signal to schwannomas on imaging. Prognosis is poor.[108]

CPA lymphomas are rare and occur as an extra-axial lymphoma, as extension from an intra-axial lymphoma, or as a leptomeningeal lymphoma presenting as a CPA lesion. Aggressive removal is not necessary, but radiotherapy to the lesion should be performed.[109]

BENIGN TEMPORAL BONE LESIONS INVOLVING THE CPA

Lesions originating from the structures of the skull base, especially the temporal bone, may reach the CPA by direct extension.

Cholesterol granulomas

Cholesterol granulomas arise from the apex of the petrous bone and may enlarge to reach the posterior fossa and produce nerve dysfunction (**Figure 105.4**).[44] Symptomatic cases may be decompressed via a transmastoid or endoscopic transnasal approach depending on its position.[110]

Glomus tumours (paragangliomas)

Large jugular foramen paragangliomas (Fisch type D) may present in the CPA by extension from the jugular foramen. Very rarely, primary CPA paragangliomas have been reported.[111] They are usually benign but locally aggressive, and destroy the petrous bone to enlarge to the CPA. Symptoms include pulsatile tinnitus, headache or VIIIth nerve symptoms. Examination may reveal a red pulsatile mass behind the tympanic membrane with a conductive hearing loss. Arteriography should be performed to demonstrate the extent of the tumour and the nature of blood supply. CT appearances are of a well-defined tumour with adjacent bone erosion and marked enhancement after contrast injection. They produce a characteristic 'salt and pepper' image on both T1- and T2-weighted MRI images because of intratumoral haemorrhages (**Figure 105.6**). Glomus tumours enhance intensively after gadolinium administration. Indications for treatment include brainstem compression and significant tumour growth with around 40% demonstrating growth following diagnosis.[112] Radiotherapy effectively controls growing tumours in 90–100% of cases and surgery has become less common as a result.[113–115] It is usually reserved for patients with significant brainstem compression, radiosurgery failure and those patients who already have lower cranial nerve compromise as post-operative cranial nerve deficits are common with unacceptably high morbidity.

MALIGNANT TEMPORAL BONE LESIONS INVOLVING THE CPA

Squamous cell carcinoma of the temporal bone accounts for 0.3% of head and neck malignancies. They are aggressive malignancies that invade adjacent structures.[116, 117] Lymph node metastases occur in 20%. Invasion of the carotid canal, cervical node involvement and poorly differentiated histology are poor prognostic factors. For cases that are operable, radical *en bloc* resection with preservation of the carotid artery, selective neck dissection and post-operative radiotherapy is recommended.[116, 117] It has a disease specific survival ranging from 19% to 48%.

Chondromas and chondrosarcomas are extremely rare and develop from embryonic cartilaginous remnants enclosed in the bones of the skull base.[44, 118] Both lesions are usually treated surgically.

Chordomas are very rare midline tumours arising from notchordal remnants around the vertebral axis. Intracranially they occur at the clivus although primary intradural chordomas have been reported. Whilst they are malignant they are generally fairly indolent in

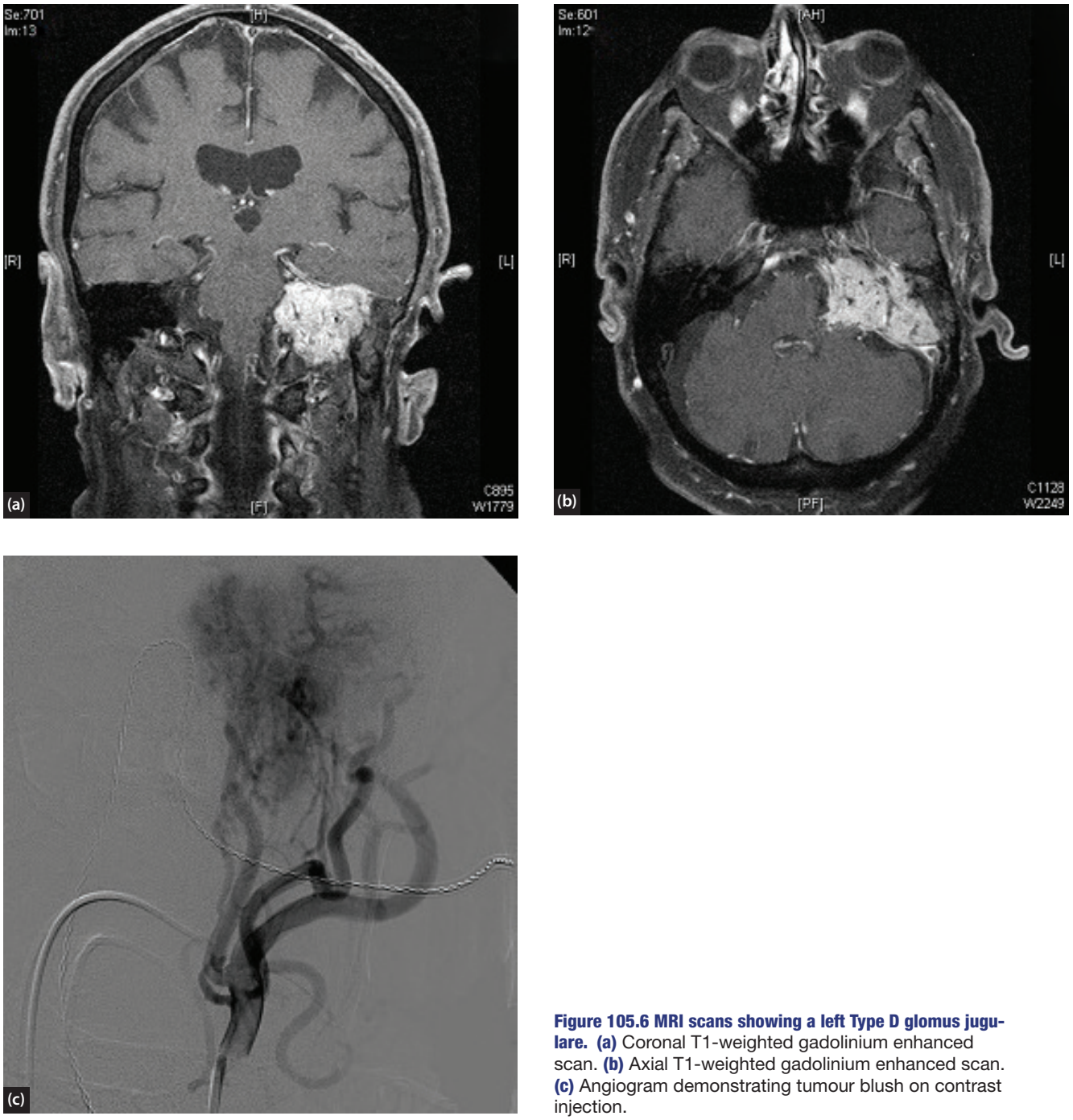

Figure 105.6 MRI scans showing a left Type D glomus jugulare. **(a)** Coronal T1-weighted gadolinium enhanced scan. **(b)** Axial T1-weighted gadolinium enhanced scan. **(c)** Angiogram demonstrating tumour blush on contrast injection.

their behaviour. Treatment is difficult but extended endoscopic endonasal approaches in combination with open approaches have increased the chances of complete resection. This is not always possible, however, particularly if the tumour extends into the inferior clivus.[119, 120] Resection should be followed by radiotherapy with proton beam therapy becoming increasingly the modality of choice. Recurrence rates are high.

Endolymphatic sac tumours are rare low-grade adenocarcinomas of the endolymphatic sac.[121, 122] Twenty per cent are sporadic but most are associated with Von Hippel Lindau Disease (4% of patients with this condition have endolymphatic sac tumours).[123] They are slow growing but locally destructive and rarely metastasize. Their presentation is similar to that of other CPA lesions. CT shows bony destruction centred on the endolymphatic sac. They have heterogenous increased signal on both T1 and T2-weighted imaging with patchy enhancement with gadolinium (**Figure 105.7**). Treatment is by wide local resection via retrolabyrinthine, translabyrinthine or retrosigmoid approaches. Cure can be achieved in 90% of moderate sized tumours but large tumours are difficult to cure. There may be late recurrence. Adjuvent radiotherapy may also reduce recurrence.

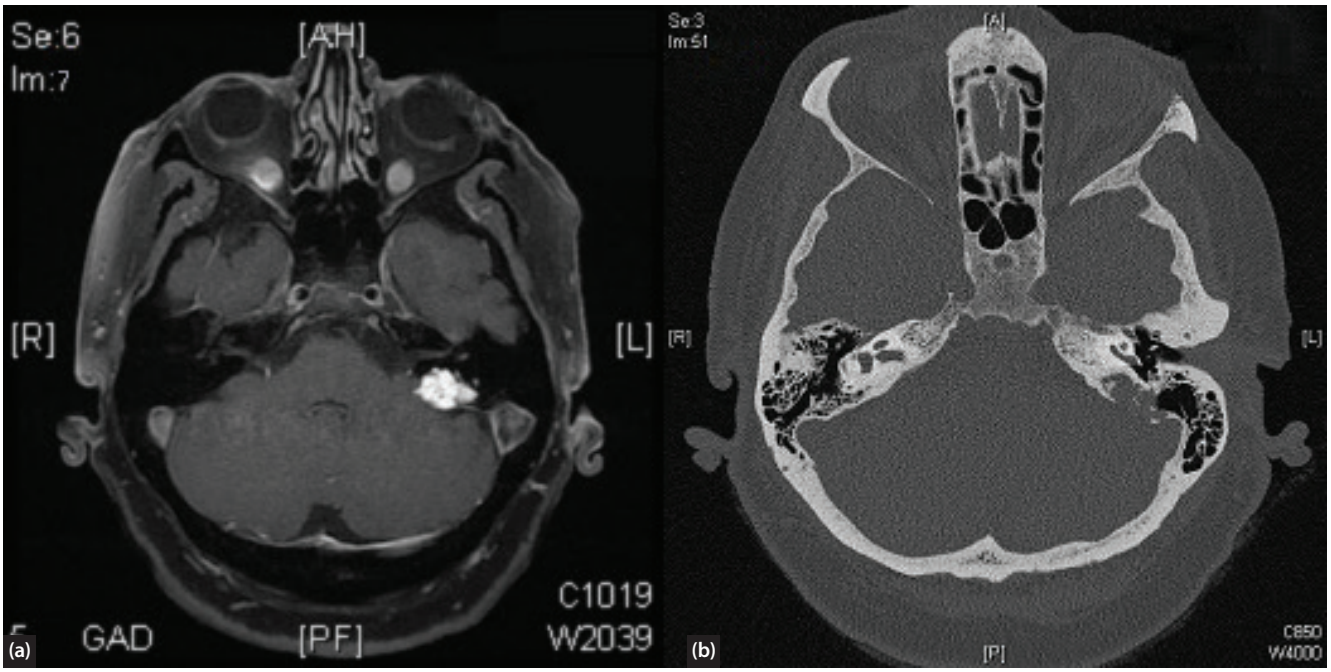

Figure 105.7 MRI scans showing a left endolymphatic sac adenocarcinoma. **(a)** Axial T1- weighted MRI scan with gadolinium enhancement. **(b)** CT scan.

BENIGN AND MALIGNANT INTRA-AXIAL LESIONS INVOLVING THE CPA

Rarely, intra-axial or intra-ventricular tumours invade the CPA. Diagnosis is difficult but subtle image signs, such as narrowing of the cisterns and oedema at the site of tumour origin, as well as the history of the patient, are sometimes helpful.

Primary central nervous system neoplasms

As few as 0.3–2% of the lesions in the CPA originate from primary brain tissue. Presenting symptoms may be typical of a CPA lesion, but an intra-axial lesion may be suspected because of the rate of progression of symptoms and the degree of non-acoustic cranial nerve symptoms.[45] The most common types of primary central nervous system tumours are medulloblastomas, astrocytomas, ependymomas and other gliomas of the brainstem.[124] It may not be possible to distinguish these lesions from vestibular schwannomas by CT although MRI may demonstrate their intra-axial status more reliably. Stereotactic biopsy has an accuracy rate of about 75% in these patients. Treatment regimens include surgery, radiotherapy or a combination of both and in some cases chemotherapy.

BEST CLINICAL PRACTICE

- ✓ All skull base pathology is best managed in a multidisciplinary setting with a core team including otolaryngology, neurosurgery and neuroradiology.
- ✓ Consider diagnoses other than vestibular schwannoma when scans are not typical and hearing loss is not the predominant symptom. All patients should have MR imaging with contrast and, if necessary, fat suppression sequences.
- ✓ Carotid angiography is helpful for certain pathologies, for example glomus jugulare tumours. Pre-operative embolization can reduce morbidity.
- ✓ The aim of surgery should be complete removal pathology but not at the expense of function. Stereotactic radiotherapy or radiosurgery are effective alternatives to surgery for some forms of growing tumour and may be used in combination with surgery in some situations.

FUTURE RESEARCH

Current understanding of the natural growth pattern of non-acoustic CPA tumours and the consequences of watchful waiting is insufficient. Future areas of research should include:

- ➤ assessment of the efficacy of subtotal surgical excision with adjuvent radiotherapy compared with radical excision
- ➤ treatment strategies for residual and recurrent tumours
- ➤ possible alternatives to surgical treatment (e.g. chemotherapy or brachytherapy)
- ➤ possible markers of tumour growth.

KEY POINTS

- One in five CPA tumours is not a vestibular schwannoma.
- Compared with vestibular schwannomas, VIIIth cranial nerve symptoms and signs are less frequent, and other cranial nerve and cerebellar symptoms and signs are more frequent in non-acoustic CPA tumours.
- The number of pathologies in the differential diagnosis of a CPA lesion is large but MRI and CT imaging often demonstrate features leading to correct diagnosis.
- Treatment most often involves surgery but some lesions may be treated conservatively or with radiotherapy.

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CHAPTER 106

MIDDLE FOSSA SURGERY

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: middle fossa surgery and middle fossa approach, combining with cerebrospinal fluid leak, facial nerve surgery, vestibular schwannoma, acoustic neuroma, superior semi-circular canal dehiscence (SSCD) syndrome, petrous apex lesions and vestibular neurectomy.

INTRODUCTION

The middle fossa (MF) approach can be used as an extradural access route to approach the MF floor, the internal auditory canal (IAC), the posterior fossa and the petrous apex. The access through this approach is via a small temporal craniotomy and visualization can be difficult owing to the limited extradural space available and desire not to apply too much pressure on the underlying temporal lobe. The access to the posterior fossa is somewhat limited and it is only when considering the many intra-temporal indications for this approach that the advantages of the MF can be fully appreciated. This chapter will focus widely, considering all the applications of this approach, and will attempt to demonstrate why it is an important skill for all neurotologic surgeons.

HISTORICAL PERSPECTIVE

The earliest description of the MF approach was by William Rose of King's College Hospital, London in 1890.[1] Rose used the approach as an access route to the trigeminal ganglion in cases of trigeminal neuralgia. In 1904, Parry[2] was the first to describe its use to access the IAC. In the early twentieth century, many authors described the use of the MF for surgery of the facial nerve, superior semi-circular canal and petrous apex. Surgical outcomes in the first half of the twentieth century were rather poor and, as a result, the approach was rarely used and fell into disrepute.

The technique was then reintroduced by William House[3] who proposed this as a technique for decompression of the cochlear nerve in cases of otosclerosis. Subsequently, it was popularized again to access and remove small and medium-sized acoustic tumours, as with it residual hearing could be preserved. Significant technical contributions have been made by Fisch,[4] who refined the approach for a variety of conditions, including the treatment of facial nerve lesions. The approach gained further support with the contributions by E and JL Garcia-Ibanez[5] on surgical landmarks in the region in relation to a large case series of vestibular neurectomies. Neurosurgeons and neurotologists considering undertaking this approach are encouraged to consider three-dimensional (3D) computerized tomographic (CT) reconstruction of the temporal bone and middle and posterior fossae prior to surgery, in order to understand the microsurgical anatomy and relations of neurovascular structures, especially where bony landmarks may be absent.[6]

SURGICAL TECHNIQUE

Surgical anatomy

The learning curve to deal with intratemporal pathology via the MF approach involves operating while at the head end of the patient and getting the 3D orientation from above downwards. The most important landmarks in this approach are the middle meningeal artery,

tegmen plate, greater superficial petrosal nerve (GSPN), facial hiatus, arcuate eminence, superior petrosal sinus and the meatal plane. Of these by far the most useful for the surgeon is the GSPN, which serves as a guide not only to the depth of dissection but also to the position of the facial nerve (**Figure 106.1**). Bento et al., in 2002, recommended opening up the tegmen tympani early in the dissection to expose two additional landmarks of importance – the cochleariform process and the tympanic portion of the facial nerve – which could effectively guide the surgeon onto the labyrinthine segment of the facial nerve more directly.[7]

The arcuate eminence has a variable relationship to the superior semi-circular canal as demonstrated by Tsunoda et al.[8] A cadaveric study on 26 temporal bones showed arc-like eminences in 92% of the specimens, but they did not necessarily correspond to the site of the superior semicircular canal. Some of these eminences corresponded to sulci of the temporal lobe, of which most were traces of the occipitotemporal sulcus. It is advisable to use landmarks in addition to the arcuate eminence in order to reach the IAC safely.[8]

There are a number of variations on the MF approach. The transtemporal MF approach as described by Fisch[4] has the advantage of minimizing dural retraction but requires consummate skill. Gjuric et al.[9] described an enlarged MF approach involving the removal of additional bone either side of the IAC and providing greater access to the posterior fossa.

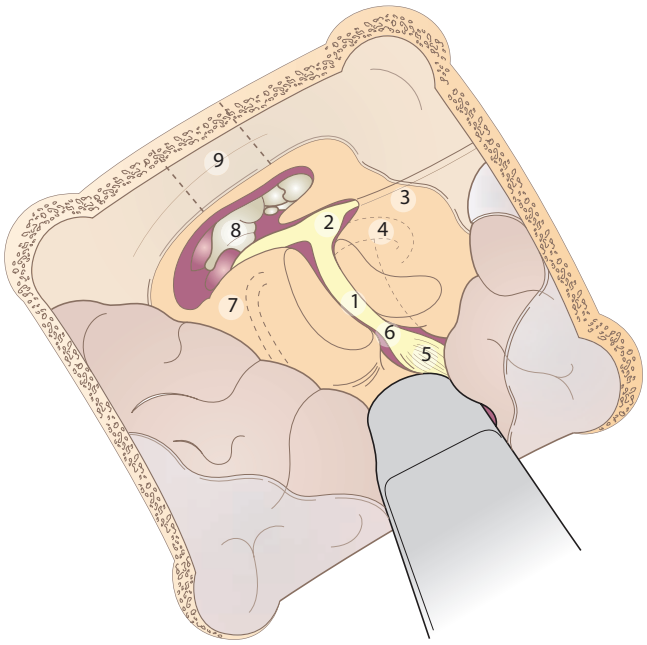


Figure 106.1 Left middle fossa anatomy with facial nerve exposed and internal auditory canal opened. 1, Labyrinthine VII; 2, geniculate ganglion; 3, greater superficial petrosal nerve; 4, cochlea; 5, internal auditory canal; 6, meatal foramen; 7, superior semi-circular canal; 8, removal of tegmen showing heads of ossicles; 9, external auditory canal position.

Patient position

The surgeon sits at the head of the operating table and addresses the floor of the middle cranial fossa from above. This is an unfamiliar orientation for most otologists and will also necessitate a change in the position of the other members of the operating team. The patient lies supine with the head rotated with the pathologic ear uppermost and with the intermeatal line perpendicular to the floor. A head holder is usually not required and a head ring stabilizes the head. Facial nerve monitoring is used routinely and it is advisable to insert a urinary catheter for the patient's comfort. Some, but not all, surgeons give mannitol to reduce intracranial pressure and obtain a larger operative field without undue compression of the temporal lobe.

Incision

This is either an inferiorly based U-shaped flap or a vertical line. It begins 0.5 cm anterior to the base of the helix, at the level of the zygomatic arch, and extends approximately 7 cm superiorly. Branches of the superficial temporal artery that are encountered at this stage should be ligated to avoid post-operative bleeding. The temporalis fascia plane is developed by finger dissection. An incision is placed in the temporalis muscle along its insertion line and it is elevated inferiorly and anteriorly taking care to preserve its neurovascular supply. Elevation of the temporalis exposes the squamous part of the temporal bone. The root of the zygoma indicates the level of the MF floor and it is crucial that the initial exposure adequately identifies this both anteriorly and inferiorly.

Craniotomy

This is sited two-thirds anterior and one-third posterior to the external auditory canal (EAC). An opening of 5 cm × 5 cm is adequate in most circumstances. It is bevelled posteriorly to minimize entry into the mastoid air cell system. The craniotomy can be cut either with an otologic burr or a craniotome to fashion a small bone flap. Utmost care should be taken not to injure the underlying dura during drilling. The opening then needs to be lowered to the level of the MF floor anteriorly and above the root of the zygoma. Any air cells entered should be sealed with bone wax.

Exposure of the middle fossa floor

Under low power of the operating microscope, dural elevation is commenced posteriorly. The superior petrosal sinus and the sulcus at the transverse–sigmoid junction are identified. A self-retaining retractor such as the Fisch, Yasergill's or House-Urban retractor is applied when the dura is sufficiently elevated. Care must be taken not to injure the geniculate ganglion as it can be dehiscent in up to 15% of temporal bones.[10] The arcuate eminence and the GSPN are then identified. It may be necessary to separate the dura using sharp dissection from the GSPN as

it can be densely adherent to it. The middle meningeal artery is anterolateral to the GSPN and dissection here is always bloody and, unless access to the apex is required, may not be necessary. If the vessel is divided, the foramen spinosum will need to be sealed with bone wax. The bone anteromedial to the arcuate eminence and posterolateral to the GSPN is termed the 'meatal plane' and lies above the IAC (Figure 106.2). It is often marked by a shallow depression. The angle between the GSPN and the arcuate eminence is bisected to identify the axis of the IAC, which was popularized by Garcia-Ibanez in 1980.[5]

Finding the internal auditory canal at its medial end (Porus Acousticus)

In medial approaches to the IAC, the dura is elevated over the meatal plane and the retractor is then inserted into the petrous ridge with its tip lodged into the bony groove of the superior petrosal sinus (as illustrated in Figure 106.2). If the ridge is not clearly identified, the placement of the retractor can be too far lateral and there is a risk of entering the inner ear when undertaking the initial bony removal. No identification of the superior semi-circular canal (SSC) is required and the GSPN is exposed only as far as its hiatus. The EAC and IAC are roughly in line, which helps with orientation.

Gentle and careful bone removal is undertaken with a diamond burr over the meatal plane, slowly reducing it over a broad area from the arcuate posteriorly to the limit of the dural elevation anteriorly. The temporal bone is usually pneumatized or filled with bone marrow anterior to the IAC. As the meatal plane is lowered, the IAC becomes visible. Its medial end is then defined and troughs are drilled both anteriorly and posteriorly to give more extensive exposure and sufficient space for safe tumour removal. At this stage, a thin layer of overlying bone is left to protect the dura of the IAC. The IAC is then followed laterally. Great care has to be exercised at this stage to ensure that no inadvertent entry into the cochlea or the SSC happens.[5]

Finding the internal auditory canal at its lateral end (Fundus Acousticus)

The margin of error at the lateral end of the IAC is of the order of 1 mm, representing the distance between the fallopian canal and the cochlea. Very precise identification is an absolute necessity if hearing is to be preserved. The lateral end of the IAC can be identified either by first finding the GSPN as described by House[3] or by using the SSC as advocated by Fisch.[4] In the former technique, the GSPN is delineated and followed proximally through its hiatus to the geniculate ganglion. Then, by tracing the labyrinthine segment of the facial nerve, the IAC is identified (Figure 106.3). A diamond burr with continuous irrigation suction is used to minimize the incidence of traumatic facial paresis post-operatively.[11–12]

The Fisch technique[4] was developed to limit the degree of dural retraction and the risk of damage to the labyrinthine segment of the facial nerve. In his technique the bone of the tegmen is removed and the SSC 'blue lined'. Having identified this, the IAC is then located within an angle of between 45 degrees and 60 degrees subtended from the ampulla of the SSC.

Completion of internal auditory canal exposure

Bone removal in the meatal plane needs to be more extensive in vestibular schwannoma surgery than for vestibular neurectomy. More radical removal of bone is carried out for access to larger vestibular schwannomas and is

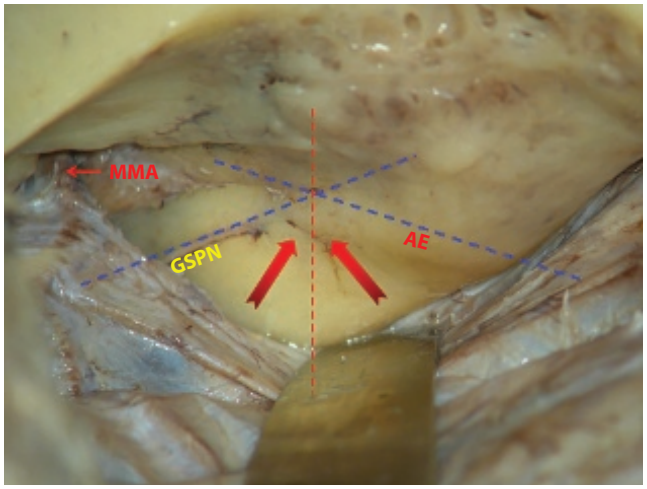


Figure 106.2 Right middle fossa floor: defining the 'meatal plane'. The IAC is identified in a tangent that bisects the angle formed by the superior semi-circular canal, SCC (identified as the arcuate eminence, AE) and the greater superficial petrosal nerve (GSPN). MMA, middle meningeal artery.

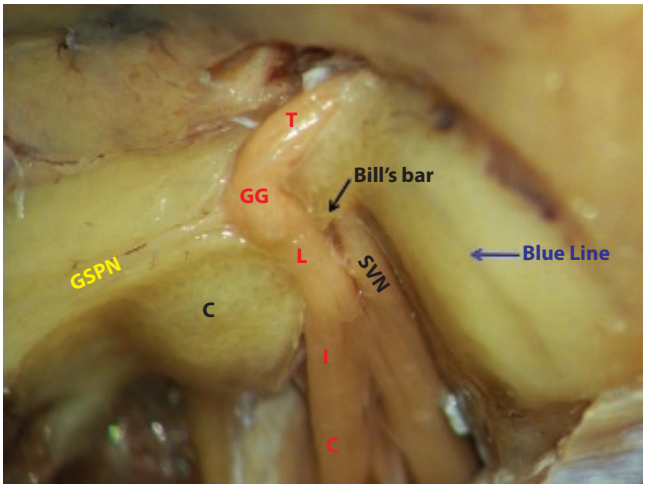


Figure 106.3 Anatomical dissection of the fundus area (right middle cranial fossa). GG, geniculate ganglion; GSPN – greater superficial petrosal nerve; T, tympanic segment facial nerve; C, cochlea; L, labyrinthine segment facial nerve; SVN, superior vestibular nerve. Also demonstrated is the blue line over superior semi-circular canal.

sometimes referred to as the enlarged MF approach.[9] Access can be improved further by division of the superior petrosal sinus.

Approximately three-quarters of the circumference of the IAC at the porous acousticus is exposed. This degree of exposure is not possible at the lateral end of the IAC because of the proximity of the ampulla of the SSC and the cochlea. Bill's bar, the vertical crest of bone separating the facial nerve from the superior vestibular nerve, is identified at the lateral end.

The fine eggshell of bone covering the dura is now carefully removed and the dura incised along the posterior aspect of the IAC, thereby avoiding inadvertent damage to the facial nerve. A dural flap is fashioned and the contents of the IAC identified.[11]

Closure

Any exposed air cell tracts must be waxed and a muscle plug is placed in the IAC. If the tegmen has been removed, it should be repaired with a bone graft or a bone pate slab to prevent dural herniation. The dura can be hitched to the skull by dural sutures to minimize the size of any extradural collection. The temporal bone flap is then fixed back into position.

CLINICAL APPLICATIONS

The indications for the MF approach can be divided into three distinct groups (**Table 106.1**):

- exposure of the MF floor
- access to the IAC and cerebellopontine angle (CPA)
- access into and through the petrous apex to anterosuperior CPA.

Initial elevation of the dura provides good access to the region of the tegmen that is ideal for repair of defects in this region. More medial dural elevation uncovers the cochlea, superior canal and facial nerve, allowing access to these structures. More medial dissection still exposes the meatal plane overlying the IAC. Bone removal in this region will reveal the IAC and can be extended to allow limited exposure of the CPA. In addition, dural elevation more medially and anteriorly exposes the petrous apex from above.[9] Pathology within the apex can be dealt with and if the apex is removed this can provide access to the anterio-superior CPA. This MF-petrosectomy extension can be combined with a posterior fossa craniotomy to access large petroclival lesions preserving inner ear function.

Internal auditory canal/cerebellopontine angle surgery

VESTIBULAR SCHWANNOMA SURGERY

The majority of small tumours are currently managed by either a conservative approach or by radiosurgery. Traditional surgical approaches remain an option in selected cases. The MF approach has been used for the removal of small vestibular schwannomas (VS) and for decompression of the IAC in bilateral tumours. The primary objectives of VS surgery are the control or complete removal of the tumour with preservation of facial nerve function and, where possible, preservation of hearing.[13] Both the MF and retrosigmoid (RS) approaches have been used for attempted hearing preservation in VS surgery. The perceived advantage of the MF approach is better visualization of the lateral end of the IAC when compared with the RS approach. In both the MF and RS approaches, there is a blind spot at the fundus, this being smaller in MF surgery.[14, 15] It is proposed as the hearing preservation approach of choice in tumours extending far into the lateral third of the IAC.[13] The main disadvantage is relatively poor access to the CPA and many surgeons would be hesitant in utilizing this approach for tumours with an angle component greater than 15 mm. In MF surgery, the facial nerve is generally found superiorly between the tumour and the operator. This has the advantage of ease of facial nerve identification but the disadvantage in that greater manipulation of the nerve may be required to remove the tumour. Additionally, control of bleeding in the CPA can be more difficult with the MF approach.[15]

Proponents of the MF approach report excellent results for hearing preservation and claim superiority over the RS in this regard. The reasons why hearing preservation should be better by this route are difficult to understand, but may possibly relate to the direction of tumour dissection. In the MF approach, small tumours can be removed in a medial-to-lateral direction, avoiding avulsion of the fine cochlear nerve endings entering the modiolus of the cochlea. The data on hearing preservation in RS when compared with the MF approach is, however, contradictory. There have been few comparative series[14] and only one prospective randomized study,[15] which reported no advantage of the MF over the RS in terms of hearing preservation. In addition, facial nerve function appears to be worse in the early post-operative period in the MF group.[14]

TABLE 106.1 Clinical applications of the middle fossa approach

IAC/CPA surgery	Middle fossa floor	Petrous apicectomy
Vestibular schwannoma	Repair of CSF leaks	Petrous apex lesions
Resection of IAC/CPA tumours	Superior canal dehiscence	Petroclival tumours
Vestibular neurectomy	Facial nerve surgery	Basilar aneurysms

VESTIBULAR NEURECTOMY

Section of the vestibular nerve can be carried out through a MF, RS or retrolabyrinthine approach. The main advantage of the MF approach is that it offers access at a more distal location where the VIII nerve is naturally divided into its vestibular and cochlear branches. The main indication for this is in patients with incapacitating Ménière's disease, unresponsive to more conservative treatment and with serviceable hearing.[5]

Middle fossa floor

FACIAL NERVE SURGERY

Indications for the MF approach have expanded to address facial nerve pathology in its intracranial, intracanalicular, labyrinthine, geniculate and tympanic segments (**Figure 106.4**). The facial nerve can be accessed through the MF floor for a spectrum of indications, namely: temporal bone fractures involving the intracranial and petrous facial nerve; benign intrinsic tumours involving the supra-tympanic facial nerve segments; nerve decompression in idiopathic recurrent facial palsy; and nerve reanimation by cable grafting it in its internal auditory meatus (IAM) and labyrinthine segments. Such an approach allows direct exposure of the proximal parts of the nerve with preservation of inner ear function, which is otherwise not possible via the trans-mastoid route alone. It is perhaps when considering pathology of the facial nerve that the MF approach clearly exhibits advantages over all others.

The MF approach to the traumatized facial nerve has proven to be a successful route. Bento et al.[16] in 2004 reviewed 220 cases where they advocated a combined MF and transmastoid approach to decompress the facial nerve for injury sustained in an unclear location but presenting with good cochlear reserve. Recently, da Franca Pereira et al. have described in detail the steps of decompression of the tympanic and labyrinthine segments of the facial nerve by middle cranial fossa approach with anatomical measurements in 20 cadavers to conclude that this is a safe, timesaving and reliable technique.[17] Aslan et al. reported a series of 13 patients who underwent facial nerve decompression via MF approach for grade VI traumatic palsy and were able to achieve grade 2 recovery in 7 (58%) patients by decompressing the geniculate ganglion within 1 month of trauma.[18] Cannon et al. have reported a series of 18 patients with traumatic complete paralysis and poor facial prognosis on electrophysiology, all of whom achieved a long-term outcome of HB III or better after MF approach was performed for primary decompression in 11 (64%) patients and repair of the facial nerve by grafting in 7 (36%) patients.[19]

The concept of decompression surgery for facial nerve paralysis of non-traumatic and non-tumorous origin remains controversial. Fisch[20] demonstrated encouraging results with surgical decompression of the nerve in its labyrinthine segment in cases of Bell's palsy and herpes zoster oticus. Marsh and Coker [21] present evidence suggesting that the meatal segment of the facial nerve is the probable site of entrapment. Unimpeded access to this region of the facial nerve can only be achieved via a MF craniotomy. Only one randomized study has attempted to address this issue and it concluded that the outcome in Bell's palsy was improved by MF decompression surgery.[22]

Cannon et al. reviewed long-term outcomes in a series of 14 patients who underwent surgical decompression for Bell's palsy within 14 days of symptom onset from 2000 to 2012.[23] Surgical criteria included greater than 90% degeneration on electroneurography (ENoG) testing and no voluntary electromyography (EMG) potentials. MF

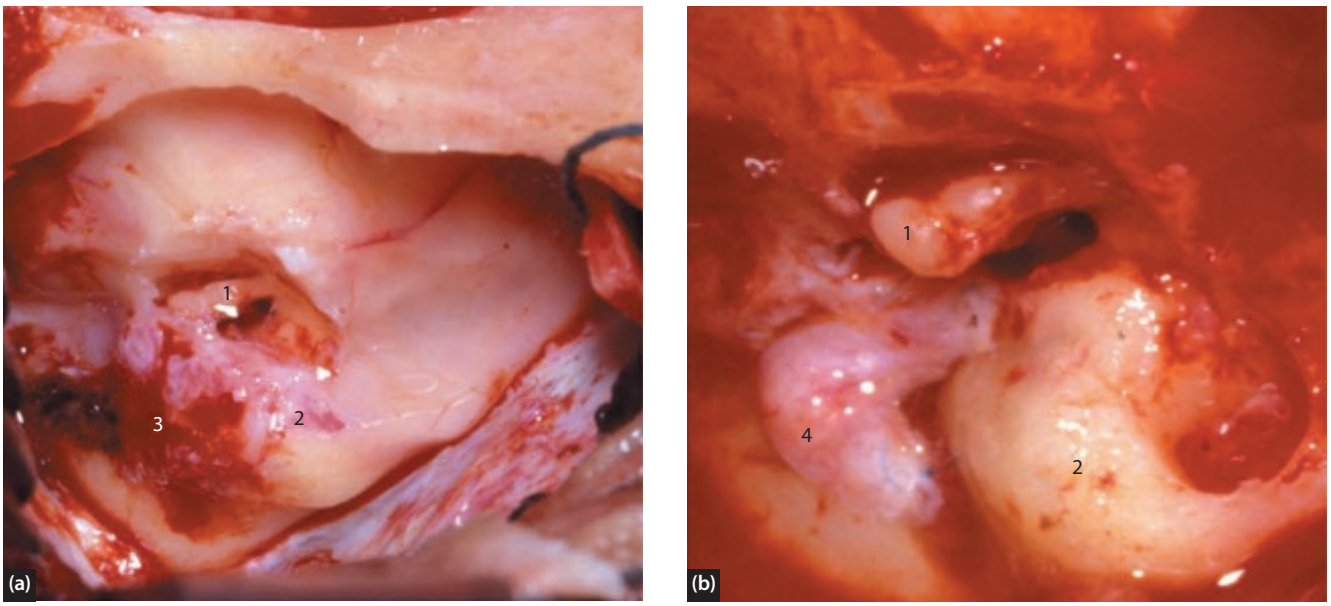


Figure 106.4 View of right middle fossa floor showing facial nerve graft (b) following removal of facial nerve haemangioma (a). 1, Heads of ossicles; 2, superior semi-circular canal; 3, facial haemangioma; 4, facial nerve graft (labyrinthine, geniculate and proximal tympanic segments).

bony decompression of the facial nerve, including the meatal foramen, labyrinthine segment, and geniculate ganglion was performed. Ten patients (72%) had regained normal facial nerve function while four cases improved to HB grade III function, with minimal morbidity in the case series. All these patients had no hearing loss of significance, which suggests MF is a viable route with hearing preservation.[23]

Decompression surgery is particularly appealing in cases of Melkersson–Rosenthal syndrome (MRS) and recurrent facial paralysis of unknown origin. MRS is a triad of recurrent alternating facial paralysis, recurrent facial and labial oedema (cheilitis granulomatosa) and fissured tongue (lingua plicata).[24] The logical conclusion is that the oedematous process affects the entire nerve within a tight bony canal, causing entrapment neuropathy. Total decompression of the entire length of the nerve using a combined transmastoid and MF approach is recommended in cases of MRS where there is a significant increase in frequency, duration and severity of facial paralysis to prevent disabling sequelae, such as synkinesis and residual facial paralysis.[24]

The benefits of MF decompression of the facial nerve in cases of recurrent facial paralysis has been demonstrated by Nyberg and Fisch.[25] They operated on a total of 14 patients, including 11 with acute paralysis with ENoG evidence of more than 90% amplitude reduction within the 10 days following the attack. Their series also included three patients who underwent decompression prophylactically to prevent further recurrences. Graham and Kartush[26] demonstrated excellent results with complete resolution in six patients with recurrent facial paralysis, who underwent total facial nerve decompression. Similarly, facial nerve decompression via MF seems to achieve better outcomes of facial nerve function than conservative treatment according to a recent report by Zhu et al., who were able to prevent further episodes by surgical decompression, providing an HB grades I–II recovery in all their cases.[27] Doshi and Irving[28] provide further evidence to support the effectiveness of MF decompression in recurrent facial nerve paralysis, with no recurrences in four cases with hearing preservation.

There is as yet insufficient evidence to propose facial nerve decompression in Bell's palsy beyond a prospective randomized trial; however, the results of decompression in cases of recurrent paralysis as mentioned above are encouraging.[25–28]

The MF approach provides a route of access to tumours involving the proximal facial nerve. Mowry et al. recommend the MF approach for debulking and decompressing facial nerve schwannomas involving the IAM. They achieved decompression with more than 70% debulking of the tumour via this approach while preserving motor fibres good enough to provide HB grade I function postoperatively at serial follow-up to 1 year.[29] Kusumi et al. also support this fact in their case report where they used a combined extradural and intradural MF approach to remove an intra-petrous GSPN schwannoma involving Glasscock's triangle, while preserving the tumour capsule in the MF floor to safely protect the geniculate ganglion and the main trunk.[30] Decompression alone without tumour debulking is an option for small tumours difficult to separate from the main nerve trunk, and with recurrent facial paralysis, with good medium-term outcomes reported in two cases.[31]

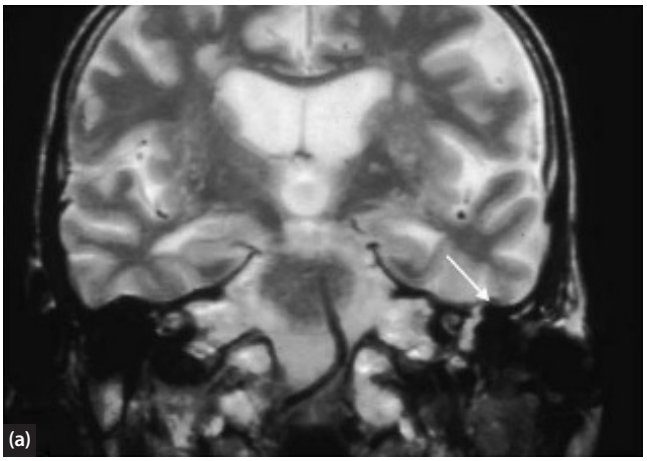
REPAIR OF TEGMEN DEFECTS, CEREBROSPINAL FLUID LEAKS AND MENINGOENCEPHALOCOELES

The conventional approach to repair of tegmen plate defects causing cerebrospinal fluid (CSF) leaks and brain hernias has been the transmastoid approach. The vast majority of spontaneous CSF leaks take place through the tegmen plate, rather than through a posterior fossa defect. Traumatic leaks are more unpredictable and many have both posterior fossa and MF components. Good outcomes are achieved with defects sealed via the MF approach to the tegmen plate when this is the site of the problem.[32–35] The major advantage of the MF approach over the transmastoid is that the repair can be carried out without disturbing the middle ear and ossicles. Also, large or multiple defects can be detected more easily and dealt with by the MF approach.[33]

The procedure can be carried out through a 'mini' temporal craniotomy with a window of less than 4 cm.[22, 23] While drilling, bone dust is collected using a bone-pate collector that is essentially a filter-trap attached to the suction apparatus. After elevation of the dura, all the defects in the tegmen are exposed and sealed with an oblong slab of bone pate mixed with blood and fibrin glue (Tisseel; Immuno, Vienna, Austria). This pliable graft material is insinuated into every defect and crevice in the tegmen using neuropatties. A large free graft of temporalis fascia placed between the dura and the bone-pate slab provides additional reinforcement. Recurrence of CSF leakage has been reported after soft tissue repairs and hence the rationale for using bone pate, which over time is believed to form an adequate layer of viable bone (**Figure 106.5**). More recently, Braca et al. have used autologous dural grafts with synthetic polymer glue to seal successfully tegmen defects with CSF leaks and encephalocoeles in eight patients via the MF approach.[36]

SUPERIOR SEMI-CIRCULAR CANAL DEHISCENCE SYNDROME

Sound- or pressure-induced vertigo caused by a bony dehiscence of the SCC into the middle cranial fossa is a rare cause of otologic symptoms including autophony and vertigo.[37] Disabling vertigo in two of these patients from the initial series prompted plugging of the dehiscent canal via a middle cranial fossa approach with good results.[37] Alternative approaches to address the dehiscence have been subsequently described, including the transmastoid and MF/transmastoid routes. Debate continues as to which is the most appropriate and effective although in some cases, especially where there is an associated encephalocoele the MF approach may be preferred.



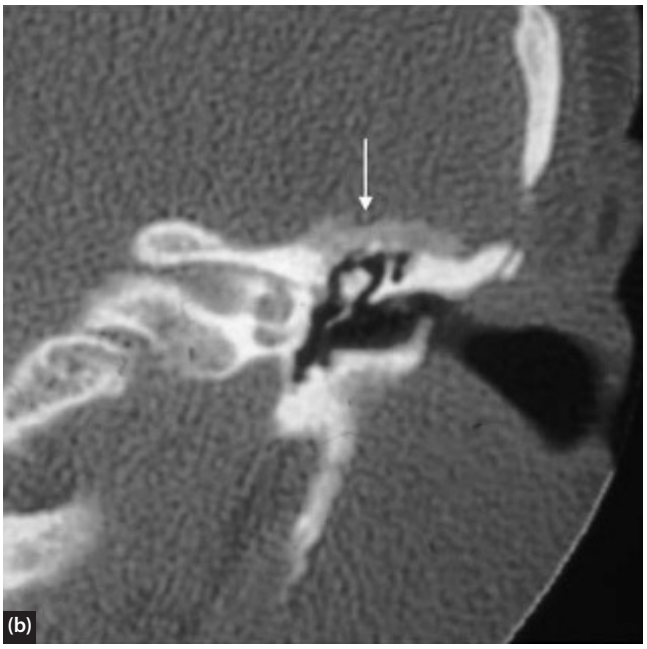


Figure 106.5 (a) Pre-operative coronal T2-weighted image demonstrating a tegmen CSF leak. Arrow shows site of leakage. **(b)** Post-operative coronal CT scan demonstrating bone pate repair. Arrow shows site of repair.

A series with 43 cases of superior canal dehiscence syndrome (SCDS) who underwent surgical plugging by the MCF approach has been reported by Ward et al.[38] Plugging of the canal was performed using fascia strips, bone dust and bone chips, which are gently but securely placed inside the dehiscent canal to obliterate the canal lumen for 2–3 mm beyond either end of the dehiscence. Careful avoidance of unnecessary force on or suction near the membranous labyrinth was observed throughout the procedure. The repair was then covered with hydroxyapatite cement, followed by a layer of fascia and fibrin glue. The authors concluded that low frequency air–bone gap decreases following surgical plugging and appears to be due to both increased bone-conduction (BC) thresholds and decreased air-conduction (AC) thresholds. Surgical plugging via a middle cranial fossa approach in SCDS is associated with mild high frequency sensorineural hearing loss that persists in 25% but no change in speech discrimination.[38–39]

Petrous apicectomy

The MF craniotomy provides the shortest and most direct route to the petrous apex. By elevation of the dura medial and anterior to the IAC, the anterior apex can be exposed as far as Meckel's cave and the ipsilateral cavernous sinus. Primary lesions within the apex, the most common being cholesterol granulomas, chordomas, cholesteatomas and chondrosarcomas, can be approached in this way (**Figure 106.6**). Lesions in Meckel's cave, including schwannomas and meningiomas, when small, can be accessed solely by a MF approach, whereas larger lesions may require an orbitozygomatic craniotomy.[40–42] The bone of the anterior petrous apex conforms to a rhomboid shape bounded by the IAC and cochlea laterally and posteriorly, the intrapetrous carotid anteriorly, and medially by the Gasserian

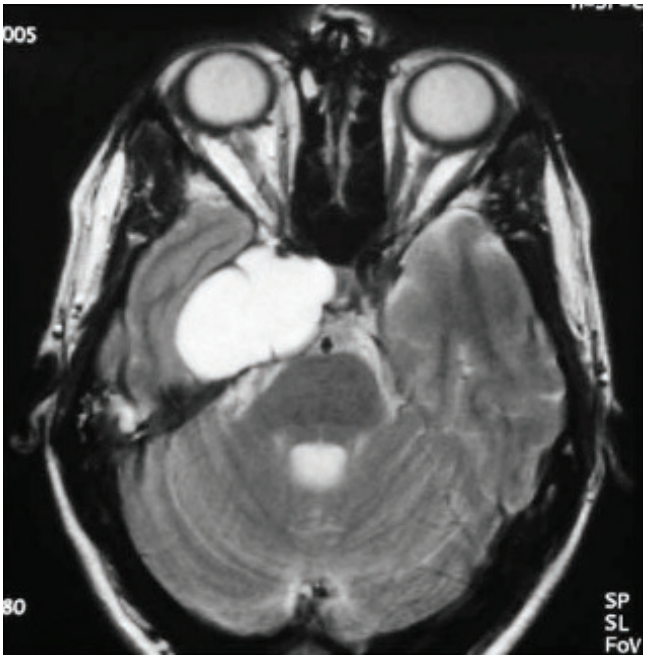


Figure 106.6 Petrous apex chondrosarcoma with large middle fossa and small posterior fossa components. This large lesion could be removed by a middle fossa transpetrous apex approach.

ganglion. If this rhomboid of bone is removed, the dura of the anterior–superior CPA is exposed and opening this provides limited access to the CPA. Additional exposure can be obtained by transection of the superior petrosal sinus and the mandibular branch of the trigeminal nerve. Access is provided to the ventral surface of the pons and upper clivus. This approach has been used for basilar tip aneurysms and petroclival and Meckel's cave tumours with limited CPA extension.[40–42]

COMBINED APPROACHES

The MF approach can be combined with any of the existing skull base approaches of the anterior, lateral and posterior skull base. While the MF approach is an extradural, subtemporal route consisting of an anterior petrosectomy, an extended approach (combined petrosal) anterior to this is used by neurosurgeons for intradural lesions of the superior CPA and prepontine clivus and cavernous sinus lesions. The 'rule of two fans' technique wherein vascular, nervous, fibrous and osseous structures are localized within two bordering fans, one centred around the geniculate ganglion in the MF floor and one centred around the Gasserian ganglion (perpendicular to the geniculate fan structures) is popular in dealing with lesions such as sphenopetroclival tumours, neoplasms with transtentorial extensions and vertebrobasilar aneurysms.[43]

Combining the MF approach with the transmastoid approach for clearance of extensive lesions is popular and has its advantages. A large defect with CSF otorrhoea after a mastoidectomy is best managed by a combined approach.[44] O'Connell et al. have described a combined transmastoid-middle cranial fossa approach for repair of lateral skull base CSF fistula and encephaloceles using a suture 'pull-through' technique. This method facilitates reliable placement of a composite graft in the centre of lateral skull base defects through a small craniotomy that minimizes temporal lobe retraction.[45]

A middle ear cholesteatoma with intracranial extension would necessitate a MF craniotomy.[46] A giant facial nerve schwannoma extending from the middle cranial fossa to the mastoid region is best cleared by a combined MF and transmastoid approach.[47] In the extended MF and transpetrous approaches, a thorough understanding of the horizontal segment of the petrous internal carotid artery (pICA) (**Figure 106.7**), its normal anatomy with variations and relations to surrounding neural and osseous structures is essential.[48]

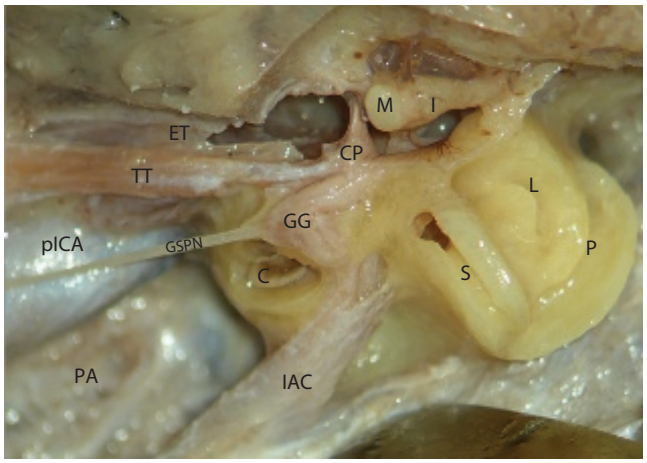


Figure 106.7 Extended dissection of the right middle cranial fossa and petrous region to demonstrate the intrapetrous internal carotid artery (ICA) and its relations. S, superior canal; P, posterior canal; L, lateral canal; GG, geniculate ganglion; GSPN, greater superficial petrosal nerve; C, cochlea; IAC, internal auditory canal; TT, tensor tympani; ET, Eustachian tube; PA, petrous apex; CP, cochleariform process; M, malleus; I, incus.

INFORMED CONSENT IN MIDDLE FOSSA SURGERY

The risks and complications that are discussed with a patient undergoing MF surgery will vary depending upon the precise pathology that is anticipated.

Inadvertent entry into the inner ear, damage to its blood supply or to the VIIIth nerve, can result in hearing loss, tinnitus or balance disturbance. Weakness of the face may develop and be accompanied by damage to the sensory component of the facial nerve. An extradural haematoma may accumulate and can be limited by suspending the dura to the edges of the craniotomy. CSF leakage is less common than in posterior fossa surgery but, nevertheless, can be equally tedious and dangerous as there is a definite risk of infection or meningitis. There has been much debate regarding the possibility of temporal lobe damage following MF surgery. The risk is in the order of 1 in 50 patients having a single early post-operative seizure following a MF exposure of the IAC.[10] Aggarwal et al.[49] described two cases of single ictal events which had the effect of prohibiting the patients from driving for a period of one year. A long-term predisposition to seizures has not been described. Retraction trauma leading to cortical injury, aphasia or hemiparesis has not been described either, but there is some suggestion that temporal lobe function is affected at least temporarily following surgery and may lead to some transient memory loss. There are additional risks in MF transpetrous surgery that include damage to the intrapetrous carotid artery, trigeminal neuropathy and ophthalmoplegia.

KEY POINTS

Middle fossa approaches:

- provide access superior and medial to the otic capsule preserving inner ear function
- provide excellent access to the proximal intratemporal facial nerve
- allow for the repair of tegmen defects with preservation of middle ear function
- small- and medium-sized VS can be removed with preservation of hearing.

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CHAPTER 107

JUGULAR FORAMEN LESIONS AND THEIR MANAGEMENT

Rupert Obholzer

SEARCH STRATEGY

In this chapter we review the anatomy, pathology, and management options for jugular foramen lesions. Data in this chapter are based on a Medline search using the keywords: jugular foramen and neoplasm (or cancer or tumour), surgery, conservative treatment (or therapy), radiotherapy, radiosurgery and diagnosis.

INTRODUCTION

A number of pathological lesions and conditions can develop in the jugular foramen, all of which are quite rare. There is only a scant amount of data on the incidence and prevalence of jugular foramen lesions, but several hundred cases have been described in the literature. Most are solitary case reports or record small series of patients and emphasize surgical techniques and outcomes. No controlled studies have been undertaken on this subject, so the scientific level of evidence in the body of literature is fairly low. This applies to many aspects of jugular foramen lesions, such as their diagnosis, biological behaviour and therapeutic options. At present, there are no exact or universally accepted management protocols. Surgical intervention in the region of the jugular foramen is often difficult and sometimes hazardous, due to the close proximity of nerves, arteries, veins and intracranial structures.

Surgery should therefore not be the default treatment, but one strategy to be considered in parallel with assessing the merit of conservative management or radiotherapy.

A team approach is often the key to success. Therefore, it is generally agreed that diagnostic examinations, decision-making and treatment should be carried out in a multidisciplinary setting in tertiary referral centres.

ANATOMY

The jugular foramina are the second largest openings in the skull base, after the foramen magnum. Their anatomy varies considerably.[1, 2] The left and right jugular foramina are asymmetrical. Usually the left is smaller than the right, which is presumed to have some relation with the dominance of right cerebral venous drainage. They are extremely important anatomical structures, because they harbour vital vascular and neural pathways.

The lateral part of the jugular foramen is a sigmoid-shaped tunnel, while the medial part looks like a canal in the cephalocaudal direction. The joint between the petrous bone and the occipital bone is part of the petrosphenooccipital suture of Gruber (named after the Russian anatomist Wenaslaus Leopoldovich Gruber) and constitutes the ventromedial aspect of the jugular foramen. The end of the occipital mastoid suture between the mastoid and the occipital bone forms the dorsolateral aspect of the jugular foramen. The incisura jugularis (the curved indentation in the occipital bone) constitutes the dorsomedial wall of the jugular foramen. Its counterpart in the petrous bone forms the ventrolateral wall of the jugular foramen. At the caudal aspect of the jugular foramen, both incisurae jugulares have a so-called intrajugular process. These processes protrude into the lumen of the jugular foramen (**Figure 107.1**) and divide it into

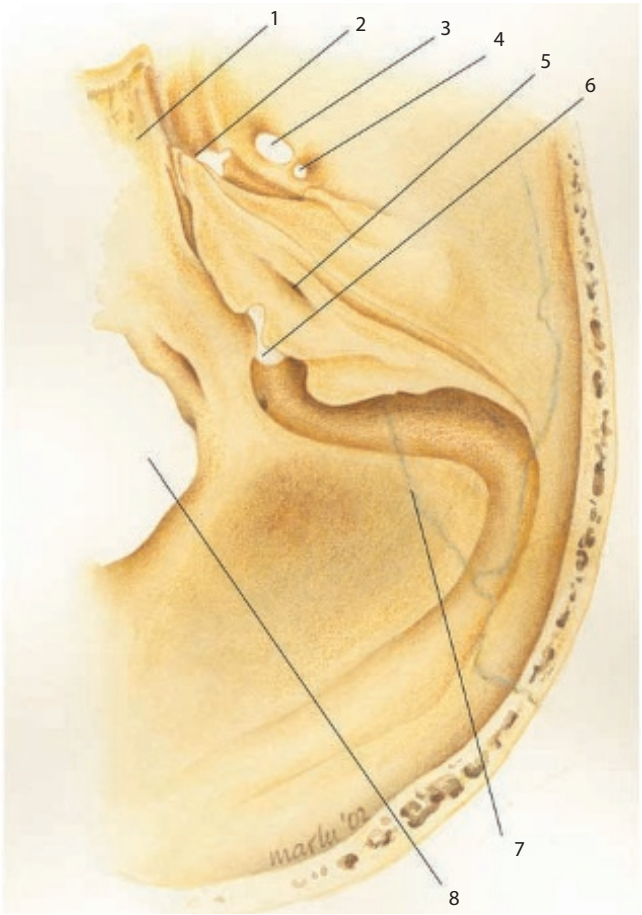


Figure 107.1 Superior view of the skull base (right side) as shown from above. 1, clivus; 2, foramen lacerum; 3, foramen ovale; 4, foramen spinosum; 5, internal auditory canal; 6, jugular foramen; 7, suture of Gruber; 8, foramen magnum.

lateral and medial parts. The lateral part (pars venosa) is filled by the sigmoid–jugular complex, while the medial part (pars nervosa) contains the inferior petrosal sinus, the cranial nerves IX, X and XI, the superior ganglion of the glossopharyngeal nerve and the jugular ganglion of the vagus nerve.[3]

The transverse sinus is an important structure in the venous drainage system of the brain, which opens into the sigmoid sinus. Venous flow proceeds via the jugular foramen through the skull base towards the IJV in the neck. Several venous pathways drain into the sigmoid–jugular complex: the superior and inferior petrosal sinuses, the occipital sinus and the mastoid and condylar emissary veins. The most important is the inferior petrosal sinus that contains the effluence of the cavernous sinus and the basilar plexus. The dome of the jugular bulb is in close contact with the floor of the hypotympanum, the vestibule, the posterior semicircular canal, the vestibular aqueduct and the internal auditory canal. The lateral side of the jugular bulb is close to the mastoid (vertical) segment of the facial nerve. The jugular foramen lies in close proximity to the internal carotid artery: only a small osseous spine separates the vertical part of the carotid canal from the jugular foramen (**Figures 107.2** and **107.3**).

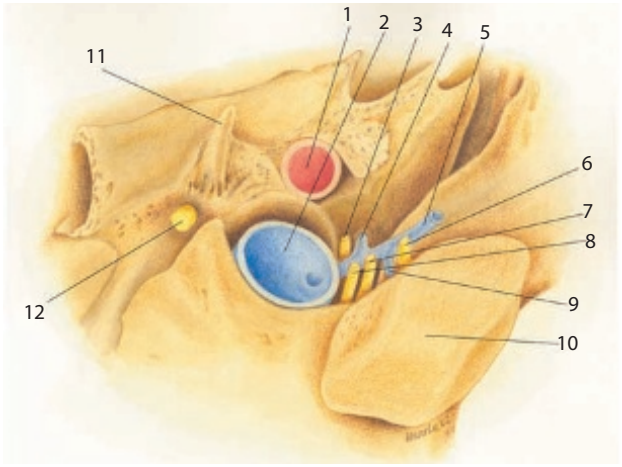


Figure 107.2 View of the jugular foramen (right side) as shown from below. 1, internal carotid artery; 2, internal jugular vein; 3, glossopharyngeal nerve; 4, inferior petrosal sinus; 5, pharyngeal vein; 6, hypoglossal nerve; 7, vagus nerve; 8, spinal accessory nerve; 9, condylar emissary vein; 10, occipital condyle; 11, styloid process; 12, facial nerve.

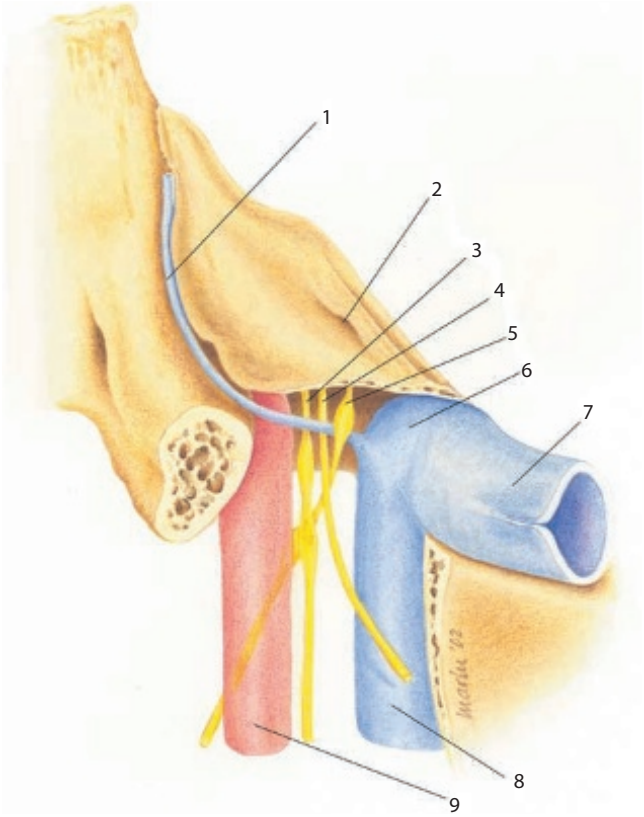


Figure 107.3 View of the jugular foramen (right side) as shown from behind. 1, inferior petrosal sinus; 2, internal auditory canal; 3, vagus nerve; 4, spinal accessory nerve; 5, glossopharyngeal nerve; 6, jugular bulb; 7, sigmoid sinus; 8, internal jugular vein; 9, internal carotid artery.

SYMPTOMATOLOGY

Disease in the jugular foramen causes a variety of symptoms and signs. These are discussed in Chapter 111, Clinical neuroanatomy. In clinical practice, perhaps the

most common is the jugular foramen syndrome, also known as Vernet's syndrome (named after the French neurologist Maurice Vernet). This syndrome comprises paralysis of the cranial nerves IX, X and XI. Obstruction or thrombosis of the sigmoid–jugular complex by tumour or infection may develop and is frequently asymptomatic because the venous drainage system of the brain has sufficient alternative routes or pathways. In rare cases, a thrombosed sigmoid–jugular complex may give rise to retrograde thrombosis of the inferior petrosal sinus and eventually even to thrombosis of the cavernous sinus. This condition then leads to the cavernous sinus syndrome, that is, paralysis of cranial nerves III, IV and VI, oedema of the conjunctiva and upper eye lid, venous congestion in the fundus of the globe and proptosis. Blockage of the cerebral venous drainage through the jugular foramen can also cause increased intracranial pressure and give rise to epileptic seizures and visual obscurations.[4] This is a life-threatening situation that needs urgent attention if multiple neurological deficits are to be avoided.

The symptoms caused by lesions that develop in the jugular foramen are not just confined to their effect on local anatomical structures. Sometimes symptoms are related to more extensive or distant pathology. For example, thrombosis in the jugular foramen is frequently the result of ear pathology, such as chronic otitis media, with or without cholesteatoma. Other factors that might induce thrombosis in the venous structures in the jugular foramen include trauma, various coagulopathies and vessel wall pathology from tumour invasion or systemic vasculitis. Jugular foramen pathology may cause facial nerve palsy and audiovestibular symptoms as a result of the close proximity of the jugular foramen and the vertical part of the facial nerve, cochlea, labyrinth, internal auditory canal and the cerebellopontine angle. Tumours are not the only cause of pulsatile tinnitus; arteriovenous malformations, high jugular bulb or jugular bulb diverticulum are also associated with this symptom. In these latter conditions, the patient should notice a decrease or disappearance of their tinnitus when the IJV in the neck is compressed.

DIAGNOSIS OF JUGULAR FORAMEN LESIONS

Patients in whom a jugular foramen lesion is suspected should undergo a standard triad of diagnostic procedures: first, a clinical examination; second, additional investigations such as audiometry; and third, imaging. The presence of jugular foramen pathology can be substantiated with a high level of probability by the first two steps, but imaging techniques are absolutely necessary to prove the existence and extent of a pathological process.

History and physical examination

The clinical history of patients with jugular foramen pathology is variable. Features to be sought have been discussed in Chapter 99, Evaluation of the skull base patient. Symptoms may result from damage to the contents of the jugular foramen (i.e. cranial nerves IX, X and XI) or to the venous structures of the sigmoid–jugular complex. There may also be symptoms that result from dysfunction of the cochleovestibular system or the facial nerve. For example, paragangliomas of the jugular foramen may present with facial palsy, the insidious development of lower cranial nerve palsies having gone largely unnoticed. In cases with extensive intracranial involvement, ataxia resulting from the compression of cerebellar structures, visual disturbances and vomiting caused by obstructive hydrocephalus may be more prominent features. Infectious disorders of the jugular foramen, such as those caused by chronic otitis media with or without cholesteatoma, may be accompanied by purulent otorrhoea. In some rapidly progressive cases, malaise, fever, headaches and stiffness of the neck may be present and in this situation there should be concern that patients might develop meningitis.

Physical examination should include a complete inspection of the ears, nose and throat and neck. Cranial nerve function must be documented accurately. If the patient has visual symptoms, an ophthalmological opinion is essential.

Additional examinations

Pure-tone and speech audiometry should be performed along with appropriate vestibular tests. Patients with paragangliomas should have their blood pressure checked and either 24-hour urinary collection for catecholamine metabolite assessment or an assay of plasma free metanephrines. This is indicated for two reasons, the identified head and neck paragangliomas may rarely have the capacity to secrete catecholamines, such as noradrenaline and dopamine, and secondly, the patient is at increased risk of having an intra-abdominal paraganglioma or pheochromocytoma, with a greater propensity to secretion.

Imaging

High resolution computed tomography (CT) and magnetic resonance imaging (MRI) are the methods of choice and should be acquired in all patients.[5] T1- and T2-weighted MRI sequences before and after the administration of gadolinium can detect most common lesions in the jugular foramen, such as schwannomas and meningiomas, and portray the precise extent of the tumour both within the infratemporal fossa and intracranially. Paragangliomas, however, require a different policy: besides visualization of the size and extent of the tumour, adequate mapping of vascular structures is a prerequisite to accurate diagnosis. This can be achieved by either magnetic resonance or CT angiography (MRA / CTA) or conventional carotid angiography. MRA with gadolinium enables precise mapping of the vasculature and its relationship with the tumour and surrounding anatomical structures. Moreover, this method accurately displays the size and extent of the tumour. CT images should be made in at least two planes. CT gives more precise information about bone destruction and gives all the information a surgeon would need in relation to temporal bone anatomy if surgery were envisaged.

It is important to visualize the fallopian canal, the middle ear with its ossicles, the absence or presence of a bony lamina between the jugular bulb and the hypotympanum, the position and shape of the internal auditory canal and the carotid canal.

Various scintigraphic techniques may be useful to diagnose some types of pathological condition in and around the jugular foramen. In patients with chronic infections, diagnostic information can be obtained with scintigraphy using radioisotopes, such as technetium-99 methylene diphosphanate and gallium-67 citrate. The former isotope identifies osteoblastic activity, whereas the latter documents the activity of the infectious process. Endocrine activity in paragangliomas can be demonstrated with iodine-123 metaiodobenzylguanidine. Octreotide scintigraphy may contribute to the detection of paragangliomas at multiple locations.

Patients presenting with a jugular foramen paraganglioma should also be screened for other paragangliomas, which are particularly common as manifestations of succinate dehydrogenase gene mutations, typically SDHB or SDHD.[6]

This can be done using positron emission tomography (PET) with 18F-DOPA or 18FDG glucose, although MRI imaging of head, neck, mediastinum, abdomen and pelvis will achieve the same result without radiation exposure, and is therefore the preferred modality for ongoing screening of such patients.

PATHOLOGY

Broadly speaking, pathological conditions involving the jugular foramen can be divided into three categories: neoplasia; infectious conditions; and miscellaneous. The pathological conditions that have been found in the jugular foramen are listed below, the majority being neoplastic disorders. Most of the lesions originate in the jugular foramen or in adjacent structures. The list does not include incidental lesions that originate from more distant head and neck regions and occasionally spread into the jugular foramen, for example, parotid tumours and nasopharyngeal carcinoma, or metastases from distant lesions:

- paragangliomas (also known as glomus tumours)
- schwannoma
- meningioma
- osteoclastoma
- myxoma
- neurofibroma
- haemangiopericytoma
- chondromyxoid fibroma
- angioma
- ceruminoma
- giant cell tumour
- plasmocytoma
- endolymphatic sac tumour
- cholesteatoma
- cholesterol granuloma
- cholesterol cyst
- neurenteric cyst
- amyloidoma
- rhabdomyosarcoma
- adenoid cystic carcinoma
- chondrosarcoma
- sarcoma
- malignant schwannoma.

Neoplasia

Paragangliomas are the most common lesions in the jugular foramen. Schwannomas and meningiomas are the second and/or third most frequent lesions. Schwannomas usually have developed from the cranial nerves IX, X or XI. Meningiomas generally originate intracranially and eventually invade the jugular foramen, although intraosseous meningiomas may occur.[7] Reports of lesions other than paragangliomas, schwannomas and meningiomas are scant and therefore our knowledge of less common jugular foramen lesions is somewhat fragmentary.

PARAGANGLIOMAS

The term paraganglioma is derived from the site of origin of the tumour. In the temporal bone, paraganglia are present in the adventitia of the jugular bulb and along the IXth and Xth cranial nerves, and in the middle ear in association with Jacobsen's plexus. Chromaffin and non-chromaffin paragangliomas have been distinguished according to their intrinsic ability to take up and stain with chromium salts. In the past, a chromaffin paraganglioma was considered capable of producing adrenalin, whereas its non-chromaffin counterpart was not. This distinction between chromaffin and non-chromaffin paragangliomas has since become outdated, as both tumours are now known to synthesize all types of catecholamines. The term chemodectoma should be reserved for tumours that originate from the chemoreceptor system. The paraganglia in the temporal bone do not belong to this histological entity, in contrast with those in the carotid sinus. Therefore, the term chemodectoma is less appropriate for lesions in the jugular foramen and in other parts of the temporal bone.

The term glomus tumour is also inaccurate, because the word glomus means a small, circumscribed histological structure in which arterioles connect directly with veins, a situation found in small cutaneous lesions also known as glomus tumours. However, the term glomus or glomus tumour is commonly used in the historical literature to refer to paragangliomas.

Temporal bone paragangliomas can be divided into one of three categories: jugular paragangliomas; jugulotympanicum paragangliomas; and tympanic paragangliomas. Only the tympanic paraganglioma is confined to the tympanic cavity. These tumours originate in the middle ear, as opposed to jugular paragangliomas, which develop from the adventitia of the jugular bulb. The term jugulotympanic is appropriate for those tumours in which it is impossible to define the site of origin, and for tympanic tumours that have extended to involve the jugular foramen and widely invade the temporal bone.

There is a female predominance.[8] The appearance of the lesion is lobular, pulsatile and red-purple in colour. Its microscopic appearance is dominated by the presence of groups of characteristic neurosecretory cells.

Up to 40% of patients with head and neck paragangliomas have a mutation of the succinate dehydrogenase gene that makes them prone to developing multiple paragangliomas. A proportion of these patients will have multiple tumours at presentation, which may include intra-abdominal tumours with a higher propensity to secrete catecholamines. Paragangliomas are considered to belong to the amine precursor uptake and decarboxylation (APUD) tumours. Consequently, associations have also been described between paragangliomas and a variety of other APUD tumours, such as various forms of multiple endocrine adenomatosis. Moreover, concomitant occurrence has been described with Von Hippel–Lindau disease, renal cell carcinoma, neurofibromatosis and vestibular schwannoma.

Several classifications have been proposed for paragangliomas in the temporal bone, based on symptoms and/or the size and extent of the tumour. Nowadays, staging is performed by means of MR and CT imaging. The most frequently used classification was the one developed by Fisch (**Table 107.1**)[9] in which tumours are classified from A to C based on extension within the temporal bone with tumours that affect the jugular foramen belonging to class C. Class C is subdivided according to the relationship between the tumour and the carotid artery, and Class D is used in addition to the A–C moniker to describe the extent of intracranial involvement where this is present.

The biological behaviour of paragangliomas is usually indolent: it can take many years or even decades for slight growth to become apparent. However, even without any substantial increase in the volume of the lesion, symptoms of progressive cranial nerve deficits may develop, presumably as the result of local erosion and compression by the tumour. In **Figures 107.4** and **107.5**, two illustrative cases are shown.

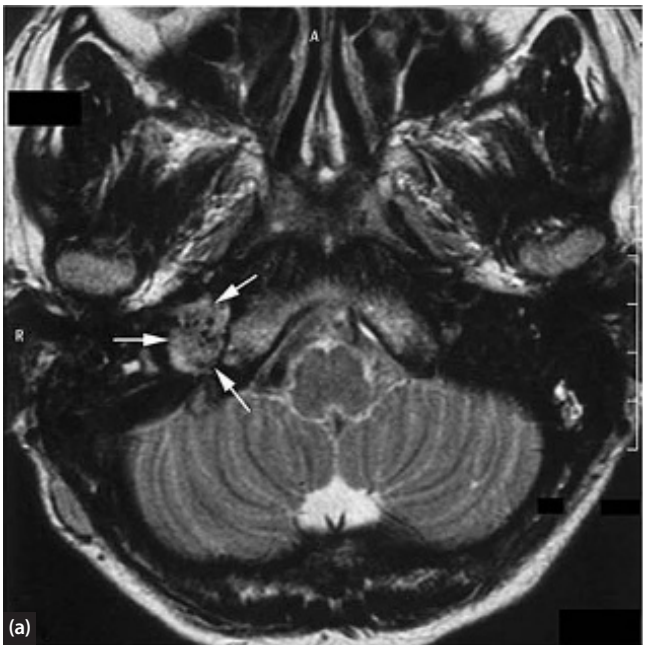
TABLE 107.1 Classification of paragangliomas in the temporal bone according to Fisch

Classification	
Class A	Limited to the middle ear (mesotympanum)
Class B	In the middle ear (meso- and hypotympanum) and the mastoid
Class C	Tumour originates in the dome of the jugular bulb, destroying the overlying bone; the tumour may spread inferiorly, posteriorly, superiorly, laterally and/or medially; class C is subdivided into four categories, according to the size and extension of the tumour
Class D	Intracranial extension; class D is subdivided into two categories according to the presence or absence of intradural extension; these two categories are subdivided again according to the depth of invasion of the posterior fossa and the degree of medial displacement of the posterior fossa dura, respectively

Reproduced with permission from Fisch.[9]

SCHWANNOMAS

Synonyms for schwannoma include nerve sheath tumour, neuroma, neurilemoma and neurinoma. Nowadays, schwannoma is the generally agreed term because the lesion develops from the Schwann cells in the perineurium. The pars nervosa of the jugular foramen is the site of origin, and the cranial nerves IX, X or XI are primarily affected.



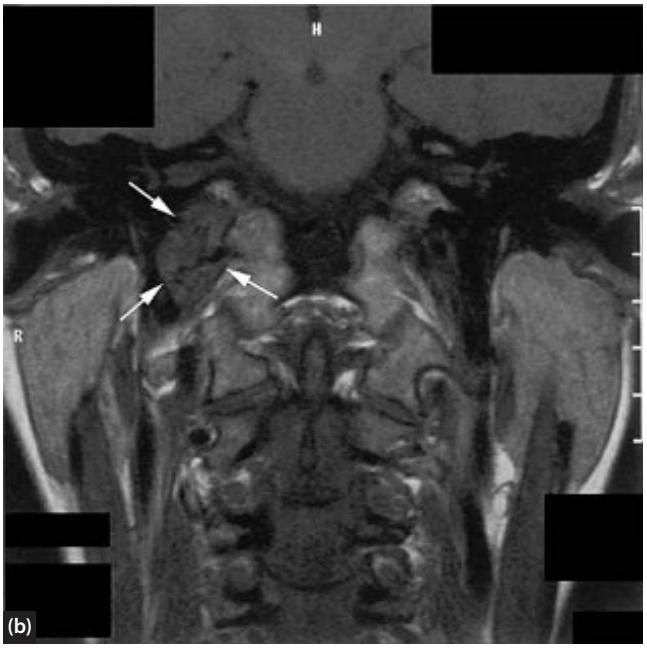


Figure 107.4 A 42-year-old woman presented with a mixed sensorineural-conductive hearing loss of about 50 dB on the right side in combination with a reddish-blue discolouration of the tympanic membrane. (a) T2-weighted axial MRI showing the lesion in the axial plane (arrows). **(b)** T1-weighted coronal slices, showing the involvement of the jugular bulb and the sigmoid–jugular complex (arrows). *(Continued)*

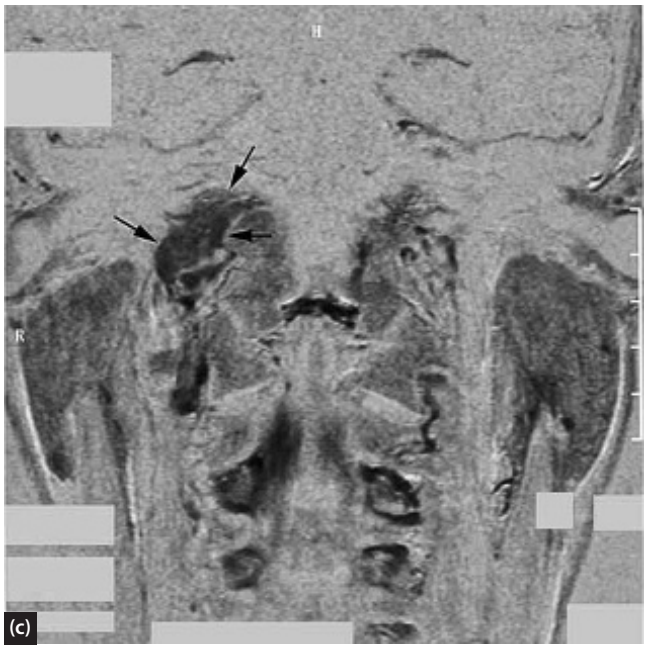
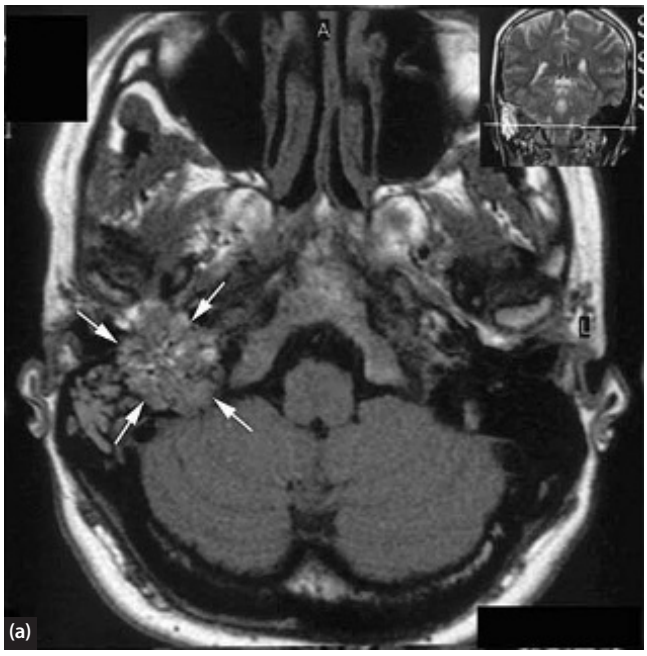
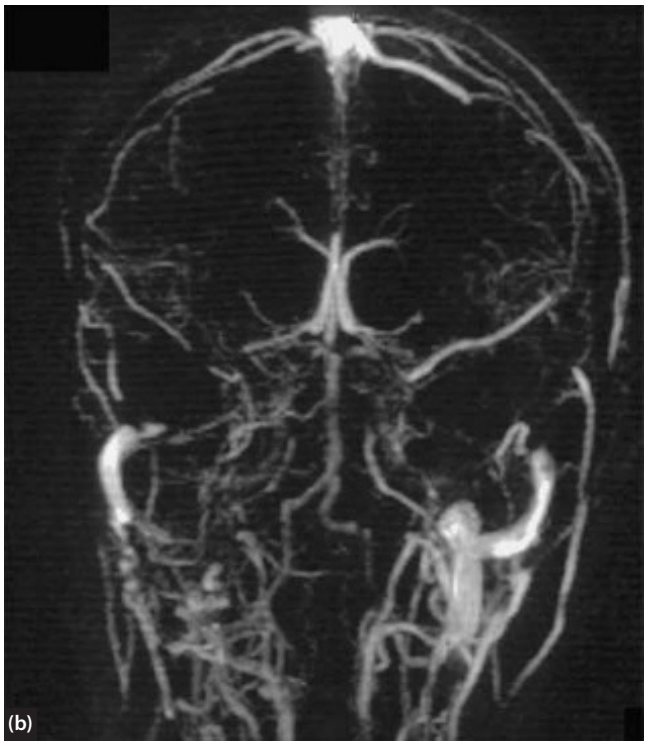


Figure 107.4 (Continued) A 42-year-old woman presented with a mixed sensorineural-conductive hearing loss of about 50 dB on the right side in combination with a reddish-blue discolouration of the tympanic membrane. (c) Subtraction image (that is, T1 with gadolinium minus T1). Diagnosis: Jugular paraganglioma, presumably a class C lesion according to the classification of Fisch.[9]





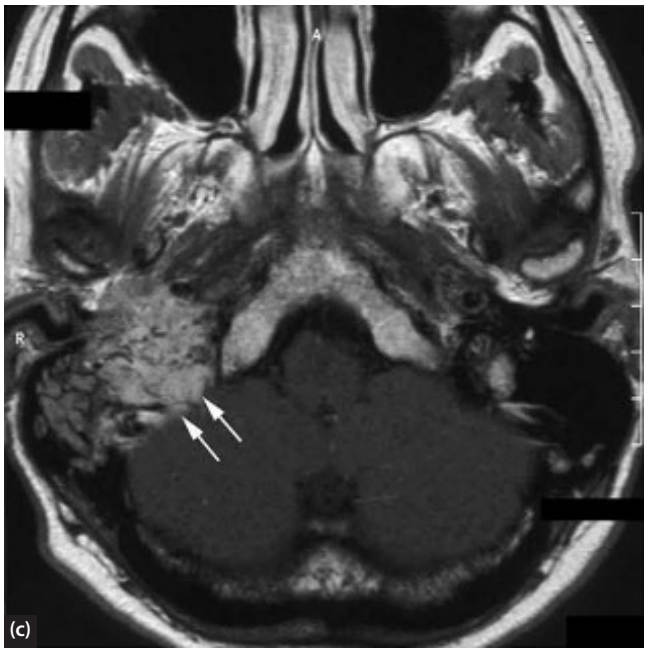


Figure 107.5 A 25-year-old woman presented with right-sided mixed sensorineural-conductive hearing loss of about 60 dB and pulsatile tinnitus. The right tympanic membrane had a reddish-blue discolouration. (a) Axial T1-weighted MRI showing a mass lesion around the right jugular foramen (arrows) with the characteristic appearance of a paraganglioma. **(b)** Coronal MRA; absence of flow in the right sigmoid–jugular complex and internal jugular vein. **(c)** Axial T1-weighted MRI with gadolinium demonstrating involvement of the posterior fossa dura (arrows). *(Continued)*

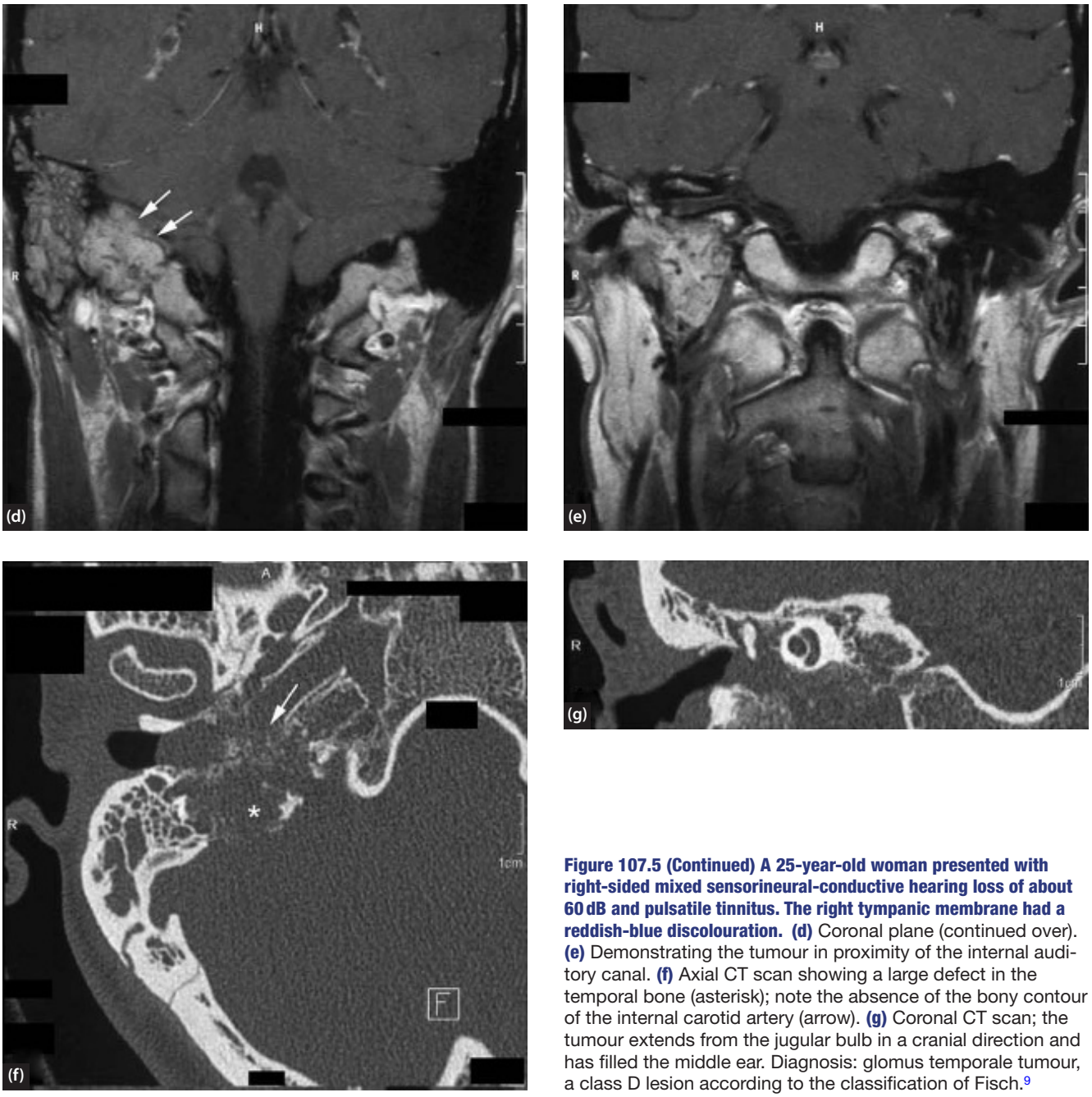


Figure 107.5 (Continued) A 25-year-old woman presented with right-sided mixed sensorineural-conductive hearing loss of about 60 dB and pulsatile tinnitus. The right tympanic membrane had a reddish-blue discolouration. (d) Coronal plane (continued over). **(e)** Demonstrating the tumour in proximity of the internal auditory canal. **(f)** Axial CT scan showing a large defect in the temporal bone (asterisk); note the absence of the bony contour of the internal carotid artery (arrow). **(g)** Coronal CT scan; the tumour extends from the jugular bulb in a cranial direction and has filled the middle ear. Diagnosis: glomus temporale tumour, a class D lesion according to the classification of Fisch.[9]

As a result, a schwannoma is usually localized in the medial part of the jugular foramen. Kaye et al.[10] and Pellet et al.[11] classified jugular foramen schwannomas according to their size and extension (Table 107.2). A further classification has been proposed by Franklin et al. (Table 107.3).[12]

Their histopathological appearance is identical to that of sporadic vestibular schwannomas. Antoni type A and type B tissues can be distinguished. Type A tissue is characterized by densely packed cells, whereas type B tissue is fairly hypocellular with a myxoid stroma. Both types can develop in different proportions. Fatty degeneration, haemorrhage, necrosis and cyst formation may also be seen. The biological behaviour of schwannomas in the jugular foramen does not differ from that in the internal auditory meatus or the cerebellopontine angle, often slow growing or apparently static. Rapid increase in size may be seen and is usually the result of intratumoral haemorrhage and cyst formation.

