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Frey's syndrome: treatment with botulinum toxin

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Abstract

Frey's syndrome, i.e. gustatory sweating on the cheek, is a fairly common embarrassment after parotid gland surgery. New surgical techniques have been proposed to avoid this complication, but are not widely in use. Hence, there is need for treatment of Frey's syndrome. All surgical and topical treatments have drawbacks. This study was set up in order to evaluate a recently described treatment. One hundred and two patients were interviewed after parotidectomy. Thirty-one of them had noticed gustatory sweating and 15 patients underwent Minor's starch iodine test before, and after, treatment with intracutaneous injections of botulinum toxin A (Botox®, Allergan Inc., USA). Thirteen of the patients did not experience any gustatory sweating at follow-up (one to 13 months). Minor's starch test showed total disappearance of gustatory sweating in 12 of the 15 treated patients. The only side effect was a discreet, transitory affection of the orbicularis oris muscle in one patient. As this treatment is minimally invasive it could be an attractive treatment for Frey's syndrome if the effect is maintained. Complaints of local hypoaesthesia and pain were also common after parotid surgery.

Key words: Auriculotemporal syndrome; Sweating, gustatory; Hyperhidrosis; Botulinum toxins, Surgery, parotid gland

Introduction

Frey's syndrome is a phenomenon comprising sweating and flushing of the skin on the cheek, forehead or in the submandibular region (Young, 1956). The symptoms appear during meals. Some foods, e.g. apples, trigger the sweating more easily. The very first description of the syndrome is attributed to Duphenix in 1757. Both in this one, as in the second case in the literature documented by Lucie Frey in 1923, injury was the cause of their problems. Nowadays gustatory sweating usually develops after parotid gland surgery, radical neck dissection (Spiro and Martin, 1967) or submaxillary gland surgery. It has also been seen after thoracocervical sympathectomies (Haxton, 1948). Diabetic neuropathy is a rare cause of gustatory sweating (Mealey, 1994). The incidence of Frey's syndrome after parotidectomy has been reported to be as high as 100 per cent (Laage-Hellman, 1958), when the Minor's starch test was used for diagnosis. Although many of these patients are asymptomatic, Spiro and Martin (1967) found that 30 per cent were severely embarrassed by sweating after parotidectomy.

The cause of Frey's syndrome is said to be a misdirected regeneration of damaged axons (Ford and Woodhall, 1938). When the skin is raised during parotidectomy the postganglionic sympathetic fibres to the sweat glands in the flap are severed. Unlike most postganglionic sympathetic fibres these nerves are cholinergic, not adrenergic. Postganglionic parasympathetic fibres from the auriculotemporal branch of the mandibular nerve feeding the parotid gland are also severed when the salivary gland is removed. This opens the possibility of abnormal regeneration to parasympathetic, secretory innervation of the sweat glands. Sweating consequently appears on gustatory stimulation.

One of the first prophylactic approaches to Frey's syndrome was to resect the auriculotemporal nerve during parotidectomy (Kidd, 1955). Others used the sternomastoid muscle flap to prevent anastomotic nerve communication with the sweat gland and to avoid the concave deformity due to the removal of parotid tissue (Kohnblut *et al.*, 1974). Singleton and Cassisi (1980) found that the incidence of Frey's syndrome was lower when using thick skin flaps. Later, Bonanno and Casson (1992) included the superficial musculoaponeurotic system (SMAS) in the flap for the same purpose. Dermis-fat grafts (Harada *et al.*, 1993), expanded polytef (Shemen, 1995) and temporoparietal fascial flaps (Sultan *et al.*, 1995) have also been used to cover the defect and attempt prevention of Frey's syndrome.

Treatment of Frey's syndrome with topical administration of 20 per cent aluminium chloride in alcohol solution (Erickson, 1985) or one per cent glycopyrrolate roll-on lotion (Hays *et al.*, 1982)

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TABLE I
DESCRIPTION OF THE 102 INTERVIEWED PATIENTS

Mean age	58.3 years	
Range	20–89 years	
Gender	65 women, 37 men	
Side of operation	54 right, 48 left	
Type of operation	Resection of parotid gland	17
	Superficial parotidectomy	68
	Total parotidectomy	17
Diagnosis	Pleomorphic adenoma	75
	Warthin's tumour	14
	Sialoadenosis	4
	Mucoepidermoid carcinoma	2
	Angioma	2
	Monomorphic adenoma	2
	Acinic cell carcinoma	1
	Epithelial-myoepithelial carcinoma	1
	Benign lymphoepithelial lesion	1

