Management options for gustatory sweating (Frey syndrome)

Laurent Laccourreye, MD,* Raimundo Gutierrez-Fonseca, MD,† and Ollivier Laccourreye, MD‡

Gustatory sweating (Frey syndrome) is a universal problem after surgery of the parotid region and might be encountered in a large number of pathology cases. Numerous treatment techniques and options have been offered to manage this condition; however, none has met with universal acceptance. This article reviews the history, pathophysiology, incidence, prevention, and management options for gustatory sweating.

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*University Hospital, Angers 49000, France; †Fundación Jimenez-Diaz, Madrid, Spain; and ‡Hôpital Laënnec, Assistance Publique des Hôpitaux de Paris, University Paris V, Paris, France

Correspondence to Ollivier Laccourreye, MD, Department of Otorhinolaryngology–Head & Neck Surgery, Laënnec Hospital, 42 Rue de Sèvres, 75007, Paris, France; email: ollivier.laccourreye@lnc.ap-hop-paris.fr

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Duphenix in 1853 was the first author to report the symptoms of gustatory sweating [1]. Considerable dispute existed in the medical literature during the 19th century regarding liquid production (sweat versus saliva) until Bergounhioux in 1859 demonstrated that the secretion produce was sweat and not saliva [1,2•]. In 1923, Lucie Frey, neurologist at the University of Warsaw, suggested a possible role for the auriculotemporal nerve in the pathophysiology of local skin flushing and sweating at the level of the face during meals after an initial trauma to the parotid region [1,2•]. It was André Thomas in 1927 who suggested an aberrant innervation of the parasympathetic to the sympathic as the possible cause of gustatory sweating [3]. In 1932, Peter Bassoe reported the first case of gustatory sweating after parotidectomy, and during the 20th century parotid surgery appeared to be the main etiologic factor for gustatory sweating [2•]. However, in her landmark study Lucie Frey [1] mentioned that German anatomist Henle had developed gustatory sweating after parotiditis induced by typhoid fewer, and since then, as depicted in Table 1, numerous other causes have been reported as etiologic factors for gustatory sweating.

Pathophysiology of gustatory sweating

Various theories have been advanced to explain gustatory sweating after parotid surgery. Currently, the most commonly accepted theory is the aberrant-regeneration theory initially suggested by French neurologist André Thomas [3]. The auriculotemporal nerve carries (1) sensory fibers to the preauricular and temporal areas, (2) postganglionic sympathetic fibers that innervate the subcutaneous arterioles and eccrine sweat glands, and (3) postganglionic parasympathetic fibers that innervate the salivary parotid gland. Trauma to the auriculotemporal nerve or its branches results in a retrograde degeneration of these fibers. The likely mechanism of gustatory sweating is considered to be a misdirection of the regenerating postganglionic parasympathetic fibers along the postganglionic sympathetic fibers. An aberrant reflex is made possible because the postganglionic sympathetic and parasympathetic fibers share the same mediator—acetylcholine. The misdirected regeneration of postganglionic parasympathetic fibers towards the eccrine sweat glands causes sweating, whereas regeneration towards the subcutaneous arterioles accounts for erythema when eating and explains the delay in emergence of symptoms

Table 1. Etiologies for gustatory sweating

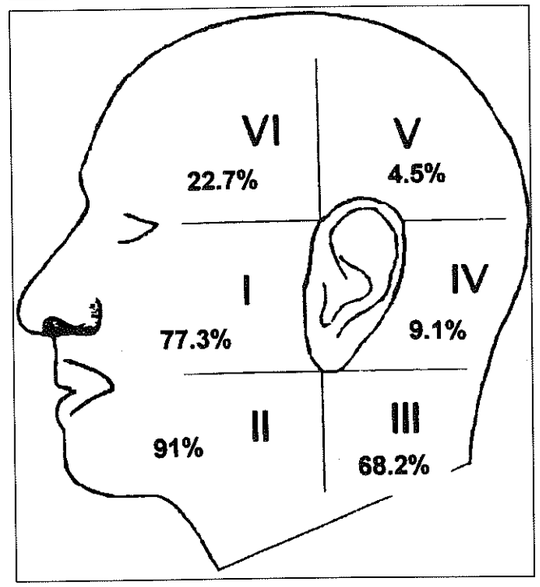
Penetrating wound of the parotid region
Chronic infection to the parotid region
Parotiditis
Parotid surgery
Jugulo-carotid lymph node dissection
Surgery of the submandibular gland
Carotid endarterectomy
Trauma of the auriculotemporal nerve after delivery with forceps
Fracture (condylar, mandible, malar)
Surgery of the temporomandibular joint
Pseudoaneurysm of the internal maxillary artery
Injury to the chorda tympani
Cervico-thoracic sympathectomy
Tumor invasion of the upper node of the sympathetic plexus
Diabetes mellitus
Herpes zoster infection
Platinum-induced neuropathy
Central nervous diseases (*eg*, encephalotrophy, encephalitis, syringomyelia, stroke)
Loss of the insulation between the postganglionic sympathetic and parasympathetic nerve sheaths within the auriculotemporal nerve