MENINGIOMAS

Intracranial meningiomas represent about 15–20% of all brain tumours. Basal meningiomas can penetrate the skull base through any of the natural foramina (e.g. the foramen magnum, the optic canal and the jugular foramen). Locally aggressive meningiomas sometimes invade

TABLE 107.2 Classification of jugular foramen schwannomas, according to Kaye et al.[10] and Pellet et al.[11]

Classification	
Type A	Primarily growing intracranially into the cerebellopontine angle
Type B	Growing into the jugular foramen
Type C	Primarily growing extracranially into the neck
Type D	Dumb-bell-shaped tumour, growing from the jugular foramen intracranially and extracranially

TABLE 107.3 Classification of jugular foramen schwannomas, according to Franklin et al.[12]

Classification	
Type A	Confined to the neck
Type B	In the neck and extending into the jugular foramen
Type C	In the jugular foramen and extending along the internal carotid artery
Type D	In the jugular foramen and extending intracranially

Reproduced with permission from Franklin et al.[11]

TABLE 107.4 Meningiomas: World Health Organization classification

Classification	
Grade I (typical)	• Meningothelial (syncytial) • Fibrous (fibroblastic) • Transitional (mixed) • Psammomatous • Angiomatous • Microcystic • Secretory • Clear cell • Chordoid • Lymphoplasmocyte-rich • Metaplastic
Grade II (atypical)	Papillary
Grade III (anaplastic)	Malignant

Reproduced with permission from Kleihues et al.[13]

bone and form new openings (e.g. from the anterior fossa through the cribriform plate into the nasal cavity and from the middle fossa into the temporal bone). About one in five intracranial meningiomas have such extracranial extensions. The histopathology and vascularity of these tumours varies widely. Some classifications have been proposed mainly based on morphological characteristics. The World Health Organization classification is the most generally accepted (Table 107.4).[13] About 10 percent of meningiomas undergo malignant transformation and very occasionally metastasize to the lung, liver or kidney. Females are more frequently affected than males. The peak age of incidence is in the fifth decade.

The medial aspect of the jugular foramen is invaded by meningiomas whose site of attachment lies either anteriorly or at the level of the lower clivus. The lateral aspect is invaded by lesions that originate more posteriorly at the dorsal aspect of the petrous bone. The lower cranial nerves are more susceptible to damage when the medial part of the jugular foramen is involved. Sometimes the tumour also erodes bone and grows through the jugular foramen into the infralabyrinthine bone and tympanic cavity. The tumour can also extend through the jugular foramen into the upper neck, occasionally within the lumen of the internal jugular vein (IJV). Biological activity varies, but slow progression is the most usual pattern.

METASTATIC LESIONS

The common malignancies that arise in the lung, breast, prostate, kidney, stomach and thyroid gland can metastasize to the skull base, including the jugular foramen. Less common malignancies that develop in adjacent structures such as the posterior fossa, temporal bone, infratemporal fossa and nasopharynx, can also spread into the jugular foramen. Some histological types, such as adenoid cystic carcinoma, are more common than others. This tumour may originate in the deep lobe of the parotid gland and spread into the skull base. Metastases from haematological neoplasms and extramedullary plasmocytomas are also seen in the temporal bone and in the jugular foramen, usually as a result of haematogenous spread. Lymphatic spread of malignancies into the jugular foramen is very uncommon. Like many other jugular foramen lesions, metastases make their presence known by causing cranial nerve dysfunction (VII to XII). Erosion of bone usually accompanies metastatic disease and this is clearly seen on CT images as radiolucent areas in bony structures.

Infectious conditions

The most frequent infectious conditions that affect the jugular foramen are:

- acute otitis media
- chronic otitis media
- chronic otitis media with cholesteatoma
- varicella zoster virus
- osteomyelitis
- epidural empyema
- necrotizing skull base osteomyelitis.

The majority are related to otitis media, predominantly the chronic type, with or without cholesteatoma. Intracranial disorders that result in jugular foramen pathology, such as meningitis and epidural empyema, are also frequently related to some type of otitis media.

Miscellaneous disorders

A high jugular bulb is defined as reaching beyond the level of the inferior border of the tympanic annulus. It is a well-known entity that protrudes anteriorly and laterally, and is visible behind the tympanic membrane or in the external auditory canal. It may even reach the ossicular chain and give rise to conductive hearing loss. In patients with a high jugular bulb, myringotomy and tympanoplasty may lead to severe haemorrhage if the condition is not recognized pre-operatively.

Jugular bulb diverticulum is another vascular disorder. The diverticulum develops from the jugular bulb and extends towards the posterior semicircular canal, the internal auditory meatus or the posterior fossa. Vestibular symptoms, sensorineural hearing loss or even facial nerve palsy may be associated with this. The condition can also cause symptoms similar to those in Ménière's disease. In Figures 107.6 and 107.7, two illustrative cases are shown.

MANAGEMENT

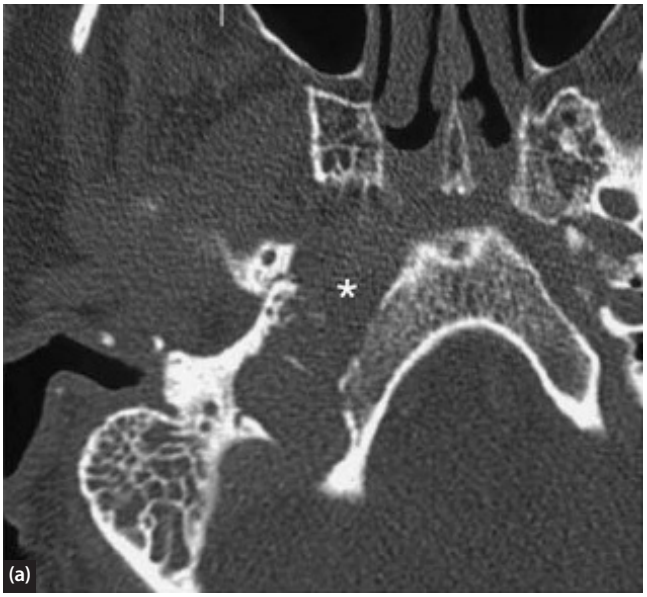
The goals of management must be clearly defined in this complex area, and the following discussion pertains primarily to the three commonest pathologies in this area, paragangliomas, schwannomas and meningiomas, all of which typically have a relatively indolent natural history.

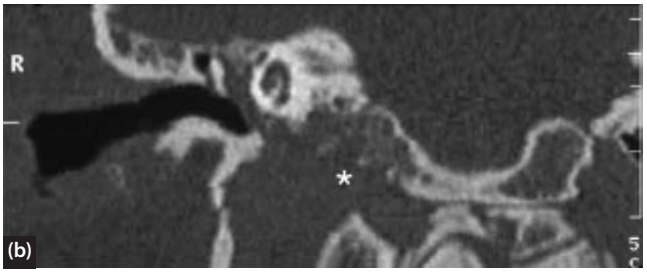
It is generally the case that the gradual onset of venous outflow obstruction is relatively well tolerated, as collateral veins develop, although exceptions occur.

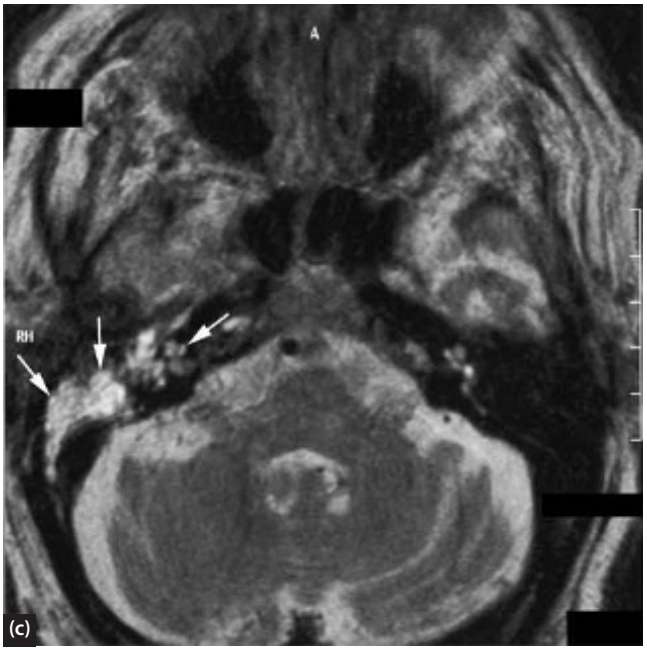
The primary goals of treatment are therefore:

1. to address presenting symptoms
2. the preservation of remaining neurological function (that which has been lost will generally not return)
3. to avoid intracranial disease extension and the associated risk of brainstem compression.

For the majority of processes affecting the jugular foramen, the likelihood of these occurring in the next few years if







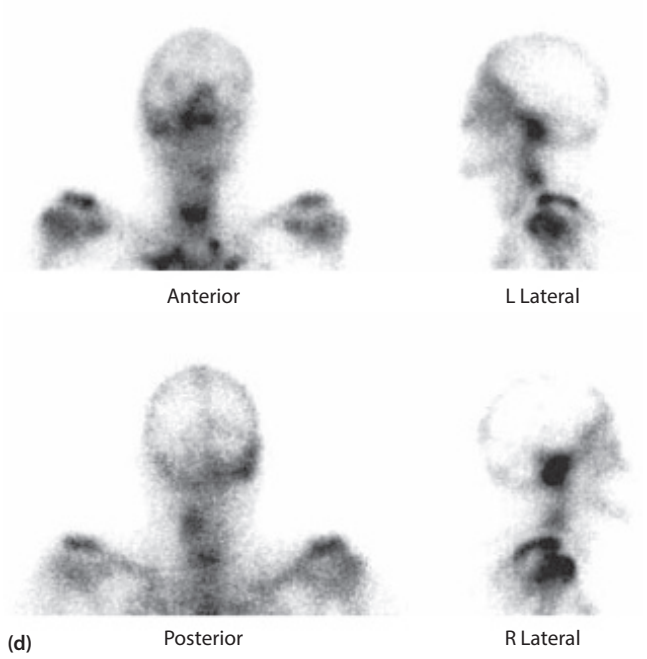


Figure 107.6 A 78-year-old man with a history of diabetes mellitus, polyneuropathy and chronic otitis media presented with right-sided facial palsy (House-Brackmann grade III) and signs of involvement of cranial nerves IX, X and XI. (a) Axial CT scan showing an irregular defect in the right petrous apex (asterisk) extending towards the jugular bulb. **(b)** The coronal plane (asterisk). **(c)** T2-weighted MRI; the right mastoid and some petrous apex cells are filled with fluid (arrows). **(d)** Scintigram (technetium-99m diphosphanate) with signal enhancement in the area of the right temporal bone. Diagnosis: jugular foramen syndrome as a result of petrositis/osteomyelitis of the skull base.

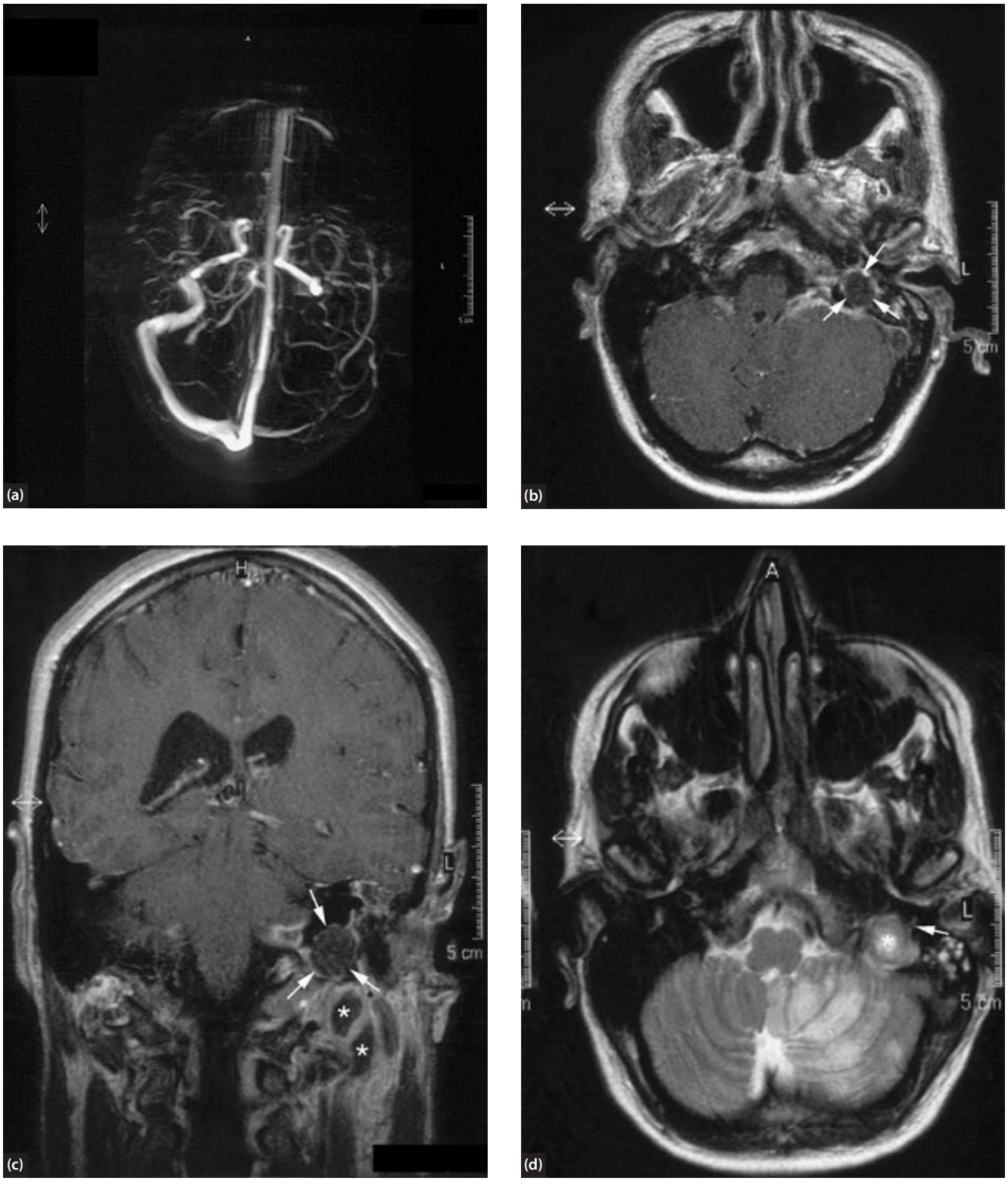


Figure 107.7 A 42-year-old man presented with fever, headache and 40 dB conductive hearing loss on the left side. Moreover, there were clinical signs of involvement of the cranial nerves VII (House-Brackmann II), IX, X, XI and XII. **(a)** MRA showing absence of flow in the left transverse sinus and sigmoid–jugular complex. **(b)** T1-weighted coronal MRI after administration of gadolinium. Mass lesion in the left jugular foramen (arrows). Multiple cystic lesions in the upper neck (asterisks). **(c)** T1-weighted axial MRI after administration of gadolinium. Note mass lesion in the jugular foramen (arrows). **(d)** T2-weighted axial MRI. The lesion in the left jugular foramen is depicted as a hyperintense area (asterisk); a small band suggests the presence of a connection with the middle ear (arrow); this was confirmed during surgery. Diagnosis (made intra-operatively): cholesteatoma in the left jugular foramen with thrombosis of the sigmoid–jugular complex and multilocular abscesses in the upper neck.

the disease is left untreated is low, and it is important that well intentioned intervention does not hasten the onset of disability.

Historically, the presence of a space-occupying lesion once formed sufficient grounds to proceed directly to surgery. It was believed that something that should not be there had to be removed, in view of the threat to adjacent vital structures.

Although the body of literature on jugular foramen lesions still focuses on surgical treatment, much can also be said for non-surgical or conservative management.

Which approach is appropriate depends not only on the nature and extent of the lesion but also on the patient. Advanced age or poor physical condition are contraindications for surgery. As conservative management becomes more widely practised there is also an increasing body of evidence that while paragangliomas, schwannomas and meningiomas may progress rapidly, the majority do not, and spontaneous regression of schwannomas is well recognized. In many cases, progression of the disorder may be extremely slow, sometimes so slow as to be undetectable.

An initially expectant policy may therefore be justified. In general, the choice of surgery, non-surgical or conservative management should not be made until a wide range of aspects concerning the patient and the disorder have been fully considered.

Wait-and-see policy

The size of a jugular foramen lesion can now be accurately measured, monitored and documented with the available imaging modalities of CT and MRI.

In many cases, the lesions do not pose a threat during the whole of the patient's life. However, there are also a number of lesions that show considerable progression and cause progressive neurological deficits and risks to life.

The main problem is therefore to identify those lesions that will progress in the future. Although theoretically histological features of the tumour could provide some insight into its biological behaviour, in most cases taking a biopsy from a jugular foramen lesion is not feasible, and for the commoner pathologies even histology is often unable to distinguish between aggressive and indolent forms of the disease. One potential surrogate marker for future behaviour of paragangliomas is metabolic activity as evidenced by standardized uptake value (SUV) max on FDG PET (fludeoxyglucoze), with higher SUV correlating with an increased tendency to growth.

It is logical to assume that larger tumours are more likely to pose an early threat to the patient than smaller lesions, and one might therefore be more inclined to treat these surgically. However, post-operative morbidity and mortality is also potentially more significant in patients with larger tumours, hence patients with minimal symptoms may be tempted to explore non-surgical options. Conversely, patients with small tumours may tolerate surgery relatively well; however, the risk associated with leaving the lesion is also minimal.

It must be emphasized that these considerations only apply to the three most common jugular foramen lesions. Conditions other than a paraganglioma, schwannoma or meningioma require a different approach, depending on the nature of the lesion. In many of these lesions, it is questionable whether surgery or any other form of treatment will be beneficial to the patient.

Medical therapy

There are very few indications for medical treatment for jugular foramen lesions. Antibiotics are important for all infectious conditions of the jugular foramen, such as those associated with chronic otitis media. Acute sepsis and its complications cannot usually be cured by even the most potent antimicrobial medication, so surgery will invariably be part of the therapeutic strategy. Necrotizing osteomyelitis in contrast is not amenable to surgery, other than to provide tissue for culture, and must be addressed with long term antimicrobial therapy.

Radiotherapy

Conventional fractionated radiotherapy has been demonstrated to be as efficacious as surgery in providing long-term tumour control in jugular and vagal paragangliomas, with a lower risk of iatrogenic cranial nerve damage.[14–16]

The aim is to destroy the microvascular tissue and bring about sclerosis and fibrosis, hence the tumour will not disappear, but may regress over time.

With modern radiotherapy techniques it is relatively straightforward in the vast majority of tumours to limit the dose delivered to the brain to within its tolerance. The cochlea is likely to be affected, however, and treating the middle ear component of a jugular paraganglioma with radiation will invariably compromise the tympanic membrane and risk radiation induced exposure of the bony ear canal floor.

Radiotherapy may be an option for patients whose paraganglioma is impossible to remove surgically (i.e. to patients with extensive class C and D tumours), although in some cases the degree of brainstem compression may present a contraindication, and debulking surgery may be a prerequisite.

In the elderly and those whose life expectancy is limited by other conditions it may be more appropriate not to treat the jugular foramen lesion at all, although a rapidly progressive tumour may be treated with radiotherapy.

The role of radiotherapy in meningiomas is neither sharply delineated nor universally accepted. The indolent nature of these lesions impairs assessment of the contribution that radiotherapy might make to slowing down or stopping progression. Moreover, meningiomas represent a fairly heterogeneous histological group of lesions, which may all react differently to irradiation. A clinical trial randomizing WHO grade 1 meningiomas subtotally resected to either radical radiotherapy or conservative management was instituted by the EORTC clinical trials group but it was abandoned due to low enrolment (EORTC 22021–26021). A similar trial looking at WHO grade 2 and 3 meningiomas is ongoing

but is yet to report results (as of March, 2018, EORTC 22042–26042), although in this cohort of patients radiation is generally considered of more benefit.

In addition, the anatomical localization and extension of meningiomas in and around the jugular foramen differ from one patient to another to a greater extent than for other pathologies, complicating the comparison of different treatments.

All these factors complicate the realistic evaluation of the value of radiotherapy as a treatment for meningiomas.

The jugular foramen lies in close proximity to delicate and vulnerable structures. Therefore, single-dose stereotactic radiosurgery is likely to be chosen in preference to conventional radiotherapy for common benign lesions in the jugular foramen, such as meningiomas and schwannomas.

Stereotactic radiosurgery

Stereotactic radiosurgery is rapidly gaining popularity as a treatment modality for tumours of less than 3 cm maximum diameter. It forms an alternative to microsurgical removal of a variety of benign lesions in the skull base, including those arising in the jugular foramen. The principles of this method of treatment are described in Chapter 103.

Most experience with stereotactic radiosurgery in skull base tumours has been gained on vestibular schwannomas, and for suitable tumours (i.e. predominately solid tumours of less then 3 cm maximum diameter results are excellent). Smaller series of non-vestibular and jugular foramen schwannomas demonstrate similar high rates of tumour control, with a lower incidence of cranial neuropathy than that associated with surgery.[17, 18]

Stereotactic radiosurgery for jugular paragangliomas has been demonstrated to be as efficacious as external beam radiotherapy, with a similar low rate of iatrogenic cranial neuropathy, and has the merit of being a single fraction treatment.[14]

The role of both radiotherapy and radiosurgery in the management of meningiomas throughout the skull base remains ill defined, and this also applies to this subsite. In view of the ambiguous nature of the evidence, clinical trails are now underway that should better define this issue, in particular for WHO grade 2 meningiomas.[19]

Generally, stereotactic radiosurgery can be considered for patients with small volume progressive disease and minimal symptoms, residual disease after surgery, inoperable tumours and in patients of advanced age or with poor physical condition.

SURGICAL MANAGEMENT

Surgical treatment for lesions in and around the jugular foramen is one of the most challenging procedures in head and neck surgery. Various surgical approaches have been described; lateral transtemporal techniques are the most widely used. A major key to success is the surgeon's knowledge of anatomy, particularly in view of the close proximity of a considerable number of important anatomical structures in this delicate area.[20]

The facial nerve nearly always causes a major obstruction to the direct surgical access of the jugular foramen. It goes without saying that it is absolutely imperative to avoid severing or damaging this important nerve. Various surgical approaches have been described, all with the intention of preserving the anatomical integrity of the facial nerve in combination with adequate surgical exposure.[21] During surgery in the region of the jugular foramen, cranial nerves VII–XII are particularly vulnerable. It should be emphasized that any damage to the VII cranial nerve results in far more serious morbidity than impairment of one or more of the other cranial nerves. Therefore, continuous intra-operative facial nerve monitoring should be performed routinely. Monitoring of X and XII nerves is also advisable in cases where pre-operative function is normal.

The internal carotid artery is another major issue for concern. The vertical part of the carotid canal lies close to venous and nervous structures in the jugular foramen. Some lesions invade the petrous carotid artery, which makes preservation of this vessel problematic. In rare occasions pre-operative stenting or balloon occlusion of the carotid may be appropriate.

Pre-operative embolization

Paragangliomas are the most common lesions found in the jugular foramen. If surgical removal is planned embolization should be considered. Selective arteriography is performed and the tumour embolized via branches of the external carotid artery. There is general agreement that pre-operative embolization significantly reduces blood loss during surgery and this facilitates complete removal of the tumour; however, embolization itself carries a small risk of stroke. The timing of embolization is subject to debate, consensus appears to be that it should take place within 48 hours of surgery, although some surgeons advocate waiting 4–6 weeks after embolization prior to surgery.

Similarly, intra-operative haemorrhage is also the main cause of problems during the surgical removal of meningiomas, particularly those that are extremely vascular. Excessive bleeding can lead to incomplete tumour resection, damage to adjacent structures and post-operative morbidity. It is therefore sensible to assess their vascularity by angiography and undertake superselective embolization in selected cases. Thus, two of the most common lesions in the jugular foramen – paragangliomas and meningiomas – should be investigated with conventional angiography and embolization undertaken where indicated.

Permanent balloon occlusion of the proximal and distal petrous carotid artery should be undertaken where it is likely that the artery is not salvageable. In this situation, the tumour can be embolized via the nutrient vessels that branch off the internal carotid artery by means of inserting a catheter proximal to the balloon. This should be done at least a month prior to definitive surgery, to minimize the risk of a watershed cerebral infarct in the event of intra-operative hypotension.

If carotid occlusion is not tolerated the artery can be reinforced with a covered stent, which minimizes the risk of iatrogenic bleeding at the time of tumour resection.

Surgical approach

The requirement of the surgical approach is that it provides adequate exposure of the tumour, and of the key structures at risk in tumour resection. In the management of jugular foramen lesions, these key structures are the facial nerve and the internal carotid artery.

A wide range of approaches has been described, and choice of approach will be dictated by the patient's anatomy and pathology, the goal of surgery (debulking versus complete resection) and surgical preference.

The basic concepts of all the lateral transtemporal surgical approaches described in the literature are fairly similar. A wide retroauricular incision is made to gain access to the lateral aspect of the temporal bone (**Figure 107.8**). This incision is extended downwards into the neck to expose the structures in the infratemporal region. Then, a wide cortical atticomastoidectomy is performed with skeletonization of the sigmoid sinus. A cranially based tympanomeatal flap can be developed if exposure of the tympanic cavity, in particular the hypotympanic region, is required. After detachment of the tendon from the sternocleidomastoid muscle, the mastoid tip is removed. The mastoid segment of the fallopian canal is skeletonized, from the second genu towards the stylomastoid foramen. The bone anterior to this part of the facial nerve is removed and, at the same time, the dome of the jugular bulb is exposed. A diamond burr is used to remove as much bone as possible that covers the sigmoid sinus and the jugular bulb, so that the fallopian bridge is the only structure that overlies the jugular bulb. As a result, the facial nerve may impair adequate exposure of lesions involving the jugular foramen, but the degree of access required also depends on the pathology. In many cases, the vertical segment of the facial nerve has to be transposed, particularly if the lesions are extensive and bulky. There are two ways to deal with this problem. The first method preserves the ear canal, tympanic membrane and middle ear structures, whereas the second method involves performing a subtotal petrosectomy to gain wide access to the facial nerve. Another possibility is not to transpose the facial nerve. Von Doersten and Jackler[22] reviewed the different ways of handling the facial nerve in jugular foramen surgery.

CONSERVATIVE FACIAL NERVE MANAGEMENT

According to some authors, lesions can be removed without any interference to the facial nerve (**Figure 107.9**).[23–25] There is no doubt that this is possible in certain cases. It typically requires the axis of surgical approach to move postero-inferiorly, to the so-called far-lateral approach. However, the anatomical relationship between the mastoid segment of the facial nerve and the jugular bulb varies considerably. When the space between the two is small, it may be difficult to achieve adequate exposure. In patients with a relatively small tumour and sufficient working space between the vertical segment of the nerve and the jugular bulb, it is usually possible to leave the facial nerve undisturbed. The nerve should preferably remain covered

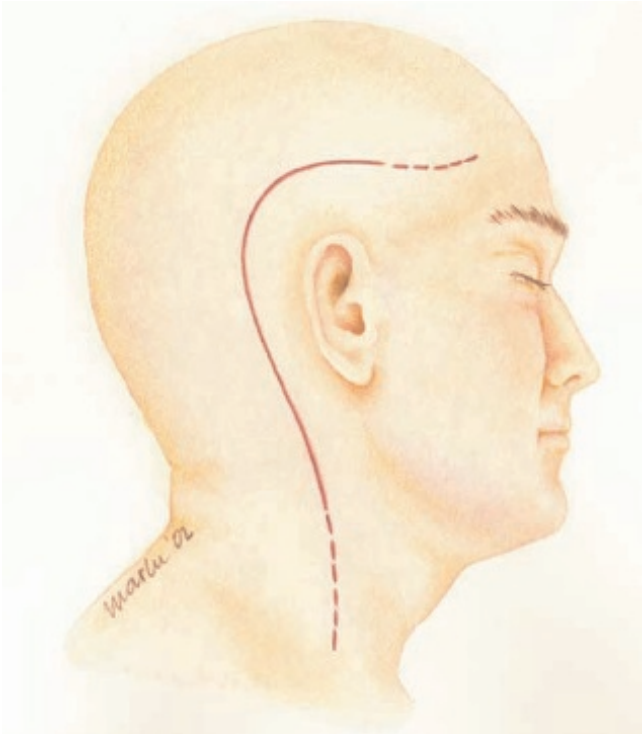


Figure 107.8 The skin incision for the several types of transtemporal approaches to the jugular foramen region.

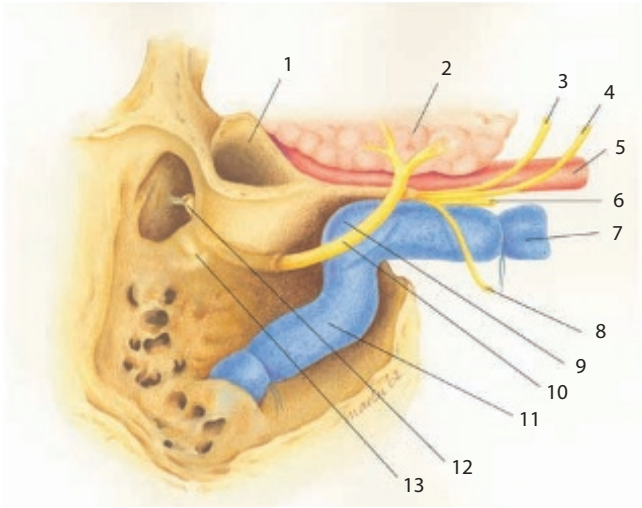


Figure 107.9 Conservative facial nerve management. The right jugular foramen region is exposed without transposition of the facial nerve. After the atticomastoidectomy, the sigmoid–jugular foramen region is exposed. The facial nerve is skeletonized and left *in situ*. The sigmoid–jugular complex is controlled by sutures around the sigmoid sinus and the internal jugular vein. 1, External auditory canal; 2, parotid gland; 3, glossopharyngeal nerve; 4, hypoglossal nerve; 5, internal carotid artery; 6, vagus nerve; 7, internal jugular vein; 8, spinal accessory nerve; 9, jugular bulb; 10, facial nerve; 11, sigmoid sinus; 12, incus; 13, semicircular canals.

by a bony shell (fallopian bridge). In these cases, a large amount of bone anterior to the facial nerve has to be removed to enable wider access to the jugular foramen. Some type of facial nerve transposition may need to be considered if visibility is poor and there is always the risk of incomplete tumour removal.

LIMITED FACIAL NERVE TRANSPOSITION, CANAL WALL UP

This technique involves complete removal of the bony covering of the mastoid segment of the facial nerve, from the second genu down to the stylomastoid foramen. Outside the stylomastoid foramen, the nerve is followed and mobilized over its intraparotid course: first the main trunk and then the temporozygomatic and cervicofacial branches. The subdivisions of these branches are also mobilized and the overlying parotid tissue is removed. Care should be taken to preserve the stylomastoid artery at this stage, to minimize the risk of post-operative facial weakness. After this part of the procedure there is some mobility of the nerve, such that it can be pulled anterolaterally, away from the jugular bulb (**Figure 107.10**). Whether this provides enough exposure is a subject of controversy. It has been stated that this is sufficient for all jugular foramen lesions, but this opinion is not shared universally.[26] According to Fisch,[9] far greater access is needed to achieve adequate exposure and enable total resection of the tumour.

FACIAL NERVE TRANSPOSITION, CANAL WALL DOWN

In order to be able to mobilize the facial nerve more extensively, atticomastoidectomy should be extended to subtotal petrosectomy. This involves removal of the skin of the external auditory meatus along with the tympanic membrane, the malleus and incus, drilling away the posterior canal wall and extensive exenteration of pneumatic cells. As a result, the facial nerve can be uncovered, not only in its mastoid segment, but also in its tympanic part. Then, after mobilization of the intraparotid facial nerve as described above, the nerve can be rerouted anteriorly. The hinge point (pivot) may be located at the second genu, but wider exposure is achieved when the nerve is displaced anteriorly with the hinge point at the first genu (**Figures 107.11** and **107.12**).[22]

MANAGEMENT OF THE SIGMOID–JUGULAR COMPLEX

Damage to the sigmoid sinus or the jugular bulb is a serious risk during jugular foramen surgery. If the vessel wall is punctured, the initial bleeding is fairly simple to control, but retrograde haemorrhage from the IJV may follow. Therefore, the venous blood flow must be blocked at two levels: cranially and caudally to the lesion (i.e. upstream and downstream) (**Figures 107.9–107.12**). It is logical to start with blocking the main flow on the cranial side, the sigmoid sinus. Two methods have been described, ligating the vessel or packing it with Surgicel, both preferably below the level of a preserved mastoid emissary vein. The upper neck can be explored by extending the retroauricular incision downwards. Accordingly, the IJV can be found easily in a later stage of the procedure, after the sternocleidomastoid muscle has been detached from the mastoid process and the mastoid tip has been removed. After identifying the surrounding structures, such as the

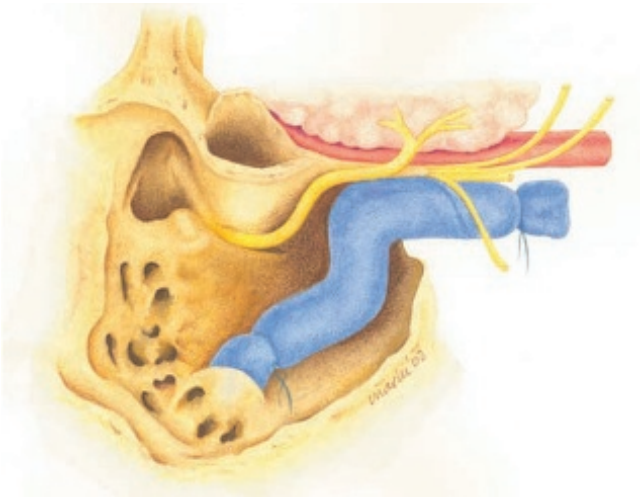


Figure 107.10 Facial nerve transposition, canal wall up. The right jugular foramen region is exposed with a limited transposition of the facial nerve. After an atticomastoidectomy, the mastoidal segment part of the facial nerve is uncovered. The intraparotid part of the nerve is exposed and mobilized. The nerve can then be pulled anteriorly in order to provide access to the jugular bulb. (See also **Figure 107.5**.)

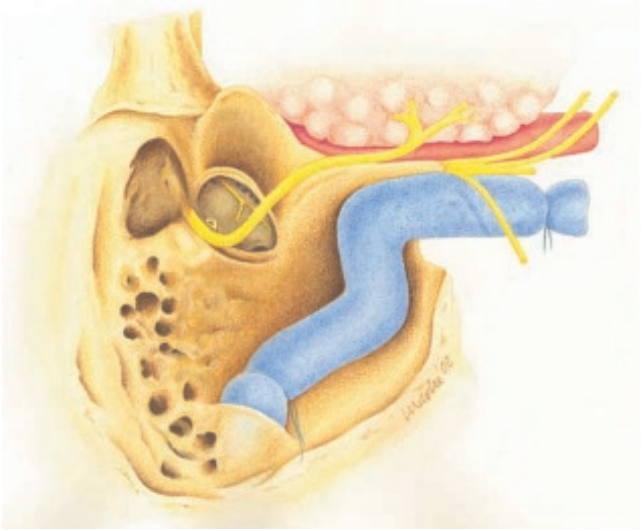


Figure 107.11 Facial nerve transposition canal wall down. The right jugular foramen region is exposed using a more extensive transposition of the facial nerve. After a canal wall down atticomastoidectomy, the tympanic membrane, the malleus and the incus are removed. The facial nerve is uncovered in its mastoidal and tympanic segments. The intraparotid part of the nerve is exposed and mobilized. The nerve can then be rerouted anteriorly with the hinge point at the second genu. (See also **Figure 107.5**.)

internal carotid artery and the cranial nerves IX, X, XI and XII, the IJV should be ligated as high up as possible to avoid bleeding from veins that drain into it in the upper neck. The inferior and superior petrosal sinuses and the mastoid and condylar emissary veins drain into the sigmoid–jugular complex. Usually in a later stage of the procedure, the sigmoid sinus and the jugular bulb have to be opened to remove the tumour. Then bleeding can be expected from these sinuses and emissary veins, which should be dealt with by the use of haemostatic agents.

MANAGEMENT OF THE INTERNAL CAROTID ARTERY

Preservation of the internal carotid artery is of crucial importance during surgery for jugular foramen lesions. The tumour may be attached to the internal carotid artery or be in close contact with it. Visualization of the plane between the tumour and the petrous carotid artery is extremely important. Therefore, the operative field should be as bloodless as possible. All sources of venous haemorrhage must be meticulously controlled, either by ligation or by packing with haemostatic agents. Management of the internal carotid artery is particularly important in patients with paragangliomas. This artery is less likely to be threatened by schwannomas or meningiomas. Paragangliomas may invade the carotid canal, first in its vertical part and eventually along the horizontal part on to the foramen lacerum. They will typically receive part of their blood supply from the petrous carotid artery, via its caroticotympanic or dural branches. In very large tumours, permanent balloon occlusion of the internal carotid artery must be considered, but only if there is sufficient collateral circulation. The latter can be tested pre-operatively during the angiography procedure by temporary occlusion with clinical and radiological surveillance. According to Andrews et al.,[27] permanent balloon occlusion is a safe procedure and does not cause any serious ischaemic deficits, as long as the tolerance test shows sufficient patency of the circle of Willis.

Extensive lesions and malignant tumours may require wide resection with sacrifice of the internal carotid artery. It should also be emphasized that not all patients have sufficient collateral circulation to allow permanent balloon occlusion. In these cases the artery may be stented, with a covered stent to provide reinforcement, or an extracranial–intracranial bypass procedure may be considered.

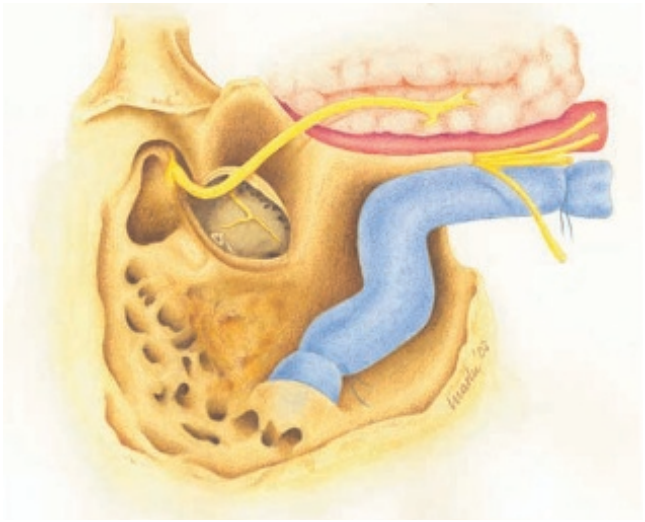


Figure 107.12 Facial nerve transposition, canal wall down. Maximum exposure of the right jugular foramen is achieved by rerouting the facial nerve anteriorly with the hinge point at the first genu. (See also **Figure 107.5**.)

Surgical approaches other than the lateral approach

Although lateral transtemporal surgical approaches are widely accepted, various other surgical techniques have been described (**Table 107.5**).[11, 28–32] These methods invariably involve combinations of well-known neurosurgical techniques. It should be noted that there is not the slightest scientific evidence to suggest that one technique is better than another. Comparative randomized controlled studies have not yet been introduced in this field. Actually, this would hardly be possible for three reasons:

1. the variability and incomparability of pathology in the jugular foramen
2. differences in surgical skills (the human factor)
3. non-uniformity in the way the outcomes are presented. It cannot be expected that this situation will change in the near future.

TABLE 107.5 Surgical approaches other than lateral transtemporal techniques

Approach	Reference
Combined suboccipital and infralabyrinthine–transcervicomastoid approach	Kim et al.[28]
Retrosigmoid suboccipital and combinations with transtemporal approaches	Lee et al.[29]
Extreme-lateral transjugular approach	Salas et al.[30]
Petrooccipital trans-sigmoid approach and combinations with transtemporal approaches	Mazzoni et al.[31]
Widened transcochlear approach	Pellet et al.[11]
Juxtacondylar approach	George et al.[32]
Endoscopic assisted retrosigmoid	Samii et al.[33]

Tumour resection

The close proximity of the internal carotid artery to the jugular foramen seriously complicates the surgical management of a variety of lesions in this area. The aim of all surgical strategies is complete tumour resection with maximum anatomical and functional preservation of nervous and vascular structures. Whether this goal can be achieved depends mainly on the skills of the surgeon and the nature and extent of the pathology. As stated under 'Neoplasia' above, the three most common tumours that affect the jugular foramen are paragangliomas, schwannomas and meningiomas. Paragangliomas usually arise in the lateral part of the jugular foramen (**Figure 107.13**), whereas schwannomas tend to be primarily located in the medial part (**Figure 107.14**). Meningiomas originate in the meninges of the posterior fossa and may eventually fill one or both parts of the jugular foramen, and are likely to encase rather than displace nerves, making functional preservation particularly challenging (**Figure 107.15**). Dumb-bell-shaped tumours are fairly common, because they can extend intracranially as well as into the infratemporal fossa. Factors that play a role in the final outcome of the surgical procedure are control of haemorrhage, appropriate surgical orientation and, last but not least, meticulous microsurgical tissue handling by a skilled surgeon.

Control of venous haemorrhage has been dealt with in Chapter 100, Vascular assessment and management in skull base surgery. Damage to the internal carotid artery is likely to be followed by uncontrollable arterial haemorrhage. This is a serious complication that deserves special attention. Avoiding this situation is a major concern in patients whose tumours infiltrate the carotid canal, such as class C paragangliomas.

After tumour resection, the cavity is filled with abdominal fat. Lumbar drainage may be considered if the resection of a bulky tumour has left a voluminous cavity with wide access to the posterior fossa. Blind sac closure of the external ear canal is performed if the middle ear has not been preserved.

Post-operative management and rehabilitation

In the period immediately following surgery, the patient should be admitted to a well-equipped high dependency care unit for at least 24 hours. Cardiovascular stability must be monitored and safeguarded. Afterwards, the recovery period can be continued in a standard hospital ward. Post-operative care also focuses on the early detection of cranial nerve palsies, because these are the most common complications after jugular foramen surgery. Facial nerve palsy, hearing loss, vertigo, dysphagia and hoarseness are the most obvious symptoms. Functional deficits of cranial nerves XI and XII are usually less embarrassing to the patient. It cannot be expected that function will recover in a nerve that was already compromised pre-operatively.

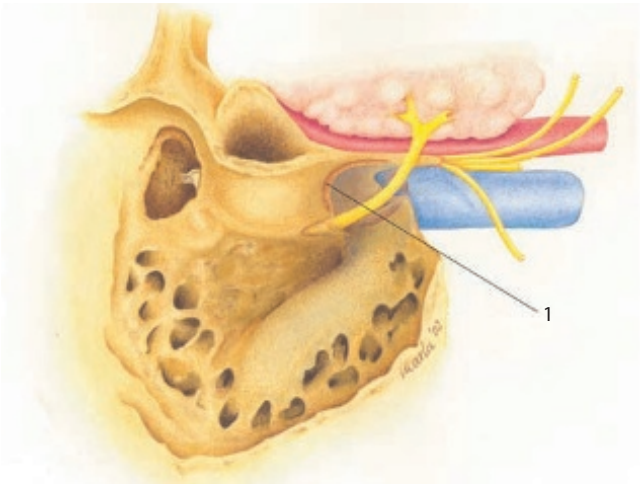


Figure 107.14 1, Right-sided schwannoma in the jugular foramen: localization primarily in the medial part. (See also **Figure 107.5**.)

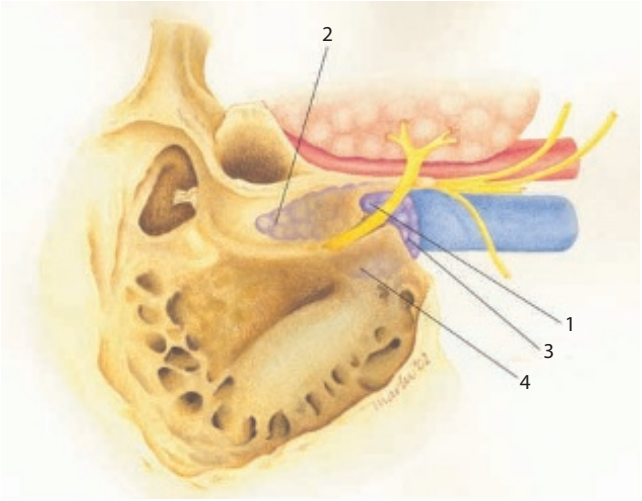


Figure 107.13 1, Right-sided paraganglioma arising from the jugular bulb; 2, extension usually takes place into the hypotympanum; 3, the jugular vein; 4, the sigmoid sinus. (See also **Figure 107.5**.)

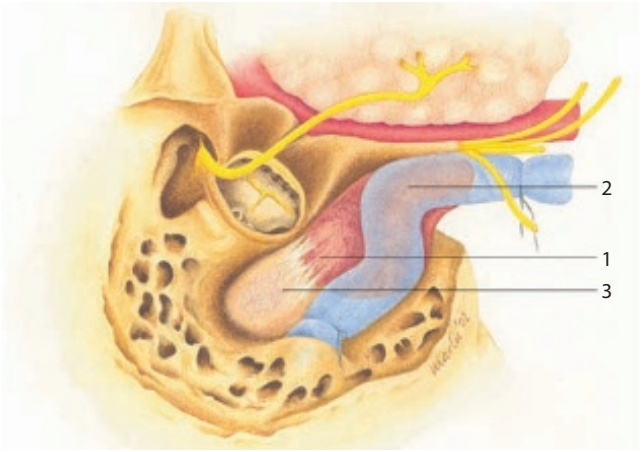


Figure 107.15 1, Right-sided meningioma arising intracranially; 2, extending into the jugular foramen; 3, the facial nerve rerouted and the dura of the posterior fossa exposed. (See also **Figure 107.5**.)

Eye protection is the first step in the care for patients with facial nerve palsy. Lower cranial nerve deficits result in speech and swallowing problems. A specialized multidisciplinary team is required to plan an adequate rehabilitation programme. Depending on the neurological status, a variety of patient-customized measures can be taken.

BEST CLINICAL PRACTICE

- ✓ An in-depth risk versus benefit analysis has to be carried out when deciding on the best management for jugular foramen lesions, in which the risk of progression of the lesion is weighed against the risks of treatment, including surgery.
- ✓ Planning of the treatment should be customized to the patient and to the nature and extension of the lesion. The choice is between radiotherapy stereotactic radiosurgery, microsurgery and a wait-and-see policy, or a combination of these.
- ✓ Only a minority of patients are best served by immediate surgical resection.
- ✓ Among the variety of surgical techniques, the lateral transtemporal approach has received the most attention and widest acceptance. This approach is mostly applied by otologist/head and neck surgeons, because it requires experience with microsurgery on the temporal bone.

FUTURE RESEARCH

- ➤ There are two major issues in the deficiencies of our current knowledge: the biological behaviour of the majority of the jugular foramen lesions and the value of different therapeutic strategies. The best treatment for many jugular foramen lesions is still the subject of controversy. In particular, there are uncertainties about the question whether proceeding to some type of (invasive) therapy is justified or not.
- ➤ There is a need for more knowledge on the biological behaviour of the most common pathologies in the jugular foramen, that is, paragangliomas, schwannomas and meningiomas, to facilitate stratification into those that require aggressive treatment and those that do not.
- ➤ The age threshold at which the long-term risks of radiation to a benign tumour outweigh the immediate risks of surgery remains unclear.
- ➤ The role of radiotherapy and stereotactic radiosurgery in the treatment of meningioma still has to be defined.

KEY POINTS

- The jugular foramen can be involved in a large number of pathological processes. Paragangliomas, schwannomas and meningiomas are by far the most common lesions found in the jugular foramen. All three are characterized by indolent biological behaviour in the majority of cases. However, in the long term, insidious progression may result in serious morbidity and even life-threatening situations.
- The anatomy of the jugular foramen is complex and due to its close proximity to nerves, arteries, veins, meninges, brain tissue and the cochleovestibular system, any treatment modality carries intrinsic risks, particularly surgical treatment.
- Even with regard to the most common lesions, there is no uniformity of opinion and no unequivocal guideline on the best therapeutic approach.
- None of the existing therapies are able to restore functions that have been lost due to the pathological process.
- All the surgical series in the literature describe a considerable risk of functional loss. In selected cases, however, post-operative morbidity is limited to mild inconveniences (e.g. some lower cranial nerve deficits or unilateral hearing loss).
- The skills and experience of the surgeon have a considerable influence on the operative result, while the surgical approach may also play an important role.

ACKNOWLEDGEMENTS

I would like to acknowledge the work of Professor Kees Graamans, who wrote this chapter for the previous edition of Scott-Brown, which was used as the basis for this chapter. I would also like to thank my colleague Professor Michael Gleeson for the time and effort he dedicated to sharing his knowledge of this complex field.

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CHAPTER 108

PETROUS APEX LESIONS

Michael Gleeson

SEARCH STRATEGY

Data in this chapter are mainly supported by personal experience and the relatively few papers on the subject that have appeared in journals and congress proceedings since 1985.

INTRODUCTION

The petrous apex remains a huge challenge as it is situated at the frontier between otology and neurosurgery. In other words, it is not within the comfort zone of most practising otologists or neurosurgeons. To make matters worse, disease within it or involving it is relatively uncommon, and so few have regular exposure to its access. Added to this is the fact that it contains two very important structures, the cochlea and the horizontal segment of the intra-temporal carotid artery. It also abuts the cavernous sinus anteriorly and the surgeon has to be familiar with the courses of the IVth, Vth, VIth and greater superficial petrosal nerves.

For some considerable time, the petrous apex remained an elusive and relatively silent part of the temporal bone. It was the occasional site of a spreading mastoid infection, signalled by excruciating pain and a VIth nerve palsy – Gradenigo's syndrome. Much less commonly, it was recognized as a potential site of congenital cholesteatoma. Modern imaging techniques have made today's otologist more aware of a wide range of abnormalities and disease processes that are found at this site. Computed tomography (CT) and magnetic resonance imaging (MRI) have given a better understanding of the natural history of many of these conditions and identified those that can be safely watched and those that need to be treated. In recent years surgical techniques to access this part of the skull base have been developed and the expertise to undertake this surgery is being acquired by those designated to work in skull base centres. In this chapter, the issues that surround the management of petrous apex lesions are summarized.

ANATOMY

Situated lateral and adjacent to the clivus, the petrous apex is that part of the temporal bone anterior to the internal auditory meatus that is wedged between the posterior border of the greater wing of the sphenoid and the basilar part of the occipital bones (**Figure 108.1**). The superior surface is part of the floor of the middle cranial fossa, while its posterior face marks the anterior part of the cerebellopontine angle. The two faces are separated by the tentorium, which is attached to the petrous ridge. Its borders and boundaries are marked by major blood

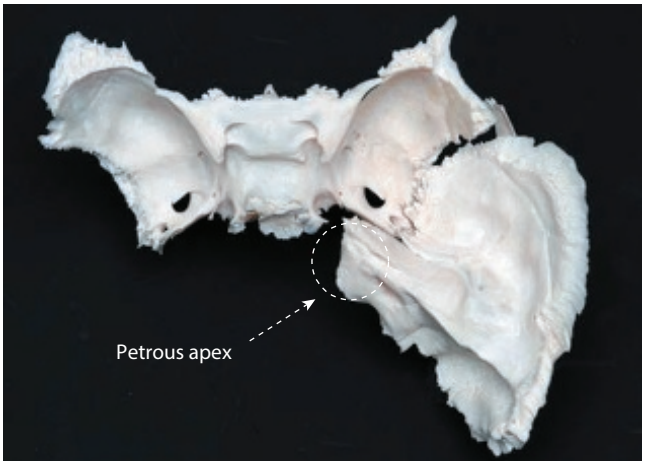


Figure 108.1 The petrous temporal and sphenoid bones. The apex is outlined to clarify its precise position.

vessels and structures, the superior and inferior petrosal sinuses above and below, and the horizontal segment of the internal carotid artery (ICA) and Eustachian tube laterally. Indeed, the apex forms the posterolateral boundary of the foramen lacerum. As an integral part of the petromastoid component of the temporal bone, the apex is preformed in cartilage. The trigeminal ganglion lies in a depression on its posteromedial aspect and the VIth nerve crosses its superior surface beneath the petro-sphenoid ligament. Like other parts of the temporal bone, the degree of pneumatization is variable. The peritubal area is frequently pneumatized, while the rest of the apex is not.

LESIONS AND THEIR PRESENTATION

Infection

As stated previously, in former times the most common disease process affecting the petrous apex was infection. The accumulation of pus or development of an osteitis may give rise to all or part of a triad of symptoms and signs that constitute Gradenigo's syndrome. The full triad of middle ear infection, deep-seated homo-lateral orbital or retro-orbital pain and a homo-lateral lateral rectus palsy may not be present, but will develop in the fullness of time if the infection is not controlled or drained.

Anatomical variants

Defects in the superior surface are occasionally seen and allow the meninges to prolapse into the apex to form a meningocele.

Cysts

Epidermoid cysts (congenital cholesteatoma) may develop in the petrous apex from sequestrated cell rests associated with Seessel's pocket. Mucosal cysts (giant petrous apex cysts) are also found in the apical part of the temporal bone and are thought to develop as a consequence of haemorrhage into the marrow spaces or isolation of a cell tract system with subsequent mucocoele formation. Mucosal cysts are generally found in well-pneumatized temporal bones. Inspection of the CT appearances of the contralateral bone can give some idea of what the state of pneumatization in the affected bone might have been before the development of the cyst. Both epidermoid and mucosal cysts develop over a long period of time, during which constant pressure on the horizontal segment of the ICA causes lateral displacement.

Unilateral hearing loss is the predominant presenting symptom associated with both of these cysts. Patients with cholesterol cysts often have a fluctuating, conductive loss presumably caused by interference with normal Eustachian tube function, while those patients with epidermoids are more likely to have a profound sensorineural deficit acquired in a slow and insidious fashion. Progressive facial weakness or palsy has always been considered the hallmark of epidermoid cysts. In contrast, facial weakness at presentation is uncommon in patients with cholesterol cysts. Regardless of the type of cyst, some patients who present with normal facial nerve function have experienced recurrent episodes of facial weakness or intermittent ipsilateral spasm in the past. Perhaps the most striking distinguishing feature is pain. A large number of patients with mucosal cysts describe a form of trigeminal neuralgia, generalized headache or otalgia and this is most uncommon in patients with epidermoid cysts.[1]

Tumours

Chordomas are derived from notochord remnants and are found in relation to the axial skeleton, most often in the sacrum and skull base. The estimated incidence is 0.5 per million. Both sexes are affected equally and most patients present in the fourth decade of life. Chordomas are slow-growing tumours and so patients often give a long protracted history that starts in a relatively benign fashion with headache or facial pain for which no cause has been found or suspected. Any symptoms are the result of pressure on cranial nerves or dural stretching. Those that develop in the clivus and petrous apex ultimately present with visual disturbance, diplopia, trigeminal deficits or neuralgia, hearing loss, voice disturbance or swallowing problems. These tumours are locally malignant and have a tendency to recur. A few, those with a relatively high proliferative index as assessed by Ki67 staining, are more likely to recur locally than others, often within one or two years of the original resection. Some have the potential to metastasize to regional lymph nodes. Patients with this form of aggressive tumour usually undergo multiple operations and eventually succumb to the disease.

Chondrosarcoma may also develop in the petrous apex, presumably from cartilaginous remnants associated with early development. The tumours are classified according to their mitotic activity and degree of differentiation. Most are low grade and as such have a very slow growth potential and long life expectancy. Like chordoma, with which they were often previously confused, chondrosarcoma produce their symptoms and signs by slow destruction of the temporal bone and its contents, dural stretching and pressure on cranial nerves. Eventually, they break through the cortex of the temporal bone and extend into the cerebellopontine angle, cavernous sinus, middle cranial fossa or into the neck. Those that extend into the cavernous sinus present with trigeminal deficits and diplopia, which is usually caused by an abducens nerve palsy. Chondrosarcomas that extend into the cerebellopontine angle cause trigeminal deficits and varying degrees of hearing loss, while those that break through the base of the skull into the neck are often relatively asymptomatic, possibly found when investigating an isolated hypoglossal palsy.

Meningiomas are the most common intracranial tumour and tend to develop around the venous sinuses. Within the temporal bone, they may develop from meningeal remnants trapped within the bone during development, but may also infiltrate the bone from an

extraosseous site. In the latter situation, they are usually part of an en-plaque tumour that covers a large part of the skull base. The adjacent bone is typically sclerotic as a result of induced osteoblastic activity. Despite their extent, trans-temporal and temporal meningiomas do little harm to the structures that they surround and encase. Growth is usually extremely slow and it may well be decades before any cranial nerve deficit becomes apparent. Some are visible as a mass in the middle ear cavity not dissimilar to, and frequently mistaken for, a glomus tumour.

Other tumours are found in the petrous apex. They are so uncommon that experience of them is largely anecdotal. Among these are plasmacytoma and histiocytosis. It should be remembered also that most of these tumours present in or after the fourth decade of life. For patients of this age, the most common bony tumour is a metastasis. A search for the primary should be undertaken if the scanning features are not characteristic of a defined entity. In the author's experience, renal cell and bronchial carcinomas have both presented in this way before the primary site became symptomatic.

INVESTIGATIONS

The main dilemma that faces the surgeon is the precise characterization of the apical lesion. Only once that is known can an appropriate management plan be devised. Fortunately, many of these tumours have specific characteristics that enable a confident diagnosis to be made from CT and MR images without resorting to open biopsy.[2] Nevertheless, there are occasions when open biopsy is the only option and the surgeon is left with the task of obtaining a diagnostic biopsy without compromising further therapy or inflicting unacceptable morbidity.

For most lesions, a combination of MR and CT imaging will determine the likely diagnosis. CT is pivotal as aggressive bone destruction is suggestive of a malignant process, whereas well-defined expansion is indicative of a benign process. T1-weighted images will distinguish between epidermoid and mucosal cysts. Epidermoid cysts give low signal on T1-weighted images, while mucosal cysts give high signal. Both types of cyst give high signal on T2-weighted images and produce a circumscribed area of bone destruction that can be detected by CT (**Figures 108.2** and **108.3**). High signal in the petrous apex without bone destruction is usually caused by either an effusion or marrow fat. The consistency or uniformity of the signal on T2-weighted images of mucosal cysts can be variable. This probably reflects the contents of the cyst, which may contain large quantities of semi-organized material.

The image characteristics of these cysts still confuse radiologists who are not familiar with the differential diagnosis and protocols necessary to establish their precise nature. Erroneous diagnoses have become more common since the advent of fast spin echo images that are used to screen patients with suspected cerebellopontine

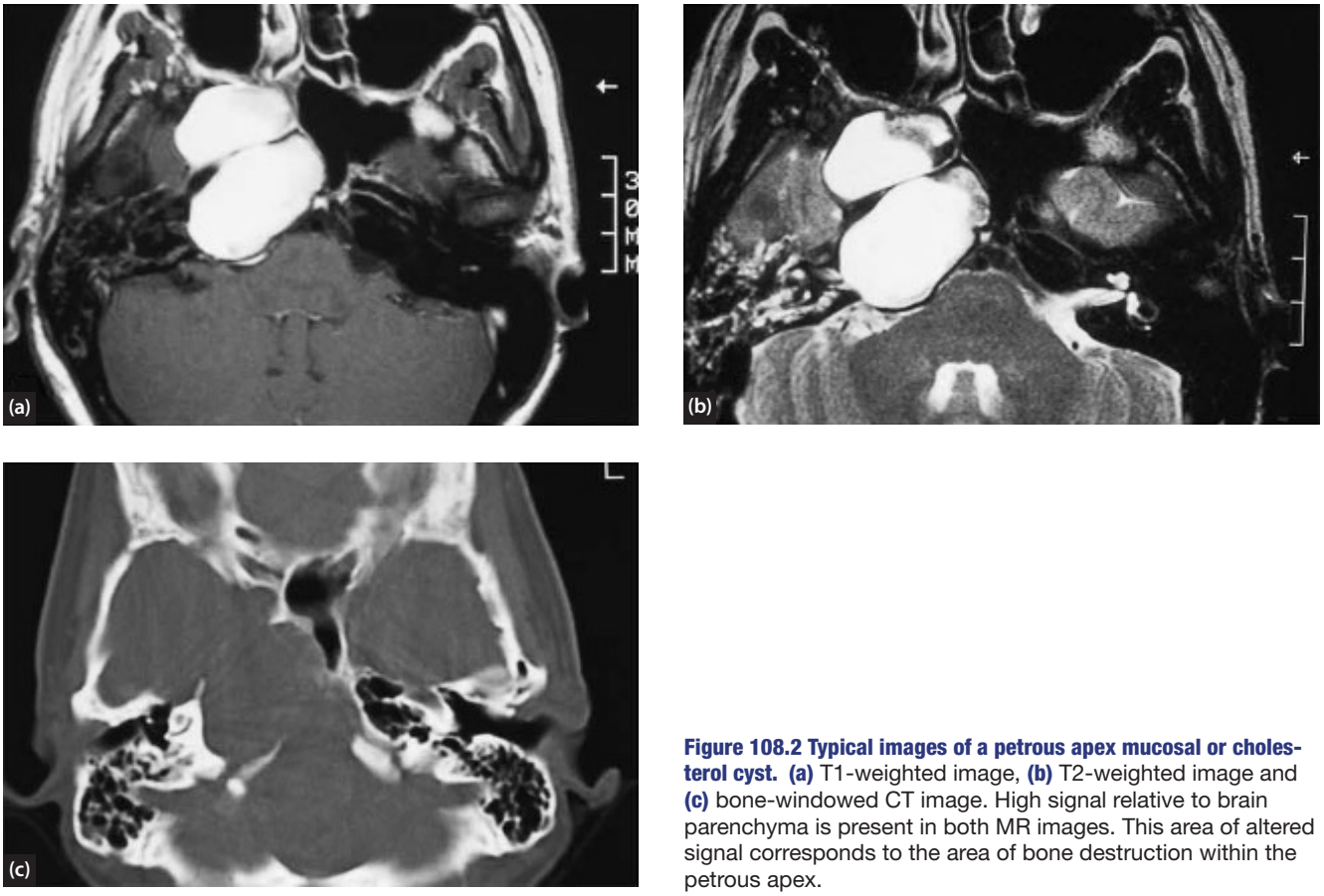
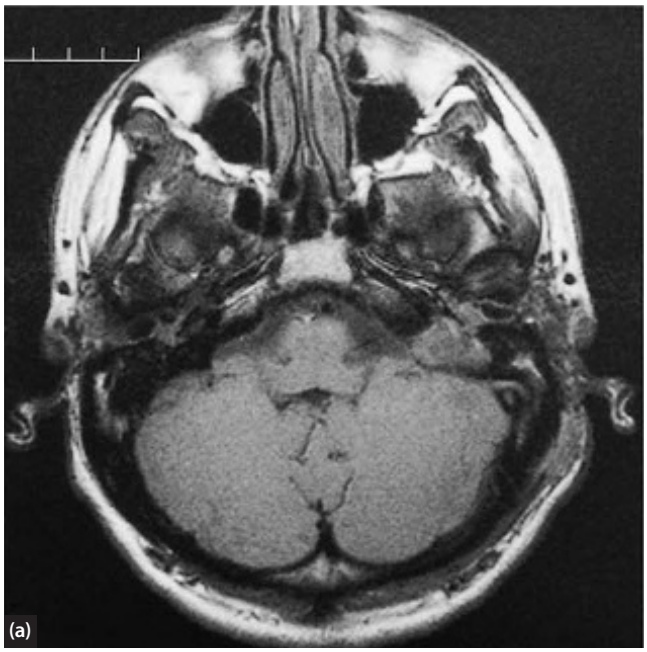
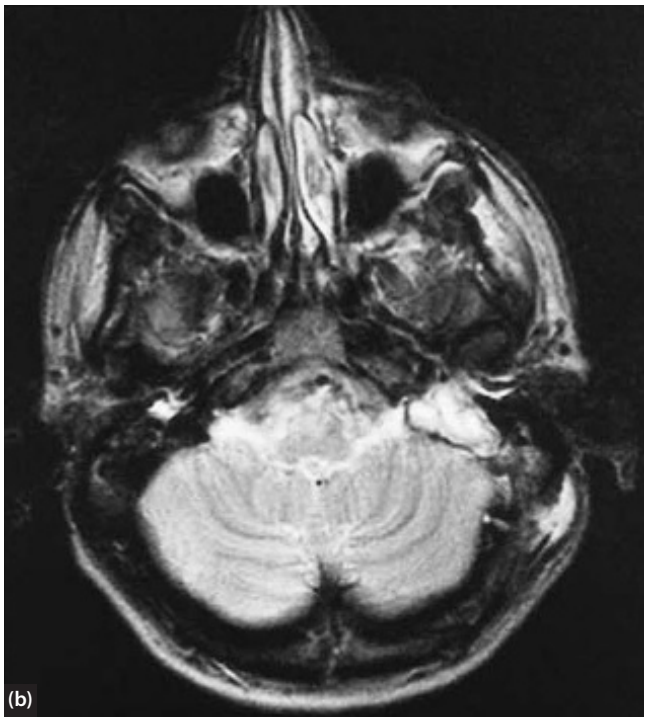


Figure 108.2 Typical images of a petrous apex mucosal or cholesterol cyst. (a) T1-weighted image, **(b)** T2-weighted image and **(c)** bone-windowed CT image. High signal relative to brain parenchyma is present in both MR images. This area of altered signal corresponds to the area of bone destruction within the petrous apex.





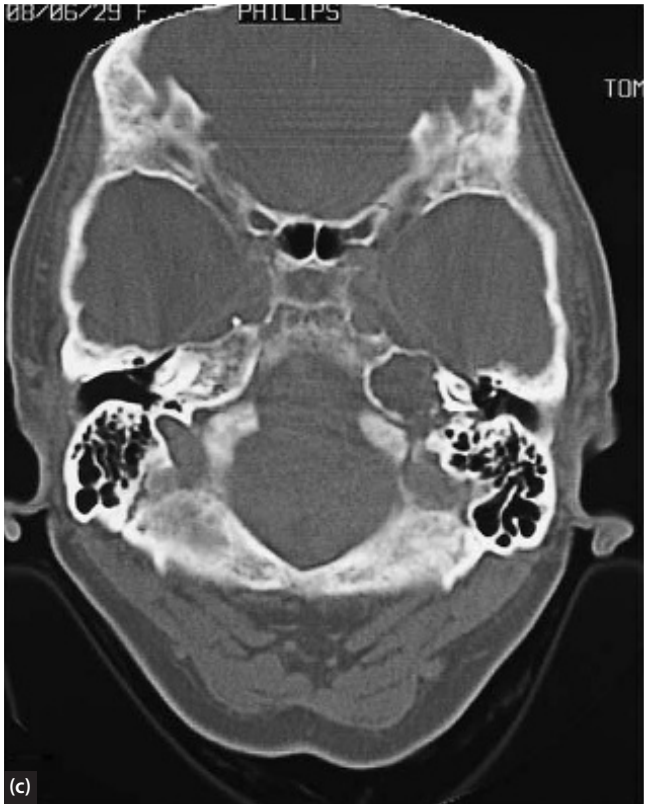
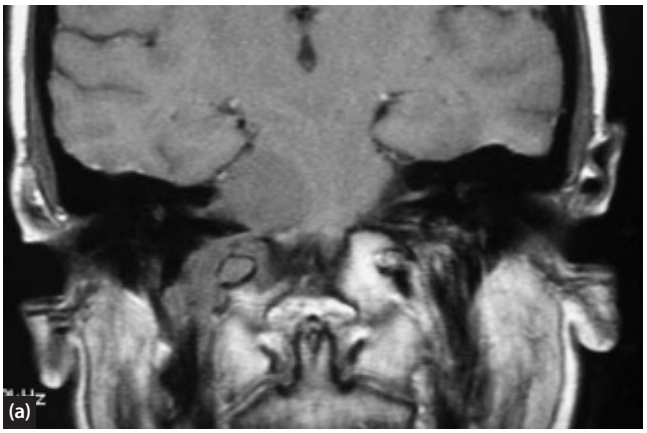


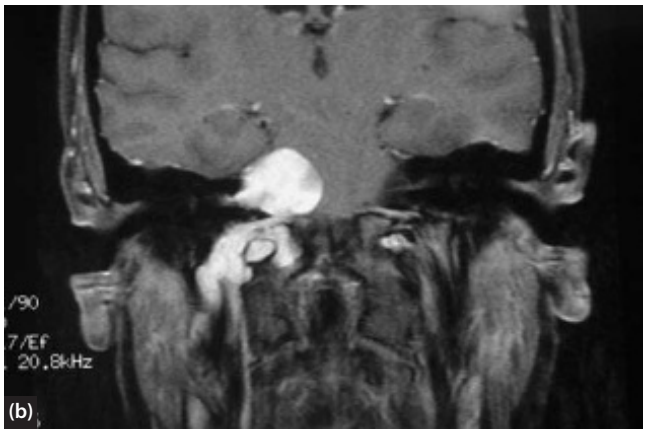
Figure 108.3 Characteristic features of left-sided, apical epidermoid cyst. (a) T1-weighted image with low signal from the petrous apex lesion; **(b)** T2-weighted image with high signal from the petrous apex lesion; **(c)** Bone-windowed CT scan showing well demarcated destruction of the left petrous apex indicative of a slow growing benign lesion.

angle tumours. These sequences do not suppress fat and cannot be used in isolation to make any comment about areas of high signal situated within the petrous apex. The diagnosis can only be made with confidence on the basis of T1, T2, inversion recovery sequences and diffusion weighted images.[3, 4]

Bone destruction with foci of calcification within it is typical of chondrosarcoma. Low or iso-intense with brain on T1-weighted images, high signal is obtained on both T2-weighted images and T1-weighted images enhanced with gadolinium (Figure 108.4).

It should be remembered that chordoma almost always arise in the midline, though a few have been described in the petroclival region. Spread from the midline into the petrous apex is common. Chordoma are generally non-homogenous on T1- and T2-weighted images and characteristically have a honeycomb structure on gadolinium-enhanced images.





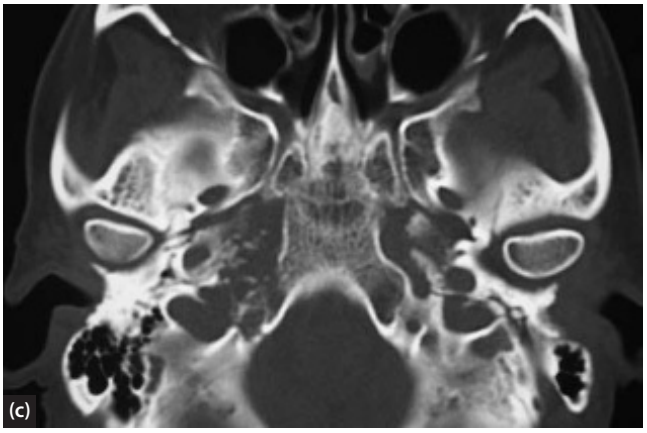
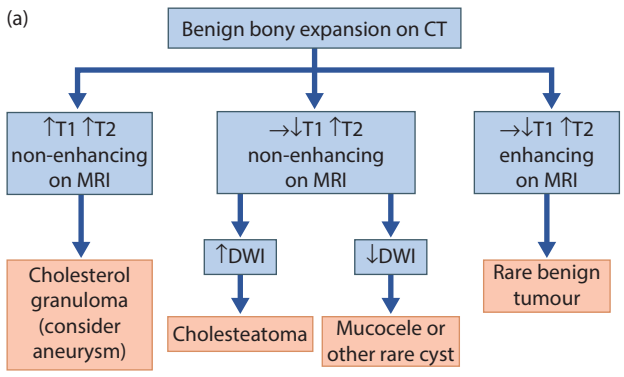


Figure 108.4 Chondrosarcoma of the right petrous apex that has spread into the cerebellopontine angle. **(a)** T1-weighted image, **(b)** gadolinium-enhanced T1-weighted image and **(c)** bone-windowed CT image of a chondrosarcoma that had spread into the cerebellopontine angle. The T1-weighted image shows low signal from the tumour, which becomes high with gadolinium enhancement. The CT scan shows foci of speckled calcification within the tumour that is characteristic of chondrosarcoma.



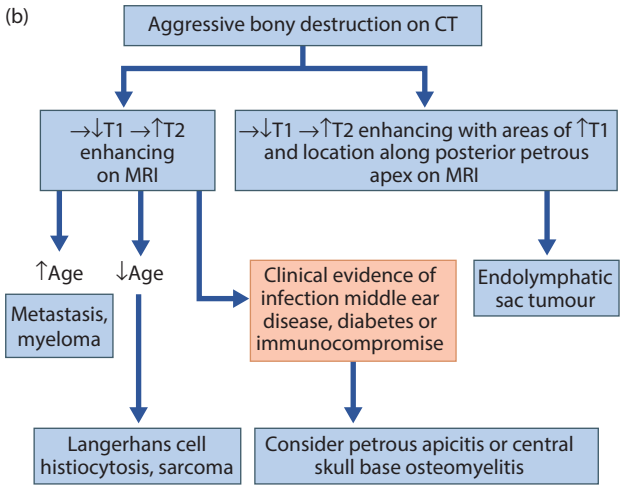


Figure 108.5 Differential diagnosis of petrous apex lesions. **(a)** Benign bony expansion on CT; **(b)** Aggressive bony destruction on CT.

MANAGEMENT

General guidance

The management of infection is dealt with elsewhere in the text (see Chapter 14, Acute otitis media in children). As stated earlier, many cysts and tumours develop over years or decades. A number are probably better observed rather than treated. Growth and its effects can be safely monitored by sequential scans and clinical examination. It is prudent to consider a number of factors before deciding what the optimal and most appropriate management should be for each and every patient. Factors such as the patient's health, their age and life expectancy, the severity of their symptoms and the nature of the cyst or tumour are of prime importance. Ipsi- and contralateral cochlear function must be considered in those where hearing on the side of the lesion might be lost. The temporal bone architecture, in particular the height of the jugular bulb and relationship of the cyst or tumour to the ICA, is also critical.

Epidermoid cysts and tumours can be resected or observed. A third option, drainage, is possible for cholesterol cysts. There is no doubt that for some patients no treatment whatsoever is indicated regardless of the nature of their petrous apex lesion. In general, these are the elderly who are relatively asymptomatic. Neural deficits are rarely reversed by surgery and, if sensorineural hearing loss and tinnitus are the only complaint, a strong case can be made for a policy of 'watchful waiting'. Patients with pain and incipient facial palsy must be considered differently. For them surgical intervention is probably the only solution and each case must be evaluated on its own merits. Figure 108.7 is a flow diagram to guide management of petrous apex cysts.

Approaches

DRAINAGE

The majority of cholesterol cysts can be decompressed by drainage into the mastoid or sphenoid sinuses.[5–7] In this way, serviceable hearing can be retained. The choice largely depends on the height of the jugular bulb when contemplating drainage into the mastoid or hypotympanum. In the first instance, access to the cyst is made through a channel drilled in the space above the bulb, inferior to the posterior semi-circular canal and medial to the facial nerve (Figure 108.8). At best, this measures 4–5 mm in diameter and in patients with high jugular bulbs may not be possible. Similarly, the infra-cochlear route exploits a tract of air cells that runs between the jugular bulb, basal turn of the cochlea and ICA. Again, in patients with large or high bulbs, this potential space may not exist.

The relationship of the ICA to the cyst and posterior wall of the sphenoid sinus are the determinant factors when considering an endoscopic trans-nasal approach. If the ICA is stretched over the anterior surface of the cyst or the posterior wall is too thick, safe or adequate access to the cyst is probably not possible and it would be wiser to explore an alternative option. Serviceable hearing can be maintained by these drainage procedures and this is their main attraction. Unfortunately, some cysts are loculated, others reaccumulate and become symptomatic, while a few become infected. Total resection is then the only alternative for these unfortunate patients.

