[CASE REPORT]

Frey Syndrome in a Patient with Facial Melanoma:

Auriculotemporal Syndrome Presenting with Gustatory Sweating Following Wide Local Excision, Sentinel Node Biopsy, and Superficial Parotidectomy

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ABSTRACT

Frey syndrome is characterized by erythema, flushing, and gustatory sweating in the preauricular area. It most commonly occurs after parotid surgery. A 21-year-old man who had a wide local excision, sentinel node biopsy, and superficial parotidectomy for a right temple superficial spreading melanoma and who subsequently developed gustatory sweating in the preauricular area is described. The presentation, diagnosis, pathogenesis, and treatment options of Frey syndrome are reviewed. (*J Clin Aesthet Dermatol.* 2012;5(7):48–52.)

Frey syndrome most commonly occurs after parotid surgery and refers to a combination of hyperhidrosis, warmth, flushing, and erythema that occurs with gustatory stimulation after injury to the auriculotemporal branch of the trigeminal nerve. A young man who developed Frey syndrome following the wide local excision of a facial melanoma is described. The presentation, pathophysiology, and treatment of this disorder are reviewed.

CASE REPORT

A 21-year-old Caucasian man with a history of recently diagnosed melanoma presented for cutaneous evaluation. His melanoma had been diagnosed when he was 20 years of age. A 1.5cm pigmented lesion on his right temple showed invasion into the reticular dermis (Clark level IV) to a Breslow depth of 1.6mm. The patient was referred to a surgical oncologist who specializes in head and neck surgery.

A wide local excision was performed. The lateral margins for the surgery were 1.5cm, and tissue to a level of the superficial fascia was taken. Sentinel node mapping showed positivity of the tracer within the parotid; therefore, he also underwent a superficial parotidectomy with sparing of the facial nerve branches, which were dissected away. Two upper right cervical nodes were positive for tracer and taken.

Five days later, with permanent section margins negative for the melanoma, the resulting 4.5cm defect was closed with a large scalp rotational flap. The patient's sentinel node biopsies were also negative for the melanoma. His postoperative period was notable only for a minor transient marginal mandibular nerve palsy that subsequently resolved.

Eleven months after his surgery, the patient reported that shortly after eating he developed moisture on his right face that was worse with sour food (Figures 1 and 2). A diagnosis of Frey syndrome was established based upon the correlation of his surgical history and his symptomatology. Treatment with oral glycopyrrolate, 1mg twice daily, was initiated. This therapy successfully decreased his symptoms without an increase in body sweating.

DISCUSSION

History. Frey syndrome, also known as auriculotemporal syndrome, is characterized by various symptoms upon gustatory stimulation including flushing, warmth, erythema, and sweating in the preauricular and

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Figure 1. The lateral view of the right side of a 21-year-old man affected with Frey syndrome. The purple line delineates the area that was affected with gustatory sweating. Scar from his surgical reconstruction can be seen from the patient's reconstruction anterior to the right ear and extending along the cervical neck.

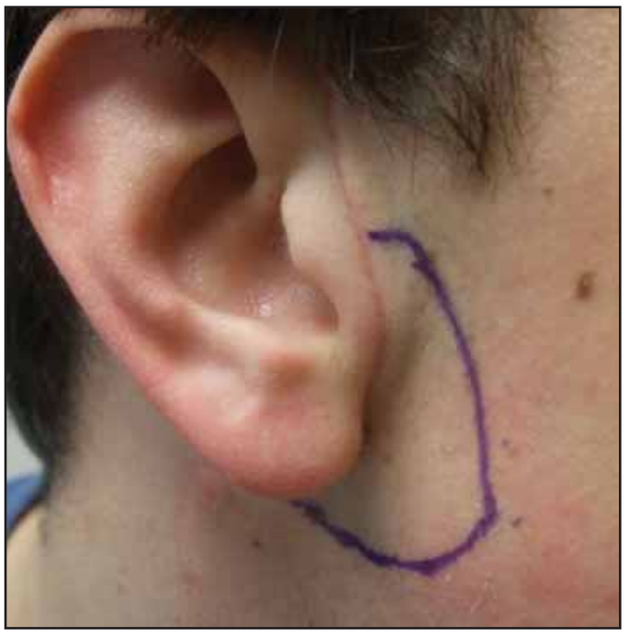

Figure 2. A closer view of the area affected by gustatory sweating shows that the surgical scar is in the area of the parotid. He also has a mild dermatitis on his face; however, it is interesting to observe that the skin affected by Frey syndrome did not develop eczematous changes.

