Chapter 5

Treatment of Frey's Syndrome

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Pavel Dulguerov

Contents

Core features

- Understand the anatomy of the autonomic innervation of the parotid gland and facial skin.
- Frey's syndrome is secondary to the sympathetic denervation of sweat glands – the reinnervation through the auriculotemporal nerve is a secondary event.
- The aberrant regeneration theory explains the physiopathology of Frey's syndrome; other described variants do not represent true Frey's syndrome cases.
- A topographic and quantitative testing for Frey's is required prior to its treatment – the ISPH test described has the majority of desired features.
- Frey's syndrome incidence after parotidectomy, without prevention techniques, is 40–80% by clinical questioning and 80–100% by objective testing.
- Intradermic botulinum toxin injection is a well-tolerated and efficient treatment. The recommended dilution is 50 IU/1 ml, inter-injection distance is 1 cm, and injection volume is 0.1 ml.

Complications to Avoid

- Facial muscle paralysis (rare and reversible complication): inject only intradermally and avoid injecting toward the midline
- Pain during injection: if bothersome could be decreased by the prior application of topical anesthetic cream

Introduction

Frey's syndrome or gustatory sweating and flushing is characterized by sweating and flushing of the facial skin during meals [44]. The area involved is on the lateral aspect of the face and upper neck, usually around the parotid region. There is no direct relation with chewing [44]. Once present, the gustatory sweating and flushing remain unchanged, i.e., there is no spontaneous resolution, even after numerous years [76].

Frey's syndrome is named after Dr. Lucia Frey, a neurologist at the University of Warsaw, who published a landmark paper on the "syndrome du nerf auriculotemporal" in 1923 [44], despite the fact that similar cases were already reported in the nineteenth century [33].

Anatomy and Physiology

During eating, a reflex arc is stimulated leading to increased salivary secretion of minor and major salivary glands, including the parotid gland. The origin of the afferent limb is at the level of the gustatory papillae of the oral cavity and oropharynx. The afferent neurons terminate in the nucleus solitarius and project to the inferior salivary nucleus.

Preganglionic parasympathetic efferent fibers leave the inferior salivary nucleus and the brain stem with the glossopharyngeal nerve. After passing through the jugular foramen and the superior and inferior glossopharyngeal ganglions, the parasympathetic fibers follow the tympanic (Jacobson's) nerve. Jacobse's nerve enters the temporal bone on its inferior aspect and travels in the inferior tympanic canaliculus toward the middle ear cavity. A plexus is formed on the promontory, but the parasympathetic fibers not supplying the middle ear unite to form the lesser superficial petrosal nerve. This nerve exits the temporal bone and travels on the floor of the middle cranial fossa. The fibers then exit the skull through the foramen ovale and reach the otic ganglion where they synapse with postganglionic parasympathetic fibers. These postganglionic parasympathetic fibers then join the auriculotemporal nerve and reach the parotid gland through its medial aspect in the parapharyngeal space. Like all postganglionic parasympathetic neurons, the neurotransmitter of these fibers is acetylcholine. The muscarinic receptors of the parotid gland are of the M3 subtype [21].

The secretion of the parotid gland is controlled predominantly by the parasympathetic system. In cats, stimulation of the parasympathetic fibers produces an important increase of salivary output, while sympathetic stimulation results only in a discrete increase [111]. In human volunteers undergoing stapedectomy for otosclerosis, electric stimulation of the tympanic plexus resulted in an increase of parotid salivary output proportional to the intensity of the applied current [113].

The sympathetic fibers for the cutaneous vessels and sweat glands follow the cervical sympathetic chain and a synaptic relay is found in the sympathetic cervical ganglions. The fibers then follow the periarterial plexuses of the internal and external carotid arteries and their branches before joining and following the branches of the trigeminal nerve supplying the cutaneous sensation of the skin [89, 93]. Thus, for the preauricular skin, these sympathetic fibers also travel within the auriculotemporal nerve. While the overall organization is described in anatomic textbooks, the exact pathway is still debatable [143] and it remains unclear at what exact level of the lower face, a switch from sympathetic fibers traveling along the internal carotid artery to sympathetic fibers traveling with the external carotid artery takes place [32, 93, 143]. It is also possible that at midface there is some overlap, with double sympathetic innervation coursing along the trigeminal nerve and along the external carotid artery [32, 121].

The result of sympathetic activation is increased secretion from sweat glands [116] and vasoconstriction [93]. A vasodilatation role of the parasympathetic facial system [17] has been demonstrated [12] and found to follow the facial nerve and then the greater superficial petrosal branch [82]. Fibers probably synapse in the sphenopalatine ganglion before joining the corresponding branches of the trigeminal nerve [82], in our case the auriculotemporal nerve.