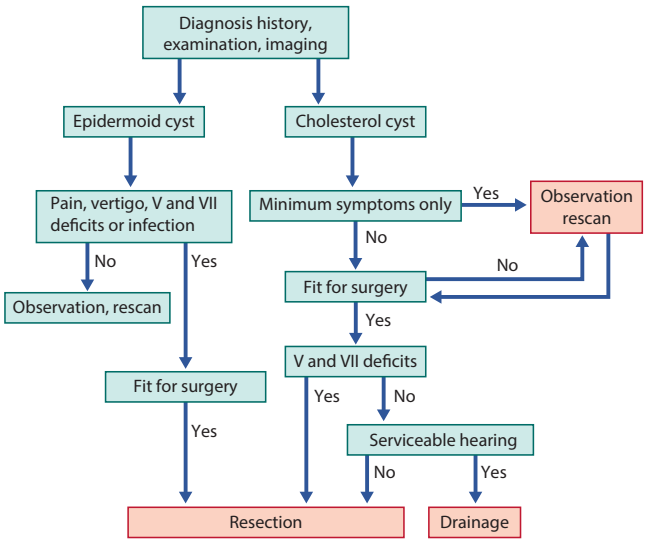


Figure 108.7 Management strategy of petrous apex epidermoid and mucosal cysts.

RESECTION

Drainage procedures are not an option for patients with epidermoids, tumours and cysts that have recurred, become infected or are incipiently inflicting a neural deficit that might be avoidable.

A number of approaches can be used to resect these lesions. Small epidermoids, cholesterol cysts and tumours can be accessed by a subtotal petrosectomy with removal of the cochlea or via the middle fossa. It is impossible to remove the lining of large cysts, epidermoids or tumours completely through these relatively narrow field techniques. For these, a wider exposure as provided by the Fisch type B infra-temporal fossa approach is necessary.[8] In this approach, following a blind sac closure of the external auditory canal, a subtotal petrosectomy is extended anteriorly by inferior displacement of the zygomatic arch, resection of the glenoid fossa of the temporomandibular joint and skeletonization of the vertical and horizontal segments of the intratemporal ICA. In this way, the ICA can be displaced and open access to the apex achieved (Figure 108.9).

The management of patients with chordoma and chondrosarcoma nearly always requires neurosurgical input.[9–12] Staged operations are the rule. For chondrosarcoma, it is probably best to remove disease in the cerebellopontine angle first. Tumour in the petrous bone can be removed at a second stage, after a suitable interval. Chondrosarcoma spreading into the cavernous sinus and sphenoid is probably best managed through a combination of a medial maxillectomy and orbitozygomatic approach. Proton beam therapy has proved successful in a large percentage of patients after radical debulking.[13] Low-grade chondrosarcomas progress very slowly indeed. After initial resection or subtotal resection, it is usually quite adequate to

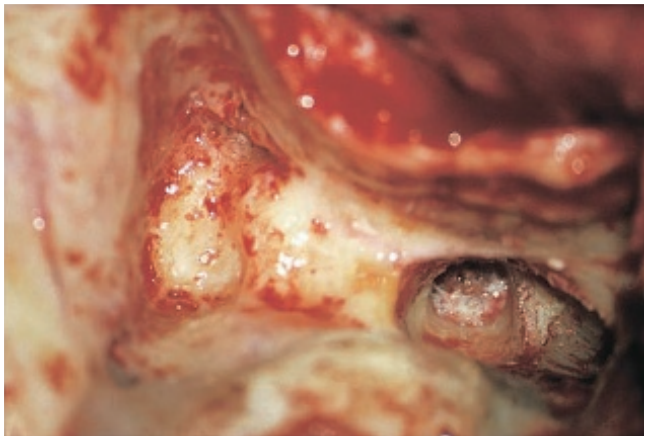


Figure 108.8 Infra-labyrinthine exposure for drainage of a petrous apex cyst. A channel has been developed beneath the fallopian canal, inferior to the posterior semi-circular canal and above the jugular bulb.

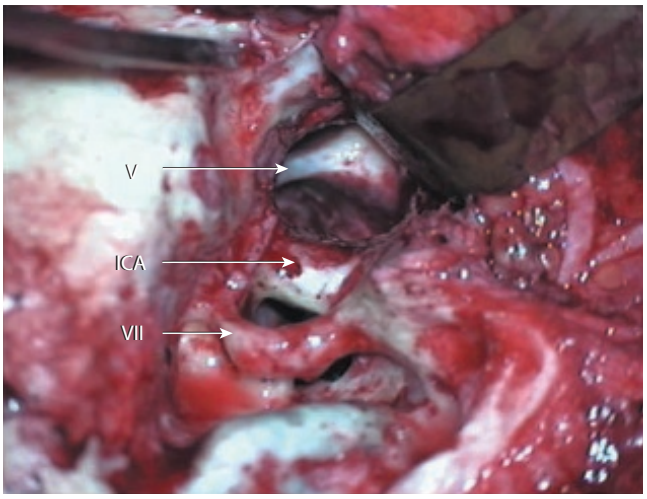


Figure 108.9 Exposure of the petrous apex by the Fisch type B approach. The facial nerve has been skeletonized in the mastoid segment and traced out into the parotid gland. The cochlea has been removed and the ICA exposed. The petrous apex is medial to the ICA and the mandibular nerve can be seen crossing the cavity.

observe clinically with interval scans. Further debulking procedures may become necessary.

Eccentric chordomas are extremely rare and chordoma in the petrous apex is far more commonly the result of spread from the clivus. It is then usually part of an extensive, multifocal tumour. Total eradication is rarely possible and even achieving a reasonable subtotal resection can be difficult. Proton beam therapy (PBT) does have a part to play in the management of this disease and has gained some popularity.[3] Figure 108.10 is a flow diagram that outlines current concepts of chordoma management.

Open cavity surgery is not an option for any of these patients. Leaving a patient with an open cavity after apex surgery is fraught with danger. Infected keratin tends to accumulate in the depths of these cavities and is difficult to remove by suction, as there is often a bottleneck between the deep and superficial portions of the cavities. Furthermore, large areas of exposed dura are usually present on the medial aspect of these cavities and so the risk of recurrent episodes of meningitis is ever present.

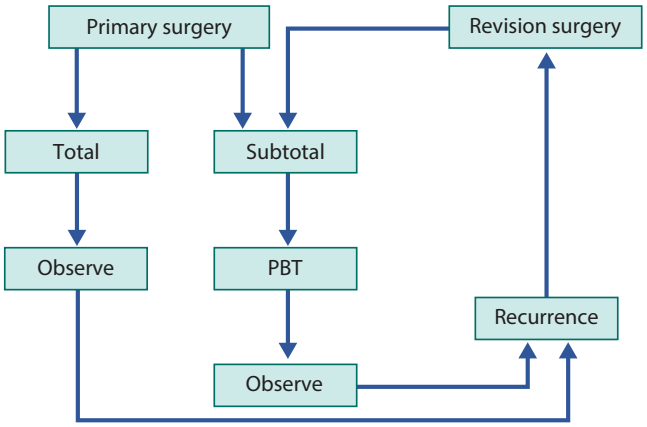


Figure 108.10 Management strategy for chordoma involving the central skull base. Redrawn with permission from Crockard et al.[9]

Complications

Drainage procedures may fail and few ever achieve permanent aeration of the cyst cavity. That the contents reaccumulate is disappointing but in itself is not an indication for further surgery. This is only indicated when the cyst becomes symptomatic.

Open access, trans-temporal access to the apex is always accompanied by a sensorineural hearing loss. This is inevitable and for most this is of no consequence as cochlear function has already been lost. Removal of the glenoid fossa has little impact on the patient and their ability to masticate. It can be reconstructed with a slip of temporalis muscle, which maintains the vertical height of the joint. Most patients experience a temporary occlusal derangement that resolves with the passage of time. Patients are usually able to eat what they like, but choose to eat hard foods on the other side. A temporary weakness of the forehead is acquired by some.

BEST CLINICAL PRACTICE

- ✓ The best exposure to the apex is afforded by the type B infratemporal fossa approach.
- ✓ Open cavity surgery should be avoided and is potentially dangerous. It leaves an inaccessible space medially that accumulates debris that inevitably becomes infected.

FUTURE RESEARCH

- ➤ Long-term outcome studies are required to determine the effect of surgical intervention on patients with low-grade chondrosarcoma, chordoma and cysts.

KEY POINTS

- Many petrous apex lesions have taken years, if not decades to develop. A large number can be managed conservatively by 'watchful waiting'.
- The diagnosis for most lesions can be made on the basis of appropriate CT and magnetic resonance imaging.
- In a middle-aged adult, always consider the possibility of a metastasis.

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CHAPTER 109

APPROACHES TO THE NASOPHARYNX AND EUSTACHIAN TUBE

Gunesh P. Rajan

SEARCH STRATEGY

Data in this chapter may be updated a Medline search using the keywords: anterior and lateral skull base approaches, extended endoscopic approaches, TORS, Eustachian tube, nasopharynx, outcome, focusing on technique, surgery and results.

INTRODUCTION

In this chapter we describe and discuss the indications for, and surgical access to, the Eustachian tube and the nasopharynx. The approaches we use nowadays are the distillation of the efforts made over the years by countless surgeons who have attempted to remove disease from this particularly challenging part of the skull base. Just the briefest consideration of the passage of the Eustachian tube from its origin in the hypotympanum across the lateral skull base, through the infra-temporal fossa to the nasopharynx gives some insight to the complexity of surgery in this region. Any surgical approach must give safe and wide exposure to achieve removal of disease minimizing the associated morbidity. The last decade has seen tremendous changes with the way we access the skull base; the extended transnasal endoscopic approaches have largely replaced the open procedures to the nasopharynx, midline and paramedian skull base, especially for all benign pathology and selected malignant disease. Recently, the emergence of transoral robotic surgery has again added new possibilities to what we can potentially do in the management of the midline skull base lesions. To do justice to these recent developments we have included the transnasal endoscopic approaches into this chapter. The detailed description of these approaches is provided by Snyderman and his colleagues in Volume 1, Chapter 116, Extended anterior skull base approaches.

What follows is a brief description of the established approaches to the nasopharynx and the Eustachian tube that have withstood the test of time. The strengths and weaknesses of each approach are identified. Each of these approaches can be used in isolation or in combination if necessary.[1–14]

As with various fields in surgery, the new technologies being introduced constantly challenge us surgeons to learn and incorporate new techniques into our surgical armamentarium. This in turn means that training of future skull base surgeons will also have to change with the aim of establishing the competence in open, endoscopic and perhaps robotic techniques. It must be remembered that every patient's needs are different and that treatment has to be planned to suit the individual patient and his/her disease. It should not be forgotten that for patients with a malignant pathology, the surgical resection is the only hope of cure or respite as other therapies are ineffective alone. As with all skull base surgery, a multidisciplinary team approach is essential, utilizing the skills of all the specialities involved.

CLASSIFICATION OF APPROACHES

The aim of the skull base techniques has been to gain maximal surgical exposure while minimizing brain retraction, aesthetic and functional handicaps as far as possible.

There is often more than one way to approach a lesion, each method offering something different. Several approaches to the Eustachian tube and nasopharynx have been described. Most are entirely extradural and extracranial, while a minority access the midline skull base by intracranial and intradural pathways. Numerous surgical variations of each approach have been described but most would agree that each variation can be listed under one of the three categories: the anterior approaches; the anterolateral approaches; or the lateral approaches.

PRE-OPERATIVE ASSESSMENT AND PREPARATION

It almost goes without saying that the evaluation of the stage of disease is absolutely vital. There is no point in subjecting a patient to a major intervention and its morbidities unless there is a reasonable prospect of eradicating their disease or reducing its bulk sufficiently to alter the course of disease. Most tumours in this part of the skull base are intimately involved with the internal carotid artery (ICA) and some displace or infiltrate the cavernous sinus. It is therefore imperative that the relationship of these structures to the tumour is known as precisely as possible and the consequences of damage to the ICA are fully assessed. Most patients will require computed tomography (CT), magnetic resonance angiography (MRA) and balloon occlusion tests. The introduction of neuronavigation has proven to be very useful in this context, enhancing surgical accuracy.

The larger disassemblies of the facial skeleton and the prevertebral skull base are better undertaken after a preliminary tracheostomy. The endoscopic techniques have simplified the sleeve resections of the nasopharynx and adjacent Eustachian tube segments. Dural resection or damage is not infrequent and the possibility of cerebrospinal fluid (CSF) leaks into the nasopharynx is ever present. The addition of a lumbar drainage helps manage the persisting CSF leak post-operatively along with adequate antibiotic coverage. While some patients may be able to take food orally relatively soon after surgery, those in whom extensive osteotomies have been undertaken will not. Another consideration is that the majority of patients with malignant disease will undergo post-operative radiotherapy. For this group of patients, oral feeding may be significantly delayed, therefore considering a pre-operative PEG-insertion.

ANTERIOR APPROACHES

Transnasal extended endoscopic approaches[1, 2]

INDICATIONS

- Tumours of the nasopharynx and anterior infratemporal fossa
- Juvenile neuroangioma
- Access to tumour extension into the clivus and craniocervical junction.

CONTRAINDICATIONS

- Malignant tumours with significant dural invasion and intracranial extension (these tumours can frequently be resected using a combined open–endoscopic approach to minimize morbidity)
- Malignant lesions that require a degree of lateral access, those that extend into the lateral parapharyngeal space, cavernous sinus, posterior infratemporal fossa and posterior peritubal space.

PRINCIPLES OF THE PROCEDURE

Most extended transnasal endoscopic approaches (EEAs) are done with two surgeons using the four-hands technique and the patient in a supine position. Depending on the location of the lesion, various modifications of the transnasal endoscopic routes provide a targeted access to the different midline and paramedian skull base lesions. The transnasal, transmaxillary route with removal of the posterior maxillary wall gives the most lateral trajectory to access the anterolateral infratemporal fossa, the addition of the transpterygoid access opens up the anterior infratemporal and the peritubal compartment, which can be extended posteriorly to access the foramen lacerum and petrous apex (**Figure 109.1**). The classic transnasal pathway after reduction of the vomer and posterior septum provides the workspace to address the nasopharynx and clival lesions.[2] The reconstruction after endoscopic

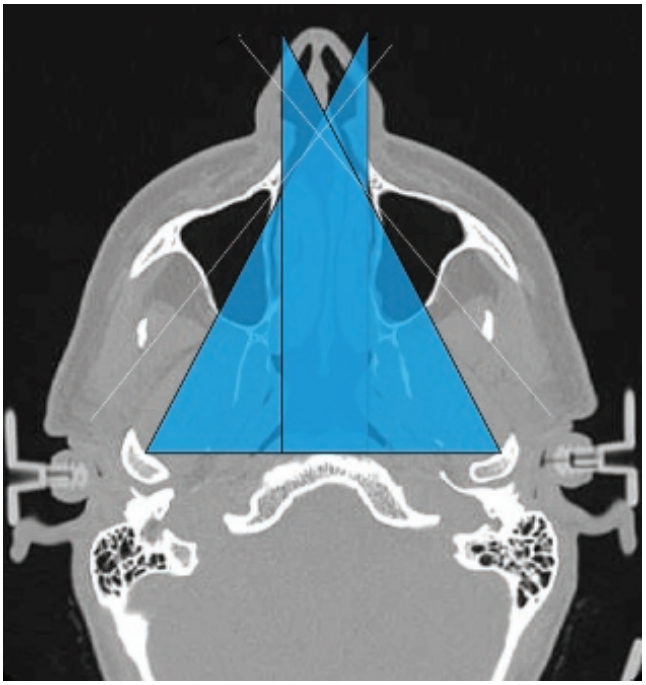

Figure 109.1 Trajectory for the endoscopic access to the anterior Eustachian Tube, peritubal space and medial infratemporal fossa (blue zone). The white lines indicate the lateral extent of the endoscopic access to the infratemporal fossa.

resections in the hostile environment of the nasopharynx and oropharynx in terms of the microbial fauna, saliva exposure and the frequent clearing movements poses a key challenge and is dealt with Volume 1, Chapter 116, Extended anterior skull base approaches. The introduction of the nasoseptal or Hadad flap has certainly simplified the reconstruction of local defects; reliable closure techniques for dural defects are constantly evolving to address this specific weakness of this treatment modality.[2]

ADVANTAGES AND DISADVANTAGES

The EEAs have revolutionized the surgical treatment of midline lesions of the skull base. With the improvement of the scope optics and HD technology, the visualization of the operation field is unparalleled. This together with the increasing portfolio of endoscopic instruments has resulted in the EEA largely replacing the open transoral and transpalatal procedures described below. The EEAs offer direct access and visualization of the pathology and allow for two surgeons to work simultaneously using the four-hands technique. Benign tumours with lateral extension into the parapharyngeal and infratemporal spaces can be accessed by these routes as in most cases the tumour extensions can be medialized into the working field.

KEY POINTS

- Advantages:
  - simple technique
  - direct approach
  - excellent visualization of the operating field.
- Two surgeon – four-hands technique.
- Limitations and drawbacks:
  - limited access to the lateral infratemporal and parapharyngeal space
  - difficult assessment of the margin status in malignant disease
  - limited data of reconstruction outcomes
  - dural reconstruction challenging
  - risk of meningitis due to wound contamination.

Transoral robotic surgery[3]

INDICATIONS

- Benign tumours of the nasopharynx and parapharyngeal space
- Indications are evolving.

CONTRAINDICATIONS

- Malignant tumours with lateral extension, significant dural invasion and intracranial extension (these tumours can frequently be resected using a combined open–endoscopic approach to minimize morbidity)
- Malignant lesions that require a degree of lateral access, those that extend into the lateral parapharyngeal space, cavernous sinus, posterior infratemporal fossa and posterior peritubal space.

PRINCIPLES OF THE PROCEDURE

Transoral robotic surgery (TORS) is the most recent surgical modality that has the potential to further improve surgery in this anatomic region. The range of the 'wrist'-mediated instrument mobility combined with the 3D-visualization of the operating field opens up a new paradigm in our specialty as exemplified by its utility in the management of HPV-positive oropharyngeal tumours. The upcoming introduction of the single-port version of the DaVinci system offers hope in the management of midline lesions. Current limitations of the technology are related to lack of haptic feedback and the lack of instrumentation to remove and remodel bone effectively.

There are several case series reporting excellent outcomes for resections of parapharyngeal tumours with no reported cases of 'first-bite syndrome' so far, which occurs frequently after transcervical removal of these tumours. More recently, salvage surgery for small recurrences of nasopharyngeal carcinoma in the posterior nasopharyneal wall has been performed using TORS with promising outcomes.[3] Detailed descriptions of TORS will be found in Volume 3, Chapter 22, Transoral laser microsurgery.

ADVANTAGES AND DISADVANTAGES

At this stage it is too early to talk about the pros and cons of TORS to address pathologies in the nasopharynx or peritubal space. More clinical data are required to provide any objective interpretation of its utility.

KEY POINTS

- Advantages:
  - direct approach
  - unparalleled instrument dexterity and mobility
  - HD 3D-visualization of the operating field.
- Limitations and drawbacks:
  - high set-up costs
  - utility and indications yet to be defined
  - current case series report on confined lesions of the posterior nasopharyngeal wall and benign tumours of the parapharyngeal space
  - clinical outcomes data evolving.

Transoral and transpalatine approaches[4, 15, 16]

INDICATIONS

- Malignant tumours of the posterior nasopharyngeal wall that are no larger than 2 cm
- Access to tumour extension into the clivus and craniocervical junction.[13, 15, 16]

CONTRAINDICATIONS

- Malignant nasopharyngeal tumours > 2 cm
- Tumours with significant dural invasion and intracranial extension

- Lesions that require a degree of lateral access, those that extend into the parapharyngeal space, cavernous sinus, infratemporal fossa and peritubal space.

PROCEDURE

The patient is placed in the supine position with their head extended as much as possible. Mayfield clamp fixation may be required if neuronavigation is employed or if it is anticipated the cranio-cervical junction might become unstable. There is no doubt that access is easier with the patient's head in a horseshoe rest that permits intraoperative manipulation of the head but this is rarely possible. A preliminary tracheostomy is established so that an unobstructed view of the oropharynx is obtained and to secure the airway post-operatively, as most patients will develop significant lingual and oropharyngeal oedema. Lumbar CSF drainage is inserted if the dura is to be opened. As this approach provides relatively narrow access through a long working distance, appropriate retracting instrumentation is crucial if sufficient exposure is to be obtained. Most surgeons opt for the Crockard wide field retractors and dissecting instruments that have been specially designed for this purpose.

After insertion of the mouth gag and retraction of the oral cavity, the soft and hard palate are infiltrated with 1:200000 adrenaline. The soft palate is split to one side of the midline. The hard palate mucosa is incised along the ipsilateral junction of the hard and soft palate within 5 mm of the maxillary dentition. This mucosal incision is extended along the palatal aspect of the alveolar ridge up to the level of the first molar and then taken in an arc across the palate to the opposite side (**Figure 109.2a**). A mucoperiosteal flap is elevated exposing the bony hard palate. The greater palatine neurovascular bundle is coagulated and divided. Exposure of the nasopharynx is increased by dissection of the muscular insertions of the soft palate from the hard palate. Great care must be taken to maintain the integrity of the remaining greater palatine vascular pedicle while doing this (**Figure 109.2b**). A self-retaining retractor is then inserted to keep the two halves of the soft palate out of the field.

Dissection through the posterior nasopharyngeal wall gives access to the lower clivus. If the lesion extends towards the sphenoid floor or the upper clivus the operative field must be enlarged. In some cases this can be achieved by removal of some palatal vomerine bone. In others, it will be necessary to perform a Le Fort I osteotomy and then split the palate in the midline, displacing each maxilla laterally. This latter approach, known as an 'open door maxillotomy', can offer unrivalled exposure of the entire clivus and cranio cervical junction.

A suitable mucosal flap is raised, hinged either laterally or inferiorly. The length of this flap varies according to the extent of the lesion being removed. The larger the flap, the better the chance of being able to approximate it at the end of the procedure (**Figure 109.2c**). If the lesion is submucosal, it is usually unnecessary to split the prevertebral fascia. But, if it is necessary to access the clivus, the prevertebral fascia and muscles have to be opened and this is best undertaken in the midline. The most helpful anatomical landmark is the anterior arch of the atlas, which is easily palpable. The narrow field afforded by this approach is insufficient for an *en bloc* resection of most tumours, so resection is usually performed in a piecemeal fashion.

Apart from very small dural tears or defects that can be plugged with muscle, primary watertight closure is virtually impossible; however, the advent of new dural sealing materials might alter this condition. The dead space created by tumour resection can be filled with autograft soft tissue secured in place by fibrin glue. It is best covered by pedicled local mucosal or mucoperichondrial flaps raised from the nasal septum and rotated into place. As much as possible prevertebral fascia, musculature and pharyngeal mucosa are reapproximated. The soft palate is readapted, preferably through a three-layered closure. In this way, the chance of an oro-nasal fistula developing is minimized (**Figure 109.2d**). If the maxilla has been split, bone plates are applied for fixation. Removal of the tracheostomy is determined by the clinical progress of the patient in terms of swallowing and resolution of oedema.

ADVANTAGES AND DISADVANTAGES

With the emergence of the EEAs the role of the transoral approaches has slipped into the background. There is much to commend the transoral approaches as they are relatively simple and straightforward to perform. They offer direct access to the lesion and, as a consequence, the surgeon is unlikely to inadvertently stray off target. Inadequacies of exposure can be resolved by local extensions in a stepwise fashion. On the other hand, a covering tracheostomy is required in most cases, the working distance is relatively long and this brings with it difficulties for the surgeon in terms of instrumentation, manipulation and visibility. Tumours with extension laterally into the parapharyngeal and infratemporal spaces cannot be accessed by these routes. Similarly, it is essential that the patient has good mouth opening otherwise a mandibulotomy might become necessary. The repair of the palate can be difficult and, despite every effort, fistulae develop in up to 40% of patients.

KEY POINTS

- Advantages:
  - simple technique
  - direct approach.
- Extendable through the LeFort I-palatal split approach.[13, 17]
- Limitations and drawbacks:
  - tracheostomy requirement
  - narrow working field and long working distance
  - possible palatal dehiscence and oronasal fistula as late complication in 30–40%
  - patients with trismus or impaired jaw opening require transmandibular approach
  - no access laterally to the parapharyngeal and infratemporal spaces
  - risk of meningitis due to wound contamination.

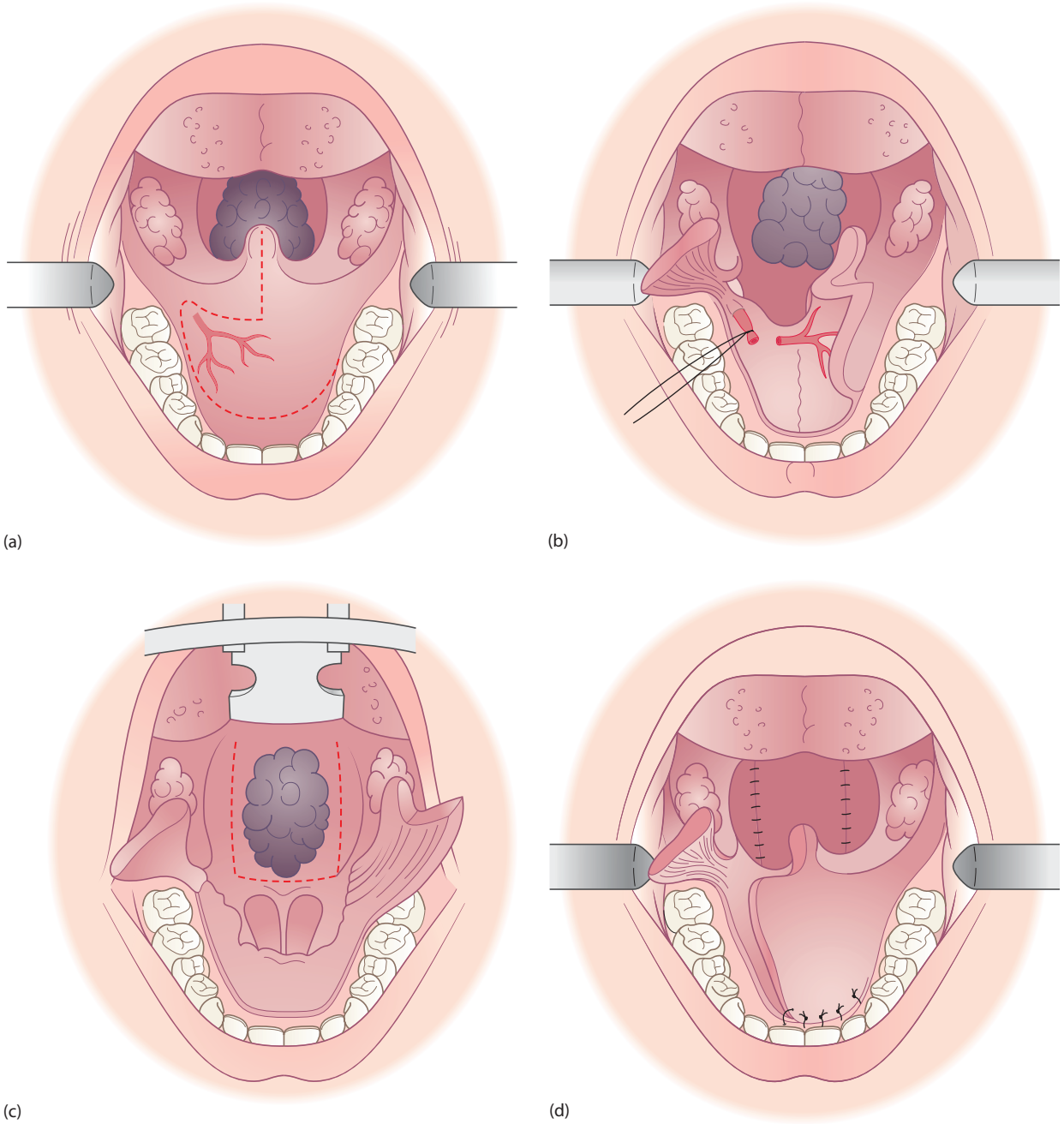

Figure 109.2 Transoral-transpalatinal approach. Redrawn from original illustrations by Margrit Pirker.

Transmandibular-transcervical approach[17, 18]

INDICATIONS

- Nasopharyngeal tumours extending into the anterior infra-temporal fossa.[15, 18]

CONTRAINDICATIONS

- Dural invasion (>2 cm²) and intracranial involvement
- Invasion of the parasellar and posterior infra-temporal region.

PROCEDURE

The patient is placed in the supine position and a tracheostomy established. An extended submandibular incision is made about 4 cm below the mandible from the mastoid tip posteriorly to rise anteriorly and split the lip (Figure 109.3a). The platysma is divided and the dissection directed beneath the submandibular gland. The tendons of the digastric and stylohyoid muscles can be released from their hyoid attachment and reflected superiorly along with the submandibular gland. This aids exposure of the mandible (Figure 109.3b). The great vessels in the carotid sheath are then identified together

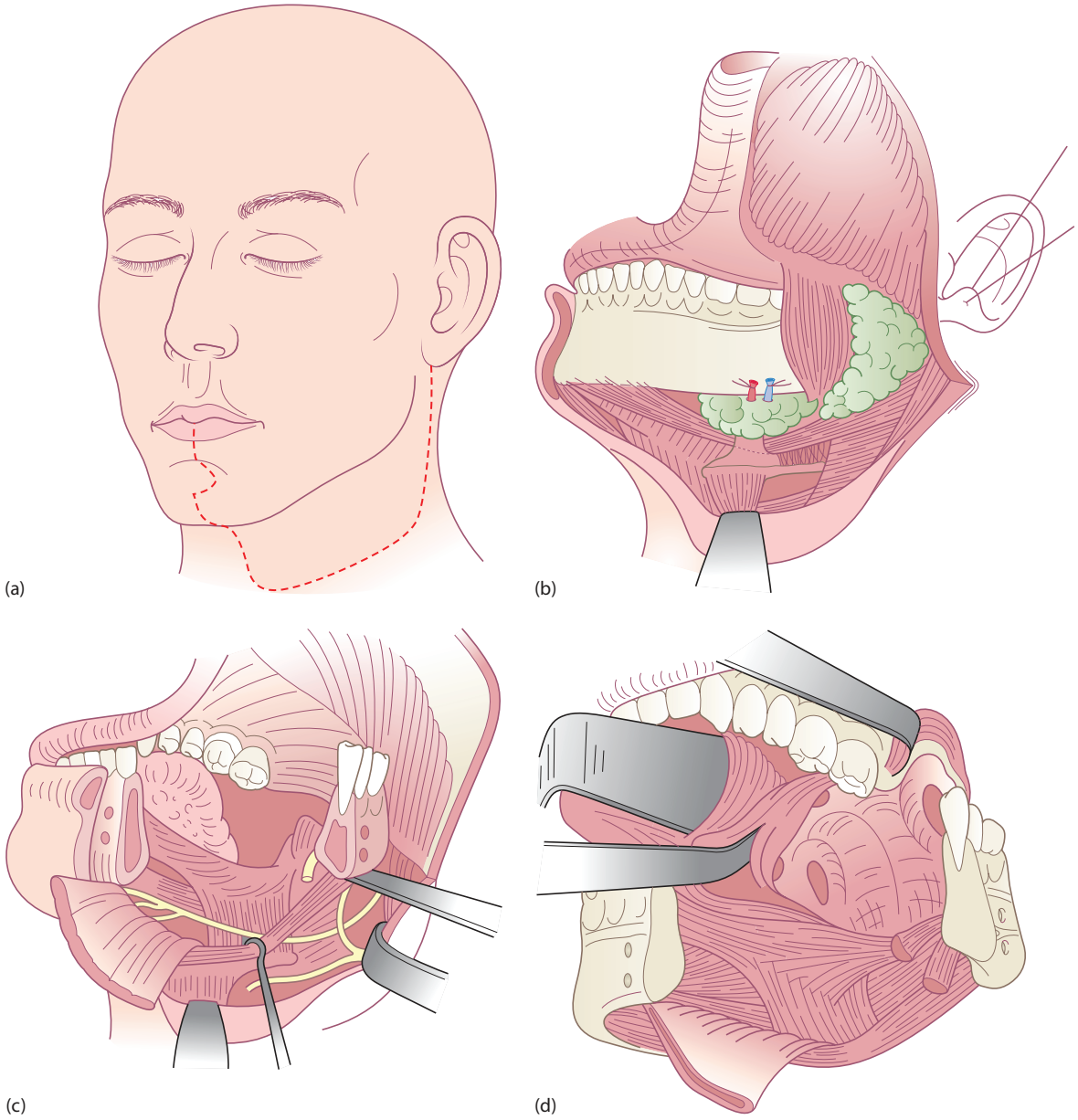

Figure 109.3 Transmandibular-transcervical approach. Redrawn from original illustrations by Margrit Pirker.

with the adjacent cranial nerves. The internal and external carotid arteries are dissected free and followed as close as possible to the skull base. A median mandibular osteotomy is performed after prefitting of mini-plates. Obviously the precise site of the mandibulotomy will be determined by the state of patient's dentition. In patients with poor dental health it is preferable to select an edentulous area (Figure 109.3c).

Dissection then proceeds across the floor of the mouth toward the parapharyngeal space. The tongue is retracted to the opposite side, the mucosa incised, mylohyoid muscle divided together with the anterior belly of the digastric muscle The lingual and hypoglossal nerves are identified and preserved (Figure 109.3c). During this stage of the approach the mandible can be steadily retracted laterally allowing entry into the parapharyngeal space which can then become continuous between the mouth and neck. Additional lateral retraction of the mandible is achieved by ligation of the external carotid artery distal to the lingual artery. By this manoeuvre access to the nasopharyngeal part of the parapharyngeal space and the anterolateral infratemporal fossa is gained (Figure 109.3d). If access to a midline lesion is required the incision is extended upward towards the hard palate and pterygoid plates ending about 1 cm medial to the gingival margin. A hemi-palatal flap is created, thereby producing an 'oropharyngeal sleeve'. Further blunt dissection lateral to and behind the superior and middle constrictor muscles produces a surgical working space (Figure 109.3d). Additional posterolateral division of the styloid musculature and glossopharyngeal nerve together with superior dissection along the retropharyngeal–prevertebral plane

allows release and retraction of the oropharynx to the contralateral side and widening of the retropharyngeal space. The precise position of the ICA should then be established and the tensor and levator muscle of the soft palate sectioned. With this, the pharyngeal and cartilaginous part of the Eustachian tube becomes accessible. Further exposure of the posterior nasopharyngeal wall can be obtained by dividing the tube and releasing the nasopharynx from the skull base at level of the pharyngeal tubercle. In this way, the whole of the pharyngeal sleeve can be displaced to the opposite side and the central skull base is exposed. Further enlargement of the operative field is achieved by removing the posterior portion of the hard palate thus widening access to nasopharynx, choanae and upper sphenoid body.

The intracranial extent of the lesion determines the amount of skull base that needs to be removed. However, if the lesion reaches the posterior aspect of the infratemporal fossa, combination with a lateral approaches may be required to allow *en bloc* resection.

Surgical closure begins with a watertight reconstruction of any dural defects. Smaller defects (< 4 cm²) can be sealed with fascial or pericranial flaps, while larger defects require musculo-fascial or microvascular free flaps. The remaining pharyngeal sleeve is reattached to the pre-spinal muscles at the skull base; exact realignment of the pharynx is achieved by suturing the Eustachian tube around an intratubal splint. The palatal muscles are reapproximated and the mucoperiosteal palatal flap is repositioned and the mucosa sutured. A palatal splint is recommended by some to encourage adherence of the flap to the hard palate. The floor of the mouth is reconstructed with resorbable sutures and the mandible fixed with the pre-fitted miniplates. A large suction drain is placed along the carotid sheath exiting though a separate stab incision in the lower neck. Finally, the lower lip is closed in three layers, taking care to achieve precise approximation of the vermilion border.

The patient should be fed by nasogastric tube for the first week, following which oral alimentation can begin. Removal of the tracheostomy tube is performed after 24 hours of uneventful plugging of the tracheostomy tube. Subsequent build-up of oral feeds is monitored by the speech pathologists.

KEY POINTS

- Advantages:
  - good access to the epipharynx, the parapharyngeal and anterior infratemporal space
  - direct approach
  - good vascular control.
- Limitations and drawbacks:
  - potential infection hazard through oral contamination
  - possible mandibular non-union
  - prolonged need for tracheostomy
  - restoration of normal or adequate swallowing often significantly delayed (mean 7 weeks)
  - temporary PEG frequently required.

ANTEROLATERAL APPROACHES

Maxillary swing technique[19]

INDICATIONS

- Nasopharyngeal tumours with limited extension into the anterior infra-temporal region.

CONTRAINDICATIONS

- Lesions involving the petrous ICA
- Lesions extending into to the petrous apex, parasellar and/or posterior infratemporal region (combination with lateral approach required).

PROCEDURE

The patient is intubated and placed in a supine position and draped. A Weber–Ferguson–Longmire incision is made, extending laterally onto the zygoma (**Figure 109.4a**). The vertical incision limb goes through the upper lip and is continued between the central incisors and onto the hard palate. After reaching the border of the hard and soft palate the incision is curved laterally to run behind the maxillary tuberosity. The facial incision is made through the subcutaneous, muscular and periosteal layers. Gentle, minimal elevation of these tissues exposes the planned osteotomy line (**Figure 109.4b**). The osteotomy is started by separating the zygoma from the maxilla, moving medially along the infraorbital rim until the frontal process is divided from the anterior maxillary wall. Then the medial maxillary wall is separated from the midline nasal complex in an antero-posterior fashion. The posterior wall is released without direct vision using an osteotome inserted through the antrum. The palatal bone is incised and a midline osteotomy fashioned. Finally, the pterygoid plates are separated from maxillary tuberosity by using a curved osteotome (**Figure 109.4c**). The entire maxilla can be swung laterally attached to the cheek flap and the masseter muscle (**Figure 109.4d**). The epipharynx is widely exposed including the cartilaginous Eustachian tubes of both sides, thus allowing *en bloc* resection of confined pathologies in this region.

After the resection has been completed, an ipsilateral turbinectomy provides useful tissue for a free graft that can placed on exposed bone in the epipharynx. Nasal packing keeps the graft in place. Closure is achieved by returning the maxilla to its anatomical position and fixation to the zygoma and contralateral maxilla with miniplates. Exact alveolar ridge alignment can be facilitated by using a pre-operatively fashioned dental splint. The facial and intra-oral incisions are closed in layers. If cartilaginous portions of the Eustachian tube were resected, a grommet should be placed on the affected side in order to prevent a chronic middle ear effusion.

Oral feeding is usually started after 72 hours. Any non-resorbable nasal packs should be removed on the 7th post-operative day and the dental plate after about a month or when all the mucosal wounds have healed.

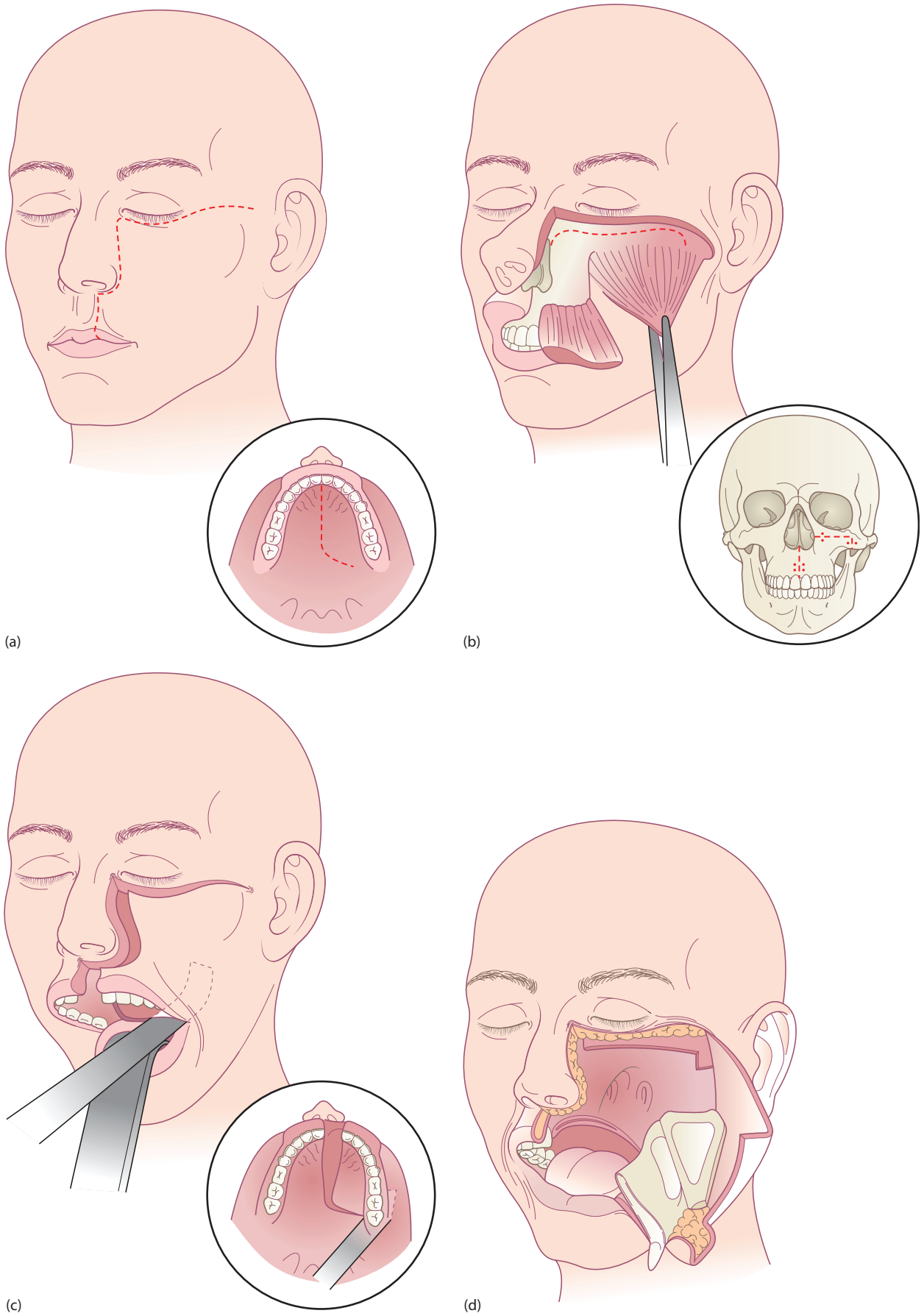

Figure 109.4 Maxillary swing approach. Redrawn from original illustrations by Margrit Pirker.

KEY POINTS

- Advantages:
  - simple technique
  - wide exposure
  - good cosmetic and functional results.
- Limitations and drawbacks:
  - limited parapharyngeal and infratemporal exposure
  - lack of vascular control
  - post-operative trismus
  - necrosis of the maxilla in some cases.

LATERAL APPROACHES

Infra-temporal approach type C[20–22]

INDICATIONS

- Infratemporal fossa tumours that extend into the temporal bone with involvement of the epipharynx
- juvenile angiofibroma Class III b–IV (Fisch)
- nasopharyngeal carcinoma.

If the lesion does not extend to the vertical portion of the petrous ICA, a variation of this approach, the preauricular Type D approach, can be used, thus avoiding blind sac closure and subtotal petrosectomy.

CONTRAINDICATIONS

- Advanced disease with extension into the sella, contralateral middle fossa or anterior skull base.

PROCEDURE

A postauricular C-shaped incision is made that extends superiorly into the temporal region and inferiorly into the neck (Figure 109.5a). The temporalis muscle, mastoid and zygoma are exposed. A periosteal flap is elevated and the external auditory canal is transsected and closed as a blind sac. The pinna and skin flap are reflected anteriorly. As a precaution, the neck is dissected so that control of the carotid and jugular vessels can be achieved. The main trunk of the facial nerve is identified together with its frontal branch so that the zygomatic arch can be exposed and divided anterior to the temporomandibular joint and again just behind the orbital rim without damaging the frontal branch. The zygomatic arch is reflected inferiorly attached to masseter muscle (Figure 109.5b). The temporalis muscle and fascia is elevated from the temporal fossa and reflected inferiorly to expose the superolateral quadrant of the infra-temporal fossa.

A subtotal petrosectomy is undertaken, skeletonizing the sigmoid sinus, ICA and middle fossa dura with preservation of the labyrinth and removal of all vestiges of skin. The temporomandibular joint capsule is exposed followed by excision of the articular disc and subsequent inferior displacement of the mandibular condyle. Additional space can be established by release of the sphenomandibular and stylomandibular ligament. The glenoid fossa is resected to give extensive exposure to infratemporal fossa and this can be enlarged further by division of the mandibular nerve and middle meningeal artery (Figure 109.5c). Access to the anterior third of the Eustachian tube and nasopharynx can be achieved by removal of the pterygoid process with its lateral and medial plates and dissection along the tube. The nasopharyngeal cavity is entered through incision of the pharyngobasilar membrane and nasopharyngeal mucosa.

After completion of the resection, closure of the nasopharynx is accomplished by rotating some of the temporalis muscle into the defect. Alternatively a bulky free flap such as the latissimus dorsi-flap can be used. The temporomandibular joint is reconstructed by interposing temporalis muscle between the condyle of the mandible and the middle fossa dura. The skin and subcutaneous tissue are closed in layers, after drain placement in the infratemporal fossa.

Normal oral feeding can be started on the first post-operative day.

KEY POINTS

- Advantages:
  - wide access to infratemporal, parasellar and temporal region
  - direct approach
  - short working distance.
- Limitations and drawbacks:
  - temporary post-operative trismus and malocclusion
  - hypaesthesia of the lower half of the face and ipsilateral tongue (V3)
  - permanent post-operative conductive hearing loss
  - temporary frontal facial paresis in 30%.

COMBINED APPROACHES

Subtemporal-preauricular infratemporal fossa approach[23]

INDICATIONS

- Large tumours (T4) of the infratemporal space extending into the nasopharynx, the cavernous sinus and the middle cranial fossa.

CONTRAINDICATIONS

- Bilateral involvement of the ICA
- Bilateral involvement of the optic chiasm[24]
- Lesions that extend into the posterior cranial fossa for which a combination with a retrosigmoid or transotic approach is required.

PROCEDURE

A preliminary tracheostomy is performed if resection of the naso-and/or oropharynx is anticipated. The ipsilateral scalp, face, neck, lower abdomen and thigh are prepared and draped. An extended Blair incision is made (Figure 109.6a) and a cervico-facial flap raised. The facial nerve trunk is identified and its major branches

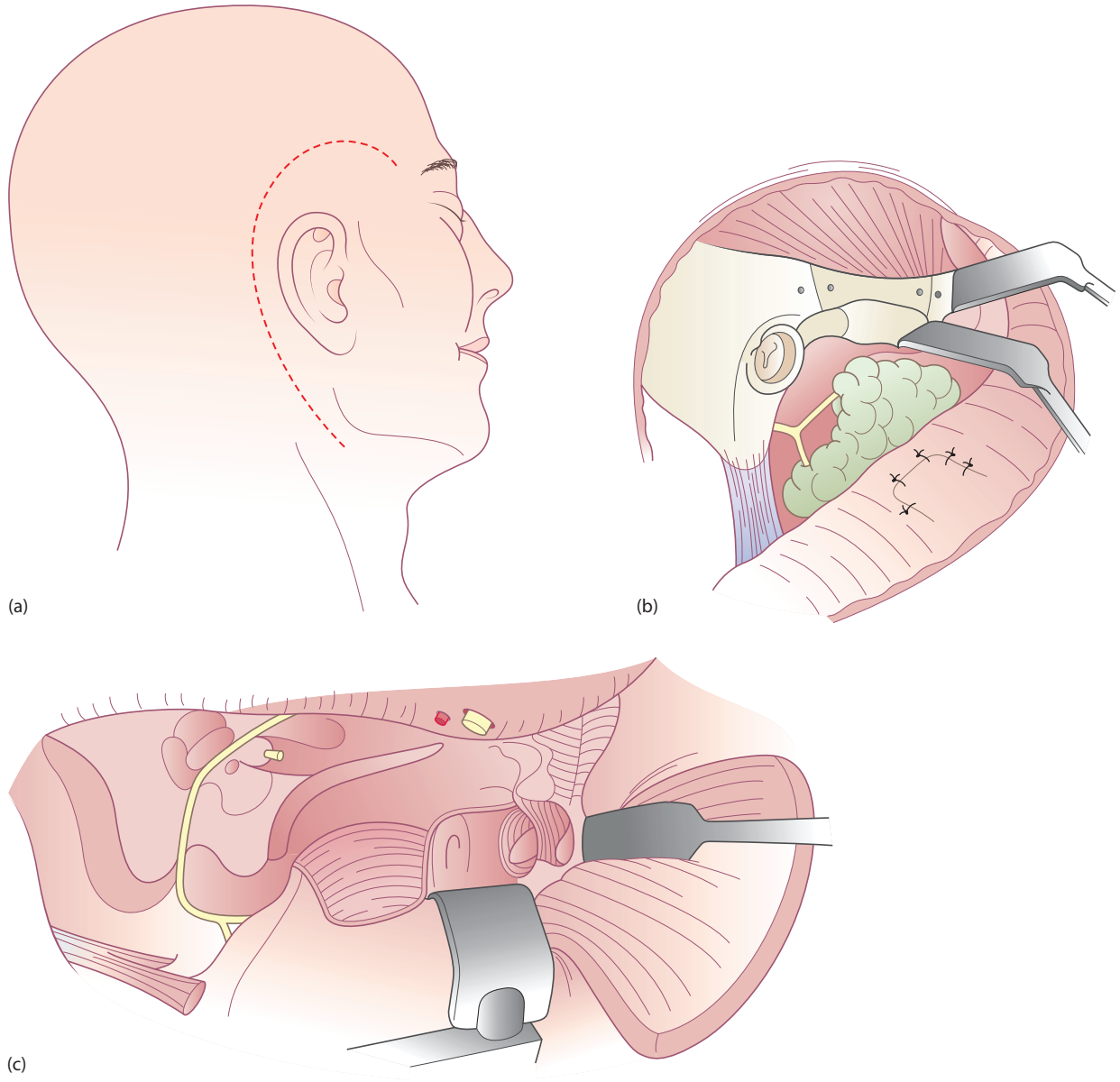

Figure 109.5 Infratemporal approach Type C. Redrawn from original illustrations by Margrit Pirker.

are dissected peripherally. The parotid gland is elevated from the masseteric fascia, the superficial temporal vessels are ligated and the temporalis muscle is elevated from the temporal squama. Osteotomies of the zygomatic arch (Figure 109.6b) permit inferior reflection of the temporalis muscle. A fronto-temporal craniotomy is then fashioned that includes the root of the zygomatic arch, glenoid fossa and the floor of the middle fossa lateral to the foramen spinosum and ovale, extending anteriorly to the pterion (Figure 109.6c).

Using a microscope, further medial dissection elevates the dura to expose the arcuate eminence, greater superficial petrosal nerve, middle meningeal artery and the mandibular nerve (V3). The middle meningeal artery is ligated and divided while the V3 can be retracted if it is not invaded by the lesion. Through this exposure, lesions around the middle third of the Eustachian tube can be addressed. Removal of more bone medial to the glenoid fossa and antero-medially along the greater wing of the sphenoid gives further access to the anterior Eustachian tube and pterygopalatine fossa. Selective removal of the pterygoid process allows access not only to the anterior third and pharyngeal ostium of the Eustachian tube but also to the posterolateral aspect of the nasopharynx. Further dissection along the pharyngobasilar membrane exposes the entire nasopharyngeal soft tissue sleeve allowing circumferential resection. If the lesion extends to the cavernous and petrous ICA, the Eustachian tube is removed completely, which gives access to the horizontal and vertical petrous segments of the ICA. Unroofing the horizontal segment of the ICA exposes the floor of the cavernous sinus. Further exposure of the inferior and medial border of the cavernous ICA is be attained by removal of the pterygoid root and the lateral walls of the sphenoid

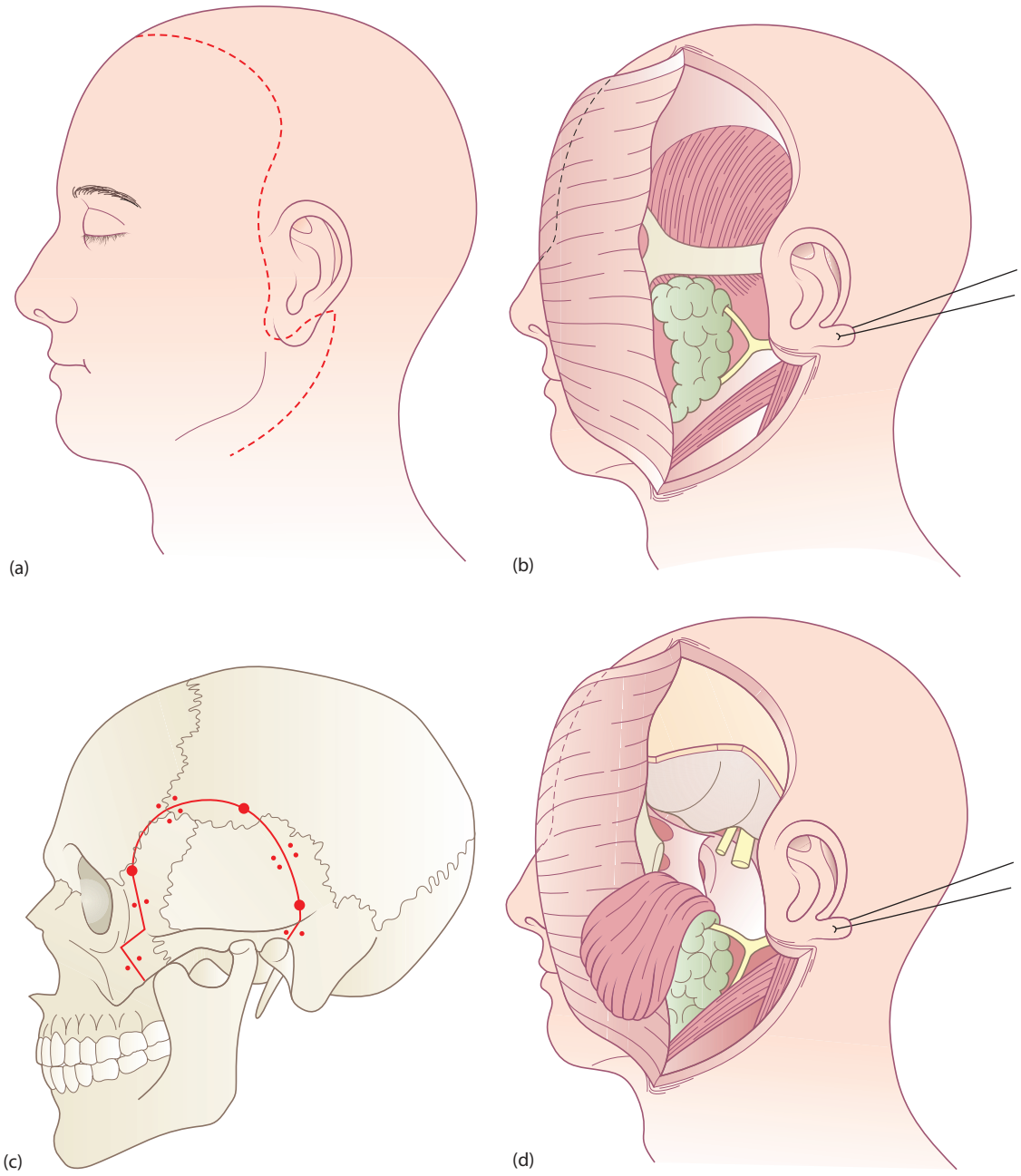

Figure 109.6 Subtemporal preauricular approach. Redrawn from original illustrations by Margrit Pirker.

body; this, however, requires transaction of the maxillary nerve (Figure 109.6d).

After removal of the tumour, dural defects can be repaired with pericranial regional flaps or with autologous fascial grafts such as temporalis fascia or fascia lata. The craniectomy bone flap is replaced and fixed with miniplates. If the defect cavity communicates directly with the nasopharynx, paranasal sinuses or skin, the exposed dura and the major vessel must be sealed off and protected by vascularized musculofascial flaps such as the radial forearm, anterior thigh or latissimus dorsi flap. Simple, passive wound drains are placed and skin closure completed.

Oral feeding can start on the first post-operative day.

KEY POINTS

- Advantages:
  - interdisciplinary approach
  - wide exposure of the infratemporal region, the petrous and cavernous segments of the internal carotid and the cavernous sinus.
  - good access for reconstruction.
- Limitations and drawbacks:
  - craniotomy required
  - CSF drainage required
  - high incidence of post-operative CSF leakage (15–20%)
  - insufficient exposure of the posterior petrous bone and otic capsule.

Facial translocation[24, 25]

INDICATIONS

- Extensive tumours (T4) of the anterior and middle skull base extending into the orbit, paranasal sinus and posterior cranial fossa with intracranial involvement.

CONTRAINDICATIONS

- Bilateral involvement of the ICA
- Bilateral involvement of the optic chiasm.[24]

PROCEDURE

The patient lies supine with the head turned 30–40 degrees to the contralateral side and positioned in an open head rest or Mayfield clamp. The ipsilateral scalp, face, neck, lower abdomen and thigh are prepared and draped. A modified Weber–Ferguson incision is made in order to create a wide cheek flap pedicled on the facial and inferior labial vessels (**Figure 109.7a**). The cheek flap includes the lateral third of the upper lip, the entire cheek soft tissue including the maxillary periosteum, lower lid, facial nerve and the parotid gland. The incision starts from the philtrum of the lip and is continued along the nasal silhouette. It then passes horizontally transsecting the medial canthus, follows the fornix of the inferior eyelid dividing the conjunctiva and the lateral canthus. It then joins the preauricular incision. By necessity, the frontal branches of the facial nerve are transsected and tagged for later reconstructive neurorrhaphy. The soft tissues of the cheek

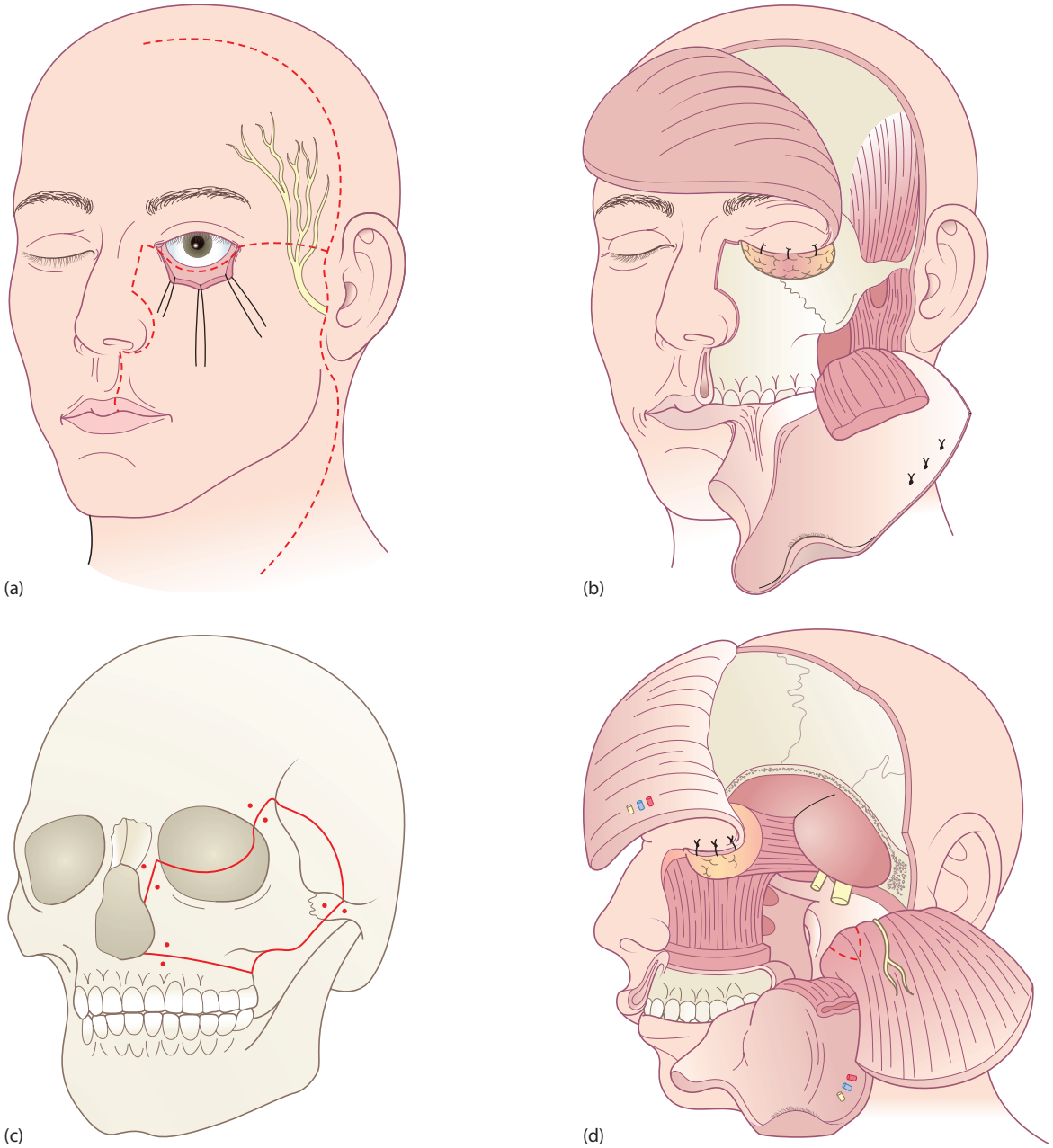

Figure 109.7 Facial translocation approach. Redrawn from original illustrations by Margrit Pirker.

are elevated from the facial skeleton and in doing so the infraorbital nerve is transsected and the masseter muscle is divided just below the zygomatic arch. A bicoronal incision is then made that meets the lateral extension of the previous transfacial incision. This allows elevation of the soft tissues from the temporal muscle and frontal bone thus creating a fronto-temporal scalp flap (**Figure 109.7b**). The latter is reflected towards the midline, while the cheek flap along with transsected masseter muscle are reflected inferiorly to the level of the hard palate. This manoeuvre requires division of the upper lip and extension of the lip incision along the gingivolabial sulcus as far as the last molar tooth (**Figure 109.7b**).

An orbito-maxillo-zygomatic free bone flap is created. Osteotomies pass through the frontozygomatic and temporozygomatic sutures laterally, inferiorly through the maxilla at the level of the nasal floor parallel to the hard palate to reach the pterygopalatine fossa; medially through the orbit in line with the inferior part of the lacrimal fossa and the tip of the inferior orbital fissure; laterally it is continued along the lateral orbital wall to join the transected frontozygomatic suture (**Figure 109.7c**). The posterior wall of the maxilla is freed from the pterygoid plates with a chisel. A subperiosteal osteotomy of the coronoid process and mandibular neck allows the temporal muscle and fascia to be mobilized from the temporal fossa and reflected inferiorly along with the mandible. This gives access to the nasopharynx, the pterygoid process, anterior surface of the sphenoid as well as the infratemporal fossa (**Figure 109.7d**). Further removal of the pterygoid processes and muscles exposes the lateral wall of the nasopharynx and foramen rotundum with the maxillary nerve. If even more access is required, it can be achieved by removal of bone from any of the exposed surfaces and by doing this the entire infratemporal, petroclival and cavernoclival borders can be visualized (**Figure 109.7d**).

Reconstruction follows the previously described steps, starting with watertight sealing of the dura with bulky microvascular free flaps (e.g. rectus abdominis, latissimus dorsi), which also eliminate the dead space and provide a well vascularized barrier between the dura and the nasopharyngeal mucosa. The free bone flaps are replaced and fixed with mini-plates. The cheek flap is realigned and the medial and lateral canthal ligaments reattached with stents being placed in the lacrimal duct. Finally, the frontal branches of the facial nerve are reanastamosed and the skin soft tissue closed in layers. Nasal packings are introduced to prevent obliteration of the nasal airway by encroachment of the reconstructive tissue in the operative defect.

Nasogastric feeding is necessary for a few days but oral alimentation can begin during the first week. Any non-resorbable nasal packs are removed on the eighth day and the lacrimal stents are left in place for 3 weeks.

KEY POINTS

- Careful patient selection and regular unit exposure are crucial for successful outcomes.
- A multidisciplinary management is mandatory.
- The detailed assessment and knowledge about the biology of pathology is the key for approach selection.
- An individually tailored approach decreases morbidity. This can frequently be achieved by a combining an endoscopic with a limited open approach.
- The endoscopic extended approaches have largely replaced the open approaches to benign lesions of the epipharynx and Eustachian tube.
- Swallow and hearing rehabilitation are key factors for quality of life.

FUTURE RESEARCH

Over the last few decades the development of multidisciplinary skull base approaches has rendered previously 'inoperable' lesions operable with minimal peri-and post-operative morbidity. The diseases managed by these approaches are not common and there are few centres with a large experience or with long-term results that would bear any form of analysis.

Improvements in the future may be achieved by:

- the expanding use of endoscopic approaches and procedures and the evolving endoscopic technology, thus further reducing post-operative morbidity and hospitalization length and improving functional outcomes
- TORS for the skull base
- new bone surgery and modelling tools
- new navigational techniques
- new dural repair techniques and products
- establishment of validated, defined indications for the established approaches
- multi-centre case-controlled or cohort studies for the most common skull base pathologies using skull base registries
- employment and evaluation of alternative or adjuvant therapies such as targeted immunotherapy, chemotherapy or Gamma Knife in an attempt to increase local tumour control.

KEY POINTS

- Advantages:
  - direct wide exposure of the anterior and middle cranial base
  - good access for reconstructions
  - radical resection of extensive tumours possible.
- Limitations and drawbacks:
  - complex multi-step surgical technique
  - craniotomy required
  - CSF drainage required
  - reconstruction and tubing of nasolacrimal system required
  - temporary or permanent palsy of the frontal branches of the facial nerve[24]
  - increased risk of post-operative osteonecrosis.

ACKNOWLEDGEMENTS

We would like to thank Margrit Pirker for bringing our intra-operative views onto paper and thus creating the essential illustrations for this chapter.

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CHAPTER 110

TUMOURS OF THE TEMPORAL BONE

Marcus Atlas, Noweed Ahmad and Peter O'Sullivan

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: external auditory canal, middle ear, temporal bone and skull base neoplasm. More specific searches were made on glandular tumours, adenoma, carcinoid tumour, endolymphatic sac tumours, inverted papilloma, haemangioma, haemangiopericytoma, osteoma, chordoma, chondrosarcoma, rhabdomyosarcoma and Langerhans cell histiocytosis, focusing on their presentation, diagnosis and management.

INTRODUCTION

The most common tumours that develop in the temporal bone, glomus tumours and squamous cell carcinomas of the external auditory canal, are discussed in greater detail elsewhere in the text (see Chapter 115, Squamous cell carcinoma of the temporal bone and Chapter 107, Jugular foramen lesions and their management). This chapter is devoted to those tumours that are less common and about which relatively little is known. Some surgeons may never encounter any of these during their career.

There are two key aims of this chapter: first, to provide sufficient information for surgeons so that these uncommon conditions can be suspected at an early stage; second, to provide an overview of what is considered best practice for managing these rare entities.

All three embryonic primordial layers contribute to the normal structure of the temporal bone and, therefore, the spectrum of neoplasms that can develop within it is vast. The difference in growth rate of these tumours, in addition to their sites of origin, account for the varied presentations of these rare tumours. To complicate matters further, initially some may mimic other more common conditions such as cholesteatoma, Wegener's granulomatosis or fibrous dysplasia. Furthermore, the complex anatomical relationships of the temporal bone can make the management of tumours in this region particularly challenging.

RISK FACTORS FOR THE DEVELOPMENT OF TEMPORAL BONE TUMOURS

Genetic

To date, more than 200 mutations of the *NF2* gene have been identified (located on the long arm of chromosome 22–22q12.2). Three separate genes have been identified that are pathogenically linked to hereditary paraganglioma (on chromosome 11q23). An association has also been demonstrated between Von Hippel–Lindau (VHL) disease and endolymphatic sac tumours, the gene for VHL having been identified on chromosome 3p25. The molecular genetics of temporal bone tumours will almost certainly play a key role in the understanding and management of some temporal bone tumours in the future.[1–2]

Radiation

Ionizing radiation has been implicated in the aetiology of temporal bone tumours. Cahan et al.[3] established criteria

that needed to be fulfilled in order to make the diagnosis of radiation-induced sarcoma in bone. Some 50 years later, Lustig et al.[4] defined similar criteria for radiation-induced temporal bone tumours as follows:

- The second neoplasm must develop in the irradiated field.
- A latent period of at least several years must elapse between radiation exposure and the development of a second primary.
- The previous condition must show histological, radiographic and microscopic evidence of neoplasia.
- The second tumour must be of a different histological type from that previously irradiated.

Radiation-induced tumours of the temporal bone are rare, but there are reports in the literature of tumours, such as squamous cell carcinoma, fibrosarcoma and osteosarcoma, which fulfil the above criteria. These tumours are aggressive and tend to metastasize early. Treatment is difficult and management of reported cases has included surgical resection, chemotherapy and adjuvant radiotherapy. Reported outcomes are generally poor with 22–32% of patients surviving 2 years and a 5-year survival of 11–32%.[4]

Chronic suppurative otitis media and papillomatosis

Despite the fact that very few patients with chronic suppurative otitis media (CSOM) develop carcinoma of the temporal bone, a relationship is postulated between the development of squamous carcinoma of the temporal bone and CSOM. Many patients, 68% in one series,[5] have been treated for this condition prior to development of their tumour. The pathogenesis of this association is not understood, but the natural assumption is that cellular trauma must be a contributory factor. Jin et al.[6] isolated human papillomavirus (HPV) 16/18 at both the tissue and molecular levels in patients with carcinoma of the middle ear and associated chronic otitis media. This finding may provide a model to explain the relationship between the two. Although HPV 11 is regarded to be a low-risk variant in the uterine cervix, its behaviour in the head and neck region includes pathogenesis of squamous carcinoma in the temporal bone.[7] The transformation to squamous carcinoma of both benign and inverted papillomas of the temporal bone, recently described, suggests the question whether there should be further genetic analysis of biopsied papillomas to assess their susceptibility to malignant transformation.[8–9]

CLINICAL EVALUATION

Presentation of temporal bone tumours

The presentation of tumours of the temporal bone may be very subtle. Early diagnosis relies heavily on the level of awareness and index of suspicion of the clinician.

The presentation of a tumour can mimic that of less sinister otological conditions, such as otitis externa or CSOM. At the outset, patients present with otalgia, otorrhoea, hearing loss and vertigo. It is not surprising that early diagnosis is difficult and biopsy, the only way to make the diagnosis, is often delayed (or even misleading if taken superficially) until a relatively late stage when other more alarming clinical features such as facial palsy or bleeding have developed. Sadly, only at that stage is the true severity of the patient's pain appreciated by the clinician. Pain caused by these tumours is generally far more severe than that experienced with non-neoplastic conditions. Tumours of the temporal bone described in this chapter tend to spread locally through the Haversian system of the bone and anatomical fissures. These canals contain blood vessels and nerves in the temporal bone and provide additional pathways for tumour spread. Leonetti et al.[10] highlighted a number of ways that this group of neoplasms tended to spread. For example, tumours of the external auditory canal often extend anteriorly into the parotid gland and temporomandibular joint (**Figure 110.1**). Tumours of the middle ear spread anteriorly to involve the Eustachian tube and the postnasal space while extension superiorly rapidly involves the middle cranial fossa (**Figure 110.2**). The otic capsule and the labyrinth become involved by medial growth. Inferior spread involves the jugular foramen and lower cranial nerves. The internal carotid artery not infrequently becomes encased when

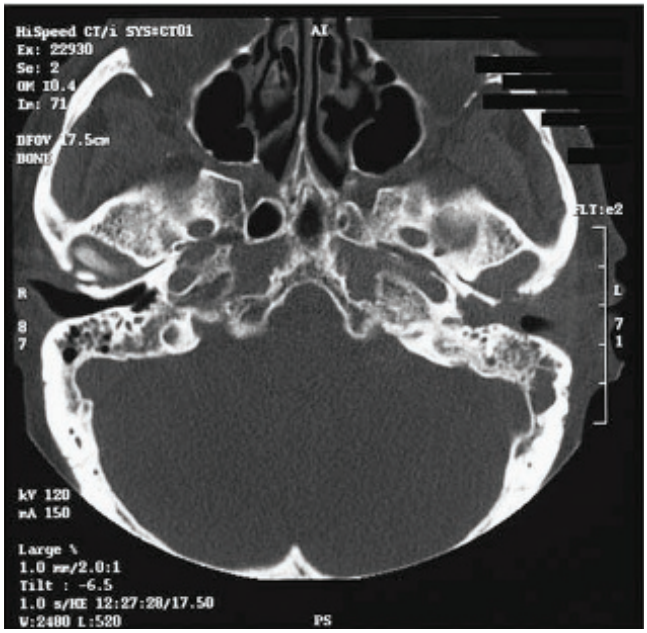

Figure 110.1 Adenoid cystic carcinoma of the left external auditory canal. High resolution axial CT of the skull base revealing soft tissue opacificaton of the left bony external canal with perforation of the anterior wall extending into the temporomandibular joint. There is slight irregularity of the posterior wall of the bony external canal with opacification of the adjacent mastoid air cells. Courtesy of Professor Andy White, Perth Radiological Clinic, Perth, Western Australia.

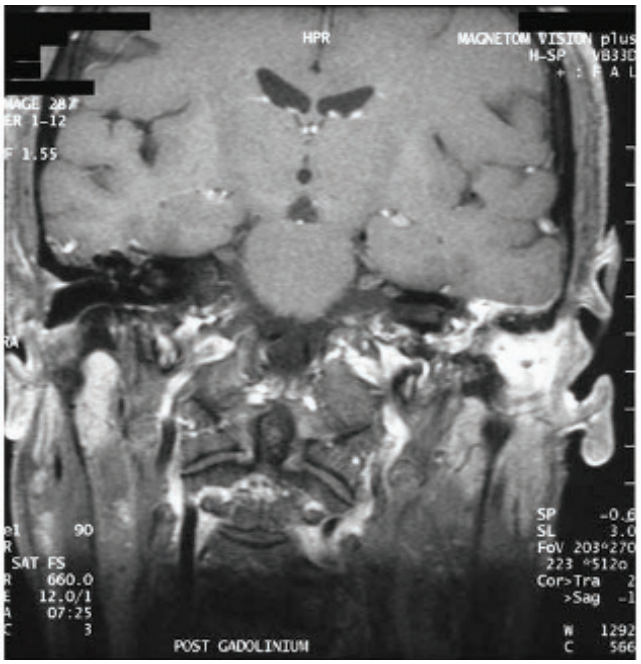

Figure 110.2 Adenoid cystic carcinoma of the left external auditory canal. Postgadolinium fat saturation T1 cranial scan of the skull base revealing extensive ill-defined enhancing tumour in the left external auditory canal and middle ear cleft. Tumour surrounds the ossicular chain and erodes the tegmen with dural thickening on the undersurface of the left temporal lobe. Courtesy of Professor Andy White, Perth Radiological Clinic, Perth, Western Australia.

tumour extends into the petrous apex. Thus, the clinical features of temporal bone tumours may include:

- trismus
- hemifacial spasm or progressive facial weakness
- lower cranial nerve palsies (IX, X, XI and XII)
- headache and localized pain
- cervical metastases.

Investigation of temporal bone tumours

Multimodality imaging is essential to provide sufficient information to assess the stage of disease from which a sensible management plan can be derived. Thin section computed tomography (CT) will demonstrate bone erosion and gadolinium-enhanced magnetic resonance imaging (MRI) the full extent of soft tissue infiltration. Image merge techniques can contribute much to the assessment of tumour stage. The surgeon must make every effort to evaluate potential dural involvement and extent of spread to the infratemporal fossa.

The tumour should be biopsied for definitive diagnosis based on histological confirmation of tumour type, but this may not be possible until after extirpation of the lesion itself.

Staging of temporal bone tumours

Neither the American Joint Committee on Cancer (AJCC) nor the International Union against Cancer (IUCC) has a system specifically for classifying temporal bone tumours. An AJCC T4 tumour grading applies to both extensive tumours with deep temporal bone involvement and small tumours that superficially invade auricular cartilage – despite what is likely a vast difference in prognosis! A number of alternative staging systems have therefore been proposed that depend on the site and type of tumour.

Stell and McCormick[11] proposed a system for staging carcinoma of the external and middle ear that was subsequently updated by Clarke and Narula[12] (see also Chapter 115, Squamous cell carcinoma of the temporal bone). Arriaga et al.[13] have also proposed a system for staging tumours of the external auditory canal. Fisch, Glassock-Jackson and De La Cruz have all provided systems for the staging of glomus tumours. None of these classification systems have been proven in terms of prognosis, but can be used to aid multidisciplinary discussion and for selection of a suitable surgical approach if appropriate.

Classification of tumours of the temporal bone

Tumour types are summarized in Table 110.1.

TABLE 110.1 Classification of tumours of the temporal bone

Cutaneous neoplasms	Glandular neoplasms	Vascular/ haematological	Paraganglioma	Bone	Neural	Developmental and congenital
Squamous cell papilloma and carcinoma	Ceruminous adenoma and adenocarcinoma	Haemangioma	Glomus tympanicum	Osteoma	V, VII, VIII, IX, X, schwannoma	Chordoma
Basal cell papilloma and carcinoma	Pleomorphic adenoma	Haemangiopericytoma	Glomus jugulare	Secondary tumours	Meningioma	Dermoid
Malignant melanoma	Adenoid cystic carcinoma	Leukaemia	Glomus vagale	Rhabdomyo-sarcoma		Teratoma
	Middle ear adenoma	Lymphoma		Chondrosarcoma		Choriostoma
	Endolymphatic sac tumours	Plasmacytoma		Ewing sarcoma		
		Langerhans cell histiocytosis		Osteogenic sarcoma		

MANAGEMENT OF TEMPORAL BONE TUMOURS

Glandular tumours of the external auditory canal

The glandular components of the external auditory canal consist of sebaceous glands and modified apocrine glands, called 'ceruminous glands'. Previously, glandular tumours of the external auditory canal had been classified under the umbrella term of ceruminoma, but this term is non-specific and should not be used without qualification. There has been some confusion in the literature with no agreed system of nomenclature for these tumours[14] but classification of glandular tumours of the external ear by Wetli et al.[15] is relatively less complicated:

- ceruminous adenoma
- pleomorphic adenoma
- adenoid cystic carcinoma
- ceruminous adenocarcinoma.

CERUMINOUS ADENOMA

Ceruminous adenomas are well-differentiated tumours derived from the ceruminous glands. These tumours exhibit solid, cystic and papillary patterns. Ceruminous adenomas consist of an inner layer of cells that are cuboidal or columnar and are of apocrine origin with an outer layer that is myoepithelial in origin. These tumours should be widely excised because local recurrence is common. Radiotherapy has no role to play in the treatment of this type of tumour.

PLEOMORPHIC ADENOMA

Pleomorphic adenoma should also be excised. Care must be taken to avoid seeding of the local tissues by spillage of tumour during resection. Recurrence may develop many years after resection in much the same way as is seen in the major salivary glands.

ADENOID CYSTIC CARCINOMA

Adenoid cystic carcinoma of the temporal bone may display cribriform, tubular or solid growth patterns surrounded by cystic spaces. Adenoid cystic carcinoma has the propensity for significant local tissue destruction (**Figure 110.1**), perineural and perivascular invasion. It also tends to metastasize to the lymph nodes of the neck. There are no established treatment regimens. This condition is thought best managed by aggressive surgical resection followed by radiotherapy. The long-term prognosis is poor with distant (lungs, lymph nodes, skeletal) metastatic disease developing years later. Bone invasion, perineural spread and tumour extension outside the external auditory canal are considered indicators of poor prognosis.

CERUMINOUS ADENOCARCINOMA

Ceruminous adenocarcinoma is often difficult to distinguish from ceruminous adenoma as it may show very few malignant features apart from evidence of invasion into local tissue. These tumours grow slowly and tend to spread by local invasion. Metastases have been reported. Ceruminous adenocarcinomas are extremely rare and advice on treatment is largely anecdotal. Surgical resection with post-operative radiotherapy is considered to be the appropriate therapy.

In summary, benign glandular tumours of the external ear should be treated by wide surgical excision. The optimum treatment for malignant tumours has not been established and is unlikely to be forthcoming in the near future. Current opinion would suggest aggressive surgical resection followed by adjuvant radiotherapy.[16]

Glandular tumours of the middle ear

Debate continues about the nomenclature, pathology and behaviour of glandular tumours of the middle ear. The distinction between terms such as adenoma, adenomatous tumours, adenocarcinoma and carcinoid tumour of the middle ear has not always been clear, partly because of overlapping pathological features, but also because of uncertainty about the behaviour and natural history of these tumours.

MIDDLE EAR ADENOMA

In 1976, Hyams and Michaels[17] presented 20 primary middle ear tumours with an adenomatous pattern that were strictly confined to the middle ear cleft and thought to be derived from the middle ear mucosa. The tumours described in this series expanded locally. There was no evidence of bony erosion or of distant metastases. All of the patients were treated by local excision. A tympanotomy or mastoid approach was used and no patients were radiated subsequently. Follow-up data were available for 18 patients and all but one was free of tumour 4–24 years after surgery. Similar tumours have been described by other authors,[18] and Torske and Thompson[19] reviewed 48 cases of middle ear adenoma that had been referred to the Armed Forces Institute of Pathology over a period of 25 years. These tumours displayed features consistent with the diagnosis of middle ear adenoma. They lacked features of aggressive malignancy such as mitotic activity, perineural or vascular invasion. The authors suggested that the presence of neuroendocrine markers made these neoplasms indistinguishable from carcinoid tumours. It was argued that the relatively small size of these tumours, together with the relatively poor blood supply of the middle ear, explained the lack of paraneoplastic syndromes. In contrast to other carcinoid tumours, metastatic disease was not seen with middle ear adenoma. It was suggested that 'neuroendocrine adenoma of the middle ear' might be a more appropriate description.

A more recent review by Saliba and Evrard[20] examined the literature on all reported cases, and recommended a new system of classification of middle ear glandular neoplams that may have prognostic significance. Based on the

presence or absence of immunohistochemical markers and metastasis, these lesions are classified into three types:

- **Type I:** neuroendocrine adenoma of the middle ear (NEAME) in 76% of cases (positive immunohistochemistry, negative metastasis)
- **Type II:** middle ear adenoma (MEA) in 20% of cases (negative immunohistochemistry, negative metastasis)
- **Type III:** carcinoid tumour of the middle ear (CTME), only 4% of tumours (positive immunohistochemistry, positive metastasis and/or carcinoid syndrome).

Wide surgical resection is generally recommended and cure can be anticipated. Hearing can often be preserved. It has been suggested that if the tumour is intimately related to the ossicles, removal of the ossicles reduces the possibility of tumour recurrence.[20] Radiotherapy does not have a role to play in the treatment of these tumours.

