

Botulinum Toxin on Frey Syndrome: Who to Treat? Case Report and Literature Review

Toxina Botulínica na Síndrome de Frey: Quem Tratar? Relato de Caso e Revisão da Literatura

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Abstract

Frey syndrome is mostly seen after parotidectomies and is an underdiagnosed surgical complication that may cause social inhibition and quality of life (QoL) deterioration. We report a case complemented with a literature review regarding the use of botulinum toxin on Frey syndrome.

We consulted the patient's file and photographed the Minor tests. We searched PubMed using the keywords: Frey syndrome; gustatory sweating; botulinum toxin.

A 43-year-old woman, diagnosed with a pleomorphic adenoma of the left parotid gland treated by parotidectomy was referred to our Physical and Rehabilitation Medicine department due to symptoms suggestive of Frey syndrome: flushing and sweating on the left parotid region during meals with impact on socialization and QoL. Minor test confirmed the diagnosis. The patient underwent intradermic infiltration of 46U of onabotulinum toxin A (Botox®) across the positive area on Minor test that matched the patient's complaints. Three weeks post-procedure, the patient denied hyperhidrosis (demonstrated on Minor test) and mentioned overall improvement on QoL.

Treatment is symptomatic and should be offered to those patients whose symptoms cause a negative impact on QoL. Botulinum toxin infiltration is currently the gold standard treatment, since it is a safe, effective and reliable procedure. The Minor test is essential to optimise botulinum toxin

dosage, thus reducing the possibility of occurring adverse effects.

Keywords: Botulinum Toxins, Type A/therapeutic use; Sweating, Gustatory/drug therapy

Resumo

A síndrome de Frey é observada maioritariamente após parotidectomias, sendo uma complicação cirúrgica subdiagnosticada que pode causar inibição social e deterioração da qualidade de vida (QV). Apresentamos a descrição de um caso clínico complementado por uma revisão bibliográfica do papel da infiltração com toxina botulínica (BoNT) na síndrome de Frey.

Efetuamos uma pesquisa bibliográfica na PubMed utilizando os termos “botulinum toxin”, “gustatory sweating” e “Frey syndrome”, consulta do processo clínico do doente e registo fotográfico do teste de Minor.

Relatamos o caso de uma mulher de 43 anos com diagnóstico de adenoma pleomórfico da parótida esquerda submetida a parotidectomia, complicada com sinais/sintomas sugestivos de síndrome de Frey: calor, rubor e sudorese na região parotídea esquerda durante as refeições, com interferência na socialização e QV. O teste de Minor confirmou o diagnóstico. Realizou-se infiltração intradérmica com 46U de BoNT Botox® na área positivada

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pelo teste de Minor coincidente com a clínica, sem intercorrências. Na reavaliação às 3 semanas, a doente negava hipersudorese (constatável no teste de Minor) e referia melhoria da QV.

A síndrome de Frey é uma complicação cirúrgica que pode acarretar inibição social e redução da QV, sendo o seu tratamento sintomático. De todas as opções terapêuticas, a infiltração intradérmica com BoNT tipo A é actualmente a primeira opção, uma vez que é segura e eficaz. O teste de Minor é essencial para otimizar a dose de BoNT, reduzindo assim a possibilidade de ocorrência de efeitos adversos.

Palavras-chave: Sudorese Gustativa/tratamento farmacológico; Toxinas Botulínicas Tipo A/uso terapêutico

Introduction

Frey syndrome or auriculotemporal syndrome consists of flushing and sweating at the cutaneous area innervated by the auriculotemporal nerve when salivating or masticating.¹⁻⁵ This clinical entity is caused by an aberrant reinnervation of the parasympathetic nerve fibers in the auriculotemporal nerve to the cutaneous blood vessels and sweat glands in the parotid region.² This aberrant reinnervation results from a mechanical or irritative lesion of these postganglionic parasympathetic nerve fibers, thus altering the salivation reflex arc response.¹ The main cause of this syndrome is parotidectomy. There is a wide range of reported incidences among the literature (43%-96%), which reflects different surgical techniques, different diagnostic criteria, underappreciation of the symptoms by the patient (with no impact on QoL) and unawareness of this syndrome by the physician.¹