TABLE II
THE QUESTIONS AND ALTERNATIVE ANSWERS IN THE INTERVIEW

Post-operative facial palsy	Grade 1–none, 5–total
	Initial or final
Pain	Grade 1–none, 5–severe
Hypoaesthesia	Grade 1–none, 5–total
Cosmetic aspects of scar	Grade 1–dissatisfied, 2–acceptable, 3–satisfied
Gustatory sweating	Grade 1–none, 2–slightly damp, 3–wet, 4–drips
	Occurrence (months post-operative)
	Duration (months)
	Symptoms unaltered, decreasing or getting worse
	Trigger mechanisms

provides only temporary relief. Use of three per cent scopolamine hydrobromide cream (Laage-Hellman, 1958) may even have systemic anticholinergic side effects.

Surgical intervention of gustatory sweating with resection of the auriculotemporal nerve is technically difficult and often only has temporary effect (Coldwater, 1954). Golding-Wood (1962) was the first to report patients treated with intratympanic sectioning of Jacobson's nerve and simultaneously he performed chorda section in some cases. Another treatment has been to raise the flap again to place fascia lata graft under the skin (Roark *et al.*, 1975). Small skin areas with sweating can actually be excised (Redleaf and McCabe, 1993). After having treated one patient successfully by destruction of the stellate ganglion by aqueous phenol solution, Duthie and Dunkley (1981) proposed this method to be performed routinely where definitive treatment was considered necessary. Thoracoscopic sympathectomy is an effective treatment for hyperhidrosis of the face (Drott *et al.*, 1995) with a satisfactory result in 80 per cent. A common complication is compensatory increased sweating in non-treated areas. Haemothorax, pneumothorax, Horner's syndrome and even mortality are also described.

The bacterium, *Clostridium botulinum* produces seven serotypes of botulinum neurotoxin (BT). These, primarily inactive, polypeptide chains of 150 kDa are released by bacterial lysis and cleaved in a heavy (100 kDa) and a light (50 kDa) chain with different roles in nerve cell intoxications (Montecucco and Shiavo, 1994). The intoxication is a four-step process: cell binding, internalization, membrane translocation and catalysation of the hydrolysis of peptide bonds in the cytosol. BT blocks the release of acetylcholine at peripheral cholinergic nerve terminals thereby preventing neurotransmission. The most important effect is at the neuromuscular junction resulting in degeneration of the intoxicated synapse and muscle paralysis. Even though BT is the most potent toxin known it does not cause death of the neurons. Consequently, within some weeks, the motor neuron sprouts around the dead synapse and after a few months a functional neuromuscular junction has reformed. Therefore, the beneficial effects of BT used in a variety of dystonias e.g.

TABLE III
DESCRIPTION OF THE 15 PATIENTS TREATED WITH BT

Name	Age (years)	Operation	Diagnosis	Debute of FS (months)	Duration of FS (months)
JL	47	S	Benign lymphoepithelial lesion	6	90
MJ	32	S	Pleomorphic adenoma	1	242
OP	20	S	Monomorphic adenoma	3	25
OK	38	S	Pleomorphic adenoma	12	27
DB	53	T	Mucoepidermoid cancer	6	105
NM	60	S	Pleomorphic adenoma	6	31
CB	69	S	Pleomorphic adenoma	6	26
PK	74	R	Pleomorphic adenoma	6	96
GE	74	T	Acinic cell carcinoma	48	54
NA	52	S	Pleomorphic adenoma	6	112
JI	59	S	Pleomorphic adenoma	6	135
KG	52	S	Pleomorphic adenoma	3	134
AA	36	S	Pleomorphic adenoma	1	55
AS	65	S	Pleomorphic adenoma	6	84
PM	69	R	Pleomorphic adenoma	3	84

R = resection of parotid gland
S = superficial parotidectomy
T = total parotidectomy

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TABLE IV
GRADING OF THE REACTION OF MINOR'S STARCH TEST

Grade	Number of spots/cm^2
1	0–4
2	5–9
3	10–19
4	>20

laryngeal dystonia, spasmodic torticollis and hemifacial spasm (Brookes *et al.*, 1995) only last for two to five months. The effects of intoxications are thus fully reversible.

