CLINICAL REVIEW

Mark K. Wax, MD, *Section Editor*

MANAGEMENT OF FREY SYNDROME

Remco de Bree, MD, PhD,[1] Isaäc van der Waal, DDS, PhD,[2] C. René Leemans, MD, PhD[1]

[1] Department of Otolaryngology/Head and Neck Surgery, VU University Medical Center, Amsterdam, The Netherlands. E-mail: r.bree@vumc.nl
[2] Department of Oral and Maxillofacial Surgery/Oral Pathology, VU University Medical Center, Amsterdam, The Netherlands

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Abstract: Almost all patients who undergo parotidectomy will to some extent develop Frey syndrome (auriculotemporal syndrome or gustatory sweating) after surgery, because of aberrant regeneration of cut parasympathetic fibers between otic ganglion and subcutaneous vessels. However, only the minority of these patients needs treatment. The syndrome consists of gustatory sweating, flushing, and warming over the preauricular and temporal areas. Thick skin flap and partial superficial parotidectomy are the most important techniques to minimize the risk of developing symptomatic Frey syndrome. Intracutaneous injection of botulinum toxin A is an effective, long-lasting, and well-tolerated treatment of Frey syndrome. If recurrence occurs, the treatment can be repeated. ©2007 Wiley Periodicals, Inc. *Head Neck* **29:** 773–778, 2007

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Frey syndrome, also known as auriculotemporal syndrome or gustatory sweating, is probably the most frequently occurring sequela of parotidectomy. The condition is characterized by sweating and erythema, and flushing of the facial skin over the parotid bed or neck which occurs during mastication and is often accompanied by general discomfort in the region.

Correspondence to: R. de Bree

Gustatory sweating was first described by Baillarger[1] in 1853, in 2 patients after drainage of parotid abscesses. Rouyer,[2] Botkin,[3] Weber,[4] and New and Bozer[5] reported patients who had gustatory sweating after drainage of a parotid abscess, a bullet wound, and other traumatic injuries of the parotid region. Later, in 1923, Lucja Frey,[6] a Polish neurologist, drew attention to the role of the auriculotemporal nerve in gustatory sweating and provided the missing link between eating and gustatory stimulation on 1 side and facial skin sweat production on the other. In 1927, Thomas[7] explained the physiopathology by postulating the aberrant regeneration theory. The pathophysiological mechanism of this theory is the misdirection of regenerating parasymphathetic fibers innervating sweat glands. The presumed process entails aberrant regeneration of cut parasympathetic fibers between otic ganglion and the salivary gland tissue, leading to innervation of sweat glands and subcutaneous vessels. Gustatory stimulation then results in sweating and redness of the involved skin. Bassoe[8] reported in 1932 the first case of Frey syndrome following parotidectomy, which is currently the most frequent etiologic factor. Frey syndrome may also occur after extirpation of the submandibular gland,

mandibular condylar fracture, and obstetric trauma caused by a forceps.[9–11] Other nontraumatic causes are sympathectomy, autonomic neuropathy in diabetes mellitus, herpes zoster infection, and metabolic diseases.[12]

INCIDENCE

The incidence of Frey syndrome varies according to the diligence with which the diagnosis is sought for and the elapsed time after the parotidectomy. If not explicitly asked for, the complaint is reported by patients in approximately 10% of cases. If asked for, approximately 30% to 40% of patients will admit to gustatory sweating. If a objective starch-iodine test according to Minor is performed, about 95% of all patients who underwent parotidectomy show evidence of Frey syndrome. In the starch-iodine test according to Minor, the affected skin area is covered with iodine solution. After the iodine solution had dried, the area is dusted with starch powder and the patient is given a lemon sweet. As a result of absorption of the wet iodine by starch, the affected area will color deep blue-purple.[13]

Regeneration of postganglionic parasympathetic nerve fibers in the skin takes a certain amount of time, suggesting a latent period between intraoperative auriculotemporal nerve injury and the onset of Frey syndrome. In most reports, this interval ranges from 2 weeks to 2 years, but latent periods of >8 years have been reported.[14]

In a study of Bremerich et al,[15] Frey syndrome was diagnosed after parotidectomy in 372 patients within 12 months in 52% and within 24 months in 83%. The remaining 17% diagnosis of Frey syndrome after parotidectomy occurred after 24 months.