In contradistinction to other postganglionic sympathetic fibers, which are adrenergic, sweat glands have acetylcholine as the main neurotransmitter [42, 86]. The cholinergic receptors on sweat glands are muscarinic, predominantly of the M3 subtype [140] similar to that of parasympathetic salivary gland nerves.

Pathogenesis of Frey's Syndrome

André Thomas [135] and later Ford and Woodhall [41] postulated that the severed parasympathetic fibers to the parotid gland regenerate along the wrong neurilemmal sheaths of the sectioned cutaneous sympathetic fibers, the so-called aberrant regeneration theory. Several experimental and clinical observations support the aberrant regeneration theory: (1) auriculotemporal nerve block by

local anesthetics induces a local anesthesia and an abolishment of gustatory sweating of similar cutaneous distribution [41, 48]; (2) stimulation of the tympanic plexus results in sweating in the involved skin area [113]; (3) symptoms are unaffected by anesthesia of the stellate ganglion, despite the appearance of a temporary Horner syndrome [30, 41, 48]; (4) in the involved area, there is an impairment of the normal sympathetic function, such as reduced thermoregulatory sweating [29, 41, 48, 58, 89] and absence of emotional flushing [29, 41, 58, 89]; (5) a latent period (minimum 1–2 months [77]) is present between the initial injury and the appearance of gustatory flushing and sweating [48, 58, 88, 89, 145]; (6) if patients are followed sequentially with an appropriate sweat test, the positivity of the test increases and the involved area progressively increases in size [77, 88]; (7) the symptoms can be abolished by the local injection of anticholinergic substances such as atropine [41, 48], as well as botulinum toxin (see below); (8) a localized hypersensitivity to cholinergic drugs is described with mecholine [145], acetylcholine [41, 48], and pilocarpine [48, 145]; and (9) the syndrome appears after various lesions or resections of the homolateral cervical sympathetic chain [29, 58, 89, 102, 145].

The postulated etiology is an aberrant regeneration of the sectioned parasympathetic fibers normally innervating the parotid gland (Fig. 5.1). The traumatized fibers lose their parotid targets and regenerate to innervate the vessels and sweat glands of the overlying skin. In order for this aberrant regeneration to occur, the sympathetic fibers to these vessels and sweat glands have to be damaged, a frequent event in either parotid surgery or penetrating parotid trauma. The regular function of the parotid parasympathetic fibers is to increase salivary secretion during eating. The activation following aberrant regeneration produces an activation of the new targets during meals, resulting in a local vasodilatation ("gustatory flushing") and localized sweating ("gustatory sweating"). Despite all these convincing arguments, the aberrant regeneration remains a hypothesis until the demonstration of parasympathetic neurons on reinnervated sweat glands.

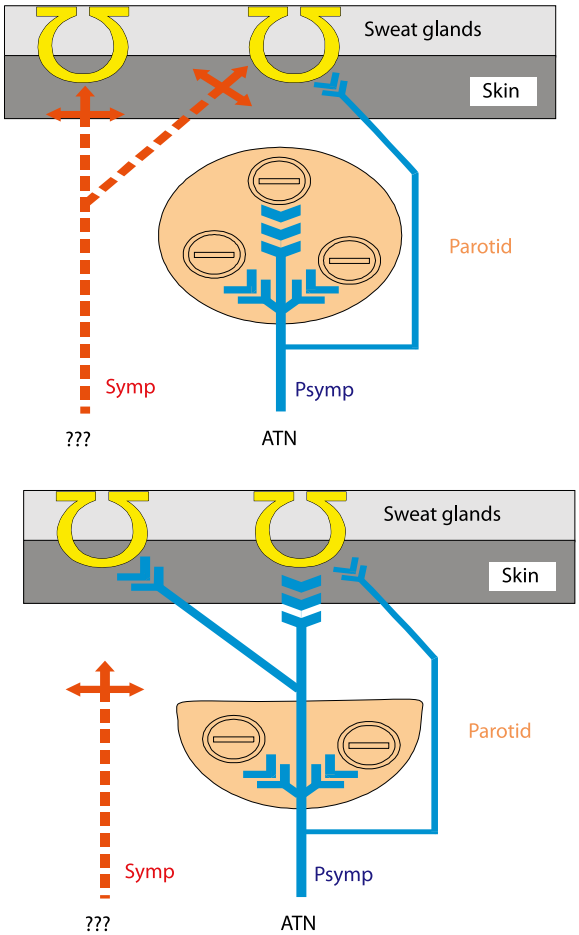

Fig. 5.1: Schematic representation of the aberrant regeneration theory. *Top* Normal situation. *Bottom* Situation after superficial parotidectomy. *Symp* Sympathetic innervation of sweat glands, *Psymp* parasympathetic innervation of the parotid and facial skin, *ATN* auriculotemporal nerve, *???* sympathetic nerve, the exact pathway of which is still unclear (auriculotemporal nerve, great auricular nerve, perivascular plexuses)

