Chapter 59 – Treatment of Gustatory Sweating (Frey's Syndrome) with Botulinum Toxin A

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Gustatory sweating, also known as Frey's syndrome, Baillarger's syndrome, auriculotemporal syndrome, or gustatory hyperhidrosis, is a consequence of parotid gland surgery, infection, or trauma. The condition is characterized by sweating and flushing of the facial skin overlying the parotid bed during mastication and may be accompanied by general discomfort in the region. Once gustatory sweating and flushing are established, there is no spontaneous resolution, even many years later. The area involved is usually in the parotid region or upper part of the neck, but it may also be seen behind the ear lobe, in the hair-bearing area in front or behind the pinna (Fig. 59-1), or even inside the external auditory canal.

Even though “Frey's syndrome” is a well-established eponym, the first case of gustatory syndrome was actually reported in a French study by Baillarger in 1853.[1] Later, in 1897, Weber was the first to describe Frey's syndrome in the English literature, which was also noted to be the first case of bilateral Frey's syndrome.[2] Finally, in 1923, Lucie Frey, a neurologist at the University of Warsaw, described a 25-year-old soldier in whom facial sweating and flushing during meals developed after a gunshot wound to the parotid region.[3] Although Lucie Frey did not describe the first case of gustatory facial sweating and flushing, she correctly identified the relevant autonomic innervation of the parotid gland and facial skin, thereby implicating the auriculotemporal nerve in its pathogenesis.

Mechanistically, Frey's syndrome is caused by misdirected regeneration of the severed postganglionic parasympathetic secretomotor fibers of the parotid gland to the severed postganglionic sympathetic fibers of the sweat glands of the overlying facial skin. The action of both these nerves is mediated by acetylcholine. Clinically, this results in facial sweating and flushing during mastication. Although many patients who have undergone parotidectomy do not report any symptoms when asked about gustatory sweating, Frey's syndrome has been reported in 50% of patients with symptomatic hyperhidrosis.[4]

Initial management of gustatory hyperhidrosis should consist of the use of topical anticholinergics (scopolamine, glycopyrrolate, diphemanil methylsulfate) or aluminum chloride. In advanced cases, surgical management of symptomatic Frey's syndrome includes elevation of a skin flap with the interposition of vascularized tissue, free fat, or AlloDerm. In addition, division of preganglionic parasympathetic nerves has been reported. However, this is associated with only temporary relief and symptoms recur 6 to 12 months later.

In 1995, Drobik and Laskawi first described the intracutaneous injection of botulinum toxin type A (Botox) as an effective therapeutic option for treating gustatory sweating.[5] Injection of Botox leads to temporary chemodenervation with loss or a reduction of the activity of the target organ. At the level of the presynaptic nerve fibers, the biotoxicity of Botox results from proteolysis of SNARE (soluble *N*-ethylmaleimide–sensitive factor attachment protein receptor) proteins, which are required to mediate vesicle membrane fusion and subsequent release of acetylcholine for transmission of nerve impulses. Recently, intracutaneous Botox injection has emerged as the first-line treatment of Frey's syndrome because of its long-lasting effects in patients with symptomatic gustatory sweating, coupled with its relatively low complication rates.