TUMOURS OF THE ENDOLYMPHATIC SAC

In 1988, Gaffey et al.[18] proposed the term aggressive papillary middle ear tumour (APMET) for adenomatous middle ear tumours that have a primarily papillary architecture. As distinct from the middle ear adenoma described above, these tumours were extremely aggressive locally invading bone and possibly extending intracranially. In Gaffey's series, brain invasion was seen in one patient and no patient had evidence of distant metastases. All of these patients were treated with surgery and, in some, adjuvant radiotherapy. In 1989, Heffner proposed that the middle ear tumour previously described as the papillary middle ear tumour was in fact derived from the endolymphatic sac.[21] Li et al.[22] confirmed their findings in 1993 using similar histochemical and histopathological techniques. Terms such as Heffner tumour, low grade adenocarcinoma of endolymphatic sac origin, and aggressive papillary middle ear tumour are now obsolete and it should be described as endolymphatic sac tumour (ELST) according to the more recently published World Health Organization tumour classification.[23]

Progressive unilateral, sensorineural hearing loss is the most prominent feature of this tumour in addition to tinnitus and vertigo. This neoplasm grows very slowly; the average duration of time between onset of symptoms and diagnosis is 9 years.[21] In the past, some patients have presented with an acute unilateral sensorineural hearing loss and been misdiagnosed as Menière's disease, which is understandable considering the site of the lesion (**Figure 110.3**). The differential diagnosis includes paraganglioma, papillary choroid plexus tumours, ceruminous gland tumours, benign adenomatous tumours and metastatic disease. On microscopy, these tumours demonstrate a papillary ultrastructure, composed of cuboidal or low columnar cells (**Figure 110.4**). Nuclear size and shape may vary, but prominent pleomorphism and mitotic activity is not a feature. They are vascular in nature and invade bone in an aggressive fashion. Metastatic spread has not been reported. Growth and spread to the cerebellopontine angle and posterior fossa is most commonly seen. Extension into the middle and external ear has been reported, as well as into the middle cranial fossa, clivus, cavernous sinus and sphenoid sinus.[24] Mukherji et al.[25] showed a correlation between middle ear spread and the size of tumour. In a radiological review of 20 patients with a diagnosis of ELSTs that included CT imaging, MRI and angiography, eight of nine tumours less than 3 cm in size did not involve the middle ear, and eight of

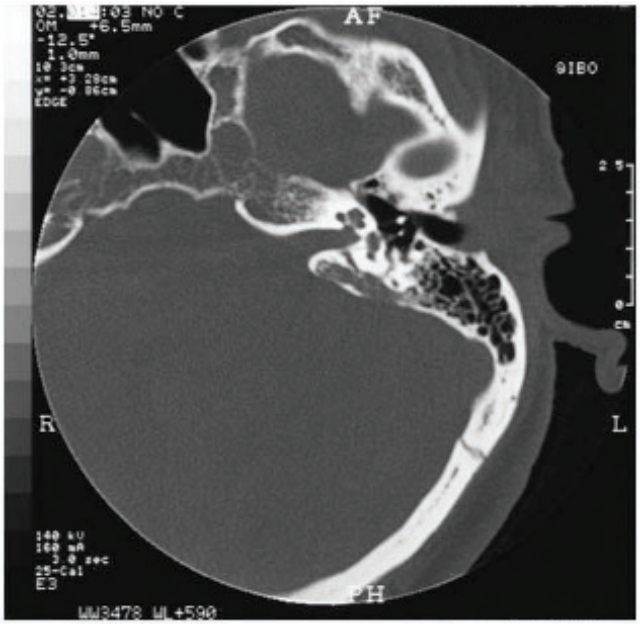

Figure 110.3 Endolymphatic sac tumour. High resolution axial CT of the temporal bone revealing permeative bone destruction along the posterior margin of the left temporal bone along the line of the vestibular aqueduct. Courtesy of Professor Andy White, Perth Radiological Clinic, Perth, Western Australia.

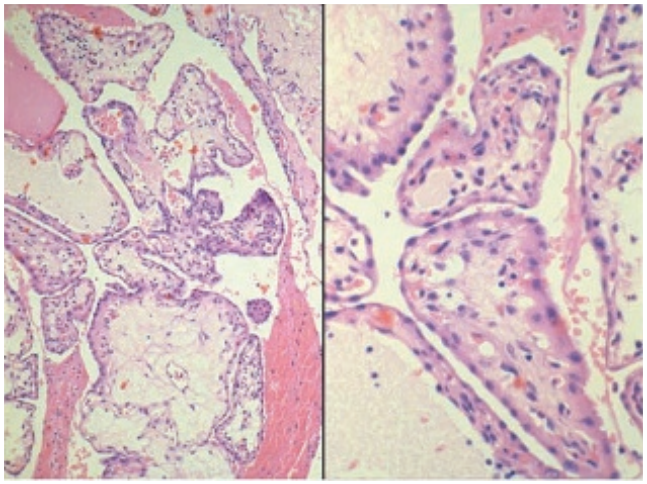

Figure 110.4 Endolymphatic sac tumour. Aggressive papillary middle ear tumour of temporal bone and endolymphatic sac. This tumour occurred in a 35-year-old female. There are papillary formations consisting of oedematous fibrovascular cores lined by a single layer of plump, cuboidal epithelial cells. Courtesy of Drs P Robbins and D Spagnolo, The Western Australian Centre for Pathology and Medical Research, Perth, Western Australia.

nine tumours of at least 3 cm demonstrated soft tissue involvement of the middle ear.[25] It was also demonstrated that the vascularity of the tumour was related to tumour size. Tumours less than 3 cm are supplied solely by the external carotid artery and, as the tumour enlarges, it obtains a blood supply from the internal carotid artery. Ultimately, the tumour may also obtain a blood supply from the posterior circulation (i.e. the anterior and inferior cerebellar arteries).

An association had been established between tumours of the endolymphatic sac and Von Hippel–Lindau (VHL) disease.[24] This autosomal dominant condition predisposes the patient to a number of conditions, including haemangioblastoma of the cerebellum, angiomatous lesions of the retina and renal cell carcinoma. The gene for this condition has been identified in the short arm of chromosome 3 (3p25) and a mutated suppressor gene has also been identified in both abnormal and neoplastic tissues of patients suffering from this condition. Gaffey et al.[18] pointed out that 15% of patients with ELSTs are known to have VHL disease. A review of the literature published in 2012 indicated an earlier age at presentation with ELST in VHL disease (31.3 years versus 52.5 years) with a female preponderance (female-to-male ratio of 2:1 for VHL disease patients versus 1:1 for non-VHL disease patients) and propensity for bilateral ELSTs in VHL disease.[26]

Recent studies have demonstrated an excellent prognosis (in terms of survival and hearing preservation) with early surgical resection without the need for radiotherapy.[27–29] Removal of the tumour is therefore advised (with pre-operative embolization if needed), the extent of the resection being determined by a number of factors that include its size, vascularity, existing neural deficits and those that might be acquired as a result of surgery. Most patients are young adults and incomplete tumour removal can lead to significant long-term morbidity. Partial tumour removal can be justified for some when complete removal might inflict unacceptable morbidity. In this respect, it is worth remembering that this is an extremely slow-growing tumour and the elderly might outlive their disease. Adjunctive radiotherapy has been used in the treatment of these tumours but its role in the treatment of ELSTs is far from established. Radiation therapy may be considered when surgical treatment is not an option or as a palliative measure following partial tumour removal.

Miscellaneous tumours of the middle ear

INVERTED PAPILLOMA

These are extremely rare tumours of the middle ear and are similar to inverted papilloma of the sinonasal system. HPV has been implicated in their pathogenesis. Like its nasal counterpart, surgery is the mainstay of treatment. It is essential that the specimen be examined for evidence of carcinoma as malignant transformation has recently been demonstrated.[9] In those patients with evidence of carcinoma, radical resection with post-operative radiotherapy has been advocated.[30]

HAEMANGIOMA

These benign vascular tumours are derived from arterioles, venules and capillaries. They develop at a number of sites in the temporal bone with the geniculate ganglion being the most common. In the middle ear they have been found coincidentally, but usually present with symptoms of conductive hearing loss. The differential diagnosis includes that of paraganglioma, high jugular bulb and adenomatous tumour. Some haemangioma may regress spontaneously, while others continue to grow and are locally destructive. Surgical excision is the treatment of choice in these cases, but as some tumours may regress spontaneously an expectant approach may be appropriate particularly if surgery might compromise middle ear function.[31]

HAEMANGIOPERICYTOMA

These are rare vascular tumours that consist of proliferating pericytes surrounding capillaries. About 15–25% of haemangiopericytomas develop in the head and neck region. Cases have been reported in the middle ear and temporal bone, although they are extremely rare. Fifty per cent are malignant, although the behaviour of even the benign form is unpredictable. Treatment is by wide surgical excision. Pre-operative embolization may be helpful. These tumours appear to be radioresistant, but it has been suggested that radiotherapy has a role to play if excision is incomplete.[32]

OSTEOMA

These are benign tumours consisting of mature lamellar bone. While well documented in the external auditory canal, they are otherwise very rare in the temporal bone. The most common site of origin appears to be the mastoid with about 20% developing in the middle ear. In half of these, the osteoma causes a conductive hearing loss and the condition is often discovered coincidentally. While easy to remove from the mastoid, an expectant approach is probably more advisable, particularly in the asymptomatic patient with middle ear disease where removal of the osteoma might compromise structures such as the ossicular chain or the VIIth nerve.[33–35]

CHORDOMA

Chordomas are rare tumours that originate from the primitive notochord. A loss of heterozygosity (LOH) study centred on the short arm of chromosome 1 (1p36 region) revealed an high incidence of 1p36 losses among sporadic chordomas.[36] They are subclassified according to site of development: spheno-occipital (35%), vertebral (15%) and sacrococcygeal (7%). Three types of chordoma are recognized: conventional, chondroid and dedifferentiated, the chondroid form being the most common. Chordomas may present more laterally in the skull base, such as at the petrous apex, the carotid canal or the jugular foramen where they are thought to arise from dendritic processes at the cephalic end of the notochord. These tumours may present at any age, but the mean age at diagnosis is

TABLE 110.2 A comparison of symptoms at presentation of chordoma and chondrosarcoma

Symptom	Chordoma (%)	Chondrosarcoma (%)
Headache	67	49
Diplopia	54	70
Intermittent diplopia	25	28
Decreased visual acuity	8	13
Facial numbness	2	23
Decreased hearing/tinnitus	2	9
Facial weakness	2	11
Dysphagia/dysarthria	2	9

Reproduced with permission from Volpe et al.[37]

between 35 and 45 years. The male to female ratio is 2:1. The most common symptoms at presentation are summarized in Table 110.2.[37]

Conventional chordoma has been misdiagnosed as chondrosarcoma in the past. Chondrosarcoma is the main differential diagnosis and despite its name has a less aggressive clinical course. It is essential to achieve accurate histological diagnosis before outlining a management plan for these unfortunate patients. CT-guided fine-needle aspiration may be useful in this respect.

Surgical removal of chordoma is the mainstay of treatment. Complete resection may be difficult but does provide the best long-term survival and lowest risk of recurrence. Successful resection depends on the degree of spread of the tumour and the degree of involvement of vital structures, such as the carotid artery and the brain. A number of skull base approaches have been described, but most fall into the category of anteromidline and lateral techniques. Successful removal also depends on accurate pre-operative assessment of the tumour and the ability of the surgeon but in many cases subtotal resection with post-operative radiotherapy is the only viable management option.

Radiotherapy as an adjunctive treatment has a significant role to play in the management of these tumours. Although a number of delivery techniques have been used, proton beam therapy is now considered the gold standard radiotherapy modality, and a prospective randomized phase III trial is underway comparing it with a newer modality – carbon ion radiation therapy.[38] However, it must be noted that if surgery (such as salvage) is needed after radiotherapy the tumour can be both fibrotic and adherent, making preservation of vital structures particularly difficult.

Crockard et al.,[39] in a review of 42 patients treated over a 12-year period, reported 5- and 10-year survival rates of 77% and 69% respectively, treated by maximum surgical cytoreduction and photon radiation therapy. A smaller, more recent study reported a higher 5-year survival of 82.5%.[40] Stacchiotti et al.[41] have demonstrated a response to chemotherapy in advanced or recurrent chordomas no longer amenable to surgery or radioresistant tumours. Molecular marker analysis of histological specimens could inform prognosis in the future as a study has demonstrated the lack of 1p36 LOH, or the presence of tumour necrosis factor receptor superfamily gene *TNFRSF8* expression, may be associated with a better prognosis.[42]

CHONDROSARCOMA

The precise origin of chondrosarcoma is not known, but one theory is that these tumours may arise from chondrocytes that persist as embryonal cell rests at or about the foramen lacerum. A number of histological types are recognized, such as hyaline, myxoid, clear cell, mesenchymal and dedifferentiated. Immunohistochemistry can help differentiate chondrosarcomas from chordomas.

Hyaline and myxoid types are more common and are sometimes referred to as 'conventional' chondrosarcoma. Evans et al.,[43] in a review of 81 patients with chondrosarcoma from varying sites, graded these tumours I–III, based on their mitotic rate, cellularity and nuclear size. A 5-year survival of 90%, 81% and 43% in grades I, II and III, respectively, has been reported. There was also a correlation between grade and metastatic rates, with a 0% metastatic rate with grade I tumours, 10% with grade II tumours and 71% with grade III tumours.

The common symptoms at presentation of chondrosarcoma of the skull-base tumours are presented in Table 110.2. These tumours grow slowly and have significant potential for local expansion. Before diagnosis, patients may have been treated for many years with non-specific symptoms, such as headaches or non-specific neurological symptoms. The mean age at presentation is in the fourth decade and the male to female ratio is approximately equal, although some studies have shown a male predominance.[44] Chondrosarcomas typically develop around the foramen lacerum, parasellar region, petrous apex and cerebellopontine angle, rather than the midline predilection of the chordoma.

Treatment protocols for chondrosarcoma continue to evolve and are multidisciplinary in nature. Surgical resection is the mainstay of treatment. Complete removal is not always possible but adjunctive radiation therapy, particularly proton beam, is used in the treatment of these tumours and has an increasing role to play in their management. Rosenberg et al., in a review of 200 patients with a diagnosis of conventional chondrosarcoma treated at the same institution, reported a 5-year local control rate of 99% and a 10-year local control rate of 98%. Both 5- and 10-year disease-specific survivals of 99% were reported when surgery was combined with high-dose fractionated proton beam radiation.[45] A recent systematic review with meta-analysis of 560 patients with cranial chondrosarcoma has demonstrated that surgical resection with post-operative adjuvant radiotherapy has the lowest 5-year recurrence rate (9% vs. 19% for radiation alone, $p < 0.011$) and is significantly better than surgery alone (9% vs. 44%, $p < 0.0001$).[46] It should be noted that chondrosarcoma has a much better overall prognosis than that of chordoma, despite similar aggressive treatment protocols.

SECONDARY TUMOURS OF THE TEMPORAL BONE

Secondary tumours of the temporal bone are classified into three types: local spread of a tumour from an adjacent site such as pharynx, parotid or sinus; distant spread of a cancer; and manifestation of a haematological malignancy (e.g. leukaemia). The spread of a tumour from an adjacent head and neck site is dealt with elsewhere (see Volume 3, Chapter 18, Metastatic neck disease). Haematological malignancies have a significant propensity to spread to the temporal bone and are not addressed further in this chapter. Gloria Cruz et al.,[47] in a review of 212 patients with primary non-disseminated malignant neoplasms, found an approximately 22% prevalence of metastases to the temporal bone. The average age of presentation corresponded to the age at which most primary tumours have their onset (i.e. the fifth to sixth decade). There was a slight male to female preponderance.

Table 110.3 summarizes the site of origin of secondary tumours of the temporal bone. The mode of presentation varies from patient to patient and up to 36% of patients have no symptoms attributable to the head, neck or ear. The most common symptom at presentation is hearing loss, followed by vertigo and facial paralysis.[47] Secondary tumours can develop throughout the temporal bone, but the petrous apex is the most common site followed by the internal auditory meatus.[47–48]

The prognosis for patients with secondary temporal bone tumours is poor. Management may involve a number of different modalities and is dependent upon the origin and nature of the original primary. Treatment, therefore, has to be individualized. Diagnosis is difficult, because so many patients are asymptomatic. In their series, Gloria Cruz et al.[47] found that all patients with temporal bone metastases had metastases at other sites. It is important to realize that metastatic disease should be excluded in any patient with a history of a previous malignancy who develops otological symptoms, particularly sensorineural hearing loss.

TEMPORAL BONE TUMOURS IN CHILDHOOD

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is an extremely aggressive tumour of striated muscle origin that has the potential to spread locally and to metastasize. It is the most common soft tumour of childhood. In the head and neck region, RMS of the ear is the third most common site of origin after the nasopharynx and the orbit. Most of these tumours present under the age of 12 years. Four histological types are recognized: embryonal, alveolar, pleomorphic and botyroid.

Table 110.4 summarizes the most common symptoms and signs at presentation. In addition to the normal histological and radiological work up for tumours of the temporal bone, investigations should include a CT scan of the chest, bone scan and a lumbar puncture. Further investigation may then be carried out as indicated.

Definitive treatment of these tumours continues to evolve and consists of a multidisciplinary, multimodality approach that includes chemotherapy, radiotherapy with less of a role for surgery. One study, the Intergroup Rhabdomyosarcoma Study (IRS), was introduced in 1972 to establish the optimum treatment for RMS in general. A summary of the IRS classification system for staging these tumours, as introduced by Maurer et al.,[50] is shown in Table 110.5.

RMS of the temporal bone tends to be diagnosed late due to symptoms that mimic more common conditions. As a result, most patients are staged in group III and included under the umbrella term of 'parameningeal' tumours. The IRS study continued to recruit patients and investigate treatment regimes for RMS, altering the chemotherapeutic regimes and radiation fields as was deemed necessary. IRS results have been reported in every decade since the 1970s. Results of treatment for all groups have improved over the study period with the group III, 5-year survival rates overall improving from 52% in IRS-I to 59% for IRS-II to 65% for IRS-III and 73% for IRS IV.[51–53]

TABLE 110.3 Site of origin: secondary tumours of the temporal bone

Site of origin	Incidence (%)
Breast	25
Lung	11
Kidney	9
Stomach	6
Bronchus	6
Prostate	6

Reproduced with permission from Streitman and Sismanis.[48]

TABLE 110.4 Rhabdomyosarcoma: the most common symptoms and signs at presentation

Symptom	Frequency (%)
Mass in the ear region	56
Aural polyp	54
Ear discharge	40
Bleeding from the ear	30
Ear pain	22
Hearing loss	14
Facial paralysis	14

Reproduced with permission from Prat and Gray.[49]

TABLE 110.5 The IRS classification system

Group	
I	Localized disease completely resected
II	Grossly resected disease, with microscopic residual disease with or without lymph nodes
III	Gross residual disease
IV	Metastatic disease present at onset

Reproduced with permission from Maurer et al.[50]

While still a potentially aggressive and fatal condition, the outcome for childhood RMS of the temporal bone is slowly improving, with the key to survival being early diagnosis through biopsy of unhealthy tissue.

Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH), formerly called histiocytosis X, is a condition that is characterized by the proliferation of histiocytes that share the characteristic of Langerhans cells (normally located in the dermis). These cells are recognized by the presence of inclusion bodies in the cytoplasm, called Birbeck granules. Proliferation and infiltration of these cells may develop in any organ in the body, including bone, skin, lung, liver, spleen and nervous system. LCH is now the collective name for the following conditions that were previously thought to be three distinct entities, but are now recognized as one condition:

1. **Eosinophilic granuloma:** Generally refers to osseus disease alone and may be unifocal or multifocal
2. **Hand-Schuller-Christian disease:** A systemic disease identified by multifocal osseus lesions, with limited involvement of extraskeletal sites, such as lymph nodes and viscera
3. **Letterer-Siwe disease:** The most serious and rapidly progressive disease, characterized by disseminated disease with multiorgan involvement.

In the series of cases reviewed by Irving et al.,[54] 73% of patients presented with head and neck involvement, 24% of patients had involvement of the skin of the external auditory meatus and 19% had involvement of the temporal bone. The mean age of presentation was 3.2 years and the male-to-female ratio was 1.7:1. These relative percentages of head and neck and temporal bone involvement vary slightly from series to series.[55, 56]

Symptoms and signs of ear and temporal bone involvement are often indistinguishable from that of CSOM and may include a conductive or sensorineural hearing loss. Thirty per cent of patients with temporal bone involvement have bilateral involvement. The characteristic radiological appearance of the temporal bone is that of a 'punched out' or lytic appearance. While extensive destruction of the temporal bone can take place, there are only limited reports of otic capsule involvement with disease often confined to the external and middle ear.

The ultimate prognosis of patients with LCH depends on whether the disease is unifocal, multifocal or disseminated. Age at presentation of less than 2 years with organ dysfunction is an indicator of a much poorer prognosis. Unifocal disease, on the other hand, has a very good prognosis responding to local treatment, which may include local resection or radiotherapy. Most series have a 95–100% cure rate. Multifocal disease also has a good response to treatment,[57] but disseminated disease can be rapidly fatal.[54–56] Involvement of the temporal bone often implies multifocal disease, which is best treated in a multidisciplinary, multimodality fashion with a combination of chemotherapy, radiotherapy and steroid therapy (in order of preference according to current trends). Surgical treatment of temporal bone LCH is now being utilized much more selectively (for isolated disease), recognizing that there is a high risk of complications, particularly to structures such as the facial nerve.

FUTURE RESEARCH

Perhaps because of the rarity of tumours of the temporal bone, there are still large gaps in our knowledge. With some tumours, such as those of the middle ear, there is still uncertainty with regard to their nomenclature, pathology and behaviour.

- There is no generally accepted system for the classification of temporal bone tumours.
- While there are staging systems available for some individual tumour types, there is no overall agreed system for staging tumours of the temporal bone.
- The lack of accurate classifications in addition to the paucity of multicentre trials make treatment guidelines difficult.
- Randomized, multicentre therapeutic trials should be devised to address these problems and it is heartening to see that these are now taking place in the management of chordomas and chondrosarcomas.
- It is hoped further advances in molecular biology and immunohistochemistry will advance new therapeutic options.

KEY POINTS

- Temporal bone tumours are exceedingly rare and can be extremely variable in their presentation and prognosis.
- There is often considerable delay in the diagnosis of temporal bone tumours. Biopsy of any unhealthy tissue in the ear is advisable. Early diagnosis and treatment improves outcomes.
- Appropriate radiological investigation is the cornerstone of management.
- The development of unilateral hearing loss in a patient who has had a previous malignancy may indicate a secondary tumour in the temporal bone.
- Management strategies for many of these tumours rely on level 4 evidence.
- Intracranial spread is not uncommon and a multidisciplinary approach is advisable.

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CHAPTER 111

CLINICAL NEUROANATOMY

John J.P. Patten

SEARCH STRATEGY

Data in the chapter may be supplemented by recourse to the standard textbooks of neuroanatomy e.g. *Gray's Clinical Neuroanatomy: The Anatomic Basis for Clinical Neuroscience*.[1]

INTRODUCTION

A neurological examination is critical in the assessment of patients with skull base disease. In this chapter, applied aspects of skull base neuroanatomy are reviewed and the differential diagnosis of neural deficits considered. In some instances, gross anatomy is of great importance and in others complex central connections require detailed elaboration to illustrate and explain the accompanying clinical disorders. The following account is always biased in the direction of practical applications, and information of limited or uncertain clinical importance has been excluded.

THE CRANIAL NERVES

The cranial nerves fall into three major groupings sharing common anatomical relationships and pathology. Differing patterns of involvement within these groups allows a very accurate differential diagnosis to be advanced, based on both the sequencing and ultimate extent of damage to the nerves in these groups. The advent of computed tomography (CT) and three-dimensional magnetic resonance imaging (MRI) has added remarkably to our ability to confirm or refute clinically suspected diagnosis in what used to be an investigational no-man's land. Scan interpretation still requires a very good knowledge of gross anatomical relationships of the intracranial and extracranial courses of the cranial nerves and these anatomical features form the bulk of this chapter.

The groupings are:

1. Cranial nerves I, II, III, IV, the ophthalmic division of V and VI and the final distribution of the cervical sympathetic
2. Cranial nerves V, VII and VIII
3. Cranial nerves IX, X, XI and XII and the cervical components of the sympathetic chain.

The influence of altered cerebellar, pyramidal, extrapyramidal and corticobulbar function on the nerves and peripheral evidence of disordered brainstem function will be detailed at the end of the chapter, or where appropriate in general discussion.

GROUP 1

In the first group, the close relationship of the olfactory and optic nerves and the varying relationship of the three nerves supplying the extraocular muscles is considered. It is also necessary to include the relationships of the first division of the Vth nerve, which traverses the orbit, to these structures, although the detailed anatomy of this nerve is dealt with in Group 2.

The olfactory nerve (I)

ANATOMY

The olfactory epithelium lies in the olfactory cleft that occupies the upper 10 mm of the nasal septum, the roof of the nasal cavity and down the lateral wall towards the origin of the superior concha (Figure 111.1). In humans, its total surface area is some 5 cm^2 and is a yellowish colour. In other species, increasing pigmentation is associated with increased sensitivity to odours. The mucosa is bathed in a lipid-rich secretion from the epithelial Bowman's glands, indicating that lipid solubility may be a critical factor in odour detection. The olfactory receptor cells, some 5 million in all, lie on the basal epithelium and extend vertically to the surface from which the terminal enlargement protrudes and gives rise to 8–20 olfactory cilia. Although these have the standard '9 + 2' fibril arrangement found in mobile cilia in other areas of the body, they are thought to be nonmotile and form a dense mat of fibrils lying on the surface of the epithelium. Pinocytic vacuoles have been demonstrated in the terminal enlargement of the receptor cells, but their functional significance remains uncertain.[1]

The receptor cells are derived from ectoderm and are unique in being replaced from stem cells every 30–50 days. They also enter the central nervous system (CNS) as very thin (0.1–0.4 µm), non-myelinated axons without synapse. These axons become grouped and ensheathed by Schwann cells forming some 20 fasciculi which are invested by pia and arachnoid mater, and pass through the orifices of the cribriform plate to enter the olfactory bulbs lying each side of the crista galli in the floor of the anterior cranial fossa. These axons synapse with dendrites of the large mitral cells of the olfactory glomeruli and each glomerulus receives axons from a wide area of the epithelium. There seems to be no functional grouping of axons. This arrangement allows a relatively small number of receptor cells to distinguish a large number of different odours. The axons of the mitral cells form the bulk of the olfactory tract but centrifugal axons of uncertain origin also pass to the olfactory bulb and undoubtedly modify activity in the olfactory glomeruli, perhaps having both inhibitory and facilitatory actions. The olfactory tracts pass posteriorly and slightly laterally crossing the floor of the anterior cranial fossa, the optic nerves and immediately above the optic chiasm. Just in front of the anterior perforated substance, each divides into medial, intermediate and lateral olfactory striae.

The termination of the medial striae is uncertain. Many fibres decussate to the opposite medial striae and these may become the centrifugal fibres of the opposite olfactory tract noted above, having facilitatory and inhibitory effects on the opposite olfactory bulb. The intermediate striae terminate in the olfactory tubercle but their further functional anatomy is unknown. The lateral olfactory striae synapse with neurons in the lateral anterior perforated substance, the lateral olfactory gyrus, the prepyriform cortex and the medial group of amygdaloid nuclei – the group of tissues that in humans represent the primary olfactory cortex. These are the only sensory pathways in humans that do not relay in the thalamus. The subsequent distribution via the limbic system then contributes to both pleasurable and unpleasant consequences of odour detection at conscious level and the appropriate

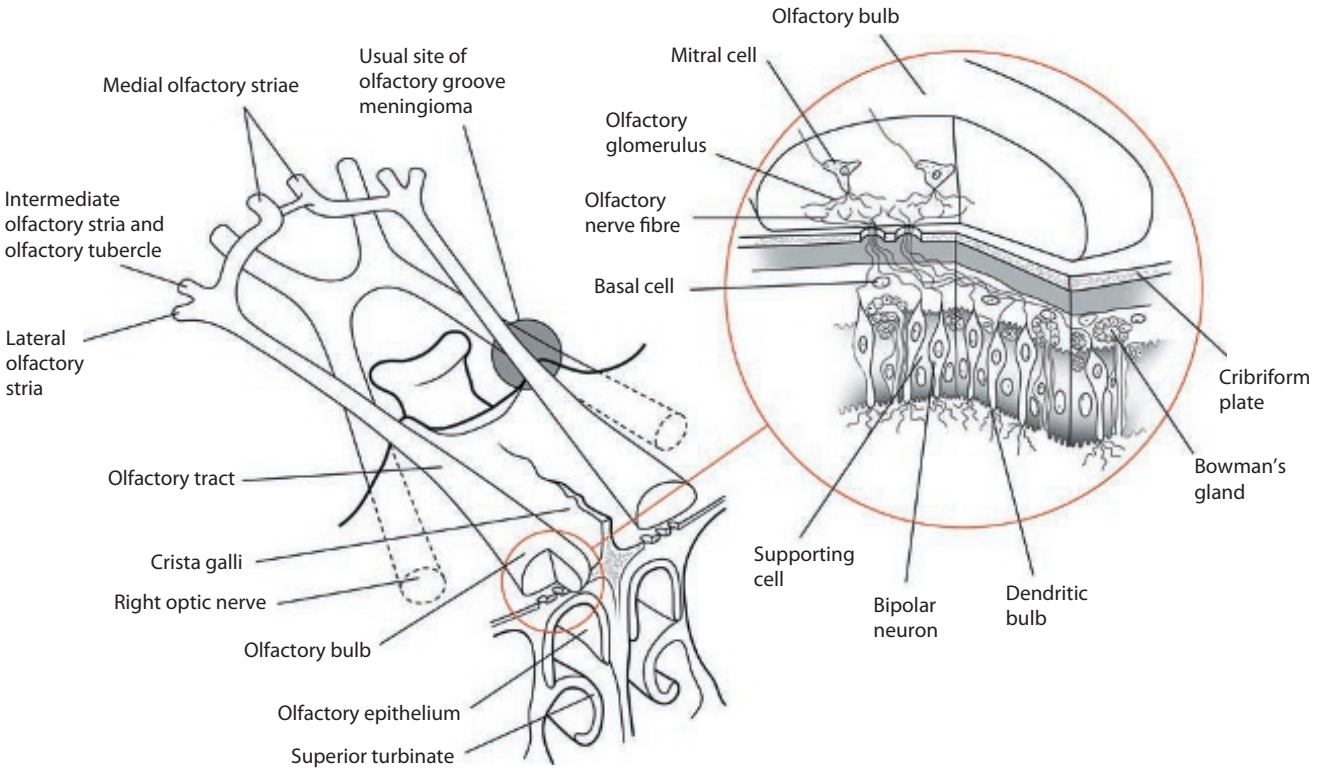

Figure 111.1 The olfactory pathways.

unconscious autonomic responses via the hypothalamus. This is related to activity in the secondary olfactory cortex located in the entorhinal complex, which includes the uncus and a tertiary olfactory cortex in the posterior orbitofrontal cortex. Descending pathways from these areas enter the pontine reticular formation in the brainstem and mediate reflex activity, such as salivation.[2]

There are also ascending projections from the midbrain raphé, the locus caeruleus and the midbrain tegmentum. These may well heighten olfaction in response to hunger and other emotional states, which emphasizes the role of olfaction in behavioural conditions, including sexual and maternal bonding, and in animals recognition of parent and offspring.[3]

PHYSIOLOGY

The receptor proteins lie in the olfactory cilia and it is likely that many different types of protein are involved. An odour must be volatile to enter the nasal cavity, actively sucked into the area of the olfactory epithelium by sniffing, which creates turbulent flow in the nasal passages, and lipid soluble to facilitate access to the fluid-bathed cilia.

Once stimulated, the resulting activity in the neuron is difficult to study. Attempts at single fibre analysis are technically almost impossible and such studies as are available demonstrate no similarities in evoked potentials from similar groups of substances or stimuli.

There is considerable evidence that some odours inhibit as well as excite and to this one must add an anatomical arrangement that allows not only local inhibition and excitation, but also crossed and possibly centrally mediated modulation by both lateral and negative feedback mechanisms. This permits humans to identify some 3000 different odours. The central pathways allow further discrimination and perhaps clarification of odour recognition. In contrast is the remarkable process of adaptation that allows continuous exposure to an unpleasant smell to diminish perception, so that the smell no longer registers. This phenomenon is interesting to consider in those patients who complain bitterly of a persistent unpleasant smell present 24 hours a day – a syndrome that commonly has a psychogenic basis, in striking contrast to patients with severe halitosis who are seemingly unaware of their problem. Further details on the physiology of the sense of smell are found in Volume 1, Chapters 89, Physiology of the nose and paranasal sinuses and 110, Abnormalities of smell.

APPLIED ANATOMY AND PHYSIOLOGY

Of obvious otolaryngological concern are simple mechanical factors interfering with access of the odour to the receptors, with simple airway obstruction, complicated by oedema or drying up of the mucosa as the most common causes of anosmia. Mechanical destruction or blockage of the nasal passages by pathology ranging from allergic rhinitis to complex vascular diseases, such as Wegener's granulomatosis, can occur. Simple polyps, nasal fractures and foreign bodies all have adverse effects on olfaction. Many drugs and generalized medical conditions that can damage or interfere with the function of a highly metabolically active tissue with a 30–50-day turnover rate, can also affect smell. These conditions include generalized metabolic disorders, such as renal failure and hepatic failure, and endocrine disorders, including diabetes, pregnancy and influenza.

Drugs affecting membrane moistness (antihistamines), cell turnover (antibiotics, antimetabolites) and cell function (anti-inflammatory agents, antithyroid drugs) may all affect both smell and taste adversely.[4]

Traumatic lesions of the olfactory fasciculi are usually caused by the shearing effect of brain movement when the head decelerates during a head injury. This complicates some 30% of serious head injuries particularly where immediate anteroposterior forces are applied to the head and a blow squarely on to the occiput is particularly likely to result in this complication. In such cases, little or no recovery can be anticipated. Severe injury of this type may actually tear the arachnoid cuffs and lead to cerebrospinal fluid (CSF) rhinorrhoea with a significant risk of subsequent meningitis.

There is circumstantial evidence that viral infections may gain access to the meninges via the same route in the absence of prior injury, *Herpes simplex encephalitis* being the most notable example. In this condition, the initial localization of the infection in the anterior temporal lobes adds support to this theory of aetiology, the virus presumably gaining access along the olfactory tract, possibly by axonal transport.[5] This is not the whole answer as in 25% of cases the virus isolated from the CSF is a different strain to that found in the oropharyngeal mucosa. Inside the skull, tumours of the olfactory groove, notably meningiomas, can cause unilateral anosmia, often unrecognized by the patient. Due to the local anatomy, progressive visual loss in the ipsilateral eye ensues – also often unrecognized by the patient. It is therefore very important to test the sense of smell in any patient with sudden loss of vision in one eye.

At central level, disorders of smell appreciation are not recognized, although behavioural, endocrinological and biochemical factors undoubtedly modify olfaction, as discussed above. Patients who complain of a continual bad smell are usually suffering from a depressive or psychotic illness. The most readily identifiable centrally based disorder of olfaction is found in uncinate epilepsy, in which an epileptic event originating in the medial temporal lobe is ushered in by the hallucination of an unpleasant smell (and occasionally taste). These olfactory hallucinations are characterized by being both unpleasant and of extremely short duration, usually only a matter of seconds, often insufficient to enable the patient to identify the odour as other than unpleasant – burning rubber or rotting rubbish being the most common descriptions volunteered.

Considerable degeneration of the olfactory glomeruli occurs with age, and olfaction is the first sensory modality to be significantly impaired by increasing age. This probably accounts for the decreasing appetite and loss of interest in food noted by the elderly with their definite tendency to over-season food.[6]

The optic nerve (II)

The orbit is entirely surrounded by structures of otolaryngological significance, only the lateral border being relatively spared from possible infection or invasive pathology other than that arising in the lacrimal gland. The frontal, ethmoid and maxillary sinuses and the lateral wall of the nose bound the orbit superiorly, medially and inferiorly, and are all prone to infection or malignant pathology.

The optic nerve enters the orbit through a tight bony canal, the optic foramen. The nerve is a direct extension of the brain and is invested with glial-derived tissue to the back of the globe, consisting of three membranes. The inner pial sheath invests the nerve and sends septae into the nerve itself, dividing the nerve into a bundle of fascicles. The intermediate arachnoid sheath is very delicate with a potential subarachnoid space inside and a subdural space outside. Both are covered by a thick extension of the dura, which merges with the sclera at the back of the globe. These membranes and enclosed spaces form a direct communication to the intracranial cavity and permit the direct transmission of raised intracranial pressure to the optic disc causing papilloedema, although the exact mechanism of the disc swelling remains uncertain, with venous compression almost certainly playing a major role.

The myelinated fibres of the optic nerve are derived from the rods and cones of the retina. As these cell processes form the most superficial layer of the retina, they are normally non-myelinated until they enter the optic disc. Occasionally, patches of persistent myelination of these fibres produce a characteristic white, fan-shaped lesion in the retina with an associated field defect, which remains unnoticed by the patient, in the same way that one is unaware of the normal blind spot. The most important papillomacular fibres conveying macular vision lie in the medial part of the nerve, only assuming their central position in the nerve as it reaches the optic foramen. In spite of this anatomy, extrinsic compression of the nerve in the orbit and the optic canal preferentially affects these papillomacular fibres, producing a central scotoma rather than a defect spreading in from the periphery, as might be anticipated on purely anatomical considerations (**Figure 111.2**).

There are 1.2 million nerve fibres in each optic nerve, just over half of which decussate in the optic chiasm. The fibres that cross are those derived from the nasal retina, conveying the temporal half field, entering the contralateral optic tract. The temporal half fibres (conveying the nasal field) pass straight into the ipsilateral optic tract.

Lesions within the orbit tend to produce mechanical displacement of the globe with consequent proptosis and diplopia. The optic nerve itself seems remarkably resistant to damage by pressure and displacement in the orbit, although an infective process may be more damaging by vascular mechanisms particularly venous thrombosis.[7, 8]

Lesions in the optic canal readily cause visual disturbance and a central scotoma is often the first evidence of a lesion at this site. This may be followed by extraocular nerve palsies and very much later, proptosis. Meningiomas or neurofibromas are the most frequent tumours arising in the posterior orbit. Neoplastic infiltration from the paranasal sinuses and nasopharynx can occur and metastatic spread from remote sites, such as the prostate in adult males or suprarenal gland in children, are well recognized. In general, the tempo of development of the signs and the presence or absence of pain will indicate the likely diagnosis.[9] The slow painless onset of symptoms usually indicates a benign lesion, while rapidly evolving symptoms, accompanied by pain, indicate a metabolic, neoplastic or infective process in the area.

Involvement of the optic nerve immediately behind the optic foramen can produce bilateral visual problems.

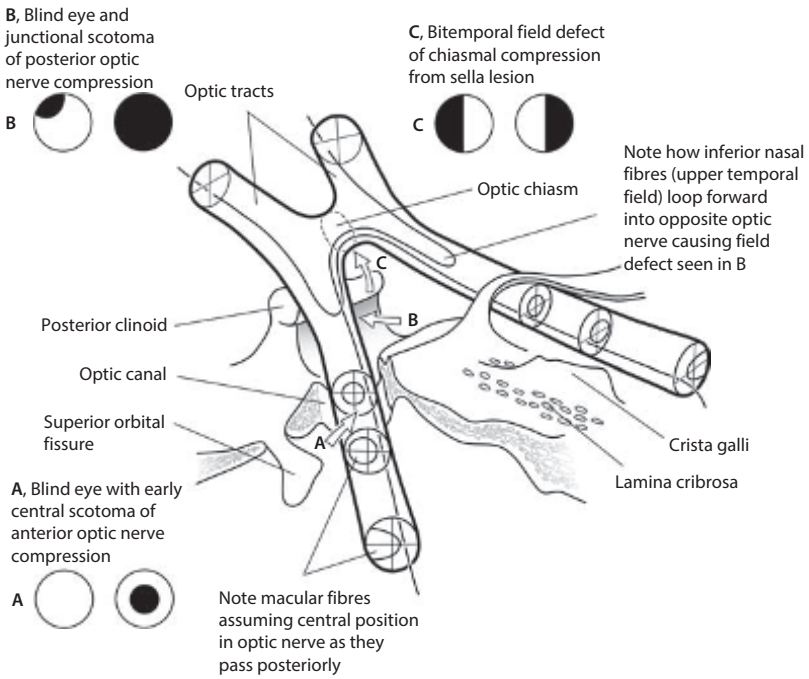

Figure 111.2 The visual pathways.

The inferior nasal fibres of the opposite optic nerve not only cross in the chiasm but also sweep forwards into the optic nerve before turning sharply to head posteriorly into the chiasm and optic tract. They can therefore be damaged by a lesion just anterior to the chiasm. A meningioma of the tuberculum sellae is the most likely lesion to be found at this site. This can produce a blind eye, an upper temporal field defect in the contralateral eye (called a junctional scotoma) and, if large, may cause loss of smell on the same side as the blind eye and eventually papilloedema in the opposite eye, the swelling in the blind eye being prevented by the compressing lesion. This constitutes the well known, but extremely rare, Foster–Kennedy syndrome.

The optic chiasm itself lies more posteriorly than is generally appreciated. It lies above and behind the pituitary gland, not on the sulcus chiasmaticus in front of the pituitary fossa of the skull. Pathological processes in the pituitary region include not only pituitary tumours but neoplasia arising in the ethmoid or sphenoid sinus, mucocoele of the sphenoid sinus and aneurysms arising from the circle of Willis or the great vessels themselves. The importance of excluding vascular anomalies or aneurysms before embarking on the transnasal approach to the pituitary fossa cannot be overemphasized. Lesions extending upwards from the pituitary, damage the underside of the chiasm anteriorly. This produces a bitemporal hemianopia, which starts in and spreads down from the upper temporal field (the lower fibres derived from lower retinal cells – therefore upper field). This field defect is rarely noticed by the patient at this early stage or indeed occasionally even when complete. When testing the temporal visual fields, particular attention should be paid to the upper temporal field to avoid missing a junctional scotoma (see 'Group 1' above and **Figure 111.2**) or the earliest signs of a developing bitemporal hemianopia. In contrast, lesions damaging the chiasm from above and behind tend to affect the lower fields first. These pathologies include craniopharyngiomas, hypothalamic tumours and a dilated third ventricle. Field defects in this area are much more readily identified by the patient as they intrude into all activities, especially reading and walking downstairs.

Because there are many situations in which visual acuity and the visual fields are of help in otolaryngological diagnosis, it is worth describing simple field examination at the bedside. Carefully examined fields, using a red and white hatpin, should be as accurate as screen testing and should only take a few minutes. The examiner should sit in front of the patient (in the traditional otolaryngological position) about 1 m from the patient. The patient should cover one eye. A white 5 mm hatpin, preferably mounted on the handle of a tendon hammer, should be brought into the patient's field of vision on four arcs, upper and lower temporal and upper and lower nasal, respectively. If all are seen at the periphery, no field cut is likely. The pin should then be brought across from the temporal field on the horizontal meridian, the patient keeping the examiner's pupil in view. The blind spot should be detected readily and can usually be compared with that of the examiner, both parties losing the object in the same area. Taking the pin across into the nasal field will detect any small scotoma as the pin will disappear again. The size and shape of the detected scotoma can then be explored and even a small scotoma can be easily confirmed by this technique. At a more sophisticated level, the very earliest evidence of a field defect can be found with the red pin. A 5 mm red pin is used. The visual field is smaller than with a white pin and for reasons that are not clear, the field defect accompanying pregeniculate optic pathway lesions affects red vision first. It is possible to detect a considerable loss of the red field before any intrusion into the white field is apparent. In the early stages, the red object may appear to change to brown or black, but care has to be taken not to confuse the normal loss of brightness of a red object as it passes into the temporal half field, as indicating an early field defect. Ultimately, of course, the red pin will not be detected at all in the affected area.

DIFFERENTIAL DIAGNOSIS OF THE PAINFUL RED EYE

Otolaryngologists are often consulted in cases where blurred vision and diplopia occur in the setting of an inflamed, proptosed eye and may even be the first opinion sought. It is therefore appropriate to consider this diagnostic situation in more detail.[10] Diagnosis falls into four main groups of disorders: inflammatory, vascular, infective and neoplastic.

Inflammatory causes

Acute thyroid exophthalmos

The eye is often injected with chemosis. Lid lag is especially noticeable on downward gaze. There may be diplopia simply due to globe displacement, but actual paralysis of the superior and lateral rectus muscles is a specific feature. In spite of its metabolic basis, the condition is usually unilateral. Vision may be threatened and acute high-dose steroids may be of value in treatment. A CT or MRI scan will usually show marked swelling of the extraocular muscles.

Pseudotumour of the orbit This is an immunologically based inflammatory disorder affecting all tissues in the orbit. It can complicate sarcoid, systemic lupus erythematosus, tuberculosis, Wegener's granulomatosis, polyarteritis nodosa or Tolosa–Hunt syndrome. Proptosis, pain and diplopia associated with a very high sedimentation rate might at first sight all seem to indicate infection. As steroids are indicated, urgent exclusion of infective disease in the paranasal sinuses is vital. CT or MRI scans show normal extraocular muscles in the midst of oedematous orbital contents and will exclude coexistent sinus infection. The condition occurs in two main age groups – between 10 and 30 years and the over 60s.

Vascular causes

Acute caroticocavernous fistula This condition usually follows known trauma with a skull base fracture. Occasionally, an aneurysmal dilatation of the carotid may

rupture into the cavernous sinus producing acute pulsating exophthalmus with marked arterial pulsation visible in the fundal veins. Carotid ligation or embolization is the procedure of choice.

Cavernous haemangioma This condition causes a gradually increasing degree of exophthalmus with proptosis aggravated by bending or straining. There is usually no diplopia or field defect and little pain. The acute proptosis on bending is both dramatic and diagnostic.

Infective causes

Local infections can readily spread into the orbit. Small boils on the nose, eyelids or face in the preantibiotic era had lethal potential and even now are extremely dangerous in diabetics and patients with impaired immunity. Paranasal sinus infection, especially of the ethmoids, can easily extend directly into the orbit. Frontal sinusitis may cause oedema of the eyelid and ptosis. In the diabetic patient, fungal infections, particularly mucormycosis, are a specific problem. The first vesicles of the viral infection *Herpes zoster ophthalmicus* usually erupt in the eyebrow after several days of severe pain and an acute red eye with eyelid oedema is often mistaken for bacterial infection until the vesicles appear.

Neoplastic causes

Any primary or secondary neoplasm may involve the orbit, by direct extension or from remote sites. Chemosis and injection may be minimal. In the elderly, pseudotumour of the orbit can be a presenting symptom of lymphoma and, as always, the importance of a general physical examination must be emphasized, in spite of such a local presentation.

The benign primary orbital tumours most often seen include lipomas, angiomas and haemangiomas. Less frequently, fibromas, myxomas and leiomyomas may be encountered.

Primary malignant orbital tumours are usually rhabdomyosarcomas that are locally invasive and usually occur in childhood. Rarely, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma and haemangioendotheliomas may occur. Lacrimal gland tumours of variable malignancy occur and tend to be locally invasive through the roof of the orbit into the intracranial cavity.

Metastatic tumours in the orbit are secondary to carcinoma of the breast in 50% of cases. Tumours originating in the lung and kidney account for the rest. Malignant melanoma has been reported but is hard to distinguish from a primary melanoma of the ciliary body or retina. In children with neuroblastoma, orbital metastases occur in 20–50% of cases.[11]

PUPILLARY ABNORMALITIES

As the main determinant of pupil size is the incident light, it is appropriate to discuss the major pupillary abnormalities at this stage.

In a blind eye, assuming that the cause of the blindness has not simultaneously damaged the iris mechanism, the pupil will dilate or constrict in proportion to the light falling on the unaffected eye. The direct light reaction will be absent, but the consensual light reflex from the opposite eye will be intact. No consensual reflex in the normal eye will be seen when the affected eye is illuminated. This is a useful check for suspected non-organic visual loss in one eye.

In acute retrobulbar neuritis, which presents as sudden impaired central vision in one eye, the pupil reaction may be sluggish and the pupil may dilate after initial constriction in spite of a constant light source being maintained (pupillary escape phenomenon). In a patient with eye pain, aggravated by movement with blurred vision, this Marcus–Gunn pupil reaction is strongly indicative of demyelinating disease. The postulated mechanism is a decrease in the number of fibres conveying light sensation.

In IIIrd nerve lesions, damage to the efferent pupilloconstrictor fibres produces a fixed dilated pupil even though the patient perceives light normally. Incomplete lesions may merely cause a slightly dilated pupil with a sluggish reaction – an important stage in the evolution of a IIIrd nerve palsy in a patient who is deteriorating following a head injury. A useful clue in a conscious patient developing a IIIrd nerve lesion is the almost invariable accompanying ptosis. This may be followed by diplopia due to paralysis of the superior rectus muscle (see 'The oculomotor nerve (III)' below). Argyll Robertson pupils due to meningovascular syphilis have become a great rarity. This is a small pupil, usually irregular, that does not react to light but reacts normally to accommodation.[12]

A sympathetic nerve lesion (Horner syndrome) will be detected by only the most alert clinician. Due to loss of the less important pupillodilator fibres, the pupil is slightly smaller with a normal light reaction because the light reflex pathway mechanisms are unaffected. A slight and variable degree of ptosis will occur, which rarely droops lower than the edge of the pupil. As the cervical sympathetic pathway courses in and out of otolaryngological territory, a full understanding of the syndrome is essential to the otolaryngologist (see also 'Group 3' below, and **Figure 111.16** under 'The cervical sympathetic' below).[13]

A Holmes–Adie (myotonic) pupil may present as a painful eye as the affected pupil fails to constrict in bright light. The affected pupil may be larger or smaller than the other, depending on the incident light, which produces either a slower constriction or slower dilatation than in the unaffected eye. The light reaction is a very slow, with definite constriction followed by a slow dilatation. This slow myotonic reaction is often best demonstrated by maintained forced convergence for about one minute, which is a much stronger stimulus to pupil constriction. Alternatively, if the patient sits in a dark room, the pupil will become very large, but if they have just come into the clinic from a sunlit room, at first the affected pupil may be smaller than the normal pupil.[14] Vision will be blurred when the pupil is large as close focusing is impossible.

The nerve supply to the extraocular muscles

The three nerves supplying the extraocular muscles and controlling eye movements have complex central control mechanisms and peripheral courses that render them vulnerable both individually and as a group, to a wide range of surgical and medical disorders. They are of special interest to otolaryngologists because of their involvement in local neoplastic disease and in infective processes originating in the paranasal sinuses, nose and nasopharynx.

The oculomotor nerve (III)

The IIIrd nerve exits from the brainstem in the interpeduncular fossa and runs forwards, laterally and slightly downwards in the subarachnoid space towards the roof of the cavernous sinus (**Figures 111.3**, **111.4** and **111.5(a)**). In its distal subarachnoid course, it runs parallel to the posterior communicating artery, hence its unique vulnerability to damage by aneurysms, which commonly arise at either end of this short vessel. It enters the roof and then the lateral wall of the cavernous sinus in between the two layers of dura, dividing into two branches before it enters the superior orbital fissure. In the wall of the sinus it picks up sympathetic fibres from the sympathetic plexus on the carotid artery and additional parasympathetic fibres from the ophthalmic division of the Vth nerve.

The superior ramus supplies the levator palpebrae superioris and the superior rectus muscle. The inferior ramus supplies the medial and inferior recti, the inferior oblique and carries the sympathetic and parasympathetic elements to the ciliary ganglion via the branch to the inferior oblique.

The anatomy of the pupillary fibres within the nerve is of great significance. The fibres at first lie dorsolaterally, then medially and finally inferiorly, but always in the periphery of the nerve. Their blood supply is derived from the pial plexus on the surface of the nerve, while the core of the nerve is supplied by a vasa nervorum. If this latter vessel is occluded by vascular disease (diabetes, arteriosclerosis, arteritis), the pupillary fibres lying peripherally are usually spared. Conversely, if the nerve is damaged by an external compressive surgical lesion (aneurysm, tumour, abscess), the peripheral pupillary fibres are those most easily affected. In a patient who has a IIIrd nerve lesion, the involvement or otherwise of the pupil is a major diagnostic pointer. Furthermore, pain tends to be a feature of surgical lesions, so the painful onset of a IIIrd nerve lesion with pupil involvement is almost certain to indicate a compressive lesion. The absence of pain and a spared pupil is almost certain to indicate a medical cause.[15] The major exception to these generalizations is that a lesion due to diabetes can be both painful and involve the pupil, mimicking a surgical lesion. A serum glucose estimation can be a very inexpensive way of resolving this dilemma.

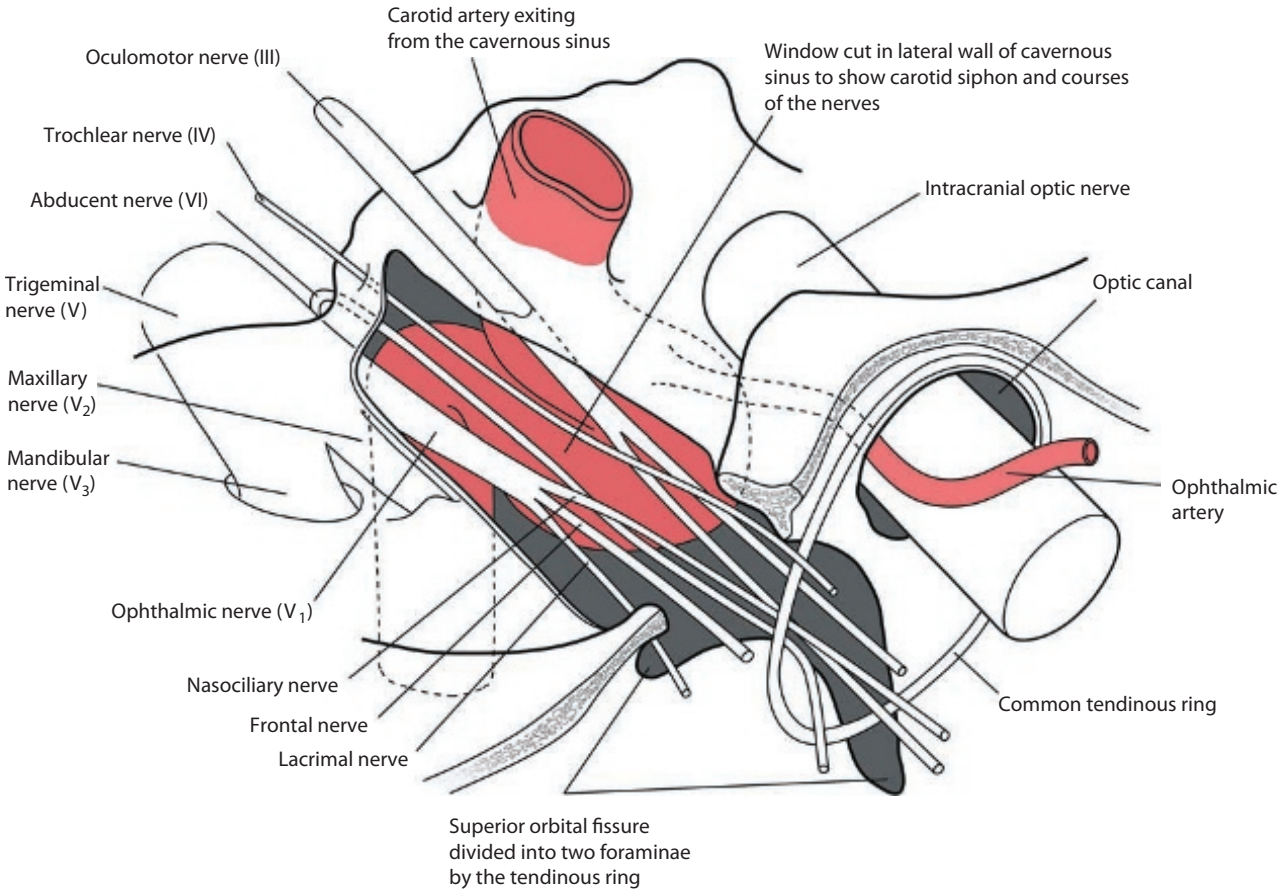

Figure 111.3 The cavernous sinus and orbital foramina.

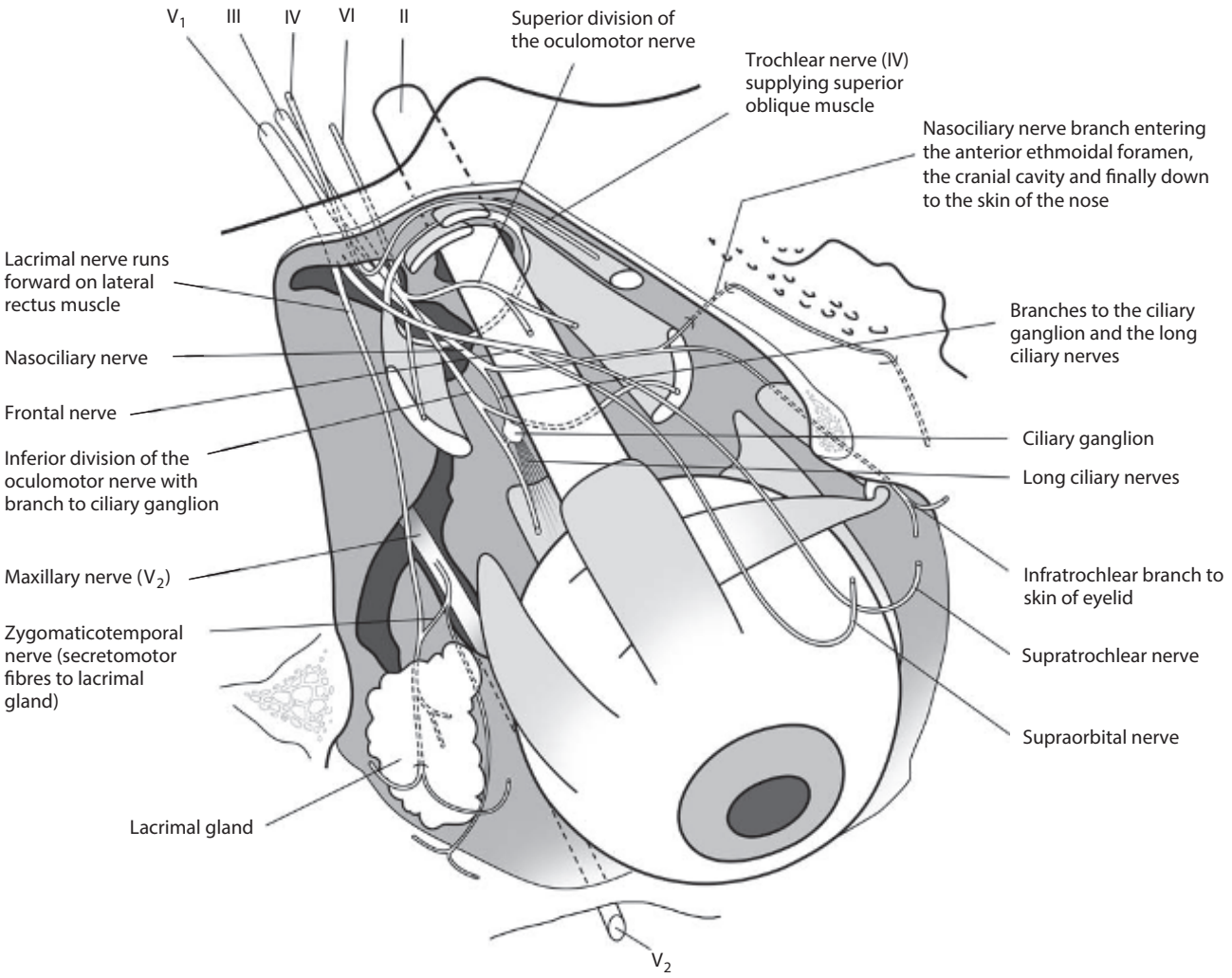

Figure 111.4 The orbital contents (right orbit from above and lateral).

CENTRAL ANATOMY

The detailed anatomical features of the oculomotor nucleus are beyond the scope of the present text. Briefly, the nucleus is shaped like an inverted V, straddling the midline (see **Figure 111.5(a)**). The lateral nuclear columns supply the eyelid and the four extraocular muscles, the superior, medial and inferior rectus and the inferior oblique. The midline nuclei have mainly parasympathetic function especially the upper midline Edinger–Westphal nucleus, which is the main central control mechanism for pupil size. The fascicles of the IIIrd nerve fan out, course towards the anterior midbrain traversing the red nucleus and the substantia nigra, converging to form the main nerve trunk, which emerges just lateral to the midline in the interpeduncular fossa.

The trochlear nerve (IV)

The IVth cranial nerve is unique in several ways. It arises in the dorsal aspect of the brainstem at the level of the inferior colliculus. It then decussates within the superior medullary velum so that the right nucleus supplies the left superior oblique muscle and vice versa (see **Figures 111.4** and **111.5(b)**). It also has the longest intracranial course and is very slender, properties that possibly protect it from damage by extrinsic pressure around the brainstem and in the subarachnoid space. It enters the wall of the cavernous sinus beneath the IIIrd nerve, but crosses it to reach a higher position as it enters the superior orbital fissure to supply the superior oblique muscle. The nerve is rarely damaged in isolation in cavernous sinus lesions, the IIIrd and VIth nerves being much more vulnerable. A vascular lesion of the nerve due to diabetes is the most common cause. Of particular importance to the otolaryngologist is the small fibrocartilaginous loop attached to the trochlear fossa in the upper medial orbit through which the muscle tendon loops. Accidental or surgical trauma in this region may easily damage the tendon interfering with the action of the superior oblique muscle, mimicking a IVth nerve palsy.[16]

The abducent nerve (VI)

The VIth nerve exits from the brainstem anteriorly at the pontomedullary junction (see **Figures 111.3**, **111.4** and **111.5(c)**).

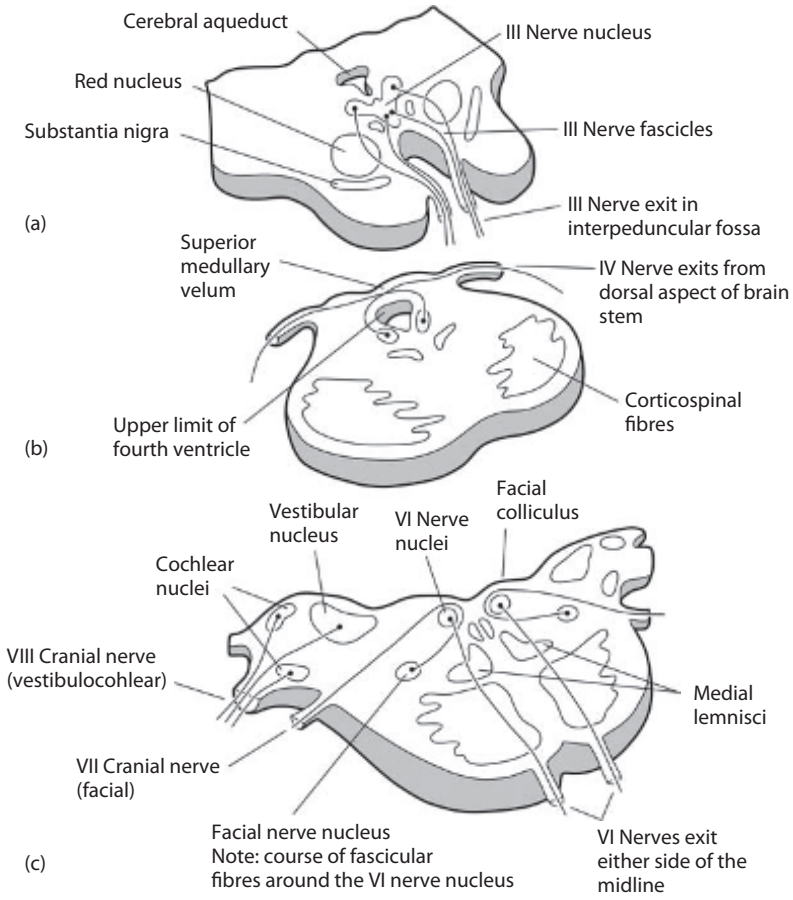

Figure 111.5 Brainstem connections of the extraocular nerves.

It is the most medial of the three nerves which exit from this groove, and ascends on the front of the pons before it angles forwards across the tip of the petrous bone to enter the bottom of the cavernous sinus in which it lies free, in close relationship to the intracavernous portion of the carotid artery. This long subarachnoid and meningeal course adjacent to the meninges renders this nerve particularly liable to damage in acute and chronic meningitis or any other meningeal process. This notably includes the remote or direct spread of malignant disease. The angulated entry into the cavernous sinus renders it vulnerable to stretch when the brainstem is pushed downwards by raised supratentorial pressure, causing the classical false localizing VIth nerve palsy, which may ultimately become bilateral if unrecognized. The nerve may become involved in inflammation of the petrous bone, secondary to otitis media. This may be combined with severe pain in the Vth nerve territory and loss of hearing, which is Gradenigo's syndrome. Inflammatory disease in the cavernous sinus and aneurysmal dilatation of the carotid siphon within the cavernous sinus are particularly likely to involve the VIth nerve, the IIIrd and IVth being involved later by the same process. Nerve trunk infarction secondary to diabetes, arteritis and arteriosclerosis occurs exactly as for the IIIrd and IVth nerves discussed above. Intracranially, both cholesteatomas and vestibular schwannoma could involve the nerve, but such involvement is surprisingly rare. As it enters the orbit it passes laterally to reach its single supplied muscle, the lateral rectus (see **Figure 111.3**). At this point it is particularly liable to damage by carcinoma infiltrating the orbit through the inferior orbital fissure from the nasopharynx.[17]

CENTRAL ANATOMY

The nucleus of the VIth nerve lies in the floor of the IVth ventricle just lateral to the midline (see **Figure 111.5(c)**). The fibres of the facial nerve sweep round it. Although derived from the same nuclear column as the IIIrd and IVth nerve nuclei, it migrates downwards during the massive developmental enlargement of the pons, but remains intimately linked to the other nuclei by the medial longitudinal bundle (see 'Central mechanisms of nerves III, IV and VI' below). The fascicles of the VIth nerve have to traverse the whole depth of the pons to reach their point of emergence at the pontomedullary junction. In its fascicular course, it lies in close relationship to the ascending medial lemniscus and the descending corticospinal pathways.

CENTRAL MECHANISMS OF NERVES III, IV AND VI

The central control mechanisms for eye movement comprise a complex group of pathways that adjust eye position to movement and posture, mainly under the influence of vestibular and extrapyramidal pathways (**Figure 111.6**).

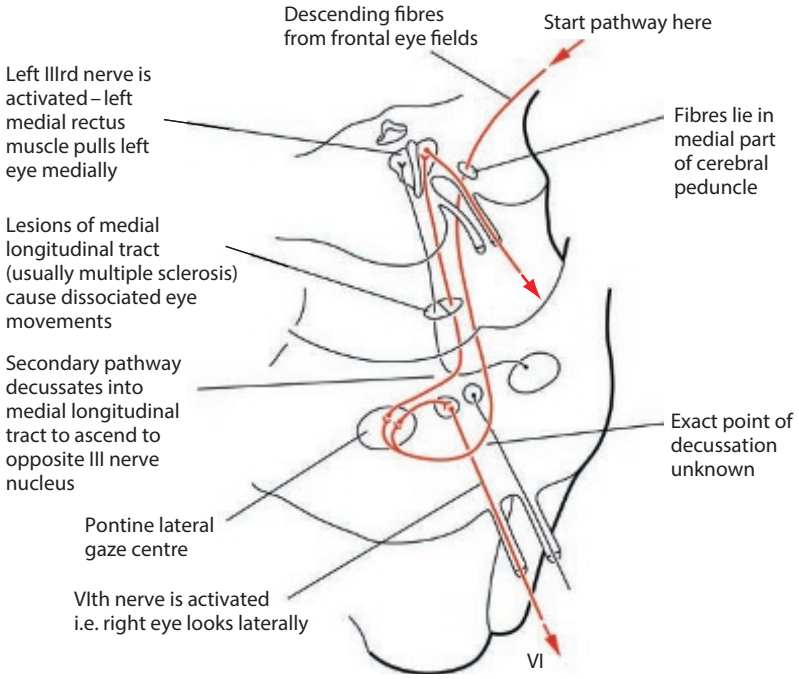

Figure 111.6 The internuclear pathways. Pathway shown moves both eyes to the right side.

There are two forms of voluntarily controlled eye movement:

1. Visual pursuit, where a specific target is fixed and followed, using parietal gaze centres closely integrated with the adjacent visual cortex
2. The ability to select a new target and relocate vision to suit, via frontal gaze centres utilizing direct voluntary pyramidal motor pathway mechanisms.

Damage in either of these areas will cause a conjugate gaze palsy, but because the range of movement of both eyes is identically affected, there is no diplopia. At brainstem level, the need to integrate eye movements controlled by three different cranial nerve nuclei widely spaced in the brainstem requires complex and extremely rapidly conducting internuclear pathways. The most critical of these is the medial longitudinal fasciculus. Damage in this pathway causes internuclear ophthalmoplegias, with disconjugate gaze palsies. These will always cause diplopia as the eyes then move independently.

The cortical influences have final relays in the brainstem in the pons bilaterally, the lateral gaze centres. There are also four gaze centres in the midbrain, two on each side, one to look up and one to look down. Eye movements occur in saccades, a series of little jerk movements without over- or undershoot, until the new position is reached. This is achieved by rapid bursts at 1000 cycles per second by cells in the gaze centres. These bursts are initiated by voluntary information from the frontal eye fields through the anterior limb of the internal capsule. Automatic movements as required in reading are controlled by visual information carried through the optic tract without projection to the visual cortex. Feedback from stretch receptors in the ocular muscles is also of great importance in this type of movement. Tracking movements are integrated in the superior colliculi, once the object to be followed has been located, using stereooptic control.

Vergence mechanisms require the voluntary frontal eye fields to work in conjunction with the parietal cortex simultaneously inhibiting those brainstem mechanisms that normally prevent convergence and divergence. Only animals with binocular stereoscopic vision have the need to converge to focus close objects.

PARIETAL LOBE LESIONS

Poor object following or pursuit gaze problems are often difficult to demonstrate clinically as lesions in these areas also tend to cause a hemianopic field defect, so that the following movement ceases as the object moves into the blind half-field. If, however, the examiner is careful to keep the object in the patient's retained field of vision, a full range of pursuit movement should be achieved if there is no gaze palsy. A tendency to ignore objects on one side in the absence of a hemianopia (an attention field defect) may be related to the inability of the eye to scan peripherally due to lack of visual input.

FRONTAL LOBE LESIONS

An active irritative lesion, such as a tumour or abscess in the frontal pole, will drive the eyes away from the lesion. A right frontal tumour may cause focal epileptic fits preceded by movement of the head and eyes to the left hand side before the patient loses consciousness. An inactive destructive lesion, such as surgical extirpation or a cerebrovascular accident, will permit the eyes to gaze preferentially towards the side of the lesion, due to the unopposed push from the intact side. This phenomenon is most readily seen in a drowsy, anaesthetized or unconscious patient.

MIDBRAIN LESIONS

Midbrain visual mechanisms are mainly concerned with up and down gaze. The classical lesion causing Parinaud's syndrome is a pineal tumour damaging the superior colliculus and the region of the posterior commissure. A lesion here blocks the light reflex relays, producing fixed dilated pupils, impairs upward gaze and causes loss of convergence.

Conversely, lesions of the inferior colliculus will impair downward gaze only. In some instances, the ineffective movements of the extraocular muscles attempting to produce up or down gaze may pull the eyeball in and out of the socket, resulting in the very rare phenomenon known as retractory nystagmus.

Lesions affecting the thalamic nuclei, either structural or pharmacological, may cause fixed deviations of up or down gaze. In patients with postencephalitic Parkinson's disease, episodes known as an oculogyric crisis were a classic feature. This can still be seen in some patients provoked by phenothiazine hypersensitivity, usually young females. Thalamic lesions may cause complex eye movement disorders with divergence with one eye up and one eye down (skew deviation) and see-saw nystagmus on attempted lateral eye movement. A midline haemorrhage between the IIIrd nerve nuclei or acute multiple sclerosis in the same area can produce a divergent squint with both eyes at the extremes of lateral gaze with retained up and down gaze limited only by the mechanical factors operating at this extreme position.

DISORDERS AFFECTING THE MIDBRAIN

Anteriorly, aneurysms of the upper basilar artery or a tortuous basilar artery (basilar ectasia) may damage and distort the emergent IIIrd nerves. Posteriorly, pineal tumours or distortion and dilatation of the posterior end of the IIIrd ventricle due to aqueduct stenosis may cause Parinaud's syndrome. Infiltration of the superior medullary velum by direct spread of a medulloblastoma may cause bilateral IVth nerve lesions and impaired down gaze. Intrinsic lesions due to vascular occlusion, haemorrhage, demyelinating disease and tumour, may all cause an anterior internuclear ophthalmoplegia (i.e. a divergent squint with loss of convergence but preserved up and down gaze).

There are three named vascular syndromes of the midbrain due to combinations of IIIrd nerve lesions and local pathway damage:

1. **Nothnagel's syndrome**: a IIIrd nerve lesion with ipsilateral ataxia due to infarction of the superior cerebellar peduncle
2. **Benedikt's syndrome**: a IIIrd nerve lesion with contralateral cerebellar movement disorder due to a lesion of the red nucleus
3. **Weber's syndrome**: a IIIrd nerve lesion with contralateral hemiparesis due to a lesion of the basis pedunculi.

These syndromes have become extremely rare with the demise of meningovascular syphilis, but are still occasionally encountered in patients with small vessel disease (diabetes, cranial arteritis, lupus erythematosus, polyarteritis nodosa, polycythaemia rubra vera, etc.). Unfortunately, the resurgence of sexually transmitted disease means that these classical syndromes should not yet be consigned to history.

PONTINE LESIONS

The pontine lateral gaze centres are often damaged by vascular lesions and demyelinating disease. This results in loss of gaze to the same side as the lesion, as the descending pathways have already decussated. In a drowsy or unconscious patient, this will result in the eyes deviating towards the unaffected side.

DISORDERS AFFECTING THE PONS

Anteriorly, the VIth nerves are often involved in bacterial, fungal or malignant meningitis due to their long meningeal course. Pontine tumours may involve the nerve nuclei or fascicular fibres and the posterior internuclear pathways. These tumours usually occur in children or adults with neurofibromatosis. Tumours blocking or infiltrating the IVth ventricle cause headache and vomiting due to CSF pathway block and VIth nerve palsies, due to stretching of the nerves by raised intracranial pressure. If the VIth nerve palsy is due to direct tumour infiltration, the VIIth nerve should also be involved, as the VIIth nerve fibres encircle the nucleus. These tumours include ependymoma, medulloblastoma, cerebellar astrocytoma or haemangioblastoma. Multiple sclerosis, haemorrhage and infarction, metabolic disorders (vitamin B deficiency), drug intoxication, fluid balance disturbance, viral infection and *Listeria monocytogenes* infection of the brainstem may all cause conjugate gaze palsies if the damage is in the lateral pons or an internuclear ophthalmoplegia with nystagmus, if the lesion is in the central pons. Vascular occlusive lesions cause strictly unilateral internuclear ophthalmoplegia as the lesion extends only to the midline. There are numerous named vascular syndromes of the pons due to a variety of combinations of damage to the nuclei of nerves VI and VII and their fascicles and the sensory, motor and cerebellar pathways. There is no special advantage in learning these by heart, but the named syndromes include those of Millard–Gubler, Foville, Grenet, Raymond-Céstan, Marie-Foix and Gasperini.[18] As a cautionary note, any hint of variability in diplopia should always raise the possibility of ocular myasthenia gravis. If combined with variable dysarthria or intermittent swallowing difficulty, a brainstem lesion may be incorrectly suspected. This is a very difficult diagnostic trap into which even experienced neurologists may fall.

INTERNUCLEAR LESIONS

Internuclear lesions are typically caused by multiple sclerosis (bilateral) or vascular disease (strictly unilateral unless haemorrhagic) (see **Figure 111.6**). In these instances, the lateral gaze centre is intact and abducts the ipsilateral eye normally. It is the relay to the opposite IIIrd nerve nucleus

that is blocked and the eye that should adduct in unison fails to move beyond the midline. If the lesion is bilateral, neither eye adducts, while the abducting eye moves normally and the mobile eye shows marked nystagmus at full abduction. This syndrome is almost diagnostic of multiple sclerosis. The integrity of the upper brainstem in such cases can be readily demonstrated by intact vertical gaze and convergence.

NYSTAGMUS

Nystagmus is covered in detail in Chapter 49, Physiology of equilibrium; and Chapter 62, Evaluation of balance. From a simplistic neurological point of view, it is a less valuable physical sign than is often thought.

The distinction into the different types (jerk, pendular, rotatory, etc.) is often less easy to make than is suggested in most descriptions. Ultimately, one is seeing the effect of a breakdown in the vestibular mechanisms as they affect the smoothness and stability of eye movements. Weak support from vestibular mechanisms will lead to poor maintenance of gaze (slow phase) and a quick restorative movement (the jerk phase), which is the feature used to define the direction of nystagmus. This is maximal when looking away from the side of a vestibular lesion, be it in the end organ, VIIIth nerve or vestibular nuclear connections.

The controlling influence over vertical eye movements also becomes apparent in the phenomenon of vertical nystagmus, which occurs with structural or metabolic lesions of the brainstem. It is important to note that vertical nystagmus means vertical displacement of the eyes, not side-to-side nystagmus when attempting upward or downward gaze. As defined, vertical nystagmus always indicates brainstem dysfunction.

Another feature of brainstem disease is jelly nystagmus, which is probably due to failure of inhibitory 'pause' neurons, which normally stop the 'burst' neurons from producing visible little saccades. In this condition, the eyes wobble with no clear-cut fast or slow component. Congenital nystagmus produces a similar type of nystagmus – the diagnostic feature being that the patient is quite unaware of it in spite of very dramatic wide amplitude nystagmus.

Cerebellar lesions, especially those affecting the flocculonodular lobes, result in nystagmus due to the loss of the stabilizing effect of input from head posture receptors. In general, the fast and therefore most readily observed phase of cerebellar nystagmus is towards the side of a cerebellar lesion.

GROUP 2

The second major grouping of cranial nerves comprises those lying in the cerebellopontine angle. The medial extent of the angle is defined by the VIth nerve, the upper extent by the Vth nerve and the lower extent by the IXth nerve. The VIIth and VIIIth nerves pass in close proximity across the subarachnoid space to enter the internal auditory canal at the start of their long intraosseous courses.

The trigeminal nerve (V)

The trigeminal nerve is the largest cranial nerve and arises from the middle of the lateral side of the pons and passes forwards and laterally across the subarachnoid space. Its large ganglion lies over the tip of the petrous bone where the nerve divides into its three divisions.

The opthalmic nerve (V_1)

The first division of the Vth nerve lies below the VIth nerve in the lateral wall of the cavernous sinus (see **Figures 111.3** and **111.4**) and is prone to damage by the same pathologies that cause extraocular nerve palsies (see above). Due to its extensive sensory distribution, severe pain in the eye, forehead, nose and scalp, extending back as far as the vertex, may result from such damage. The nerve divides into three branches as it enters the superior orbital fissure:

1. The lacrimal nerve runs along the lateral rectus muscle to supply the lacrimal gland. It also supplies the skin over the lateral eyelid and brow. It picks up secretomotor fibres from the zygomaticotemporal nerve, which it conveys to the lacrimal gland. In the skin, it receives proprioceptive filaments from the facial nerve.
2. The frontal nerve divides into two, the supratrochlear and supraorbital nerves, which supply the skin of the forehead and scalp to the vertex. They are prone to damage by minor injuries over the brow and a causalgic syndrome may follow local trauma.
3. The nasociliary nerve has important autonomic and cutaneous functions:
   a. The main trunk traverses the orbit and enters the anterior ethmoidal foramen into the intracranial cavity, runs forwards across the cribriform plate and exits the skull through a slit in the crista galli to enter the nose. It supplies the mucosa of the nasal cavity and emerges at the lower end of the nasal bone to supply the skin over the tip of the nose, alar and vestibule.
   b. In the orbit, the nasociliary nerve gives off branches to the ciliary ganglion and two or three long ciliary nerves which carry the pupillodilator sympathetic fibres and convey sensation from the cornea. This is of cardinal importance for the protection of the very delicate cornea.
   c. The infratrochlear branch is given off just behind the anterior ethmoidal foramen and lies on the medial wall of the orbit and supplies the skin of the upper medial eyelid and upper side of the nose.

THE CORNEAL REFLEX

It is essential that otolaryngologists know how to elicit this reflex correctly. The afferent limb of the reflex is via the nasociliary nerve, as above, and the efferent limb is via the facial nerve. A pointed wisp of cotton wool should be used. The examiner should ask the patient to look upwards, then, resting the hand on the patient's cheek, the wisp should be applied to the lower cornea but taking

care not to bring it into vision or a blink reflex will result. The patient will flinch, the eyeball will roll up and the eye will attempt to close. Even if the VIIth nerve is paralyzed, the eyeball will roll up and the discomfort will be felt. The opposite eyelid will also close as this is a consensual reflex. Absence of the corneal reflex is often the first clinical evidence of Vth nerve damage and should be tested obsessionally in any patient presenting with symptoms of vertigo, deafness or facial pain.