Etiology

Since Frey, emphasis has been placed on the auriculotemporal nerve [113] and the regeneration of the parasympathetic fibers it contains [41, 135] to explain gustatory sweating and flushing. Although parotidectomy is the most frequent etiology [35], the syndrome has been described with other surgical procedures in the parotid region such as mandibular surgery [54, 72, 138], drainage of parotid or other local abscesses [6, 50, 98, 103, 107, 144] and neck dissection [56, 84, 99, 133]; with regional trauma such as mandibular fractures [47, 52, 85, 148] or penetrating wounds [5, 37]; and with surgery or lesions of the cervical sympathetic chain [20, 58, 83, 89, 102, 105, 145] (Table 5.1).

Table 5.1. Etiology of Frey's syndrome

Typical Frey's syndrome etiologies:
1. Trauma in the parotid region • Parotidectomy • Other surgical procedures in the parotid region (mandibular surgery, drainage of parotid abscess, neck dissection) • Penetrating trauma parotid region • Closed mandibular fractures
2. Trauma to the cervical sympathetic chain
3. Other aberrant regeneration locations • Cerebellopontine angle • Middle ear • Otic ganglion
4. Autonomic neuropathies • Diabetic neuropathy
Atypical variants of gustatory sweating:
1. Physiologic
2. Pediatric gustatory flushing
3. Gustatory neuralgia

The development of gustatory sweating after cervical sympathectomy can only be explained if one is to admit that the primary event of gustatory sweating is a degeneration of the cervical sympathetic neurons. The initial event is the loss of postganglionic sympathetic neurons and the resulting denervation of the corresponding facial sweat glands. Regeneration of parasympathetic fibers, within the degenerating sympathetic neurilemmal sheets, is a secondary event although it accounts for the observed symptoms. If sympathetic degeneration is the primary event then Frey's syndrome could occur in any location where close contact between parasympathetic sialogogue fibers and sympathetic sudomotor efferents is present. This perspective allows the explanation of the location of Frey's syndrome outside the auriculotemporal nerve territory [84], the presence of gustatory sweating away from the flap elevation area [84], as well as such etiologies as cervical sympathectomy, diabetic and possibly other autonomic neuropathy [91].

Often in the preantibiotic literature, gustatory sweating is described as following "parotitis." A closer look at most of these publications shows that most of the cases described had had drainage of a parotid abscess, although in these publications various etiologies were proposed. The cause of Frey's syndrome is not the infection but the surgical drainage. No recent case of gustatory sweating resulting from parotid infection has been reported.

More bizarre etiologies for facial gustatory sweating, in single case reports, include herpes simplex of the mandibular division of the trigeminal nerve [31], a case of a large cerebellopontine angle tumor [123], and "gustatory otorrhea" [115]. These cases could also be explained by the aberrant regeneration theory, with the locus of cross-fiber regeneration being at the level of the maxillary division of the trigeminal nerve [123], at the level of the middle ear [115], or in the deep portion of the auriculotemporal nerve instead of the parotid space portion of the auriculotemporal nerve [31]. A similar explanation, i.e., peripheral parasympathetic sprouting to degenerated sympathetic fibers, has been offered for the observed facial, and often neck and upper chest, gustatory sweating seen in patients with severe diabetic neuropathy [13, 15, 43, 59, 65, 134, 139, 142].

A certain amount of "physiologic" gustatory sweating and flushing can be induced by certain spicy foods such as chilies in normal subjects [86]. A variation of the threshold of individual cutaneous regions appears to be present, since only certain head and neck areas are

found to respond in a given individual [86]. In contradistinction to Frey's syndrome, this "physiologic" gustatory sweating and flushing is bilateral and usually symmetrical [86], similar to physiologic thermal sweating [109]. In fact the cutaneous distribution of this physiologic gustatory sweating was found to be similar to that of hyperthermic head and neck sweating and flushing [86].