after initial trauma [4,5••]. It has been postulated that such a regeneration may occur either by direct regrowth of misdirected postganglionic parasympathetic fibers that reach the distal cut ends of sympathetic fibers to eccrine glands and subcutaneous arterioles or by way of a "sprouting" that might occur at various sites (*eg*, otic ganglion) upstream from the trauma to the auriculotemporal nerve, where parasympathetic and sympathetic postganglionic fibers are in close contact. This notion is supported by (1) numerous clinical reports documenting a reduction of incidence and severity of Frey syndrome after interposition of various components between the elevated skin flap and the transected auriculotemporal nerve and (2) the notion that gustatory sweating was less often noted after parotid surgery for Sjogren disease or chronic infection (caused by increased scarring and fibrosis that impair the establishment of nerve anastomosis) [5••,8]. This concept might also be transposed to damage to other nerves (*eg*, chorda tympani, lingual nerve) that carry postganglionic parasympathetic fibers involved in the production of saliva and postganglionic sympathetic fibers involved in the thermoregulation of various skin regions, explaining the wet-ear syndrome and gustatory sweating after submandibular gland excision [6•,7••]. Furthermore, the aberrant-regeneration theory provides an explanation that allows the patient to understand his/her symptoms easily. However, this concept does not answer the following questions:

(1) Why, as recently demonstrated by Laskawi *et al.* [7••], do all regions affected by gustatory sweating after parotid surgery not coincide with the regional distribution of the auriculotemporal nerve?
(2) How can gustatory sweating in skin regions where no skin flap elevation was performed at the time of parotid surgery (*eg*, nasolabial fold, concha, temporal hair-bearing region, occipital region) be explained (Fig. 1)?
(3) How can regenerated nerve fibers, through postoperative fibrosis, bridge over the long gap between the transected postganglionic parasympathetic fibers at the level of the auriculotemporal nerve and reach the distal ends of the postganglionic sympathetic fibers located sometimes more than 10 centimeters away?
(4) How can gustatory sweating be explained when the auriculotemporal nerve was not traumatized and no skin flap was elevated (*ie*, cervicothoracic sympathectomy, diabetes mellitus)?

To answer such questions, Laskawi *et al.* [7••] recently reviewed the pathophysiology of gustatory sweating. In this well-conducted study, the authors suggested that other nerves such as the facial nerve, the anterior and posterior branches of the greater auricular nerve, and the lesser occipital nerve, served as guiding structures for the regenerated parasympathetic fibers. The authors introduced a very interesting concept based on a clinically orientated classification (Table 2) into three main pathophysiological schemes that could be used to explain the numerous etiologies that might result in gustatory sweating [7••].

Figure 1. Schematic representation of the areas involved in gustatory sweating after parotid surgery in a series of 180 patients



From [7••], with permission.

Table 2. Classification of gustatory sweating according to pathologic state and etiologic basis

Type	Pathologic state	Pathologic basis
Type I Sympathetic/parasympathetic	Salivary gland surgery, salivary gland diseases, neck dissection	Lesion of thermoregulated sympathetic fibers + a lesion of gustatory-controlled parasympathetic fibers
Type II Sympathetic	Sympathectomy, neck surgery with sympathetic (trunk) lesions, cervical and cephalic trauma	Lesion of thermoregulated sympathetic fibers + a lesion of preganglionic (cholinergic) gustatory-controlled sympathetic fibers
Type III Central	Normal persons, feeble persons, central nervous diseases (*eg*, encephalotrophy, encephalitis), spinal processes such as syringomyelia, emotional stress	Central nervous lesion of thermoregulated or (?) gustatory regulation centers; low reflex threshold of gustatory sweating

From [7••], with permission.

