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BOTULINUM TOXIN FOR TREATMENT OF FREY'S SYNDROME

Report of two cases

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ABSTRACT - Frey's syndrome is a phenomenon of hemifacial flushing and sweating after gustatory stimulus, usually secondary to surgical trauma over the parotid gland, although other injury mechanisms may be seen. It is accepted as a result of aberrant regeneration of facial autonomic nerve fibers. Treatment evolved from ineffective medical and surgical approaches to botulinum toxin. We evaluate the effectiveness and safety of botulinum toxin in the treatment of this complication in two patients.

KEY WORDS: Frey's syndrome, botulinum toxin, gustatory sudoresis.

Toxina botulínica para o tratamento da síndrome de Frey: relato de dois casos

RESUMO - A síndrome de Frey é caracterizada pela presença de sudorese e rubor hemifacial, que ocorre após estímulo gustatório, usualmente secundário a trauma cirúrgico da glândula parótida. Acredita-se que esta disfunção ocorra como resultado de regeneração aberrante de fibras autonômicas do nervo facial. O tratamento inclui abordagens clínicas e cirúrgicas, geralmente ineficazes, bem como o uso de toxina botulínica. Avaliamos a eficácia e segurança do uso de toxina botulínica no tratamento desta complicação em dois pacientes.

PALAVRAS-CHAVE: síndrome de Frey, toxina botulínica, sudorese gustatória.

Frey´s syndrome (FS) was defined by Young in 1956 as a phenomenon secondary to gustatory stimulus, manifested by flushing and sweating of parotid, frontal and submandibular areas consequent to trauma on parotid or another major salivary gland[1]. It was first described by Duphenix in 1757, and named after Lucie Frey´s detailed description in 1923[2]. FS is a common complication of parotidectomy. May and McGuirt[3] found 50% of their postoperative patients to be affected by facial sudoresis after gustatory stimulus. Fifteen percent of these patients reported severe symptoms. Laage-Hellman found an almost 100% prevalence in post-parotidectomy patients, using Minor starch-iodine test as a diagnostic criterion [4]. This test, brought to light in 1921, is performed by painting the affected hemiface with iodine staining and waiting for it to dry. This area is subsequently powdered with starch, which renders visible the sweating reaction. To elicit salivation, the patient is then asked to chew a lemon slice for 5 minutes. Appearance of black spots over the starched field constitutes a positive result, generated by a chemical reaction between iodine, dissolved starch and sweat, confirming sudoresis secondary to gustation. The margins of the black spots are drawn with a ball-point pen. Although FS is more commonly seen after parotid exeresis, suggestive symptoms were related as a consequence of parotid abscess drainage, fire arm injury over parotid gland, forceps delivery[5,6] and associated to central nervous system (CNS) diseases as syringomyelia, encephalitis and epilepsia[7].

This paper focuses on the effects of subcutaneous botulinum toxin (BT) in the treatment of two patients with FS.

CASES

Patient 1. A 16 years-old woman submitted to, parotidectomy for muco-epidermoid carcinoma. One year after surgery the patient presented a clinical picture compatible with FS. Minor test was positive for an area of 14 cm^2 (Fig 1). She received 35 units of BT, about 2.5 units per square centimeter of affected skin (Botox® 01 vial with 100 units diluted to isotonic saline 4 mL, achieving a 2.5 units /0.1mL concentration), applied subcutaneously in the region previously delineated on Minor test. She had symptomatic improvement from the thirdy day following application,

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corresponding to a negative Minor test on days 7 and 90 after treatment (Fig 2), with sustained response for 1 year.

Patient 2. A 56 year-old woman, submitted to parotidectomy due to pleomorphic adenoma. Two years after surgery she complained of FS symptoms, confirmed by Minor test, which demonstrated a 20cm2 area of gustatory sweat. BT 50 U led to significant improvement of symptoms for 10 months, confirmed by Minor test on day 7.

DISCUSSION

The proposed pathogenic process underlying FS is an aberrant regeneration of damaged axons[8]. Traction and detachment during parotidectomy tear post-ganglionic sympathetic fibers projecting over skin´s sweat glands. Cholinergic post-ganglionic parasympathetic fibers, most of them part of temporal auricular branch of mandibular nerve, are equally affected in their pathway to salivary glands. Therefore, abnormal regeneration leads parasympathetic fibers to supply sweat glands, lacking sympathetic innervation due to surgery, resulting in facial sweating secondary to gustation. FS was first believed to result from disoriented regeneration of temporal auricular nerve fibers only, which explains its initial designation "temporal auricular nerve syndrome". Laage-Heelman[9] found parotidectomy to injure nerve fibers from cervical plexus as well.