The few cases of gustatory sweating in the pediatric age group that have been described [7, 8, 22, 40, 68, 70, 130, 147] merit careful review because they possibly represent the only etiology, not easily explained by the aberrant regeneration theory. The majority of the cases described are normal children with unilateral [7, 8, 22, 40, 70, 130, 147] or bilateral gustatory facial flushing [22, 68], without any sweating. The absence of facial sweating, a hallmark of Frey's syndrome, in these cases tends to make us consider them as variations of normal. Maybe the term "gustatory flushing syndrome," as proposed by Kozma and Gabriel [70], might be more appropriate. Another argument against accepting these few cases as Frey's syndrome is that, with a follow-up of several years, a gradual resolution of the symptoms occur [22, 70, 95], in contradistinction to typical gustatory sweating. A final consideration is the possible role of traumatic forceps delivery, pointed out by Balfour and Bloom [7] because about half of the pediatric "gustatory flushing" cases follow a forceps delivery [7, 8, 22, 68, 130].

In addition, a "gustatory otorrhea" in a two patients without any previous pathology has been reported [110, 131].

Recently several cases of facial pain in the territory of the auriculotemporal nerve have been described [24, 124, 127, 136] and the name "gustatory neuralgia" proposed [124]. Other specific characteristics of gustatory neuralgia include an electric, burning (neuralgic) pain, pain distribution in the territory of the auriculotemporal nerve, triggering of the pain by eating, numbness in the auriculotemporal territory because of surgery, and lack of response to anticonvulsant medication [124]. Gustatory neuralgia should be differentiated from classical Frey's syndrome because of the absence of sweating and flushing and because pain is not a symptom in patients with Frey's syndrome [30, 38]. The authors describing this "gustatory neuralgia" refer to the 1979 paper of Hanowell et al. [56] as a justification for the presence of pain in Frey's syndrome patients, however Hanowell's patients had composite resections and neck dissections which was probably responsible for the observed pain.

Investigation of Gustatory Sweating

Since the most troublesome symptom of Frey's syndrome is sweating, testing for Frey's syndrome has in general been limited to the evaluation of sweating. Only Laage-Hellmann investigated flushing, and this was done by simple direct observation and without any quantification [74, 77]. We attempted to study skin color changes, without being convincingly able to demonstrate them in patients with Frey's syndrome (Dulguerov, unpublished). Temperature skin changes were demonstrated in four patients in one study [64] and another used lactate content in an attempt to quantify the amount of sweat [79].

Testing for gustatory sweating is, therefore, assessing the function of eccrine sweat glands. The major function of sweat glands in humans is thermoregulation [118]. About 2–4 million sweat glands are distributed over the entire human body with a density varying from 60 glands/cm^2 on the back to 600 glands/cm^2 on the palms and soles [117]. The maximal sweat rate is about 2–20 nl/min per gland [118]. The face has about 250 glands/cm^2 and thus the maximal facial sweat rate should be about 0.5–5 µl/min per cm^2 or 5–50 ml/min per m^2. Sweat is a hypotonic solution that contains mainly sodium chloride, potassium, and bicarbonate, as well as certain inorganic compounds such as lactate, urea, and ammonia [116, 118].

Tests of autonomic thermoregulatory function are complex [90] and the measure of sweat output is just one of the aspects assessed. Tests of sweat output function measure the production of sweat by a group of sweat glands and these tests could be classified as: (1) topographic, where a chemical reaction provides a view of the anatomic location of sweat secretion; (2) electric, where a change of skin impedance by the humidity of sweat is measured; and (3) thermodynamic, where the skin humidity is evaporated and a "sudometer" measures the thermal mass of the air stream [90]. Advantages of the electric and thermodynamic tests include the possibility of repeated and dynamic measures, while topographic tests give a better representation of surface and anatomic distribution.

The ideal test method for gustatory sweating should provide topographic information and quantification of the amount of sweating. While dynamic measures might be interesting in investigational studies, their use in clinical practice is of limited value. Further characteristics of the test should include: (1) simplicity (one-step); (2) sensitivity; (3) reliability; (4) adequate dynamic range, so that different sweating rates could be appreciated; (5) absence of toxicity and allergenicity of the agents used; (6)

easy removal from the skin of the applied agents; and (7) low cost [36, 117].

The most frequently used method of sweat secretion assessment for gustatory sweating was originally described by Victor Minor, a Russian neurologist [96]. The original solution described contains 1.5 g iodine, 10 g castor oil, and 88.5 g of absolute alcohol and is painted on the skin to be tested. Actually, any colored iodine solution used for disinfections, such as Betadine, will work [49]. After drying, the areas are powdered with starch (regular baking corn starch works fine). The water in the sweat produces blue coloring by a reduction reaction of the iodine-starch mixture. With limited sweat production, the apertures of individual sweat glands are marked as small blue dots, while with larger amounts of sweat secretion the blue dots are larger and eventually become confluent. Therefore, the Minor test is seen as a topographic method allowing accurate mapping of the involved surface.