The maxillary nerve (V_2)

The middle branch of the Vth nerve ganglion lies in the extreme lower lateral wall of the cavernous sinus and exits via the foramen rotundum, passes through the pterygopalatine fossa and enters the floor of the orbit via the inferior orbital fissure (**Figure 111.7**). At first, it lies in a groove in the orbital floor and then enters the short canal and exits on to the face via the infraorbital foramen. It supplies the skin of the cheek, midlateral nose and lateral part of the alar, lower eyelid and the mucous membrane of the cheek and upper lip. In its course, it gives off the following branches:

1. Meningeal branches to the floor of the middle cranial fossa
2. Two branches to the sphenopalatine ganglion, conveying the secretomotor fibres destined for the lacrimal gland
3. The zygomatic nerve, which lies on the floor of the orbit, dividing into the zygomaticotemporal nerve (secretomotor to the lacrimal gland and carrying cutaneous sensation from the temporal area) and the zygomaticofacial nerve which, after penetrating the zygomatic bone, carries cutaneous sensation from the prominence of the cheek
4. The three alveolar nerves convey sensation from the teeth, gums and adjacent palate via the superior

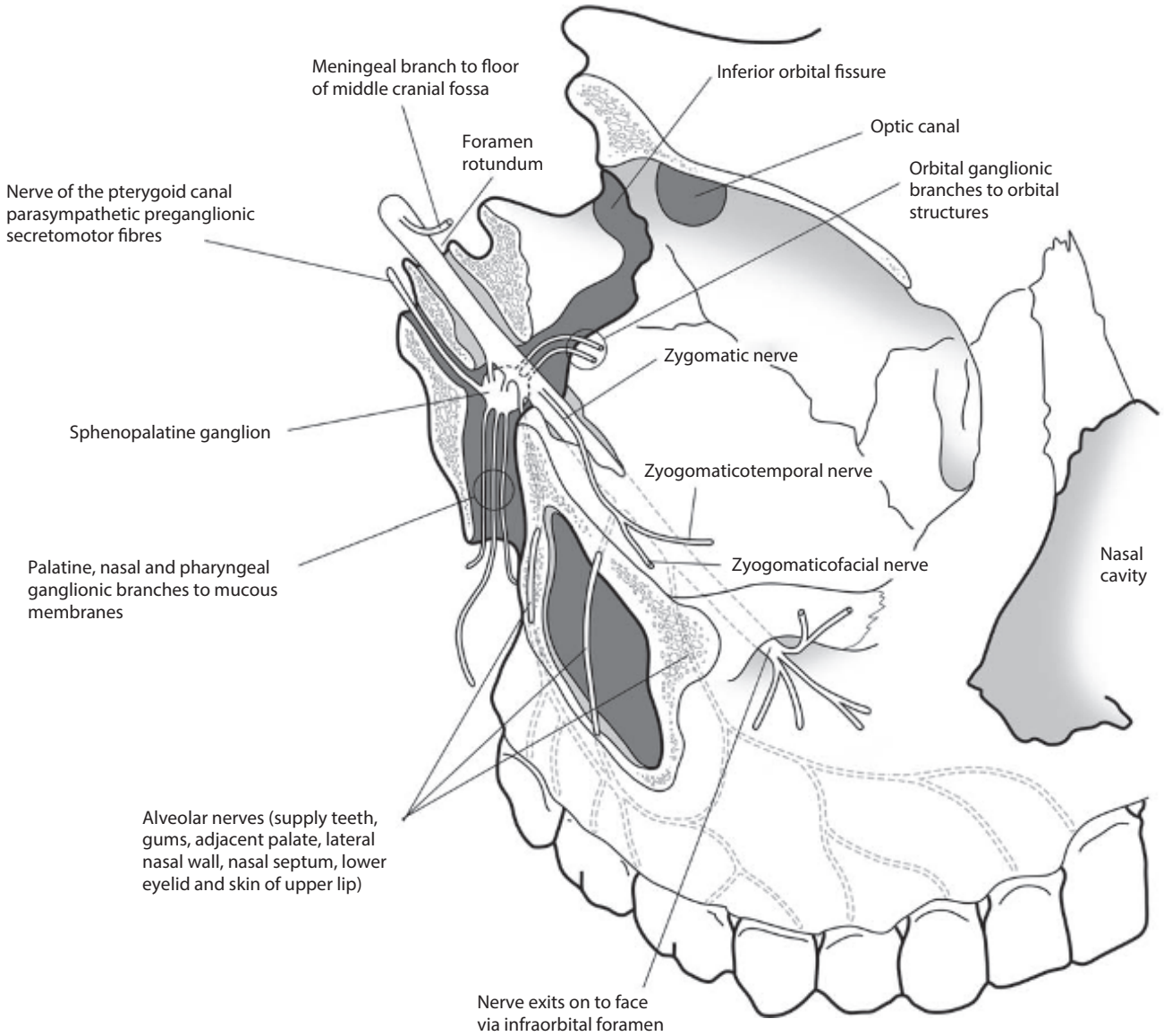

Figure 111.7 The maxillary nerve (V_2).

dental plexus. The anterior superior branch is the largest and supplies not only the incisor and canine teeth, but also the lateral nasal wall, nasal septum, the lower eyelid and the skin of the upper lip.

THE PTERYGOPALATINE (SPHENOPALATINE) GANGLION

This very large ganglion is suspended from the maxillary division, deep in the pterygopalatine fossa. It receives its main contribution from the nerve of the pterygoid canal. This carries preganglionic, parasympathetic fibres derived from the pontine lacrimatory nucleus via the nervus intermedius (VIIth nerve) and sympathetic elements derived from fibres on the middle meningeal artery. Both groups of fibres are then relayed via their subsequent complex course to the lacrimal gland in the lacrimal branch of the nasociliary nerve. The main outflow of the ganglion is via the orbital, palatine, nasal and pharyngeal nerves to the mucous membranes of the orbit, nasal passages, pharynx, palate and upper gums.

The mandibular nerve (V_3)

This is the largest branch of the Vth nerve and includes the motor branch. It exits from the skull base through the foramen ovale, the main sensory trunk being joined by the much smaller motor root, in Meckel's cave, just outside the skull (Figure 111.8). A meningeal branch re-enters the skull with the middle meningeal artery through the foramen spinosum and conveys sensation from the lateral, middle and anterior cranial fossae. A small branch, the nerve to the medial pterygoid, supplies medial pterygoid, tensor tympani and tensor veli palatini. The main nerve then divides into anterior and posterior trunks.

The anterior trunk conveys the bulk of the motor root to supply the masseter, temporalis and lateral pterygoid muscles. The main branch of the anterior trunk is the buccal nerve, which merges with the buccal branches of the facial nerve to convey sensation from the skin over buccinator, the mucous membranes of the cheek and the posterior part of the buccal surface of the gum.

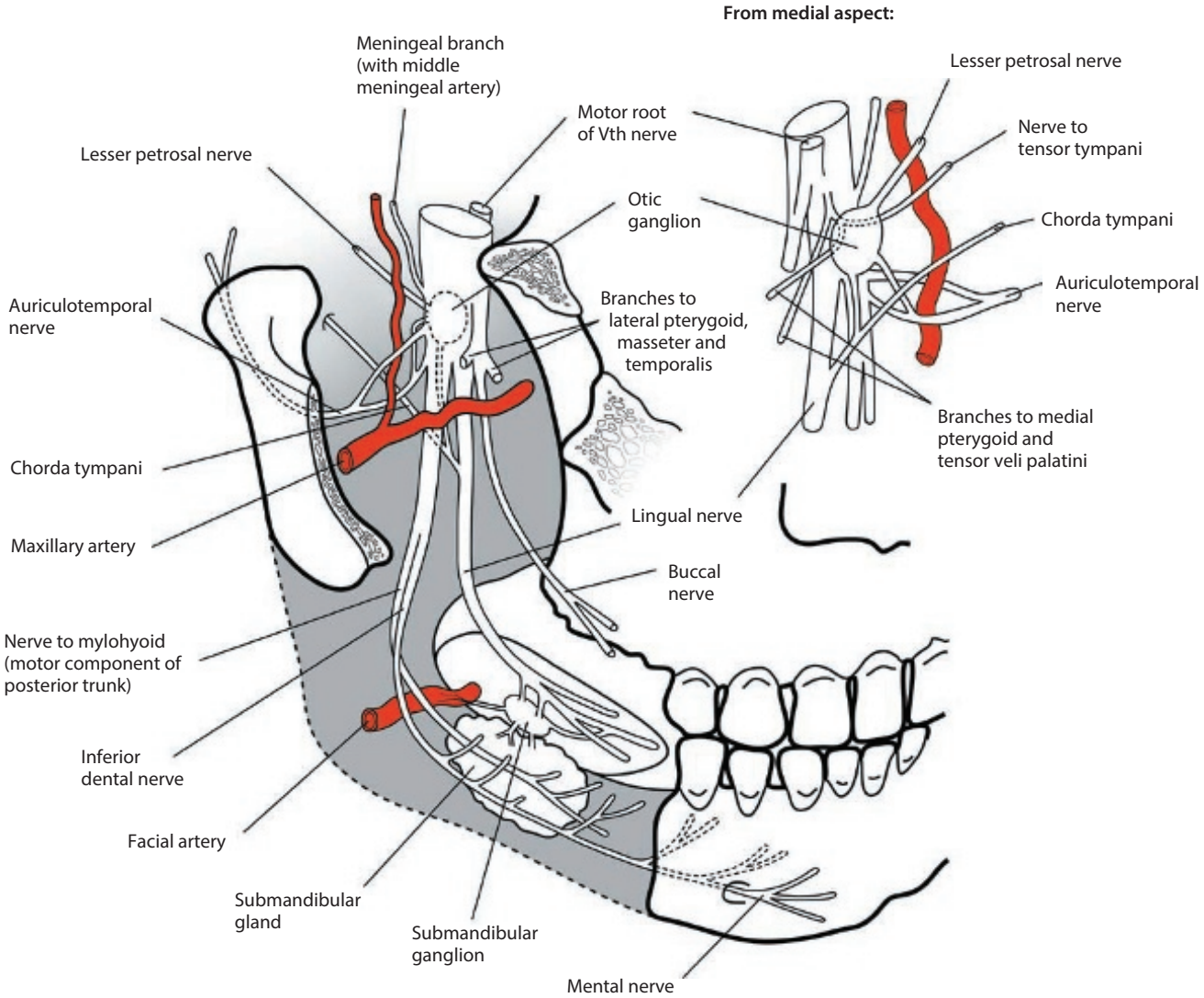

Figure 111.8 The mandibular nerve (V_3).

The posterior trunk is mainly sensory and divides into three main nerves:

1. **The auriculotemporal nerve**, which passes behind the temporomandibular joint to join the facial nerve with which it is distributed to supply the skin over the tragus, helix, auditory meatus and tympanic membrane and, via superficial temporal branches, to the skin over temporalis. It also conveys the secretomotor fibres to the parotid gland and fibres derived from the tympanic branch of the glossopharyngeal nerve via the otic ganglion (see 'The facial nerve (VII)' below).
2. **The lingual nerve**, which carries sensation from the presulcal tongue, the floor of the mouth and lower gums. It also carries the taste fibres of the chorda tympani from the mucous membranes of the anterior two-thirds of the tongue and conveys secretomotor fibres from the submandibular ganglion to the sublingual and anterior lingual glands. It communicates with the hypoglossal nerve.
3. **The inferior alveolar (dental) nerve** enters the mandibular canal running forwards in the mandible to re-emerge on the chin at the mental foramen dividing into the incisive and mental branches, supplying sensory fibres to the skin and mucous membrane of the lower lip, jaw, incisor and canine teeth. The motor component of the posterior trunk leaves the inferior alveolar nerve, just before it enters the mandibular canal, as the mylohyoid nerve supplying mylohyoid and the anterior belly of digastric.

CENTRAL MECHANISMS OF THE VTH NERVE

The central anatomy of the Vth nerve is very complicated. The small motor nucleus lies in a midposition in the upper lateral pons opposite the nerve root. It receives bilateral supranuclear innervation from corticobulbar fibres, which leave the main pyramidal pathways at the level of the nucleus (**Figure 111.9**). Direct connections with proprioceptive fibres in the adjacent main sensory nucleus allow a simple stretch reflex for mastication to operate. The jaw jerk tests the integrity of this pathway and, if greatly enhanced, indicates a bilateral upper motor neuron lesion above midpontine level, the highest stretch reflex that can be elicited.[19]

The sensory nucleus is very extensive. The cell bodies of the sensory fibres lie in the gasserian ganglion overlying the petrous apex. At least 50% of the fibres do not enter the main sensory nucleus but are concerned solely with stretch reflex activity. The other fibres form ascending and descending branches. The ascending fibres enter the mesencephalic nucleus of the Vth nerve. Their subsequent course and exact function is not understood. The descending fibres convey pain and temperature sensation and synapse in the nucleus of the descending tract of the Vth nerve, which lies adjacent to the descending tract itself and extends as low as C2 cord level. The sensory fibres derived from the facial, glossopharyngeal and vagus nerves all join the same tract and relay in the same nucleus. The secondary ascending pathway fibres swing across the brainstem, ventral to the central canal to become the secondary ascending tract of the Vth nerve, which is adjacent to the medial lemniscus,

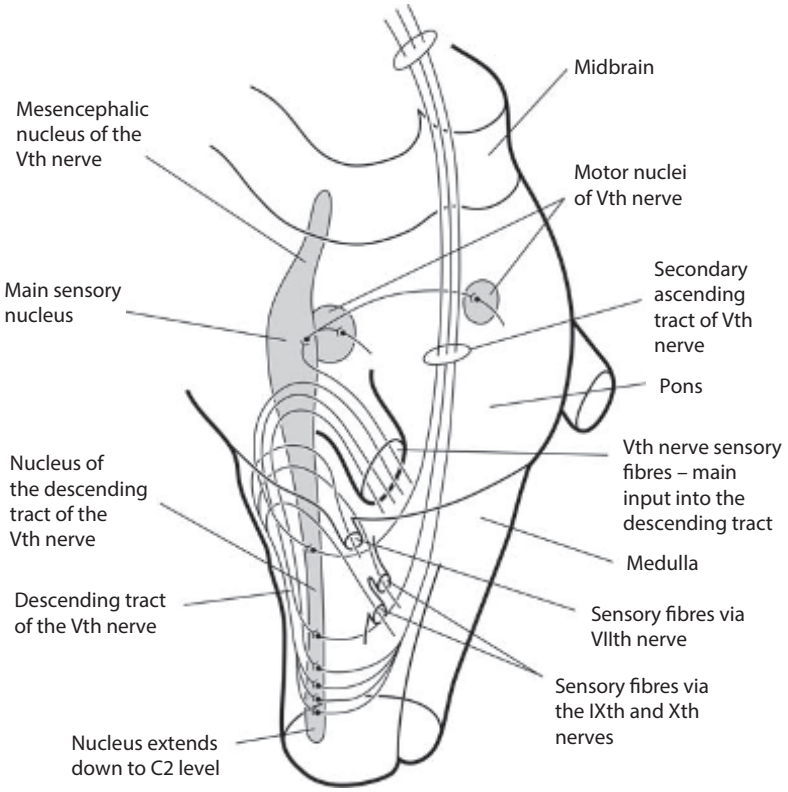

Figure 111.9 Central sensory pathways.

adding sensation derived from the face to that of the arm and leg in the latter pathway. In the decussation, these fibres are very vulnerable to damage by midline lesions, such as syringomyelia and syringobulbia, producing a classical sensory deficit, typically extending forwards from the back of the head. This is the so-called 'onion peel' or 'balaclava' sensory deficit, which may leave sensation intact only over the nose and central face in the final stages of its development.

CLINICAL ASPECTS OF THE VTH CRANIAL NERVE

Damage to the Vth cranial nerve is very important to the otolaryngologist. Branches of the nerve and its associated ganglia lie in areas often involved by otolaryngological disease, especially oropharyngeal and nasopharyngeal neoplasms. Involvement of the motor root of the Vth nerve is quite rare as it seems to be remarkably resistant to pressure or distortion. If damaged, the wasting of the masseter is usually visible and easy to demonstrate by palpation as the patient clenches the teeth. The pterygoids are tested by attempted jaw opening against resistance, the jaw deviating towards the paralyzed side.

Painless or painful loss of sensation over any part of the face, but particularly over V_2, is a very ominous finding and malignant disease in the antrum or nasopharynx is the most likely pathology. Repeated examination under general anaesthesia if necessary and biopsy of the nasopharynx are vital in such cases, to attempt to establish the cause, even if CT or MRI scanning do not clearly indicate an abnormality.

Involvement of V_1 is usually painful and nearly always accompanied by extraocular nerve palsies. It is most often damaged by lesions in and around the cavernous sinus, but may also be involved by malignant disease entering the orbit via the inferior orbital fissure.

Nasopharyngeal tumours most commonly arise in the fossa of Rosenmüller or near the orifice of the Eustachian tube. They are usually squamous carcinomas. Tumours originating in the maxillary antrum or ethmoids are usually either squamous cell carcinomas or adenocarcinomas. Some 40% of such tumours present as neurological problems. In 70% of cases, the Vth nerve is involved; in 50% of cases, the IIIrd, IVth and VIth nerves are involved. Visual pathways are affected in 8.5% of cases, and the lower cranial nerves in 10% of cases. The favourite routes of entry into the skull are through the inferior orbital fissure or via the foramen lacerum alongside the carotid artery.[20]

The maxillary division runs past the mouth of the Eustachian tube and the fossa of Rosenmüller, through the orbital floor just above the antrum and on to the face. Nasopharyngeal and antral carcinomas are particularly likely to damage this division and can cause loss of sensation as frequently as pain. The surface branches of both V_1 and V_2 are easily damaged by blunt trauma around the orbit and cheek, or divided by lacerations.

The mandibular division is involved in oropharyngeal, tonsillar and mandibular tumours and, as noted earlier, painless numbness over the chin may be the presenting symptom, rather than pain. This remains a paradox when we consider that the most common benign condition, trigeminal neuralgia, causes exquisite facial pain and yet the most serious conditions are often quite painless.

Trigeminal sensory neuropathy is a very rare condition in which painless numbness develops over the Vth nerve territory, usually starting in the second division and eventually becoming bilateral. Only the passage of time and continued failure to demonstrate an underlying lesion, allow this diagnosis to be made with certainty.[21]

The sensory root of the Vth nerve is particularly sensitive to distortion and pressure and loss of the corneal reflex is an important early sign of a lesion in the cerebellopontine angle. Rarely, extensive loss of sensation over the face may be the presenting symptom of a vestibular schwannoma, but again it is worth stressing the rarity of pain as the presenting symptom.

TRIGEMINAL NEURALGIA

This is probably the most painful condition known, the cause of which seems to be due to ageing changes in the nerve or seemingly trivial irritation by adjacent aberrant arteries. From a practical, anatomical point of view, the very strict localization of the pain in Vth nerve territory is a vital diagnostic feature. There is no such thing as atypical trigeminal neuralgia and it is not acceptable to allow the pain to radiate behind the ear, onto the neck or across the midline, and the anatomically precise distribution is the linchpin of diagnosis. The pain is usually described in two characteristic distributions. The first runs from the lower canine tooth along the lower jaw to just in front of the ear and sometimes round into the upper jaw (i.e. it involves both V_3 and V_2). The second less frequent type runs from the upper incisor or canine, up the side or inside the nose and encircles the eye, involving both V_2 and V_1. It is probably this spread over two divisions that makes simple surgical section of the peripheral branches unsuccessful in managing the condition long term, although triggering is occasionally reduced. Although it is claimed that transient sensory deficit may follow a spasm of pain, any evidence of sensory loss, impaired corneal reflex or Vth motor weakness should invalidate the diagnosis. Although trigeminal neuralgia may complicate multiple sclerosis, it is very rare as a presenting symptom of this disease.

HERPES ZOSTER OPHTHALMICUS

Most patients with this condition develop very severe pain in the distribution of V_1. The pain lasts between four and five days and during this time the diagnosis of ruptured aneurysm, cranial arteritis or acute frontal sinusitis may all have to be seriously considered. The vesicles usually appear in the inner eyebrow on day five or six and involve the entire distribution of the nerve branch. Severe chemosis of the eye and extraocular nerve palsies may further complicate the initial picture. Often, only the appearance of the vesicles will finally indicate the correct diagnosis.

ANEURYSMAL DILATATION OF THE CAROTID ARTERY

This is the other major condition in the elderly that can cause very severe pain in a V_1 distribution, with chemosis, extraocular nerve palsies and even blindness. This is usually of very sudden onset and typically develops in elderly females with long-standing hypertension.

The facial nerve (VII)

The VIIth nerve is primarily motor to the muscles of facial expression. It also carries the important taste fibres from the anterior two-thirds of the tongue via the chorda tympani and taste from the palate via the nerve of the pterygoid canal (Figure 111.10). A small but clinically important cutaneous supply to the skin of the external ear is mediated in fibres carried from the nerve via the vagus. These sensory fibres are contained in a separate trunk, the nervus intermedius, which runs with the VIIIth nerve rather than the VIIth nerve in the subarachnoid space. The cell bodies of the sensory root lie in the geniculate ganglion. The nervus intermedius also carries preganglionic, parasympathetic secretomotor fibres to the lacrimal, submandibular and sublingual salivary glands. These fibres originate in the lacrimatory nucleus and superior salivatory nucleus.

Several important branches arise from the intrapetrous part of the nerve:

- The greater petrosal nerve arises from the geniculate ganglion, carrying taste fibres from the palate and conveying preganglionic, parasympathetic fibres to the pterygopalatine ganglion, and thence via the zygomaticotemporal and lacrimal nerves to the lacrimal gland. It is joined by the deep petrosal nerve (derived from the sympathetic plexus on the carotid artery) to form the nerve of the pterygoid canal.
- A branch from the ganglion joins the lesser petrosal nerve and is then carried to the otic ganglion. This conveys secretomotor fibres via the auriculotemporal nerve to the parotid gland. It also carries sympathetic fibres derived from the carotid artery to supply the blood vessels of the parotid gland.
- A small twig, the nerve to stapedius, arises 6 mm above the stylomastoid foramen.
- The chorda tympani arises at the same level and runs forward across the middle ear and enters a canal in the petrotympanic fissure, grooves the spine of the

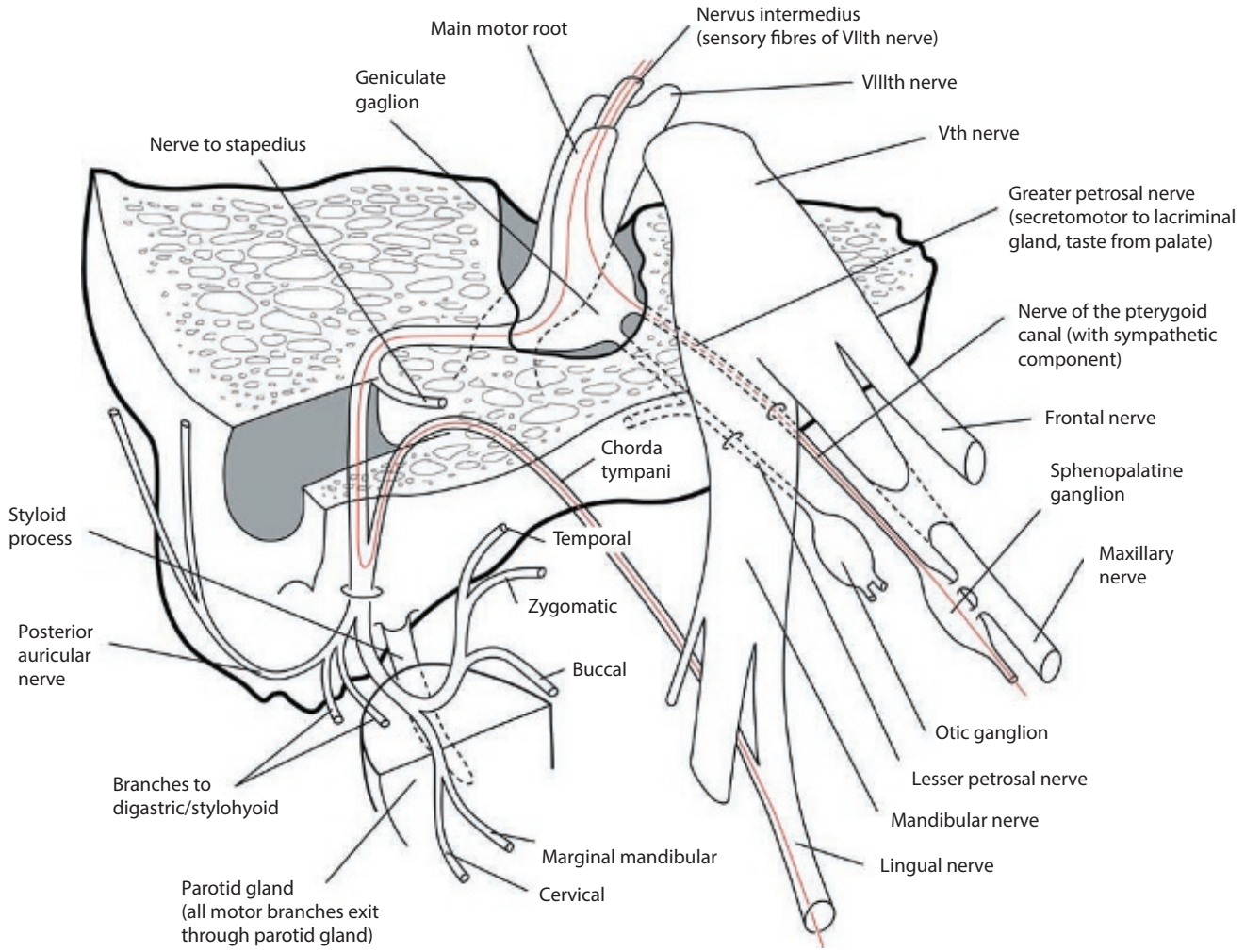

Figure 111.10 The facial nerve.

sphenoid and joins the lingual branch of the Vth nerve with which it is distributed to the presulcal part of the tongue.
- At the stylomastoid, foramen twigs join both the vagus and glossopharyngeal nerve.
- The posterior auricular nerve supplies the muscles of the ear and occipital belly of occipitofrontalis.
- The branches to the muscles of facial expression are, from above down, the temporal, zygomatic, buccal, marginal and cervical. They pass through the substance of the parotid gland before emerging in the skin and are vulnerable to disease in the parotid gland and to local surgical procedures.
- Cutaneous fibres are distributed with the auricular branch of the vagus supplying the skin on both sides of the auricle and part of the external auditory canal and tympanic membrane.

THE SUBMANDIBULAR GANGLION

The submandibular ganglion hangs from the lingual nerve. Its preganglionic fibres are derived from the superior salivatory nucleus and reach it via the facial nerve, chorda tympani and lingual nerve. These fibres are secretomotor to the submandibular and sublingual glands. The sympathetic components are derived from the sympathetic plexus on the facial artery and pass uninterrupted through the ganglion to the blood vessels of the same glands.

THE CENTRAL CONNECTIONS OF THE FACIAL NERVE

The nucleus lies in a deep position in the central pons (see **Figure 111.5**). The dorsal part of the nucleus receives bilateral supranuclear innervation, whereas the lower part of the nucleus receives mainly contralateral supranuclear innervation. This has important consequences for the clinical varieties of VIIth nerve lesions. The nucleus is closely related to the Vth nerve and this proximity is vital for the important corneal reflex and its own reflex activity via the nucleus of the tractus solitarius. The fascicular course of the nerve is unusual in that the fibres course towards the floor of the IVth ventricle, wrap around the nucleus of the VIth nerve, producing a visible enlargement in the floor of the IVth ventricle (the facial colliculus) and then retrace their course across the entire depth of the pons to exit at the pontomedullary junction. This complex arrangement is thought to be due to the embryological migration of the nucleus from its original position in the floor of the IVth ventricle to achieve its close relationship to the nucleus of the Vth nerve and the nucleus of the tractus solitarius.

TASTE MECHANISMS

Taste is mediated via taste buds; some 50 cells arranged in a pear-like cluster. These are found on the tongue, undersurface of the palate, palatoglossal folds, posterior wall of the pharynx, posterior surface of the epiglottis and the upper third of the oesophagus. They are most numerous on the lateral tongue and decrease in number with age by about 1% per annum. Each taste bud opens on the surface of the mucous membrane as a pore. The buds are found in the vallate, fungiform and foliate papillae. The life span of these cells, which are renewed from epithelial cells surrounding the bud, is about 10 days. They are therefore very vulnerable to factors inhibiting rapid cell turnover.

Two main receptor cells have been identified although they are possibly different types of the same cell. Some receptor cells have receptor sites for afferent neurons and small presynaptic vesicles. Others contain larger vesicles and have more definite ciliary processes at their tip just inside the pore. There is evidence of considerable cross-innervation of taste buds, which may indicate inhibitory and facilitatory control similar to that seen in the smell receptors. It is thought that patterns of taste over a wide area of receptors is critical in perceiving different tastes, rather than that there are specific receptors for specific tastes. There is some evidence that sweet is more readily detected on the tip and medial dorsum of the tongue, salt and sour over the lateral tongue and bitter over the posterolateral tongue, where the circumvallate papillae are most numerous.

The neural connections of the taste receptor cells are the unipolar processes of cells in the geniculate ganglion of the VIIth nerve, the inferior ganglion of the IXth nerve and the inferior ganglion of the Xth nerve. The central processes of these cells form the tractus solitarius and they synapse in the adjacent nucleus of the tract. These fibres then ascend in the medial lemniscus to the opposite nucleus ventralis posterior medialis of the thalamus. The final pathway is via the internal capsule to the sensory cortex and insula. Some information from the pons relays direct to the hypothalamus for autonomic reflex purposes.

The anatomy of the peripheral taste pathways is complex, but for practical purposes, the supply to the anterior two-thirds of the tongue is carried by the chorda tympani, but finally distributed via the lingual branch of the mandibular division of the Vth nerve (**Figure 111.11**). The facial nerve also conveys sensation from the taste buds on the palate, through the middle and posterior palatine nerves, via the greater petrosal nerve and the nerve of the pterygoid canal. Taste sensation from the vallate papillae, pharyngeal tongue and palatoglossal folds is conveyed by fibres carried in the IXth nerve. Taste sensation from the lowest part of the tongue, epiglottis and hypopharynx is carried by the vagus in fibres derived from its superior laryngeal branch. Free nerve endings of the Vth nerve are also widespread, conveying somatic sensation from these same areas. They also undoubtedly contribute to the perception of extremely strong taste stimuli, such as curry powder, carbonated drinks and acid substances. Modifications of this pattern of gustatory and simple physical stimuli, such as temperature, can alter taste sensation, heightening the unpleasant features of such highly flavoured compounds. It is clear that taste mechanisms are rather more complex than simple permutations of sweet, bitter, salt and sour. Parallel smell appreciation adds savour to taste. Patients with anosmia describe all food as ‘tasting like cardboard’

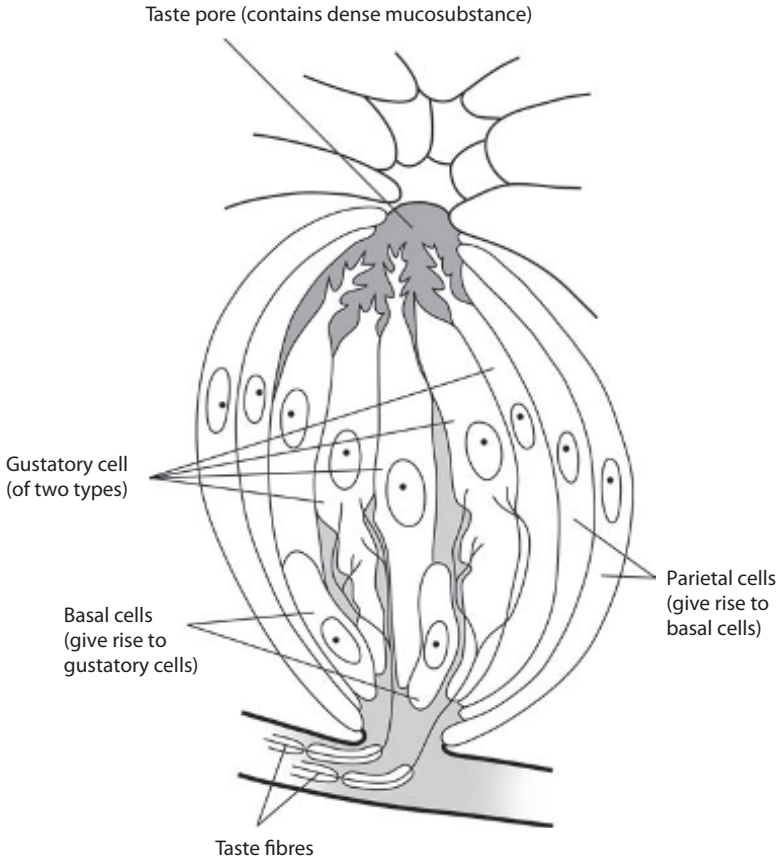

Figure 111.11 The taste bud.

and only highly spiced or flavoured foods make any impact and often not necessarily a pleasant one. Adaptation again plays a role. The modification of fruit juice flavours by the previous use of mint toothpaste, is a universally appreciated phenomenon. Because of the vital role of smell in taste appreciation and the frequent simultaneous impairment of smell, it is difficult to isolate specific disorders of taste. For example, in Bell's palsy, patients identify tastes as having a 'metallic' flavour, in spite of the lesion being strictly unilateral and there being no impairment of the sense of smell. Chemicals and systemic diseases that modify taste and smell are listed under 'The olfactory nerve (I)' above.

The chemistry of taste sensation is described in Volume 1, Chapter 110, Abnormalities of smell.

CLINICAL DISORDERS OF THE VIITH NERVE

The VIIth nerve is frequently damaged by diseases of otolaryngological origin inside the skull, in the petrous bone and in the parotid gland.[22]

For reasons noted above, a cortical lesion affecting VIIth nerve function, such as a vascular lesion or tumour in the motor strip, will cause weakness maximal in the lower face which is almost exclusively contralaterally innervated. The upper face, in particular forehead movement and eye closure, is relatively spared, due to bilateral supranuclear innervation. Thus, upper motor neuron facial weakness is, in many instances, more apparent on spontaneous smiling and speaking than during deliberate attempts to move the face to command.

Lesions affecting the whole facial nucleus or the peripheral part of the nerve should cause total unilateral facial weakness. In some instances, weakness may be more marked in the lower face, which can happen in the early or recovery phase of a simple Bell's palsy and an upper motor neuron lesion may be incorrectly suspected. Much less commonly, a very dense upper motor neuron lesion may mimic a lower motor neuron lesion by affecting all facial movements. These difficulties are stressed as the distinction is of immense diagnostic importance and mistakes are easily made. It is also worth stressing that ptosis of the eyelid is not a feature of either a lower or upper motor neurone facial palsy – a droopy eyelid should never be accepted as part of a facial weakness.

Lesions in the brainstem affecting the VIIth nerve usually also involve the VIth nerve because of the intimate anatomical relationship in the floor of the IVth ventricle. Careful examination may reveal long tract signs, such as brisk reflexes or extensor plantar responses, if the brainstem is distorted or infiltrated by the causative lesion.

The VIIth nerve lies in very close relationship with the VIIIth nerve as they both cross the subarachnoid space to enter the internal auditory foramen. This is in the region of the cerebellopontine angle and a vestibular schwannoma is the lesion most frequently found at this site. Vestibular schwannomas, although inevitably grossly distorting the

VIIth nerve, very rarely present as a VIIth nerve palsy. If there is clinical evidence of a cerebellopontine angle lesion and if the VIIth nerve is involved, alternative pathology is more likely.[23] Permanent damage to the VIIth nerve following surgical removal of a vestibular schwannoma is unfortunately very common and often unavoidable.

In the facial canal, the nerve is liable to ischaemic damage and this is the probable mechanism of Bell's palsy, where the nerve is thought to be damaged by compression, secondary to the inflammatory response to an antecedent viral infection. In nearly all cases very severe pain in the ear is experienced in the 24 hours before the onset of the Bell's palsy, particularly if herpes zoster is responsible (Ramsay Hunt syndrome). The accompanying pain and local swelling may suggest bacterial infection until the vesicles appear three to four days later. The facial paralysis is usually complete on the second day and includes occipitofrontalis and platysma.

In a straightforward Bell's palsy, hearing distortion, due to paralysis of stapedius, and impaired taste, due to simultaneous involvement of the chorda tympani, do not always occur and in mild cases the lower half of the face may be more severely affected than the upper half, mimicking an upper motor neuron lesion, as discussed above.[24] Seventy-five per cent of patients make a good recovery over three to six weeks with or without treatment. Twenty per cent make an acceptable but slow recovery complicated by the development of facial synkinesis. This is due to nerve sprouting with subsequent loss of fine control, which can turn a smile into a snarl and eye closure into a distorted grimace. Five per cent of cases make little or no recovery and may ultimately require plastic surgical repair. In some cases, aberrant regeneration may lead to lacrimation instead of salivation on eating, so-called crocodile tears.[25] It is most important that patients with Bell's palsy are not told that they have had a small stroke. Exclusion of underlying hypertension, diabetes, sarcoidosis and inflammatory arterial disease is important and more recently the recognition of Lyme disease in southern rural England suggests blood tests for *Borrelia burgdorfii* be added to the diagnostic work up in appropriate areas, typically where there is a large deer population.

Middle ear infection carries a considerable risk of damaging the nerve by similar mechanisms. Fractures through the petrous bone are often complicated by facial nerve palsy. Those of immediate onset are usually due to nerve laceration. Those of delayed onset, usually two to three days after trauma, are due to oedema and carry an excellent prognosis. Trauma to the nerve as it emerges from the stylomastoid foramen is a well-recognized complication of forceps delivery.

Benign hemifacial spasm occurs in both sexes at any age, but is most common in elderly hypertensive females. Since the advent of scanning, a surprising number of underlying lesions are found in this condition, such as cholesteatoma, vestibular schwannomas, meningiomas or aneurysms of the basilar artery. CT or MRI scanning should now be regarded as necessary investigations in all cases. The symptoms consist of a constant flickering and twitching of the facial muscles. This usually starts around the eye, producing involuntary winking, and later extends to involve the mouth. It is usually worse in company, but continues 24 hours a day. It may respond to carbamazepine (Tegretol) but if the patient's age and condition permits, posterior fossa exploration to identify vascular irritation by a small vessel may be considered.[26] Excellent control can be obtained using botulinum toxin injections in many cases. At present, the need for repeat injection every two to three months and the expense limits the use of this valuable treatment, but once a gross underlying lesion is excluded, botulinum is the treatment of choice.

CLINICAL TESTING OF THE VIITH NERVE

A standard sequence of movements should be tested. Wrinkling the forehead, followed by forced eye closure will usually detect weakness in the upper half of the face. The ability to flare the nostrils and wrinkle the nose should then be tested, followed by asking the patient to forcibly show the teeth and attempting to blow out the cheeks. Eversion of the lower lip is difficult to achieve, but tests the perioral muscles and produces striking contraction of platysma. It should only take about 30 seconds to perform these tests. Hearing should not be impaired to simple clinical testing, although the patient may report distorted hearing. In the same way, formal testing of taste with standard test flavours may be performed, but often the patient's own perception and description of altered taste will be adequate for diagnostic purposes.

Whenever the VIIth nerve is damaged, it is important to exclude coexistent Vth nerve damage, in particular to confirm the presence of the corneal reflex. Not only will the absence of the corneal reflex exclude a simple Bell's palsy, but the considerable danger to an unprotected and anaesthetic cornea will be identified. Eye movements should be carefully tested to exclude a VIth nerve lesion, which could indicate a brainstem lesion, and simple clinical tests of hearing should be performed, particularly if the corneal reflex is depressed, as simultaneous involvement of the Vth, VIIth and VIIIth nerves would strongly indicate a lesion in the cerebellopontine angle. It should be remembered that herpes zoster may affect several cranial nerves simultaneously and can cause severe pain, which, when accompanied by multiple cranial nerve palsies, can present a very difficult diagnostic situation until the vesicles appear.

The vestibulocochlear nerve (VIII)

The anatomy and physiology of the specialized end organs of the VIIIth nerve are described in Chapter 47, The anatomy of the cochlear and vestibular system: Relating to ultrastructure to function. Discussion here is therefore confined to the role of hearing impairment and balance disorders in the diagnosis of neurological disease.

Due to the anatomical proximity of the VIIth and VIIIth nerves, simultaneous involvement under many circumstances would seem likely. In reality, such damage

is quite unusual, with the exception of acute traumatic lesions of the petrous bone where both nerves are simultaneously lacerated. This peculiarity is of considerable clinical importance.

THE CEREBELLOPONTINE ANGLE SYNDROME

The classical tumour arising in the cerebellopontine angle is a vestibular schwannoma (**Figure 111.12**). Although originating on the vestibular division of the nerve, the rate of growth is usually so insidious that a purely vestibular presentation is extremely unusual. Gradual and often unrecognized impairment of hearing is the rule. Similarly, the VIIth nerve may become grossly distorted but either benign facial hemispasm or weakness as a presenting symptom is similarly unusual. In contrast, minimal pressure on the Vth nerve root as the tumour extends upwards or perhaps stretching of the Vth nerve root as the pons is displaced medially, commonly produces impairment of the corneal reflex. In spite of such distortion, pain or numbness of the face is also very unusual. Obviously, a cerebellopontine angle tumour may present as facial hemispasm, facial weakness, facial numbness or a trigeminal neuralgia-like syndrome, but in all such instances an alternative cause, such as a cholesteatoma or meningioma in the cerebellopontine angle, becomes a more likely diagnosis. If the clinical picture has evolved extremely rapidly, both metastatic carcinoma or lymphoma could be responsible. Less often, and usually in the 5–15-year age group, pontine glioma or cerebellar medulloblastoma can extend into the cerebellopontine angle, to produce this typical combination of nerve lesions.

BALANCE DISORDERS AND VERTIGO

Unsteadiness is a common symptom prompting leading to referral for an otolaryngological or neurological opinion. The most important historical feature to establish is what the patient means by their description using the terms: 'off balance', 'giddy', or 'dizzy'. So often close questioning reveals that they actually mean 'light-headed', 'floaty' or 'woozy', all non-specific symptoms usually due to anxiety. They do not include the obligatory illusion of movement of either themselves or their surroundings, which is necessary to establish that they have true vertigo and therefore justify extensive and expensive otoneurological investigations to define the cause.

Disorders of balance, such as Ménière's disease, vestibular neuronitis and benign positional vertigo, are discussed in Chapters 62–67. The frequency with which vertigo is a symptom in migraine attacks also deserves mention. A feature of all these situations is that the attacks are episodic or provoked by change of position and in the case of migraine often accompanied by or associated with headache. Disorders of balance due to structural organic disease in the CNS tend to produce continuing difficulty with balance and non-stop vertigo. The most frequent causes are multiple sclerosis and cerebrovascular accidents affecting vestibular and cerebellar connections in the brainstem. Pure cerebellar lesions are less likely to produce vertigo, unless they also distort the brainstem. They also tend to produce impaired coordination or a tendency to veer to one side while walking, rather than the drunken reeling in all directions seen in association with vertigo in patients with brainstem lesions.

GROUP 3

The final group of cranial nerves are not only anatomically bunched at their major exit, the jugular foramen, but share common nuclear origins. They also have peripheral cross-connections for final distribution that make for poor physiological distinction of function, as well as complex anatomy. Only the hypoglossal nerve with its discrete nuclear origin

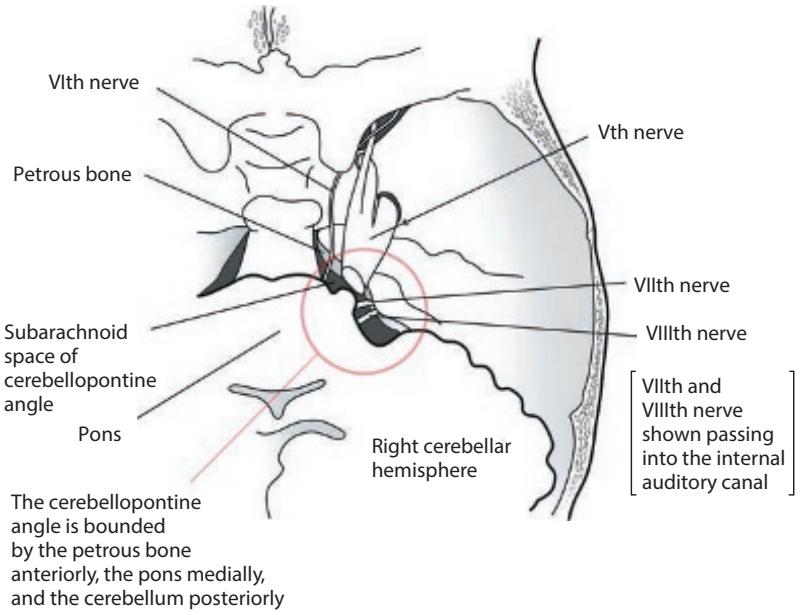

Figure 111.12 The cerebellopontine angle.

and separate hypoglossal canal can be discussed in isolation. Even then, its peripheral course brings it into close anatomical relationship with the other three nerves.

The glossopharyngeal nerve (IX)

The glossopharyngeal nerve has sensory, motor and autonomic components. The sensory ganglion cells lie in the superior and inferior ganglia of the nerve (**Figures 111.13**, **111.14** and **111.15**).

The central processes pass to the nucleus of the tractus solitarius, conveying taste sensation, and to the nucleus of the spinal tract of the Vth nerve, conveying somatic sensation. The motor nucleus lies in the upper part of the nucleus ambiguous, which receives bilateral supranuclear innervation from corticobulbar fibres. This nucleus supplies the stylopharyngeus. The autonomic parasympathetic fibres arise in the inferior salivatory nucleus. These fibres are carried in the lesser petrosal nerve via the tympanic branch to the otic ganglion. The postganglionic fibres are distributed to the parotid gland via the auriculotemporal nerve.

The glossopharyngeal nerve emerges from the brainstem in line with the vagus and accessory nerves and exits from the skull via the jugular foramen. It descends between the jugular vein and carotid artery, picking up sympathetic fibres from the carotid plexus as it loops forwards and medially to reach the soft tissues of the oropharynx, posterior tongue and palate. In its course, it gives off the lesser petrosal nerve conveying the secretomotor fibres for the parotid gland to the otic ganglion. An important nerve, the carotid branch, conveys chemoceptor and stretch reflex information, respectively, from the carotid body and carotid sinus centrally for respiratory and circulatory reflex function. The final branches of the glossopharyngeal nerve are the pharyngeal, tonsillar and lingual branches, conveying general sensation and taste sensation from the posterior third of the tongue and oropharynx.

THE OTIC GANGLION

The otic ganglion lies just below the foramen ovale, attached to the mandibular nerve but functionally carries secretomotor fibres from the glossopharyngeal nerve. These parasympathetic fibres relay in it and supply the parotid gland via the auriculotemporal nerves originating from V_3. Sympathetic fibres derived from the middle meningeal artery pass through the ganglion and are also distributed to the blood vessels of the parotid gland in the auriculotemporal nerve.

GLOSSOPHARYNGEAL NEURALGIA

This is a rare condition that presents at about one-tenth the frequency of trigeminal neuralgia. It consists of excruciatingly severe pain in the palate, throat and external auditory canal, locations demonstrating the somatic sensory distribution of the glossopharyngeal nerve. The pain has the typical burning, electric shock quality of neuralgia and is triggered mainly by swallowing. The incidence of underlying lesions inside the skull is very much higher than in trigeminal neuralgia. Both phenytoin and carbamazepine may control the pain, but MRI scanning would seem a wise precaution in all instances. Intracranial root exploration is necessary if medical treatment fails. Peripheral glossopharyngeal section has little to commend it and can seriously interfere with normal swallowing mechanisms.[27]

The vagus nerve (X)

The vagus nerve (the wanderer) is the most widely distributed cranial nerve, hence only aspects essential to otolaryngologists will be detailed. The central connections are similar to the IXth nerve (see **Figures 111.13**, **111.14** and **111.15**):

- The dorsal nucleus of the vagus contains motor and sensory components. The motor fibres are general visceral efferent to the smooth muscle of the bronchi,

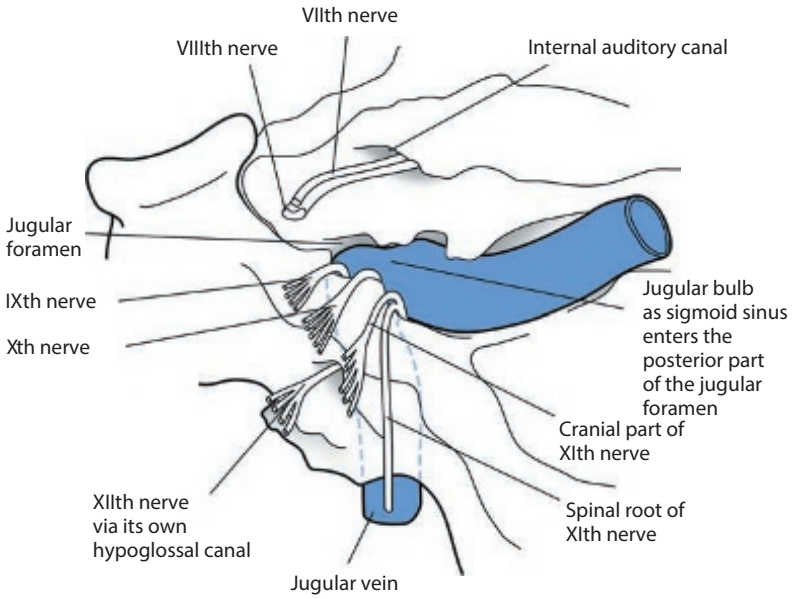

Figure 111.13 Schematic diagram of internal jugular foramen.

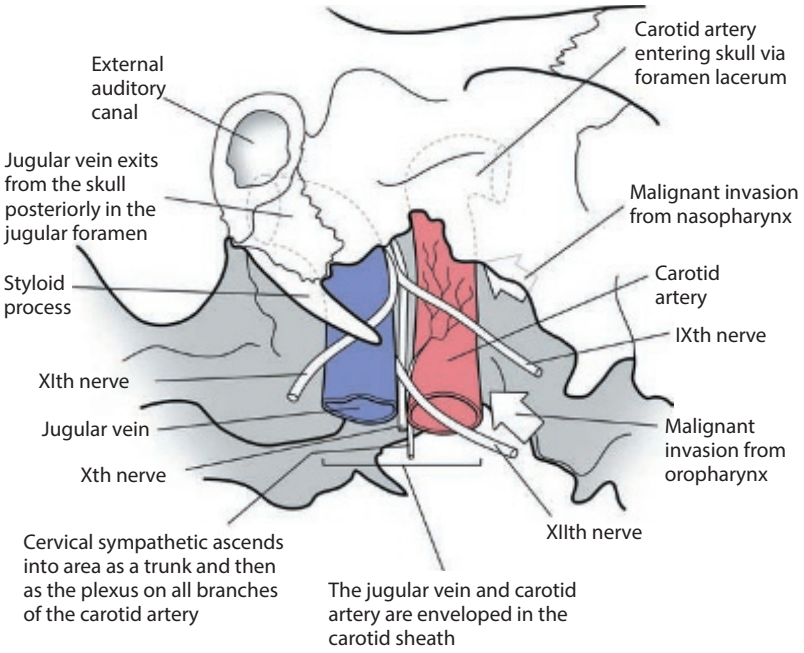

Figure 111.14 Schematic diagram of external jugular foramen. (See also Figure 111.16.)

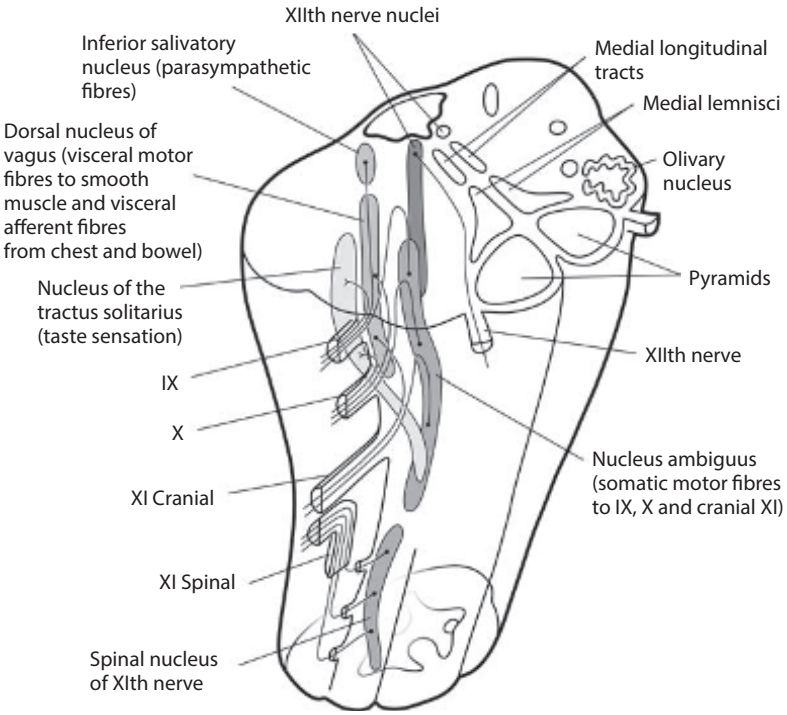

Figure 111.15 Central connections of nerves IX, X, XI and XII, viewed anterolaterally from the right side. (See also Figure 111.9 for central sensory connections via the nucleus of the descending tract of the Vth nerve.)

heart, oesophagus, stomach and intestine. The sensory fibres are general visceral afferent, originating in the oesophagus and upper bowel with cell bodies in the superior and inferior vagal ganglia.

- The nucleus ambiguus gives origin to those fibres controlling the striated muscle of the pharynx and intrinsic muscles of the larynx. It has a bilateral supranuclear innervation.
- The nucleus of the tractus solitarius is shared with the glossopharyngeal nerve and receives fibres from the taste buds of the epiglottis and vallecula.
- General somatic afferent fibres from the pharynx and larynx are found in the nerve and are believed to terminate in the spinal nucleus of the Vth nerve.

Because of these extensive nuclear connections, multiple rootlets emerge from the brainstem and form a flat cord, which enters the jugular foramen.

The superior and inferior ganglia lie in the foramen and just below an identical arrangement to the glossopharyngeal nerve. Both ganglia make connections with the accessory and hypoglossal nerves and the sympathetic

plexus on the carotid artery. Below the inferior ganglion, the cranial root of the accessory nerve merges with the vagus nerve, which then distributes its fibres to the pharynx and larynx.

The vagal branches of practical importance are as follows:

- A meningeal branch supplying the dura of the posterior fossa is given off in the jugular foramen.
- The auricular branch arises from the superior ganglion and is joined by a branch from the glossopharyngeal nerve and conveys sensation from the skin of the external ear with the branch of the facial nerve. These fibres eventually all enter the nucleus of the descending tract of the Vth nerve.
- The pharyngeal branch arises just above the inferior ganglion and distributes the spinal accessory nerve components to the pharyngeal plexus, supplying the pharynx and palate.
- The superior laryngeal nerve comes off the inferior ganglion and divides into two branches: the internal laryngeal nerve, which carries sensation from the mucous membrane of the larynx and conveys proprioceptive information from the neuromuscular spindles and stretch receptors of the larynx; and the external laryngeal nerve, which supplies cricothyroid and contributes to the pharyngeal plexus, which is of considerable importance in speech mechanisms.
- The recurrent laryngeal nerve has differing courses on each side. On the right, it loops under the subclavian artery and on the left under the aortic arch. On both sides it then ascends on the side of the trachea. It supplies all the muscles of the larynx except cricothyroid and carries sensory fibres from the mucous membranes and stretch receptors of the larynx.

The spinal accessory nerve (XI)

The cranial part of this nerve is a detached portion of the vagus and the spinal part is motor to the sternocleidomastoid and trapezius (see **Figures 111.13**, **111.14** and **111.15**).

The cranial portion arises from the lower part of the nucleus ambiguus and a small component from the dorsal efferent nucleus of the vagus. The nerve rootlets emerge in line with the vagus and are joined by the ascending spinal component and run laterally to enter the jugular foramen. The cranial portion merges with the vagus at the level of the inferior vagal ganglion and is then distributed with the pharyngeal and recurrent laryngeal branches of the vagus. These fibres probably supply the muscles of the soft palate.

The spinal root arises from ventral horn cells in the cord between C1 and C5. These fibres emerge from the cord laterally between the anterior and posterior spinal nerve roots to form a separate nerve trunk, ascending into the skull through the foramen magnum. This then exits from the skull via the jugular foramen in the same dural sheath as the vagus. It runs posteriorly as soon as it emerges to supply the sternocleidomastoid and the upper part of the trapezius and receives a major contribution from branches of the anterior roots of C3 and C4, to form the neural plexus, which supplies the cervical musculature. Evidence from surgical procedures suggests that these additional root components make important contributions, as upper cervical root section is required to denervate completely the sternocleidomastoid and trapezius. The peripheral portion of the nerve is easily damaged in lymph node biopsy and other operations in the posterior triangle of the neck.[28]

The accessory nerve is unusual in that clinical evidence indicates that the supranuclear innervation of the motor cells supplying sternocleidomastoid is ipsilateral. In hemiparetic vascular lesions, the weakness in sternocleidomastoid is on the same side as the lesion. In epileptic fits originating in the frontal pole, the head turns away from the side of the lesion (i.e. the ipsilateral sternocleidomastoid is contracting). Failure to recognize this unanticipated distribution may to the novice seem to indicate that a patient with a left hemiparesis also has a right accessory nerve lesion, and therefore a lower brainstem lesion, rather than a typical capsular cerebrovascular accident. This is an easy mistake to make unless this anatomical peculiarity is appreciated and the normality of the upper trapezius on the side of the weak sternocleidomastoid is confirmed.

The hypoglossal nerve (XII)

The hypoglossal nerve arises from a nuclear column lying in the floor of the IVth ventricle and derived from the same cell group as the nuclei of nerves III, IV and VI (see **Figures 111.13**, **111.14** and **111.15**). Like nerves III and VI, the fascicular fibres of XII have to traverse the full sagittal diameter of the brainstem to reach their exit from the ventral surface of the medulla between the pyramid and olive. The numerous rootlets combine and become two main roots with their own dural sleeves and exit the skull via the hypoglossal canal just below the jugular foramen. The nerve therefore emerges deep to the other neural structures and has to course downwards and anteriorly to emerge between the jugular vein and carotid artery, cross the inferior vagal ganglion and then pass upwards and anteriorly on hyoglossus, distributing branches to all the muscles of the tongue. It receives sympathetic fibres from the superior cervical ganglion, some fibres from the vagus and the motor roots of C1 and C2 via the ansa cervicalis. In addition, numerous filaments connect to and are distributed with the lingual nerve.

Motor fibres derived from the hypoglossal nucleus itself supply styloglossus, hyoglossus, geniohyoid and genioglossus. The fibres derived from the C1 components are distributed to sternohyoid, sternothyroid, omohyoid, thyrohyoid and geniohyoid. Although a XIIth nerve lesion paralyzes one side of the tongue as its most demonstrable feature, the larynx also pulls across to the opposite side on swallowing, because the hyoid fails to elevate on the paralyzed side.

The supranuclear innervation of the hypoglossal nucleus is usually bilateral but can be mainly contralateral, so that in some cerebrovascular accidents transient weakness of one side of the tongue may be found. The nerve is

particularly vulnerable to surgical trauma in operations on the submandibular gland and ducts and during carotid endarterectomy.[29] Paralysis following central venous catheterization has also been reported.[30]

THE CERVICAL SYMPATHETIC

Horner's syndrome due to damage to the cervical sympathetic is one of the most frequently missed physical signs in medicine. In the present context, its detection is of vital importance.

The cervical sympathetic originates in the ipsilateral hypothalamus, descends through the entire dorsolateral brainstem to the central grey matter of the cervical spinal cord at TI level (**Figure 111.16**). The sympathetic fibres leave the cord via the ventral root, join the sympathetic chain and ascend through the various ganglia to end as a plexus on the carotid artery, on which they re-enter the intracranial cavity. This ultimately distributes sympathetic fibres to all the cranial nerves innervating the pupil, glands and blood vessels of the head and neck.

The external evidence of Horner's syndrome is said to be fourfold:

1. Enophthalmos is rarely visible and of dubious authenticity.
2. Loss of sweating over the face and forehead is rarely noted, unless specifically tested by warming the patient.
3. Ptosis of the eyelid may be very subtle and somewhat variable, as the nerve endings become sensitized to circulating adrenalin due to denervation hypersensitivity. The lid rarely drops lower than the edge of the pupil.
4. Pupilloconstriction, or more accurately the failure of pupillodilatation, leads to an entirely normally reactive pupil to light and accommodation, but through a smaller range. At rest, the affected pupil is small.

Horner's syndrome may be congenital and this is associated with failure of pigmentation of the iris on the affected side, which remains blue.

The causes of Horner's syndrome are:

- lesions in the dorsolateral brainstem, especially vascular lesions in the medulla, multiple sclerosis at any level or pontine glioma
- lesions in the central cervical cord: syringomyelia, ependymoma, glioma or traumatic damage
- lesions of the TI root: apical carcinoma of the lung, cervical rib, aortic aneurysm or avulsion of the lower brachial plexus
- lesions of the sympathetic chain in the neck: thyroid carcinoma, thyroid surgery, neoplastic lesions, local trauma, accidental surgical damage or surgical extirpation for various vascular syndromes of the arm
- lesions of the carotid plexus: carotid artery surgery, carotid artery thrombosis, migrainous spasm, local neoplastic destruction of the skull base or involvement by aneurysm or malignancy in the region of the carotid siphon or jugular foramen.

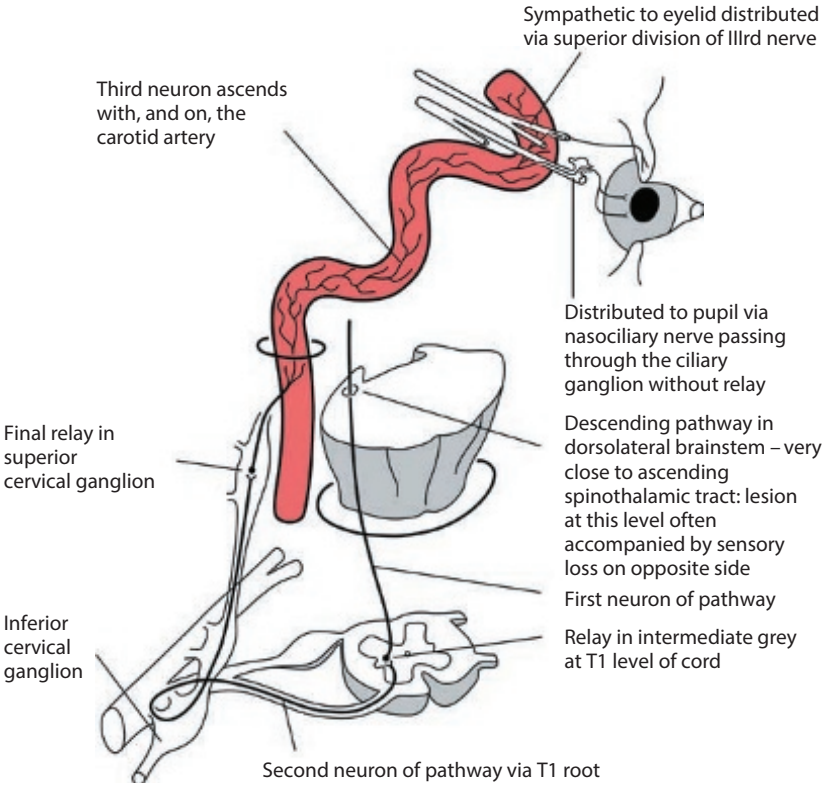

Figure 111.16 Schematic course of the cervical sympathetic nerve.

Clinical evaluation of the last four cranial nerves

Multiple involvement of these nerves is extremely common, so that the symptoms and signs of individual nerve lesions can be difficult to isolate, both from the history and on examination. Disorders of swallowing, speaking, coughing and pain syndromes are the usual presenting symptoms.

A glossopharyngeal nerve lesion will cause impaired taste sensation over the posterior third of the tongue, but this is usually asymptomatic and impossible to test. The loss of somatic sensation over the palate and oropharynx will cause impaired swallowing reflexes as the initial stimulus to deglutition is the arrival of the bolus against the palate. This will lead to occasional choking on food and fluids. Pain in the throat and ear may develop with sensory fibre irritation and then true glossopharyngeal neuralgia may follow. This characteristically will be triggered by swallowing.

Sensation over the palate should be tested by touching the palate with an orange stick and if sensation appears blunted, this can be further explored using a long sharp point. A further check can also be made by touching the posterior pharyngeal wall, while the patient says 'Ah' to elevate the palate.

A vagal nerve lesion at brainstem or jugular foramen level will affect the palate and vocal cords. Unilateral weakness of the palate causes nasal speech and a tendency for food to come back up the nose. Vocal cord paralysis will cause a hoarse, soft voice and prevent explosive coughing. The failure of airway protection when swallowing is initiated, leads to spluttering of food and fluids, with secondary regurgitation through the nasal passages. Pain in the ear may result from irritation of the sensory fibres in the nerve.

In a peripheral recurrent laryngeal nerve lesion, the palate will not be affected, but the voice symptoms will be similar, as will a tendency to choke on fluids. It has also been shown that the external laryngeal nerve with its supplied muscle, cricothyroid, has a greater role in speech than previously realized. Damage causes more severe and lasting speech problems than will result from a recurrent laryngeal nerve lesion.[31]

The integrity of the vagus can be assessed by the patient's voice, ability to cough, direct inspection of the palate and laryngoscopy.

An accessory nerve lesion is really a spinal root lesion, as the cranial part of the nerve is distributed with the vagus. Weakness and wasting of sternocleidomastoid and the upper part of trapezius is readily detected, provided it is carefully sought. Like Horner's syndrome, this is a physical finding that is very easily missed.

A hypoglossal nerve lesion produces paralysis of the intrinsic musculature of the tongue on the supplied side. This causes surprisingly little disability and is often accidentally discovered by the patient or their dentist. Once recognized, some slight difficulty with chewing may then be appreciated by the patient. In an established lesion, on examination at rest, the affected side of the tongue will be shrivelled and fasciculating. On attempted tongue protrusion, the tongue will deviate towards the affected side.

CLINICAL INVOLVEMENT OF IX, X, XI, XII AND CERVICAL SYMPATHETIC NERVES

As the last four cranial nerves lie in close proximity inside the skull and even closer outside the skull (see **Figures 111.13** and **111.14**), multiple involvement is the rule and a variety of named syndromes have been reported. Of immediate practical importance are four major anatomical features:[32]

1. The proximity of the nucleus of nerves IX, X and XI to the spinothalamic tract and descending cervical sympathetic in the brainstem produces a combination of multiple nerve involvement, sparing nerve XII and affecting spinothalamic sensation on the opposite side of the body and associated with an ipsilateral Homer's syndrome. This is seen in Wallenberg's syndrome (dorsolateral medullary infarction).
2. The XIIth nerve lies in a different brainstem vascular territory and the nerve emerges lateral to the pyramid. A vascular lesion of this area will produce a XIIth nerve lesion with contralateral hemiplegia and contralateral impairment of posture, sense and touch. As the nerve exits through a separate foramen, it is often spared by a lesion involving the jugular foramen structures inside the skull.
3. Outside the skull, all four nerves lie so close together that the XIIth nerve is more likely to be involved and is often the first structure affected by lesions infiltrating the area from the oropharynx. Any mass in this region may be palpable.
4. As the cervical sympathetic ascends into the region from below, its involvement (provided there is no evidence of a brainstem lesion, such as a spinothalamic sensory loss on the opposite side) is certain evidence of a lesion external to the jugular foramen.

The named syndromes

Eponymous syndromes have been applied to every conceivable permutation of nerve and tract involvement affecting the last four cranial nerves. Those traditionally accepted are as follows:

- **Vernet's syndrome** (of the internal jugular foramen) is characterized by involvement by nerves IX, X and XI only (an identical syndrome has been attributed to Schmidt).
- **Avellis's syndrome** (of the brainstem) involves only nerve X and the spinothalamic tract (loss of pain and temperature on the opposite side).
- **Tapia's syndrome** involves nerves X and XII. It is difficult to see how this syndrome could occur at either brainstem or peripheral level for anatomical reasons. Presumably this is a chance association.

- **Jackson's syndrome** is characterized by involvement of nerves X, XI and XII. Again it is difficult to see how this combination could develop on any logical basis. Presumably it is also a consequence of a chance combination of peripheral lesions.
- **Collet–Sicard syndrome** (of the posterior lacerocondylar space) is basically the external jugular foramen syndrome involving nerves IX, X, XI and XII, but sparing the cervical sympathetic.
- **Villaret's syndrome** (of the posterior retropharyngeal space). This is involvement of nerves IX, X, XI and XII and the cervical sympathetic and is diagnostic of a complete external jugular foramen syndrome.
- **Wallenberg's syndrome** (infarction of the dorsolateral medulla). This consists of lesions of nerves IX and X, the cervical sympathetic, contralateral spinothalamic loss in the limbs, ipsilateral spinothalamic loss in the limbs, ipsilateral spinothalamic loss over the face and severe vertigo, vomiting and hiccoughs. This is the most classical brainstem vascular syndrome encountered.

Causes (excluding cerebrovascular accidents affecting the brainstem)

- Intracranial lesions:
  - neurinomas of the XIIth nerve, less frequently nerves IX, X and XI, and rarely a vestibular schwannoma may extend down into the internal jugular foramen
  - meningioma of the lateral recess
  - cholesteatoma (particularly likely to affect nerves VII and IX)
  - meningitis (especially malignant or chronic fungal meningitis)
  - fracture of the skull base.
- Extracranial lesions:
  - thrombosis of the jugular bulb
  - metastatic tumour in carotid sheath lymph nodes
  - retropharyngeal abscess or neoplasm
  - carotid body tumour (of the glomus jugulare) may start externally and erode in through the petrous bone or start in the petrous bone and erode out through the skull base.

Clinical symptomatology

The presenting symptoms in these cases may include:

- persistent occipital headache often resembling migraine
- persistent otalgia, which may be worse on swallowing
- hoarse voice, pain in the throat or persistent sore throat
- difficulty in swallowing, choking on fluids or nasal regurgitation.

CT and MRI scanning have revolutionized the investigation of these syndromes. Previously, plain skull films, tomography and carotid angiography were used and often failed to establish a diagnosis. CT scanning will reveal very early evidence of skull base erosion or infiltration by tumour; conversely, MRI scanning can detect even a small neuroma within the jugular foramen – impossible by any other technique.

BULBAR PALSY

The differential diagnosis of lower cranial nerve lesions includes those conditions destroying motor nuclei in the brainstem. Poliomyelitis, previously a common cause, has fortunately become a historical condition, as has diphtheritic bulbar palsy. The most common cause is now bulbar motor neurone disease.

The presenting symptoms consist of a tendency to cough and splutter initially on fluids, but then extending later to include all consistencies of food. Nasal regurgitation and aspiration are common. Speech becomes progressively unintelligible and the patient typically arrives in the clinic clutching a handkerchief to the mouth and a written list of complaints. In the early stages, poor palatal movements, poor tongue movements and weakness of jaw closure and opening may be detected, but the symmetry of involvement may make it difficult to identify mild disability. Fasciculation may be seen in the tongue and facial muscles, or palpated in the masseter. Long tract signs are important and a brisk jaw jerk, increased reflexes and extensor plantar responses would provide strong supporting evidence for the diagnosis.

Myasthenia gravis of the bulbar type is the most important differential diagnosis. Although variability ought to be the hallmark of this disorder, occasionally non-fatiguable and apparently progressive difficulty can produce a confusing picture. This is further compounded by the typical occurrence of bulbar myasthenia gravis in the elderly, the same age group that is liable to develop bulbar motor neurone disease.

PSEUDOBULBAR PALSY

In earlier discussion, the fact that motor cranial nerve nuclei usually have equal, bilateral, upper motor neurone innervation has been emphasized. Only the part of the facial nerve nucleus controlling the lower face shows a major difference in having mainly contralateral supranuclear innervation. Occasionally, both the palate and tongue may be visibly affected by an upper motor neurone lesion, suggesting a variable pattern of supranuclear innervation with mainly contralateral innervation of X and XII in some cases. The accessory nerve is unique in having mainly ipsilateral supranuclear innervation.

The evidence for and the significance of these variations is found in the occurrence of pseudobulbar palsy. This is usually of acute onset consequent upon vascular disease, but is occasionally seen evolving slowly in motor neurone disease and the degenerative condition Steele–Richardson syndrome. These latter conditions produce symmetrical, bilateral, supranuclear degeneration. In vascular disease, a unilateral lesion will usually cause little or no dysfunction of the lower cranial nerves.[33] Occasionally, a patient with a classical, capsular cerebrovascular accident (CVA), in addition to the usual upper motor neurone facial weakness, will demonstrate transient ipsilateral weakness of sternocleidomastoid and upper trapezius and weakness of the palate in the early hours following the onset. Later, a stroke in the opposite internal capsule will acutely deprive

the lower cranial nerves of the residual 50% of their supranuclear innervation. This will result in the instant inability to speak and swallow and is often accompanied by severe emotional lability. In stroke-related disease, these problems will always be of acute onset. In degenerative disease, such as Steele–Richardson syndrome or motor neurone disease of upper motor neurone type, the onset is insidious. In all instances, the end result is pseudobulbar palsy.

EXTRAPYRAMIDAL DISEASE

Fine control of articulation, swallowing and the facial movements associated with speech are achieved by extrapyramidal mechanisms.

PARKINSON'S DISEASE

The loss of spontaneous facial expression and infrequent blinking constitute two of the cardinal features of this disease. In the later stages, hypophonic, tachyphemic speech is characteristic, the short, sharp whispered phrases becoming virtually unintelligible. Chewing food is extremely slowed and the patient may seem to lack the will to initiate swallowing. When one adds the slowness of cutting up and transporting food to the mouth, the cachectic state of a patient with terminal Parkinson's disease is easy to understand. The apparent sialorrhoea of Parkinson's disease actually represents a decreased swallowing rate with a normal production of saliva; it is not due to excessive secretion.

CHOREIFORM SYNDROMES

Choreiform movements of the tongue, palate and mouth conspire to produce spluttering, slurred, explosive speech. This may be seen acutely in Sydenham's chorea as a transient phenomenon or as a severe and progressively disabling problem in Huntington's chorea.

DYSKINETIC SYNDROMES

The so-called buccal–lingual–masticatory syndrome is usually a complication of prolonged neuroleptic therapy, but is also seen in mental subnormality and dementia. In these conditions, the movements do not seem to interfere with speech or swallowing, as the movements subside while speaking and eating. They are mainly a feature at rest.

The oromandibular syndrome (Meige's syndrome) in which slow dystonic opening of the jaw and mouth, in association with tongue protrusion and blepharospasm, is usually seen without neuroleptic provocation. In this condition, attempts to talk and eat aggravate the movements.

Another possibly related dystonic syndrome is spasmodic dysphonia, a disorder characterized by choking of the voice while speaking due to laryngeal spasm, especially on initial vowel sounds. The patient can usually whisper, hum and sing normally. During the choking phase, spasms in the face and neck muscles and blepharospasm may be observed.[34] Treatment with botulinum toxin is a successful form of treatment.

CEREBELLAR DISORDERS

Dysarthria is a feature of generalized cerebellar disease. It typically consists of a slurred, spluttering or scanning type of dysarthria, as breathing mechanisms are desynchronized from speech. It is associated with incoordination of tongue, palatal and facial movements. Inherited cerebellar degenerative disorders and multiple sclerosis are the most common causes, although in the latter condition the disability is often compounded by coexistent spastic dysarthria, producing the typical scanning dysarthria of this disease. Cerebellar neoplasms rarely seem to produce definite speech disturbance.

CONCLUSION

Much clinical material has been included in this chapter to illustrate the functional features of the anatomy and physiology of the cranial nerves in the clinical situation. The coverage is by no means comprehensive. It is hoped that the clinical physiology of cranial nerve function included here will enable the reader to perform a competent clinical examination of cranial nerves in those situations where the symptoms have prompted otolaryngological referral, but have a basis in neurological dysfunction.

KEY POINTS

- Abnormalities of cranial nerve function may be important manifestations of skull base and otological disease.
- A clinical neurological examination is critical in the assessment of patients with skull base pathology.
- In some instances, gross anatomy is of great importance; in others complex central connections require detailed elaboration to illustrate and explain the clinical findings.
- The advent of computed tomography (CT) and magnetic resonance imaging (MRI) has enhanced our ability to unravel suspected diagnoses in what used to be an investigational 'no-man's land'. Scan interpretation requires a very good knowledge of gross anatomy, particularly of the cranial nerves.

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CHAPTER 112

THE FACIAL NERVE AND ITS NON-NEOPLASTIC DISORDERS

Christopher Skilbeck, Susan Standring and Michael Gleeson

SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: facial nerve, anatomy, physiology, imaging, Bell's palsy, Ramsay Hunt, trauma, surgery, facial nerve grading system, electrophysiological tests and focusing on diagnosis and management.

INTRODUCTION

Facial palsy is a devastating handicap for our patients and probably the foremost complication that otologic and parotid surgeons fear and try to avoid. Leaving aside the potential medico-legal issues that might flow from a palsy that could have been avoided or the risk of acquiring it reduced, it has a huge negative impact on the quality of life of our patients. In recent years, otologic surgery has expanded into the cerebellopontine angle (CPA) as otologists have worked closer with their neurosurgical colleagues. It is now important that we become more competent and familiar with the management of the facial nerve in the angle as well as the temporal bone and neck. In this chapter, the surgical anatomy of the facial nerve is discussed and demonstrated in fine detail together with the non-neoplastic processes that might affect its function. The management and expected standard of care for patients with facial palsy is detailed including the levels of evidence that underpin current protocols.

SURGICAL ANATOMY OF THE FACIAL NERVE

The facial nerve can be exposed through a number of surgical windows, each of which requires a detailed three-dimensional understanding of the relevant anatomy to avoid causing iatrogenic injury intra-operatively.[1] The nerve contains motor, sensory and parasympathetic axons (Figure 112.1). Cadaveric studies have found that the total number of myelinated axons ranges between 7000 and 9000 in the motor root of the facial nerve and between 3000 and 5000 in the nervus intermedius.[2, 3] Both nerves also contain unmyelinated axons. (For an extensive account of some of the important variations of facial nerve anatomy that have been described in the literature, consult Shoja and Tubbs).[4]

INTRAPARENCHYMAL ELEMENTS, ORGANIZATION AND COURSE

Special visceral/branchial efferent (SVE) motor axons supply muscles derived from the second branchial arch, namely the mimetic facial muscles, buccinator, stapedius, platysma, the posterior belly of digastric and stylohyoid. The axons arise from neurons in the facial nuclear complex in the lateral part of the central tegmentum of the pons just rostral to the pons-medulla transition[5] and run posteromedially through the pons, arching over the abducens nucleus to raise the facial colliculus on the floor of the fourth ventricle (which may be seen in axial MRI sections), before turning anterolaterally to leave the brainstem. Neurons in the face area of the motor cortex (supranuclear neurons) project bilaterally to facial motor neurons that control muscles in the upper face (frontalis, orbicularis oculi) but contralaterally to facial motor neurons that innervate the muscles of the middle and lower face. However, sparing of the forehead in facial paralysis is not necessarily pathognomonic of a central lesion (see 'Physical examination' below). Axons supplying

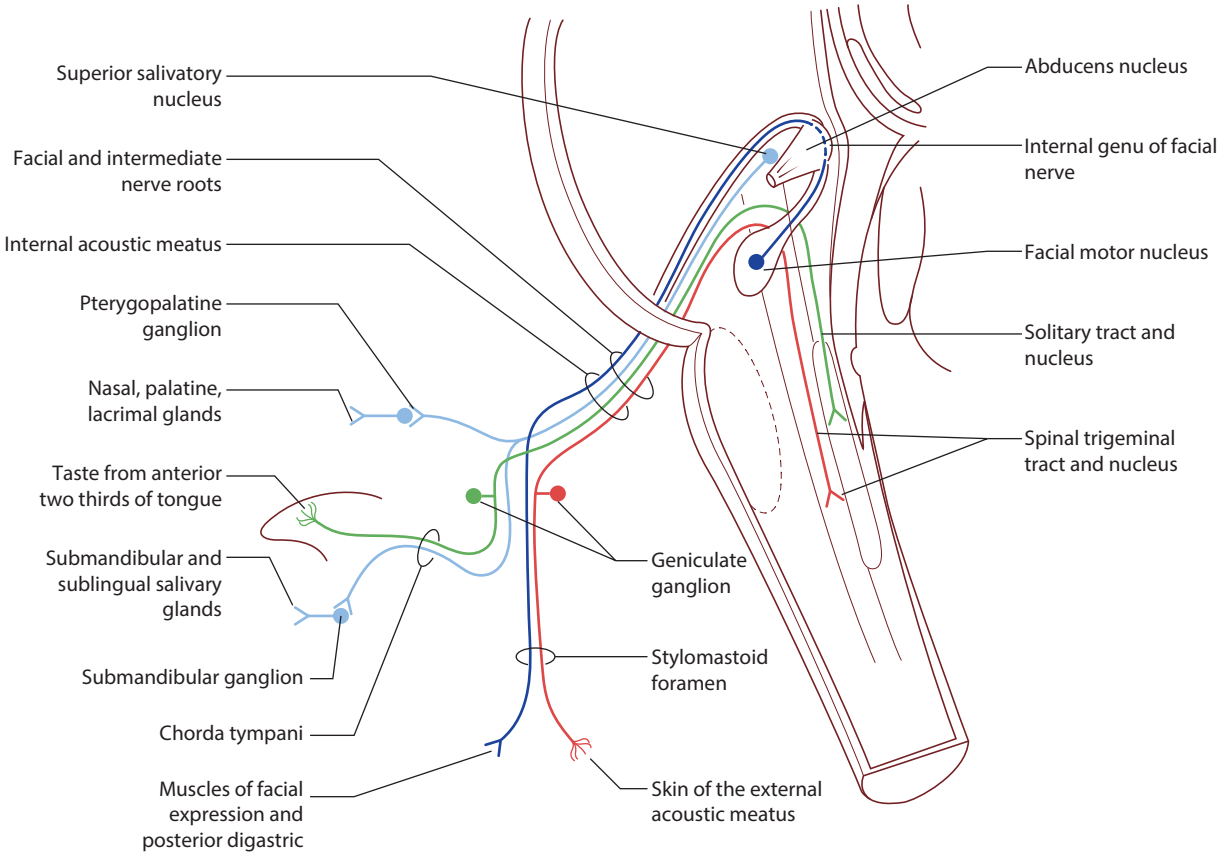

Figure 112.1 GVA axons (nasopharynx, palate, submandibular and sublingual salivary glands) not shown. Cell bodies of origin in the geniculate ganglion, project to more caudal regions of the solitary nucleus. With permission from Haines, D.E. 2013 *Fundamental Neuroscience for Basic and Clinical Applications.*[7]

orbicularis oculi constitute the efferent limb of the corneal reflex. Detailed information about the spatial organization of human stapedial motor neurons is unavailable, but findings in guinea pigs, cats and rats suggest that nerve to stapedius may arise from motor neurons that lie outside the main facial motor nucleus.[6] The stapedial reflex is used to test for topographical assessment of a facial nerve lesion and to assess cochlear function as it is elicited by a sound impulse of threshold + 80 dB.

