

Frey syndrome

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Abstract

Frey syndrome is a condition of gustatory sweating and hyperemia related to damage of the auriculotemporal nerve. It affects around 80% of patients after parotidectomy. Syndrome may be easily diagnosed with an iodine-starch test, even in patients without symptoms, which are about 20% depending on studies. Authors searched PubMed and Google Scholar using searchterms Frey syndrome, auriculotemporal nerve, greater auricular nerve, tympanic nerve, parotidectomy. We manually searched the references of selected articles for additional relevant articles. We selected articles relevant to a general medicine readership and

prioritized systematic reviews, clinical practice guidelines and cases. The literature contains the latest reports on Frey syndrome. Symptoms of Frey syndrome are: reddening of the skin due to vasodilatation, excessive sweating or tingling and burning sensation of the cheek skin. Clinicians should pay attention to Frey syndrome in patients after parotid gland surgery. Treatment includes botulinum toxin type A most commonly, topical injection of alcohol, scopolamine, glycopyrrolate and less common surgical treatment including transection of auriculotemporal nerve. Frey syndrome is not such a rare disease and should be always considered by clinicians because it may worsen the quality of patients' life.

Keywords: Frey syndrome, auriculotemporal nerve, tympanic nerve, greater auricular nerve, parotidectomy

Introduction

Frey syndrome is a condition named after Polish neurologist, Lucia Frey, who described it in 1923 as auriculotemporal syndrome. It may be also known as Dupuy syndrome, Baillarger's syndrome and gustatory hyperhidrosis.[4] Studies show that it is a common sequela of parotidectomy, which affects up to 64% of patients after procedure.[1] Other conditions highly connected to this condition are: submandibular gland surgery, radical neck dissection, infection, traumatic injuries in the parotid region, forceps delivery, thoracic sympathectomy or burns.[2,7] It is caused by aberrant regrowth of facial autonomic nerve fibres.[3] The most common symptoms includes unilateral sweating, flushing of the cheek skin occurred during eating and heating sensation of the facial skin. This syndrome may significantly worsen the quality of life of the patients and this is why it should be well diagnosed and clinicians should aim to completely cure patients suffering from this disease. [7]

Epidemiology

The disease after parotid gland removal occurs in 4% to 96% of individuals.[4–6] The large variation in symptom intensity, reporting and being diagnosed is the reason for the sizable range of indicators.[3,4,7] In about 80% of patients undergoing parotid removal, the syndrome is detected by the starch-iodine minor test. The percentage of patients reporting symptoms is in the range of 30-60%, which can indicate that some patients are without symptoms.[4,8]

Diagnosis

Diagnosis in children is more complicated because it is quite difficult to differentiate the symptoms of Lucia Frey syndrome from food allergy, particularly in bilateral cases.[9] The first diagnostic method from 1927 is Minor's iodine-starch test. It is simple, effective and affordable.[3] During this test, iodine and starch should be placed on the temporal facial area, then the patient should be given a sour candy, which is a salivary stimulant.[3,10] The color of starch applied to dry iodine changes to blue or brown when sweat interacts with iodine.[1]

To examine the affected area more closely, UK authors proposed to use a thermal imaging camera.[11,12]

Given the availability of thermal imaging equipment on hospital wards, this method of diagnosing Frey syndrome is recommended. It is quick and less invasive for the patient than the Minor starch-iodine test. Accurate identification of temperature fluctuations allows more precise treatment with Botox injections.[12] Another method for detecting auriculotemporal syndrome is the presence of L-lactate on undamaged skin after the impulse. The method is harmless and dependable, but unused. The method described above is based on the biosensor enzyme electrode system.[3,13]

Differential

diagnosis

1. In children, Frey syndrome should most often be differentiated from food allergy. This syndrome has a quick onset after eating, characteristically sour and sweet foods that usually do not cause food allergies. It is located near the parotid gland and there are no other allergic manifestations.[4]

2. Emotional sweating is caused by high emotions. It manifests itself later in the armpits, palms and soles. During sleep, it does not occur.[4,14]

3. First-bite syndrome is caused by sympathetic nerve damage. It manifests as pain while eating and drinking. It subsides after eating is finished.[15–17]

Etiology and pathomechanism

Considerations on the etiology, etiopathogenesis as well as the mechanisms and theory of Frey syndrome should begin with an outline of the anatomy of the innervation of the preauricular and mandibular regions.[3]

