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Hyperhidrosis of the Axilla

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Sweat stains under the armpits sometimes extending downwards to the waist may not necessarily be considered a life-threatening disease, yet they can substantially impede one's quality of life. Axillary hyperhidrosis can produce social and physical discomfort, skin maceration and subsequent microbial infection [20, 21]. Moreover, textiles may be ruined due to the corrosive effect of sweat. Consequently, patients suffering from this condition have been consulting many physicians in the past, often to no avail. With the use of botulinum toxin A for axillary hyperhidrosis, however, such odysseys have come to an end: For patients unresponsive to topical agents (e.g. aluminium salt solutions), intradermal injection of botulinum toxin A is an easy, quick, highly efficient and safe remedy satisfying patients and physicians alike. In contrast to invasive surgical procedures, such as excision, curettage or liposuction of the axillary area, botulinum toxin A injections can be conveniently performed as an outpatient procedure. It requires little time and does not require any cut-backs on working or leisure activity for the patient.

Definition and Prevalence of Axillary Hyperhidrosis

The axillary type is the single most prevalent form of focal hyperhidrosis. In more than half the patients, axillary hyperhidrosis is associated with other forms of localized sweating. Together with palmar and plantar hyperhidrosis it is referred to as primary or idiopathic hyperhidrosis [20, 21]. Primary hyperhidrosis is defined by excessive sweating independent of thermoregulatory impulses and in the absence of detectable organic causes for sweating such as

hyperthyroidism, infections or malignancies. There are no representative epidemiological data on how many people suffer from this condition and what might be considered a *normal* sweat rate. The diagnosis is usually based on the patients' history and visible signs of excessive sweating. The extent of hyperhidrosis can be measured gravimetrically as sweat rate in milligrams per minute. Gravimetric values >50 mg/min have been used in a recent clinical study to select patients with frank axillary hyperhidrosis [10]. The iodine-starch test and planometry, which are helpful to visualize the active hyperhidrotic area, are not pertinent for the exact quantification of sweating.

Aetiology of Axillary Hyperhidrosis

Focal hyperhidrotic patients do not show any histopathological deviances such as an increased number or size of sweat glands. The condition is purely based on hyperfunction, not on hypertrophy. Sweat bursts are mediated by escalating sympathetic activity channelled through sudomotor fibres which innervate eccrine sweat glands. This has been nicely demonstrated for focal plantar hyperhidrosis: when hyperhidrotic individuals were exposed to mental stress, there was a more than 10-fold activity of sudomotor fibres compared to non-hyperhidrotic controls exposed to the same stress level [13]. Thus, overstimulation which is detached from thermoregulation may result in a paradoxical state: patients sweat even though they are freezing.

Association with atopic disease, allergies, smoking habits or overweight have been assumed but never been proven in any representative epidemiological studies. Likewise, a familial predisposition may be present in some patients, yet there is no known genetic background for hyperhidrosis. Most patients report the onset of axillary hyperhidrosis after puberty, while other focal hyperhidroses of the palms, soles or forehead may already be observed in infants. The reason for that is not quite clear, as eccrine sweat glands are already present and functional in infants. In contrast, apocrine glands are evolving as a functional unit during puberty but are not thought to be relevant for the excessive sweat production characterizing axillary hyperhidrosis and cannot be blocked by botulinum toxin A. The existence of apo-eccrine glands has been demonstrated by electron microscopy studies [22]. The function and significance of these glands is still awaiting further elucidation. They may, however, play a role in axillary hyperhidrosis and/or bromhidrosis. They are found exclusively in the axillary area after puberty and they are strongly responsive to acetylcholine which may explain how axillary hyperhidrosis typically occurring after puberty can be blocked by botulinum toxin A.

Efficacy and Safety of Botulinum Toxin A for Axillary Hyperhidrosis

Axillary hyperhidrosis was the first condition to be described as a possible target for the antihyperhidrotic effect of botulinum toxin A [1]. A fair number of pilot studies confirmed the expected efficacy of this therapeutic approach [2, 5, 8, 9, 12, 17, 18, 23–25]. The therapeutic benefit after botulinum toxin A injections could be objectively quantified by gravimetry comparing not only *before* and *after* treatment, but also left-versus-right sides which appears to be more appropriate in order to eliminate the impact of body and ambient temperature as well as physical and psychological conditions which may affect sweating variably at different time points [8].

In view of the conspicuous psychosomatic background of hyperhidrosis the question of placebo effects has to be addressed critically. One placebo-controlled double-blinded clinical trial (n = 13) did not show any placebo effects [24], while such effects appear to be present in a larger multicentre trial including some 24 centres (study conducted by the hyperhidrosis study group, presently in progress). All published papers, however, attest to an overwhelming and reliable efficacy of intradermal botulinum toxin A injections for axillary hyperhidrosis. What is rather diverse, however, in the available literature are the variable protocols specifying the pharmaceutical products of botulinum toxin A, the total dose and the number of injections [7, 19].