The facial skin area exhibiting gustatory sweating gradually becomes larger during follow-up. This progressiveness is compatible with different lengths of time required by regenerating nerve fibers to reach effector organs at varying distances from the proximal nerve endings. Linder et al[16] noticed also an increase in incidence of subjective complaints, incidence of objective findings and involved skin area during the first 12 months.

QUALITY OF LIFE

Frey syndrome may cause considerable social embarrassment and social incapacity due to profuse flushing and sweating when eating. Most patients (80%) complain of gustatory sweating only, 40% notice erythema, and 20% experience a raised skin temperature.[9]

Unfortunately, no standardized questionnaire for quality of life in Frey syndrome is available. Nitzan et al[17] conducted a quality of life study in patients undergoing parotidectomy to define the morbidity and its impact on quality of life. In a questionnaire, the mean score for local effects was 77 (scale 0–100): erythema or sweating during eating but not bothersome. The importance to overall quality of life was 2.7 on a scale from 1 to 5: a little bit to somewhat important.

Hays[18] determined the severity of Frey syndrome by the frequency of wiping: less or more than 3 times a meal. Ahmed and Kohle[19] included also the incidence (occasional – every meal) and social embarrassment. Beerens and Snow[20] introduced the Frey questionnaire card for answering the question "Did you, for the past 2 weeks, have annoying flushing or perspiration of the cheek during meals?" Luna-Ortiz et al[21] proposed a grading system to determine the severity of Frey syndrome. According to this system, which scores clinical perception of symptomatology by the patient, extent of the affected area, intensity, and smell of sweat, 12 of the 28 (43%) patients with Frey syndrome were classified as mild and 16 (57%) as severe.[21]

Prevention. Probably the most important way to prevent Frey syndrome is to minimize the parotid wound bed while adequately removing the pathology.[22] Therefore, partial superficial parotidectomy, if possible, is recommended to minimize the risk of Frey syndrome.

Singleton and Cassisi[23] found a significant lower incidence of Frey syndrome after parotidectomy if a thick skin flap is made using a scissor dissection as compared to the use of a extremely thin skin flap at the level of the base of the hair follicles made using a scalpel. Although in their study only thick and extremely thin flaps were compared, it is likely that the thickness of the skin flap indeed influences the incidence of Frey syndrome.

Radiotherapy significantly reduces the incidence of gustatory sweating. In a study of Casler and Conley,[24] only 14% of 14 patients receiving radiotherapy complained of gustatory sweating, whereas, 51% of 93 patients who did not receive radiotherapy had the same complaints. Although effective, prevention of gustatory sweating alone is of course not justified as a single indication

Table 1. Techniques to prevent Frey syndrome.

	Subjective incidence of Frey syndrome			Objective incidence of Frey syndrome			
	No. of patients (%)			No. of patients (%)			
	With	Without	Significance	With	Without	Significance	Reference
Partial superficial parotidectomy	64/615 (0.3)	329/1298 (25)	+				22
Thick skin flap	3/116 (3)	6/48 (13)	+				23
Radiotherapy	2/14 (14)	47/93 (51)	+				24
Temperoparietal fascia interposition	2/24 (8)	10/23 (44)	+	4/24 (17)	13/23 (57)	+	19
SMAS interposition	0/16 (0)	49/104 (47)	+				24
	1/112 (1)			1/112 (1)			25
Superiorly based SCM interposition				34/35 (97)	33/35 (94)	–	27
	2/16 (13)	49/104 (47)	+				24
	0/11 (0)	2/11 (18)	–	2/11 (18)	9/11 (82)	+	28
	8/26 (31)	8/26 (31)	–	8/26 (31)	6/26 (23)	–	30
	0/24 (0)	9/19 (47)	+	0/24 (0)	7/19 (37)	+	29
Inferiorly based SCM interposition	2/15 (13)	4/9 (44)	–	3/15 (20)	2/9 (22)	–	31
Platysma-fascia-SCM interposition	2/9 (22)	4/10 (40)	–				32
Implants	1/38 (26)	11/21 (53)	+	5/38 (13)	16/21 (76)	+	33
	1/10 (10)	5/10 (50)	+	2/10 (20)	8/10 (80)	+	34

Abbreviations: SMAS, superficial musculoaponeurotic system; SCM, sternocleidomastoid muscle.

for postoperative radiotherapy because of side effects.