Incidence and diagnosis of gustatory sweating

The diagnosis of gustatory sweating is clinical and does not require any paraclinical exam. The symptoms of gustatory sweating are often dismissed, but they can also cause considerable social problems. The typical features of gustatory sweating after parotid surgery include unilateral flushing and sweating during meals in the skin area anterior to the ear over the angle of the mandible, the parotid bed, the cheek, and the temporal hairline region associated with a sensation of warmth or discomfort [4,5••]. However, Laskawi *et al.* [7••], in an inception cohort of 180 patients, recently demonstrated that numerous other regions, such as the occipital region, the cervical region, the ear region, and the temporal hair region, could be involved with gustatory sweating after parotid surgery (Fig. 1). Although gustatory sweating occurs typically during mastication (masticatory sweating), this syndrome may also be stimulated by thermal, tactile, and electrical stimuli, and this has been related to central synapses between the trigeminal nerve and the afferent tracts of the glossopharyngeal nerve [5••]. Furthermore, in rare cases the symptoms might be isolated [5••].

The differential diagnosis for gustatory sweating includes physiological sweating, food allergy, and parotid fistula [4,5••]. Physiological sweating is located at the forehead, nose, upper lip, and occasionally the trunk [4,5••]. Sweating related to food allergy is bilateral, occurs usually in children, involves the front as well as the cheek region, and occurs immediately after ingestion of foods. Parotid fistula occurs within 5 weeks of parotid surgery, while gustatory sweating takes at least 5 weeks to occur [4,5••].

Numerous methods have been used to document gustatory sweating [5••]. Patient self-evaluation and clinical evaluation by a physician or by way of a survey always underestimate the incidence of gustatory sweating. The oldest and most used objective test is the Minor starch iodine test described in 1927 by a Russian physician, Victor Minor [5••,8]. The Minor starch iodine test relies on a colorimetric reaction between the ion Cl- and the iodine of a solution applied to the skin.The test identifies the precise location of the syndrome. However, this test is difficult to use in hair-bearing regions of the skin and does not allow evaluation of the severity of gustatory sweating. Numerous other methods (weighting filter papers, thin facial tissue papers, iodine paper histogram, one-step methods using dyes, impression methods using silicone or polyvinyl, biosensoring methods with enzymatic electrods, infrared medical thermography, and evaluation of evaporation) have been suggested to evaluate Frey syndrome incidence and severity [5••,7••,8]. Unfortunately, none has gained widespread acceptance, and currently the Minor starch iodine test must still be considered the reference method when evaluating gustatory sweating.

The incidence of gustatory sweating is highly variable. This is due to the diligence with which the syndrome is sought, the time interval from the trauma, the different methods used to evaluate the syndrome, the etiology of the syndrome, and the wide variation in the quality and quantity of sweat from one patient to another. In patients with diabetes mellitus, the incidence of gustatory sweating has been reported to vary from 36% in patients with diabetic neuropathy to 69% in patients with diabetic nephropathy [9•]. Similarly, as depicted in Table 3, the incidence of gustatory sweating has been reported to vary from 9% to 100% after parotid surgery [5••]. In fact, as demonstrated by Laage-Helman [4] more than 30 years ago, gustatory sweating is constantly noted after parotid surgery if sought for at least 8 months from the initial trauma and if a Minor starch iodine test was used to document the syndrome.

Prevention of gustatory sweating after parotid surgery

In medical literature available on parotid surgery, low amount of parotid tissue resected, ligation and cauterization of the proximal extremity of the transected auriculotemporal nerve, and elevation of a thick skin flap are suggested frequently as efficient preventive measures that reduce the incidence and the severity of gustatory

Table 3. Incidence of gustatory sweating after parotidectomy in a series of more than 100 patients with a minimum 1-year follow-up

Author	Nb	Evaluation method	Incidence, %	Follow-up
Laage-Helman, 1957 [45]	123	Minor test	100	1 y
Morfitt *et al.*, 1961 [18]	100	Survey	54	1 y
Spiro *et al.*, 1967 [19]	165	Oral test	59	> 1 y
Owen *et al.*, 1989 [20]	112	Oral test	11	> 1 y
Yamashita *et al.*, 1991 [21]	306	Oral test	18	> 3 y
Laccourreye *et al.*, 1993 [22]	229	Oral test	65	> 5 y
Leverstein *et al.*, 1994 [23]	192	Oral test	9	6 y
Linder *et al.*, 1997 [10]	167	Survey	22	> 5 y

