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Frey's Syndrome

Treatment with Botulinum Toxin

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Gustatory sweating is a common sequela following parotid gland surgery and was first noted by Duphenix [1] and Baillarger [2]. As a separate entity, a syndrome known as the *auriculotemporal syndrome* was described in detail in 1923 by Lucie Frey [3].

Following gustatory stimulation, the clinical picture (fig. 1, 2) includes pathological sweating in certain areas of the skin of the face, and also a 'flush' may occur as a reaction involving skin vessels [4–9]. It is important to know that the patients' complaints do not exclusively depend on the extent of the sweating area. The handicap for the patient can be enormous even if the area of hyperhidrosis is small.

Some 50% of patients experience gustatory sweating (Frey's syndrome) after parotidectomy, and about 15% consider their symptoms severe [10, 11]. Typically, gustatory sweating develops within 6 months of parotid gland or neck surgery [10–14] or following other lesions such as infection or trauma [15, 16], and it can also appear after submandibular gland excision [17, 18].

Following parotid gland surgery, the most likely explanation for the condition is a misdirected resprouting of postsynaptic salivomotor parasympathetic fibers that have lost their 'glandular target organ'. The misdirected fibers then come into contact with sweat glands, normally innervated by sympathetic (cholinergic) fibers, if these fibers have already been damaged before. The localization of the sweating area varies and cannot usually be influenced by surgical techniques.

To simplify the description and discussion of gustatory sweating we suggest a classification into three types (type 1: lesion of parasympathetic and sympathetic fibers, type 2: lesion of sympathetic fibers, type 3: lesion of central structures of the nervous system) which includes the various mechanisms of induction of gustatory sweating [for details, see 10].

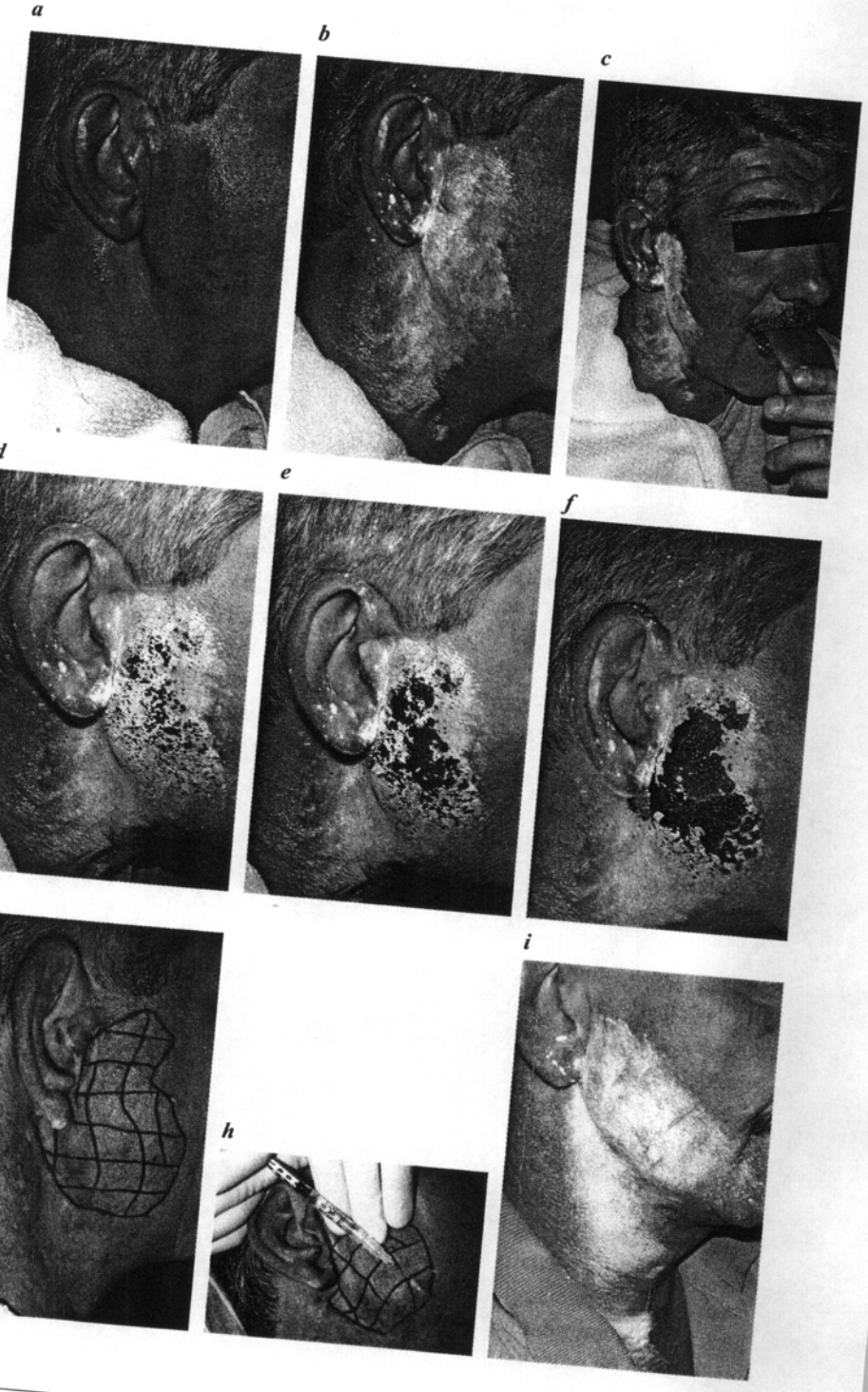
Treatment of sweat glands with *botulinum toxin* to reduce pathological sweating (here patients with *gustatory* sweating) was first described and practiced by our group (first patient treated in December 1993) [19–23], and its value has, in the meantime, been confirmed by many authors [24–30]. The treatment is effective not only for gustatory sweating but also for other forms of pathological sweating, such as axillary or palmar hyperhidrosis [31–34]. The effect of botulinum toxin on the reduction of sweat production was already described by Kerner [35] in 1820 who observed this phenomenon in patients poisoned with the toxin. Bushara and Park [36] reported a reduction in physiological sweating as a *side effect* after treating patients with facial movement disorders and suggested possible therapeutic aspects.