Interposition of barriers to prevent aberrant reinnervation of parasymphatetic fibers have been described. The temporoparietal fascia flap is a reliable and versatile flap in close proximity to the parotid bed, which can be harvested by extending the parotidectomy incision well hidden within the temporal hair line. Ahmed and Kohle[19] reported a significant lower subjective (8% of 24 patients vs 44% of 23 patients) and objective (17% of 24 patients vs 57% of 23 patients) incidence of Frey syndrome after temporoparietal fascia flap interposition. Drawbacks are the risk of injury to the frontal branch and alopecia. Ligation of the superficial temporal artery during parotidectomy limits the use of this flap.

Allison and Rappaport[25] were the first to describe a rotation of the superficial musculoaponeurotic system (SMAS) to ameliorate the defect after parotidectomy. This technique involves plicating the SMAS layer and the remaining gland capsule to the sternocleidomastoid muscle and perichondrium of the ear canal. The incidence of Frey syndrome was only 1% in their series of 112 patients. Casler and Conley[24] found in none of the 16 patients with SMAS plication subjective symptoms, whereas 47% of the 104 patients without SMAS plication had subjective symptoms of Frey syndrome. Hönig[26] proposed a hybrid SMAS, in which a vicryl mesh is embedded in folded SMAS to prevent the development of gustatory sweating.

The sternocleidomastoid muscle receives its blood supply superiorly from the occipital artery, in the midportion from the superior thyroid artery and inferiorly from the transversal cervical artery. This allows the muscle to be used as superiorly- or inferiorly-based flap. Kornblut et al[27] were the first to report on the use of a superiorly-based sternocleidomastoid muscle flap to prevent Frey syndrome. In their initial series, the sternocleidomastoid muscle flap was useful for cosmetic filling out of a cheek or upper neck depression created by the parotid surgery, but it was ineffective in preventing the occurrence of gustatory sweating.[27] In contrary, some other studies found a significant lower incidence of symptomatic Frey syndrome after parotidectomy in patients in whom a superiorly or inferiorly based sternocleidomastoid muscle flap was used as compared with those without.[24,28,29] This difference in incidence of Frey syndrome could not be confirmed in all studies in which a sternocleidomastoid flap interposition was used (Table 1).[30–32] Moreover, the incidence of abnormal greater auricular nerve function and abnormal facial sensation was higher in patients who underwent this interposition.[31] It is difficult to reconcile these differences given the

Table 2. Results of botulinum toxin A treatment.

Reference	Effective, no. of patients (%)	Follow-up	Recurrence, no. of patients (%)	Interval
38	3/3 (100)	6–8 mo	0/3 (0)	
39	12/15 (80)	1–13 mo	2/15 (13)	3–13 mo
40	45/45 (100)	6 mo	0/45 (0)	
41	18/18 (100)	11–33 mo	8/18 (44)	8–19 mo
42	16/16 (100)			
43	33/33 (100)	>18 mo	32/33 (97)	6–30 mo
44	7/7 (100)	17–23 mo	0/7 (0)	
45	8/8 (100)	–	–	
20	11/13 (85)	6–24 mo	10/13 (77)	3–24 mo
46	11/11 (100)	6–23 mo	1/11 (9)	16 mo

wide variety of techniques and follow-up and different patient populations.

Dulguerov et al[33] suggested implantation of lyophilized dura, polyglactin, and expanded polytetrafluroethylene to reduce the incidence of Frey syndrome. Also other materials like acellular human dermal matrix have been used to reduce the incidence of Frey syndrome.[34] Although most implants decrease the incidence of Frey syndrome, the risk of parotid fistula is increased significantly. The less resorbable an implant, the better the barrier is and the greater the risk of fistula.[33]

Because it is difficult to predict preoperatively which patients will likely have subjective complaints of Frey syndrome after parotidectomy, accurate selection of patients who might benefit from preventive surgical procedures is problematic. Interposition of tissue or other materials may form a barrier placed between the parotid wound and the overlying skin. It is not clear if these barriers hamper or only delay aberrant reinnervation of nerve fibers. In most series, follow-up is too short to answer this question. Furthermore, bulky muscle flaps and implants may potentially mask recurrences in the operative bed.