It is important to notice that the symptoms do not appear immediately after surgery, with asymptomatic periods ranging from 2 to 22 months after surgery, which reflects the amount of time necessary for nervous regeneration and

subsequent aberrant reinnervation.¹⁻³

The diagnosis is clinical and can be confirmed by the Minor test. This test can be performed by applying an iodine solution at the pre-auricular, retromandibular, temporal and cervical areas. Once dry, a thin layer of dry starch is applied to the painted area and an oral stimulus with food or lemon juice is given to the patient. If sweat glands are active, a blue or violet punctiform area appears.²

The impact on QoL should be attained. Patients can have positive Minor Test, without reporting social inhibition or negative impact on QoL. As such, the Minor test should always be evaluated minding the patient's clinical context.

Primary prevention consists of surgical techniques that minimize the surgical wound, namely superficial partial parotidectomy *versus* total parotidectomy, and incorporation of a barrier between the parotid lie and the overlying cutaneous tissue. However, the results are often not satisfying.^{1,2}

Case Report

Forty-three-year-old female, with past medical history of right ovarian teratoma (treated with hysterectomy and right oophorectomy in 2016, medicated with tibolone), underwent a superficial parotidectomy in 2014 due to a left parotid pleomorphic adenoma.

As a complication of this last procedure, she developed an ipsilateral peripheral facial palsy (treated successfully with corticotherapy and rehabilitation program) and symptoms suggestive of Frey syndrome in 2015. The patient was kept under clinical surveillance and was referred to our Physical and Rehabilitation Medicine (PRM) department in September of 2018. A timeline of the patient's history is shown on Fig. 1.

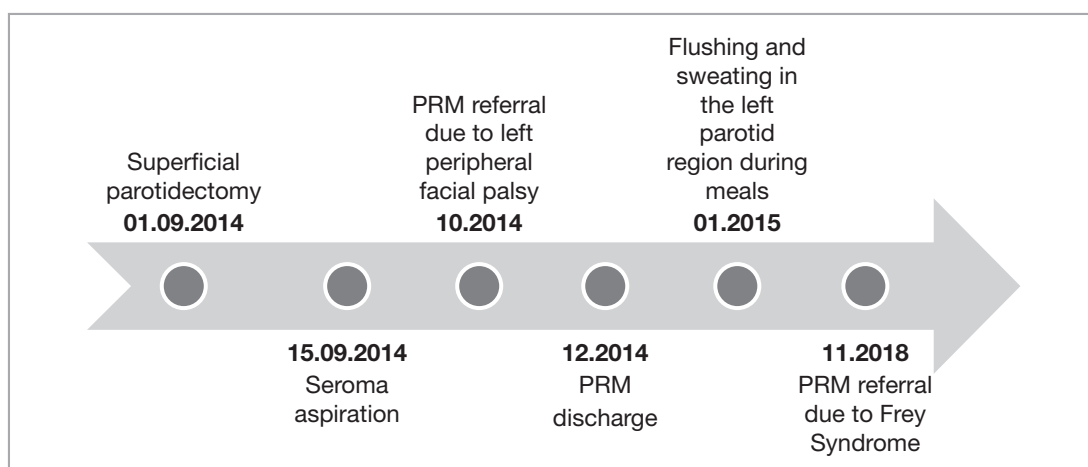


Figure 1 - Patient's history timeline.



Figure 2 - Minor test before botulinum toxin treatment.



Figure 3 - Minor test 3 weeks after botulinum toxin treatment.

At the first appointment, the patient complained of flushing and sweating at the left parotid area during meals with a negative impact on socialization and QoL. On inspection, she had a normotrophic scar, with no facial asymmetry. The Minor test confirmed the diagnosis and identified the affected area (Fig. 2).