The preganglionic parasympathetic fibers originate in the inferior salivary nucleus in the upper part of the medulla.[3,18] They travel along the glossopharyngeal nerve, through the middle ear as the tympanic nerve to the tympanic plexus where the cervico-tympanic sympathetic nerves join. Hence, as a lesser petrosal nerve, they go to the auricle ganglion and autonomously supply the parotid gland via the auriculotemporal nerve. The auriculotemporal nerve from the mandibular nerve wraps around the mandibular condyle and goes sideways and upwards between the temporomandibular joint and the external auditory canal, medially from the parotid gland. It gives articular, ganglion, parotid, auricular and superficial temporal branches.[3,6,18,19]

The postganglionic sympathetic fibers come from the upper jugular ganglion of sympathetic trunk. They mainly affect the vasoconstriction and innervation of the sweat glands.[6] Although most of these nerves have norepinephrine as their primary mediator, the fibers leading to the sweat glands are sympathetic cholinergic fibers.[3,19,20]

Lucia-Frey syndrome is a known and frequently described complication occurring as a result of damage to the auriculotemporal nerve containing fibers of the autonomic system that affect the secretion of saliva in the parotid gland and the secretion of sweat from the sweat glands, and dilatation and constriction of blood vessels in the pre-ear and temporal areas of the scalp.[7,19,21] Destruction of nerve fibers may occur during craniofacial injuries, parotidectomy, forceps delivery, thoracic sympathectomy or burns.[6] Frey syndrome may also show after removal of the submandibular gland, mandibular condylar fracture. Other

nontraumatic causes are sympathectomy, autonomic neuropathy in diabetes, herpes zoster infection, and metabolic diseases.[22] In general, the parasympathetic fibers regenerate abnormally and begin to innervate the sweat glands and blood vessels of the scalp. Consequently, the taste stimulus, that increases the activity of the parasympathetic system in order to increase saliva secretion, causes: sweating, redness and warming of the pre-ear area, the angle of the mandibula and directly above the parotid gland.[1,6,7,19,23]

The FS mechanism with the theory of improper regeneration was developed in 1927 by Andre Thomas, and 8 years later additionally supported by Ford. This theory says that the split parasympathetic fibers of the auriculotemporal nerve tend to regenerate along sympathetic pathways.[24] It is widely accepted and explains the asymptomatic period between nerve injury and the onset of clinical symptoms.[10] The Minor test consists in applying iodine and starch to the temporal area of the face and administering to the patient the factor causing increased salivation. Upon the onset of gustatory sweating, iodine and starch combine, resulting in a purple color change. The test detects the functioning of the sweat glands very accurately and therefore indicates that FS is almost always followed by a parotidectomy. This frequency of positive minor test results suggests that the parasympathetic fibers must somehow cling to the sympathetic pathways and not accidentally regenerate along them.[10,22]

Another theory is that gustatory sweating is a primordial phenomenon that is inhibited by the ATN nerve. If it were plausible, there would be no pre-symptomatic latency, only sweating immediately after the nerve was injured.[1]

The other thesis claims that the stimulation of the parotid gland leads to the fact that the tissue scar causes deterioration of the sympathetic fiber endings, leading to the initiation of the sweat secretion process.[25] However, FS occurs after total parotidectomy, so it would not be able to stimulate the nerve endings.[26]

A more likely postulation is that severed parasympathetic nerve endings may snag to the scar and cause acetylcholine release and sweating.[25]

After all, the first theory is considered to be the most credible, especially when it is extended to include the missing elements such as neurotrophic factors.[10]

These factors play a key role in the prenatal development of the nervous system. The nerve target secretes neurotrophic factors that act as a means of attracting nerve fibers. Those who manage to win the competition for these substances survive and innervate the organ, while the rest enter the pro-apoptotic path.[27] Neurotrophic substances are involved in the survival of neurons, keeping them alive, influencing the expression of neurotransmitters and controlling the growth path of neurons towards a structure in the future innervation.[10]

One of the most important groups of neurotrophic elements is the family of GDNF ligands (the glial cell-derived neurotrophic factors) [10]. They bind to GDNF receptors (GFRs) expressed on developing neurons. In addition to GDNF, there are such neurotrophic factors as neurturin (NRTN), artemin and persephin. By binding to GFR α receptors, they affect the direction of growth and the tendency to elongate neurons of the autonomic system (playing a major role in the etiopathogenesis of FS) towards the target organ or structure that is to be innervated by them.[10,28]