BT also acts on cholinergic autonomic nerve terminals (Sellin, 1981). Both the parasympathetic nerves stimulating salivary gland secretion and the sympathetic fibres that cause sweating are cholinergic autonomic fibres. This is why the regeneration of axons can be misdirected and why BT inhibits both salivation and sweating.

In 1994 Drobik and Laskawi proposed treatment of Frey's syndrome with injections of BT. The following year they presented a case with 12 months follow-up (Drobik and Laskawi, 1995) and in the same year 14 cases with a maximum follow-up of 13 months (Drobik *et al.*, 1995). They distributed 0.1 ml BT in areas of 4 cm^2 i.e. 0.5 U/cm^2. The last contribution in evaluating this new treatment was made by Schulze-Bonhage *et al.* (1996). In this report three cases with successful treatment followed for six to eight months were presented. These three articles, with a total of 17 treated patients, suggest that BT injection is a simple, secure and effective treatment. Long-term follow-up results are, however, lacking.

Materials and methods

Between 1985 and 1995, 460 patients have undergone major salivary gland operations by eight surgeons in our department. Two hundred and eighty-nine of these patients had operations on the parotid glands. Of this last group, 102 patients were randomly selected. A description of these patients appears in Table I. The 102 selected parotidectomized patients were interviewed more than six months after the operation. The questions and the alternative answers are outlined in Table II.

Thirty-one patients had noticed sweating on the cheek during meals. Fifteen of these patients accepted participation in the study and had the sweating documented by Minor's starch test (Minor, 1927). This group is described in Table III. Informed consent was given and the study was approved by the Medical Products Agency.

The area on the affected cheek was painted with a solution of iodine, 15 g, ricine oil, 100 g, and alcohol, 900 g (Minor, 1927). After drying, potato starch was powdered onto the iodine-coloured skin. Chewing a

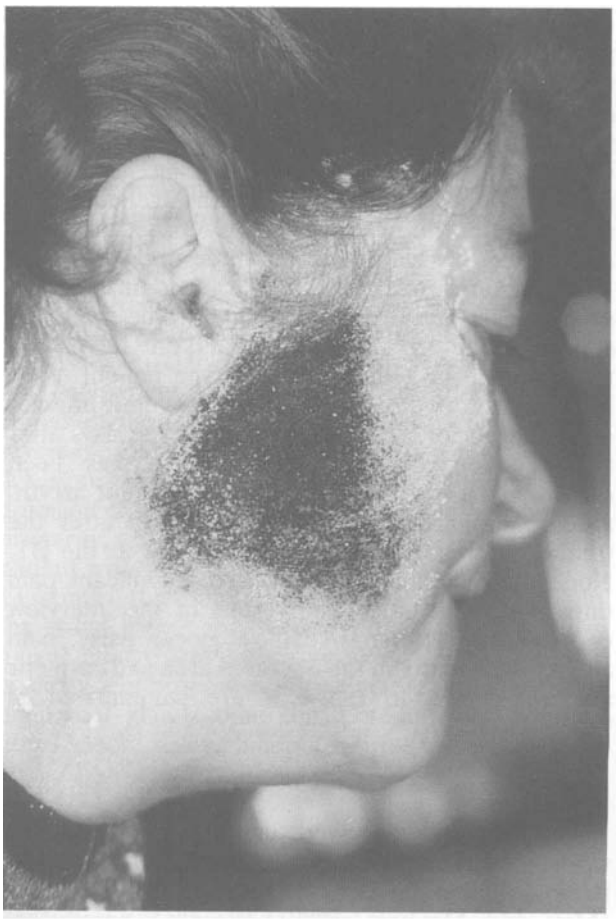

FIG. 1
Profuse gustatory sweating demonstrated with Minor's starch test before treatment in patient JI.