temporal areas. It has a somewhat contentious history in that many articles attribute this first report of gustatory sweating syndrome to French surgeon M. Duphenix in 1757.[1] However, in their review of the history of the syndrome, Dulgeurov et al suggest that 1) Duphenix's report was actually a parotid fistula and 2) the first account of the syndrome was written by Baillarger in his series of five patients, two of whom had the disorder.[2,3] The eponym for the syndrome honors a Polish neurologist, Dr. Lucja Frey, who was the first individual to not only describe the symptoms, but also elucidate the correct underlying neuroanatomy of the condition in 1923.[4]

Etiology. There are several predisposing causes that have been associated with the development of Frey syndrome (Table 1).[5–19] The most common etiology for the condition is a preceding parotidectomy; the proposed mechanism of pathogenesis is aberrantly regenerated parasympathetic and sympathetic fibers that have been transected during surgery. Symptoms may develop months or years after the inciting injury because of the slow nature of neural regeneration as exemplified in the patient described in this case who developed symptoms 11 months after his surgery.

The parotid lymphatic basin is not only the most common site of metastatic spread for melanomas involving the scalp and face, but also the most common lymphatic basin to undergo sentinel lymph node biopsy.[20] In one series of children undergoing parotidectomy for various reasons, 19 percent of them developed mild Frey syndrome.[6] In another retrospective evaluation of people with Frey syndrome, similar to the patient in this case, only 10 percent of the individuals voluntarily presented their symptoms to the physician. If asked about Frey syndrome-related symptoms, another 30 to 40 percent admitted to having them. Yet, up to 95 percent of the patients actually had gustatory sweating when evaluated with the iodine-starch test.[21]

The incidence of Frey syndrome following parotidectomy varies not only based upon the type of assessment conducted, but also the type of parotidectomy performed. Specifically, Frey syndrome is more frequently discovered following a quantitative assessment (such as a starch iodine test) than on a clinical inquiry for the syndrome-related symptoms. In addition, the incidence of Frey syndrome is higher in patients with a total rather than partial parotidectomy and in those individuals with repeat surgeries.[14]

Clinical presentation. Frey syndrome most commonly occurs after parotid surgery and refers to a combination of hyperhidrosis, warmth, flushing, and erythema that occurs with gustatory stimulation. The patient who develops this condition may experience only one or a combination of the symptoms that comprise the syndrome. The key component is that gustatory stimulation elicits the symptoms. In addition, usually the stimulus has a solid component to elicit the

TABLE 1. Frey syndrome: Associated causes

CAUSE	REFERENCE
Carotid endarterectomy	5
Chronic abscess	6
Cisplatin chemotherapy	7
Congenital hemangioma	8
Diabetic neuropathy	9
Forceps delivery	10
Herpes zoster	11
Mandibular fracture or surgery	12,13
Neck dissection	14,15
Neurofibromatosis	16
Parotid surgery	12
Peritoneal dialysis	17
Submandibular salivary gland surgery	18
Thoracic sympathectomy	19

salivation reflex from mastication. The main exception is sour foods, which may elicit the response alone, similar to what the patient described in this case experienced. The symptoms generally begin within a few minutes after eating and may last for up to 30 minutes after eating cessation. The severity of symptoms can range from annoying to socially incapacitating and often depend on the surface area involved.[14]

Diagnosis. The diagnosis can usually be established based upon the clinical presentation of symptoms—especially in patients with a history of associated etiology, as in the patient in this case. The Minor's starch-iodine test is the most common technique that can be used to confirm the diagnosis of Frey syndrome.[22] To conduct the test, three percent iodine in ethanol is applied to the symptomatic area and allowed to dry. A starch powder is subsequently applied and the patient is asked to eat something acidic that can be masticated. If sweat is produced, the affected area will begin to turn blue-black in 30 seconds with a maximal development of the color change in five minutes.

Pathophysiology. The syndrome arises from an alteration of the complex network of nerves found in the preauricular area. The auriculotemporal nerve, a branch of the mandibular nerve (V3; cranial nerve 5, 3rd division) supplies not only sensory information to the preauricular and temporal areas, but also parasympathetic innervation to the parotid and smaller mucous glands. In addition, the auriculotemporal nerve has a minor role in the innervation of the local vasculature. Sympathetic fibers in the preauricular region originating from the superior cervical ganglion form a plexus around the carotid artery; branches from these nerves also join the auriculotemporal nerve and supply sympathetic innervation to both blood vessels and sweat glands (Figure 3).

The currently accepted pathogenesis of Frey syndrome is that trauma in the area of the parotid gland results in sectioning of both sympathetic and parasympathetic fibers. During their regeneration, parasympathetic fibers originally meant for the parotid or smaller salivary glands begin to aberrantly innervate sweat glands and cutaneous vasculature (Figure 3). This not only results in gustatory sweating, but also the flushing, warmth, and erythema associated with gustatory stimulation characteristic of the syndrome.