Disadvantages of the Minor test include the necessary application of several layers of reagents, the difficulty of removing the iodine paint, the possible allergy to iodine [119], and the difficulty of using the method with heavy perspiration, since the sweat tends to drip down, obscuring the assessment of the more dependently located skin [36]. While it could be seen as objective, it is not a quantitative test and therefore might not be suited for the comparison of two treatments [34, 35]. In addition the topographic information provided by the Minor test is cumbersome to use with the newer treatments involving local intradermal injections, because the applied reagents should be removed and the skin disinfected prior to injection while maintaining the topographic mapping.

Several modifications of the Minor test have been proposed but all of these share the inconveniences of the original test [1, 36]. Randall [109], noting that some papers have starch coatings, modified the method by using paper instead of starch, but continued to paint the skin with the iodine-based mixture. Dole and Thaysen [26] further simplified the process by the use of paper that was coated with iodine. Unfortunately this method seems to have been forgotten until recently [36].

We recently applied two techniques for the evaluation of gustatory sweating [36]. The blotting paper method simply uses the difference in weight of a piece of blotting paper before and after gustatory stimulation. In the iodine-sublimated paper histogram (ISPH) method, regular office paper is sublimated with iodine and acquires the property of changing color when wetted. The paper is than digitized and a histogram algorithm applied to measure the area of color change [36]. A calibration of these tests with known and appropriate quantities of saline was performed and an excellent correlation found.

These tests (blotting paper and ISPH) satisfy most of the requirements of an ideal sweat test: quantitative test, simplicity, sensitivity, reliability, adequate dynamic range, absence of toxicity and allergenicity, easy removal from the skin of the applied agents, and low cost. In addition, these two tests give complementary data. While the quantitative data obtained with the blotting paper method is excellent, the topographic information is suboptimal. The topographic data of ISPH technique is excellent, providing a mirror image of the facial sweating area.

Incidence

The reported incidence of gustatory sweating after parotidectomy is highly variable and "depends on the diligence with which it is sought and the time-interval from surgery" [132]. The publications of Laage-Hellmann [74–77] in the late 1950s constitute the first serious attempt to study this problem. A group of 123 patients who underwent a parotidectomy was evaluated retrospectively with a questionnaire and clinical testing. On questioning, 62% of the patients complained of problems during eating: 22% had both sweating and flushing, 26% had sweating only, and 14% had only flushing. When a gustatory stimulus was used, flushing was observed in 92% of patients, and 98% of patients exhibited a positive Minor test. Laage-Hellmann [74–77] concluded that gustatory sweating is an unavoidable sequel of parotidectomy that is not overtly symptomatic in all patients. The incidence of clinical and objective gustatory sweating following parotidectomy in publications using an objective evaluation technique is summarized in Table 5.2.

The severity of the gustatory sweating was judged moderate by 58% of patients, important by 15%, and embarrassing by 27% [74]. Lower percentage of important and embarrassing symptoms have been found in other studies [88]. The correlation between the severity of sweating and intensity of the Minor test was not good [39, 74].

More recently, the clinical severity has been correlated to the surface involved [79, 88] and to the extent of parotid surgery (superficial versus total) [46, 53, 79]. There has been an ongoing debate on the role of the thickness of the flap raised prior to the actual parotidectomy, as originally suggested by Singleton and Cassisi [129]. Others have not substantiated this point of view [88].

Table 5.2. Incidence of Frey's syndrome

Author	Year	Number of patients	Incidence of clinical Frey's syndrome (%)	Incidence of objective Frey's syndrome (%)
Laage-Hellman [74]	1958	123	62	98
Kornblut et al. [69]	1974	35	43	97
Gordon and Fiddian [53]	1976	50	34	100
Farrell and Kalnins [39][a]	1991	21	14	43
Yu and Hamilton [146]	1992	35	6	14
Allison and Rappaport [2]	1993	35	83	87
Linder et al. [88]	1997	26	43	96
Nosan et al. [104]	1991	23	44	70
Dulguerov et al. [35]	1999	24	53	76
Laskawi et al. [84]	1998	81	63	100
Cavalot [16]	2000	86	47	86

Incidence of Frey's syndrome in the literature using questioning (clinical) and objective testing. No Frey's syndrome prevention techniques were used in these patient cohorts

[a]Farrell and Kalnins [39] used a modified Minor test with Betadine and four of their patients underwent postoperative radiation therapy. Modified from Dulguerov et al. [35]

The delay between parotidectomy and the appearance of gustatory sweating was examined by sequential Minor tests by Laage-Hellman [77]. The minimal delay was 5 weeks and the median delay for a positive Minor test was approximately 8 weeks. The test was positive before patients started to complain about gustatory sweating. In some patients, the test became positive at 9 months and in less then 1% of patients did gustatory sweating appear after 1 year. While most other authors [84, 88] have confirmed this timeframe, clinical manifestation of gustatory sweating have been reported to appear up to 8.5 years after parotidectomy [60].