As they pass through the anterolateral part of the pons the SVE motor axons are joined by general visceral efferent (GVE) preganglionic parasympathetic axons from neurons in the superior salivatory nucleus that will ultimately synapse on postganglionic neurons in either the pterygopalatine ganglion (PPG) or submandibular ganglion.

The facial nerve contains two, possibly three, types of sensory axon. Special visceral afferent (SVA) axons carry taste from the anterior two thirds of the tongue via the chorda tympani. General sensory afferent (GSA) axons carry cutaneous sensation, including pain, from the posterior aspect of the external auditory meatus (EAM),[8, 9] with the caveat that the innervation of this region is complex and largely contributed by Arnold's nerve:[10, 11] these axons are thought to be responsible for coughing during cerumen removal, idiopathic otalgia, Hitselberger's sign[12] and to be the site of vesicular eruptions in Ramsay Hunt syndrome. Several authors have suggested that the nervus intermedius also contains general visceral afferent (GVA) axons mediating pain from the tongue and oropharynx.[13] The evidence appears to be based almost exclusively on Ramsay Hunt's description[14] of the occasional distribution of vesicles on the palate in the region of the anterior pillar of the fauces and on the anterior two-thirds of the tongue in the distribution of the chorda tympani in cases of *herpes zoster oticus*. In 1915, Ramsey Hunt inferred that these clinical findings indicated the *'variable and vestigial intra-oral sensory representation'* of the facial nerve. The craniofacial muscles innervated by the facial nerve typically lack muscle spindles: proprioceptive information from these muscles may be mediated by modified cutaneous mechanoreceptors or capsular corpuscle-like structures within the muscles.[15]

The facial nerve has intra- or extracranial connections with the cutaneous branches of all three divisions of the trigeminal nerve (including branches of the auriculotemporal, buccal, mental, lingual, infraorbital, zygomatic and ophthalmic nerves); with branches of the vestibulocochlear, glossopharyngeal and vagus nerves; and with branches of the cervical plexus (including the great auricular, greater and lesser occipital and transverse cervical nerves). Various functions have been proposed for these connections.[16–18] The cutaneous connections are significant in facilitating the perineural spread of tumours that arise either within the parotid or on the face and explains why some patients

with perineural spread from cutaneous or parotid malignancies may present with vocal cord palsy.[19, 20]

The GVE, SVA, GSA (and GVA) axons form the nervus intermedius (intermediate nerve, nerve of Wrisberg) which was initially described by Heinricus Augustus Wrisberg.[21] The name reflects the fact that the nerve usually lies between the motor root of the facial nerve and the vestibulocochlear nerve as it exits the brainstem (**Figure 112.2**). The axons of the motor root of the facial nerve and the nervus intermedius intermingle within the substance of the pons but emerge separately onto the surface of the brainstem, deep in the pontomedullary sulcus. In a retrosigmoid approach, visualization of the root emerging point is impaired by the lower cranial nerves. The root entry/exit zones (REZ) of the facial nerve and nervus intermedius and the more distal transition zones (Obersteiner–Redlich zones) of these nerves, where central myelin (produced by oligodendrocytes) abuts peripheral myelin (produced by Schwann cells), are both targets in microvascular decompression for hemifacial spasm.[22–24] Surgical landmarks to the REZ on the brainstem are the pontomedullary sulcus; the junction of the glossopharyngeal and vagus nerves with the medulla; the foramen of Luschka and choroid plexus; the cerebellar flocculus (the last three structures are related to the lateral recesses of the fourth ventricle).

The subsequent course of the facial nerve is conventionally divided into intracranial (cisternal), intratemporal and extratemporal portions.

Cisternal portion

The cisternal portion is approximately 24 mm long. The motor root of the facial nerve and the nervus intermedius course anterolaterally through the CPA cistern (pontocerebellar cistern) to the porus of the internal auditory meatus (IAM), accompanied by, and usually anterior to, the cisternal segment of the vestibulocochlear nerve. The nervus intermedius may adhere to the vestibulocochlear nerve for a variable distance.[25] The nerves are ensheathed only by a delicate layer of arachnoid mater: the absence of a more robust connective tissue covering renders them not only extremely vulnerable in CPA tumour surgery but also difficult to identify during dissection of a schwannoma.

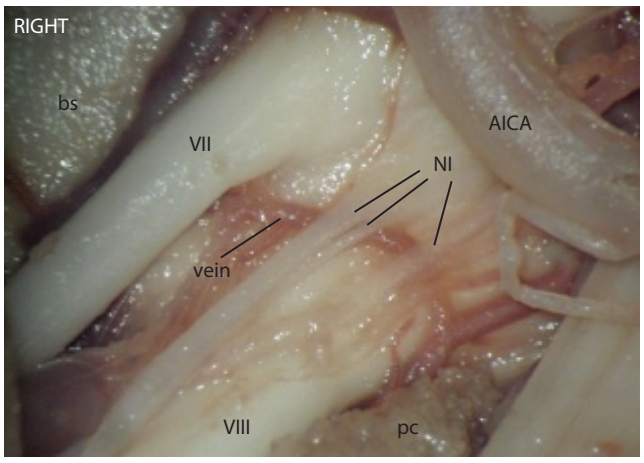

Figure 112.2 Right sided specimen showing the facial nerve (VII), the vestibulocochlear nerve (VIII), the nervus intermedius (NI), and a vein between cranial nerves VII and VIII. In this case, the NI (three bundles) arises separately from the brain stem (bs). The choroid plexus (pc) is located antero-inferiorly to the VII at the entry of the foramen of Luschka. From Alfieri et al. with permission.[22]

Intratemporal portion

The intratemporal portion is 28–30 mm long and subdivided into meatal, labyrinthine, tympanic (horizontal) and mastoid (vertical) segments. The meatal segment runs in the IAM; the labyrinthine segment runs laterally to the geniculum (first turn or genu) and the geniculate ganglion; the tympanic segment runs backwards from the geniculate ganglion to the second genu; the vertical segment runs from the second genu to the stylomastoid foramen; the extratemporal segment runs forwards into the parotid gland where it usually divides into temporofacial and cervicofacial branches. The first three segments do not display any obvious fascicular organization, which may explain why a very selective partial lesion in this part of the nerve is likely to produce a slight overall paresis of the face and also why regeneration following injury usually results in some degree of synkinesis (reinnervation of inappropriate facial muscle groups by regenerating facial axons). These proximal segments are invested by arachnoid mater but lack epineurial and perineurial sheaths, rendering suture technically challenging if not contra-indicated in favour of glue. Arachnoid cysts have been reported within the IAM and facial nerve canal, where they may compress adjacent nerves.[26] Discernible fascicles defined by perifascicular, interfascicular and intrafascicular connective tissue only appear distal to the geniculate ganglion. The number of fascicles increases proximodistally as axons are progressively segregated into specific named nerves. Although the spatial relationship of the fascicles is highly variable,[3] a very selective partial lesion affecting the lower part of the mastoid segment will produce total paralysis of the denervated muscles.

MEATAL SEGMENT

The meatal segment is 5–12 mm long. The motor root of the facial nerve and the nervus intermedius run through the IAM from its porus (medial) to its fundus (lateral wall), accompanied by the cochlear nerve and the superior and inferior vestibular nerves and the labyrinthine artery (**Figure 112.3**). The bundles that make up the nervus intermedius join the facial nerve within the IAM, typically 3 mm from the porus.[22] Different degrees of rotation between the facial and vestibulocochlear nerves have been reported within the IAM.[27] The components of the vestibulocochlear nerve rotate 90 degrees as they travel from the brainstem to the inner ear. The facial nerve remains anterior in its course to the porus acusticus and within the IAM and so lies anterior to the superior vestibular nerve in the lateral end of the meatus.[1] On cross-section, the fundus is divided into four quadrants. It is divided horizontally by a thin bony septum, the crista falciformis (transverse septum) and vertically into anterior and posterior compartments above the crista

by an important bony landmark, Bill's bar (named after **William Fouts House**). The motor root of the facial nerve and the nervus intermedius lie anterior to Bill's bar in the anterior superior quadrant; the superior vestibular nerve lies posterior to Bill's bar in the posterior superior quadrant; the cochlear nerve and inferior vestibular nerve lie below the crista, the cochlear nerve lying anterior to the inferior vestibular nerve (Figure 112.3). The close anatomical relationship between the motor root of the facial nerve, nervus intermedius and vestibulocochlear nerve along their cisternal and meatal portions explains the disturbances in lacrimation, taste, salivary flow, hearing, balance or facial motor control that may result from lesions in either the CPA or IAM.

LABYRINTHINE SEGMENT

The labyrinthine segment is the shortest (3–5 mm) and narrowest part of the facial nerve (average diameter of 0.68 mm). It is the only segment of the facial nerve that lacks anastomosing arterial cascades and so is vulnerable to embolic phenomena, low-flow states and vascular

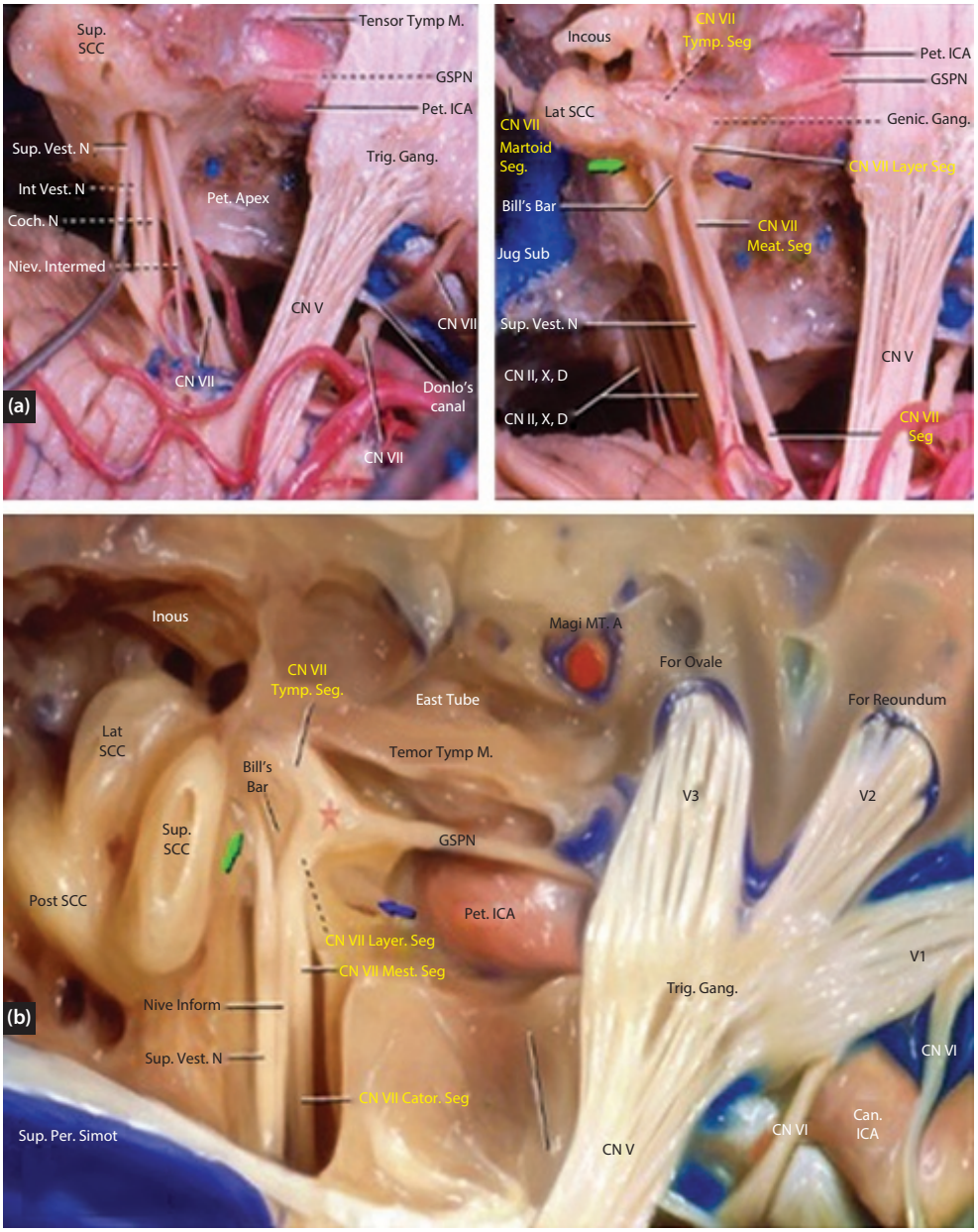

Figure 112.3 When operating using the middle fossa approach, the facial nerve runs laterally, anterior to the superior vestibular nerve and parallel to it within the IAM. This relationship is maintained in a translabyrinthine approach where the facial nerve is found to lie anterior to the superior vestibular nerve and covered by it from the surgeon's perspective, parallel to the cochlear nerve. A significantly different relationship may be encountered in vestibular schwannoma surgery as a result of displacement by tumour. However, it would normally allow the recognition of such a relationship at the level of the fundus when Bill's bar and the crista falciformis become readily identifiable. From Tanriover et al. with permission.[28]

compression: it is most likely to be affected by ischaemia in the event of oedema following trauma or inflammation.

At the distal end of the labyrinthine segment, the geniculate ganglion forms part of a sharp 'hairpin' turn, the geniculum or first genu of the facial nerve, that marks the start of the tympanic segment. At the geniculum, the nerve is cradled by the superior semicircular canal posteriorly and the cochlea anteriorly and inferiorly (**Figure 112.4**). The nerve may be accompanied by the subarachnoid space as far as the geniculate ganglion.[18]

The geniculate ganglion is a sensory ganglion: it does not contain synapses. The central processes of the GSA neurons in the geniculate ganglion carry pain from the EAM and terminate somatotopically in the spinal tract nucleus of V. The central processes of the SVA neurons in the geniculate ganglion that carry taste from the anterior two thirds of the tongue via the chorda tympani terminate somatotopically on second order neurons in the gustatory nucleus (rostral end of the solitary tract) (see **Figure 112.1**). The chorda tympani is thought to modulate trigeminal and glossopharyngeal sensitivity.[29, 30]

Preganglionic parasympathetic axons destined to synapse on postganglionic neurons in either the PPG or submandibular ganglia pass through the geniculate ganglion without synapsing. Those destined for the PPG form the greater petrosal nerve (formerly termed greater superficial petrosal nerve), the first branch of the facial nerve.

The greater petrosal nerve is an important landmark in directing operative approaches through the middle cranial fossa (MCF) to the IAM, petrous apex, trigeminal nerve and petrous portion of the ICA (**Figure 112. 4**).[28, 31] It runs anteriorly and medially from the geniculate ganglion, receives a branch from the tympanic plexus and traverses a hiatus on the anterior surface of the petrous part of the temporal bone to enter the middle cranial fossa, where it runs forwards in a groove on the bone above the lesser petrosal nerve and then passes beneath the trigeminal ganglion to reach the foramen lacerum. Here it is joined by the deep petrosal nerve (which carries postganglionic sympathetic axons from the internal carotid sympathetic plexus), to become the nerve of the pterygoid canal (Vidian nerve) destined for the PPG. Axons travelling in the nervus intermedius pass to the lesser petrosal nerve in the region of the geniculate ganglion. Contrary to their depiction in most anatomical texts, the greater and lesser petrosal nerves are not parallel but usually diverge in the area medial to the geniculate ganglion.[32]

The geniculate ganglion lies in a fossa covered by a very thin layer of bone that separates it from the floor of the MCF. Dehiscences here are not uncommon: when present they render the nerve vulnerable during middle fossa surgery and bring it into direct contact with the meninges. The geniculate ganglion may be injured by bone spicules or directly contused by a shock wave: an enlarged fossa on temporal bone CT strengthens a diagnosis of geniculate ganglion fossa (GGF) fracture in patients with traumatic facial paralysis.[33]

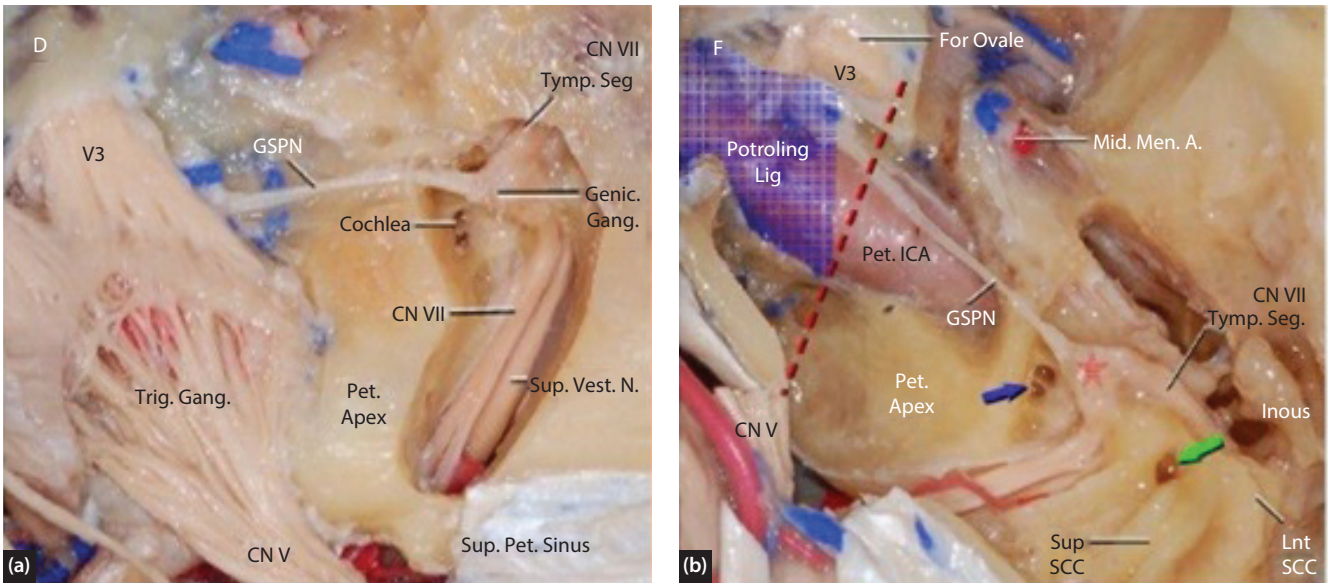

Figure 112.4 **(a)** The superior vestibular and the facial nerves have been exposed within the IAM along with the geniculate ganglion and the cochlea. The cochlea lies below the floor of the middle fossa in the angle between the labyrinthine segment of the facial nerve and the GSPN. The posterior border of the cochlea is the fundus of the IAM, and, posterolaterally, it is related to the geniculate ganglion. The cochlea should not be violated during the exposure of the lateral part of the IAM to preserve the hearing during a middle fossa approach. The bone over the tympanic segment of the facial nerve distal to the geniculate ganglion has been removed. **(b)** The trigeminal nerve has been sectioned to expose the full course of the GSPN and the petrous ICA. The interrupted red line corresponds to the posterolateral limit of the V_3 and the GSPN passes 1.7 cm from this point to the geniculate ganglion (marked with a red star). The cochlea (marked with a blue arrow) and the vestibule (marked with a green arrow) are the main structures to be preserved during the middle fossa approach. The petrous segment of the ICA passes under the petrolingual ligament to enter the cavernous sinus. The petrolingual ligament has been removed; however, the approximate position has been shown in the blue area. From Tanriover et al. with permission.[28]

During a translabyrinthine approach the labyrinthine segment is at risk while drilling along the superior semicircular canal. The ampullated ends of the superior and the lateral semicircular canals (the 'cat's eyes') should be identified; the facial nerve lies just anterior to this area. The labyrinthine segment is the part of the facial nerve that is most likely to be injured in temporal bone fractures, when it is likely to be compressed by bony fragments.

TYMPANIC SEGMENT

The tympanic segment is 8–11 mm long. It runs the length of the superior edge of the medial wall of the tympanic cavity, perpendicular to the long axis of the petrous part of the temporal bone, taking a posterior path that inclines downwards and laterally from the geniculate ganglion to the second genu at the level of the pyramidal eminence.[34] Proximally it passes just above and medial to the posterior edge of the cochleariform process and the tendon of tensor tympani. The cochleariform process is a consistent landmark, when other landmarks are obscured or have been destroyed by pathology. More distally the nerve lies above the oval window niche, just anterior and inferior to the prominence of the lateral (horizontal) semicircular canal before bending at the second genu to enter the bony mass of the styloid complex. The second genu hugs the inferior aspect of the lateral semicircular canal; this relationship is extremely constant. The pyramidal eminence is a useful landmark for the second genu. The retrotympanum contains several small sinuses around the facial canal: the sinus tympani lies medial and anterior to the canal and the facial and lateral tympanic sinuses lie lateral and posterior to the canal.[35–37] The distal aspect of the tympanic segment can be located surgically via a facial recess approach. The chorda tympani nerve and the fossa incudis can be used to identify the nerve when performing a facial recess approach. The second genu of the facial nerve runs inferolateral to the lateral semicircular canal (a relatively constant relationship). The posterior semicircular canal lies just posterior to the second genu: it also marks the superior end of the retrofacial air cells, which are helpful in delineating the medial aspect of the facial canal (**Figure 112.5**).

Developmental dehiscences are not uncommon at this level, making the nerve vulnerable during middle ear surgery, especially around the oval niche.[38–43] A dehiscent or prolapsed facial nerve should always be anticipated in the tympanic segment, especially in patients with congenital ear deformities. The tympanic segment is vulnerable to traction along its axis in longitudinal fractures of the temporal bone.

MASTOID SEGMENT

The mastoid (vertical) segment is the longest of the petrous segments (10–14 mm). It runs vertically downwards in the posterior wall of the tympanic cavity and the anterior wall of the mastoid, from the second genu just distal to the pyramidal process to the stylomastoid foramen on the base of the skull. The digastric ridge (seen on well-pneumatized bones as the medial aspect of the mastoid tip) points to the lateral and inferior aspect of the mastoid segment: a line drawn between the anterior end of the digastric ridge and the tip of the short process of the incus marks the path of the mastoid segment. The nerve may be identified by removing the mastoid tip, skeletonizing the digastric ridge and outlining the inferior part of the vertical segment of the nerve. This is particularly helpful when the extracranial trunk of a functioning nerve is encased in benign tumour recurrences at the stylomastoid foramen.

The nerve travels from the second genu posteromedially to the stylomastoid foramen anterolaterally, which means that expanding a posterior tympanotomy inferiorly in the same plane as it was fashioned could risk injury to the facial nerve. The plane of the facial nerve is almost always lateral to the level of the tympanic anulus, but it may cross it, or lie medial to it in its lower half.[44] The nerve may be damaged when elevating the tympanic anulus or when lowering the mastoid ridge overlying the nerve, as in a modified or radical mastoidectomy.

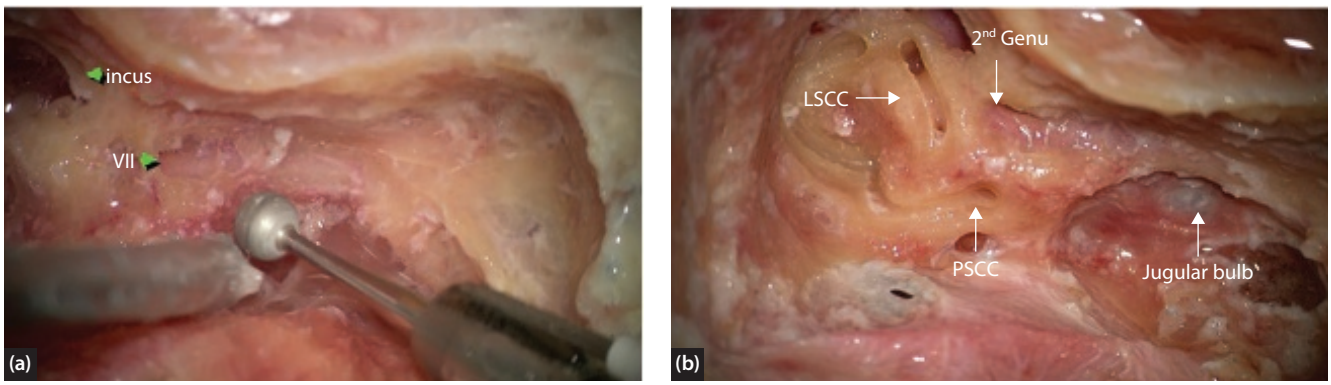

Figure 112.5 **(a)** Right-sided cadaver dissection of the temporal bone. The facial nerve has been exposed in the mastoid segment along an imaginary line from the anterior part of the digastric ridge to the tip of the short process of the incus in the mastoid antrum. **(b)** The semi-circular canals have been skeletonized and opened to demonstrate the relationship of the posterior canal to the second genu (arrowed). If the remaining bone is removed inferior to the lateral semicircular canal, there would be good access to the posterior part of the tympanic segment of the facial nerve.

Most commonly, iatrogenic injury is caused by failure to identify the mastoid antrum properly or being impeded by an overhanging tegmen. It should be remembered that the positions of both the tympanic anulus and the mastoid segment of the facial nerve change during childhood.[45]

The mastoid segment of the facial nerve has three branches, namely the nerve to stapedius muscle, the chorda tympani and the sensory auricular branch. The nerve to stapedius is a small twig given off behind the pyramidal eminence that passes forwards through a small canal to reach the muscle. The chorda tympani is usually given off approximately 5 mm proximal to the stylomastoid foramen and runs anterosuperiorly in a canal to enter the tympanic cavity via the posterior canaliculus. It then curves anteriorly across the pars flaccida of the tympanic membrane between its mucous and fibrous layers, adjacent to the posterior and anterior mucosal folds of the malleus, medial to the upper part of the handle or neck of the malleus and above the insertion of tensor tympani, lateral to the long process of the incus, to reach the anterior wall of the tympanic cavity, where it enters the anterior canaliculus (canal of Huguier) within the medial part of the petrotympanic fissure.[46] Upon exiting the skull at the petrotympanic fissure, the chorda tympani enters the infratemporal fossa where it joins the lingual nerve. A small branch communicates with the otic ganglion. The chorda tympani carries axons mediating taste from the anterior two thirds of the tongue and preganglionic parasympathetic axons that will synapse on postganglionic neurons in the submandibular ganglion. The nerve is a commonly used landmark when performing posterior tympanotomy and serves as the lateral margin of the facial recess. It is sometimes used as the medial limit of lowering the facial ridge when performing a canal wall down technique. Occasionally the chorda tympani may arise extratemporally.[47]

The facial nerve is usually surrounded by thick fibrous tissue at the styolomastoid foramen: to avoid irrevocable damage during anterior transposition of the nerve it is advisable to lift the segment *en bloc* together with fibres of the posterior belly of digastric and slivers of bone around the foramen. On leaving the stylomastoid foramen, the facial nerve initially lies below the tympanic plate, lateral to the bases of the styloid process and the carotid sheath and posterior to the parotid gland. It immediately gives off the posterior auricular nerve which passes upwards behind the ear between the parotid gland and the anterior border of sternocleidomastoid and then in the notch between the EAM and the mastoid process to supply the occipital belly of occipitofrontalis, auricularis superior and the intrinsic auricular muscles. A second muscular branch divides to supply the posterior belly of digastric and the stylohyoid muscle.

EXTRACRANIAL SEGMENT

The main trunk of the extracranial facial nerve enters the parotid gland high up on its posteromedial surface and passes forwards and downwards behind the mandibular ramus. It divides within the gland, usually just behind and superficial to the retromandibular vein and external carotid artery (ECA) into an upper temporofacial trunk and a lower cervicofacial trunk. The relationship between the nerve and vein may vary.[48, 49] In cadaveric studies of adult heads, the length of the facial nerve trunk from stylomastoid foramen to the initial intraparotid bifurcation has been found to range between 8 mm and 22 mm.[50]

The temporofacial trunk contains more axons but fewer fascicles than the cervicofacial trunk.[3] The trunks branch further to form a parotid plexus (pes anserinus) from which five main terminal branches, temporal, zygomatic, buccal, marginal mandibular and cervical, ultimately emerge. These branches diverge within the substance of the parotid and leave the gland via its anteromedial surface, medial to its anterior margin. Numerous microdissection studies have demonstrated considerable individual variations in branching patterns and anastomoses between branches, both within the parotid and on the face.[51–55] While there is no evidence to suggest that a particular classification pattern is associated with increased risk of surgical complications, it is reasonable to assume that nerves that are truly plexiform sustain surgical injury better than those that are not, since accidental division or deliberate sacrifice of a small branch in a plexiform nerve is rarely accompanied by a significant or noticeable facial weakness. While the subsequent distribution of the branches of the facial nerve on the face is variable they retain a relatively constant relationship to soft tissue planes.[4, 56]

Facial nerve injury is the most significant complication of parotidectomy.[57] In addition to intra-operative functional nerve monitoring, a number of landmarks are commonly used to identify the facial nerve trunk during surgical procedures. They include the tragal pointer, the posterior belly of digastric muscle, the junction of the bony and cartilaginous portions of the ear canal, the transverse process of the axis and the tympanomastoid suture. The main trunk of the facial nerve usually lies 1 cm medial and inferior to the tragal pointer (the medial aspect of the tragus which points inward, forming the anterior and inferior wall of the EAM). The trunk can also be identified 6–8 mm below the inferior 'drop off' of the tympanomastoid fissure or by retrograde dissection along the posterior belly of the digastric muscle towards its insertion into the mastoid process: the main trunk bisects the angle between the upper border of the muscle and the EAM. In spite of numerous cadaveric studies there is no general consensus as to which of these landmarks is the most consistent.[58, 59] Landmarks for retrograde parotidectomy, undertaken when the landmarks used in anterograde parotidectomy are not easily accessible intra-operatively, will vary according to which peripheral branch of the facial nerve is being followed retrogradely. The retromandibular vein is a commonly used landmark for the marginal mandibular branch of the facial nerve.[60] The marginal mandibular nerve may also be identified by following the facial vein proximally within the parotid tissue, where the nerve crosses lateral

to the vein. The buccal branch runs parallel and 1 cm below the zygomatic arch and often along the inferior aspect of the parotid duct.

The anatomical course of the facial nerve is subject to variations and anomalies. Because the facial nerve is the nerve of the second branchial arch, any malformations in the derivatives of Reichert's cartilage should raise suspicion of possible anomalies. Otolaryngologists should be cautious when exploring patients with external ear malformations, congenital conductive hearing loss and craniofacial anomalies.

BLOOD SUPPLY OF THE FACIAL NERVE

The arterial supply of the segments of the facial nerve is derived from branches of the vertebrobasilar and ECA systems (**Figure 112.6**).[61, 62] The labyrinthine artery (internal auditory artery) supplies the cisternal, meatal and labyrinthine segments. It usually arises directly from the AICA as it loops between the cisternal segments of the motor root of the facial nerve, the nervus intermedius and the vestibulocochlear nerves, projecting towards and often into the IAM, but it may arise from the basilar, vertebral or superior cerebellar arteries.[63] The greater petrosal nerve is supplied by the petrosal branch of the middle meningeal artery which usually passes through the bone enclosing the geniculate ganglion and tympanic segment of the nerve, less commonly it passes through the hiatus of the greater petrosal nerve: the vessel and nerve are at risk during procedures where the dura is elevated from the floor of the MCF.[64] The tympanic and mastoid segments are supplied by the facial arch, an anastomotic network formed by the superficial petrosal branch of the middle meningeal artery and the stylomastoid branch of either the occipital or posterior auricular arteries, which enters the facial canal via the stylomastoid foramen. The lowest branch from the stylomastoid artery to the facial nerve is given off at the level of the origin of the chorda tympani: collaterals of the stylomastoid artery supply the chorda tympani. Branches from the facial arch anastomose with vessels supplying the bone marrow of the facial canal and with anterior and superior tympanic branches of the maxillary artery, the posterior tympanic branch of the posterior auricular artery, and the inferior tympanic branch of the ascending pharyngeal artery.[65] The posterior auricular and occipital arteries and their branches, including the stylomastoid artery, supply the facial nerve from the stylomastoid foramen to the parotid gland. The temporofacial and cervicofacial branches that exit the parotid gland are supplied by collaterals of the superficial temporal, transverse facial, facial and maxillary arteries.

The labyrinthine portion is supplied exclusively by meatal arteries and therefore more likely to suffer from ischaemic damage than the other segments. That said, any part of the intratemporal portion of the nerve that becomes oedematous is susceptible to compression and subsequent ischaemic damage. Vascular lesions causing pulsatile compression of sensory axons likely produce neuralgia, whereas compression of motor axons will produce hemifacial spasm.

PATHOPHYSIOLOGY OF NERVE INJURY

Peripheral nerves (cranial and spinal) may be injured in a variety of ways, broadly classified as local (trauma, whether blunt or penetrating; compression: chronic traction or acute stretch; local chemical or freeze injury) or systemic (immune-mediated inflammation; diabetes

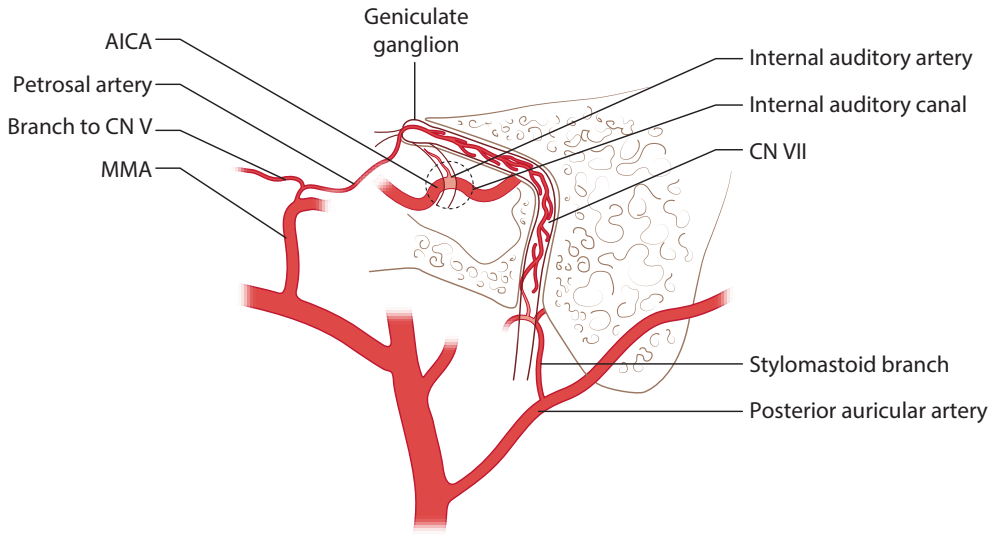

Figure 112.6 The tympanic and mastoid segments of the facial nerve are supplied by the facial arch formed by the petrosal branch of the middle meningeal artery (MMA) and the stylomastoid branch of the posterior auricular artery. AICA, anterior inferior cerebellar artery; CN, cranial nerve. Redrawn from Chen et al.[66]

mellitus; vasculitis; drug-induced). Ischaemia induced by mild pressure may produce transient paraesthesia but no obvious structural changes, recovery is usually rapid and surgical intervention is not required. Prolonged ischaemia or immune-mediated attack may cause specific loss of myelin (primary or segmental demyelination) without loss of axonal integrity, resulting in an increased refractory period of transmission and conduction slowing, followed by conduction block. If the causative agent, such as a spicule of bone or a haematoma, is removed, remyelination typically takes place within 2–4 months, usually with little residual loss of function; surgical intervention is not required. In marked contrast, any injury that physically separates axons from their neuronal cell bodies triggers a programme of molecular and cellular events at the site of the lesion and in distant parts of the injured neurons and their target organs that has a significant impact on outcome. Therapeutic intervention cannot (yet) manipulate responses that happen many centimetres from the injury and that may influence functional outcome months or even years later. Centrally, nerve injury induces reprogramming of synaptic connectivity in the cortex and spinal cord as well as responses in affected sensory ganglia that may mediate the development and maintenance of chronic neuropathic pain. Variable numbers of neurons will die when injury isolates them from their supply of retrogradely transported neurotrophins, particularly if the insult is close to the neuronal cell body. Peripherally, atrophy of chronically denervated sensory end organs and muscles may preclude their reinnervation. (The term 'Wallerian degeneration' refers specifically to the process of degeneration that takes place along a nerve distal to an injury and is named after Augustus Waller: in a seminal report read to the Royal Society of London on February 21, 1850. Waller summarized the degeneration that would come to bear his name, describing the gradual disintegration of the glossopharyngeal or hypoglossal nerves of frogs after axotomy).

The microenvironment of an acutely denervated distal stump facilitates axonal regrowth because it provides a vascularized segment of longitudinally orientated, laminin-rich basal lamina tubes filled with axon-responsive Schwann cells (**Figure 112.7**).[67] However, axonal regrowth is frustrated over time by progressive endoneurial fibrosis and Schwann cell senescence.[68–70] The cardiologists' aphorism 'time is muscle' applies equally to the consequences of delaying nerve repair too long. Early nerve repair results in improved functional outcomes.[71, 72] Surgical intervention, whether direct coaptation of stumps by gluing or suturing; or bridging a long inter-stump gap by either grafting a segment of nerve (end-to-end or end-to-side) or some form of tissue-engineered device; or by nerve transfer, may be required to enable regrowing axons to encounter and interact with Schwann cells. The mitigation of endoneurial fibrosis, muscle and sensory end organ atrophy and Schwann cell senescence remain key clinical challenges.[73]

Based on his wide experience of traumatic nerve injuries, Sir Herbert Seddon distinguished between three types of localized injuries to peripheral nerves and

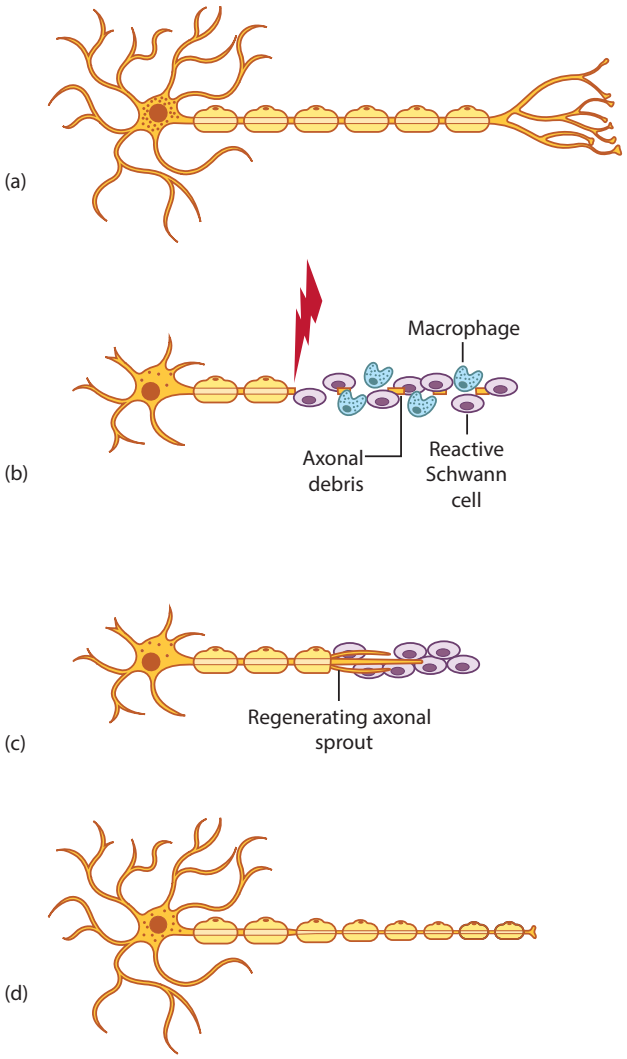

Figure 112.7 **(a)** Normal neuron and nerve fibre. **(b)** Wallerian degeneration. Axotomy results in fragmentation of the distal axon and myelin sheaths. Schwann cells proliferate and macrophages invade the distal nerve segment and phagocytose degrading materials. **(c)** Schwann cells in the distal segment line up in bands of Büngner. Axonal sprouts advance embedded in the Schwann cells and attracted by gradients of neurotrophic factors. **(d)** Axonal reconnection with end organs and maturation and remyelination of the nerve fibre. Re-drawn from Allodi I, Udina E, Navarro X.[67]

introduced the terms neurapraxia, axonotmesis and neurotmesis to describe them.[74] Neurapraxia occurs when compression or stretch produces an anoxic, physiological block of both axoplasmic transport and ion channel functions along affected axons: loss of function is usually temporary and release of the compressive agent usually results in rapid and complete recovery of function and relief of pain. Compression or traction resulting in prolonged ischaemia produces demyelination. Birch[72] points out that … '*the term neurapraxia is best reserved for those situations where electrodiagnosis has conclusively shown that demyelinating conduction block is solely responsible for the neural lesion.*' Axonotmesis occurs when a blunt injury to a nerve results in Wallerian

degeneration distal to the injury, but the connective tissue layers (epi-, peri- and endo-neurium) remain intact. Conduction ceases throughout the distal extent of the nerve within a few days of injury. With the caveat that the distance from injury site to end organ(s) may ultimately defeat successful reinnervation, there is no *a priori* reason why regrowing axon sprouts should not extend to their appropriate targets within the Schwann cell tubes that housed their parent axons: if their progress is unimpeded, recovery progresses proximo-distally (as judged by an advancing Tinel's sign) at a rate of ~1 mm/day. It must be appreciated that even when an axon reaches its target organ, subsequent reinnervation of that target is neither guaranteed nor is it synonymous with full functional recovery. Neurotmesis occurs when a nerve is either completely divided or so badly disorganized by injury that recovery without some form of surgical intervention is impossible. All the connective tissue layers of the nerve as well as the axons are disrupted at the site of injury: a wide inter-stump gap may be produced either by the injury or during subsequent intra-operative wound debridement.

Spontaneous axonal regeneration following this type of injury will be imperfect and disorderly, and may not occur at all. Distance is a significant factor in recovery, particularly after proximal injuries in limb nerves, because regrowing axons may fail to reach their target organs before the latter disappear. Changes in fibre type and loss of striated muscle mass begin within days after denervation; up to 80% of muscle volume may be lost by 4 months and irreversible muscle fibrosis and fatty infiltration occurs after 2 years.[75–77] Some reconstructive surgeons regard functional reinnervation as unlikely beyond 12–18 months. Even after repair, muscles usually exhibit weakness, impaired coordination and reduced stamina; regeneration of the largest diameter axons and coactivation of α and γ efferents may fail. Cutaneous sensory receptors undergo a slow degenerative change after denervation and may disappear after 3 years. Their reinnervation tends to reverse these changes, particularly if the injury occurs close to the end organs and the nerves involved are sensory, however, the longer the period of denervation, the less complete will be the regeneration. Attempts to increase the rate of axonal regrowth in various experimental animal models remain disappointing.

Sir Sydney Sunderland amplified Seddon's category of axonotmesis to describe progressively more invasive levels of injury to the endoneurial contents, perineurium and epineurium, respectively, correlating these new levels with more accurate prognoses of outcomes in axonotmesis injuries.[78] Recovery is typically complete after Sunderland's grade 1 (equivalent to neurapraxia) and 2 (axonal degeneration with intact endoneurium) injuries; grade 3 injuries recover partially; grades 4 and 5 (equivalent to neurotmesis) usually require surgical intervention (**Table 112.1**). Depending upon the level of tissue disruption, misdirection of regrowing axons into modality-inappropriate Schwann tubes in the distal stump is inevitable (For a review of the molecular mechanisms that have been implicated in axonal pathfinding after injury refer to the biology of chronically denervated Schwann cells).[67, 68] Regrowing axons and their associated Schwann cells may form a mechanosensitive neuroma at the end of a proximal nerve stump or a neuroma – in-continuity with the distal stump, phenomena that also compromise recovery. In 1988, MacKinnon

TABLE 112.1 Nerve injury classification and electrophysiological correlates (modified from Birch, 2011)[72]

Seddon	Sunderland	Pathology	Electrophysiological correlate
Neurapraxia	Grade 1	A transient light compression causing endoneurial oedema but no significant morphological changes. A more substantial and prolonged mechanical compression or stretch is most likely to cause a focal demyelination that may be paranodal or affect whole internodes. Anoxia plays a role in the pathogenesis	Conduction block ± conduction slowing. Nerve distal to 'lesion' shows normal conduction
Axonotmesis	Grade 2	Axons degenerate distal to the site of the lesion, irrespective of calibre or modality Endoneurium, perineurium and epineurium remain intact. Schwann cell basal lamina tubes either remain continuous across the lesion or are minimally separated within a morphologically intact perineurium and epineurium	Fibrillation Mild diminution to complete absence of SNAP and CMAP responses, in proportion to degree of axonal loss ± varying degrees of conduction block and slowing associated with demyelination
Axonotmesis	Grade 3	Endoneurium disrupted, axons degenerate distal to the site of the lesion	Fibrillations, absent SNAP and CMAP responses
Axonotmesis	Grade 4	Perineurium disrupted, axons degenerate distal to the site of the lesion	Fibrillations, absent SNAP and CMAP responses
Neurotmesis	Grade 5	Epineurium disrupted, axons degenerate distal to the site of the lesion	Fibrillations, absent SNAP and CMAP responses

'Mixed' is an additional category that combines Grades 2–4 to produce a classification that better represents common clinical scenarios (Mackinnon and Dellon, 1988).[79] SNAP, sensory nerve action potential; CMAP, compound muscle action potential.

and Dellon[79] added a Grade VI injury to Sunderland's classification to better reflect the common clinical scenario of a mixture of crush and transection injury occurring within a damaged nerve. Their classification resonates with an earlier comment by Bowden and Gutmann[75] that … '*In some cases of lesions in continuity there is a mixture of neurotmesis and axonotmesis and if there is much intraneural disturbance, the quality of spontaneous recovery may be poor.*'

The distinction between cases of conduction block (non-degenerative lesions) and those causing axon degeneration is important in prognosis. However, this can be difficult to diagnose early after an injury because Wallerian degeneration usually takes place over several days following injury which means that distal nerve excitability is usually maintained for several days. This timescale has implications on the timing of electrical testing of an injured nerve (see 'Electroneuronography (ENog)' below). In 2016, Hems summed it up well: '*The most important issue is the difference between lesions where the nerve is in-continuity (neurapraxia and axonotmesis) and those where recovery will not occur without surgical repair (neurotmesis).*[80]

Other than a sharp transection, most other injuries or disorders involving the facial nerve will not cause an all-or-nothing lesion, i.e. there is usually a mixture of all three types of injury.

May and colleagues correlated Sunderland's classification with evoked electromyography, histological change, onset of clinical recovery and final recovery according to House and Brackmann's grading.[81] May suggested that the first three degrees of injury can develop with viral inflammatory immune disorders such as Bell's palsy and herpes zoster cephalicus. It is important to remember that the time course for improvement and the extent of recovery is significantly different for incomplete facial nerve paresis compared with total paralysis: 'palsy' includes both entities, whereas 'paralysis' denotes total loss of nerve function.[82] Multiple factors affect the progress of facial nerve regeneration, including the type and severity of the injury and local wound conditions, and more general criteria such as age, nutritional status and comorbidities (e.g. diabetes mellitus).

CLINICAL EVALUATION OF PATIENTS WITH FACIAL PALSY

The history and physical examination are absolutely crucial in the evaluation of a patient with a facial nerve disorder. Every effort must be made to determine the cause. This is particularly the case for patients who present with a facial palsy when their history does not quite fit with an idiopathic palsy (Bell's palsy). In a study of 974 patients referred with a presumptive diagnosis of Bell's palsy, 96 had been misdiagnosed and of these, 47 patients had tumours.[83] Schaitkin and May[84] studied 273 patients who were seen consecutively for evaluation of acute facial nerve palsy. They found that in all cases patients or their families were satisfied if three questions could be answered: (1) what was the cause? (2) when could recovery be expected? (prognosis); (3) what could be done to promote recovery? In most patients who present with an acute facial palsy, these three questions can be answered after a thorough evaluation during the initial office visit.

History

Most patients with a facial palsy consult their general practitioner in the first instance and a large number of them will be assumed to have an idiopathic palsy. Although suggestive, the history of the onset of palsy, whether complete or incomplete, sudden or progressive, is not diagnostic. All these patterns have been noted with idiopathic palsy as well as with infections or neoplasms. Progressive facial nerve palsy over a period of more than 3 weeks, or an incomplete facial nerve palsy that does not start to recover after 3–6 weeks, should make the clinician suspect an underlying neoplasm as the cause and should dictate the need for further investigations.

Ipsilateral recurrent facial nerve palsy is occasionally seen in patients with idiopathic palsy, Melkersson–Rosenthal syndrome and tumours. In fact, the incidence of recurrent facial nerve paralysis in patients with idiopathic palsy is approximately 13% of which 38% are ipsilateral and 62% are on the contralateral side.[85] Pitts et al.[86] reported a mean interval of 9.8 years between recurrences of idiopathic palsy (range : 1 month to 43 years). They also noted that patients with a recurrence were 2.5 times more likely to have a positive family history. Recurrence is common in herpes simplex type I infection but rare with herpes zoster. May and Hardin[87] reported that in 6 of 20 patients with ipsilateral recurrence, a tumour involving the facial nerve was the cause. They recommended that a tumour be suspected in every patient who presented with an ipsilateral recurrent facial palsy. In contrast to recurrent ipsilateral facial paralysis, contralateral recurrence is almost always benign. Alternating recurrent facial nerve palsy is rare and is a feature of Melkersson–Rosenthal syndrome, a condition also characterized by facial oedema, fissured tongue and a positive family history (**Figure 112.8**). Bilateral concurrent facial nerve paralysis is most probably associated with a systemic condition, the most common being Guillain–Barré syndrome, but is also seen in patients with cerebral lymphoma, leukaemic infiltration, sarcoidosis, Lyme disease, rabies, infectious mononucleosis and Moebius syndrome.

Physical examination

A thorough head, neck, otologic and cranial nerve examination is the absolute minimum required when evaluating facial nerve dysfunction. Facial weakness can be extremely subtle, apparent only to a trained examiner and, almost

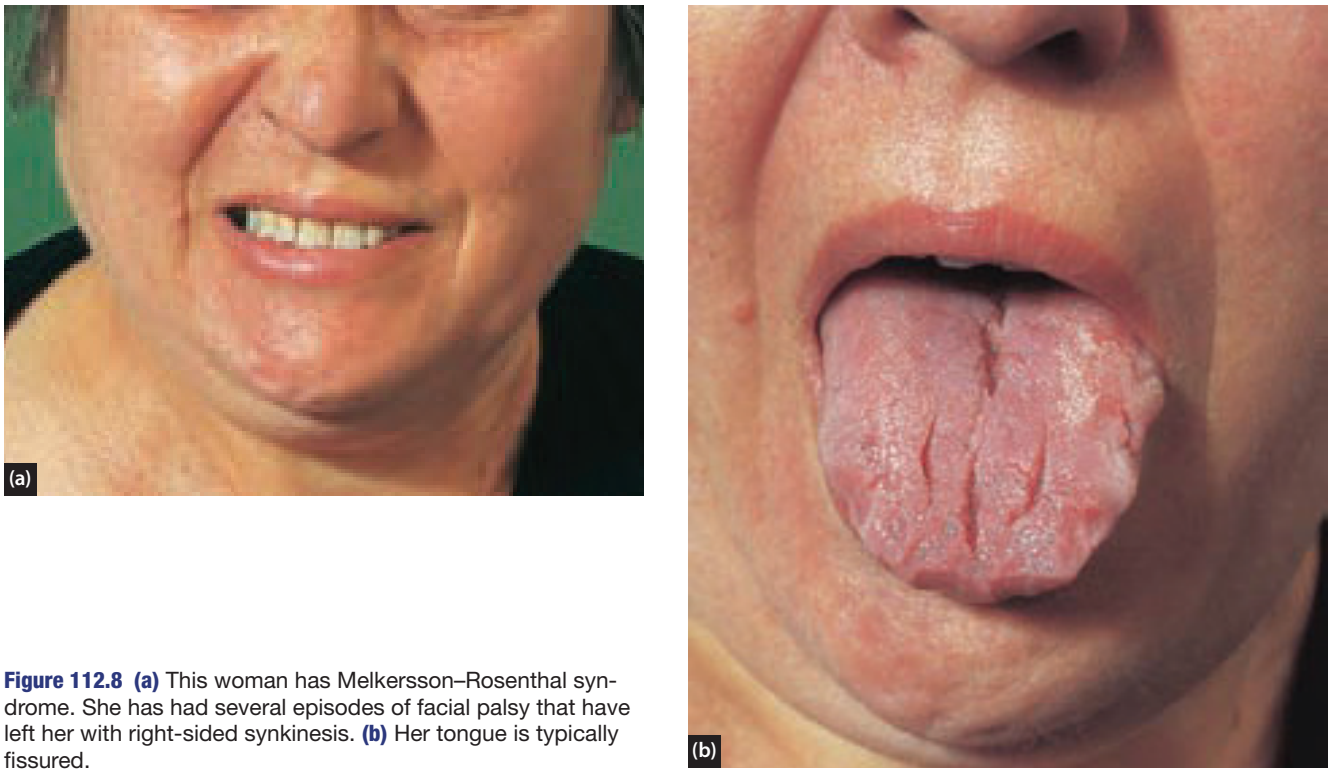

Figure 112.8 **(a)** This woman has Melkersson–Rosenthal syndrome. She has had several episodes of facial palsy that have left her with right-sided synkinesis. **(b)** Her tongue is typically fissured.

certainly, to the patient and their close friends or carers. Examination must be expanded as indicated by the individual patient's history. The degree of facial weakness must be recorded from the outset and an attempt made to localize the precise site of the cause along the course of the facial nerve i.e. intracranial, intratemporal or extratemporal. An open mind to the potential cause is essential since facial nerve palsy may be the first presentation of a systemic illness.

If symptoms or signs of other cranial nerve deficits are present, a central or systemic cause should be suspected. Sparing of forehead movement is considered to be characteristic of a central lesion but is not always the case. Normal movement can be seen in facial nucleus lesions and even peripheral lesions of the temporal branch of the facial nerve. An isolated lower facial palsy is therefore not necessarily indicative of a central lesion. A partial palsy of one or two branches strongly suggests disease localized distal to the stylomastoid foramen and a parotid malignancy should be suspected. If the parotid gland is enlarged and the patient has impaired vision or iritis, sarcoidosis is a possibility.

Facial palsy grading systems

Several systems of clinical measurement of facial nerve function have been described. In 1983, House proposed a six-point scale for reporting the recovery and outcomes of surgery for vestibular Schwannomas. This system was modified and called the House–Brackmann Staging System and has become the most widely used scheme and endorsed by the American Academy of Otolaryngology – Head and Neck Surgery.[81] It has become engrained in clinical practice and will remain so despite its shortcomings as a scientifically accurate assessment tool. In the House–Brackmann system, grade I is normal function, grade VI is complete absence of facial motor function and grades II–V are intermediate (Table 112.2).

As stated above, the House–Brackmann staging system does have limitations with respect to precision and inter-observer error. It emphasizes the characteristics of facial nerve palsy from two assessment domains. The first is gross observation and the second is movement of the forehead, eye and mouth. The fusion of static and dynamic criteria may have contributed to some disagreement between examiners. When only a global score is used, the risk of disagreement among different examiners can range from 13% to 44%.[88, 89] Yen et al.[90] reported the efficacy of the House–Brackmann grading in patients with differential facial nerve function and concluded that a single global grading number was inadequate to describe facial function and primarily reflected the function of the eye. They recommended that regional assessment using the House–Brackmann grading system should be carried out in patients with facial nerve palsy and the result should be reported for the forehead, eye, nose and mouth separately to get a more precise evaluation.

The wide acceptance of the House–Brackmann system has not prevented others from proposing new systems. Burres and Fisch[91] described a method requiring multiple measurements of movement in different parts of the face. Croxson et al.[89] showed the expected correlation between the Burres–Fisch and House–Brackmann systems in 42 patients and found considerable overlap of

TABLE 112.2 House–Brackmann staging system

Degree of injury	Grade	Definition
Normal (1°)	I	Normal symmetrical function in all areas
Mild dysfunction (barely noticeable) (1–2°)	II	Slight weakness noticeable only on close inspection
		Complete eye closure with minimum effort
		Slight asymmetry of smile with maximal effort
		Synkinesis barely noticeable, contracture or spasm absent
Moderate dysfunction (obvious difference) (2–3°)	III	Obvious weakness, but not disfiguring
		May not be able to lift eyebrow
		Complete eye closure and strong but asymmetric mouth movement with maximal effort
		Obvious, but not disfiguring synkinesis, mass movement or spasm
Moderately severe dysfunction) (3°)	IV	Obvious disfiguring weakness
		Inability to lift eyebrow
		Incomplete eye closure and asymmetry of the mouth with maximal effort
		Severe synkinesis, mass movement, spasm
Severe dysfunction (3–4°)	V	Motion barely perceptible
		Incomplete eye closure, slight movement of the corner of the mouth
		Synkinesis, contracture and spasm usually absent
Total paralysis	VI	No movement, loss of tone, no synkinesis, contracture or spasm

This system was proposed by House and Brackmann and adopted by the Facial Nerve Disorders Committee of the American Academy of Otolaryngology, Head and Neck Surgery.

Burres–Fisch scores for House–Brackmann grades III and IV. Murty et al.[88] proposed and tested the Nottingham system of subjective estimation of movement at each of several points on the face. This method correlated better with the House–Brackmann system than did the Burres–Fisch, and it was simpler to perform.

Facial nerve dysfunction includes secondary effects that complicate facial nerve injury. They usually result from aberrant neural regeneration and include synkinesis, hemifacial spasm, contracture, crocodile tears, epiphora, dysgeusia, pain and hyperacusis. These effects do not accompany the primary weakness in an orderly fashion or predictable way and have a significant influence on the patient's perception of disability, handicap and quality of life. Both the Nottingham and Sunnybrook scales have attempted to include these secondary effects in their overall score.[92] To date, none of the current measurement systems have been validated against patient self-assessment in a robust fashion. The ideal system should be user-friendly, reliable and reproducible, reflect patho-physiological events and correlate well with self-assessment.

The advent of computerized technologies prompted more accurate and objective measurements of facial function and secondary effects such as synkinesis, spasm and velocity of facial movement. These techniques have utilized superficial reflective facial fiducials, pixel subtraction techniques, the movement of standardized facial landmarks against registered static points in the midline of the face and even Moiré topography to obtain objective scores or grades. A detailed summary and critique of these techniques has been made by Brenner and Neely.[93] Their conclusion was that computer-based systems offer refinement beyond that available by all other assessment scales. However, they require specialized equipment and considerable investment of time on the part of the clinician, which is almost certainly not possible outside the research setting.

In reality, it is the effect of facial palsy, incomplete recovery and the secondary effects caused by aberrations of regeneration on the patient's quality of life that matter. Functional impairments that include difficulties in eating, drinking, speaking and conveying intimate human information and emotion are simply not captured in any of the surgeon-ranked clinical scales used in practice. Psychological consequences such as decreased self-esteem, anxiety when meeting strangers, depression and social isolation are not even considered. Patient-reported outcomes should be quoted alongside those of surgeon-ranked scales. In a thorough, systematic review undertaken by Ho et al.[94] that analyzed 598 articles indexed by the recognized databases, the Facial Clinimetric Evaluation,[95] the Facial Disability Index[96] and a questionnaire developed to study aberrant facial nerve regeneration[97] were the only instruments that satisfied all inclusion and exclusion criteria. Even these had limitations in domains that addressed self-perception of facial appearance and procedure-related symptoms or satisfaction. Ho et al. concluded that future

research was necessary to develop and validate a new patient-reported outcome instrument.

Topodiagnostic tests

Topodiagnostic evaluation of facial palsy refers to the functional testing of an individual facial nerve branch in an attempt to locate the anatomical level of dysfunction or injury. These tests are of some value but have a slightly limited correlation with the precise site of nerve damage and do not have any prognostic value. These studies are summarized in Table 112.3.

Electrophysiological tests

Electrophysiological tests have been developed to evaluate the degree of dysfunction and assumed viability of the facial nerve in the anticipation that results would provide prognostic information for recovery. This information has been used to influence management, particularly the potential impact of any surgical intervention. These tests are not normally used in the assessment of incomplete paresis, which has a higher probability of full, functional recovery. They are only used in patients with complete established paralysis, when they can aid management decisions concerning facial reanimation. Repair of the facial nerve is contraindicated when the motor end plate muscle units are no longer functional, a process that continues inexorably along with muscle atrophy in the months after total denervation. Reinnervation procedures when no muscle end plate activity can be detected by electromyography are contraindicated because they will not be successful.

The traditional tests using transcutaneous stimulation of the facial nerve to establish the minimum current required to provoke muscle movement, the nerve excitability test (NET), and the current required to achieve maximal muscle response without causing any discomfort to the patient, maximal stimulation test (MST), are rarely used nowadays (Table 112.4). Both these tests compared the response on the normal to the palsied side and could be undertaken at the bedside or in the clinic using a Hilger Stimulator: they had their limitations in terms of accuracy, reproducibility, inter-observer variation and prognostic value (Table 112.4).[98]

The two techniques most commonly used now by otorhinolaryngologists in clinical practice are electroneuronography (ENoG) and electromyography (EMG). A third technique, transcranial magnetic stimulation, also has a role in clinical practice, particularly in neurology, but has yet to be employed widely by otorhinolaryngologists.

ELECTRONEURONOGRAPHY (ENoG)

In ENoG, a supramaximal stimulus is delivered to the facial nerve trunk as it exits the stylomastoid foramen and the evoked biphasic compound muscle action potential (CMAP) is recorded using surface electrodes. The response of the paralyzed side is compared with that of the normal side, which serves as a control, and is expressed as a percentage of the normal. It has been shown that reduction in CMAP correlates well with histological axonal loss.[99] This means that if the CMAP amplitude on the affected side is 10% of the normal side, then it is assumed that

Figure 112.9 Schirmer's test. The patient had sustained a longitudinal fracture of the left temporal bone that had transected the greater petrosal nerve. She had a dry eye as is demonstrated in this test.

TABLE 112.3 Topodiagnostic tests

Test	Nerve branch assessed	Technique considerations	Assessment/ Outcome
Schirmer's test (Figure 112.9)	Greater (superficial) petrosal nerve	Strips of paper are placed in the inferior conjunctival fornix for 5 minutes and the length of paper moistened is compared between eyes	>75% unilateral decrease in lacrimation, or a bilateral decrease in lacrimation (less than 10 mm wetted for both sides at 5 minutes)
Stapedial reflex	Nerve to stapedius muscle	See Chapter 51, Psychoacoustic audiometry	Present or absent
Electrogustometry	Chorda tympani	The tongue is stimulated electrically to produce a metallic taste and the two sides are compared	Threshold of the test is compared between sides
Salivary flow testing	Chorda tympani	Wharton's ducts are cannulated and salivary flow is measured over time following a gustatory stimulus (6% citric acid on anterior part of tongue)	A reduction of 25% is considered abnormal

TABLE 112.4 Comparison of NET and MST

Test	Technique	Outcome measure	Prognostic value
NET	Compares transcutaneous current threshold required to elicit minimal muscle contraction between two sides	>3.5 mA difference is considered significant	Indicates poor recovery
MST	Compares muscle contraction at maximal nerve stimulation (~5 mA) between two sides	Equal response, reduced response or absent response	Loss of response within 10 days is associated with incomplete recovery.

90% axonal loss has been sustained. ENoG is said not to be useful until the fourth day of facial nerve paralysis. Neural conduction disappears quite rapidly after an injury that transects an axon because a degenerating axon is incapable of conducting an action potential, and most axons have at least started to degenerate within 3–4 days of such an injury.

ENoG is considered the most valuable prognostic indicator among current electrophysiological tests and its main indication is acute onset complete facial nerve paralysis. Both the percentage of amplitude reduction and rate of degeneration have been used as prognostic indicators of facial nerve recovery. In idiopathic palsy, degeneration of >90% within 14 days of complete paralysis indicates a probable poor recovery in >50% of cases.[100] ENoG does not appear to be useful in Ramsay Hunt syndrome because of multiple sites of nerve involvement. Fisch has recommended surgical intervention within three weeks in patients where traumatic injury has resulted in >90% amplitude reduction by ENG within 6 days of the injury.[101, 102] Great care has to be taken interpreting these data. Although there is good correlation between the natural history of idiopathic palsy and ENoG findings, there are no definitive data on the natural history of facial nerve injury due to other causes. The assumption that ENoG data is valid regardless of whether the paralysis was of immediate or delayed onset cannot be justified from the literature.[103]

ELECTROMYOGRAPHY (EMG)

EMG records active motor unit potentials of the orbicularis oculi and orbicularis oris muscles during rest and voluntary contraction. EMG can be used to determine:

- if a nerve in question is in continuity (volitional activity recorded)
- if there is evidence of Wallerian degeneration (fibrillation potentials)
- if there are early signs of reinnervation (polyphasic innervation potentials).

Fibrillation potentials typically arise 2–3 weeks following injury, and polyphasic reinnervation potentials may precede clinical signs of recovery by 6–12 weeks.

In cases of acute onset and complete paralysis with unfavourable ENoG recordings (>90% degeneration), the finding of active motor unit potentials indicates that some fibres are intact and suggests a favourable prognosis. As long as some active motor units can be recorded one week following a complete paralysis, severe degeneration is unlikely to take place. EMG has a role in decision making regarding surgical intervention in long-standing paralysis as follows:

- Polyphasic motor unit potentials indicate regenerative processes and surgical intervention is therefore not indicated. In this case, close follow-up studies of nerve regeneration are advocated.
- Fibrillation potentials indicate lower motor neuron denervation, but viable motor end plates. Surgical exploration is therefore indicated with a view to achieving nerve continuity, either by end-to-end anastomosis, interposition grafting, re-routing or re-innervation techniques.
- 'Silence' on EMG (no electrical output) indicates long-term denervation and suggests that muscle has been replaced by fibrous tissue. In this case, static or dynamic (microvascular innervated free muscle transfer or muscle transposition) facial reanimation is indicated.

LIMITATIONS OF ELECTROPHYSIOLOGICAL TESTING

Although electrophysiological testing may provide useful prognostic information and serve as a guide to the management of facial palsy, there are some important shortcomings.

- The electrical impulse can only stimulate normal or neurapraxic fibres and cannot distinguish whether the remaining fibres are in a state of axonotmesis or neurotmesis. Thus, it cannot distinguish between injuries which have different prognoses.
- It provides no useful information in cases of incomplete facial paralysis.
- It fails to provide information on the immediate post-paralysis period (first 72 hours).

An overview of ENoG and EMG is given in Table 112.5 and should be read in conjunction with the Nerve Injury Classification in Table 112.1.

TRANSCRANIAL MAGNETIC STIMULATION

While electrodiagnostic tests provide information about the facial nerve distal to the stylomastoid foramen, transcranial magnetic stimulation is able to stimulate the facial

TABLE 112.5 ENoG and EMG

Study	Measurement	When to measure	Use in acute onset paralysis	Use in long-standing paralysis
ENoG	Evoked CMAP compared to normal site	Between 3 days and 3 weeks	>90% of degenerated fibres suggests poor prognosis	Not useful because of desynchronization
EMG	Active motor unit potentials after voluntary forceful contraction	Complementary to ENoG, after 2 weeks	Presence of active motor potentials in response to voluntary contractions indicates good prognosis	Fibrillation potentials suggest Wallerian degeneration
		In long-standing paralysis		Polyphasic potentials suggest reinnervation

nerve within the cranium. Magnetic impulses induce an electric current within the brain and stimulate neuromuscular tissue in exactly the same way as conventional electrostimulation. The design and type of coil determines the penetration and site of stimulation. A double coil is normally employed for facial nerve studies and has the ability to focus on the infranuclear portion of the nerve, probably at the root entry zone or temporal bone itself. It is this capability that has opened up the potential to clinical and research studies of palsies caused by temporal bone pathologies and link these with information derived from MRI data.[104, 105]

INTRA-OPERATIVE NERVE MONITORING

Intra-operative monitoring is now widely used though yet to be considered a standard of care for every operation at which there is a risk of damaging the facial nerve. A number of devices are marketed that employ continuous EMG monitoring from peripheral facial muscle groups for spontaneous and electrically evoked stimulation of the facial nerve trunk or its branches. Their role in preventing facial nerve injury remains controversial, but there is little doubt that intra-operative nerve monitoring makes the trainees' learning curve safer for the patient. There are no prospective, randomized studies that have proven its efficacy in reducing the incidence of facial nerve paralysis. However, intra-operative monitoring has established itself in CPA tumour surgery, revision mastoidectomy, parotidectomy and in surgery of congenital ear abnormalities. Other considerations should be medico-legal issues that may arise in cases of facial nerve injury when the monitor was not used even though it was available, and the use of monitoring during supervised resident training.

In CPA tumour surgery it is particularly helpful for identification of the nerve at the brainstem, its displacement and distortion around the tumour, where it can be almost invisible, and within the IAM: in other words, throughout the whole of the procedure. Jackler et al.[106] have reported a reduced incidence of complete permanent paralysis following removal of CPA tumours with the use of intra-operative monitoring, while Axon et al.[107] have found a good correlation between intra-operative CMAP amplitude following tumour resection and immediate post-operative facial nerve function. Kirkpatrick et al.[108, 109] reported that intra-operative facial nerve monitoring in CPA tumour surgery appeared to predict eventual facial function accurately in small tumours, but did not predict facial nerve recovery reliably following surgery for larger tumours. Wilson et al.[110] looked at the cost-effectiveness of intra-operative facial nerve monitoring in middle ear or mastoid surgery. They found that a strategy to monitor both primary and revision surgeries had the greatest effectiveness and lowest cost. Noss et al.[111] reported that the absence of monitoring would have led to facial nerve deficits in 1–2% of their cases. Pensak et al.[112] felt that the overall outcome of mastoid surgery was definitely affected in a positive way by the presence of the monitor in 0.4% of cases during residents' training. As far as parotid surgery is concerned, several studies have demonstrated that there is no significant difference in the incidence of permanent paralysis of monitored versus unmonitored groups, but its use may have an effect on the intensity of post-operative palsy and on the recovery time in revision surgery.[113, 114] Only one study demonstrated that intra-operative monitoring led to a significantly decreased incidence of post-operative temporary paralysis (62% versus 44%), although no difference in permanent paralysis was seen.[115] These results support the observation that continuous intra-operative EMG monitoring may not affect post-operative facial nerve outcomes and EMG abnormalities do not predict facial nerve injury in parotid surgery. Pitfalls and caveats are shown in **Table 112.6**.

Blood investigations

While most patients present in a truly idiopathic fashion, some patients do not and the cause of their palsy is far from clear. In retrospect, the following blood tests might have helped to identify or exclude other less common causes: Angiotensin Converting Enzyme titres, Anti-neutrophil Cytoplasmic Antibody profile, HIV serology, Lyme serology and Syphilis serology. Obtaining the results of tests sooner rather than later is wise.

Facial nerve imaging

RADIOLOGICAL IMAGING OF THE NORMAL FACIAL NERVE

Computed tomography (CT) of the temporal bone allows identification of the Fallopian canal from the fundus of the IAM to the stylomastoid foramen (**Figure 112.10a,b&c**). The technique of high-resolution acquisition with overlapping thin sections of 0.6 mm, reconstructed into 0.3–0.4 mm sections, allows equivalent voxels of 0.3 mm^3.

TABLE 112.6 Pitfalls and caveats of intra-operative monitoring

Pitfalls and caveats
Always ask the anaesthetist to avoid neuromuscular blockade
The closer the bipolar electrodes are placed, the fewer the muscle fibres that will be represented in the EMG response
Use transparent drapes for backup
Test the integrity of the system with the anaesthetic nerve stimulator before starting the operation and check the system periodically during surgery
Even after nerve transection, the distal segment can still be stimulated for a few days, creating evoked EMG responses that may be falsely interpreted as evidence of continuity
The mastoid segment is least sensitive to nerve stimulation, so a higher setting is needed (0.5 mA in mastoid surgery as opposed to 0.05–0.1 mA in CPA tumour surgery)

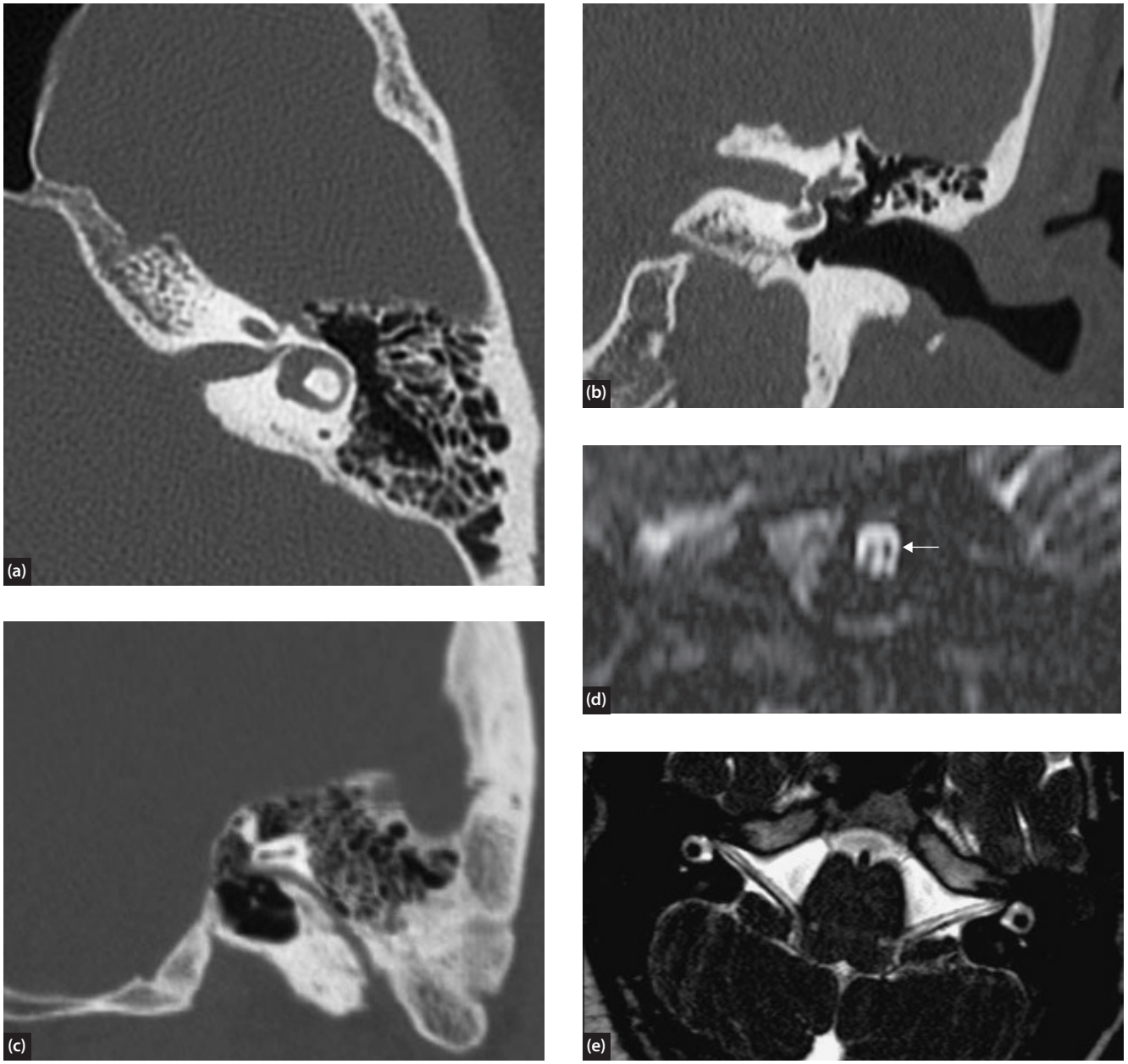

Figure 112.10 **(a)** Axial CT scan of the labyrinthine segment of the facial nerve and first genu; **(b)** coronal CT of tympanic segment of facial nerve which lies just inferior to the lateral semicircular canal; **(c)** oblique sagittal CT view of the mastoid segment of the facial nerve and second genu; **(d)** T2 DRIVE oblique sagittal MRI of facial nerve in the IAM (arrowed); **(e)** T2 DRIVE axial MRI of facial nerve in the IAM running alongside the superior vestibular nerve.

In contrast, the thin collimation performed as part of a trauma sequence CT head/brain may not provide an adequate level of detail to assess the facial nerve canal. The tympanic portion is probably easiest to identify on axial scans at the level of the body of incus and its short process. From there it can be followed proximally and distally towards the labyrinthine and descending segments respectively. The labyrinthine segment is characteristically banana-shaped on axial sections. On coronal images it may be visualized as the medial of the two circular 'eyes' directly above the cochlea. The sulcus for the geniculate ganglion is also well demonstrated in coronal sections. The mastoid segment is best visualized in coronal or sagittal views. In coronal views it is easier to follow the nerve from the stylomastoid foramen to its more proximal part. It is more difficult to identify in axial views, especially in well-pneumatized temporal bones. One way is to try and locate the pyramid or the stapedius muscle; the facial nerve lies immediately behind.[116, 117] Bance and Erb[118] have described the 'B-line': a tangent line extrapolated from the posterior border of the basal turn of the cochlea, which falls within 1 mm of the facial nerve on average. The intra-parotid facial nerve cannot be identified on CT scans. The facial nerve plane is extrapolated as a line connecting the stylomastoid foramen to a point immediately lateral to the retromandibular vein.

The intra-parotid facial nerve is not identified on CT scans. The facial nerve plane is extrapolated as a line connecting the stylomastoid foramen to a point immediately lateral to the retromandibular vein.

Cone-beam CT scanning is becoming increasingly utilized for pre-operative planning for middle ear surgery including cochlear implantation and provides good anatomical detail, particularly in respect of the facial nerve location, while exposing the patient to less ionizing radiation.

The rich perineural arteriovenous plexus which surrounds the normal facial nerve facilitates visualization on contrast enhanced T1-weighted MRI. It is usually observed in more than one segment, more commonly in the geniculate ganglion and the tympanic segments and it may enhance asymmetrically between right and left. Enhancement previously considered pathological has more recently been noted in the fundus of the IAM in normal subjects. Most radiologists believe that the intra-parotid facial nerve cannot be routinely identified on MRI. The linear, low-intensity signal seen on axial T1 scans most probably represents intra-parotid ductal ramification (**Figure 112.10**).

Imaging strategies in facial nerve palsy

The imaging strategy is largely determined by the suspected nature of the lesion. In general, a high-resolution CT (HRCT) enables superior visualization of the intratemporal segment of the facial nerve and is particularly useful in cases of temporal bone trauma, Fallopian canal involvement in chronic suppurative otitis media (CSOM) or temporal bone malignancies. MRI using paramagnetic contrast agents such as gadolinium-DTPA is known to provide better visualization of soft tissues and is particularly useful in neoplastic or inflammatory lesions. It should be remembered that both imaging techniques are complementary and may be used in combination.

IDIOPATHIC PALSY

Imaging of patients with idiopathic facial palsy who present in a typical fashion is not cost-effective. The degree of enhancement on MRI carries no significant prognostic value and the chance of acute facial nerve palsy in a tumour is remote. Imaging is only recommended if the presentation is atypical, an alternative diagnosis is suspected, surgical decompression is planned or recovery is incomplete at 6 months. MRI may be normal in the first 10 days following the onset of palsy. Post-gadolinium enhancement is characteristically asymmetric, diffuse, intense and linear (not nodular). It involves the entire intratemporal segment of the facial nerve, but is more distinct in the fundus of the IAM and labyrinthine segments and may well persist for several months after full recovery (**Figure 112.11**). However, in a case of presumed idiopathic facial nerve palsy the authors consider contrast-enhanced MRI scanning 3 months following the initial weakness if the clinical condition has not improved. In cases where the weakness is progressing, the patient should be scanned earlier.

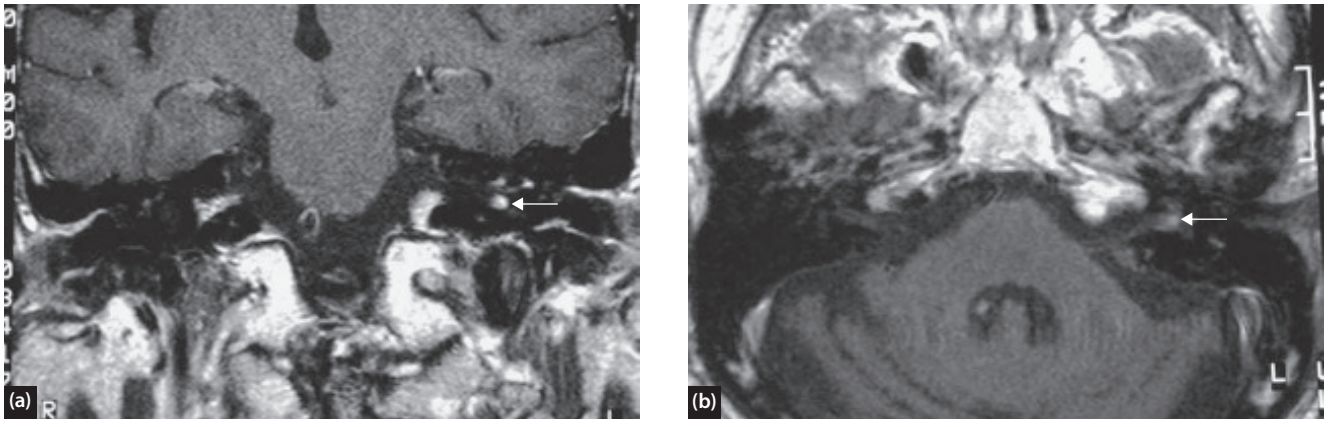

Figure 112.11 **(a)** Coronal and **(b)** axial MRI of a patient with a left-sided idiopathic palsy. Increased signal is clearly visible in the geniculate region (arrowed).

Different departments will employ various imaging protocols to ensure an idiopathic case is not masking a more sinister diagnosis. Pre- and post-contrast T1 sequences through the temporal bone, in combination with T2 sequences of the whole brain and parotid-specific fat suppression imaging can be considered a comprehensive approach.

ACUTE AND CHRONIC OTITIS MEDIA

Imaging in facial nerve paralysis in the presence of acute or chronic otitis media is generally directed towards identifying coexisting intratemporal or intracranial complications rather than the site of nerve damage. A CT scan of the temporal bone can delineate the site of erosion of the Fallopian canal, but MRI cannot differentiate between the increased signal of the facial nerve from that of surrounding inflamed granulation tissue.