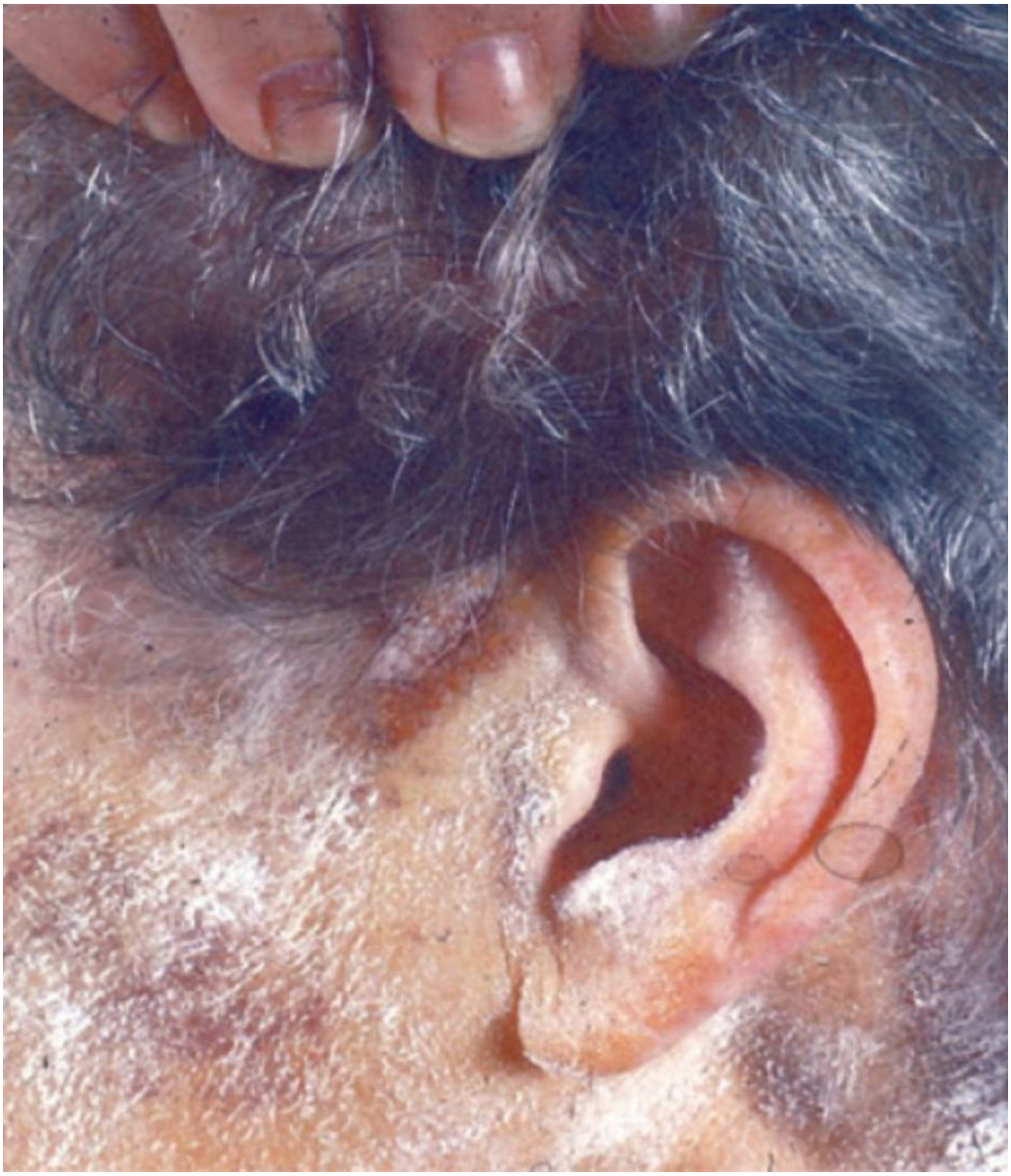

Figure 59-1 The area typically involved in gustatory sweating is usually overlying the parotid region; however, it may also be seen behind the ear lobe and in the hair-bearing area in front or behind the pinna.

PATIENT SELECTION

Patients with Frey's syndrome are often identified after surgical resection of the parotid gland or after incision and drainage of a parotid abscess. However, it has also been reported several weeks to months after various injuries to the parotid gland, including blunt trauma, bullet wounds, condyle fractures, infections (e.g., herpes zoster), and inflammatory parotid disorders; in association with central nervous system diseases such as syringomyelia, encephalitis, and epilepsy; and in surgical treatment of meningioma of the cerebellopontine angle.[6] In addition, gustatory sweating has developed as a result of iatrogenic causes, such as a rare case after reconstruction with a deltopectoral flap (Fig. 59-2). Because of the location, one might suspect that the cause is related to severing of postganglionic parasympathetic fibers from the submandibular gland. Moreover, idiopathic causes with no history of antecedent injury have been reported.[7]