Diagnosis

Exact data on a patient's history (parotid gland surgery, trauma, infections, neurological diseases) and the present clinical picture must be obtained from a thorough anamnesis. It is important to allow patients to describe the extent of the sweating area themselves to determine what areas of the skin must be tested. To establish the exact dimensions of the affected skin area (fig. 1), we used the iodine-starch test according to Minor [37]. Other possible procedures have been described elsewhere [38]. Large cotton swabs soaked with a solution containing 15 g iodine, 100 ml castor oil and 900 ml ethanol are used to paint the skin of the affected region. Sometimes the hair-covered skin of the temporal region has to be included. After evaporation of the alcohol, all these areas must be uniformly powdered with starch. Then the patients should eat an apple since the fruit acid in combination with the masticatory effort needed constitute a particularly strong stimulus to induce gustatory sweating. In most cases, it starts 30 s later and causes a deep blue reaction between starch and iodine in the treated skin area. The borders of the sweating area become clearly visible after 2 min. Once established, they normally do not change so that the test does not exceed 5 min.

At the end of the test, the applied starch-iodine paste can easily be removed with soap and water. Before the skin is cleaned, the borders of the sweating field should be marked with a waterproof pen to prepare for exact injection (see above).

The results of the starch-iodine test are *photographically* documented to record the exact extent of pathological sweating in order to compare control tests with the pretreatment state. To control the effect of treatment, exact anamnesis has to be repeated in combination with a second Minor test.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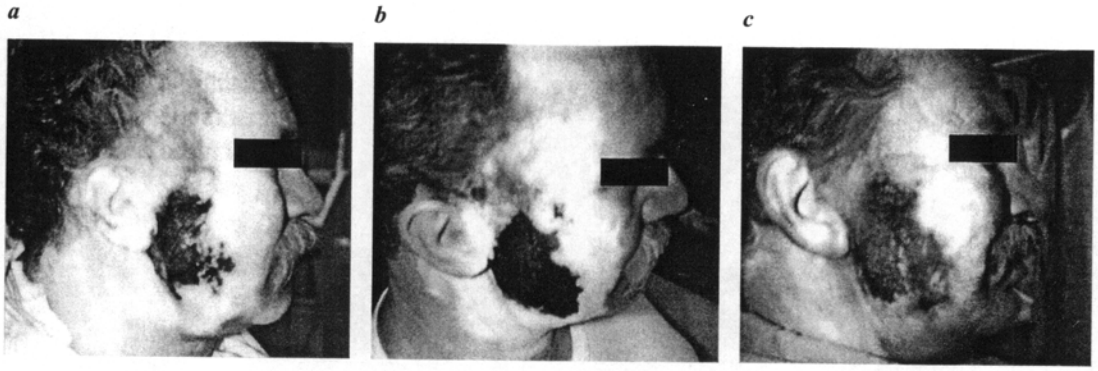

Fig. 2a–c. Patient with recurrent gustatory sweating. ***a*** The state of the skin before the second injection is shown, 1 year after the first treatment. After the second injection, gustatory sweating recurred after almost exactly the same time (***b***). The time between the last control (***c***) after the previous injection and complete recurrence was approximately 1 year. It is recognizable that the area of hyperhidrosis was identical each time (***a–c***). The therapeutic effect was a complete stop of pathological sweating in the treated area.