Available Treatments

The treatment modalities proposed for gustatory sweating can be classified in five main groups: (1) external radiotherapy; (2) local or systemic application of anticholinergic drugs; (3) section of some portion of the efferent neural arc; (4) interposition of a subcutaneous barrier, as used for Frey's syndrome prevention; and (5) injection of botulinum toxin in the involved skin. Considering that the symptoms are not always very troublesome, it is important that the treatment itself does not result in more serious side effects.

Radiotherapy

Radiotherapy was first attempted by Needles [101]. In Laage-Hellman's studies irradiated patients had a lower incidence of gustatory sweating [74], with the involved surface often outside the radiotherapy fields. Similar hints can be drawn from other publications [4, 23, 88], indicating that should radiotherapy be indicated, the expected incidence and severity of gustatory sweating will be low.

Anticholinergic Medication

The attempts to treat gustatory sweating with systemic anticholinergic medications [101] were put to rest by the study of Shelley and Horvath who showed that none of the substances available could be used in accepted doses to reduce the sweating produced by 0.1 cc intradermal

injection of pilocarpine [128]. In addition, these authors showed that local iontophoresis or application of anticholinergic drugs such as scopolamine could be used to reduce sweating [128]. Laage-Hellman was the first to apply scopolamine (3% cream) for the treatment of gustatory sweating [77], with symptom reduction in male and abolition in female patients. The difference was tentatively explained by a thinner female skin. Double-blind studies, have shown topical glycopyrrolate [60, 61, 94], aluminum chloride [11, 63, 122], and diphemanil methylsulfate [80] to be superior to placebo. Few patients experienced minor side effects such as dry mouth. However, the population in each of these studies was small, and only one publication is available on patients treated with these drugs for longer periods [61]. Despite the effectiveness of these preparations, patients seem, in the long run [88], to abandon the cumbersome daily application requiring skin drying with a hairdryer and avoiding shaving for 12 h [132]. In addition, skin wounds or infection, as well as application to the mucosa of the eyes, mouth, and nose result in an enhanced absorption and side effects [60].

Interruption of the Efferent Pathway

Section of the auriculotemporal nerve was originally described by Leriche for the treatment of traumatic parotid fistula [87]. Coldwater [19] and more recently Debets and Munting [25] attempted auriculotemporal nerve section, with only partial and temporary decrease of the symptoms [57]. Also, the access to this deeply located region is complex and carries the risk of injuring several important structures, including the facial nerve. At the other end of the efferent pathway, a division of the intracranial portion of the glossopharyngeal nerve was done by Gardner and McCubbin [45], with a good result lasting 5 years in one patient and a short period of relief in a second one. Because of the extensive surgery, this therapy has not been pursued.

Hemenway [62] in 1960 suggested interrupting the efferent neuronal pathway at the level of the middle ear, by sectioning the tympanic nerve of Jacobson. The first such procedure for gustatory sweating was carried out by Golding-Wood, who named it "tympanic neurectomy" [51], in three patients with apparently excellent results. Other authors' experience [57, 60, 106, 113] has been less enthusiastic: all patients were initially improved, but a longer follow-up was associated with recurrence of symptoms in most cases. While tympanic neurectomy appears to be based on solid physiopathologic grounds, does not seem too risky, and can be done under local anesthesia, the paucity of recent reports probably attests its lack of effectiveness.

Surgical Interposition

Sessions et al. [125] pioneered the use of a barrier between the facial skin and the parotid bed in the treatment of established Frey's syndrome. They used the surgical interposition of a fascia lata graft in four patients with excellent results. This technique appeared to be effective in the small group of patients reported [125, 141]. Probably a major deterrent of its use is the risk of facial nerve paralysis during reoperation, since the nerve lies just under the skin after superficial or total parotidectomy. A variation of this technique with the use of a pedicled temporal fascia has been reported [114] in a case without prior facial nerve dissection.

Botulinum Toxin

The injection of botulinum A toxin in the skin involved by gustatory sweating was recently proposed by Drobik and Laskawi [28]. Following their case report, the technique has been progressively adopted [3, 9, 10, 16, 28, 34, 38, 55, 73, 78, 81, 84, 100, 108, 137]. Numerous advantages can be cited for the use of botulinum toxin in the treatment of Frey's syndrome. The substance is relatively well known and has been used for a variety of pathologies in the last 25 years with few side effects [66]. Its use is rather simple in the office setting, and avoids complex procedures in the operating room. The only disadvantages are the pain associated with the needle sticking and the secondary reluctance of some patients to be stuck, especially on the face.

