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Improvement of diabetic autonomic gustatory sweating by botulinum toxin type A

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Abstract—Fourteen diabetic subjects with gustatory sweating were treated by intracutaneous injections of botulinum toxin type A into the affected facial skin areas. In all subjects, sweating (measured by Minor starch iodine test) ceased within 4 days, with the maximal follow-up time lasting 24 weeks. This therapeutic approach, which could be used to reduce the severity of diabetic gustatory sweating, appears to be long lasting, adverse effect free, and minimally invasive.

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The association of gustatory sweating (GS) with diabetes mellitus has been known for several years.[1,2] GS commonly occurs in patients with diabetes with nephropathy or neuropathy, and often involves sympathetic autonomic fibers.[3] A similar condition known as Frey syndrome can be found in patients without diabetes as a consequence of parotidectomy and sympathectomy.[4,5]

The main clinical finding of GS is localized hyperhidrosis of the facial skin during meals. The sweating process is controlled by sympathetic cholinergic fibers. When these fibers are lesioned, the sympathetically denervated sweat glands are thought to become reinnervated by misdirected cholinergic parasympathetic fibers.[4,5] In diabetic autonomic neuropathy, the sympathetic denervation that occurs in sweat glands might be compensated by reinnervation of aberrant parasympathetic fibers stemming from the minor petrous nerve and normally innervating the parotid gland, via the auriculotemporal and facial nerve, after being relayed in the otic ganglion. Thus, sweating occurs in the reinnervated area when salivation is induced upon cholinergic stimulation.

Although GS is not a cause of major morbidity, it is troublesome and embarrassing.[6] Traditional treatment of diabetic GS includes oral[1,7] or topical[1] anticholinergic drugs. However, these treatments are poorly tolerated or have a short-term action.[1]

Recently, treatment with botulinum neurotoxin type A (BoNT/A) has been shown to be effective in abolishing GS in Frey syndrome.[8] The effects of percutaneous injection of this neurotoxin, which are due to the block of the presynaptic release of acetylcholine, last several months. Because BoNT/A has demonstrated to be effective in treating GS due to Frey syndrome, we hypothesized that, for the same reason, a long-lasting block of the cholinergic parasympathetic fibers might be useful in treating and preventing GS in subjects with diabetes with autonomic neuropathy.

Subjects and methods. Fourteen subjects with diabetes (11 men, 3 women; age range 56 to 67 years; 10 insulin-dependent and 4 non–insulin-dependent) with a history of frequent facial, scalp, or neck sweating during or immediately after eating underwent treatment with BoNT/A. The mean GS duration was 8.7 ± 3.4 years. The diagnosis of diabetic neuropathy was based on clinical and neurophysiologic criteria. Somatic neuropathy was ascertained by either the modified neuropathy disability score[3] or the vibration perception threshold, which was assessed by a neurotensiometer at the great toe of the dominant foot. Autonomic neuropathy was diagnosed by calculating of the

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mean expiratory:inspiratory heart rate ratio (R-R ratio) during deep breathing. Serum creatinine and 24-hour urinary protein loss were also measured. All subjects had been previously treated for sweating with glycopyrrolate with poor improvement.

Assessment. Minor iodine starch test was performed before treatment in order to localize and circumscribe the affected skin areas. Zones where sweating occurs turn dark-brownish with this method. The hyperhidrotic area was then marked with a pencil and subdivided into squares of 1.5 × 1.5 cm each (2.25 cm^2). Photographs were taken 10 minutes after beginning the meal and 4 weeks after the treatment. Subjects were asked to record the severity of the hyperhidrosis during and after eating in a diary and to compare their condition before and after the BoNT/A treatment. For this evaluation, three subjective severity levels were considered: + = mild hyperhidrosis; ++ = discrete hyperhidrosis; +++ = severe hyperhidrosis. Level 0 indicated the absence of hyperhidrosis. Other than before and 4 days after treatment, the patients were clinically re-examined 4, 12, and 24 weeks after BoNT/A injection. Minor iodine starch test was performed at each control.

Ethics. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethical committee. The patients gave their written informed consent to the treatment.