However, the main innervation that the sweat glands receive is sympathetic via the neurotransmitter acetylcholine at the postsynaptic ganglion. This innervation is maintained in Frey syndrome—even when the aberrant parasympathetic fibers are also controlling sweat gland activity (Figure 3). This dual innervation of the sweat glands by both the parasympathetic and sympathetic nerves has important implications for the treatment of the syndrome.

Prevention and treatment. A variety of medical and surgical modalities have been used to manage the symptoms of Frey syndrome. Topical therapies target either the cholinergic synapse via acetylcholine receptor antagonism (scopolamine, atropine, and glycopyrrolate) or the eccrine gland via direct inhibition of eccrine gland secretion (aluminum chloride solutions and other

antiperspirants). Topical scopolamine and atropine have the disadvantage of variable efficacy and increased risk of adverse side effects including xerophthalmia, xerostomia, blurred vision, and urinary retention.[23] Topical preparations of glycopyrrolate, ranging from 0.5 to 2% in either liquid or cream, applied once daily, every other day, or even once weekly have been found to be efficacious with few adverse effects.[24] Topical aluminum chloride, either as a 12 or 20% solution, has also been beneficial for treating syndrome-associated symptoms with minimal or no side effects.[24,25]

Systemic anticholinergic agents have also been used to treat patients with Frey syndrome. Indeed, the patient in this case was successfully managed with oral glycopyrrolate. Adverse effects associated with systemic anticholinergics may include blurred vision, urinary retention, and tachycardia; however, newer anticholinergics, such as glycopyrrolate, have less blood-brain penetration and fewer side effects.[14]

More recently, botulinum toxin A has been used for both the gustatory sweating and flushing associated with the syndrome. The toxin prevents presynaptic fusion of the acetylcholine-containing vesicle by cleavage of the synaptosomal-associated protein-25 (SNAP-25) necessary for vesicular exocytosis. Treatment consists of injecting 1 to 5 units of botulinum A toxin in a grid pattern approximately 1cm apart. Clinical improvement may have a sustained duration of more than 12 months.[26,27,28] The major theoretical adverse effect of the therapy is paresis of the facial nerve branches, but this complication is infrequent if the injections are made posterior to the anterior border of the masseter muscle.

Surgical management of Frey syndrome now aims, in part, to avoid the development of the syndrome by primarily using fascial, musculofascial, dermal collagen, or dermal fatpad grafts over the parotid defect and thereby preventing the aberrant neural reanastomoses. However, if the syndrome is already present, an additional surgery may be used that sections the lingual nerve.[14,29] Surgical management of Frey syndrome is usually reserved for the most intractable circumstances since most patients are reluctant to undergo further surgical procedures, and there are several medical modalities that can be initiated.

CONCLUSION

Frey syndrome most commonly occurs after parotid surgery and has the characteristic clinical features of gustatory sweating, flushing, and erythema in the preauricular area. The surgical treatment, including not only excision of the tumor but also sentinel node biopsy, parotidectomy, and/or more extensive head and neck lymph node dissection, of patients with primary or metastatic skin cancer that occurs in this region of the face may result in these individuals subsequently developing this syndrome. Physicians familiar with the armamentarium of hyperhidrosis treatments, such as topical or systemic anticholinergics and the administration of botulinum A toxin, may be able to provide nonsurgical treatment of this disorder.

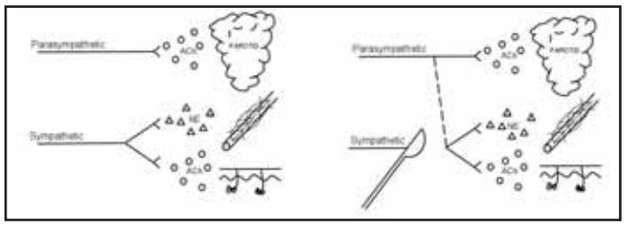

Figure 3. The parasympathetic and sympathetic nerve fibers travel within the auriculotemporal nerve. In their normal state, they provide parasympathetic input to the parotid and minor salivary glands via the neurotransmitter acetylcholine, and sympathetic innervation to the cutaneous vasculature and sweat glands via both norepinephrine and acetylcholine, respectively (left side). Damage to the parasympathetic and sympathetic nerve fibers may result in aberrant reinnervation such that parasympathetic signaling may cause gustatory sweating, erythema, warmth, and flushing (right side). ACh=acetylcholine; adnexal structures in skin=cutaneous sweat glands; dotted line=aberrant reinnervation of parasympathetic nerves; NE=norepinephrine; PAROTID=parotid gland; Scalpel=represents damage to the parasympathetic and sympathetic nerves; tubular structure=blood vessel with nerve plexus

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