The incidence of Frey syndrome and treatment with botulinum toxin in the Central Denmark Region

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Abstract
Objectives: Frey syndrome (FS) is a common complication to large salivary glands surgery. This study primarily aims to describe the incidence of FS among parotid surgery patients in the Central Denmark Region. The secondary aim is to describe predisposing characteristics to syndrome development and the effect of treatment with botulinum toxin (Botox) injection.

Methods: This is a retrospective qualitative study spanning the years 2015–2020. Data on patients diagnosed with FS after parotid surgery with symptoms severe enough to require Botox was extracted from electronic patient records. Incidence of FS development was calculated using data from all parotid gland surgeries in the same period and region.

Results: The incidence of treatment-requiring FS was 2.6% (20/775), with an annual incidence ranging from 0.8% (1/125) in 2017 to 4.5% (5/112) in 2016. Difference in FS development for men and women was not statistically significant (p = .07), although it was significantly more common after total parotidectomy compared to superficial resection (p = .003), and after malignant compared to benign diagnosis (p = .01). Complications in the postoperative period arose for 30% of FS patients. Repeated treatment with Botox was necessary after 6–12 months and at a median interval of 11 months. Forty-five percent of patients received only one injection. The average dose per injection was 48.3 IU.

Conclusion: This study revealed a rather low incidence of FS in the Central Denmark Region compared to current international literature. Total parotidectomy and malignant diagnosis predisposed to syndrome development. Botox injection had a wide-ranging effective duration but typically lasted for around 1 year.

Level of evidence: Level IV.

Keywords
botulinum toxin, Frey syndrome, gustatory sweating, parotid gland, parotidectomy

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1 | INTRODUCTION

Frey syndrome (FS) or auriculotemporal syndrome is a variable yet relatively common complication to surgery involving the large salivary glands. Symptoms are often concerning and sometimes socially debilitating for patients that develop varying intensities of localized gustatory sweating and flushing in relation to meals or other stimuli for salivation. Development of symptoms is most commonly observed 6–18 months (in some cases after several years) after large salivary gland surgery. It is also associated with cervical lymph node dissection, trauma, and facelift procedures. The syndrome was first reported in medical literature by Jules Baillarger in 1853 and named after Polish neurologist Łucja Frey who described the syndrome in detail in 1923.

Previous studies have reported wide-ranging incidences varying between 1% to 62%, depending largely upon the extent of salivary gland involvement. Currently, no studies describing incidence in a Danish population exist and all estimations refer to international literature, where the last article was published a decade ago. The Danish hospital setting presents the possibility of unique insight into FS development. Because Denmark has universal health care, all patients have equal opportunity to seek medical aid regardless of personal economy or insurance status. This is especially important in the case of FS, as this is a surgical complication impacting primarily quality of life, which patients may not prioritize as highly should they be financially challenged. Due to the quality of living in Denmark (leading worldwide according to the comprehensive Numbeo Quality of Life Index in 2020), we expect that a much larger proportion of patients who develop FS will prioritize seeking medical attention in this setting. Denmark also generally has a very high standard of surgery and aftercare meaning standardized surgical techniques, better follow-up, and more accurate diagnoses than in other settings.

In Denmark, cases of FS are referred for centralized treatment with botulinum toxin A (Botox) injections. Following salivary gland surgery, skin located superficially to the excised gland can be reinnervated by parasympathetic fibers that inherit control of the sympathetic skin response. Local injection of Botox blocks the release of acetylcholine from nerve endings, thus suppressing this response. Treatment typically takes effect 3–4 days after injection and lasts for up to approximately 12 months. A study of 100 patients reported that once Botox injections started, each injection was effective for a median of 12 months and that this interval did not change over time. A minority of patients are not sensitive to treatment with Botox (primary non-responders), and few develop neutralizing antibodies after multiple injections resulting in failure of continued treatment (secondary non-responders). Although Botox is a widely accepted form of treatment, there is very limited international data on long-term effects of Botox injection and the need for re-injection over time.

The objective of this study is to describe the incidence of FS among parotid surgery patients in the Central Denmark Region in the period 2015–2020. Secondarily, this study will describe predisposing characteristics to syndrome development such as histology, resection size, gender, age, smoking status, and surgeon experience. It will attempt to assess the effect of treatment with botulinum toxin injection based on doses and frequency of re-injection.