Treatment. BoNT/A (Dysport, Speywood, Portons Downs, UK) was intracutaneously injected in the middle of each defined square at a dosage of 5 units/2.25 cm^2 (dissolved in 2.5 mL of 0.9% NaCl) of hyperhidrotic skin. Distance between each injection was about 1.5 cm.

Statistical analysis. Data obtained during each examination were evaluated by analysis of variance (ANOVA). The level of significance was set at $p < 0.001$. Likert transformation was obtained to change the qualitative results of the self diary evaluation into a score ranging from 0 (no hyperhidrosis) to 3 (severe hyperhidrosis).

Results. Electrophysiologic and clinical data showed that an autonomic neuropathy was present in all patients (vibration perception threshold: 29.3 ± 13.8 volts, normal values: <25 volts; R-R ratio: 1.09, normal values: >1.20). In addition, in the majority (10 of 14), the serum creatinine and 24-hour urinary protein mean values were abnormally increased (creatinine: 174.5 μmol/L, normal range: 50 to 120 μmol/L; 24-hour urinary protein: 0.45 g, normal values: <0.15 g), disclosing the presence of a concomitant nephropathy. The hyperhidrotic area was evaluated by clinical examination, Minor iodine starch test, and diaries recorded by the patients. In 8 of 14 patients, the hyperhidrotic area involved the scalp, whereas in the remaining 6 patients, it did not spread into the scalp, remaining localized below the hairline. A single injection of BoNT/A for each square was performed in all patients. Thus, a mean of 8.3 ± 2.1 injections was administrated to each patient. Within 4 days (as documented in their diaries), BoNT/A treatment produced a remarkable reduction of sweating in the treated area in 8 of 14 patients and a disappearance of sweating in the remaining 6 patients (table). These changes were significant at 4 days ($p < 0.0001$), as well as at 4 ($p < 0.0001$), 12 ($p < 0.0001$), and 24 ($p < 0.0001$) weeks after BoNT/A treatment. In all patients, hyperhidrotic areas were dramatically reduced within 4 days (area before BoNT/A: 18.8 ± 4.8 cm^2; area 4 days after BoNT/A: 1.9 ± 1.1 cm^2; $p < 0.0001$). These changes remained significant at 4 ($p < 0.0001$), 12 ($p < 0.0001$), and 24 ($p < 0.0001$) weeks after the treatment. The effect peaked at 4 weeks and remained unchanged at 12 weeks. Although a reduction of the effect was observed at 24 weeks, the changes induced by BoNT/A on the hyperhidrotic area were significant. At 6 months after treatment, no recurrence of GS was observed clinically or by Minor iodine test, and no patient needed to be treated subsequently. Injections were well tolerated; occasionally, small cutaneous hematomas were observed in three patients. No other important adverse side effects were observed.

Table *Diary of subjects regarding hyperhidrosis in the affected areas before (baseline) and after botulinum toxin type A injection*

Subject no.	Baseline	4 days	4 weeks	12 weeks	24 weeks
1	+++	0	0	0	0
2	+++	+	0	0	0
3	+++	+	+	+	+
4	++	0	0	0	+
5	+++	+	+	+	+
6	+++	+	+	+	+
7	++	0	0	0	0
8	+++	+	+	+	+
9	+++	+	+	+	+
10	++	0	0	0	0
11	++	0	0	0	0
12	+++	+	+	+	+
13	++	0	0	0	0
14	+++	+	+	+	+

+++ = Severe; ++ = discrete; + = mild; 0 = absence.

Figure 1 shows typical responses visualized by Minor iodine starch test during meals in the affected areas at the basal situation (left) and 4 weeks after BoNT/A injection (right) in Subject 1. Cumulative results from all subjects are plotted in figure 2, in which values of sweating areas, calculated before injection as well as 4 days and 4, 12, and 24 weeks after injection, are reported as means. As shown, BoNT/A caused a reduction of the sweating area in all treated cases, with positive effects of the treatment peaking at 4 and 12 weeks and lasting about 6 months.