TEMPORAL BONE FRACTURE

HRCT is the investigation of choice for temporal bone fractures. Facial nerve injury is usually situated just distal to the geniculate ganglion and the first genu in longitudinal fractures and just proximal to the geniculate ganglion in transverse fractures. MRI has little if any value in these instances. There is no correlation between pathological facial nerve enhancement and ENoG findings and it may be observed up to 2 years post-trauma (**Figure 112.13**).[119]

TUMOURS

MRI is the investigation of choice in these cases. Facial nerve haemangiomas enhance intensely on post-contrast T1-weighted MRI, most commonly in the area of the geniculate ganglion, and also have a typical honeycomb matrix appearance on CT. Facial nerve schwannomas show a strong enhancement with gadolinium on T1-weighted images and, when they grow to the point of filling the internal auditory canal, they cannot be distinguished from vestibular schwannomas (**Figures 112.14, 112.15** and **112.16**). Malignant parotid tumours may track up the facial nerve and a soft-tissue intensity enhancing mass is usually observed extending from the gland through an enlarged stylomastoid foramen to involve the mastoid

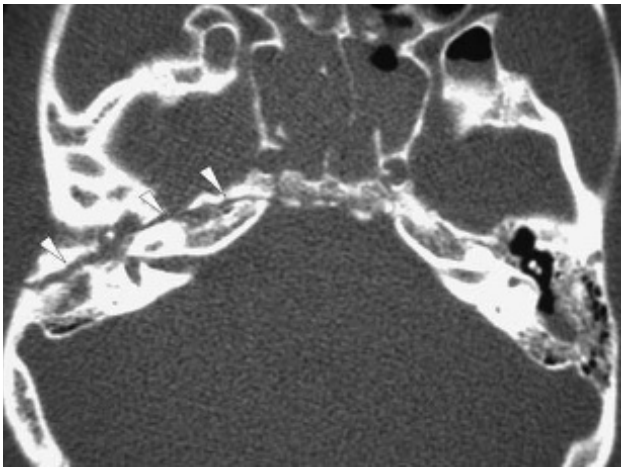

Figure 112.12 Typical CT appearance of a longitudinal fracture of the temporal bone. The fracture line (arrowed) passes anterior to the genu of the facial nerve.

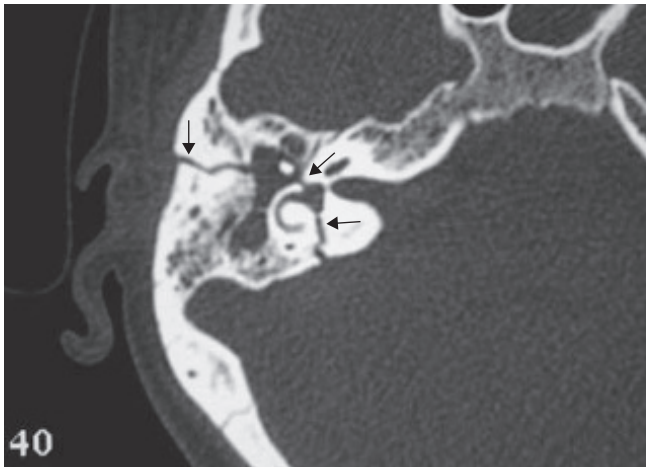

Figure 112.13 CT scan of a transverse fracture of the temporal bone. The fracture (arrowed) passes through the vestibule and across the tympanic segment of the facial nerve.

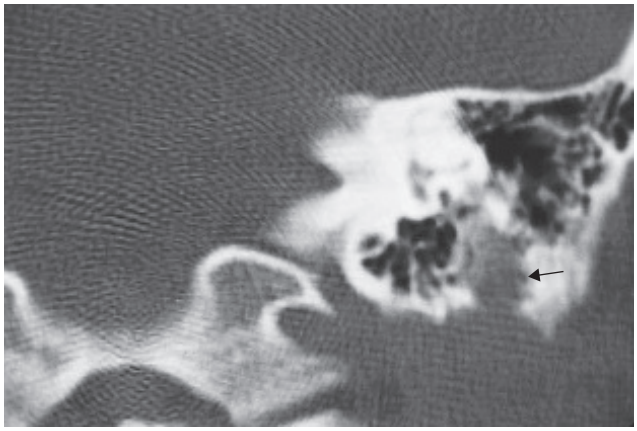

Figure 112.14 CT scan of Fallopian canal containing a facial nerve schwannoma. The canal is expanded and its bony margins are scalloped (arrowed).

Figure 112.15 T1 gadolinium MRI of facial schwannoma showing increased signal (arrowed).

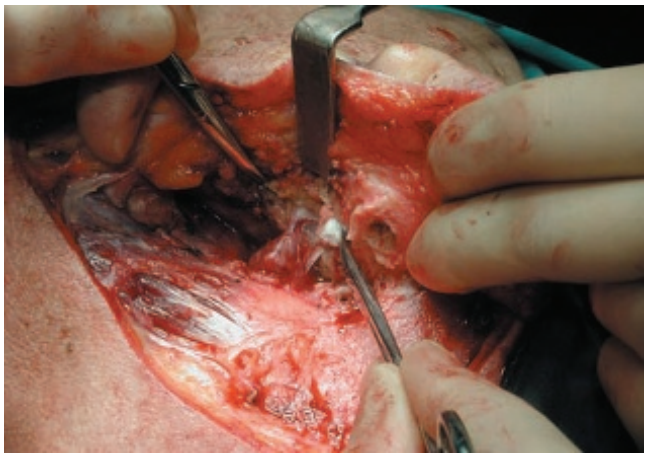

Figure 112.16 Facial nerve schwannoma, imaged in 112.14 and 112.15 seen at surgery pouting from the anterior border of the sternocleidomastoid muscle, entering the parotid gland, just beneath the transected external ear canal.

segment of the facial nerve. There is usually replacement of the hyperintense fat tissue by a hypointense signal in T1-weighted images.

DIFFUSION TENSOR IMAGING TRACTOGRAPHY

Skull base surgeons are well aware of the challenges of functional preservation of the facial nerve at the time of tumour dissection in vestibular schwannoma surgery. Intra-operative EMG is routinely employed to help locate and allow preservation of the often-thinned nerve traversing the tumour capsule. Diffusion tensor imaging (DTI) utilizes multidimensional vector algorithms to derive neural tract directional information. The aligned fibres of neural tissue can be specifically imaged. DTI has been shown to provide the surgeon with additional pre-operative information as to the location of the facial nerve with respect to the tumour within the CPA, potentially increasing the likelihood of a good facial nerve outcome.[120, 121]

MANAGEMENT OF THE PATIENT WITH A FACIAL NERVE DISORDER

As stated earlier, the management of an acute insult causing a facial nerve palsy depends to some extent on the cause, but there are also general points that apply to all (**Table 112.7**). In this section the management issues surrounding palsies resulting from the most common causes are discussed.

EYE CARE

Appropriate eye care, including advice regarding corneal protection with lubrication and patching should be instituted immediately in cases where eye closure is impaired. In those patients with severe facial weakness the blink movement is impaired and the eyelid cannot cleanse and lubricate the corneal surface. In addition, if the nerve injury involves the trunk proximal to the 1st genu, and therefore the origin of the greater petrosal nerve, the secretomotor supply to the lacrimal gland is also impaired thus compounding the problem with corneal lubrication.

Simple guidance regarding the use of large-lens sunglasses can help protect the eye from dust and debris on a windy day. Eye drops should be applied to the corneal surface frequently during the daytime, whilst at night ointment is preferred. Following the application of the ointment the eye should be taped closed. Over time, the unopposed action of levator palpebrae superioris (supplied by the oculomotor nerve) results in shortening of the upper eyelid. Patients should be advised to close their eye manually using a finger as well as attempting to stretch the upper lid to try and prevent this shortening. Upper eyelid weighting with external adhesive skin-tone coloured weights (Blinkeze™) is recommended. More formal surgical weighting or levator-lengthening procedures are used in long-standing cases of impaired eye closure. In some cases, these may be performed acutely as they can be reversed, although this is not the usual practice of the authors.[122, 123]

Idiopathic (Bell's) palsy

The term idiopathic palsy should be reserved for cases of facial paralysis that have signs and symptoms consistent with the disease and in which a diligent search for another cause is negative. The search for a cause should not simply relegate idiopathic palsy to a diagnosis of exclusion, but emphasize the diagnosis based on specific clinical features. In 1959, Taverner[124] outlined the minimum diagnostic criteria for idiopathic palsy, then known as Bell's palsy, that included: paralysis or paresis of all muscle groups on one side of the face; sudden onset; absence of signs of central nervous system disease; absence of signs of ear or CPA disease. These criteria still hold today. Classically, patients present with a prodromal illness which may include periauricular pain and general malaise. Within 72 hours they rapidly develop complete lower motor neuron facial weakness.

The annual estimated incidence of idiopathic palsy is fairly similar throughout the world, ranging between 20 and 32.7 per 100,000 in different studies.[125, 126] The condition affects approximately 1 in 65 people during their lifetime. The incidence reaches a peak between the ages of 15 and 45 years. It has a predominance in women younger than 20 years and a slight predominance in men older than 40 years, although the male to female ratio is more or less equal across the population. Recurrence rates of 4.5–15% and a familial incidence of 4.1% have been addressed in various studies. There may be genetic factors that influence the development of idiopathic palsy but quite what they might be is unclear. Idiopathic palsy is more common in pregnancy with the majority of cases being in the 3rd trimester. It is suggested that the increased incidence in the latter stages of pregnancy relates to changes in fluid balance with increased extracellular fluid leading to oedema of the nerve and subsequent compression within the Fallopian canal.[127]

TABLE 112.7 Causes of facial palsy

Causes	
Birth	Moulding
	Forceps delivery
	Dystrophia myotonica
	Moebius syndrome (facial diplegia associated with other cranial nerve defects)
Trauma	Basal skull fracture
	Facial injuries
	Penetrating injury to middle ear
	Altitude paralysis (barotrauma)
	Scuba diving (barotrauma)
	Lightning
Neurological	Opercular syndrome (cortical lesion in facial motor area)
	Millard–Gubler syndrome (abducens palsy with contralateral hemiplegia due to lesion in base of pons involving corticospinal tract)
Infection	Otitis externa
	Acute otitis media
	Mastoiditis Chronic otitis media
	Chicken pox
	Herpes zoster cephalicus (Ramsay Hunt syndrome)
	Encephalitis
	Poliomyelitis (type I)
	Mumps
	Infectious mononucleosis (glandular fever)
	Leprosy
	Coxsackie virus
	Malaria
	Syphilis
	Scleroma
	Tuberculosis
	Botulism
	Acute haemorrhagic conjunctivitis (enterovirus 70)
	Gnathostomiasis
	Mucormycosis
	Lyme disease
Metabolic	Diabetes mellitus
	Hyperthyroidism
	Pregnancy
	Hypertension
	Acute porphyria
Neoplastic	Facial schwannoma
	VIIth nerve tumour
	Jugular paraganglioma
	Tympanic paraganglioma
	Meningioma
	Haemangioblastoma
	Sarcoma
	Carcinoma (invading or metastatic)
	Anomalous sigmoid sinus
	Haemangioma of tympanum
	Hydradenoma (external auditory meatus)
	Leukaemia
	Cerebral lymphoma
	Teratoma
	Hand–Schüller–Christian disease
	Fibrous dysplasia
	Von Recklinghausen's disease
Toxic	Thalidomide (Miehlke syndrome, cranial nerves VI, VII with congenital deafness)
	Tetanus
	Diphtheria
	Carbon monoxide
Iatrogenic	Mandibular block anaesthesia
	Anti-tetanus serum
	Vaccine treatment for rabies
	Post-immunization
	Parotid surgery
	Mastoid surgery
	Post-tonsillectomy and adenoidectomy
	Iontophoresis (local anaesthesia)
	Embolization
	Dental
Idiopathic	Bell's, familial
	Melkersson–Rosenthal syndrome (recurrent alternating facial palsy, furrowed tongue, faciolabial oedema)
	Hereditary hypertrophic neuropathy (Charcot–Marie–Tooth disease, Déjérine–Sottas disease)
	Autoimmune syndrome
	Temporal arteritis
	Thrombotic thrombocytopenic purpura
	Polyarteritis nodosa
	Landry–Guillain–Barré syndrome (ascending paralysis)
	Multiple sclerosis
	Myasthenia gravis
	Sarcoidosis (Heerfordt syndrome – uveoparotid fever)
	Osteopetrosis

The prognosis for pregnant women with idiopathic palsy is notably better than among non-pregnant women with palsy. Once the child has been delivered, the clinical picture tends to improve. However, there has been reluctance among non-specialists to prescribe corticosteroids for pregnant women with facial palsy. Obstetricians and those involved with the management of pregnant women with facial palsy should be assured of the safety and efficacy of prednisolone in this special group of patients.

The aetiology of idiopathic palsy remains unclear, although microcirculatory failure of the vasa nervorum, ischaemic neuropathy, infectious, genetic and immunologic causes have all been proposed in the past. Of those possible causes, clinical and epidemiologic data lend credence to an infectious origin, which triggers an immunologic response resulting in damage to the facial nerve. Pathogens that have been implicated in the disease process include herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), human herpesvirus, varicella zoster virus (VZV), influenza B, adenovirus, Coxsackie virus and Epstein–Barr virus (EBV). Recently, it has been demonstrated that an inactivated intranasal influenza vaccine increased the risk of idiopathic palsy.[128]

Murakami et al. in 1996 explored the link between herpes simplex virus (HSV) and Bell's palsy.[129] Surgical decompression for facial nerve palsy was performed in 14 patients with Bell's palsy, 9 patients with Ramsay Hunt syndrome and 12 other controls. Viral genomes of HSV-1, VZV and EBV were analyzed in clinical samples of facial nerve endoneurial fluid and posterior auricular muscle using polymerase chain reaction (PCR) followed by hybridization with Southern blot analysis. HSV-1 genomes were detected in 11 of 14 patients (79%) with idiopathic palsy but not in patients with Ramsay Hunt syndrome or in the controls. The authors concluded that HSV-1 is the major aetiologic agent in Bell's palsy. However, these results have not been replicated. Linder et al. identified HSV-1 genomic DNA in 86% of autopsied human geniculate ganglion samples taken from control patients without any previous history of facial palsy.[82] In 43% of the specimens, viral genomic DNA for VZV was found, HSV-2 genomic DNA was not detected. In all 14 geniculate ganglion preparations, either one or even both viral pathogens were found using the highly sensitive nested PCR. HSV-1, HSV-2 or VZV could not be detected in facial muscle biopsy samples taken from acute Bell's palsy patients. Linder et al. also comment, correctly, that current PCR methods are unable to differentiate between a latent and a lytic virus state. [82] To demonstrate that reactivation of HSV virus, or its switch from a latent to a lytic state, causes idiopathic palsy, a reverse transcription PCR aimed at detecting lytic state-specific mRNAs might provide the answer. Until proven otherwise, idiopathic palsy should still be called idiopathic.

Although, the majority of patients with Bell's palsy recover facial movement completely, a significant proportion have long-term issues with facial asymmetry, tightness and synkinesis. Poor prognosis has been related to complete paralysis at onset or incomplete paralysis with late onset of recovery, old age, a dry eye, abolished taste, absent stapedius reflex and postauricular pain.[128] Normal function is usually regained within 3 months in about two-thirds of all patients. No further recovery is expected after a period of 6 months has elapsed.

The pharmacological management of idiopathic palsy primarily involves oral corticosteroid medication. Evidence from the Scottish Bell's Palsy Study[130] showed clear benefit from treatment with prednisolone within 72 hours of onset of the paralysis. There was no evidence of additional benefit from oral antiviral medication in the form of acyclovir. However, other authors have found antivirals provide additional benefit and the most recent evidence from the Cochrane Database concludes that there is evidence that the addition of antiviral medication improved the rates of incomplete recovery and reduces the long-term after-effects of idiopathic palsy.[131] Based on the above evidence, most surgeons would advocate a combination of steroids and antiviral drugs. The usual recommended regime is prednisone 1 mg/kg/day for 10 days and oral acyclovir (400 mg five times daily) for 10 days.

Facial nerve disorders of viral origin

VARICELLA ZOSTER VIRUS (VZV) INFECTION (RAMSAY HUNT SYNDROME)

The strict definition of Ramsay Hunt syndrome is a peripheral facial nerve palsy accompanied by an erythematous vesicular rash on the ear (zoster oticus) or in the mouth (**Figure 112.17**). The mechanism of disease is reactivation of the latent VZV virus in the geniculate ganglion.

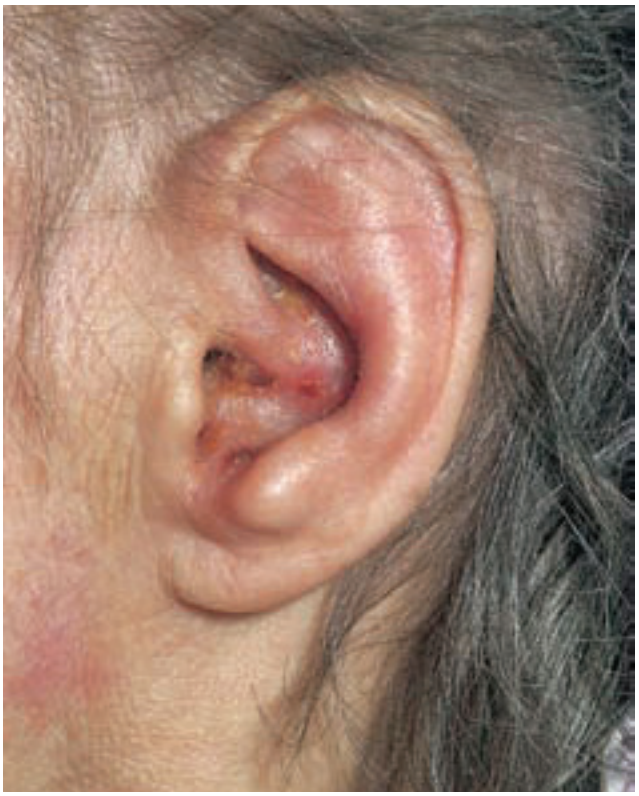

Figure 112.17 This patient has a complete left-sided facial palsy and a vesicular eruption in the conchal bowl of her ear which is typical of Ramsay Hunt syndrome.

Other cranial nerves are less commonly involved. The onset of palsy is usually preceded by pain which may persist and be excruciating. In a small proportion of patients, the facial palsy is accompanied by labyrinthine symptoms including tinnitus, vertigo and a sensorineural hearing loss. Diagnosis is clinical but may be confirmed by rising titres of antibodies to VZV. Examination of CSF and gadolinium-enhanced MRI have no diagnostic or prognostic value. PCR to detect VZV in ear exudates is more sensitive than VZV PCR performed on tears or blood mononuclear cells and may be positive before the development of vesicles.[132]

It has been shown that a small proportion of patients diagnosed as idiopathic palsy may in fact have a VZV infection. In 15% of cases vesicles may appear after the onset of palsy, and the diagnosis may be missed. Another reason for missing the diagnosis is the Ramsay Hunt syndrome *zoster sine herpete*. This is characterized by peripheral facial paralysis without ear or mouth rash, and the presence of either a four-fold rise in antibody to VZV or the detection of VZV DNA in skin, blood mononuclear cells or middle ear fluid.[132] Although further research is needed, perigeniculate region VZV PCR may help to distinguish between patients with Bell's palsy and patients with early Ramsay Hunt syndrome.

The prognosis for Ramsay Hunt is worse than idiopathic facial palsy. Persistent weakness is observed in 30–50% of patients and only 10% recover completely after complete loss of function without treatment.[133] Regarding management, the same controversies exist as in idiopathic palsy. Most advocate a combination of steroids and antiviral agents, but for a longer period of time, 2–3 weeks. The largest retrospective Ramsay Hunt syndrome treatment study showed a statistically significant improvement in patients treated with prednisone and acyclovir within 3 days of onset.[134] The recommended regime is prednisone 1 mg/kg/day for 5 days followed by a 10-day taper, as well as intravenous acyclovir (250 mg three times daily), or oral acyclovir (800 mg five times daily). Robillard et al.[135] have shown that patients with Ramsay Hunt syndrome treated with prednisone were less likely to progress to complete facial paralysis than untreated patients. The combination of steroids and acyclovir also seems to reduce otalgia, vertigo and post-herpetic neuralgia. Surgical decompression is not indicated.

OTHER VIRAL CAUSES

A variety of viral diseases have been associated with facial nerve palsy. Guillain–Barré syndrome (acute inflammatory demyelinating polyradiculoneuropathy) presents typically 2–3 weeks after an upper respiratory infection probably caused by an abnormal T-cell response against myelin components. The most prominent feature is ascending symmetrical muscular weakness and autonomic involvement with a maximum effect 2–3 weeks after the onset of illness. Facial nerve paralysis may develop and is often bilateral. Supportive management is of the essence, with attention mainly focused on respiratory support and passive physiotherapy. Steroids have been shown to have no beneficial effect and may even delay recovery. The most effective form of treatment is considered to be intravenous immunoglobulin infusion. Epstein–Barr infection (infectious mononucleosis) is clinically characterized by generalized lymphadenopathy, fever and sore throat and may be associated with facial nerve palsy. The presence of at least 10% of atypical lymphocytes on peripheral tests and positive serology will confirm the diagnosis. Forty percent of the EBV-associated facial nerve palsy cases are bilateral (**Figure 112.18**).[136] Facial nerve paralysis during the course of human immunodeficiency virus (HIV) infection can present at any stage of the disease. The presumed mechanisms of paralysis include local infection of the facial nerve or geniculate ganglion by the HIV, inflammatory demyelinating neuropathy or secondary infection precipitated by immunosuppression with agents such as VZV, HSV or EBV.[137]

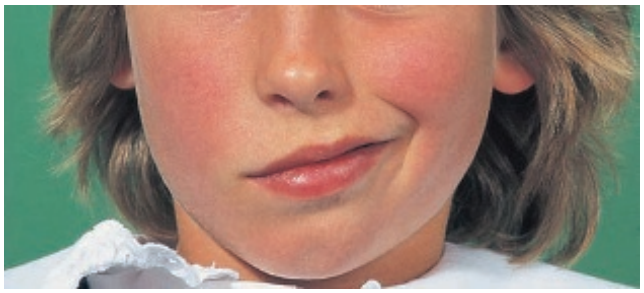

Figure 112.18 A young girl with a complete right-sided facial palsy caused by infectious mononucleosis.

FACIAL NERVE TRAUMA

As a general rule, management of facial nerve paralysis following trauma is generally deferred until the patient is both medically and neurologically stable as most cases are associated with more life-threatening injuries. This often delays treatment for a large proportion of patients and for many it dictates that a suboptimal management plan has to be adopted, for example when associated with severe head injuries.

Facial nerve paralysis can result from stab wounds to the face or mandibular fractures. If possible, it is advisable to explore the region within 3 days so that a nerve stimulator can be used to identify the distal segments of facial nerve branches. Transection of the cervicofacial or temporofacial primary divisions should be promptly repaired by end-to-end anastomosis. Mobilization to avoid unwanted tension may be necessary if a short segment of nerve is destroyed. Rarely, an interposition graft is necessary. Injuries to branches distal to the lateral canthus or nasolabial fold are too small for anastomosis and are better approximated and glued in position. This offers a better chance of some recovery without synkinesis. If the wound is dirty, it is advisable to identify and tag the facial nerve branches, clean the wound thoroughly and, in severely soiled cases, repair and close at a later stage. The major problem in knife wounds to the face is that damage to the facial nerve is often multi-segmental with transections at more than one level. With each transection the chance of a good functional outcome is diminished.

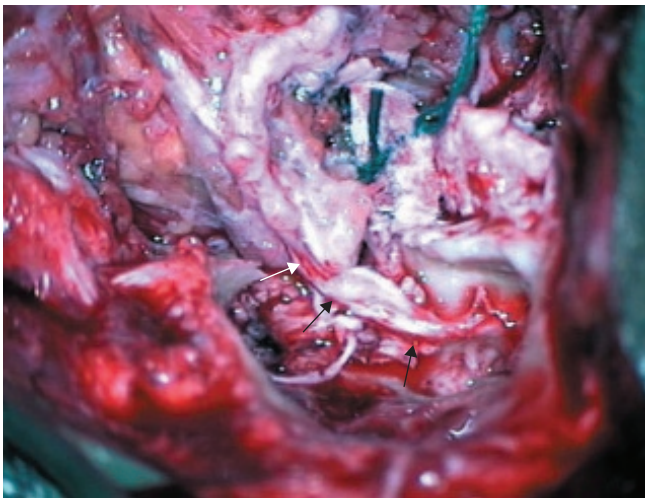

Figure 112.19 This man was shot in the ear and suffered a complete facial palsy. The nerve has been shredded over a significant distance (arrowed).

GUNSHOT INJURIES

Care must be taken when assessing facial nerve function in this type of injury as there is often significant facial oedema and both muscle tone and eye closure appear adequate when in fact they are not. This illusion can last for several days. The mastoid segment of the facial nerve is most commonly affected and often over a long segment. Low-velocity bullets may be found lodged in the mastoid tip.[138] Surgical exploration of the facial nerve should be performed as early as possible. Long delays make identification of the nerve more difficult because of granulation tissue and traumatic neuroma formation. If a segment of the nerve has been destroyed, the proximal and distal ends of the nerve must be trimmed back to a point where healthy fascicles can be seen and then an interval cable graft inserted. Good functional results are rarely achieved and other methods of reanimation should be considered.[139]

There is often considerable bony damage and the potential for subsequent cholesteatoma development should be kept in mind. Open mastoidectomy with a meatoplasty is the surgical technique of choice in this situation as there is a high risk of infection and it may not be possible to find and remove all fragments of skin and bullet (**Figure 112.19**).

FRACTURES OF THE TEMPORAL BONE

Temporal bone fractures are divided traditionally into longitudinal and transverse subtypes, although a significant proportion of these are mixed. Longitudinal fractures are associated with a 20% incidence of complete paralysis and the perigeniculate region is most commonly involved. Transverse fractures have a higher incidence of facial nerve paralysis (50%) and the labyrinthine and mastoid segments are most commonly involved (**Figures 112.12** and **112.13**). Longitudinal fractures are overwhelmingly more common than transverse fractures which is fortunate as outcomes are better. Some authors have recently proposed a different classification according to whether the otic capsule is involved or spared, as this correlates better with the incidence of complications.[140] Patients with otic capsule violating fractures are approximately twice as likely to develop facial nerve paralysis, four times more likely to have a CSF leak and seven times more likely to sustain a profound hearing loss.

The key issues to consider in the management of facial nerve paralysis following temporal bone trauma are (a) if there is an indication for surgical exploration, and if so, (b) when to operate; (c) which is the optimal surgical approach; and (d) which nerve repair technique to use. The use of high-resolution CT scans and ENoG are important in decision-making. If surgical exploration is indicated, the goals are (a) to decompress the nerve to prevent ischaemic injury; (b) to remove bony fragments that impinge on the nerve; and (c) to re-establish continuity in case of transection.

Management in the early post-injury stage

Patients with normal facial nerve function at presentation, regardless of whether they develop delayed palsy or even paralysis, or those with acute onset incomplete palsy without progression, have an excellent prognosis and do not require surgical exploration.[141] Similarly, follow-up with serial ENoG is probably not necessary, although this is not universally accepted. In cases of acute complete paralysis, surgical exploration is warranted if ENoG shows greater than 90% denervation within 6 days of the onset of paralysis and the patient is neurologically stable.[142] The same applies for incomplete palsy that progresses to complete paralysis over time with unfavourable ENoG recordings. In some patients, it is difficult to establish whether the onset of palsy was immediate as the patient may be unconscious at the time of presentation. However, ENoG can be performed on unconscious patients. Lambert and Brackmann[143] have suggested that the indication for surgery should be based on ENoG findings and that time from onset of paralysis should not be taken into account.

Timing of surgery will be dictated by the general condition of the patient: there is no general consensus on the optimal timing, although an early exploration is probably desirable. Chang and Cass[144] suggested decompression within 14 days of injury and May[145] has demonstrated superior results if nerve repair is performed within 30 days of injury. According to Quaranta et al.,[146] recovery of satisfactory facial nerve function can be achieved in more than 75% of cases treated 27–90 days after trauma. It should be noted that there are no studies reporting on the natural history regarding recovery of patients with unfavourable ENoG results.

Management in the late post-injury stage

Owing to trauma-related issues it is not rare to see a patient with facial nerve paralysis many months following injury. As discussed above, ENoG is not helpful after 3 weeks have elapsed. The decision to explore is therefore largely based on CT findings and electromyographic results. The rationale for late exploration is the

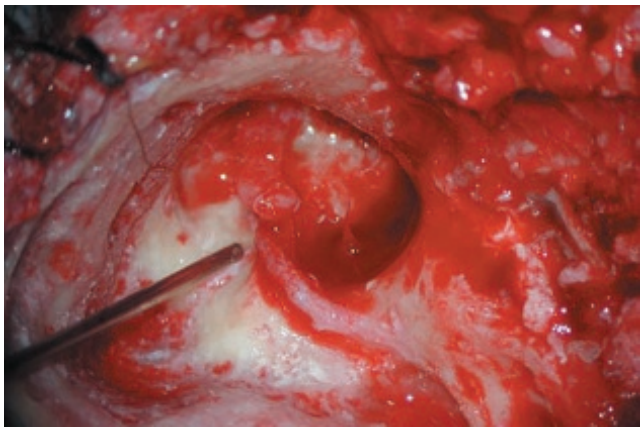

Figure 112.20 This fracture has transected the tympanic segment of the facial nerve. The proximal segment has become fibrotic as a result of organized intraneural haemorrhage and the bone shifts associated with the fracture have made approximation of the ends impossible. An interposition graft was necessary.

need to remove any fragments of bone and fibrosis that may impede regeneration. If no return of facial function is observed 6–12 months after the injury and there are no signs of polyphasic potentials that suggest reinnervation, exploration is indicated with a view to achieving nerve continuity either by end-to-end anastomosis, interposition grafting, rerouting or other reinnervation techniques. If, however, EMG findings suggest long-term denervation (no electrical output), static or dynamic facial reanimation procedures are indicated.

The surgical approach that will be used depends on the site of injury and the hearing status of the patient. In general, a middle fossa approach is preferred for longitudinal fractures in which hearing is preserved. In the very unlikely event of mixed or transverse fractures with serviceable hearing, the same approach may be employed in combination with a transmastoid exploration. In the presence of severe sensorineural hearing loss, a translabyrinthine approach is easier to use and results in less morbidity. Decompression is usually sufficient, although a severely crushed nerve is best resected and primarily anastomosed. If the nerve is transected and if it is possible, an end-to-end anastomosis without any tension on the cut ends is best. Otherwise an interposition nerve graft from the great auricular or sural nerve should be used (**Figure 112.20**). There are no controlled studies on the use of steroids in temporal bone fractures. Administration is based on the assumption that neural oedema is a contributing factor in the progression of nerve injury.

IATROGENIC INJURY

Middle ear and mastoid surgery

The incidence of facial nerve palsy has been reported to be between 0.6% and 3.6%.[146] In the Royal College of Surgeons audit it was found to be 0.8%.[147] The most common site of injury during middle ear or mastoid surgery is the distal tympanic segment including the second genu, followed by the mastoid segment.[148] If an injury to the facial nerve is recognized intra-operatively, exploration with decompression of proximal and distal segments of the nerve should be undertaken. If nerve fibres are found to be herniating, the epineural sheath should be opened with a neurotomy knife or Beaver blade. If more than 50% of the circumference of the nerve has been disrupted it should be repaired with either direct suture or inlay graft.

If facial nerve paralysis is observed immediately post-operatively, it is important to determine whether the facial nerve was identified or its integrity tested intra-operatively. If facial palsy is observed immediately after surgery and the nerve was identified or was not at risk during the operation, a few hours of observation will usually allow for any local anaesthetic-induced weakness to clear. The possibility of a tight mastoid dressing over an exposed nerve should also be considered and it is wise to remove the pack. If the paralysis is incomplete, the patient should be started on oral steroids and observed clinically. In cases of progression to full paralysis, exploration should be considered. Although immediate exploration was advocated in the past, this is no longer justified.[149] Green et al.[150] have not demonstrated a difference between early versus more than 7-day delayed exploration. HRCT imaging should be obtained even though it will probably be subject to artefact from iodine-containing compounds. Perhaps the most important thing is to make sure that a more experienced surgical colleague undertakes the re-exploration or that the patient be transferred to a regional centre where subspecialty expertise is available.

In rare cases, a delayed palsy is observed a few days after uneventful middle ear surgery with a reported incidence of 0.9–1.4%.[151, 152] The aetiology is unclear, although reactivation of HSV or VZV is postulated as the underlying mechanism. Combined use of prednisone and acyclovir should be considered and the overall prognosis appears to be good.

Parotid surgery

The likelihood of temporary facial weakness correlates with tumour location deep to the plane of the facial nerve, previous parotid surgery, previous sialadenitis and the addition of neck dissection to the parotidectomy. All parotid surgery is best undertaken with facial nerve monitoring and at the end of the procedure the main trunk should be stimulated to confirm continuity. If there is no response, the nerve and its branches should be closely inspected for areas of discontinuity. A reduced incidence of facial nerve palsy has been reported with the use of a harmonic scalpel.[153]

Cerebellopontine angle tumour surgery

Post-operative facial nerve function in CPA tumour surgery mainly depends on tumour size and surgical skill. When the facial nerve is lost during dissection, it may be possible to achieve an end-to-end anastomosis or place a cable interposition graft. Unfortunately, this is more often not the case and an expectant approach is probably best lest any fibres have been preserved. A subsequent reanimation procedure can be performed at a later date.

TABLE 112.8 Neonatal facial palsy

Developmental and inherited disorders	Clinical characteristics
Moebius syndrome	Agenesis of VI and VII cranial nerve nuclei. Bilateral facial nerve palsy, abducens palsy, possible involvement of other cranial nerves
Dystrophia myotonica	Progressive familial distal myopathy. Bilateral facial nerve palsy, without abducens palsy at birth. Muscle and extramuscular wasting, swan-like neck (wasting of muscles of mastication and sternocleidomastoids)
Alberg–Schoenberg's disease	Osteopetrosis of bony canals resulting in blindness, deafness and facial paralysis. Present later in childhood, not usually at birth
Melkersson–Rosenthal syndrome	Facial palsy, facial oedema, fissured tongue
CHARGE association	Colobomata, heart defects, choanal atresia, retarded growth, genital hypoplasia and ear abnormalities
Oculoauricular-vertebral syndrome	Abnormal formation of first and second arches
Congenital unilateral lower lip palsy	Hypoplasia of the depressor anguli oris muscle. Cardiac defects in 10%

Neonatal facial nerve injury

The frequency of neonatal facial nerve paralysis ranges from 0.05% to 0.23%.[154] Trauma is the main cause, but other rare congenital conditions should be excluded (Table 112.8). Forceps delivery is associated with a slightly increased incidence of paralysis. The superficial position of the facial nerve at the stylomastoid foramen and the softness of the temporal bone make it vulnerable to injury by this and other presumed mechanisms, such as compression against the infant's shoulder or maternal sacral prominence in cephalopelvic disproportion.[155] Facial nerve paralysis usually involves the entire distribution of the nerve and is usually unilateral. Other signs signifying trauma that may be present include Battle's sign and haemotympanum. EMG responses are present at birth with progressive decline in amplitude over time, as opposed to inherited or developmental disorders where they are absent. Unfortunately, they are rarely obtained and this leaves the surgeon with a diagnostic dilemma. Any child with facial paralysis at birth should also undergo brainstem response audiometry to test hearing as some developmental disorders are associated with cochlear nucleus abnormalities. The prognosis of neonatal facial nerve injury is excellent with more than 90% recovering completely. The indications for surgical intervention are similar to facial nerve paralysis in adults.

Facial nerve paralysis as complications of the ear infection

OTITIS MEDIA

Facial nerve paralysis may complicate both acute otitis media and CSOM. The presumed pathophysiological mechanisms include: direct involvement of the facial nerve by infection through Fallopian canal dehiscences or physiologic canaliculi for neurovascular connections; Fallopian canal osteitis with bone erosion and nerve involvement, inflammatory oedema leading to compression and secondary thrombosis of the vasa nervorum with consequential ischaemia and infarction of the facial nerve, and demyelination of the facial nerve caused by bacterial toxins. The mainstay of treatment of facial paralysis associated with acute otitis media is antibiotic therapy. Steroids may be used, although their efficacy is not supported by any studies. When spontaneous perforation is absent, myringotomy and the insertion of a ventilation tube is generally recommended. Mastoid exploration and facial nerve decompression is essential for patients with CSOM.

MALIGNANT OTITIS EXTERNA

Malignant otitis externa is an invasive *Pseudomonas* or *Aspergillus* infection of the ear canal which may lead to skull base osteomyelitis (Figure 112.21). It mainly afflicts immunocompromised patients, particularly the elderly, insulin dependent and poorly controlled diabetics. Facial palsy indicates advancing infection and invasion through the bony-cartilaginous junction and the fissures of Santorini, under the tympanic ring and posteriorly to the stylomastoid foramen. Ciprofloxacin (750 mg orally twice per day) seems to be the antibiotic of choice and prolonged treatment for a minimum of 6–8 weeks is recommended.[156] However, there are no comparative trials between antibiotics in the literature. Ciprofloxacin has also been safely administered to children with cystic fibrosis and is therefore indicated for treatment of malignant external otitis in the rare paediatric patient. In cases of resistance to ciprofloxacin, antipseudomonal β-lactam agents (ceftazidime, piperacillin, imipenem) with or without an aminoglycoside can be used. Cases attributed to *Aspergillus* infection need systemic antifungal therapy. Surgical management is currently not indicated other than diagnostic biopsies to exclude malignancy. Hyperbaric oxygen has been used on occasion with mixed results and may be considered as an adjuvant treatment for refractory cases although its efficacy remains unproven.[157]

Inflammatory disorders of the facial nerve

Sarcoidosis is an autoimmune systemic disease characterized by non-caseating granulomata mainly developing in the lungs. Facial nerve palsy is the most common otologic manifestation, which can develop either in isolation or with uveitis and parotitis as a component of Heerfordt's disease (uveoparotid fever). A raised angiotensin converting

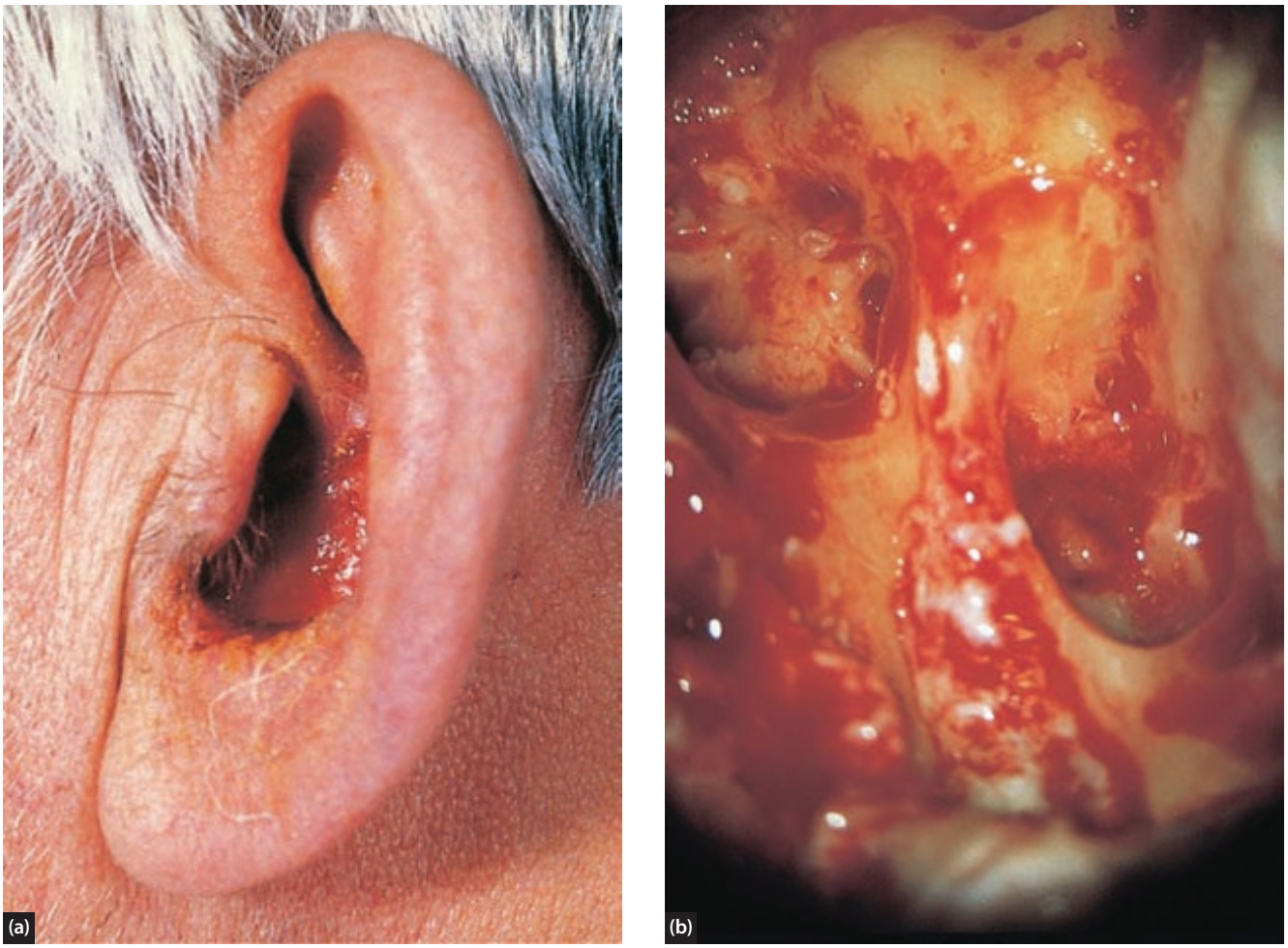

Figure 112.21 Malignant otitis externa. **(a)** discharge from left ear canal; **(b)** on opening at operation, pus was drained from the Fallopian canal. This patient's facial nerve was decompressed at a time well before the introduction of Ciproxin.

enzyme titre helps to confirm the diagnosis. Treatment with systemic corticosteroids is indicated.

Granulomatosis with polyangiitis, formerly known as Wegener's granulomatosis, is an autoimmune necrotizing vasculitis characterized by granulomata of the upper and lower respiratory tracts and kidneys. Facial nerve paralysis may be seen in this condition secondary to middle ear involvement in the presence of a dehiscent Fallopian canal. Clinical suspicion is raised by the synchronous presence of sensorineural hearing loss. Diagnosis is confirmed by elevated circulating antineutrophil cytoplasmic antigen test. Treatment of granulomatosis with polyangiitis includes a combination of cyclophosphamide and steroids. Mastoid exploration and facial nerve decompression is unrewarding and may often aggravate the problem.[158]

Lyme disease is a vector-borne, multisystem inflammatory disease caused by the spirochete *Borrelia burgdorferi*, transmitted to humans by the bite of *Ixodes ricinus* ticks. It is characterized by flu-like symptoms and erythema migrans. Facial palsy can be bilateral and should raise suspicion of the disease, especially in children. Serologic testing can confirm the diagnosis, although sero-conversion can take up to 6–8 weeks. Doxycycline or amoxicillin for 14–21 days is indicated for patients with facial nerve palsy with normal CSF findings. It should be remembered that doxycycline is contraindicated in patients younger than 8 years of age and in pregnant women. Macrolides are suitable alternatives in cases of penicillin allergy.

Multidisciplinary management of established facial palsy

In patients whose facial palsy has not resolved or when recovery is incomplete, the assessment of the degree of impairment and the impact on their physical and psychological well-being is best managed in the setting of a Multidisciplinary Facial Nerve Clinic.[159, 160] Although various models exist, most Facial Nerve MDT clinics comprise surgeons from otolaryngology and plastic surgery and highly specialized facial therapists (physiotherapy or speech and language therapy). Additional support from an oculoplastic surgeon, expert radiologist, clinical photography and psychological services is advised.[161] Patients seen in specialized clinics should expect not only a comprehensive assessment of their facial function and directed management to ameliorate the negative physical aspects of a paralyzed face, but also an attempt at securing

the diagnosis. It is not uncommon for the diagnosis to change once a patient has been seen and assessed under the auspices of the MDT clinic.

PHYSIOTHERAPY FOR INCOMPLETE RECOVERY OF FACIAL PALSY AND SYNKINESIS

Facial physiotherapy techniques for patients with facial palsy vary amongst professionals who specialize in this unique area of practice. A large proportion of the workload is devoted to patients with unresolved idiopathic palsies, although patients with other causes of unresolved facial palsy benefit from the expertise of the therapist.[162, 163] Idiopathic palsy patients may have tightness and shortening of the muscle fibres resulting in a 'frozen face' which may be associated with an aching pain which increases throughout the day. Specific guidance regarding muscle stretches allows the muscles to relax and facial symmetry to improve. Once the muscle length is restored, more active movement is usually achieved.

Given the lack of proprioceptive information from the facial musculature, patients have to relearn to make facial expressions that were previously natural. Facial therapists will spend time guiding the patient in front of a mirror in facial retraining. Novel technologies to engage patients, particularly children, have been developed to help in this regard.

CHEMODENERVATION WITH BOTULINUM TOXIN

Botulinum toxin is utilized as a second-line treatment to further release the over-tightened facial muscles and to facilitate the stretches advised above.[164] In patients with synkinesis, i.e. unwanted muscle contractions resulting from aberrent reinnervation, chemodenervation is helpful in reducing and weakening these unwanted movements.

Occasionally, chemodenervation can be judiciously used to weaken the more active 'normal' facial muscles in order to achieve a more balanced facial appearance and functional benefit for the patient.

FACIAL REANIMATION CONSIDERATIONS

The topic of facial reanimation is beyond the scope of this chapter but some basic principles exist which are considered here. It is generally accepted that a lack of recovery of facial function 12 months following the original insult is considered a permanent deficit. Throughout this period there is a steady loss of motor end-plate units and progressive muscle atrophy, such that after some months reinnervation techniques will have no beneficial effect. Therefore, techniques employing nerve grafting, or nerve transfer are only considered of value if carried out within that first 12-month period and the sooner the better. Historically, ENT surgeons have made use of a hypoglosso-facial anastomosis, providing tone and some active movement in patients with complete loss of ipsilateral facial function. Using an end-to-side neurorraphy or partially opening, rather than transecting, the hypoglossal nerve, it has been possible to preserve good tongue movement.[165] Other cranial nerves may be employed in nerve transfers including the contralateral facial nerve and the nerve to masseter (a branch of mandibular nerve). Whichever technique is employed the patient must expect a long period of rehabilitation and ongoing physiotherapy to achieve the optimum results.

Static reanimation

Given the inability to restore normal facial symmetry and achieve natural spontaneous movement, it is often appropriate for the Facial Nerve MDT to discuss simple small procedures to reduce the burden of facial weakness without the risk of larger more complex procedures. This is particularly the case in older and medically less-robust patient. Periocular surgery, including lower-lid tightening, lateral canthopexy, brow lift and upper eyelid positioning/weighting surgery may be performed under local anaesthesia and can provide benefit for the patient with troublesome eye symptoms.

Various face-lifting techniques can improve the static position of the face. These may be combined with soft-tissue procedures (e.g. wedge resection of the lower lip) to achieve a more balanced facial appearance and more importantly to improve facial function (oral competence).

Dynamic reanimation

In those patients where active movement is desired, particularly in terms of smile, it is usually necessary to bring new tissue to the area. This may be in the form of muscle transfer, for example a temporalis transfer – Labbé procedure[166] or free muscle graft using the gracilis muscle.[167] The latter is preferred in paediatric patients who have the necessary neural plasticity to achieve excellent results following physiotherapy. Depending on the aetiology of the facial nerve palsy, nerve grafting may also form an integral part of this surgery.

PSYCHOLOGICAL ISSUES IN FACIAL PALSY

Facial appearance and non-verbal communication are so central to human interaction that it is no surprise that patients who are unable to eat in public and communicate without embarrassment may suffer significant psychological distress. The development of support networks and groups has enabled patients to benefit from the experience of others and to reduce the isolation associated with living with the effects of facial palsy. Psychological support with counselling is provided in some specialist units and is available through primary care.

The over-arching principle in the management of patients with established facial palsy is to improve facial function, reduce the psychosocial consequences of the facial weakness and improve the overall quality of life for the patient.[168] These aims can be best achieved in a setting where all possible treatment modalities that might be employed in the management of a patient with facial palsy are available.

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BEST CLINICAL PRACTICE

- ✓ Intra-operative facial nerve monitoring is a wise precaution for any surgery around the facial nerve regardless of the surgeon's experience. It is a standard of care in Vestibular Schwannoma surgery.
- ✓ Decompression of the facial nerve in the acute phase after trauma is indicated when paralysis is complete from the outset, there is ENoG evidence of rapid denervation and clear CT evidence of compression or wide displacement of the Fallopian canal.
- ✓ Late exploration of the facial nerve after cranial base trauma is indicated if there is no recovery after 9-12 months and CT evidence of a significant fracture.
- ✓ If a patient awakes from mastoid surgery with an unexpected facial palsy, remove the pack and obtain a CT scan. If no recovery ensues in the first few hours, the ear must be re-explored to establish the integrity of the facial nerve or correct any damage.
- ✓ Antibiotic therapy for malignant otitis externa must be prolonged, often for several months.

FUTURE RESEARCH

- ➤ Although there is some evidence to suggest that Bell's palsy is caused by HSV, definitive evidence is still lacking.
- ➤ Further knowledge regarding aberrant reinnervation and the role of facial therapy in preventing/reducing synkinesis may have a useful benefit for patients.

KEY POINTS

- The commonest cause of facial palsy in adults is an idiopathic palsy.
- Although electrophysiological testing may provide useful prognostic information and serve as a guide to the management of facial palsy, there are some important limitations: it provides no useful information in cases of incomplete facial paralysis and it fails to provide information on the immediate post-paralysis period.
- Ipsilateral recurrent facial nerve palsy or a paralysis with progressive or incomplete recovery should raise the suspicion of malignancy.
- Any facial palsy that does not recover or is recurrent needs further investigation and imaging.

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CHAPTER 113

TUMOURS OF THE FACIAL NERVE

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SEARCH STRATEGY

The data may be updated with a PubMed or MedLine search using the following keywords: facial nerve tumour, schwannoma and neuroma.

INTRODUCTION

Facial nerve tumours are rare. The most common histological type are facial nerve schwannomas (FNS) although facial nerve haemangiomas, malignant nerve sheath tumours and 'skip' lesions from parotid malignancies, amongst others, may also occur.[1] This chapter focuses on FNS, their presentation, diagnosis and management, but will also consider the differential diagnoses for these lesions.

PATHOLOGY

As with other schwannomas, FNS are benign, slow growing tumours arising from Schwann cells within the nerve sheath. Facial nerve neuroma, neurinoma and neurilemmoma are other terms previously used. The classic histology showing Antoni type A and B tissue is indistinguishable from vestibular schwannomas. As such, diagnosis requires correlation with imaging findings and/or intra-operative confirmation of the tumour arising from the facial nerve.

INCIDENCE

Facial nerve schwannomas are rare and thought to account for between 1% and 3% of all cerebellopontine angle (CPA) tumours although are not uncommonly seen as part of neurofibromatosis type 2.[2] A previously reported cadaveric temporal bone study found 5 FNS in 600 specimens, suggesting that these tumours may grow undetected without symptoms.[3]

CLINICAL PRESENTATION

Facial nerve schwannomas can arise from anywhere along the course of the facial nerve from the CPA to the ramifications within the parotid. The presenting symptoms will vary according to the segment involved. The relative frequency of occurrence at each site varies and has been reported to be most common at the geniculate ganglion (68%), labyrinthine (52%) and tympanic (43%) and mastoid segments.[4] In addition, FNS are commonly found to involve multiple segments.[1, 5, 6]

Intratemporal FNS most commonly present with progressive weakness or spasm, although less commonly may present with sudden onset or recurrent facial weakness.[7–8] Tumours affecting purely the internal auditory canal (IAC) or CPA are reported to represent less than 2% of FNS.[9] When isolated to this segment their presentation commonly mimics that of a vestibular schwannoma (VS) with symptoms of hearing loss, tinnitus and imbalance.[9] In these cases diagnostic confirmation of FNS may only occur at surgery thereby presenting an intra-operative management dilemma. This will be considered later in this chapter. Although rare, extra temporal FNS may present simply with a parotid mass.[10]

For FNS that continue to grow and extend intracranially either from the IAC into the posterior fossa or from the geniculate ganglion into the middle fossa, neurological sequelae may develop causing symptoms of brainstem compression/hydrocephalus or seizures.

The natural history of FNS is not as well studied or understood as for VS. However, there is a growing number of published series demonstrating that a significant proportion of FNS do not grow.[5, 11] A recent study of 21 patients with FNS managed with observation for a mean follow-up of 6.4 years (range 4–9) showed that, overall, 43% grew, which corresponded to 10% growth rate in FNS <10 mm in size and 73% growth rate in those >10 mm in size. Furthermore, 18 of 21 (86%) maintained facial function of HB grade III or better.[12]

INVESTIGATIONS

Radiological investigations

The mainstay of diagnosis is with high resolution cross-sectional imaging. A T1 weighted MRI with gadolinium will show an enhancing (often fusiform) lesion at the site of involvement, which may vary in appearance depending on the location. Multiple segment involvement is common and may give a 'beads on a string' appearance.[6,9] Facial nerve schwannomas are classically described as causing smooth bony expansion of the facial nerve canal, which helps to distinguish between contrast enhancement of the facial nerve as seen following a simple Bells palsy and a true facial nerve schwannoma.

Facial nerve schwannomas that are limited to the internal auditory meatus (IAM)/CPA can be difficult to differentiate from VSs (see **Figure 113.1**). However, the advantage of a T1-weighted MRI with gadolinium over other sequences (such as FIESTA) is that it may demonstrate a 'labyrinthine tail' with enhancement of the adjacent facial nerve (see **Figure 113.1**).[6] Involvement of the geniculate ganglion with extension along the greater superficial petrosal nerve makes radiological diagnosis of FNS more obvious (see **Figures 113.2 and 113.3**).

CT of the temporal bones may be helpful in demonstrating smooth bony expansion at the site of the FNS (see **Figure 113.4**). An exception to this well defined appearance has been described when the vertical mastoid segment of the nerve is involved and growth extends into adjacent mastoid air cells giving the suggestion of an aggressive tumour (especially on MR).[13]

Facial nerve schwannomas affecting the tympanic segment of the facial nerve have been described as appearing as a pedunculated mass on imaging but, again, enhancement of the adjacent nerve should help in distinguishing it from other middle ear masses.

Other investigations

Audiometry with a pure tone audiogram and speech audiometry is essential and may influence subsequent management decisions and surgical approaches.

Topographical assessment of facial nerve function (taste, lacrimation and stapedial reflexes) has largely been superseded by other diagnostic modalities and do not usually form part of a standard assessment.

Electroneurography (ENoG) has been advocated as a method for calculating the proportion of facial nerve motor neurons lost to tumour compression. It measures the compound muscle action potential (CMAP) to maximal bipolar stimulation of the facial nerve at the stylomastoid foramen. The investigation is used as an aid in the management of acute facial paralysis because it indicates the severity of Wallerian degeneration in the days after onset of facial weakness. ENoG, however, does have its drawbacks. It relies on comparison of the maximal CMAP derived from the muscles of the affected and normally functioning side and has a poor test–retest reliability. It is particularly inaccurate

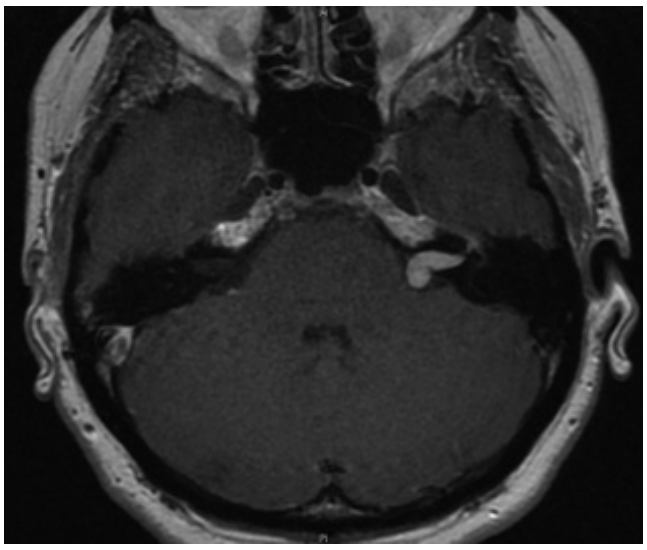

Figure 113.1 Axial T1 weighted MRI of patient who presented with facial weakness showing contrast enhancing tumour of the IAM/CPA with subtle enhancement of adjacent segment producing 'labyrinthine tail'.

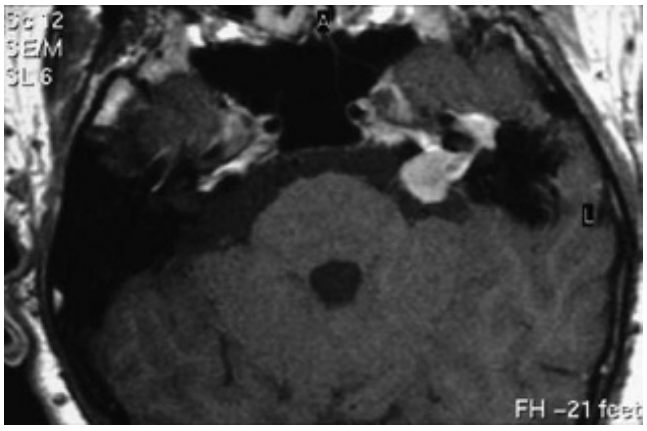

Figure 113.2 Axial T1 weighted MRI with contrast showing facial schwannoma filling the internal auditory meatus and extending along the greater superficial petrosal nerve into the middle fossa.

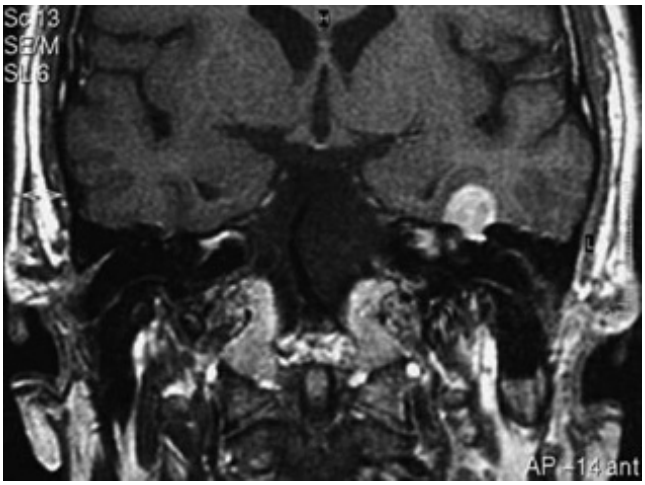

Figure 113.3 Coronal MRI showing a facial schwannoma arising from the geniculate ganglion and extending through the petrosal foramen into the middle fossa, pushing upwards into the temporal lobe.

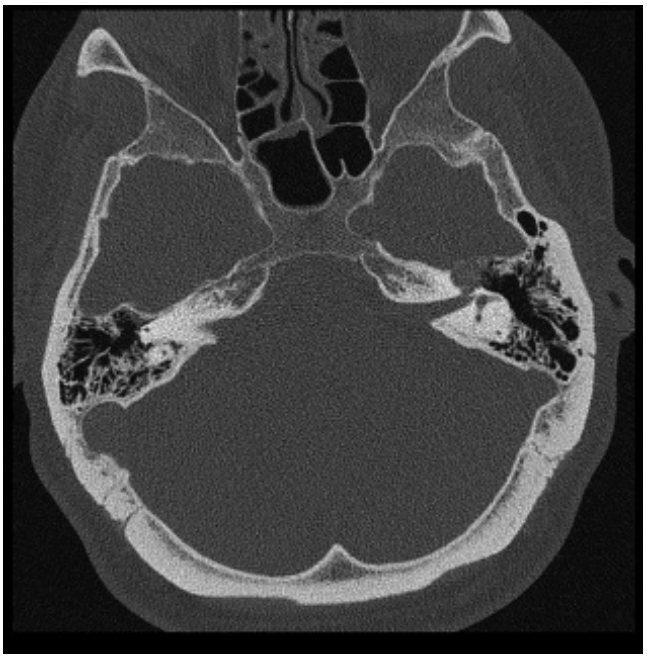

Figure 113.4 Axial CT of temporal bones at the level of the IAM/geniculate ganglion on the left with a round smooth bony expansion of the geniculate fossa caused by a facial schwannoma. (See **Figure 113.5** for corresponding MRI.)

for assessing longstanding or slowly progressive facial palsy, for two important reasons. First, it is unable to take into account terminal collateral sprouting in response to nerve injury, which increases the number of muscle fibres each motor neuron innervates. Second, it cannot differentiate between motor neurons that are functioning normally across the site of tumour compression and those in conduction block. As such, a clinical assessment of facial function using the House-Brackmann grading system provides a pragmatic assessment for guiding management decisions. Some units do advocate the use of ENoG to monitor for subclinical deterioration in nerve function as an additional factor when considering surgical intervention.[11]

Investigation of intraparotid FNS by fine needle aspiration cytology biopsy has been shown to be unreliable in retrospective analyses.[14–15]

MANAGEMENT

Due to the rarity and heterogeneity of FNS and the inherent problems of conducting prospective trials in this setting (as for VS), management of FNSs remains controversial and lacks good evidence to support any particular treatment algorithm. Overall, however, there does appear to be an evolving philosophy towards a more conservative approach with the paramount aim of preserving optimal facial nerve function for as long as possible.[5, 11] This is in contrast to the previously held wisdom that FNSs should be excised and grafted.[1, 16–17] An acceptance that facial nerve grafting can reach, at best, a House-Brackmann (HB) grade III, has lead to a reluctance to intervene surgically in patients with good facial function (HB I or II).

As for VS, the management options are: observation with serial scanning; radiotherapy (stereotactic or fractionated); and surgery. Management decisions are largely influenced by existing facial nerve function, hearing, tumour location and patient comorbidities.

For patients with an FNS and good facial function (HB I or II), unless there is evidence of significant intracranial extension with mass effect, observation with serial imaging is an appropriate initial strategy for most patients.

For FNSs that have demonstrated growth, the options include stereotactic radiation or surgery (or continued observation). In an effort to prevent deterioration in facial function in FNSs growing within a bony confine or with deteriorating facial function or ENoG, some units advocate bony decompression.[18]

STEREOTACTIC RADIATION

Published reports of stereotactic radiation (SR) treatment for FNS have increased significantly in recent years.[19–21] High tumour control rates of as high as 93% are quoted but these studies include all treated tumours and not just those that have demonstrated growth on serial MR imaging. In a recently published series from Manchester, tumours in only 2 of 11 patients that were managed conservatively with observation grew, giving a growth rate of only 18%.[5] Further larger long-term observational studies are needed to delineate the natural history of these tumours to better measure the true effect size of SR treatment. Nevertheless, given the poor surgical outcomes in terms of facial function, SR remains an attractive option for treating growing FNSs in patients who have good facial function (HB I or II).

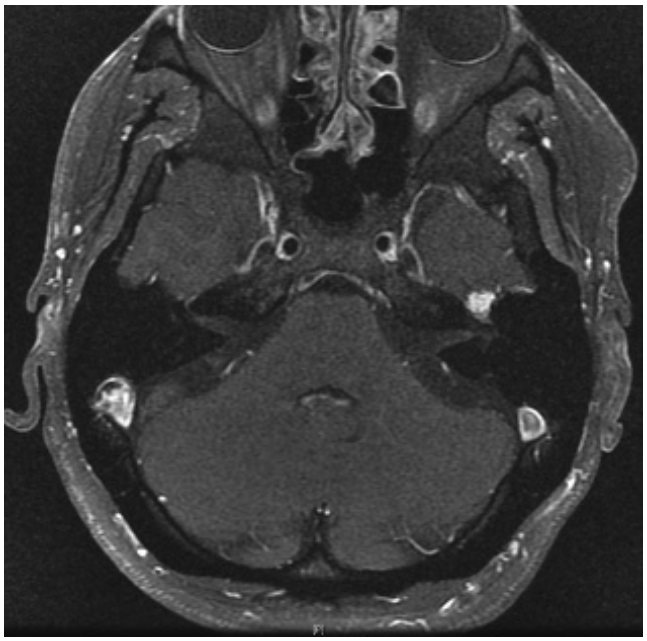

Figure 113.5 A T1 weighted MRI showing enhancing facial schwannoma of the geniculate ganglion from same patient as Figure 113.4.

SURGERY

Surgical intervention is often reserved for growing FNSs that have failed radiation treatment, tumours with significant intracranial extension with mass effect and tumours where facial function has already deteriorated to HB grade III or worse. There is, however, no consensus on the optimal time to intervene or the type of surgical intervention in this scenario. The options include:

- near total/subtotal excision in attempt to maintain nerve integrity with the option of SR treatment if the residual remnant grows
- fascicle preservation surgery/tumour stripping from intact facial nerve
- excision with primary anastamosis, grafting or other reanimation technique.

The choice of surgical approach varies depending on tumour location, levels of hearing and surgeon preference. An FNS involving the mastoid segment of the facial nerve extending through the stylomastoid foramen will require a combined transmastoid/parotidectomy approach, whereas involvement of the geniculate ganglion extending primarily along the superficial petrosal nerve will likely require a middle fossa approach. Tumours extending medially from the internal auditory meatus into the cerebellopontine angle will require a translabyrinthine or retrosigmoid approach depending on surgeon preference. For larger tumours involving multiple segments, combined approaches will be required.

Some units have adopted subtotal excision as a more conservative approach to reduce facial nerve dysfunction. Li et al. published a series demonstrating a regrowth rate of 27% for 15 FNS that had undergone subtotal or near total resection. They concluded that this was not a safe technique despite achieving HB of I or II for 93%.[22] Other centres would consider this acceptable and utilize radiation treatment for growing residual tumour. Fascicle preservation surgery (or tumour 'stripping') has been described as a surgical technique whereby a plane of cleavage can be found between the tumour and the facial nerve, thereby maintaining its integrity.[23,24] Sherman et al. described 5 patients in a series of 10 who had total macroscopic tumour removal leaving an intact facial nerve.[25] All patients achieved HB grade I or II post-operative facial function and one patient had tumour recurrence. O'Donoghue et al. maintained at least 50% facial nerve continuity in 11 of a series of 36 patients undergoing surgery; however, the post-operative results were no better than facial nerve resection and grafting.[26]

For growing FNS where the facial function has already deteriorated significantly, excision of the tumour and involved segment of the nerve offers the best chance of long-term cure. Primary end-to-end anastomosis has the highest success rate and can be performed by mobilization of the nerve when there has been minimal loss of length. More commonly a cable graft is required, such as using the great auricular (or sural nerve if longer length is required). Most would accept that the best outcome possible with this technique is an HB grade III. Techniques vary to achieve the tension free nerve anastomosis but include suturing the epineurium with 8.0–10.0 nylon, using fibrin glue[27] and the use of grafting conduits to aid coaptation such as with autologous vein, tubed fascia or collagen nerve tubules.[18] Clearly, there are many more dynamic and static facial nerve reanimation techniques utilized in this setting that cannot be covered in this chapter.

MANAGEMENT OF THE INTRA-OPERATIVELY DIAGNOSED FNS

As described earlier, the clinical presentation and radiology may not always give the diagnosis of FNS and only at surgery does it become apparent that the tumour is arising from the facial nerve. An index of suspicion in these cases may avoid inadvertent injury. During a translabyrinthine approach to a presumed VS, the finding of a normal superior vestibular nerve overlying a tumour antero-superiorly in the IAM presents a surgical dilemma. At this point the options include: abandoning the procedure; decompression; or some form of partial/total excision as described above. This decision will depend on the individual case, particularly the preoperative facial nerve function, as well as the surgical team's management philosophy.

A middle ear mass arising from the facial nerve identified intra-operatively should not be biopsied as this may cause a facial palsy. Appropriate imaging should be organized post-operatively, which is likely to aid diagnosis, with an FNS often identified on the horizontal facial nerve segment.

DIFFERENTIAL DIAGNOSIS

The main differential diagnosis of an intratemporal facial nerve schwannoma is a facial nerve haemangioma. Clinically these are associated with a significantly worse facial function at presentation, even when relatively small.[28] There may be similar appearances to FNS on imaging but with subtle differences. Bony erosion may not be smooth because haemangiomas do not have a capsule. They do not usually affect multiple segments as FNS do. Haemangiomas have been described as having a 'honeycomb' appearance on imaging.[29] Again, evidence to support management decisions is sparse but given the early loss of facial function and the possibility to resect these keeping the facial nerve intact, some advocate early intervention.[30, 31]

Malignant peripheral nerve sheath tumours can affect the facial nerve and occasionally occur in association with neurofibromatosis type 1. Treatment usually requires radical surgery, often with adjuvant radiotherapy. Other malignant tumours affecting the facial nerve include perineural spread from the parotid gland tumours as seen with adenoid cystic carcinoma and others.

CONCLUSION

FNSs are rare and usually present with disturbance of facial function, with or without audiovestibular dysfunction. Management decisions must be tailored to each patient based on existing facial and audiovestibular function and tumour location but management philosophy varies between units internationally. The primary aim of management is preservation of optimal facial function for as long as possible.

FUTURE RESEARCH

- ➤ Accurate long-term data on FNS managed with observation will provide a better understanding of the natural history of this condition, which will help better counsel patients.
- ➤ The results of long-term data assessing the efficacy of SR treatment are awaited, including the results of subsequent surgery and reanimation in those that fail radiotherapy.

KEY POINTS

- FNS should be considered in all patients with a presumed diagnosis of VS presenting with facial spasm or weakness.
- Surgical excision with facial nerve grafting can achieve a HB grade III facial function at best.
- Most surgeons avoid/delay excision of FNS whilst good facial function is maintained.

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CHAPTER 114

OSTEITIS OF THE TEMPORAL BONE

Cheka R. Spencer and Peter Monksfield

SEARCH STRATEGY

Data presented in this chapter may be updated by a National Library of Medicine PubMed search of all medical literature using the keywords: skull base osteomyelitis, malignant otitis externa, necrotizing otitis externa, limited to human, English language and full text.

INTRODUCTION

Osteitis is defined as inflammation of bone. It can be due to a number of reasons, the most common of which is secondary to infection. Acute infection of the temporal bone known as acute mastoiditis and chronic mastoid infections coupled with middle ear disease and chronic otitis media are dealt with in other areas of this book.

Temporal bone osteomyelitis, more often called skull base osteomyelitis as it progresses to other bones of the skull base, is the more invasive form of temporal bone osteitis. It usually occurs as a result of otitis externa in immunocompromised individuals. It can cause neuropathy of cranial nerves and is resistant to treatment.

Other inflammatory conditions affecting the temporal bone are rare and much of the literature is limited to case reports rather than case series or larger studies.

SKULL BASE OSTEOMYELITIS

Definition

Skull base osteomyelitis is a rare complication of otitis externa. It is a vicious infection in which the soft tissue pathogens have spread to the periosteum and temporal bone of the skull causing necrosis. This may be associated with involvement of the facial nerve, carotid artery and jugular vein, including the bulbar and hypoglossal nerves. The infection may then progress to other bones of the skull base.

Nomenclature

The condition was first described in 1959 by Meltzer and Kelemen, who named it 'pyocutaneous osteomyelitis of the temporal bone'.[1] Subsequently, Chandler coined the term 'malignant external otitis' in 1968 when presenting his series of 13 patients with progressive osteomyelitis of the temporal bone.[2] He termed it malignant due to the aggressive clinical behaviour, poor treatment outcome and high mortality rate for the patients affected by this disease. This used to be as high as 50% but has significantly reduced with better antibiotic regimens. The term 'malignant' is controversial as many authors feel some may misconstrue the inflammatory process as neoplastic and advocate 'necrotizing otitis externa' instead.[3] It has been suggested that 'necrotizing otitis externa' be used for aggressive soft tissue infection without bony involvement.[4] Otogenic 'skull base osteomyelitis' refers to the more severe clinical entity following spread of infection through the soft tissue and cartilage with histological or radiological confirmed bony involvement.

Epidemiology

Skull base osteomyelitis most frequently affects the elderly and diabetic.[2, 5–18] The national incidence of skull base osteomyelitis, according to the Hospital Episodes Statistics (see **Figure 114.1**), is increasing significantly (from 67 in 1999–2000 to 421 in 2012–2013) out of proportion to the increase of hospital admissions in general[8, 12] This is thought to be due either to the increased number of elderly

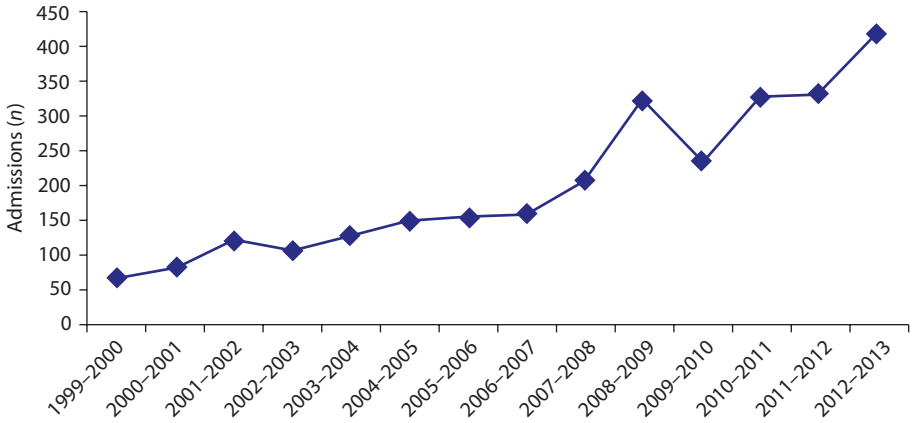

Figure 114.1 Cases of necrotizing otitis externa 1999 to 2013 according to the Hospital Episodes Statistics data.[8]

diabetics or to an increased index of clinical suspicion, and is likely to be both of these factors. The reported prevalence of diabetes in this condition ranges from 65% to 100% of patients.[2, 5, 13] It is postulated that endarteritis, microangiopathy and small vessel obliteration prevalent in the elderly diabetic in addition to their innate defects in humoral immunity, predispose them to this condition.[9, 15] Patients are usually older than 60 years of age and there is a male preponderance with a ratio of 2:1.[12, 17] Conditions causing immunosuppression such as HIV/AIDS, steroid usage, chemotherapy, anaemia, leukaemia, lymphoma, neoplasia and renal transplantation are also predisposing factors to skull base osteomyelitis.[5, 6, 8, 13] The epidemiology of skull base osteomyelitis is said to be changing, with more presentations amongst the immunocompromised.[12]

HIV-affected patients with skull base osteomyelitis tend to be younger than those with diabetes. They are also more likely to have a fungal infection (i.e. *Aspergillus sp.*), particularly when CD4 counts are less than 50 cells/mm.[5]

Skull base osteomyelitis in children is rare. It is most often seen in immunocompromised states such as immunoglobulin A (IgA) deficiency, acute monocytic leukaemia, iatrogenic neutropenia and bone marrow transplantation. Diabetes as a risk factor is not as common in children as in adults.[5, 12, 15]

Pathophysiology

Various factors are said to account for the susceptibility of diabetics to skull base osteomyelitis including their weakened immune response to *Pseudomonas aeruginosa* infection and the high pH of their cerumen.[5, 6, 9, 13–15, 17] In all cases, the infection spreads to the skull base from the external auditory canal through the fissures of Santorini. At the osteocartilaginous junction, the infection spreads medially to the tympanomastoid suture along venous canals and fascial planes invading connective tissue, cartilage, bone, nerves and blood vessels. The inflammatory process alters the morphology of the compact bone of the skull base, changing it to granulation tissue.[5, 9] As the infection progresses to the skull base foramina it causes cranial neuropathies. The facial nerve is most commonly affected due to its close relation to the external auditory canal. The disease can spread medially and subsequently affects nerves around the jugular foramen. Further spread of disease can affect abducens and trigeminal nerves around the petrous apex, and also the optic nerve. Septic thrombosis of the sigmoid sinus and internal jugular vein may also complicate skull base osteomyelitis should the infection spread there. Histologically, new bone formation is observed next to areas where bone has been destroyed. The otic capsule and middle ear structures are very resistant and are rarely, if ever, involved in the disease.[5, 9]

Diagnosis

The diagnosis of skull base osteomyelitis is based on the clinical features, microbiology for culture, radiological changes within the bone of the skull base and histology showing inflammation without neoplasia.[11] Fungal pathogens may also be identified on silver staining of histological sections.[5]

CLINICAL FEATURES

Patients with skull base osteomyelitis are usually elderly diabetics presenting with severe unremitting otalgia, unilateral otorrhoea and a hearing loss. There is usually a history of ear canal trauma, often after irrigation for wax removal.[13] Self-inflicted trauma has also been implicated and a strong relationship between laterarality of skull base osteomyelitis and handedness has been reported.[18] Otalgia that is nocturnal, deep, lancinating and disproportionate to the clinical signs is highly suggestive of osteomyelitis. It is often resistant to analgesics. It is the most common presenting symptom with a prevalence of 75–100%.[6, 7]

Purulent otorrhoea, the second most common symptom and sign, in an exquisitely tender and oedematous ear canal, is found on examination in more than half of the cases.[9] Inspection of the floor of the ear canal may reveal granulation tissue or exposed bone (see **Figure 114.2**). There may also be a polyp or granuloma in the canal obstructing the view of the tympanic membrane. The granulations should be sent for histological analysis to exclude malignancy, histiocytosis and tuberculosis.[6] Patients with HIV infection often lack granulation tissue.[13]

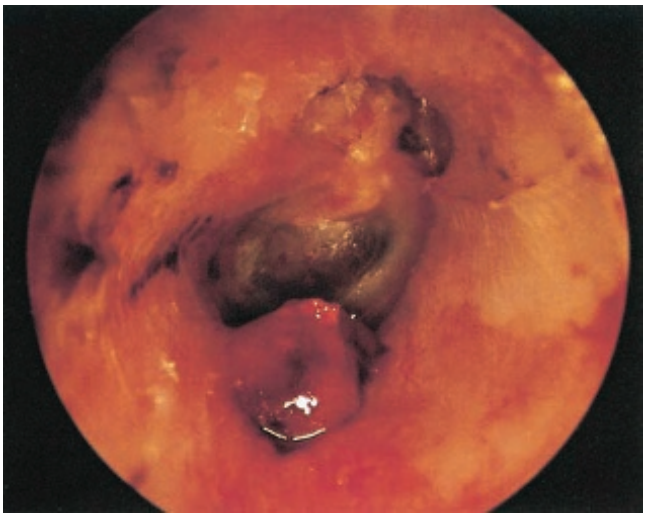

Figure 114.2 Necrotizing otitis externa with granulations of the floor of the right external auditory canal. Reproduced from Carney.[37]

The hearing loss is usually conductive due to external auditory canal obstruction by granulation or oedema. Sensorineural hearing loss is usually due to pre-existing presbycusis.[5]

As bony destruction and inflammation progresses medially through the skull base to the foramina, cranial neuropathies ensue initially with facial paralysis (in up to 25% of patients). This is followed by cranial nerves IX, X, XI, XII and then VI and II. Meningitis, cerebral abscess and sigmoid sinus thrombosis are late signs that are associated with a poor prognosis.[6, 9]

Children with skull base osteomyelitis usually develop facial nerve palsies earlier due to their more medial fissures of Santorini and their underdeveloped mastoid process.[13]

Parotitis and trismus due to masseter myositis and temporomandibular joint involvement is a rare clinical feature that has been described.[9]

A meta-analysis which sought to develop a clinically useful prognostic scoring system found the following factors to have a statistically significant negative effect on outcome: cranial neuropathies, external auditory canal granulations, bilateral symptoms and positive aspergillus cultures.[12]

BACTERIOLOGY

Pseudomonas aeruginosa, a Gram-negative obligate aerobe, is the most common bacteria species in skull base osteomyelitis.[5–7, 12–14] It is opportunistic and only a pathogen when the natural host defences are defective.[9] It has the ability to invade local vasculature and cause a focal coagulative necrosis of the surrounding tissue. Diabetics are susceptible to *P. aeruginosa* infection due to their poor phagocytosis of polymorphonuclear leucocytes. Virulent species have a mucoid surface layer that confers additional protection against phagocytosis. They may additionally produce lytic enzymes (for example, collagenases and elastases) and endotoxins, resulting in a necrotizing vasculitis.[6–9] Some strains also produce neurotoxins, which likely play a role in the development of cranial neuropathies.[6]

Staphylococcus aureus, *Staphylococcus epidermidis*, *Proteus mirabilis*, *Klebsiella oxytoca*, *Klebsiella pneumonia, Burkholderia cenocepacia, Enterobacter cloacae* and *Streptococcus constellatus* are other bacteria that have been implicated in the pathogenesis of skull base osteomyelitis.[5–7, 12]

Fungal infections are more commonly associated with the immunocompromised (e.g. HIV/AIDS) than with diabetics. In contrast to pseudomonal skull base osteomyelitis, these originate more often in the middle ear or mastoid. *Aspergillus fumigatus*, is the most common fungal organism isolated. It is associated with a worse prognosis than *Pseudomonas* when it is the causative agent. Others include *Aspergillus niger, Aspergillus flavus, Candida sp., Malassezia sympodialis* and *Scedosporium apiospermum*.[5–7, 9, 12–15, 17]

RADIOLOGY

All imaging modalities are reliant on the experience and confidence of the radiologist reporting the scans in order to help establish the diagnosis and guide treatment. A high-resolution computed tomography (CT) scan is valuable in diagnosing bony erosion and reduced density in the skull base. However, the value of CT scans is limited due to it only detecting bony demineralization of 30% or greater.[6, 9, 19] A negative CT scan must therefore be treated with caution as a potential false negative, as demineralization may take months to appear.[8, 13] A contrast-enhanced CT scan is useful in evaluating the extent and severity of extratemporal soft tissue involvement. Other features of complicated skull base osteomyelitis, such as abscess formation, mastoid and temporomandibular joint involvement, as well as progression of disease to the petrous apex and carotid canal, can also be demonstrated on CT scanning. However, CT scanning cannot reliably measure treatment response, distinguish between neoplasia and inflammation or show intracranial or bone marrow involvement.[8, 9, 14] It has been shown to depict persistent cortical changes 12 months after initiation of treatment.[11] It is nonetheless useful at the initial evaluation to outline the extent and location of the osteomyelitic process. Magnetic resonance imaging (MRI) is generally good at soft tissue differentiation and in skull base osteomyelitis can depict bone marrow oedema. Nonetheless, MRI is unable to assess response and resolution of disease and has also been shown to depict soft tissue and marrow abnormalities months after treatment has been completed.[6, 9, 11]

Nuclear imaging is useful in diagnosing skull base osteomyelitis, defining its extent and evaluating response to treatment and resolution of infection. Technetium-Tc ^{99m}-methylene-diphosphonate (^{99m}Tc-MDP) or Technetium-Tc 99-hydroxymethylene-diphosphonate (^{99m}Tc-MDP) scintigraphy has almost 100% sensitivity.[5] Its radiotracer accumulates in areas of high osteoblastic activity even in early cases of the disease. It has low specificity as it is also positive in malignancy; and so histological confirmation is important. As it

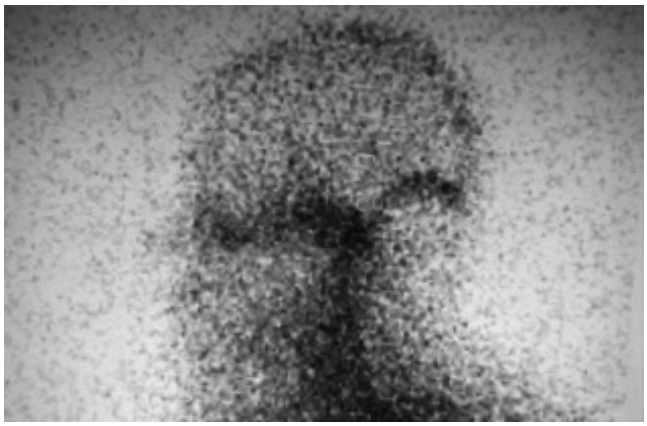

Figure 114.3 Indium labelled white cell scan of a patient with necrotizing otitis externa showing increased uptake in the left temporal bone. Reproduced from from Carney.[37]

cannot distinguish between active infection and bone remodelling, Gallium-67-citrate scanning is often utilized to monitor treatment response.[11, 14] It is based on the propensity of Gallium Ga 67 citrate to accumulate in areas of active inflammation in both soft tissue and bone. As Gallium uptake normalizes with disease resolution, unlike ^{99m}Tc MDP, it is a reliable tool to gauge response to treatment.[6, 9, 11] It should ideally be repeated every 4 weeks to monitor response to antibiotics until it is no longer positive.