Nb, number of patients.

sweating. However, the consequences of ligation and cauterization of the auriculotemporal nerve have never been analyzed objectively. Furthermore, Linder *et al.* [10] recently reported that neither the thickness of the elevated skin flap, the extent of parotid tissue removal, nor the technique used to dissect the parotid influenced the occurrence of gustatory sweating. Similarly, creation of hematoma and/or interposition of surgicel in the parotid region do not decrease the incidence of gustatory sweating [5••]. On the other hand, the use of interposition materials at the time of surgery has constantly been reported as the most valuable method to decrease the incidence and severity of gustatory sweating and cosmetic sequelae after parotid surgery [6•,11••]. Numerous flaps (skin, dermis, fat, sternocleidomastoid muscle, superficial musculoaponeurotic system, temporoparietal fascia, platysma, postauricular myoperiosteum, masseteric fascia, posterior belly of the digastric muscle, and fascia lata), resorbable materials (lyophilized dura, polyglactin 910-polydioxanone), and synthetic inert materials (polytetrafluoroethylene) might be used [5••,8,11••, 12•–14]. Recently, Dulguerov *et al.* [11••], in a well-conducted prospective nonrandomized controlled trial, documented that incidence and severity of gustatory sweating was significantly reduced when a subcutaneous implant was inserted at the time of parotidectomy.

Management options for gustatory sweating

Numerous treatment techniques and options have been offered to manage gustatory sweating. However, none has met with universal acceptance. The analysis of the literature regarding management options in patients with gustatory sweating is fraught with difficulties because of the lack of a standardized method to evaluate treatment results, the low number of patients included in the series, the lack of prospective randomized studies with a control group, and the frequent short duration of follow-up. The evaluation is complicated further by the notion that although all patients will present with gustatory sweating after parotid surgery, the severity of the syndrome will vary from one patient to another, with only 10% to 15% of the patients considering the symptoms severe enough to seek relief [5••,10,11••]. The very large number of procedures described and the heterogeneity in the therapeutic approaches for gustatory sweating also demonstrate clearly the current lack of an efficient procedure to manage afflicted patients. Such data, together with the unsettled pathophysiology, still lead numerous physicians to consider that explanation and reassurance without treatment is the best approach.

Medical approaches to gustatory sweating include topical administration of antiperspirant (20% aluminum chloride solution), topical administration of anticholinergic agents (3% scopolamine, 2% glycopyrolate, diphemanil methylsulfate), topical administration of alpha-agonist (clonidine), blockage of the parasympathetic outflow by the way of alcohol or 2% lignocaine injections at various sites (otic ganglion, auriculotemporal nerve), and intracutaneous injection of botulinum toxin type A [5••,7••,15–17•]. None of these approaches allows definitive cure, and relief is only temporary. Currently, the intracutaneous injection of botulinum toxin type A appears to be the easiest and safest method that provides the longest period of relief with the lowest morbidity rate and the lowest incidence of adverse side effects [5••,16•]. Furthermore, although two mechanisms are known to limit the duration of the synaptic action of the toxin when used at the neuromuscular junction (higher rate of resynthesis of the protein SNAP-25 and axonal sprouting), currently these mechanisms have not been documented when used in autonomic nerve endings. Similarly, the antibody formation against botulinum toxin type A resulting in secondary failure has not yet been documented in patients with gustatory sweating.

Radiation therapy to the affected skin region causes skin atrophy and is a highly efficient method in patients with gustatory sweating. However, this option is not used anymore because of the risk of radiation-induced carcinoma [5••].

Surgical approaches to gustatory sweating include tympanic neurectomy, chorda tympani transection, resection of the auriculotemporal nerve, intracranial division of the 9th cranial nerve, and reelevation of the skin flap (with or without excision of the skin involved, skin grafting, and interposition). However, none of these surgical procedures results in definitive cure because anastomotic connections between greater and lesser superficial petrosal nerves allow aberrant regeneration pathways, and none is without a significant risk of major morbidity [5••].

Conclusion

Research on gustatory sweating should still be promoted to increase knowledge of the pathophysiology of this

syndrome. Currently, gustatory sweating should be viewed as a constant consequence of parotid surgery. The advantages and risks of prophylactic measures with interposition techniques to reduce incidence and severity of this syndrome should be discussed with patients who require parotid surgery. In patients with gustatory sweating, management should be discussed if the symptoms are distressing.

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