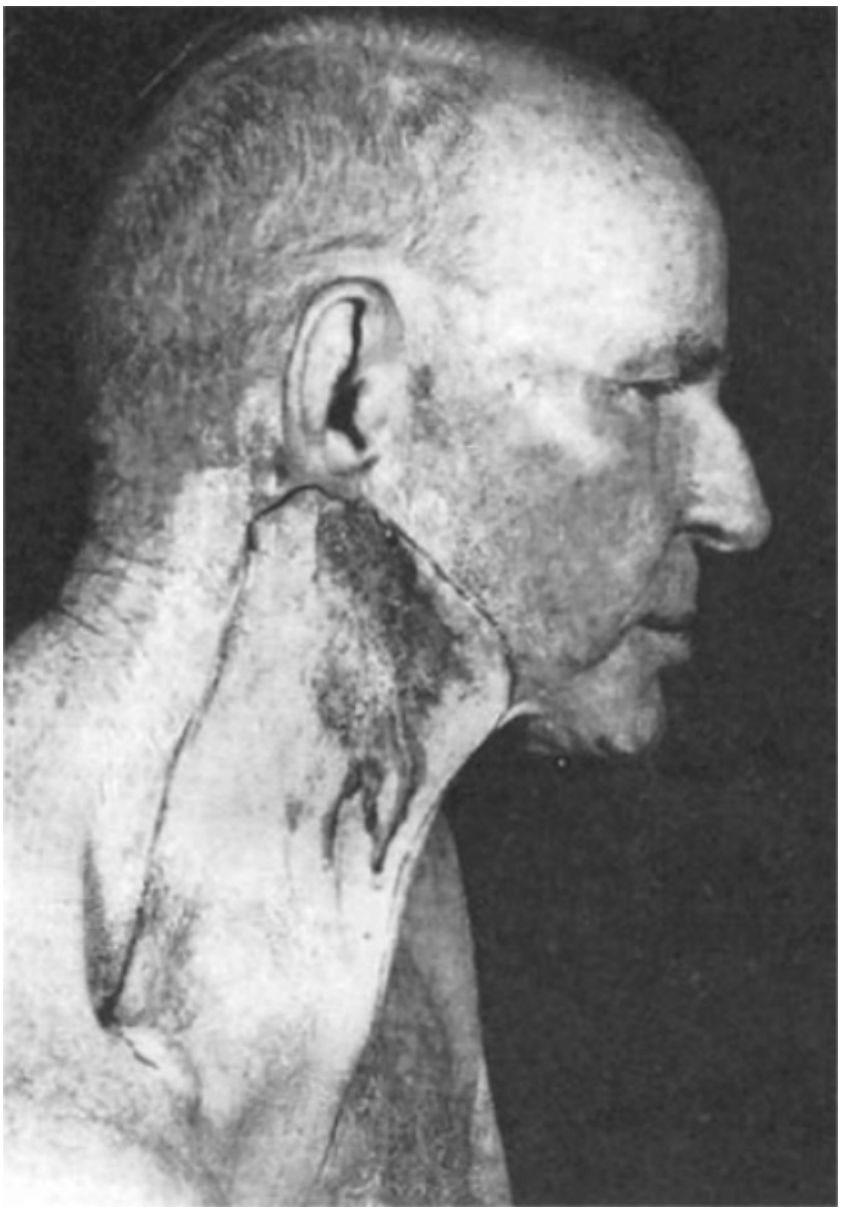

Figure 59-2 Gustatory sweating that developed in the region of a patient's distal deltopectoral flap.

Patients with symptomatic gustatory sweating after parotidectomy are closely monitored for 6 months and are initially managed with the application of topical anticholinergic products on the affected sites (nonscented deodorants, Etiaxil). For mild cases, this is often successful and further intervention is not necessary. If conservative measures fail, the patient should be evaluated with a qualitative hyperhidrosis severity questionnaire. Many validated assessment tools for primary hyperhidrosis have been reported in the literature, including the Hyperhidrosis Impact Questionnaire (HHIQ), the Dermatology Life Quality Index (DLQI), and the Illness Intrusiveness Rating Scale (IIRS).[8–10] The most current and the simplest assessment tool is the Hyperhidrosis Disease Severity Scale (HDSS), which is a reliable single-question, 4-point scale for assessing the severity of hyperhidrosis in which patients rate their tolerability of hyperhidrosis symptoms and the extent to which it interferes with daily activities (Table 59-1).[11,12] In patients with a score greater than 2 (hyperhidrosis is barely tolerable or intolerable and frequently or always interferes with daily activities), Botox treatment is recommended, with the goal being a decrease in the patient's hyperhidrosis symptoms to a more tolerable level of 1 or 2 on this scale. Because the HDSS consists of only one question, it can be completed rapidly and offers a practical, validated tool for determining the efficacy of treatment.

Table 59-1 -- HYPERHIDROSIS DISEASE SEVERITY SCALE

Question: How Would You Rate the Severity of Your Hyperhidrosis?	Score
My sweating is never noticeable and never interferes with my daily activities	1
My sweating is tolerable but sometimes interferes with my daily activities	2
My sweating is barely tolerable and frequently interferes with my daily activities	3

Question: How Would You Rate the Severity of Your Hyperhidrosis?	Score
My sweating is intolerable and always interferes with my daily activities	4