NRTN most influences the growth and innervation of the target structure through the parasympathetic neurons leaving the ganglion, interacting with GFR α 2 receptors.[29] The parotid gland, as one of the target organs for neurons, releases NRTN which helps to direct the growth of parasympathetic neurons from the otic ganglion.[10] For example, after radiotherapy of the head and neck area, the parotid gland often becomes hypoplasia and underactive. Research shows that when NRTN adenovirus is administered to a patient after such radiation therapy, the salivary glands will start producing NRTN mRNA, and NRTN will then increase the growth of parasympathetic neurons, which will ensure proper innervation of the glands and prevent their loss of function.[30]

The sweat glands innervate the cholinergic sympathetic neurons, so if the NRTN directs the parasympathetic fibers, after damage, to regenerate and innervate these glands, there will be gustatory sweating in Frey syndrome.[10] Pediatric Frey syndrome can occur as unilateral or bilateral. The unilateral form of the syndrome appears after forceps delivery, during which structures such as ATN or the facial nerve may be damaged mechanically. The bilateral form of the syndrome has no traumatic etiology.[9,10] This suggests abnormal growth of neurons without damaging them first. A hypothesis for this is that the sympathetic neurons do not innervate the sweat glands, and the parasympathetic neurons take their place and take over. This may be the case, for example, in familial dysautonomia[31] or Harlequin syndrome.[10,32]

Vasoactive intestinal peptide (VIP) is likely to have a vasodilating effect in exocrine glands such as the salivary glands, lacrimal glands and sweat glands.[33] The nerve networks associated with VIP concentrate around the sweat glands.[34] Nitric oxide regulates the release of VIP in the parasympathetic system.[35] VIP exists along with acetyltransferase in the parasympathetic ganglia. Nerve fibers containing VIP and nitric oxide synthase accumulate near the proximal parts of large arteries that supply muscles, glands, periorbital skin and mucous membranes.[36] Thus, the release of VIP from regenerating parasympathetic fibers can lead to pathological dysgeusia, inflammation, possibly by activation of vasomotor receptors previously stimulated by the sympathetic nervous system to dilatation. Confirmation of the hypothesis of VIP involvement in the pathogenesis of Frey syndrome will be possible after the development of antagonists and related neuropeptides for VIP safe for use in humans.[33]

Symptoms and clinical manifestations

According to the causes of syndrome there are various clinical manifestations of this condition. One of the examples featuring this ailment presented by Frey shows the case of 25 year-old male whose left side of the lower mandible was damaged by a pistol bullet.[37] Three months after injury he started complaining about some clinical manifestations, such as sweating and sensing warmth in the damaged area while he was eating. The symptoms occurred along with skin redness. Another thing that the patient had been annoyed about was that people in public places stared at him in some weird way. They thought that he was eating too voraciously.[38] Another case shows the 25 year-old male who experienced a traffic accident. Examination revealed superolateral dislocation of the left condyle, associated with mid-symphyseal fracture. No other damages were serious or required operation, so doctors'

decision was to reduce the disjoint and manage the crack under general anesthesia. Twenty months after successful surgery he reported sweating in the left preauricular region while eating, what finally leads to diagnose Frey syndrome.[25] It is well-known that the ailment occurs more often in adults, but among pediatric patients it is reported relatively rare, for example because of being frequently misdiagnosed.[39]

Another case represents the healthy 5 year-old male boy who was visiting a dental clinic. His medical history was notable for a delivery with forceps assistance. Boy's appointment included a dental hygiene procedure and a restoration of the right primary first molar. Local anesthesia was administered (1.8cc of 2% lidocaine with epinephrine 1:100000) right after nitrous oxide induction. 20 minutes after starting the treatment the flush appeared on the child's right cheek. It disappeared within 45 minutes, no other symptoms were seen. Father of the boy reported that several flush episodes occurred in the past, especially after consuming spicy foods or sour candies. He added that those events were considered by the pediatrician as gustatory flushings.[40]

Another case shows the 9 month-old male who was examined because of recurring and periodic flushing on the left side of face. It occurred the most frequently 30-60 minutes after eating, especially when trying new foods or sour things, and it was located over the innervation range of auriculotemporal nerve. The significant matter was that the patient's medical history revealed a delivery with forceps assistance. Further physical exam findings and characteristic manifestations led to detect Frey syndrome.[41]