Treatment. Various forms of treatment of Frey syndrome, both medical and surgical, have been tried with varying degrees of success. However, the majority of patients are satisfied by an explanation of the condition and reassurance.[16] Several surgical procedures have been used to treat established Frey syndrome. The most commonly used method consists of reelevation of the cheek skin flap and interposition of various tissue barriers like dermal graft and temporoparietal fascia between the cheek skin and the parotid gland.[35,36] Reelevation of the skin flap and excision of the involved skin followed by skin grafting have also been used. These procedures result in a donor site scar and harbor the risk of facial nerve injury.

Tympanic neurectomy is described as treatment for Frey syndrome. Resection of the parasympathetic plexus is performed after creating a tympanomeatal flap and identification of the tympanic plexus on the promontorium in the middle ear. Satisfactory control of Frey syndrome has been reported in 82% of the patients.[37] This procedure is probably abandoned due to its only temporary effect.

Topically anticholinergic medications are effective in treating Frey syndrome for several days. Scopolamine is a tertiary amine preparation, which penetrates skin easily and blocks cholinergic transmission. Scopolamine is applied in solution and cream and has a great variation in efficacy between individual patients necessitating adjustments in dosage from 0.25 or less to at least 3% in some patients with thick skin.[18] Bremerich et al[15] found that scopolamine ointment did not elicit better results compared with no treatment at all. Glycopyrrolate is a quaternary ammonium compound, which penetrates skin slowly and blocks cholinergic transmission. Glycopyrrolate is effective in both solution and cream. Topical anticholinergic medications are contraindicated in patients with glaucoma. Side effects as blurred vision and dry mouth occur more frequently in scopolamine than in glycopyrrolate treatment probably due to differences in potential to penetrate membranes and blood brain barrier.[18]

Favorable results have been reported on the treatment of Frey syndrome by intracutaneous injections of botulinum toxin A (Table 2).[20,38–46] This neurotoxin enters the cytoplasm of peripheral nerve cells by receptor-mediated endocytosis. On the cytoplasmic side of the cell membrane, the

toxin breaks down the synaptosome-associated protein SNAP-25, which is essential for exocytosis of acetylcholine vesicles. In this way, neurotransmission is blocked until reinnervation occurs by collateral growth of fibers or new SNAP-25 is produced by the cell.[47] Before treatment, the effected area, as determined by the starch-iodine test, has to be marked and divided into 4-cm^2 squares. In the middle of each square, botulinum toxin has to be administered.

Dulguerov et al[42] showed a significant reduction of sweat surface and quantity of gustatory sweating after botulinum injections. The effect on temperature and erythema was more difficult to determine.[42] In the first reports on botulinum therapy of Frey syndrome, responses in almost all cases and very low recurrence rates were reported.[38–40] However, in these studies the follow-up was probably too short for reinnervation by collateral growth. In studies with a longer follow-up, the effectiveness was temporary and recurrence rate was higher.[20,41,43] However, because the severity of recurrent Frey syndrome is reduced when compared with the severity of the initial Frey syndrome and because recurrent Frey syndrome remains amenable to reinjection of botulinum toxin A, intracutaneous injection of botulinum toxin A is suggested to be the first-line treatment option in patients with Frey syndrome.[20,43] Botulinum toxin A treatment appears to be effective in almost all patients, minimally invasive, well tolerated and long-lasting (>6 months) and can be repeated.

CONCLUSION

Almost all patients who underwent parotid surgery will develop to some extent Frey syndrome, but only the minority needs treatment. Thick skin flap and partial superficial parotidectomy are the most important techniques to minimize the risk of developing symptomatic Frey syndrome. Intracutaneous injection of botulinum toxin A is an effective, long-lasting, and well-tolerated treatment of Frey syndrome, but may need to be repeated.

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