2 | MATERIALS AND METHODS

This is a retrospective qualitative observational study using electronic patient records from the Central Denmark Region between January 2015 and December 2020. It includes the largest population of FS patients in Denmark gathered from the second largest Danish region (with a population of 1.33 million). The Department of Otorhinolaryngology, Head and Neck Surgery at Aarhus University Hospital (AUH) manages the treatment of all FS patients in the Central Denmark Region and is a primary Danish center for parotid surgery of both benign and malignant tumors. Prior to each Botox injection, all patients have their symptoms reevaluated by a Botox-specialized otolaryngologist and a Minor’s (iodine-starch) test performed to gauge the extent of the affected area needing treatment.

Permission to review patient journals was given by the Department of Quality and Patient Safety, Aarhus University Hospital, where the study was registered and confirmed as a qualitative retrospective study. The Central Denmark Region Committees on Health Research Ethics had also confirmed that no further ethical approval was necessary.

The Danish BI Portal is a database containing ICD-10 diagnosis codes for patients treated within the Danish hospital system in the Central Denmark Region. AUH manages the treatment of all patients in the region referred with FS and is one of five centers in Denmark to do so.

Using the BI-database, 12 FS patients were identified through the ICD-10 diagnoses DR610 localized hyperhidrosis and DR619 hyperhidrosis, unspecified. Diagnoses DK117 disturbances of salivary secretion, DK118 other diseases of salivary glands, and DK119 disease of salivary gland, unspecified were also assessed resulting in one additional case. Remaining cases were identified using the procedural codes for Botox injection: BDXC Injection with botulinum toxin and BEHO2 Injection of salivary gland with botulinum toxin (the latter to find any misdiagnosed patients). A few of these cases had nondescriptive diagnoses like DT983 Sequelae of complications of surgical and medical care, not elsewhere specified or DZ488 Other specified surgical follow-up care. The search was limited to the aforementioned region with eligible patients being those with active treatment periods for FS referred between 2015 and 2020.

FS cases that were referred to AUH for treatment had their electronic patient records individually reviewed. The records documented treatment courses such as diagnosis of primary parotid disease, surgery year, referral to Botox treatment, and injection course. Effects of age and smoking status on syndrome development were based on status at the time of surgery. Documentation on a few operational procedures predating the year 2000 were not accessible.

Two-tailed Fisher exact tests were used to calculate p-values for contingency tables due to small cell counts. A statistically significant p-value was defined as p < .05.
TABLE 1  Number of Frey syndrome patients and healthy patients according to procedure type, tumor histology, and sex

| Procedure type          | Patients with FS (%) (n = 20) | Patients without FS (%) (n = 755) |
|-------------------------|-------------------------------|----------------------------------|
| Total parotidectomy     | 13 (65)                       | 678 (90)                         |
| Superficial parotidectomy | 7 (35)                       | 77 (10)                          |
| Tumor histology*        |                               |                                  |
| Benign                  | 15 (79)                       | 555 (95)                         |
| Malignant               | 4 (21)                        | 27 (5)                           |
| Sex                     |                               |                                  |
| Male                    | 6 (30)                        | 393 (52)                         |
| Female                  | 14 (70)                       | 362 (48)                         |

Abbreviation: FS: Frey syndrome.
*Nontumor or no verified final diagnosis for 174 patients.

3 | RESULTS

In the period of 2015–2020, 775 parotidectomies were performed in the Central Denmark Region. During this same period, 20 new cases of FS were referred to AUH for treatment. This makes for an FS incidence of 2.6% for that period. The yearly incidence ranged from 0.8% (1/125) in 2017 to 4.5% (5/112) in 2016.

There were 20 referred patients with FS after parotidectomies; thirteen procedures were superficial (partial) resections, whereas seven procedures consisted of total extirpation of the gland (Table 1). When stratifying by procedure type, there were significantly more FS patients after total parotidectomy (8.3% of patients) compared to partial resection (1.9%) (p = .003).

Sixteen of the referred cases had surgery based on a benign diagnosis, 15 of which were benign tumor diagnoses; most commonly the pleomorphic adenoma (10/15). One nontumor case arose after surgery due to chronic sialoadenitis. The four cases of FS after malignant tumor surgery were due to basal cell adenocarcinoma, adenoid cystic carcinoma, renal cell carcinoma, and acinar cell carcinoma. Using only verified histological tumor diagnoses, it is known that 570 of parotidectomies in 2015–2020 had a benign diagnosis, and 31 had a malignant diagnosis (Table 1). Remaining operations were either due to nontumor diagnoses like chronic inflammation or sialolithiasis or did not have a final diagnosis. Using these numbers, 2.6% (15/570) of benign parotidectomies and 12.9% (4/31) of malignant surgeries had FS development. Significantly more procedures performed based on a malignant diagnosis developed FS (p = .01).