Mechanism of Botulinum Toxin Action

Eight serotypes (A, B, Cα, Cβ, D, E, F, and G) of botulinum toxins are produced by different strains of the anaerobic bacteria *Clostridium botulinum* of which only four (A, B, E, and F) are toxic to humans [71]. Although these serotypes are structurally (dimers of a large 150-kD and light

50-kD chains) and functionally (acetylcholine release inhibition) similar, they represent different pharmacologic entities because of the differences in membrane receptor binding sites and intracellular targets.

The action of botulinum toxins is that of highly specific endopeptidases that cleave cytosol proteins involved in the fusion of exocytosis vesicles with the cell membrane [97], with type A toxin acting on synaptosome-associated protein (SNAP)-25 [14] and type B toxin acting on vesicle-associated membrane protein (VAMP) [120]. This action is highly specific for cholinergic synapses because the specific membrane proteins required for the internalization of botulinum toxins are found only in the presynaptic endings of cholinergic synapses [18]. By blocking the exocytosis mechanism of the presynaptic terminal, the release of acetylcholine is inhibited. The synapse remains intact but is non-functional and for neuromuscular junctions results in muscle paralysis. The recovery of function is due to collateral sprouting from the same or other axons and the formation of new synapses.

Practical Aspects

Botulinum toxin A has been approved by the Food and Drug Administration (FDA) since 1989 and is commercially available as Botox (Allergan, Irvine, CA) and Dysport (Speywood Pharmaceuticals, Maidenhead, UK). In the USA only Botox is available and FDA approved for muscular dystonia, blepharospasm, and glabellar rhytids. Type B toxin has more recently become available as Myobloc in the USA and Neurobloc in Europe (Elan Pharmaceuticals, San Francisco, CA) and is approved by the FDA for cervical muscular dystonia [27].

A Botox vial contains 100 IU of botulinum toxin A, 0.5 mg of human albumin, and 0.9 mg of NaCl as a sterile powder that can remain in a refrigerator for at least 24 months. A Dysport vial contains 500 IU of type A toxin–hemagglutinin complex, 125 g of albumin solution, and 2.5 mg of lactose in a sterile powder form. Botox is diluted with 2–5 ml of 0.9% saline solution, while 1 ml is typically used for Dysport [27]. The solution should also remain refrigerated and is said to lose potency after a few hours. Lowe demonstrated that 1 IU of Botox was approximately equivalent in potency to 4 m.u. of Dysport for the treatment of hyperfunctional upper facial expression lines [92], however more recent data seem to indicate a factor of 3 [112].

The practical considerations for botulinum toxin treatment in Frey's syndrome include:

Mapping of the facial surface to be treated by a technique described earlier; we use the ISPH method because it gives excellent topographic information without dripping and staining [34]. With any technique the contour of the area to be injected is drawn on the patient's face.

A grid of 1 cm squares is drawn either physically on the face or an "imaginary" one is created by the physician. We prefer the latter approach and use the minute bleeding from the needle puncture sites as guides.

If anesthetic is to be used it should be applied at this time. Local anesthetic cream (EMLA, Astra, Sweden) is what we have used occasionally.

The delimited area is injected at sites 1 cm apart which are infiltrated with 0.1 ml (5 IU) of a solution containing botulinum toxin at a concentration of 5 IU/0.1 ml (2 cc per bottle of Botox powder) [34]. The injection should be strictly intradermal, rising tiny wheals at each injection site. A light massage of the area is used for local diffusion.

While a consensus on the exact botulinum toxin injection modalities for gustatory sweating treatment is lacking, experimental data favor the 10-mm inter-injection distance and an injection dose of 0.1 ml (Table 5.3). The 10-mm inter-injection distance is supported by the data of Shaari and Sanders for neuromuscular junctions [126]: injections 10 mm away from the motor end plate band of rat tibialis anterior muscle are ineffective in inducing paralysis. In the same experimental system, increasing the dose and volume of botulinum toxin resulted in increased paralysis. A 20-fold increase in dose doubled the paralysis; however, little gain was achieved with injection doses above 5 IU [126]. As far as volume is concerned, a 100-fold increase in volume was necessary to double the paralysis [126].