Shortly after, the patient underwent an infiltration of 46U of onabotulinum toxin A (Botox®) at the area previously identified by the Minor test that matched her complaints. The procedure had no complications.

At 3 weeks post-procedure, the patient reported clinical improvement with no sweating, which was confirmed with the Minor test (Fig. 3) and overall marked improvement of QoL. A slight feeling of flushing persisted.

The patient was then instructed to reach out to our department when the symptoms relapsed to evaluate the need of a new botulinum toxin (BoNT) injection and, if so, the area to be treated. Twelve months later, we contacted telephonically the patient and she reported a relapse of the symptoms (mild flushing) but without significant impact on QoL.

Discussion

Treatment of Frey syndrome is symptomatic and is recommended when symptoms have a negative impact on QoL.¹ It can be surgical, with many surgical techniques described, among them reelevation of the skin and interposition of barriers of multiple natures (temporoparietal fascia or acellular dermal matrix) between the parotid lie and the skin.^{2,4}

A second option is the excision of the affected skin followed by a skin graft.¹

Tympanic neurectomy, where the tympanic plexus is sectioned in the middle ear, at the promontory, could also be considered. However, this procedure only has a temporary effect.^{1,2}

Recently, injection of adipose tissue, previously collected from the abdominal wall, in the area identified by the Minor test, has been tested. The aesthetic effect and symptomatic treatment of Frey syndrome is achieved after several sessions of treatment.

Conservative treatment options include oral anticholinergic agents (oxybutynin, scopolamine, glycopyrrolate), topical aluminium chloride and type A BoNT intradermic infiltration, with the latter being currently the gold standard of treatment.^{1,2}

BoNT irreversibly inhibits the presynaptic release of acetylcholine at the neuromuscular junction, preventing the aberrant parasympathetic synapse and subsequent sudation.^{1,3,4} The effect is temporary, due to nervous regeneration,¹ with reported symptomatic relief lasting from 6 to 18 months³ (longer than when used for spasticity treatment⁴). After successive treatments, the relapses seem to decrease in frequency and intensity. One theory to explain this phenomenon is a progressive atrophy of the sweat glands or of the smooth muscle that encircles them.⁴ Despite BoNT being an effective option, response to treatment varies between individuals. This variability is unrelated to gender, age, surgical dissection extension or surgical indication.³

Numerous dilution protocols and doses have been described (1.9 to 2.5 U/cm² onabotulinumtoxin A / Botox^{®2} and 10 U/cm² of abobotulinumtoxin A / Dysport^{®3}). The injection area should be identified considering the patients' complaints and the Minor test and the infiltration points

should be 1cm apart from each other. During follow-up, the procedure can be repeated, if necessary.

Though uncommon, local pain, rash, bruise, dry mouth and rarely facial hypesthesia or paralysis are the reported side effects.¹

Conclusion

Frey syndrome is a fairly frequent condition in a post-surgical context, but only 10% to 15% of the patients spontaneously report their symptoms, which leads to underdiagnosis of this entity.

Botulinum toxin is currently the gold standard of treatment and there are several protocols of BoNT infiltration with different doses and dilutions. The area where the treatment is applied should be well established by confronting the patients' complaints and the Minor test, thus avoiding excessive BoNT expenditure with no benefit for the patient and the risk of causing iatrogenic peripheral facial palsy.

With this condition being able to have a negative impact on the patients' QoL, and the BoNT treatment being safe, effective and long lasting, it is important for the physicians, particularly Otorhinolaryngology and PRM doctors, to be aware of this syndrome and to provide adequate and timely treatment to these patients.

Clinical Messages

- Frey syndrome (FS) is a fairly frequent surgical complication and is underdiagnosed
- FS can have a negative impact on quality of life and socialization
- Treatment should be offered to those patients who report such impact
- Type A botulinum toxin is a safe and effective procedure and is the gold standard treatment
- The Minor test is crucial to determine the minimum dose of BoNT to provide maximum efficacy and to assess the response to the treatment

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