PREOPERATIVE EVALUATION

The area of excessive sweating can vary considerably from patient to patient. The sweat glands are distributed over the entire surface of the head and neck, except at the margins of the lips. They are most numerous in hair-bearing skin. Because of this interpatient variability, mapping the area of excessive sweating is a very important first step in the chemodenervation procedure with Botox. An objective method of mapping the hyperhidrotic area is to perform Minor's iodine-starch test, which makes direct visualization of the area possible.[13] Specifically, the symptomatic side of the face and neck is first cleaned and dried thoroughly. The area is then painted with a 2% iodine solution (2 g of iodine in 10 mL of almond or castor oil and 90 mL of alcohol). An alternative is to use povidone-iodine with alcohol (e.g., Betadine) swabs. After the solution has dried, fine starch powder (e.g., potato or rice starch) is dusted evenly over the painted site. After several minutes the patient chews on a sialagogue (e.g., lemon wedge or lemon candy) for several minutes. The appearance of dark blue-purple spots along the face confirms gustatory sweating. This discoloration is the result of reduction of the dissolved starch with iodine, which makes the location of the sweating readily discernible. The borders of the darkened, hyperhidrotic area are then outlined with a surgical pen, photographs are taken with a 10-cm ruler, and the area is reprepared with antimicrobial solution for subsequent Botox injection. Finally, the patient should be counseled regarding the risk for temporary facial weakness and should be carefully evaluated for any facial nerve weakness and synkinesis before the injection.

INJECTION TECHNIQUES

Botox injections delivered at the level of the superficial dermis diffuse radially in an approximately 5-mm radius. Therefore, intradermal botulinum toxin should be placed at regular intervals to allow overlap of the diffusion patterns. This serves to maximize the paralytic effect on the eccrine units while minimizing the local supratherapeutic dosage of Botox. After morphometric evaluation by Minor's starch test, the affected skin area is marked with a surgical pen in an evenly spaced square-grid pattern (to ensure adequate delivery, we prefer a grid with points 0.5 cm apart) (Fig. 59-3). Lyophilized botulinum toxin type A (Botox, 100 units per vial) is reconstituted with 1 mL of preservative-free, sterile saline to a final concentration of 10 U/0.1 mL (preservative may destroy the toxin). Overdilution of the product should be avoided. The total injection volume (1 mL) is then drawn into a 1-mL syringe. To minimize patient discomfort, a 30-gauge needle should be used to deliver the toxin. Intracutaneous injections are performed with 5 to 10 units of Botox injected in the center of each 0.5-cm^2 grid. Botox has the potential (determined by volume) to diffuse from the point of injection.[14] The injection should be performed slowly and carefully into the intradermal plane. A visible wheal should be present, which confirms placement of the toxin in the proper plane of the skin and decreases the likelihood of unwanted weakness of the facial muscles. Gentle pressure should then be applied to facilitate hemostasis and even distribution of the toxin. Because of the large quantities injected and the proximity of the underlying facial muscles, undesired outcomes can also occur, particularly if the injections are too deep. This mild weakness is temporary and resolves after a few weeks. After all of the grids have been injected, the skin is cleaned, the markings are removed with alcohol, and the patient is observed for potential side effects for approximately 30 minutes.