Treatment

Injection Technique

Treatment (fig. 1) is performed on an outpatient basis. All patients must desire treatment and give their informed consent. For injection, 100 units Botox® available as freeze-dried powder (Allergan Inc., USA) is dissolved in 4 ml physiological saline, yielding a concentration of 25 units/1 ml. The borders of the affected areas are marked with a waterproof pen and then the whole area is divided up into squares, each of about 4 cm^2. Into each square, approximately 0.1 ml of the Botox solution (2.5 units) is injected intracutaneously. Injections are performed with insulin syringes. Care has to be taken to distribute the substance evenly in each marked field. If patients suffer pain, the skin can be pretreated with an anesthetic ointment. The fact that in many patients the greater

Fig. 1a–i. Patient with gustatory sweating following parotid gland surgery. The different stages of Minor's test are demonstrated (***a–f***). After treatment of the skin with the iodine-starch component (***a***, ***b***), the patient begins to eat an apple (***c***). About 30 s after gustatory stimulation, a change of color becomes evident, developing to a maximum with a deeply colored area marking the full extent of the pathologically sweating skin (***d–f***). After division of the total area into squares (***g***), intracutaneous injections are performed (***h***), and, 2 weeks later, pathological sweating after gustatory stimulation has completely ceased (***i***).

auricular nerve was resected during parotid gland surgery is an advantage because the treated area is then often hypesthetic.

When we began our work, we did not inject in front of the masseteric border to avoid affecting the fascia-free mimic muscles. Wider experience has shown, however, that this is possible, as long as injections are performed exactly intracutaneously [39].

Results and Discussion

Botulinum toxin is an effective therapeutic option for the treatment of gustatory sweating [19–30]. Several authors have confirmed its successful use and some even recommend this option as the 'first-line treatment' [28].

In our experience, in all patients (100%) pathological sweating ceased in the treated skin regions. This was controlled by the patients' self-assessments and by Minor's tests [37].

In our patients, Minor's test was an adequate method to determine the extent of the sweating areas before and after treatment. It is a practical, easy, time-saving and reasonably priced diagnostic option, independent of measuring instruments and practicable at any place and any location of sweating. Some authors use other methods to reveal the exact extent of the sweating skin [38]. Further investigations will show whether there is any noticeable advantage in these new methods compared to Minor's test as far as the practicality and the comfort of the patients are concerned. In this connection, the direct contact between the skin and the starch-iodine component in regions of *hairy skin* proved to be very reliable to demonstrate the areas of hyperhidrosis. In these regions, making a 'print' with a stencil without cutting the covering hair might be problematic as far as the exact determination of the amount of sweat and the exact borders of hyperhidrosis are concerned [39]. Another important point is that regions of gustatory sweating can vary and be found in areas possibly not reachable by standardized stencils.

For our patients, we use a solution of 25 units Botox/1 ml (approx. 100 units Dysport®/1 ml). The available literature recommends a range from 20 to 50 units Botox/1 ml [22, 25, 26, 28, 30]. In our experience, preparation of the Botox solution as above has proved its worth in halting the unpleasant sweating. In most patients, a total dose of 100 units Botox (=400 units Dysport) does not need to be exceeded and in all patients 2.5 units Botox/4 cm^2 skin were effective in stopping the pathological sweating. This dose is at the lower level of the possible range.

The beneficial effect is normally observed by the patients within 2 days of injection. A few patients reported persisting sweating 2 weeks after injection therapy; the control Minor test revealed only a few small sweating areas to be

responsible for the persisting complaints. A second injection into these skin areas led to a complete cessation of hyperhidrosis.

As shown by many authors, it is interesting to note that the duration of treatment effect in patients with Frey's syndrome is much longer than in patients treated for other indications such as hemifacial spasm or blepharospasm [22, 28]. In our patients, the mean duration of the botulinum effect for Frey's syndrome was 17.3 months. Lacourreye et al. [28] confirmed this longer duration and showed, using a Kaplan-Meier analysis, that the loss of effect was linear. In his investigation, almost half (45%) of the treated patients were still free of symptoms 17 months after therapy. In our opinion, there are several possible mechanisms to explain the longer duration of the positive effect such as a loss of function of the glandular cells, a lower regeneration capacity of resprouting parasympathetic fiber terminals and changed local 'tissue circumstances' leading to a natural barrier caused by scars and connective tissue [22].

Recurrent sweating (fig. 2) normally develops in the same skin area as before the therapy [22]. This does not occur evenly over any particular subarea of the skin concerned, but, rather, differences in the time course are seen here despite evenly applied doses. Another interesting point is that in some cases of recurrence there is a difference between the subjective evaluation, based on the patients' self-assessments, and the objective evaluation by Minor's test, showing again pathological sweating, but only in parts of the original area. It can be speculated that a certain 'grade of sweat production' is necessary to make the patients feel handicapped.

After having used the concept described now for about 8 years, we have observed no severe side effects in our patients, in particular no systemic effect or paresis of the mimic musculature. The absence of severe side effects has been confirmed by many other authors reporting similar results [24–30].

In summary, it can be stated that botulinum toxin is a safe and effective option to treat gustatory sweating, a specific form of focal hyperhidrosis.

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