Fourteen (70%) of the 20 cases were female (Table 1). Compared to all parotidectomy patients, where 49% (376/775) of patients were female, more women than men (3.7%, 14/376 vs. 1.5%, 6/399) developed FS. This finding shows a trending difference but is not statistically significant (p = .07). Age ranged from 23 to 76 at the time of surgery. The mean age was 49 and cases were evenly distributed through age groups without an increased tendency to develop FS in younger or older patients. Smoking status at the time of surgery is known for 18 of the cases. Five (27.8%) of these were active smokers at the time of the procedure. When considering surgeon experience, all FS cases developed after procedures performed by senior consultants (standard practice for parotidectomies in Denmark). No single surgeon had an increased incidence of syndrome development compared to their peers.

The rate of complicating factors during the postoperative period for patients that later developed FS was relatively high. Complicated courses developed among 30% (6/20), with a mix of postoperative hematoma (3), paresis of the facial nerve (3), and additional need for postoperative radiation therapy (2).

3.1 | Treatment with Botox injection

Treatment with Botox injection was usually started 1–2 years postoperatively. Injections were offered as outpatient treatment at approximately 3-month intervals administered by a specialist in otorhinolaryngology. Treatment frequency in the patient group varied between 3 and 30 months, though most commonly with treatment at intervals of 6–12 months (Figure 1). Median time between re-injection was 11 months. This is comparable to the median effective time of 12 months found in a recent study.11 The average number of injections per patient in the study period was two, varying from zero to nine injections in total. Forty-five percent of patients were only treated once. There was no apparent correlation between time passed from operation to reference for treatment and an effect of Botox injection. Thus, a longer interval between operation and syndrome onset did not affect a need for re-injection. Three patients were first referred for treatment more than 15 years after primary surgery and had treatment courses comparable to those of the other cases.

The average dose of Botox per injection was 48.3 IU (12.5–95). This dose was always directly proportional to the size of the area affected by gustatory sweating. After the Minor test doses of 2.5 IU/cm² were administered locally. Necessary dosage size did not correlate to total number of received injections or to time between injections. The latter was true across all patients; also when assessing variance in dose size for each patient. A larger injected dose did have a longer lasting effect than a smaller dose for the same patient.

As of January 2021, seven of the 20 courses of treatment started since 2015 have been concluded. Courses have been terminated either due to patient request or after multiple years of being offered re-injection without patient reply. All of these patients were only treated once or twice before declining further treatment.

4 | DISCUSSION

Calculating an exact FS incidence in this patient group is rather difficult given that a sizable proportion of newly referred cases were operated prior to the observational period. Our results are however expected to be representative, considering that indications for parotid surgery and surgical techniques in Denmark have not changed for
decades. Thus, the proportion of new FS cases to yearly parotid surgeries should remain consistent despite not reflecting an absolute yearly incidence for syndrome development.

A potential source of bias that may influence our results is that only patients who were referred for hospital treatment for FS were eligible for inclusion. On this basis, it could be assumed that the found incidence best reflects moderate to severe cases, where patients’ quality of life was noticeably affected, thus driving them to seek treatment. Milder cases, where patients were not bothered to a degree that warranted referral for invasive treatment, would thus not be included. This is largely expected to be negated by the fact that Denmark has universal health care, significantly lowering the threshold for when patients seek medical aid. The impact of an individual’s financial situation is a potential source of bias that would be influential in another setting.

There is a risk of misdiagnosis of FS, as it is a lesser-known diagnosis among general practitioners (patients can however consult private practice otolaryngologists without referral). An unknown fraction of patients is misdiagnosed regardless of syndrome severity and these patients are not referred for relevant treatment. Despite that, this study is the largest regarding FS in a Danish population to date.

AUH has a regional function for Botox injection on the indication of FS. It is therefore safe to assume that no referred patients in the Central Denmark Region were excluded. Also, the extended observational period of this study should sufficiently account for the natural fluctuation in yearly Botox treatment referrals.