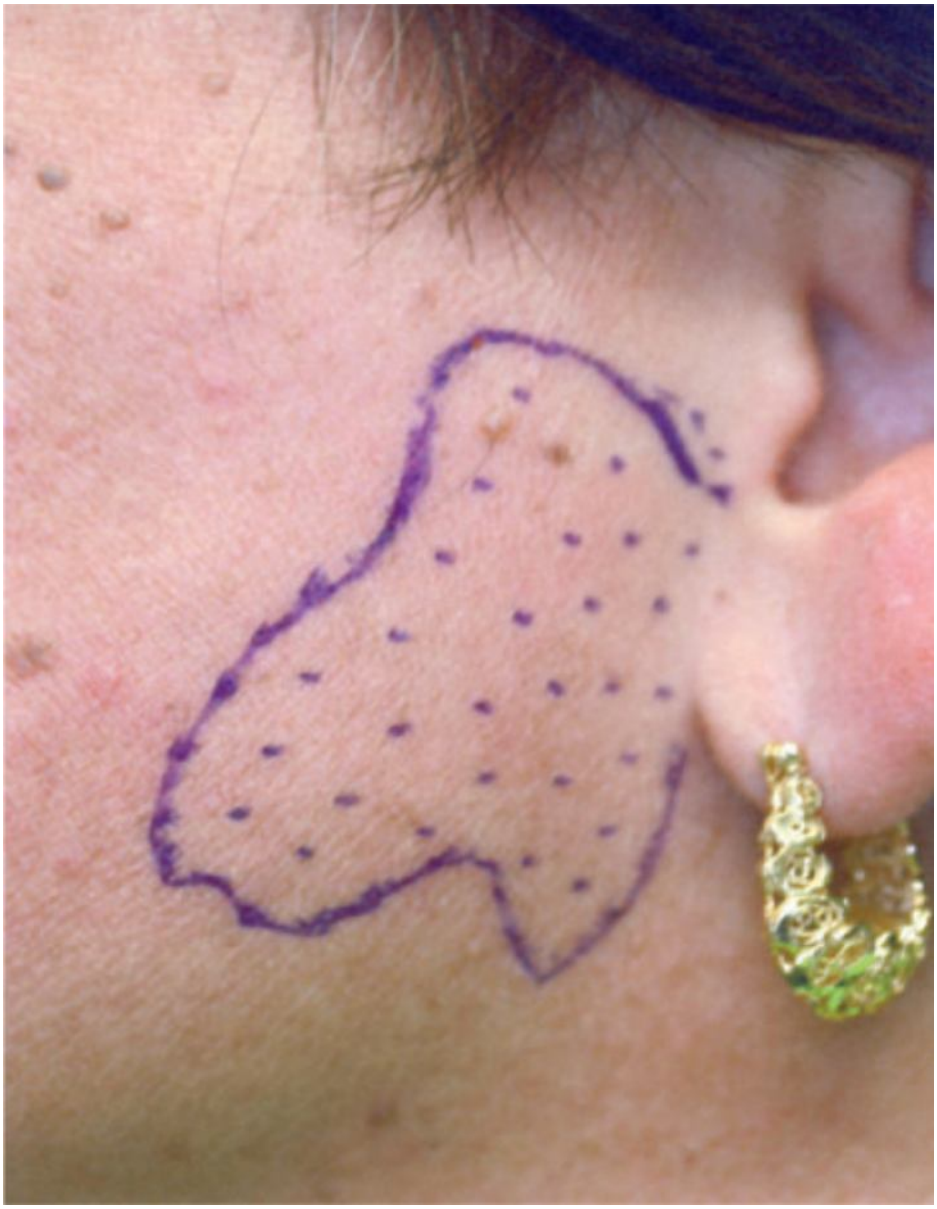

Figure 59-3 The area affected by gustatory sweating is marked with a surgical pen and a grid is drawn with points 0.5 cm apart to delineate the multiple Botox injection sites.

POSTOPERATIVE MANAGEMENT

After the procedure, the patient is advised that the therapeutic effects of the Botox treatment will not be evident for 36 to 48 hours. The patient should be seen 1 to 2 weeks after treatment to assess therapeutic efficacy. In some instances patients may show incomplete results, which generally indicates that some of the sites were injected in the wrong plane of the skin. If such is the case, the problematic area should be remapped with Minor's iodine-starch test to visualize the hyperhidrotic area, and the patient should be treated again.

PEARLS

- Because adverse effects of Botox are frequently the result of diffusion of toxin from the target tissue to adjacent tissues, many smaller-volume injections are recommended over fewer, larger-volume injections.
- The duration of treatment effects in patient's with Frey's syndrome (mean duration, 17.3 months) is much longer than in patients treated for other indications, such as hemifacial spasm, blepharospasm, or even hyperhidrosis in other locations.[15]
- Although the optimal dose has not been established (in diverse studies doses from 0.5 to 5 U/cm^2 have been used), we typically administer a total dose of 50 to 100 units.
- Botulinum toxin type A is quite stable in its lyophilized form, but once it is reconstituted in preservative-free saline, it should be refrigerated at 2° C to 8° C and used within 4 hours.[16]

- In refractory cases when patients respond poorly to treatment with Botox, injections of type B botulinum toxin (Myobloc) can be considered because it is antigenically distinct from type A and has a different mechanism of action on the release of acetylcholine.[17]
- Studies report no difference in the severity of gustatory hyperhidrosis in patients who were subjected to superficial or total parotidectomy.[18]

PITFALLS

- Overzealous injection with Botox, especially with large injection volumes, has the potential to cause numbness and temporary facial weakness on the injected side.
- The application of EMLA cream (lidocaine-prilocaine hydrochloride) 45 minutes before injection can prevent pain at the time of injection.
- Hyperhidrosis control rates after the initial Botox injection are high, and it is rare for patients to have recidivism after the first successful treatment. Treatment failure after the initial injection may indicate that the toxin was placed too deep (i.e., not producing a visible wheal) or that the injection did not adequately cover the entire target area and would therefore warrant a second procedure.
- Violent agitation or freezing of rehydrated botulinum toxin type A will denature the toxin in solution, thereby significantly decreasing its potency.
- The therapeutic dosage of type B botulinum toxin (Myobloc) is 50 to 100 times higher than that of the conventional type A Botox, so injection of Myobloc at Botox dosages can result in lack of efficacy or incomplete benefit.