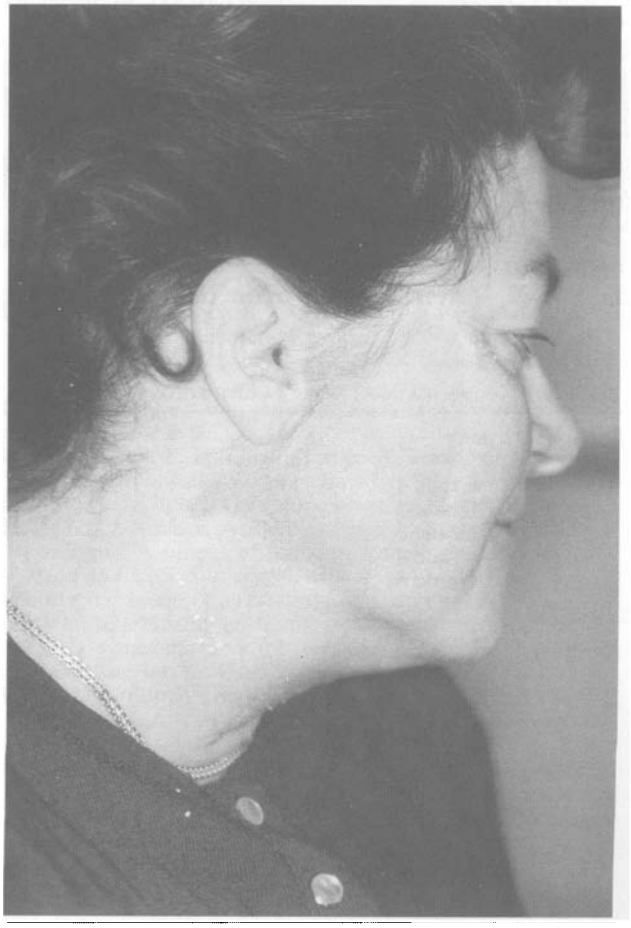

FIG. 2
Absence of gustatory sweating demonstrated with Minor's starch test after treatment in patient JI.

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TABLE V
THE EFFECT OF THE TREATMENT

Name	BT dose (U)	Follow-up (months)	Symptom before BT	Symptom at last follow-up	Minor's test before BT	Minor's test at last follow-up
JL	17.5	13	3	3	4	4
MJ	30.0	13	4	1	3	1
OP	32.5	12	4	1	4	1
OK	25.0	9	3	1	3	1
DB	45.0	9	4	1	4	2
NM	32.5	7	3	1	3	1
CB	40.0	7	3	1	3	1
PK	25.0	7	2	1	4	1
GE	45.0	6	3	1	3	1
NA	35.0	6	4	2	3	2
JI	62.5	6	3	1	4	1
KG	50.0	1	3	1	4	2
AA	50.0	1	3	1	2	1
AS	37.5	1	4	1	4	1
PM	37.5	1	3	1	3	1
Mean	37.67	6.60	3.27	1.20	3.36	1.40

sour candy for five minutes exposed the hyperhidrotic area with small, black spots when the sweat from the glands started a chemical reaction with the iodine. The reaction was graded, see Table IV. This area was photographed (Figure 1) and the margins marked with a waterproof pen before cleaning the skin with water. To avoid pain on injection a cream of lidocain and prilocain (EMLA®, Astra, Sweden) was placed on the area and covered with an occlusion dressing for 45 minutes. After cleaning, BT was uniformly intracutaneously injected using an needle with a diameter of 0.45 mm. In each site we injected 0.1 ml of a solution containing 2.5 U of Botox®. The first patient (JL) was injected at 20 mm intervals with a dose of 1.2 U/cm^2. Because of insufficient effect, the other patients were injected at 10 mm intervals with a dose of 2.5 U/cm^2. The total dose given varied with 17 to 62.5 U, i.e. seven to 25 injections. The effectiveness of the BT treatment was evaluated at about seven days, three and 12 months by Minor's starch test, interviews and photographs (Figure 2). The patients were particularly asked about side-effects.

TABLE VI
COMPLICATIONS AFTER PAROTIDECTOMY

		Initially	Finally
Facial nerve palsy			
	Grade 1	85	98
	Grade 2	3	2
	Grade 3	6	0
	Grade 4	5	1
	Grade 5	3	1
Pain			
	Grade 1	75	
	Grade 2	10	
	Grade 3	6	
	Grade 4	1	
	Grade 5	0	
Hypoaethesia			
	Grade 1	47	
	Grade 2	34	
	Grade 3	12	
	Grade 4	3	
	Grade 5	5	
Cosmetic aspects related to the scar			
	Satisfied	84	
	Acceptable	13	
	Dissatisfied	5	