Discussion. GS due to diabetic autonomic neuropathy or nephropathy is common. Traditional treatments for diabetic GS include a number of oral and topical anticholinergic drugs.[1,7] These treatments have not been effective. In fact, the oral anticholinergics oxybutynin and propantheline, as well as the centrally acting α_2 blocker clonidine, although effective in reducing sweating, have all been reported to have considerable side effects.[1,7] Topical antimuscarinic drugs, which include scopolamine and glycopyrrolate, also have been used. Scopolamine has been shown to have significant CNS side effects

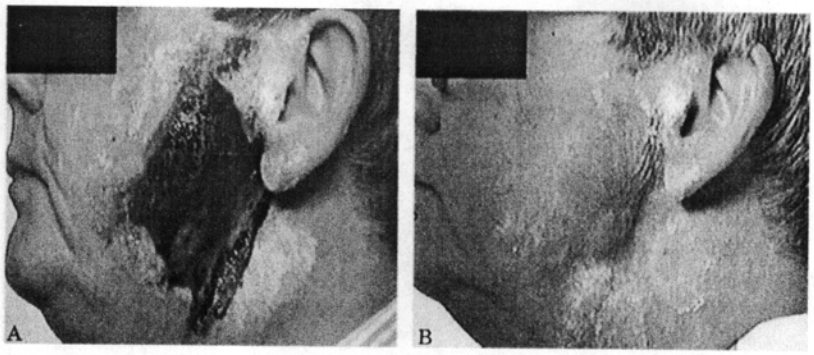

Figure 1. Minor iodine starch test during meals before (A) and 4 weeks after botulinum toxin type A injection (B) in the hyperhidrotic facial skin.

when systematically absorbed. Conversely, glycopyrrolate has been demonstrated to be an effective treatment in reducing both the severity and the frequency of GS, although not abolishing it.[3] Although this treatment has fewer side effects than scopolamine when given topically,[3,9] frequent applications are necessary. Furthermore, it cannot be used on patients with narrow angle glaucoma, can cause allergic eczematous reaction, and cannot be applied in patients who have considerable sweating on the scalp (mostly patients with diabetic GS), as it is not possible to apply it beyond the hairline.[3]

Intracutaneous injection of BoNT/A has been demonstrated to be effective in GS due to Frey syndrome.[8] BoNT/A acts by blocking the release of acetylcholine, the autonomic nerve fiber transmitter supplying eccrine sweat glands in the skin.[1]

Our study extends previous observations on Frey syndrome and demonstrates that BoNT/A treatment is a safe, simple, and highly effective therapy for patients with diabetic GS. Neither primary treatment failure nor adverse effects were present in our patients. Secondary failure, caused by antibody formation, was not observed.

In our patients the effect lasted about 6 months. A longer-lasting therapeutic effect of BoNT/A on hyperhidrosis than that in the neuromuscular system, even if unclear at present, has been previously demonstrated for other cutaneous districts[10] than the facial ones.[8] Our findings of a long-lasting effect of BoNT/A on GS are in agreement with previous observations on Frey syndrome.[8] We are unable to explain why the effect of BoNT/A lasts so long in our patients. The action of BoNT/A lasts at least 4 months in the skin, but it also has been reported that BoNT/A in GS probably has a particularly long-standing effect of more than 12 months.[8]

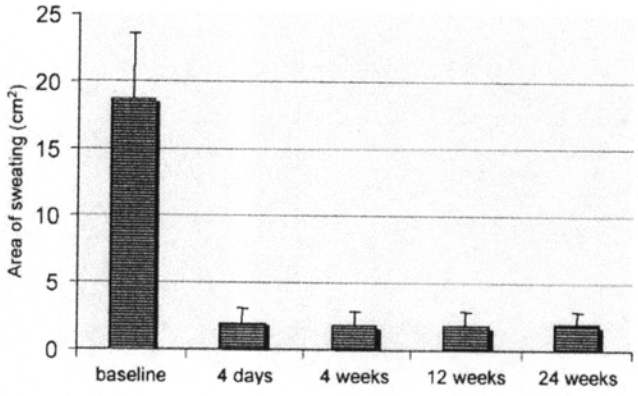

Figure 2. Pooled data of botulinum toxin type A injections in hyperhidrotic facial skin of the 14 individual subjects. Mean values and standard deviations of sweating areas during meals are displayed by all subjects before and after injection.

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