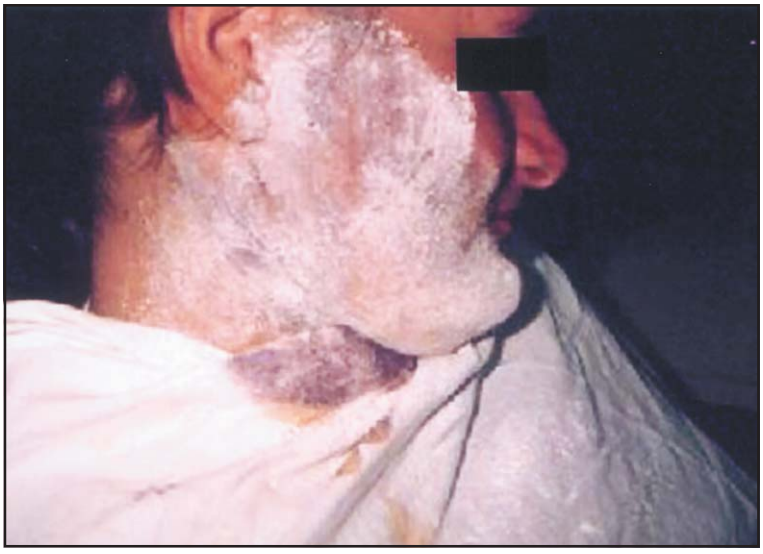

Fig 1. Patient 1. Minor test positive: there is a 14 cm² black spot over the starched area (positive to gustatory sudoresis).

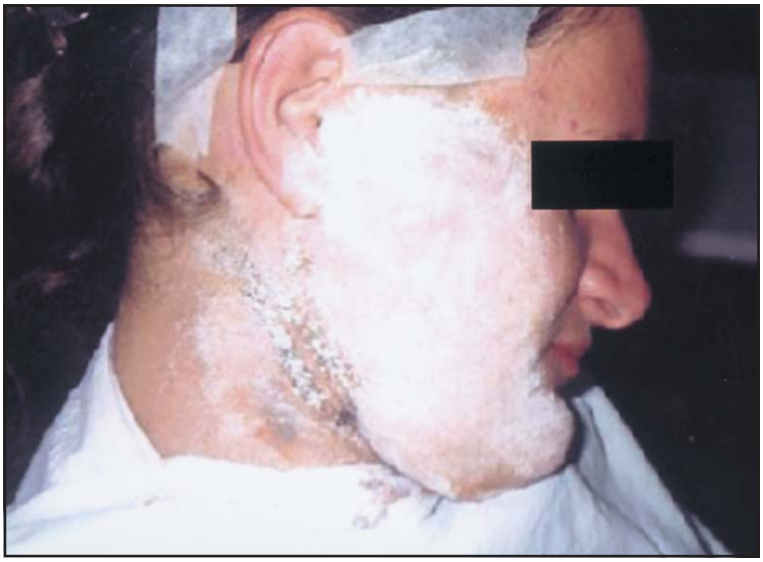

Fig 2. Patient 1. Minor test negative after use of botulinum toxin (35 units).

Many therapeutic approaches have been tried in FS, such as intratimpanical section of Jacobson nerve[4], systemic anticholinergic drugs[3] and topic aluminum chloride. Surgical procedures seem disproportionate to symptomatology and also ineffective. Anticholinergic drugs are not well-tolerated and are only slightly effective[7]. Botulinum toxin transiently blocks pre-synaptic acetylcholine release at the neuromuscular junction, leading to chemical denervation[10]. Since 1989 its effects have been assessed on dystonia, hemifacial spasm and then spasticity, myofascial pain, muscular tension-type headache and others[11]. Recently, its indications were expanded to syalorrhea, hyperhydrosis, stetical treatments, gastrointestinal disorders and gustatory sweating. Applied as subcutaneous injections, BT has a growing number of good results and adepts in the treatment of FS. It was first proposed in 1995 by Drobik and Laskawi[12], who described a 64 year old patient with gustatory sweating after total right parotidectomy. Six days after treatment with BT there was complete resolution of sweating, sustained for 7 months.

Bjerkhoel and Trobbe[13] presented results on 15 patients treated with BT for FS, with a 13 month follow-up. Seven days after application, all patients had a normal Minor test. After 13 months, one patient had total symptomatic recurrence, while 3 other patients had partial sweating in specific parts of the face. Eleven patients remained asymptomatic. One patient had transient facial paresis following BT treatment on day 3. Laccourreye et al.[14], in a follow-up study of 33 FS patients treated with BT, found recurrence rates of 27% in ther first year, 63% in the second and 92% in the thirdy year, by means of clinical assessment and Minor iodine-starch test. Nevertheless, patients reported prolonged improvement and recurrence remained amenable to reinjection of BT. Naumann et al.[15] followed 45 patients for a shorter period of 6 months, during which all patients were asymptomatic. Cavalot et al.[16] reported on 18 patients with severe FS (sweating at every meal) and 22 with intermittent episodes. More severely affected patients had satisfactory results, with reappearance of symptoms in 50%. Sixteen of 22 patients with a protracted course showed the best results, achieving symptom resolution.

Laskawi et al.[17] reported findings in 19 FS patients suited to single-application BT, with satisfactory results being obtained. About 44% of these patients reported sweat recurrence after 15 months. On examination through Minor test, sweat recurrence rate for that period was 70.5%[17]. Kuttner et al.[18] described 19 patients with severe gustatory sweating following superficial parotidectomy, treated with intracutaneous injections of botulinum toxin type A. The authors confirmed that botulinum toxin A are highly effective and safe treatment of gustatory sweating[18]. Similar results were published by Beerens and Snow with 13 patients with FS[19].

Recently, Guntinas-Lichius[20] compare the duration of effect of two dosages regimes of botulinum toxin A to treat patients with FS. This study demonstrated that using a higher concentration of botulinum toxin type A is more effective than a lower concentration in the treatment of FS[20].

Although BT is acclaimed as the safest and most effective treatment for FS, longer studies involving a more significant number of patients are needed.

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