To accurately gauge the incidence of all FS development, it would be necessary to allocate resources to long-term follow-up for all surgical patients. Currently, patients are informed preoperatively of the risk of FS, but this information is easily forgotten alongside comprehensive surgical preparation. Patients with malignant salivary gland diagnoses are all postoperatively enrolled in a 5-year follow-up program with clinical controls every 6 months for the first 2 years and yearly controls thereafter. This follow-up could be expected to increase the likelihood of recognizing even mild FS development in malignant cases and could bias results compared to benign cases. However, this follow-up alone cannot account for the increased risk of syndrome development that malignant cases face. Importantly, it should be noted that malignant cases are always treated with extirpation of the affected gland. This study has found an elevated incidence of syndrome development following total parotidectomy, which could logically be ascribed to a larger surgical

**FIGURE 1** Botulinum toxin injections per Frey syndrome patient. Each bar represents 1 of the 20 Frey syndrome cases. Each new injection is marked with a circle. Solid bars correlate to effective time in months between two injections. Time after a patient’s final injection is not visualized. Time for each patient starts upon first injection. Y-axis is marked with the start-date (dd-mm-yyyy) for each patient and ordered chronologically. Patients having never received an injection are displayed with date of first contact in parentheses.
field, resulting in a larger area with possible aberrant nerve reinnervation.

Smoking status as a predisposing factor to syndrome development should be considered with the fact that Warthin’s tumors are known to be heavily associated with smoking.\textsuperscript{14,15} As such, it would be expected that for this patient group, the prevalence of smoking would be much higher than that of the background population, thus inflating numbers for smoking among FS patients as well. In 2020, 18% of the Danish population smoked daily.\textsuperscript{16} In our study, 27.8% of FS patients were smokers at the time of surgery. If patients with Warthin’s tumor histology are subtracted, then smoking prevalence amounted to 20%, which more closely matches that of the background population. As such, smoking itself did not seem to increase the risk of FS development.

As there are few total patients receiving Botox injections in the Danish hospital setting and because treatment is a specialized function, AUH offers injections at intervals of 3 months. It is rare for patients to need re-injection at shorter intervals. The regularity in which patients would accept re-treatment serves as a surrogate for the efficacy of Botox on symptoms in this group. Once the effect of a previous injection wore off sufficiently, patients would routinely accept the callback for re-injection sent out by AUH every 3 months. The Minor test prior to re-treatment would reveal symptom relapse and the need for injection. With a median time between treatments of 11 months, it can be deduced that Botox would be effective for at least up to 8 months on average. Xie et al.\textsuperscript{17} published a meta-analysis of 22 articles in 2015. Half of these studies described more than 10 months of mean duration of effect for injections. Effect even lasted more than 20 months in some patients without symptom recurrence. The same could be expected for some of the patients in our study. The findings of one study in the meta-analysis, where duration of effect increased with subsequent treatment, could not be reproduced in our patient group.

Results from this study population are expected to be representative for the rest of Denmark. They should also be generalizable to an international setting because techniques for surgical approach and Botox injection are standardized. Our results from this medium-sized patient group correlate to those presented in earlier international studies. The incidence is low but lies within the wide margin found in other literature (1–62%). Our findings are possibly more accurate in terms of moderate to severe cases due to the quality of this study’s setting and argue that FS could be more uncommon than currently assumed.

Because this study only utilizes standard hospital records, future studies could greatly increase data quality by including additional subjective patient experience through questionnaires to more accurately gather information on treatment effect and duration (e.g., the Short Form 36 Health Survey\textsuperscript{18} could gauge both physical and mental well-being). This would allow for collection of accurate and consistent data on why patients decline further treatment; whether they do not respond to treatment, have a long-term effect, or possibly experience discomfort related to injection.

5 | CONCLUSION

The incidence of treatment-demanding FS after parotid gland surgery between the years 2015–2020 was 2.6% in the Central Denmark Region. Significantly more patients developed FS after total parotidectomy compared to partial resection (8.3% vs. 1.9%), and after malignant compared to benign diagnosis (12.9% vs. 2.6%). There were more women than men who developed FS (3.7% vs. 1.5%), although without statistical significance. Complications in the postoperative period seemed to increase the risk of syndrome development. Most patients experienced an effect of treatment with Botox injections lasting 6–12 months, but 45% of cases only received one injection. Patients received an average dose of 48.3 IU per injection.

It is the first study to describe FS incidence in a Danish patient group and includes the largest population of FS patients in Denmark. A future prospective study in collaboration with private practice otorhinolaryngologists and all hospitals treating patients with FS in a Danish setting would increase data quality and would represent a better assessment of the long-term effects of Botox injections in patients with FS in Denmark.

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The authors have no relevant financial interest in this article.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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