Indium 111 (111 In) labelled leucocyte scintigraphy detects neutrophil mediated inflammation (see **Figure 114.3**). Single photon emission computed tomography (SPECT) creates 3-D pictures using Indium 111 or Gallium 67, which optimize anatomical localization.[5]

A meta-analysis of 23 studies seeking to determine which modality was most accurate found that fluorodeoxyglucose positron-emission-tomography (FDG-PET) was most accurate in confirming or excluding osteomyelitis but not significantly better than the combination of ^{99m}Tc bone and leucocyte scintigraphy or Ga67 scintigraphy.[11] Such modalities may not be available in most acute settings.

Treatment

AURAL TOILET

Aural toilet of the external auditory canal, as with uncomplicated otitis externa, is vital. It enables control of granulations and pain. Controversy surrounds the use of topical anti-microbial therapy in these cases as it may make culture of the pathological organism difficult.[4]

CONTROL OF DIABETES

Patients with poorly controlled diabetes are more susceptible to developing skull base osteomyelitis than diabetics with satisfactory control of serum glucose levels.[18] Aggressive glycaemic control in diabetic patients can be as crucial a management strategy as systemic antimicrobial therapy.[5, 13] Achieving good control of serum glucose may be difficult with invasive infection.

SYSTEMIC ANTIBIOTICS

Long-term systemic culture-directed antimicrobial therapy is the mainstay of treatment of skull base osteomyelitis. This is on average continued for at least 6–8 weeks depending on the resolution of symptoms,[5] but in advanced cases could be administered for months. In the ideal setting, antimicrobial therapy should be continued for as long as the gallium-67 scan remains positive. Fluoroquinolones have transformed the treatment of skull base osteomyelitis.[20] They are antipseudomonal, have good bone penetration and good oral bioavailability, and have fewer side effects than such alternatives as penicillins and aminoglycosides. Monotherapy with oral ciprofloxacin (750 mg twice daily) is the preferred initial regimen[5, 21–23] although some experts, with no conclusive evidence, still advocate parenteral antimicrobials converted to oral once the serum C-reactive protein (CRP) and/or the erythrocyte sedimentation rate (ESR) start to decline.[24] The addition of rifampicin (600 mg twice daily) has also been suggested, again with no direct evidence that it confers additional benefit.[25]

The incidence of *Pseudomonal* resistance to fluoroquinolones worldwide is increasing.[16] Cephalosporins active for pyocyanin (i.e. ceftazidime, cefepime), penicillins (i.e. ticarcillin, clavulanate) and aminoglycosides either in combination or as monotherapies are suitable alternatives in the context of resistance.[5, 7] Amphotericin B is the antifungal agent of choice for skull base osteomyelitis of fungal origin.[26] Oral itraconazole may be used after a successful course of amphotericin B.[27]

HYPERBARIC OXYGEN

The use of hyperbaric oxygen as an adjunct to systemic antimicrobial therapy has been debated with reports that it confers a beneficial effect.[27–29] It increases the partial pressure of oxygen, relieving hypoxia and enhancing the oxidative killing of microbes. A Cochrane review, however, found that there was no evidence from randomized controlled trials to support this treatment.[30]

SURGERY

In contrast to the era when the condition was first described, which saw radical debridement advocated to improve survival, surgery has a limited role in the management of skull base osteomyelitis. It is primarily performed to obtain specimens for culture, to locally debride granulation tissue and to exclude malignancy.[17] In selected cases it may be necessary to remove dead sequestra and drain associated abscesses.[5] Facial nerve decompression for complete facial palsies has unproven therapeutic benefit.[16]

OTHER INFLAMMATORY CONDITIONS AFFECTING THE TEMPORAL BONE

Sarcoidosis

Sarcoidosis is a granulomatous inflammatory condition that can affect several organs. It is thought to be due to an

autoimmune response by CD4 lymphocytes and mononuclear phagocytic cells against an unspecified antigen that evolves into a granuloma.[31] The vast majority of patients will have pulmonary involvement but other organs can be affected such as the eyes, spleen, mucous membranes and spleen.

In osseous sarcoidosis, which occurs in 1% to 13% of patients with sarcoidosis, the granulomatous inflammation is within the bone marrow. The petrous apex has been shown to be pneumatized in 30% of temporal bones,[31] with the remaining cases containing bone marrow, which could be a focus for sarcoidosis.

Clinical features have been reported to include otalgia, sensorineural hearing loss, aural fullness, tinnitus, disequilibrium and vertigo. Otomicroscopy is likely to be normal. Neurosarcoidosis, which occurs in 5% of cases, may cause cranial neuropathies with the facial nerve most commonly affected.[31]

Bony involvement exhibits threepatterns of radiographic appearance: lytic, permeative and destructive.[32] ^{99m}Tc-MDP scintigraphy and CT scanning are useful diagnostic tools in identifying bony lesions.[33] Biopsy of accessible lesions is useful when the diagnosis is unclear (e.g. suspected malignancy).[31, 33] There is no consensus on the length of time serial imaging should continue but annual surveillance scanning has been suggested.[31] Oral corticosteroids are the usual treatment modality in sarcoidosis.

Paget's disease

Osteitis deformans, also known as Paget's disease, is characterized by increased osteoclast activity, resulting in bony resorption, followed by osteoblast-mediated disorganized new bone formation. This results in a thickened, hypervascular, hypodense bone that is susceptible to fracture.[34]

It affects 3% of people aged over 40 years, with males more frequently affected.[34] The temporal bone is affected in 65–70% of cases.[35] Hearing loss occurs in 30–50% and vestibular dysfunction in 20–25%.[34] CT scanning demonstrates cotton wool appearance of involved bone due to replacement of marrow with hypodense bone. ^{99m}Tc-MDP scintigraphy is very sensitive in the early stage of the disease process as it is taken up by active osteoblasts.[34] Bisphosphonates that inhibit osteoclast activity are the mainstay of treatment. Zoledronate has been found to be the most potent bisphosphonate in suppressing disease activity.[36]

KEY POINTS

- Skull base osteomyelitis is a severe infection usually arising from otitis externa.
- The incidence of this infection is increasing.
- It affects the elderly, diabetics and immunocompromised individuals.
- Treatment comprises aural toilet, diabetic control and long term systemic antibiotics.

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CHAPTER 115

SQUAMOUS CELL CARCINOMA OF THE TEMPORAL BONE

Liam Masterson and Neil Donnelly

SEARCH STRATEGY

Data in this chapter may be updated by a PubMed, EMBASE and CINAHL search using the keywords: squamous cell carcinoma, temporal bone, external auditory canal, lateral skull base and free tissue reconstruction. The evidence in this chapter is mainly level 3 or 4. The clinical recommendations are predominantly B and C.

HISTORICAL BACKGROUND

Schwartze and Wilde provided the first description of temporal bone carcinoma in 1775, but it was not until the 1880s that Kretschmann, Politzer and Zeroni confirmed the existence of this pathology.[1–3] In 1917, Newhart published the first accurate case series, which consisted of 34 patients with squamous cell carcinoma (SCC) affecting the middle ear cavity, all of whom died after a short period of observation.[4]

The principle of *en bloc* resection emerged in the 1950s after reports by Campbell et al.[5] Using this approach, 20 years later, Lewis published a 25% 5-year survival in a cohort of 100 patients.[6] Modern skull base and reconstructive surgery techniques have improved the treatment of SCC of the temporal bone. Surgery is now more effective due to a greater understanding of skull base anatomy. Imaging techniques such as magnetic resonance (MR) and computed tomography (CT) help produce accurate assessment of the disease extent with particular regard to soft tissue involvement and/or bone erosion. With this approach, recent case series have demonstrated improved control of local advanced (T4) disease with 5-year survival rates ~40%.[7–10]

EPIDEMIOLOGY

SCC is the most common tumour type to occur in the temporal bone. The reported incidence is <6 cases per million per year, which accounts for 0.3% of all cancers within the head and neck. There is a slight predisposition to the male sex and the median age at presentation is within the seventh decade.[11–17]

AETIOLOGICAL THEORIES

Established risk factors for SCC within the epithelium of the temporal bone are chronic suppurative otitis media (CSOM) and previous radiotherapy.[8, 18] Exposure to ultraviolet light may be a risk factor for SCC that originates in the external auditory canal (EAC).[11]

One theory, which may provide a connection for the various predisposing factors, is the establishment of a chronic inflammatory process leading to metaplastic or neoplastic change. No strong evidence exists for occupational exposure to radiation or chlorinated disinfectants.[19]

Chronic suppurative otitis media

Chronic otitis media and cholesteatoma are common in patients with SCC affecting the temporal bone.[8, 20] In recent years several studies[21–23] have suggested an aetiological role for high risk human papillomavirus; however, they are limited to archival samples with disparate methods of collection. As yet, no study has been conducted on a prospective basis with fresh tissue due to the infrequent nature of this condition. It is also not clear if this viral subgroup demonstrates an improved survival after treatment.

Radiation-associated tumours

A past medical history of radiotherapy is relevant and may serve as a red flag at presentation. Goh et al.[24] reported seven patients with temporal bone malignancy, all of whom were initially treated by radiotherapy for head and neck disease. The latency period before symptoms were detected ranged from 5 to 30 years.

Although radiation-associated tumours of the temporal bone occur with a low incidence, their prognosis can be poor.[25] This potential risk should be considered when deciding upon the most appropriate treatment for individuals with tumours of the head and neck – especially if the patient is young and/or the condition is benign (i.e. acoustic neuroma or vascular malformation).

Exposure to ultraviolet light

The most common type of primary cancer in the EAC is SCC. It is suggested that long-term ultraviolet light exposure to the pinna or lateral concha can lead to carcinogenic change that migrates medially.[11] This is more likely in Caucasians, who are more prone to non-melanomatous skin cancers in sun exposed areas. A genetic predisposition to skin cancer may also exist, manifesting as the development of skin cancers in sites not exposed to sunlight (in addition to the more conventional locations).

SURGICAL ANATOMY AND CLINICAL FEATURES

Tumour spread is difficult to predict due to the complex anatomy of the temporal bone. The cartilaginous portion of the EAC provides minimal resistance to malignant invasion and the foramen of Huschke and fissures of Santorini are a source of direct egress to the parotid and temporomandibular regions. Although the bony canal is more resistant to local disease spread, posterior involvement of the mastoid cavity may occur. Medial spread along the EAC can extend through the tympanic ring, allowing entrance to the middle ear cavity and increasing the probability of conductive hearing loss. Invasion of blood vessels of the EAC gives rise to bloody otorrhoea. Once in the middle ear cavity, involvement of the Fallopian canal may result in facial nerve palsy. Extension through the petrous apex and invasion of the internal carotid artery (ICA) is possible but less likely due to the resistant bone of the otic capsule. The Eustachian tube and local neurovascular structures provide a potential method of tumour spread beyond the temporal bone to the nasopharynx, infratemporal fossa or neck. Extension to the inferiorly based jugular foramen may cause dysphonia or dysphagia by involving the vagal, glossopharyngeal or hypoglossal nerves.

Superior invasion through the tegmen tympani is a frequent occurrence and will allow spread to the middle fossa dura and/or the temporal lobe. Less frequently, malignancy within the mastoid will allow direct spread to the posterior cranial fossa.

Node-positive disease is an infrequent finding for early stage tumours (T1–2) but may occur in 10–20% of cases of advanced disease (T3–4).[8, 26] The first echelon lymph nodes are often within the parotid gland and these drain into pre-auricular nodes en route to the jugulodigastric and deep cervical chain of lymph nodes.[27] The integrated pathway of the facial nerve through the temporal bone results in 10–30% of patients with suboptimal facial function at presentation.[7, 8, 14–16] Involvement of the nerve may be found at the stylomastoid foramen/mastoid tip, Fallopian canal, geniculate ganglion or intracranial pathway.

Distant metastases are rarely reported but when present will normally occur in the liver, lungs or bone.[28] Haematogenous spread from other sites to the temporal bone can be possible and should form part of the differential diagnosis.[29]

DIAGNOSIS AND INVESTIGATION

History

The clinical history is relevant if temporal bone malignancy is to be diagnosed at an early stage. Moody et al. showed that the average time from onset of symptoms to the time of primary treatment for cancer was 3.9 years.[26] Common presenting symptoms include otalgia, blood-stained otorrhea and hearing loss. As many patients have associated cholesteatoma or CSOM, a change in clinical pattern can point to the development of a more sinister pathology.[11] If cranial palsies are noted at presentation, skull base osteomyelitis is a more likely differential but a malignancy should be actively excluded.[30]

The frequency of reported symptoms for large contemporary series is reported in **Table 115.1**.

Examination

Clinical examination should include inspection of the pinna, external ear canal and middle ear for scars, ulcers,

TABLE 115.1 Frequency of presenting symptoms (%)

	Gidley[7]	Masterson[8]	Gillespie[16]	Nyrop[13]	Leonetti[15]	Pensak[14]
Otalgia	52	53	53	35	73	74
Otorrhoea	62	55	73	45	69	84
Hearing loss	44	n/a	33	25	69	62
Facial palsy	16	17	13	n/a	30	18

mass lesions or soft tissue swelling. In patients with chronic otitis externa or CSOM, it may be difficult to determine malignant change from inflammation and this fact alone can account for diagnostic delay. An endophytic or exophytic mass within the EAC is likely to be malignant and is a strong indication for an urgent biopsy (**Figure 115.1**). Facial nerve assessment should be meticulously documented along with all other cranial nerves. A complete head and neck examination is performed, looking in particular for enlarged nodes within level II, III and Va.[13] The patient's general medical condition should be evaluated as this may greatly impact treatment options and outcome.

Biopsy and histological confirmation

A trans-canal biopsy is required to determine whether the lesion is malignant or benign. A staging mastoidectomy is not appropriate as this may complicate definitive treatment once a formal diagnosis has been made. Clinically suspicious neck nodes should undergo ultrasound guided core biopsy to improve the diagnostic accuracy of clinical staging and facilitate treatment planning.[31]

Although the majority of neoplastic lesions of the temporal bone are due to SCC, it is important to be aware of a differential diagnosis that can include basal cell carcinoma, melanoma, chondrosarcoma, Ewing's sarcoma, verrucous carcinoma, adenoid cystic carcinoma and metastatic disease.

In view of the strong correlation of SCC with chronic inflammation, it is important to have a high index of suspicion in this group of patients to avoid unnecessary treatment delays caused by misdiagnosis. Deep biopsies are preferable due to the risk of misrepresentative sampling. The middle ear cavity may now also be accessible via CT-guided biopsy. Early results suggest this alternative to direct trans-canal biopsy may increase the probability of a positive biopsy result but at present the majority of the surgical community are sceptical.[32]

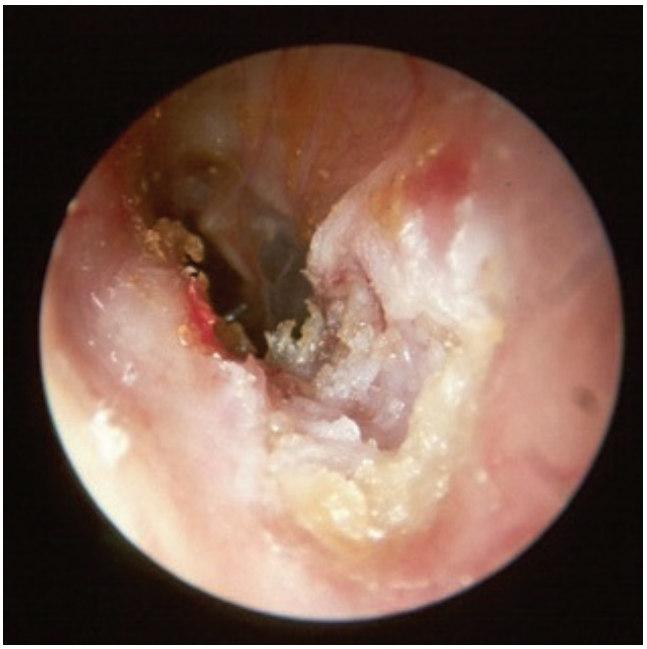


Figure 115.1 Early stage SCC right ear canal.

Audiometry

SCC temporal bone carcinoma rarely involves the sensorineural or balance system. However, an audiogram is mandatory before commencing any major ear surgery.[11] This will allow a baseline threshold for future comparison and also investigate the need for hearing rehabilitation as a result of the surgery.

This is important as Kwok et al.[33] identified poor communication in the post-surgical period as a major adverse influence on patient reported quality of life (ranked higher than cosmetic deformity).

Tumour staging

Staging systems are devised to aid classification of patients pre-operatively into groups with similar prognosis. There is now general consensus that the modified Pittsburgh staging system should be used to standardize comparison of outcomes between treatment centres and the differing surgical/non-surgical techniques undertaken.[7, 8, 10, 15, 17, 23, 26]

Arriaga et al. first conceived the Pittsburgh staging system to conform to the American Joint Cancer Committee's TNM classification system.[34] This staging system is based on clinical, pathological, and radiologic evidence. Tumours limited to the EAC are defined as early stage disease, and those that spread from the external canal to invade adjacent soft tissues, the mastoid, middle ear or cranial nerves indicate advanced disease. More recently, this scheme has been modified (**Table 115.2**) again to take into account facial nerve involvement as a prognostic indicator.[26, 35] Complete or partial facial nerve paresis would be classified as T4 regardless of the anatomical area of involvement.

It should be noted that the presence of metastatic lymph nodes in the neck are a poor prognostic indicator and consequently upstage the disease regardless of the T status.

Imaging

Physical examination alone cannot reliably characterize tumour beyond the external ear canal or middle ear cavity. Magnetic resonance imaging is the optimal modality for soft tissue analysis and can help differentiate tumour from fluid or inflammatory mucosa in the middle ear cavity, especially where bony erosion is not present.[32] MR scans with gadolinium DTPA enhancement are better for the assessment of soft tissue disease. Dural and brain involvement, infratemporal disease and perineural spread can be demonstrated when present, which may have great prognostic significance.[34]

High resolution CT (axial and coronal) portrays bone erosion accurately and when combined with MR imaging can improve pre-operative staging and give vital information to the surgical team (**Figures 115.2** and **115.3**).[36] A 1 mm fine-cut CT image is optimal for the temporal bone. The images should be carefully assessed with

TABLE 115.2 Modified Pittsburgh staging system[26,34]

Stage		Description
T Classification	T1	Limited to the EAC without bony erosion or evidence of soft tissue involvement
	T2	Limited to the EAC with bone erosion (not full thickness) or limited soft tissue involvement (<0.5 cm)
	T3	Erosion through the osseous EAC (full thickness) with limited soft tissue involvement (<0.5 cm), or tumour involvement in the middle ear and/or mastoid
	T4	Erosion of the cochlea, petrous apex, medial wall of the middle ear, carotid canal, jugular foramen, or dura; with extensive soft tissue involvement (>0.5 cm, such as involvement of the TMJ or styloid process); *or evidence of facial paresis*
N Classification	N0	No regional nodes involved
	N1	Single metastatic regional node <3 cm in size
	N2a	Single ipsilateral metastatic node 3–6 cm in size
	N2b	Multiple ipsilateral metastatic lymph nodes
	N2c	Contralateral metastatic lymph node
	N3	Metastatic lymph node >6 cm in size
Overall stage	I	T1N0
	II	T2N0
	III	T3N0
	IV	T4N0 and T1-4N1-3

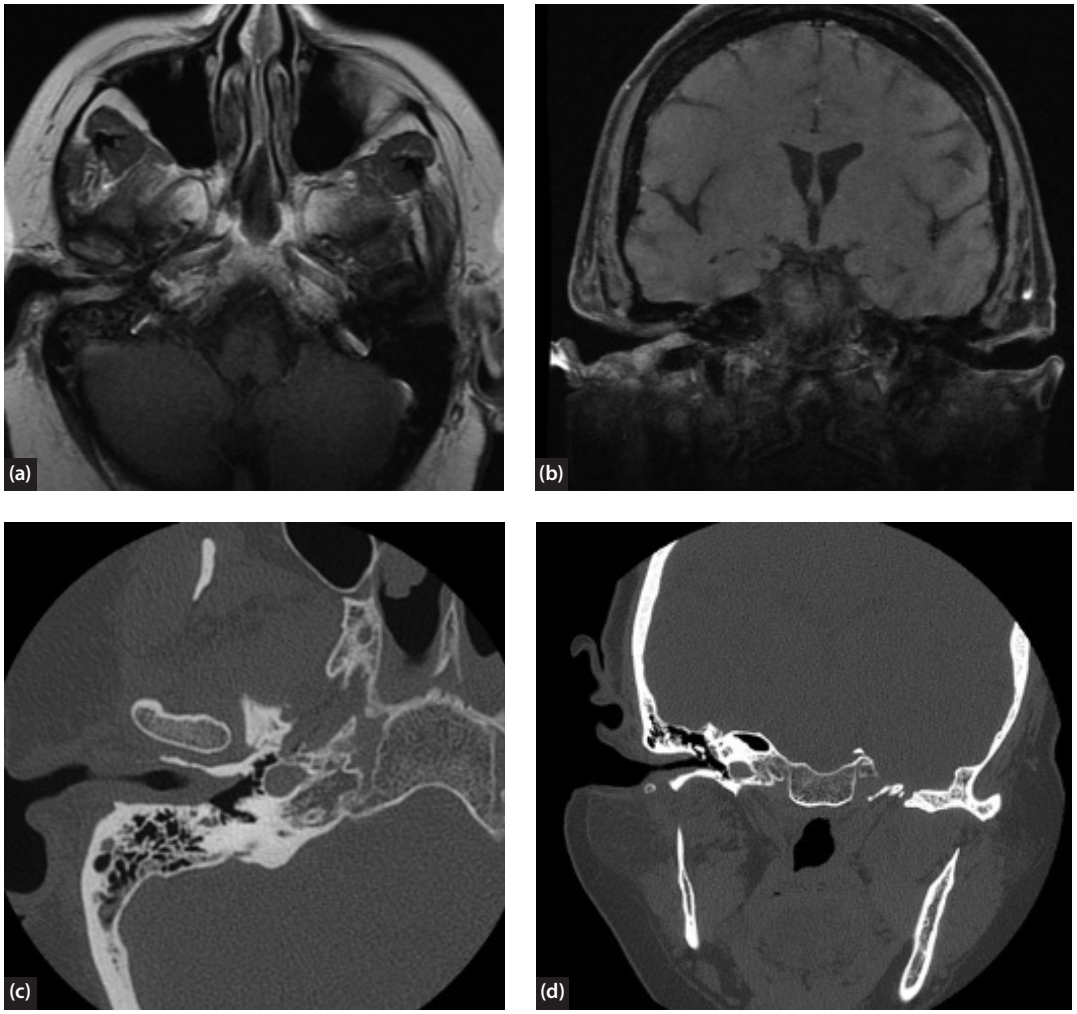


Figure 115.2 MR imaging with gadolinium enhancement showing early stage SCC within the right ear canal (a) MR axial and **(b)** MR coronal. CT imaging reveals that the same disease does not invade the middle ear cavity **(c)** CT axial and **(d)** CT coronal. Images courtesy of Colchester Hospital University NHS Foundation Trust.

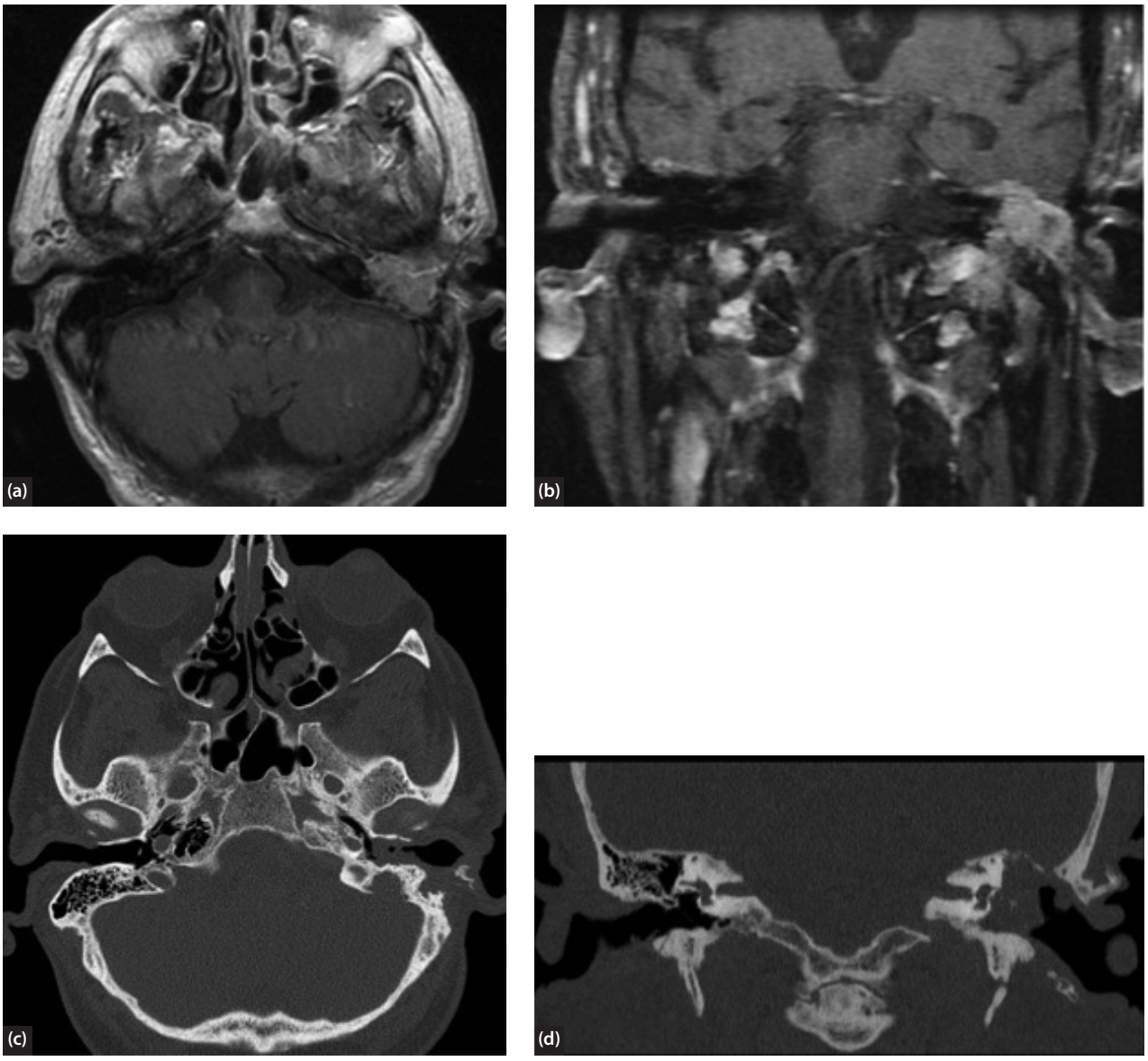


Figure 115.3 MR imaging with gadolinium enhancement (a) MR axial and **(b)** MR coronal, showing late stage SCC in the left mastoid cavity with possible invasion of the temporal lobe. CT imaging reveals that the same disease has eroded through the tegmen tympani and mastoid cavity **(c)** CT axial and **(d)** CT coronal. Images courtesy of Norfolk and Norwich University Hospitals NHS Foundation Trust.

regards to the EAC, middle ear, facial nerve, mastoid, tegmen, middle/posterior fossa dura, sigmoid sinus, jugular bulb and carotid canal. Extra features to review include the parotid gland, TMJ and infratemporal fossa.[37]

If CT or MR raises the possibility of ICA involvement, angiography with balloon occlusion should be considered, as sacrifice of the ICA may be necessary. Angiography with ipsilateral balloon occlusion testing is established to check the patency of cerebral blood flow from the other side. The venous phase is also important to determine the patency of the contralateral sigmoid/jugular system, in case surgery requires sacrifice of the sigmoid sinus or internal jugular vein. In view of the potential consequences of carotid ligation, the multidisciplinary team often makes the pre-operative decision not to sacrifice this major artery unless deemed absolutely necessary.[8, 16]

A staging scan of the neck and chest is routinely performed. CT scanning of the pelvis and abdomen is not required unless the biopsy result suggests an alternative diagnosis to SCC (e.g. lymphoma, melanoma or adenocarcinoma).[35, 36]

TREATMENT

The UK National Institute for Health and Care Excellence (NICE) document, *Improving outcomes in head and neck cancers* was first published in 2004 and subsequently revised in 2012.[38] It provided several recommendations to improve the quality of patient care, for example the establishment of a direct referral pathway and a multidisciplinary team approach (surgeon, oncologist, pathologist and radiologist) to reassess diagnosis and instigate

appropriate treatment plans. Other key recommendations included the provision of a specialist nurse service to enhance co-ordination of care, provide supportive counselling and improve opportunities for participation in clinical trials. The rehabilitation team (audiologist, speech and language therapist, occupational therapist, physiotherapist) is deemed essential to aid the anticipated hearing handicap, balance disorder and speech or swallowing problems.

At present, there is no consensus strategy for operative management of temporal bone tumours. The main surgical approaches are *en bloc* resection combined with adjuvant radiotherapy versus piecemeal resection or radical mastoidectomy with adjuvant radiotherapy.

There appear to be two underlying causes for this. First, a significant proportion of oncological procedures require a degree of piecemeal tumour removal as the main block of tissue is weakened or fragmented by the carcinoma. Second, in some patients the diagnosis is made during mastoid exploration for what seemed to be a routine cholesteatoma or another chronic inflammatory disease. A pragmatic approach entails post-operative radiotherapy alone without further surgical intervention; however, this may adversely affect patient survival.

Notwithstanding the above, recent results suggest that the most favourable survival rates are achieved with *en bloc* extended temporal bone resection and post-operative radiotherapy. This can be demonstrated by analysis of recent results from Yin, Gidley, Bacciu and Masterson et al., which all demonstrate improved survival figures despite treating a cohort of patients dominated by T3 and T4 disease.[7–10, 28]

It is useful to consider each stage or section of the operation separately to give an overview of the management that may arise in individual patients.

Surgical management of the neck

Although nodal metastases are uncommon in early stage disease, a neck dissection will allow accurate staging and provide access to the major vessels for free flap reconstruction. If suspect lymph nodes are found, these are sent for frozen section analysis and, where positive, a modified radical neck dissection is performed. Node-positive disease is associated with a poor prognosis, and neck dissection does not improve survival.[7–9, 26, 34]

Gidley et al. noted that the distribution of pathological nodes within their cohort was largely restricted to levels II/III/Va with the exception being level IV in < 10% of cases.[7] On this basis, a selective neck dissection should incorporate these anatomical zones when performed for node-negative disease. The parotid gland and intraparotid nodes are not only the anterior resection margin of the tumour but also the first echelon nodes draining the EAC. A superficial parotidectomy is routinely performed in early stage disease where a functional facial nerve is present. A total parotidectomy is reserved for advanced stage disease with sub-optimal facial nerve function.

LATERAL TEMPORAL BONE RESECTION

Tumours lateral to the tympanic membrane (T1 and T2) can be resected adequately by a lateral temporal bone resection.[39]

In view of the aggressive nature of this disease, the pinna is only preserved if a wide soft tissue margin (> 1 cm) exists between the lateral aspect of the tumour and the external auditory meatus. Pinna resection will impose a significant handicap to the patient, in terms of both aesthetics and function for those who wear spectacles.

An extended cortical mastoidectomy should be undertaken and the facial nerve identified and preserved as the medial limit of the dissection. The tegmen is followed anteriorly toward the zygoma to allow a suitable bony margin along the anterosuperior canal wall. The facial nerve is skeletonized along its inferior path towards the stylomastoid foramen. The mandibular head may also be transected and the tumour removed *en bloc*. All mucosa is removed from the middle ear cavity to optimize the flap repair and the Eustachian tube is obliterated by scarifying the mucosa and then plugged with muscle, fascia or bone wax.

The anterior border of the malignancy is the posterior limit of the temporomandibular joint (TMJ). The thin bone of the anterior canal wall can be difficult to assess pre-operatively and many studies recommend removal of the articular disc, or at least drill out the glenoid fossa. However, if the condyle is removed, this may give rise to significant dental occlusion deformity. Recent data from Cambridge (UK) would suggest no evidence of microscopic invasion into the condylar head for patients with T1-2 disease.[8] Finally, the primary tumour should be removed *en bloc* with the neck dissection and the superficial parotid gland. This is often not possible due to technical constraints, requiring the neck dissection and parotid to be detached separately.

EXTENDED TEMPORAL BONE RESECTION

An extended temporal bone resection is required when invasion extends medial to the tympanic membrane or into the mastoid (T3/T4 disease). With locally advanced disease, aggressive treatment is required due to the equally aggressive nature of the malignancy. The facial nerve is sacrificed in this procedure and the entire pinna is also removed.

The specimen includes the lateral temporal bone resection (as above) with additional dissection of the medial bony wall of the middle ear, extended mastoidectomy and removal of the otic capsule (**Figure 115.4**). The margins of resection are the ICA anteriorly, middle fossa dura superiorly, sigmoid sinus and posterior fossa dura posteriorly, petrous apex medially and the jugular bulb inferiorly.

In selected patients, resection of dura or brain may be required. A posterior and middle fossa craniotomy is achieved by resecting bone 3 cm above the sigmoid sinus and temporal line. Involved dura is removed with

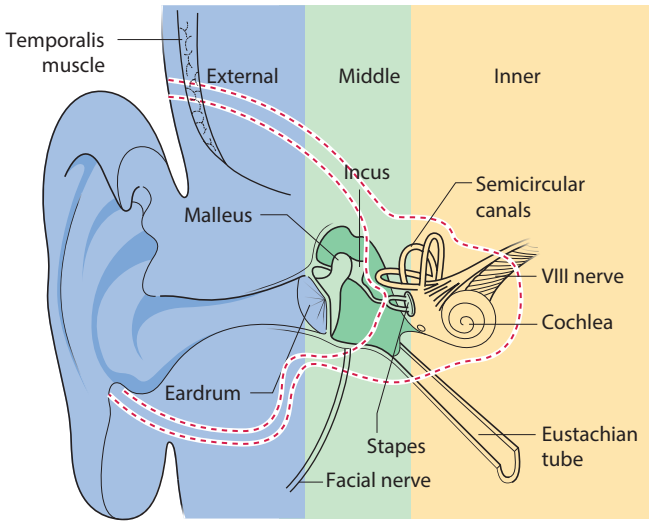


Figure 115.4 Anatomy of the left temporal bone in the coronal plane, showing the extent of a lateral temporal bone resection (outlined in red) and an extended temporal bone resection (outlined in green).

an adequate margin. The jugular bulb and sigmoid sinus are delineated as the resection extends medially. The bony labyrinth and the internal auditory canal are both resected and the intrapetrous portion of the carotid artery exposed. The middle fossa dura is retracted to allow further detailed inspection. Dura and brain, which have macroscopic tumour involvement, are removed as a separate specimen. Frozen sections from all margins of the dura are taken to ensure clear margins. The defect in the dura is then sealed with fascia lata and sutured carefully to avoid a potential cerebrospinal fluid (CSF) leak.

If a radical neck dissection has been performed, the next stage will be to divide and ligate the sigmoid sinus. Wherever possible, the lower cranial nerves (IX, X, XII) are conserved if macroscopic disease is not present. For some, removal of the condyle, coronoid process and the upper two-thirds of the ramus of the mandible together with surrounding soft tissue will be necessary after the masseter has been dissected away. This may allow greater exposure of the infratemporal fossa region to assess disease extension.

The anterior margin of the resection includes the entire parotid gland. Frozen section analysis is employed if there is concern that the surgical margin is not clear. After this stage, the whole temporal bone resection lateral to the ICA together with the neck dissection and parotid gland are removed.

RECONSTRUCTION

Free tissue transfer is routinely used to reconstruct the pyramidal defect that typically remains following ablative surgery. The anterolateral thigh flap is a common choice as it provides skin and fascial covering and can be taken with muscle if more bulk is required.[40, 41] The thigh donor site provides access for fascia lata if required for static slings for simultaneous facial palsy reconstruction. The distant flap donor site allows for concomitant flap harvest and oncological resection, minimizing the duration of surgery. Alternative free flaps, which are less commonly used, include the radial forearm and lateral arm flaps. Pedicled myocutaneous flaps and scalp transposition fasciocutaneous flaps have also been employed with good results, but are usually reserved for the minority of patients who are not good candidates for free tissue transfer due to microvascular disease (e.g. diabetic or peripheral vascular disease patients).[42]

In cases of pre-existing facial palsy or where the facial nerve has been sacrificed, simultaneous facial palsy work can be undertaken including upper eyelid gold weight insertion, browpexy, lateral tarsorraphy and static fascial slings. In patients aged <65 years, and depending on the integrity of the distal facial nerve branches, a nerve graft procedure may be possible (e.g. interposition neurorraphy or transposition of the nerve supplying masseter onto the distal stump of the facial nerve).

Following removal of the pinna and completion of post-operative treatment, patients are routinely offered a prosthesis or, less frequently, a staged autologous pinna reconstruction.

Adjuvant therapy

RADIOTHERAPY

The literature supports a beneficial effect of adjunctive radiotherapy on DSS, but as yet no well-controlled studies have been performed. Most studies report a dose ~60 Gy applied to the temporal bone and upper neck region.[7–10, 15, 43]

The effect of RT may also extend beyond adjuvant therapy based on some retrospective case series. Pemberton et al.[44] revealed a 45% 5-year DSS for 123 patients treated with 55 Gy radiotherapy alone; however, the survival benefit was significantly lower for patients who had advanced disease (T3-4), suggesting primary radiotherapy alone is not appropriate in this subgroup. In the most extreme cases in which contraindications to surgery are present, palliative radiation and/or chemotherapy may be offered.

In patients who have previously undergone treatment with radiotherapy, further doses may be given if the previously irradiated area has been resected and new vascularized tissue covers the defect.[42] Post-operative radiotherapy normally commences 6–8 weeks after surgical intervention to maximize flap viability.

CHEMOTHERAPY

Adjuvant chemotherapy was previously thought to provide little advantage. However, in 2006 Nakagawa et al.[45] reviewed series of patients all treated with either pre-operative chemoradiation or with chemoradiation alone. Four of eight patients treated with chemoradiation (5-Flourouracil + external beam radiation with a dose of 40 Gy), were free of disease at 24–47 months. The same

study also a reported a significant difference in 5-year survival for T4 patients with advanced stage disease treated surgically (75%) and non-surgically (16%). In a similar manner to radiotherapy above, the available evidence would not suggest a survival benefit for primary chemotherapy in advanced stage disease.

TREATMENT OUTCOMES AND PROGNOSTIC FACTORS

Early stage tumours generally have a favourable outcome, with most series reporting an 80–100% survival rate. However, T4 tumours have reduced survival rates even after adequate surgery and adjuvant radiation treatment (Table 115.3).

Prior surgical intervention is often a prerequisite towards making the diagnosis of malignancy, but this can complicate pre-operative staging, disrupt margins and require the surgeon to operate in an inflammatory region.[9] The literature is divided as to whether persistent/residual disease will result in significantly reduced survival when compared to patients who have not received prior treatment.[8, 14–16]

Although true *en bloc* resection is sometimes difficult to achieve because of the complicated three-dimensional nature of the temporal bone and anatomical spread of disease, more recent results confirm that it does offer the greatest chance of successful treatment.[7–10, 16, 28] Advanced stage of disease, node-positive status, dural/brain involvement, facial nerve palsy, poor histological differentiation, positive surgical margins and carotid invasion are all important adverse factors.[7, 8, 16, 17, 28, 36]

Stage of disease

The modified Pittsburg staging system predicts disease outcome by tumour size, local/distant metastatic spread and/or facial nerve involvement. Moody et al.[26] revised the University of Pittsburgh staging system in 2000 by suggesting that temporal bone SCC with evidence of facial nerve palsy should be categorized as T4. Multiple studies have since endorsed this new classification, the best evidence coming from Higgins et al.,[17] who produced a systemic review to determine the impact of facial palsy on survival outcomes. This study selected 21 articles containing information on 348 subjects and found that disease-specific survival (DSS) and overall survival in patients with facial palsy were significantly worse than for subjects without this deficit.

Dural and cerebral infiltration

Extension superiorly through the tegmen with dural and cerebral involvement is considered by some to be a particularly ominous feature. Moody et al.[26] reported that dural involvement was such a poor prognostic indicator that it may render curative surgery futile. This may directly contradict the findings in the larger study by Masterson et al., where 14/60 patients presented with brain involvement and the disease specific five-year survival was not significantly different from the rest of the group (37% versus 44% $p = 0.335$).[8]

Tumour differentiation

For this condition, most studies[7–9, 28] correlate poorly differentiated histology to an adverse prognostic outcome (Figure 115.5). Primary SCC affecting other sites in the head and neck behave in similar manner.

Surgical margins

In those patients with positive surgical margins, recurrent disease is more likely and survival reduced.[10, 16] The judicious use of intra-operative frozen sections can aid detection of safe margins.[8, 14, 18, 34]

Carotid involvement

Carotid involvement is fortunately rare, and also correlates strongly with a poor outcome.[7, 8, 28] Resection of the intrapetrous carotid artery can result in serious consequences and as such should only be attempted with appropriate caution. Malignant invasive disease may sometimes be limited to the adventitia and as a consequence the tumour can be dissected clear without need for ligation and division of the artery.

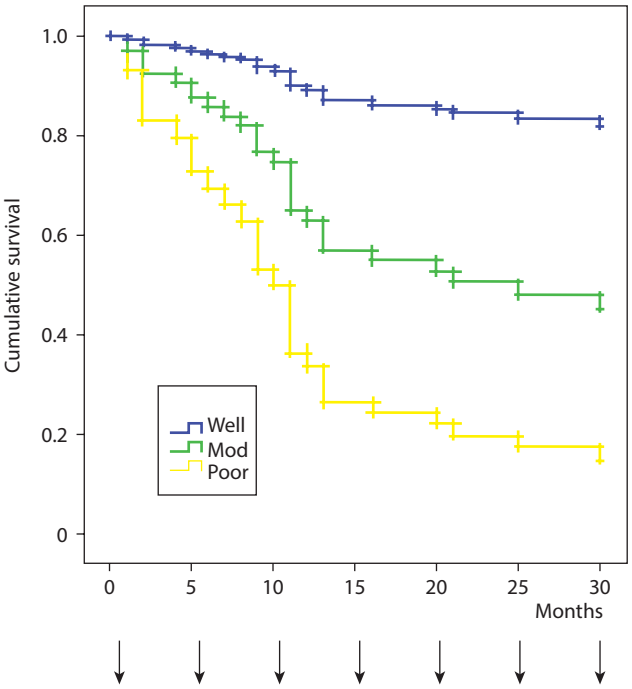
COMPLICATIONS OF TREATMENT

Complications of treatment depend on the extent of resection and the use of adjunctive radiation. Extended temporal bone resection will commonly cause or exacerbate a cranial nerve deficit. Facial palsy will cause both cosmetic

TABLE 115.3 Five-year disease specific survival stratified by stage of disease†

Study	Year	Patient number	Stage I	Stage II	Stage III	Stage IV
*Yin et al.[28]	2006	95	100	100	67.5	29.5
Moore et al.[9]	2007	35	100		53	
Gidley et al.[7]	1020	124	48		28	
Bacciu et al.[10]	2013	45	100	100	86.2	48.7
Masterson et al.[8]	2013	60	n/a	100	62	39.5

† Only studies using the modified Pittsburgh staging system are included;
* Yin et al. report overall survival only



Grade	Number of patients at risk						
Well	12	12	11	10	8	6	6
Mod	32	30	22	15	13	9	3
Poor	14	9	5	4	4	4	3

Figure 115.5 Temporal bone SCC disease specific survival stratified by histological grade (Log-Rank multiple regression analysis p = 0.05; Well, Well differentiated SCC; Mod, Moderately Differentiated SCC; Poor, Poorly differentiated SCC).[8]

and functional disability. Prompt eye care is of vital importance to prevent exposure keratitis.

Post-operative vertigo, hearing loss and other cranial nerve deficits (e.g. V, VIII, IX, X, XI) may also occur. Vagal, glossopharyngeal or hypoglossal nerve palsies may enhance patient risk of poor nutritional input and aspiration pneumonia. Speech and language expertise can be helpful but ultimately some patients will require a gastrostomy and/or temporary tracheostomy.

If the dura was resected and repaired, the risk of meningitis due to a CSF leak can be ameliorated by the use of lumbar drains inserted for 24–72 hours.[46] The main complications of adjuvant radiotherapy include osteoradionecrosis, soft tissue fibrotic change that can mask future recurrent disease, destruction of salivary gland tissue and increased risk of iatrogenic malignancy within the central nervous system (CNS).[16]

CONCLUSION

The gold standard treatment for temporal bone SCC remains undefined because of continued debate regarding staging, adjuvant radiation and the extent and nomenclature of surgical procedures. It is clear that there is a survival advantage to be gained from being managed in a tertiary centre with multidisciplinary expertise in the condition. At present, the number of patients with this condition at each individual institution restricts definitive conclusions. Multi-institutional cooperation is now required to facilitate prospective clinical trials.

Surgery and adjuvant radiotherapy alone are currently insufficient for obtaining adequate survival rates for patients with advanced T4 disease. Induction or concurrent chemotherapy should be investigated as a means of achieving improved survival.

Finally, well-validated outcome measures of quality of life parameters need to be utilized and communicated in the literature. There has been restricted work on patient-perceived outcomes of what is often referred to as disfiguring and debilitating surgery.

BEST CLINICAL PRACTICE

- ✓ Early biopsy of a suspicious lesion in the EAC will avoid diagnostic delays for patients with temporal bone SCC and improve their survival.
- ✓ All patients should have both MR and CT scans to stage their disease and facilitate treatment planning.
- ✓ *En bloc* resection with post-operative radiotherapy is the current treatment of choice.
- ✓ Management by a multidisciplinary team is essential, for example the expertise of the plastic surgeon for reconstruction of the defect, and the skills of the speech and language therapist to overcome speech and swallowing problems.

KEY POINTS

- Temporal bone squamous cell carcinoma is a rare disease that may cause severe morbidity.
- Otitis externa that does not resolve mandates formal biopsy.
- The treatment plan should be informed by careful staging with MR and CT imaging.
- Optimal management involves a multidisciplinary team with specialist expertise in squamous cell carcinoma of the temporal bone.
- The multidisciplinary team should include an otolaryngologist, neurosurgeon, clinical oncologist, reconstructive surgeon, neuroradiologist and rehabilitation team to deal with hearing handicap, balance disorders, speech and swallowing problems.
- Palliative surgery may have a role in advanced cases.

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CHAPTER 116

COMPLICATIONS OF SKULL BASE SURGERY

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SEARCH STRATEGY

Data in this chapter may be updated by a Medline search using the keywords: randomized controlled trials, meta-analysis, evidence-based medicine, review literature, skull base (focusing on surgery and complications), skull base neoplasms (focusing on surgery and complications), postoperative complications, vestibular schwannoma (focusing on surgery and complications), cerebrospinal fluid rhinorrhoea (focusing on surgery, complications, prevention and control), cerebrospinal fluid otorrhoea (focusing on surgery, complications, prevention and control), CSF lumbar drainage, antibiotic prophylaxis, meningitis (focusing on surgery, complications, prevention and control), electromyography, intraoperative monitoring, facial nerve and facial nerve injuries (focusing on prevention and control), acetazolamide (focusing on adverse effects and therapy), papaverine (focusing on therapy), intracranial hypertension (focusing on therapy), hydrocephalus (focusing on therapy and drug therapy), CSF pressure, therapeutic embolization, meningioma, angiofibroma. In addition, the Cochrane database has also been searched.

INTRODUCTION

The evolution of skull base surgery has provided an intersection between various surgical specialities including neurosurgery, otolaryngology surgery, ophthalmology, oncology, radiology, head and neck surgery, as well as craniofacial and reconstructive surgery. In addition to this, the last decade has seen dramatic advances in surgical technique, neuronavigation and optics; including the triple chip cameras, endoscopic 3D systems and high-definition screens, providing both precise surgical resection, as well as preservation of surrounding neurovascular structures. Intra-operatively, nerve monitoring has further aided the modern day surgeon when managing varying pathologies within a delicate anatomical region. An improvement in surgical interventions has been coupled with accurate radiological imaging, allowing both appropriate visualization and management of anatomically remote and complex lesions to be safely resected. A collaborative multidisciplinary team, in conjunction with the dramatic advances in surgical technique and technology, has resulted in improved patient care and reduced post-operative complications.

Despite a constant evolution, skull base surgery remains a challenging field of surgery, with important risks. As with any surgical procedure, identification and minimization of complications is essential. Skull base tumours are intimately related to vital neurological structures, cranial nerves (CN), major arteries and venous sinuses, making surgical resection challenging. These problems may be compounded when large tumours directly invade important structures. Dural breaches predispose to cerebrospinal fluid (CSF) leakage and the close proximity to contaminated aero-digestive structures may expose the patient to an increased risk of infection.

In this chapter we will detail both intra-operative and post-operative complications of skull base surgery.

INTRA-OPERATIVE COMPLICATIONS

Vascular

ARTERIAL HAEMORRHAGE

Transection of a major artery is a disastrous but fortunately rare event. Inadvertent excessive manipulation or direct forceful suction of an intracranial artery may lead to vasospasm and cerebral infarction. Gentle handling of vessels using neurosurgical patties for protection with medium/low suction and frequent irrigation with isothermic saline

are mandatory operative techniques. Infiltration of vasoconstrictive agents prior to surgery, as well as local application of patties soaked in vasoconstrictive agents produce lower rates of morbidity intra-operatively.

The primary vessels at risk during lateral skull base surgery are the basilar artery and the anterior inferior cerebellar artery (AICA). The basilar artery may be injured during translabyrinthine or suboccipital approaches to very large vestibular schwannomas (VS). The AICA is frequently in the surgical field during VS surgery. Injury to the AICA may result in Atkinson syndrome – lateral tegmental pons infarction, which is often fatal.

Major vascular complications in anterior skull base surgery primarily affect the carotid within the sphenoid sinus, particularly in transphenoidal surgery for patients with acromegaly. The specific difficulties within this cohort include the sinus being deeper, characterized by more septa and a reduced intercarotid distance, resulting in potential intra-operative surgical difficulties.[1] The intrasphenoid carotid artery can further complicate matters both pre- and intra-operatively. Its presence can mimic a sinonasal mass with variations occurring in approximately 40% of patients, as well as aneurysms of the cavernous portion, which accounts for 2–9% of all intracranial aneurysms.[2, 3] In conjunction with this, there are high rates of dehiscence shown in literature, with multiple other papers finding only a mucoperiosteal covering the intrasphenoid carotid artery coursing through the sphenoid sinus.[3] Sethi et al. described rates of dehiscence as high as 93%, although this paper did not define their criteria.[4] As a result, if the surgeon is not aware of such common variations, a damaged intrasphenoid carotid artery can result in both vascular and neurological complications and potentially death.

Embolization of selected vascular tumours such as meningiomas, paragangliomas and nasopharyngeal angiofibromas may reduce the risk of intra-operative and post-operative bleeding and even the operative time. Unfortunately, studies have yielded contradictory results and, at present, there is no consensus on its use. The majority of studies have been retrospective, and the two prospective studies to date on the preoperative embolization of meningiomas have produced conflicting conclusions.[5, 6] Major complications of such neuroradiological procedures include cerebrovascular accident (CVA), subarachnoid haemorrhage, intratumoral haemorrhage, raised intracranial pressure and CN palsies due to tumour swelling or embolization of the vaso vasorum and even death.

VENOUS HAEMORRHAGE

Venous haemorrhage may be controlled using a variety of methods depending on location and quantity of bleeding. These include bone wax if the bleeding point has a bony perimeter, bipolar diathermy or repair using 6-0 or 7-0 monofilament suture if the vessel wall is easily visible, or placement of haemostatic agents such as oxidized cellulose (Surgicel), microfibrillary collagen (Avitene) or biological tissue glue, typically for more diffuse bleeding. Occasionally, large sinus perforations may require extraluminal packing to achieve haemostasis or even formal ligation. Anatomical studies have shown a unilateral non-functioning sigmoid sinus/jugular bulb is present in only 4% of normal subjects, so adverse post-operative sequelae, such as cerebral oedema or long-term benign intracranial hypertension following ligation, is infrequent.[7]

Air embolus

Air embolus is a rare complication that usually only happens when the patient is in the sitting position. This position leads to a reduction in intracranial venous pressure; if a defect in a venous sinus is created, a pressure gradient favouring the passage of air into the circulation is created.[8] The first sign is a sucking sound or venous crepitation at the site of entry. Later, hypotension, tachycardia, dysrhythmias and diminishing end-expiratory pCO_2 develop. When this complication is detected, inhalation anaesthesia is discontinued and 100% oxygen administered, while the bleeding site is controlled by direct pressure and the jugular veins are compressed in the neck. The patient is placed in the left lateral Trendelenburg position with the head lowered in order to trap the air embolus in the right side of the heart, preventing it entering the pulmonary circulation. The air can then be aspirated through a central venous catheter or, in its absence, needle aspiration of the right ventricle via a subxiphoid approach should be attempted.

Cranial nerve injury

Cranial nerve injuries are among the most debilitating complications encountered in skull base surgery. Most pre-operative CN deficits persist post-operatively if due to tumour invasion rather than compression. Unlike sensory CN deficits, there is a good prospect of some recovery of motor CN function if a primary reanastomosis or cable graft is performed. Microdissection techniques and electrophysiological nerve monitoring enhance the preservation of CN during tumour resection.

OLFACTORY NERVE

The olfactory nerve is at risk and often unavoidable in anterior skull base procedures, specifically ethmoidal tumours or meningiomas of the sphenoid ridge and those involving stripping of the dura from the cribriform plate treated through an open approach. This is due to the position of nerve within the subarachnoid space, with only a meningeal sheath covering.

The olfactory epithelium is present at the apex of the nostrils bilaterally, covering an area of approximately 2–3 cm^2. The epithelium consists of both trigeminal and olfactory nerve fibres, with trigeminal fibres sensitive to irritation and temperature rather than olfaction. Tumours involving the anterior fossa floor often lead to unilateral anosmia, which is usually not perceived; however, it can occasionally cause permanent bilateral anosmia.[9]

Management of patients with anosmia includes safety advice and dietary advice. Smoke and gas detectors should be installed in their homes and they will require advice on healthy eating, as many foods are unappetizing without the sense of smell and this can lead to an unbalanced diet.

OPTIC NERVE

The optic nerve is at risk in anterior skull base surgery, specifically pituitary tumours close to the optic chiasm. Blindness within tumour management may also be secondary to radiotherapy, leading to radiation keratitis, or direct radiation injury to the optic nerve. Visual-evoked potentials should be monitored during surgery. Sharp dissection around the nerve using the appropriate microscopic or endoscopic techniques will lower the risk of injury.

It is interesting to note there is a high level of protrusion and dehiscence of the optic nerve, with over 30% of the population having both protrusion and dehiscence, and various papers reporting rates of protrusion as high as 70%.[3] These differences in variations are attributed to ethnic background.[3] Without careful anatomical dissection it will lead to post-operative visual difficulties, with increased risk of blindness from optic nerve damage within the sphenoid sinus.[3]

CRANIAL NERVES III, IV AND VI

The cranial nerves III, IV and VI are at risk during operations of the petrous apex adjacent to the cavernous sinus and the anterior skull base. The trochlear nerve exits the posterior brainstem and has a relatively long intracranial course, but is well protected in the tentorium and is infrequently injured. Abducens nerve palsy has been reported after lumbar drain placement – it is not known whether this is through an ischaemic or traction injury. Abducens nerve palsy management tends to be symptomatic, with recovery tending to be slow and progressive. In paediatric patients occlusive patch therapy for eyes will help avoid amblyopia, until residual palsy improves. Monitoring of extraocular movements is important in recovery.

TRIGEMINAL NERVE

The trigeminal nerve is at risk during lateral skull base surgery, such as large VSs, temporal bone resection and approaches to the clivus, nasopharynx and parasellar–parasphenoid compartments, when intentional neural section may be necessary for anatomical access. Trigeminal nerve branches are also at risk during anterior skull base procedures. With sensory innervation of the head mainly covered by the trigeminal nerve, except the occipital and maxillary joint area, disorders may lead to severe discomfort for the patient. Various forms of rehabilitation have been hypothesized and researched. With regards to conservative therapy, vitamin B6 is traditionally used as a neurotrophic substance; however, there is little clinical evidence to support its use. Nerve growth factor is a similar neurotrophin, with local use following damage increasing expression of tyrosine receptor kinase A. However, it is currently not available for clinical use and is still within research phases for possible neural repair and reconstruction. Surgically, there have been positive outcomes following reconstructions of the inferior alveolar and lingual branches of the trigeminal nerve, with suggestions that the same theories can be utilized for sensory nerve reconstruction. Possible interposition grafts include the great auricular nerve or the sural nerve for longer graft requirements. Both of these have drawbacks, with permanent sensory deficits over the ear lobe and calf respectively. If reconstruction and rehabilitation is not a realistic option, typically carbamazepine or gabapentin are used as required to treat possible facial pain from trigeminal nerve dysfunction.[10]

FACIAL NERVE

Facial nerve damage frequently leads to decrease in a patient's quality of life, despite successful lesion removal.[11] Pre-operative dysfunction is independently linked to post-operative paralysis, with informed consent essential.[11] Important anatomical variations lead to higher intra-operative complications, with appropriate knowledge of the superficial location of the stylomastoid foramen in infants integral. Other anatomical variations include absence of chorda tympani, lateralization of the vertical portion, duplication in the tympanic segment of the nerve and common bony defects of the fallopian canal. It is, however, important to be aware that the majority of facial nerve injuries in mastoid surgery occur in the presence of an anatomically normal facial nerve.[12] Seventy per cent of iatrogenic injury is located in the pyramidal segment (between tympanic and mastoidal segment) at the second genu.[11]

Orbicularis oculi and orbicularis oris muscles are typically routinely monitored intra-operatively via electromyographic (EMG) monitoring during mastoid procedures. The introduction of intra-operative facial nerve monitoring has facilitated early identification and localization of the facial nerve and is of prognostic value in predicting functional outcome.[13] Feedback from monitoring probably shortens the learning curve, as the surgeon adapts his technique to avoid manoeuvres that produce excessive EMG discharges; however, this does not replace anatomical knowledge and surgical ability.

If the nerve is transected, a primary reanastomosis avoiding tension is the optimum management. If necessary the nerve may be mobilized from the fallopian canal to gain 0.8 cm of length. Removing a portion of the tympanic bone and retracting the parotid gland with a suture can add another 0.9 cm. In total, 1.7 cm of additional length is possible following complete mobilization of the facial nerve for a primary anastomosis.[14] Failing this, the next best option is cable grafting using the greater auricular nerve or the sural nerve. If there is poor or absent facial function one year post-operatively other facial reanimation techniques, such as gold weight upper lid implants, temporalis muscle transfer, cross-facial anastomosis or faciohypoglossal anastomosis techniques may be required. Despite advances, reconstruction techniques are not capable of restoring facial nerve function grade I or II, using the House Brackmann (HB) grading system.[15]

VESTIBULOCOCHLEAR NERVE

Surgical ablation or resection causes a complete loss of audiovestibular function, with symptoms differing depending on pre-operative function. Patients with pre-operative good or near normal auditory and vestibular function will have severe vertigo and noticeable hearing loss. Patients usually achieve satisfactory central vestibular compensation over several weeks, but for some vestibular exercises are invaluable. In addition, customized rehabilitation regimes in the pre-operative phase may facilitate earlier vestibular compensation. Those patients with poor auditory and vestibular function, which is typical in those undergoing nerve resection in VS surgery, or vestibular nerve section for Ménière's, often have a minimal change in symptoms post-operatively.

The auditory nerve has no perineurium, and is therefore prone to damage from mechanical trauma, as well as from vascular injury within the internal auditory canal during tumour resection. Hearing conservation in VS surgery is an option in those with small acoustic tumours and good pre-operative hearing (minimum mean pure tone audiometry 30 dB/70% speech discrimination). It can be performed by a middle fossa or retro mastoid approach depending on tumour location and may preserve useful hearing in 40–79% of cases.[16] The chance of hearing preservation is inversely related to tumour size, with 90% of tumours > 3 cm involving the auditory nerve pre-operatively.[11] Most techniques of intra-operative auditory monitoring only provide delayed feedback to the surgeon and have not improved hearing conservation results in the last decade. Unilateral hearing loss may be rehabilitated by a contralateral rerouting of the signal (CROS) hearing aid or a bone-anchored hearing aid.

LOWER CRANIAL NERVES

The glossopharyngeal and vagus nerves travel closely together throughout most of their course in the skull base and any injuries often happen simultaneously. This may result in a potentially life-threatening complication due to chronic aspiration and recurrent pneumonia. Satisfactory functional recovery often takes place with peripheral lower CN dysfunction, so a temporary tracheostomy and gastrostomy are frequently advisable. However, brainstem dysfunction, especially involving the lower CN nuclei, often results in long-term bulbar problems necessitating laryngeal airway protection. A gastrostomy and tracheostomy will not prevent contamination of the lower respiratory tract. Epiglottopexy and epiglottic plication techniques offer an alternative management option.[17, 18]

Cardiac dysrhythmia

Vagal stimulation can cause a sinus bradycardia and hypotension. Brainstem stimulation may cause tachycardia and hypertension. Fortunately, any adverse cardiac event is invariably transient, although it is usually advisable for the surgeon to switch attention to work on another part of the tumour to allow consolidation of the recovered cardiac status in the patient.

OPHTHALMOLOGICAL COMPLICATIONS

Due to the inherent close relationship of the eyes, as well as their neurovascular supply, to skull base surgery, there are clear risks to vision. Neurovascular injury is especially important in elderly patients with fragile periobital capillaries. In certain scenarios, surgical necessity can lead to visual symptoms, with orbital floor removal producing vertical dystonia, excision of the medical canthal area causing canthal drift, as well as diplopia if two or more extraocular muscles are removed. Rehabilitation for these defects is difficult, with some surgeons opting occasionally for exenteriation of the orbit subsequently or reconstruction following radiation therapy. If reconstruction is sought, the temporalis muscle is most commonly used.[11, 19]

Nasolacrimal duct blockage and the ensuing epiphora can usually be treated effectively with dacrocystorhinostomy. Ectropion and entropions can result from open surgery, with appropriate reconstructive methods extensively used for both cosmesis and corneal surface disorders. Corneal abrasion is the most common cause of post-operative blindness secondary to surgical drape position, foreign body injury or reduced tear production from intra-operative anticholinergic agents.

LATERAL SKULL BASE APPROACH COMPLICATIONS

Lateral skull base approaches require intimate anatomical knowledge, in conjunction with precise surgical exposure of the lesion. To obtain this, an approach through the middle and inner ear may be required, resulting in careful dissection of structures.

Hearing loss can be due to drill-generated acoustic trauma, caused either by direct contact of the burr with the ossicles or endosteal membrane of the cochlea. Avoiding contacting the ossicles and systemic and local application of corticosteroids are the mainstay of protecting the inner ear against trauma.[11] If the inner ear is advertently opened, recognition, repair and avoiding suction of perilymph/endolymph can preserve underlying function.

Whilst the ideal approach to CPA lesions is still debated and will be discussed in Chapter 105, Non-vestibular schwannoma tumours of the cerebellopontine angle, the differing approaches confer different potential complications. Ten to fifteen per cent of CPA surgery procedures are complicated by a post-operative CSF leakage, with the largest risk found in the translabyrinthine approach.[20] Tumour excision through the translabyrinthine approach can either be attempted to be total, with a 57% HB I–II facial nerve preservation rate, or surgeons can perform a functional resection, accepting they are leaving a thin rim of tumour on the nerve, achieving a 77% HB I–II facial nerve outcome.[21] In relation to the retrosigmoid approach, the CSF leak and facial nerve palsy rates are lower (approximately 9% and 6% respectively); however, there is a requirement of cerebellum retraction, which is related to its own complications, and furthermore there is compromised access to the internal auditory canal fundus due to the nature of this technique.[22, 23] Further, the retrosigmoid approach, when compared to

the translabyrinthine approach, is typically used for smaller tumours, which is an independent risk factor for facial nerve outcomes. In comparison the middle fossa approach has greater risks of facial nerve damage (16%), as the anatomical course of the facial nerve may compromise tumour exposure; however, it has higher hearing preservation rates.[23, 24] As a result, although the retrosigmoid approach would seem to provide the most versatile corridor for facial nerve preservation, the middle cranial fossa approach seems safest for hearing preservation for smaller tumours. The translabyrinthine approach would be reserved for larger tumours. Detailed knowledge of potential pitfalls of surgical technique is vital when assessing skull base lesion management, based on position and outcomes desired.

ANTERIOR SKULL BASE ENDOSCOPIC SURGERY RISKS

Within endoscopic surgery, unfavourable results are typically related to learning curve and time taken to adapt to a two-dimensional (2D) environment. With vision of vital importance in surgery, the 2D nature of surgery creates drawbacks, specifically with regard to a lack of stereopsis impairing depth perception. This may impair the surgeon's ability to recognize and manage anatomical structures. With the safety of skull base procedures largely dependent on precise anatomical knowledge, this remains a key concern. Experienced surgeons compensate for this difficulty through the use of visual and tactile feedback, dynamic movements of the scope, light and shadows and detailed anatomical knowledge. Image guidance is another recent advance, with recent studies highlighting a higher number of cases of incomplete resection when image guidance is unavailable.[19, 25, 26]

A further concern with endoscopic surgery is in relation to temperature during surgery. Bone drilling and cauterization within a narrow field delivers significant levels of thermal energy, which can continue despite suctioning and flushing. Incessant increase of the temperature in the intra-operative field can potentially harm neural structures, with temperatures over 42 degrees causing cerebral harm. Regular breaks are important during these procedures.

POST-OPERATIVE COMPLICATIONS

Haematoma

This potentially fatal complication is usually due to inadequate haemostasis. With intradural haematomas, the source of bleeding is invariably vessels adjacent to the tumour. Careful bipolar diathermy effectively controls most bleeding but cannot be used immediately adjacent to important CNs as dysfunction inevitably follows. Surgicel may be helpful in many situations, but many surgeons are reluctant to allow this material to come into direct contact with CNs as increased post-operative neural oedema is possible. On occasions, application of a biological glue such as Tisseal® provides very satisfactory haemostasis in these circumstances. Very occasionally, one will encounter a patient with a previously unknown bleeding diathesis. If the administration of drugs and appropriate blood coagulation products fail, a combination of Surgicel with FloSeal® is effective.

Extradural haematomas may result from failed middle meningeal artery cautery or ligation and more superficially from branches of the superficial temporal artery. They may also arise from haemorrhage at the craniotomy site and require the judicious application of bone wax.

The rate at which neurological deficits develop varies with the location and source of bleeding. Arterial haemorrhage produces a rapid collection of blood. In contrast, venous haemorrhage results in a gradual neurological deterioration, often due to subdural haematoma formation, and may result in secondary hydrocephalus. Depending on the severity and rapidity of the patient's neurological deterioration, management varies from immediate decompression by wound opening at the bedside to surgical exploration in the theatre or computed tomography (CT) imaging. Most haematomas are rapid and precious time should not therefore be wasted on imaging studies.

Cerebrospinal fluid leak

This is the most common complication after VS surgery. CSF leak rates of approximately 10% are reported in the immediate post-operative period. However, late leaks may develop many months or years after surgery and up to 35% of leaks develop 2 weeks after VS surgery.[27] It is likely that neither the surgical approach nor the tumour size affect the post-operative CSF leakage rate and transient post-operative rises in CSF pressure may be responsible.[11, 24, 25, 27] CSF leaks are also the most common anterior skull base complication with reported rates of occurrence between 3% and 19%.[28]

To prevent the development of CSF leaks a peri-operative lumbar drain to lower CSF pressure may be left in place for up to 5 days, during which time the patient is kept on strict bed rest, with the head of the bed elevated at 15–30 degrees. Unfortunately, patients often experience low-pressure headaches.[29] There is no evidence regarding the effectiveness of prophylactic lumbar drainage, but for established leaks it eliminates 50–90%.[29, 30] Known complications of continuous lumbar drainage include brainstem herniation (may present with vagal nerve paresis and vocal cord paresis), Chiari type 1 malformation, infection, pneumocephalus and subdural haematoma.[27, 28] A compression dressing is maintained over the wound to promote watertight healing.

Symptoms of CSF leak include pain or headache (especially positional), unexplained pyrexia and, more seriously, meningitis. Rhinorrhoea may present as a salty taste in the patient's mouth. High-flow CSF leaks lead to clear rhinorrhoea and, less frequently, otorrhoea or wound discharge. A sample should be sent for immunoelectrophoretic assay for beta transferrin, which is both highly specific and sensitive for CSF.

High-flow CSF leaks require surgical exploration and repair. Low-flow CSF leaks may be managed with bed rest and elevation of the head by 20–50 degrees. In addition, a lumbar spinal drain may be used for up to 5 days. Wound

leaks are managed by the insertion of further sutures and the application of a compressive head bandage. Acetazolamide is known to lower CSF pressure by inhibiting the enzyme carbonic anhydrase and by decreasing CSF production. Some units use this therapy but there is no evidence for its efficacy in the treatment of CSF leaks.[31] The use of prophylactic antibiotics remains uncertain. There is some evidence favouring the role of prolonged prophylactic antibiotics in patients with ventricular drains but no studies exist for lumbar drains.[32] Two large meta-analyses have produced conflicting conclusions over the role of antibiotic prophylaxis in the prevention of meningitis in patients with basilar skull fractures and CSF fistulae.[33, 34] The larger meta-analysis found no reduction in meningitis.[35] It is known that prolonged antibiotic use encourages the development of resistant organisms and prophylactic antibiotics in patients with CSF fistulae are probably best avoided, due to poor penetration of the meninges.[34, 36]

Infection

The incidence of wound infections is usually low. Recognized risk factors include tumour size, operative time and haematoma. Anterior skull base procedures performed in a cleaned but previously contaminated environment, where the wound is in close contact with the aerodigestive tract, have a rate of infectious complications of between 0% and 30%.[28, 37] Frontal bone flap osteomyelitis may complicate craniofacial resection for anterior skull base tumours in certain cases.[38] Wound infection may lead to meningitis or a brain abscess. Meningitis is usually associated with a CSF fistula.

The risk of infection is minimized by the liberal use of peroperative irrigation and prophylactic antibiotics (for clean non-implant procedures and for clean contaminated procedures). Prophylactic antibiotics should be given on induction of anaesthesia to ensure high tissue levels at the time of surgery. Antibiotics given more than 4 hours after the end of surgery are not effective, either experimentally or in clinical trials.[39] The Infection in Neurosurgery Working Party of the British Society for Antimicrobial Chemotherapy recommends that surgery for clean and clean-contaminated surgery should be administered as a single intravenous dose on induction of anaesthesia, with additional doses every 3 hours for long procedures.[39] In support of these recommendations, a systematic review in the Cochrane database of prospective randomized controlled trials of patients undergoing major pulmonary, gynaecological, obstetric, urological, pelvic or abdominal surgery, who had been given either single or multiple dose prophylaxis, found no difference in surgical site infection rates.[40] This confirms the findings from an earlier review of similar patient groups.[41] In addition, prolonged antibiotic prophylaxis increases the risk of hospital acquired infection.[40]

Pneumocephalus

Intracranial air is often present after craniotomy and may be seen on CT, but usually resorbs after 7–10 days. The presence of pneumocephalus is pathognomonic for the presence of a CSF leak, with risks of meningitis as high as 30%.[42] It is rarely seen after posterior fossa surgery and is usually associated with surgery at sites that include the aerodigestive tract, as in anterior skull base procedures. Clinically significant pneumocephalus presents in 2–12% of post-operative craniofacial patients.[28] Air accumulating under pressure may create a tension pneumocephalus, which if unrecognized is a potentially fatal condition. The use of positive pressure ventilation and a lumbar catheter drain are risk factors. The lumbar drain creates a vacuum effect by lowering intracranial pressure and drawing air in through the wound. Treatment with needle aspiration via a craniotomy burr hole may be adequate. Surgical exploration to decompress the brain and seal air leaks may sometimes be necessary. About one-third are associated with CSF leaks and a thorough search for a fistula is, therefore, also advisable.

Hydrocephalus

This presents in the early post-operative period with headache, impaired consciousness, gait disturbance and incontinence. It is secondary to cerebral oedema or intracranial haemorrhage. Normal pressure hydrocephalus is due to chronic obstruction of arachnoid villi function. It has been reported following jugular bulb resection in association with unrecognized contralateral cerebral venous drainage insufficiency. The presence of post-operative hydrocephalus is approximately 6% within anterior skull base tumour resection.[43]

Epilepsy

Post-operative seizures may herald the development of haematoma, oedema, infarction or any complication causing mass effect and cerebral irritation. Temporal lobe manipulation carries a special risk of the development of this complication, which is not encountered with posterior fossa surgery. Manipulation or resection of brain parenchyma can result in an irritable epileptic focus. For high-risk procedures, consideration should be given to the use of carbamazepine, phenobarbitone or phenytoin for antiseizure prophylaxis. For post-operative seizures these drugs and diazepam are indicated. One medication is initiated at a time and the dosage increased until the seizure is controlled or the maximum serum level of the drug is reached. Another drug may then be added if necessary.

Headaches

There is a higher incidence of headache with the retrosigmoid approach for VS surgery, which may be debilitating and intractable.[22, 23] This is a feature of VS surgery, with headache not as common using this approach in other posterior fossa tumours. It has been suggested that adherence of the dura to nuchal soft tissue, neck muscle spasm and aseptic meningitis from bone dust or fibrin glue is responsible.[44, 45] It is more common following VS surgery for small tumours, although this may reflect individual psychological

factors, causing patients of a 'sensitive disposition' with mild tumour symptoms to present early and also to be more likely to report local discomfort post-operatively. Intradural drilling of the internal auditory meatus deposits bone dust into the posterior fossa, and alternatively, it is postulated that larger VSs prevent wide distribution of bony debris. The use of cranioplasty techniques with bone or titanium mesh and acrylic reduces the incidence.[44, 45]

BEST CLINICAL PRACTICE

- ✓ **General practice:**
  - performing procedures in a multidisciplinary team, utilizing the strengths of each member
  - regular frequency of surgeries; minimum once every 2 weeks.
- ✓ **Pre-operative management:**
  - otological and audiological examination – pure-tone and speech audiometry
  - vestibular examination – 1/3 of patients with profound sensorineural hearing loss report subjective hearing loss, while twice as many show pathological vestibular signs in caloric testing and/or vestibular evoked myogenic potentials
  - imaging – temporal bone imaging revealed high riding bulb in 32% (which can lead to the presence of bony defects of the hypotympanon), anterior sigmoid sinus in 34%, a low riding dura in 26% and an aberrant carotid artery in 0.02%.
- ✓ **Vascular:**
  - discontinue aspirin and clopidogrel 7–10 days prior to surgery
  - warfarin discontinued 5 days pre-operatively, which is adequate time to reconstitute the coagulation factors. If at risk of thromboembolic event, use low molecular weight heparin 2 days after stopping warfarin or 3 days prior to operation, stopping 24 hours before surgery
  - pre-operative corticosteroid administration – to reduce inflammatory mediators which cause vasodilation, transduction and oedema
  - patient positioning should be reverse Trendelenberg, as head elevation reduces mean arterial pressure in the elevated area. Patient must be tilted in and out of position slowly to avoid sudden shift in blood
  - ventilation technique maintaining normocapnia or mild hypocapnia to minimize bleeding, with some centres using high-frequency jet ventilation
  - highly vascular tumours may require pre-operative embolization and ligation of feeding vessels. Should be performed 24 to 72 hours pre-operatively to provide adequate thrombosis and prior to re-formation of collateral blood supply
  - bleeding is controlled using bone wax, bipolar diathermy, placement of haemostaic agents such as oxidized cellulose (Surgicel), microfibrillary collagen (Avitene) or a biological glue and repair using 6-0 or 7-0 monofilament suture
  - occasionally, large venous sinus perforations require extraluminal or intraluminal packing or even ligation to achieve haemostasis
  - decrease bleeding with controlled hypotensive anaesthesia.
- ✓ **Air embolus:**
  - the first sign of this complication is a sucking sound or venous crepitation at the site of entry
  - later hypotension, tachycardia, dysrhythmias and diminishing end-expiratory pCO_2 develop.
- ✓ **Cranial nerve injury:**
  - microdissection techniques and electrophysiological nerve monitoring enhance the preservation of CN during tumour resection
  - if the facial nerve is cut, primary reanastomosis avoiding tension is best. Failing this, cable grafting using the greater auricular nerve or the sural nerve is the next best option, followed by facial-hypoglossal anastomosis.
- ✓ **Cardiac dysrhythmia:**
  - vagal nerve stimulation can cause a sinus bradycardia and hypotension
  - brainstem stimulation may cause tachycardia and hypertension.
- ✓ **Temperature:**
  - regular flushing of endoscope
  - site of bone drilling to be short and varied to avoid high temperature.
- ✓ **Haematomas:**
  - arterial haemorrhage produces a rapid collection of blood in the extradural space
  - venous haemorrhage results in a gradual neurological deterioration, owing to subdural haematoma formation
  - depending on the severity and rapidity of the patient's neurological deterioration, management varies from bedside wound opening to surgical exploration in the theatre or CT imaging.
- ✓ **Cerebrospinal fluid leak:**
  - immunoelectrophoretic assay for beta transferrin is both highly specific and sensitive for CSF
  - CSF lumbar drainage is effective in eliminating 50–90% of cases of CSF leaks after skull base surgery.
- ✓ **Infections:**
  - there is a good evidence base to recommend a single intravenous dose antibiotic prophylaxis, given at induction of anaesthesia for skull base procedures
  - meningitis is usually associated with a CSF fistula.
- ✓ **Pneumocephalus:**
  - air accumulating under pressure to create an acute elevation of intracranial pressure is potentially fatal.
- ✓ **Hydrocephalus:**
  - this presents in the early post-operative period with headache, impaired consciousness, gait disturbance and incontinence.
- ✓ **Epilepsy:**
  - post-operative seizures may herald the development of haematoma, oedema, infarction or any complication causing mass effect and cerebral irritation
  - temporal lobe manipulation carries a special risk.
- ✓ **Headaches:**
  - there is a higher incidence of headache with the retrosigmoid approach for VS surgery, which may be debilitating and intractable.

FUTURE RESEARCH

Despite the wealth of data on the pathophysiology of disease and our theoretical foundations for treatment, randomized trials have produced somewhat surprising results in the past. Prospective randomized controlled trials, which may need to be multicentred, are required to improve the evidence-base on the following issues:

- the efficacy of neuronavigation technology in reducing complications
- evaluation of newer tumour ablation techniques
- the value of pre-operative embolization of highly vascular tumours, addressing selection criteria, different materials and the timing in relation to surgery
- the efficacy of CSF lumbar drainage for prophylactic prevention of post-operative CSF leaks (How long should the drain remain *in situ*? Should it drain at a certain rate or would a lowered stable CSF pressure setting be more efficacious?)
- the role of antibiotic prophylaxis in clean contaminated skull base procedures, with lumbar drains and in patients with a post-operative CSF leak
- use of novel monitoring techniques, such as four contact adherent systems for glossopharyngeal and vagus nerve monitoring during surgery. Utilize compound muscle action potentials from posterior pharyngeal wall.

KEY POINTS

- The sound of crepitation at the site of a large perforation of a venous sinus and later cardiorespiratory distress should alert the surgeon to the possibility of an air embolus.
- Manipulation of the vagus nerve or brainstem may result in cardiac dysrhythmia and surgery should be halted until sinus rhythm returns.
- Cranial nerve injuries are among the most debilitating complications encountered in skull base surgery.
- Microdissection techniques and electrophysiological nerve monitoring enhance the preservation of CN during tumour resection.
- CSF leaks are among the most common post-operative skull base surgery complications.
- There is a good evidence base to recommend a single intravenous dose antibiotic prophylaxis, given at induction of anaesthesia for skull base procedures.
- Post-operative seizures may herald the development of haematoma, oedema, infarction or any complication causing mass effect and cerebral irritation.
- Most post-operative intracranial haematomas are rapid and require prompt surgical exploration, avoiding the delay of imaging studies.
- There is a higher incidence of headache with the retrosigmoid approach for VS surgery, which may be debilitating and intractable.

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