Taking all mentioned cases into consideration, Frey syndrome is known for manifesting clinically in several ways. It is often characterized by sweating of the face in the distribution of the auriculotemporal nerve.[9] Another symptoms are feeling warmth along with flushing which are not related to other conditions, for example allergic reactions.[4] No other symptoms are observed in the development of this syndrome and the skin lesions are limited to lacking, sweating, erythema but without itching. Their manifestation usually occurs unilaterally with segmental distribution.[41] Opposite to adults, children with Frey syndrome do not often suffer from sweating.[42] Another thing that often occur as characteristic symptom in both younglings and grown-ups, is a gustatory hyperhidrosis. It is described as a local and excessive sweating involving face, scalp or forehead, due to ingesting or smelling specific food products.[43] Those nutrients appear to be carrots, candies, apples, citrus fruits, spicy dishes, coffee and chocolate.[42,43]

It may also be useful to distinguish Frey syndrome between allergic reactions. Differentiating those two conditions, Frey syndrome is often unilateral and allergies are bilateral and nonsegmental. The first one appears without any respiratory and gastrointestinal symptoms and no anaphylaxis is present, but all of those may be observed in the second one. Also common nutrients that evoke allergies are different in both conditions – in allergic reactions they are soy, eggs, wheat, peanuts, fishes, cow's milk in contrast to Frey syndrome where causative agents are other. Also skin lesions are not manifested the same in both conditions. During allergic reactions itching is present, flush isn't limited to the face and angioedema may be present. Knowing Frey syndrome characteristic clinical features and manifestations is essential to habituate an adequate treatment.[42,44]

Treatment

Due to unpleasant symptoms caused by the syndrome, several treatment methods are proposed, including topical injection of alcohol (method first proposed by Frey in 1923), scopolamine, glycopyrrolate and botulinum toxin A. Most commonly used treatment nowadays are intradermal injections of botulinum toxin.[45] First improvements after therapy can be noticed after four to seven days, with the regress of flushing and decrease of gustatory sweating.[46]

Studies show that after BTA injection, recurrence of the syndrome appears in up to 27% and 92% cases at 1 and 3 years respectively.[1] Despite the recurrence, botulinum toxin A is most effective pharmacological agent available, based on studies which has investigated dosage between 1,9 and 2,5 U/cm² in area affected by Frey syndrome.[47] However, as none randomized control studies have been documented, conclusions based on efficacy of therapy shouldn't be made.[1,2]

Methods of treatment	Year of introduction	Reiteration	Mechanism of action
Injection of scopolamine (3%)	1958, Laage-Hellman	96 hours on average [48]	Local depression of sweat production and vasodilatation [48]
Injection of glycopyrrolate	1974, Abell	Every 4-6 weeks [49]	Antimuscarinic agent
Topical injection of botulinum toxin A	1995, Drobik	Every three months [45]	Anticholinergic effect, paralyses glands and striated muscles [45]

Tab. 1 Frey syndrome treatment methods [45,48,49]

Another treatment option, historically considered by physicians, was surgical treatment of Frey syndrome. There have been reports for surgical transections of auriculotemporal nerve, tympanic nerve and greater auricular nerve, but they are not commonly used, due to the risk of facial nerve injury and limited number of studies. Surgical methods should be considered only for patients, for whom nonsurgical measures are completely ineffective.[1]

Conclusion

Frey syndrome affects around several dozen percent and it is highly unspecified. Some patients may occur without symptoms, which makes diagnostics more difficult. However, the symptoms may be very problematic and worsens the quality of life of patients. Auriculotemporal nerve may be damaged as a result of its iatrogenic cut during the surgery (for example parotidectomy) or after resection of superior cervical ganglion, craniofacial injuries, mandibular condylar fracture or burns. This may lead to redding of the skin due to vasodilatation, excessive sweating or tingling and burning sensation of the cheek skin. There has been proposed nonsurgical treatment such as alcohol topical injection, scopolamine, glycopyrrolate and botulinum toxin type A (most common) or more invasive and less used surgical treatment such as transection of auriculotemporal nerve, tympanic nerve or greater auricular nerve. Patients with described symptoms should be always considered with Frey syndrome and fully diagnosed.

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