Results

Thirty-one of the 102 interviewed patients answered that they became wet on the cheek during meals. The gustatory sweating had started after a median time of six months after surgery (range one to 242). Three of these patients considered the symptoms were getting worse and two had spontaneous regression. One week after the treatment with BT injections all patients but one (JL) observed that the gustatory sweating had disappeared completely. After 13 months JL had a total recurrence. Another patient (NA) had a slight recurrence of symptoms at three months. With Minor's starch test, 11 of the 15 patients had no sweat reaction at the last follow-up, while three had slight reaction on certain places, and one (JL) had a total recurrence (see Table V). One patient (KG) had a transitory discrete effect on the mimic muscles at the corner of the mouth starting three days after the injection. No general weakness has been observed. One patient (DB) with recurrent arrythmias experienced a fibrillation the day after the treatment, but this could not be linked to the BT. None of the patients experienced significant pain during the injections. The results of the interview concerning post-operative facial nerve palsy, pain and hypoaesthesia in the operated area and cosmetic aspects related to the scar are summarized in Table VI.

Discussion

Symptoms of Frey's syndrome after parotidectomy were experienced by 31 per cent of the patients. The incidence is comparable to that of other authors (May and McQuirt, 1989). We also noted that hypoaesthesia of the earlobe affected 59 per cent and pain or discomfort 18 per cent by the time of the interview. This is in accordance with another study

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where 43 per cent had hypoaesthesia and 24 per cent pain (Faber and Pedersen, 1996). The cause of these side effects is probably division of the greater auricular nerve. If possible, division should therefore be avoided. Only five per cent were not satisfied with the scar. Thus use of face lift incision at parotidectomy does not seem to be of great importance in most patients.

Immediate post-operative facial nerve palsy was present in 17 of the 102 interviewed patients. At the time of the interview one patient had total facial nerve palsy (grade 5) (Sandstedt *et al.*, 1981) and four had partial facial palsy (grade 2, 3 and 4). Although facial palsy is the most important complication that patients should be informed about prior to the operation, it is appropriate to also mention the possibility of these other side-effects. Few patients would reject an operation on the grounds of these minor complications, but it is better to have well-informed patients.

The gustatory sweating was totally absent in the BT treated area, both subjective and objective, in 11 of our 15 patients at last follow-up. Discrete sweat production was seen on Minor's starch test in three patients and a total recurrence in one patient. This confirms the success of the earlier studies, but also proves that total recurrence can occur. Drobik *et al.* (1995) tunnulated a 4 cm^2 skin area with the cannula giving 0.5 U Botox®/cm^2. Schulze-Bonhage *et al.* (1996) distributed the BT in 'equidistant sites' not mentioning the distance between each site. In our study, we injected 2.5 U/cm^2 in all but one patient. The quantity of Botox® used per cm^2 gives important information when discussing the lowest effective dose. The total amount of injected BT was well under the recommended maximum dose of 200 U since no patient received more than 62.5 U and the mean dose was 37.7 U (see Table V). We injected the BT in sites 10 mm apart and kept the cannula strictly intracutaneous, while the sweat glands are situated between the corium and subcutaneous layer. We also wanted to avoid the mimic muscles. Despite this, one patient developed a discreet affection in the corner of the mouth. The resulting palsy was fully reversible. Side effects of BT are related to overdoses or incorrect injections into a muscle or diffusion to a muscle. A place which is not treated primarily, can without problem be injected later. The patient with total recurrence (JL) was re-injected at 13 months. It is still unclear why the effects of BT on the sweat glands involved in gustatory sweating is longer than the effect on muscles. Is the sprouting capacity less pronounced for nerve endings regulating sweat glands than for those affecting muscle fibres? More research could resolve this issue.

Conclusion

In this study we found an incidence of Frey's syndrome of 31 per cent after parotid gland surgery. Prevention of this side-effect is preferable and consequently surgical technique utilizing interposing flaps or grafts ought to be more common. Gustatory sweating will, however, still be a problem for some patients and a secure, minimally invasive treatment with good and longstanding effect could be intracutaneous injections of BT. We treated 15 patients with 2.5 U Botox®/cm^2 except for one who received 1.2 U/cm^2. Thirteen had no symptoms of gustatory sweating at the last follow-up at one to 13 months. Since Frey's syndrome can occur after several years (Haxton, 1948) it would be wise to await the results of further follow-up before this treatment can be finally evaluated.

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