Studies on human sweat glands partially support these data [71]. Small volumes of concentrated botulinum toxin have the advantage of minimizing the diffusion and possible side effects. However, if side effects do occur they would be more disabling because of the higher concentration [126]. We [34] and others [55] used a concentration of 50 IU/ml, with the idea that a smaller volume of injection will produce less discomfort and be more efficacious. This is probably necessary in zones with intense facial gustatory sweating. Others [10, 78, 81, 84, 100] have

Table 5.3. Botulinum toxin treatment of Frey's syndrome

Study	Year	Patients	Botox dilution (U/ml)	Inter-injection distance (cm)	Dose per injection	Dose per patient (U)	Maximal dose used
Bjerkhoel [10]	1997	14	25	1	0.1 ml	38±12	62.5
Naumann [100]	1997	45	20	1.5	0.05–0.1 ml	21±14	72
Laccourreye [81]	1998	12	25	1	0.1 ml	65	88
Laskawi [84]	1998	19	25	2	0.1 ml	31	100
Cavalot [16]	2000	40	25	1	0.1 ml	?	200
Dulguerov [34]	2000	16	50	1	0.1 ml	41±22	75
Guntinas-Lichius [55][a]	2002	20	25	1	0.1 ml	37±9	?
		20	50	1	0.1 ml	62±20	?
Beerens [9][a]	2002	13	20	2	0.1 ml	25	38
Tugnoli [137][a]	2002	17	20	1.5	0.1 ml	25–55	55
Eckardt [38]	2003	33	?	1.5	1 IU	16–80	80

Principal characteristics of botulinum toxin injections used for the treatment of Frey's syndrome. Only publications with more than 10 patients were included. Data from Kuttner et al. [73] were not tabulated because several of the selected parameters could not be extracted

[a]The botulinum toxin preparation used was Dysport and the Botox equivalents are approximate, with a presumed equivalence of 1 IU Botox = 4 m.u. Dysport [92]. Modified from Dulguerov [35]

obtained good results with a lower dilution (25 IU/ml), and this dosage might be advantageous in patients who have a large surface of gustatory sweating. Guntinas-Lichius compared two concentrations of botulinum toxin and found that the higher concentration is associated with longer recurrence-free intervals [55]. However, a total dose per patient should remain limited to less than 100 IU per session.

Side Effects

We did not experience any facial paralysis side effects of the botulinum toxin injection, as reported by others [9, 10, 81]. It is difficult to understand how a strictly intradermal injection can result in paralysis of facial nerve branches, because the membrane receptors responsible for the cholinergic specificity of botulinum toxins are located only in the presynaptic terminals and not in nerve fiber trunks. Therefore, the most plausible explanation of this rare and partial temporary paresis [9] is an injection deep to the dermis and/or diffusion to facial motor end plates.

The pain associated with the needle injection was evaluated by our patients to be minimal (2/10 on an analog visual pain scale) [34], a result found also in other studies [10, 81]. The use of local anesthetic cream (EMLA, Astra, Sweden) might be tried in the few patients reluctant to undergo this procedure [10].

Since the various botulinum toxins are foreign proteins it is surprising that the incidence of antibodies and allergic reaction is low. The development of antibodies seems related to the amount of protein load injected and the shortness of the interval between injections [27]. The incidence was about 5–10% with the original Allergan batch (#79-11) but has decreases to less than 1% with current Botox preparations [27, 67]. There is no overt hypersensitivity reaction but the blocking antibodies result in decreased effectiveness of the botulinum toxin preparation. These patients could benefit from botulinum toxin B or F preparations.

Therapeutic Results

In our and most published series, all patients treated have a complete resolution of their clinical symptoms. Lower total doses per patient were used by Arad-Cohen and Blitzer resulting in the necessity to repeat the injections

several times prior to obtaining a complete response [3]. In our study, objective testing demonstrated a decrease of the surface involved from 29±22 cm^2, before treatment, to 0.6±0.4 cm^2, after treatment [34].

The duration of the effect of botulinum toxin on gustatory sweating is rather long lasting, with an average of 15 months [9, 78, 84]. An actuarial estimate puts the clinical gustatory sweating recurrence at 1, 2, and 3 years at 27%, 63%, and 92%, respectively [78]. The severity of the recurrent Frey's syndrome was found to be reduced when compared to that of the initial episode and retreatment with botulinum toxin was still effective [78]. A clear explanation for this longer timeframe relative to neuromuscular indications is lacking, but different possibilities have been suggested [84], such as an atrophy of the sweat glands, poor sprouting of autonomic fibers, and increased scarring impeding regenerating axons.

Take Home Messages

- Frey's syndrome is an almost unavoidable complication of parotidectomy, if no preventive techniques are employed.
- Frey's syndrome occurs months to years after surgery and is explained by aberrant regeneration of parasympathetic sialogogue fibers to cutaneous sweat glands.
- The treatment of Frey's syndrome with botulinum toxin is effective and is, in experienced hands, almost free of complications.

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