Diagnosis and Management of Frey Syndrome

Frey syndrome is characterized by sweating and flushing of the facial skin during meals. There is no direct relation with chewing. Once present, the gustatory sweating and flushing remain unchanged, i.e., there is no spontaneous resolution, even after numerous years. While "Frey syndrome" is a well-accepted eponym, following Lucie Frey's description [1], cases of gustatory sweating were already reported in the nineteen-century and the first description should be attributed [2] to Baillarger in 1853.

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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. Pre-ganglionic parasympathetic efferent fibres leave the inferior salivary nucleus and the brain stem with the glossopharyngeal nerve to follow the tympanic (Jacobson's) nerve in the inferior tympanic canaliculus towards the middle ear cavity. A plexus is formed on the promontory, but the parasympathetic fibres not supplying the middle ear unite to form the lesser superficial petrosal nerve, which travels on the floor of the middle cranial fossa. The parasympathetic fibres then re-exit the skull through the foramen ovale and reach the otic ganglion where they synapse with post-ganglionic parasympathetic fibres. These post-ganglionic parasympathetic fibres then join the auriculotemporal nerve and reach the parotid gland through its medial aspect in the parapharyngeal space. Like all post-ganglionic parasympathetic neurons, the neurotransmitter of these fibres is acetylcholine. The receptors are of the M3 subtype[3].

The key player in Frey syndrome are the sympathetic fibres for the cutaneous vessels and sweat glands which follow the cervical sympathetic chain and a synaptic relay is found in the sympathetic cervical ganglions. The fibres then follow the periarterial plexuses of the internal and external carotid arteries and their branches [4,5]. The result of sympathetic activation is increased secretion from sweat glands and vasoconstriction. In contradistinction to other postganglionic sympathetic fibres, which are adrenergic, sweat glands have acetylcholine as the main neurotransmitter, predominantly of the M3 subtype [6].

Pathogenesis

A number of different theories have been proposed to explain Frey syndrome. The presently accepted explanation is the so-called aberrant regeneration theory, which postulates that the severed parasympathetic fibres to the parotid gland regenerate along the wrong neurilemmal sheaths of the sectioned cutaneous sympathetic fibres. The traumatized fibres loose their parotid targets and regenerate to innervate the vessels and sweat glands of the overlying skin. The regular function of the parotid parasympathetic fibres 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").

Etiology

The causes of Frey syndrome could be grouped in three categories: 1) simultaneous lesion of the parasympathetic and sympathetic fibres, of which parotidectomy and trauma or other interventions of the parotid region are examples; 2) surgery or lesions of the cervical sympathetic chain; 3) other nerve lesions allowing for aberrant reinnervation, such as

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herpes simplex or diabetic neuropathy. To these should be added a category of "physiologic" gustatory sweating and flushing which can be induced by certain spicy foods such as chillies in normal subjects [7], as already reported by Claude Bernard and Brown-Sequard [2]. In contradistinction to Frey syndrome, this "physiologic" gustatory sweating and flushing is bilateral and usually symmetrical [7], similar to physiologic thermal sweating. The sporadic reports of children with bilateral gustatory flushing, without sweating, are probably related to this last category.

The development of Frey syndrome after cervical sympathectomy, without lesions of the parotid parasympathetics, 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 loss of postganglionic sympathetic neurons and the resulting denervation of the corresponding facial skin targets. Regeneration of parasympathetic fibres is a secondary event although it accounts for the observed symptoms.

Investigation of gustatory sweating

Since the most troublesome symptom of Frey syndrome is sweating, testing for Frey syndrome has in general been limited to sweating. The ideal test method should provide topographic information and quantification of the amount of sweating. 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; 7) low cost [8].

The most frequently used method of sweat secretion assessment of sweating was originally described by Victor Minor. A solution containing 1.5 g iodine, 10 g castor oil, and 88.5 g of absolute alcohol is painted on the skin. After drying, the areas are powdered with starch. The water in the sweat produces blue colouring 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. Among the numerous disadvantages of the Minor test [8], we were especially bothered by the difficulty of using the method with heavy perspiration, because of the dripping that obscures the assessment of the dependent skin, and by the fact that the reagents should be removed and the skin disinfected prior to botulinum toxin injection, while maintaining the topographic mapping.

We recently applied two techniques for the evaluation of Frey syndrome [8]. In the iodine-sublimated paper histogram (ISPH) method, regular office paper is sublimated with iodine and acquires the property of changing colour when wetted. The paper could than be digitized and a histogram algorithm applied to measure the area of colour change. A calibration of these tests with known and appropriate quantities of saline was performed and an excellent correlation found.

Incidence

The reported incidence of gustatory sweating after parotidectomy is highly variable, supporting Laage-Hellmann's conclusion that Frey syndrome is an unavoidable sequel of parotidectomy that is not overtly symptomatic in all patients. About 50% of patients with Frey syndrome are symptomatic and among those half judge their symptoms "important or embarrassing".[9] The correlation between the severity of sweating and intensity of the Minor test was not good. [9]

Treatment

The treatment modalities available for Frey syndrome were reviewed elsewhere.[10] Considering that the symptoms are not always very troublesome, it is important that the treatment itself does not result in side-effects that are more serious. Because of the ease of use, tolerance, and lack of side-effects of intradermal injection of botulinum A toxin [10], previously reported treatments should be regarded as historic. The only disadvantages are the pain associated with the needle injection and the reluctance of some patients to be injected, especially on the face.

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, with type A toxin acting on SNAP-25. 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. 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.

Our technique starts by mapping the involved area by the ISPH technique. Once the area is delimited injection sites 1 cm apart are infiltrated with 0.1 ml (5 IU) of a solution containing botulinum toxin at a concentration of 5 IU per 0.1 ml.[10] All patients treated so far had a resolution of their clinical symptoms. On objective testing, the surface involved decreased from 29 ± 22 cm^2, before treatment, to 0.6 ± 0.4 cm^2, after treatment. The pain associated with the needle injection was evaluated by our patients to be minimal (2/10 on an analog visual pain scale),[10] a result found also in other studies.

We did not experience any facial paralysis side-effects of the botulinum toxin injection, as reported by others.[11] It is difficult to understand how a strictly intradermic 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 fibre trunks. Therefore, the most plausible explanation of this rare and partial temporary paresis is an injection deep to the dermis and diffusion to facial motor end plates.

A consensus on the exact botulinum toxin injection modalities for gustatory sweating treatment seems necessary, prior to its generalization. There seems to be an agreement on the 10-mm inter-injection distance and on an injection dose of 0.1 ml.[10] The main differences concern the concentration of botulinum toxin: small volumes of concentrated 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 concentra-

tion. We used a concentration of 50 U per 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 [12, 13] have obtained good results with a lower dilution (25 U per ml) and this dosage might be advantageous in patients who have a large surface of gustatory sweating.

Apparently, the duration of the effect of botulinum toxin on gustatory sweating is rather long lasting, with an average of 15 months.[12, 13] An actuarial estimate was recently published,[12] with clinical gustatory sweating recurrence at 1, 2, and 3 years of 27%, 63%, and 92% respectively. The severity of the recurrent Frey syndrome was found to be reduced when compared to that of the initial episode and re-treatment with botulinum toxin was still effective.[12]

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