Type A botulinum toxin is presently available in the USA as Botox® (Allergan, Irvine, Calif., USA) and in Europe as Botox or Dysport® (Ipsen Ltd., Wrexham, UK). Although the biological activity is uniformly defined in mouse units, the respective dosage in humans has to be determined for each product individually [3, 15]. Presumably, 1 unit of Botox is equivalent to 3–4 units of Dysport [3, 15, 16] which may vary depending on dilutions and pharmaceutical composition [6, 26]. Effective doses for the treatment of axillary hyperhidrosis have been reported in a range of 50–200 units per axilla using Botox [14, 17] and 100–400 units using Dysport [9, 10]. However, detailed dose-response curves for botulinum toxin A have been established neither for hyperhidrosis nor for most other clinical uses. This may be due to the relatively small number of patients included in any given pilot study and the fact that botulinum toxin A cannot be titrated in an individual patient. Thus, future attempts to provide evidence-based information on how to optimize botulinum toxin A treatment should be welcomed. For this purpose, however, stringent study designs with larger populations and controls as well as accurate measurements of sweating and uniform follow-up schedules will be indispensable.

As costs of treatment and the risk of antibody induction against botulinum toxin A are increasing with higher doses, the simple equation 'the more,

the better' is not likely to prevail in botulinum toxin therapy. Presently, the dose for treatment axillary hyperhidrosis is chosen empirically as the amount of botulinum toxin A which is most likely to produce a satisfactory effect, which is 50 units of Botox or 100 units of Dysport.

For sustained relief from axillary hyperhidrotic symptoms, re-injections of botulinum toxin A in variable intervals are usually required. Presently, no explicit criteria for determining dose and frequency of repetitive treatments have been published except for the patients' own request for re-injection occurring anywhere from 4 to 17 months [8, 9, 11, 17, 18, 24]. Recently, high-dose botulinum toxin A has been reported to yield longer-lasting effects [14]; however, no control groups with lower doses and no uniform follow-ups have been used in this study.

Up to date, the treatment displays a very high safety profile. Severe side-effects or the induction of antibodies have not been reported, yet.

Patient Management

Botulinum toxin A for axillary hyperhidrosis is not a first-line treatment. Patients should be selected carefully based on their history of symptoms, failure of first-line treatment and subjective extent of impediment by sweating. Patients in which no previous attempts for treatment have been made should be tried on topical aluminium chloride (10–20% compositions, commercially available or prepared by a pharmacist) for 4–8 weeks before botulinum toxin A may be considered. In our hyperhidrosis clinic, also a gravimetric value of >50 mg/min is used to define frank axillary hyperhidrosis, although this is not a conditio sine qua non.

A detailed patient history should be obtained, particularly focusing on clues for secondary hyperhidrosis in which underlying causes must be addressed first. If necessary, laboratory tests determining hormone levels, signs of insidious infections or occult tumours should be carried out. General contra-indications as listed in table 1 should be ruled out, and informed written consent should be obtained (table 2). Also available treatment alternatives including topical agents, systemic drugs and operative procedures should be discussed with the patient.

One to two injections per year will usually provide sufficient control of hyperhidrotic symptoms. However, some patients tend to come back for treatment long before the therapeutic effect ceases, because they have become so comfortable with their completely dry armpits that they consider even minimal sweating (well below 50 mg/min) as disturbing. In this regard the question of when and why treatment should be repeated remains to be discussed between the individual patient and her/his physician.

Table 1. Contra-indications for botulinum toxin A treatment

Secondary hyperhidrosis due to hormonal disturbances, infections or malignancies
Neuromuscular diseases (e.g. myasthenia gravis, Lambert-Eaton syndrome)
Pregnancy/lactation
Intake of aminoglycoside antibiotics
Marcumar therapy of severe coagulopathies

Table 2. Points to be addressed for informed consent of the patient

Nature and mechanisms of botulinum toxin
Off-label use for axillary hyperhidrosis
Treatment alternatives
Minor discomfort such as a stinging sensation upon injection
Flu-like symptoms, skin rashes or fatigue within days after treatment may occur
Temporary skin rashes may occur
The effect will usually not be noticed before 2–5 days
The expected benefit (anhidrosis of the axillary area) may last between 3 and 12 months
Repeated treatments are usually required for continuing relief of symptoms

Table 3. Material needed for treatment of axillary hyperhidrosis with botulinum toxin A

Botulinum toxin A
Sterile NaCl
1-gauge and 30-gauge injection needles
1-ml and 5-ml syringes
Lugol solution
Starch powder
Skin marker
EMA ointment (optional)

Practical Considerations

The injection of botulinum toxin A into the axillary region is simple and easy (table 3). Usually no anaesthetic pretreatment is required. Optionally, EMLA® cream under an occlusive dressing can be applied 30–60 min before injection. The respective dose for one axilla is divided into 8–12 aliquots (depending on the size of the marked area) which are injected strictly intradermally by creating a visible wheal on each injection point. Generally, 0.2 ml is a convenient volume to inject into each point so that the total dose for one axilla has to be prepared in total of 2 ml for an average of 10 points. The distance between two injection points should not exceed 2.5 cm as the radial diffusion

from a given point is approximately 1.5–2 cm [4]. After the procedure, the patient may be advised to restrain from heavy exercise or sauna for the day (as heat may inactivate botulinum toxin A before it is taken up into the neurons). Otherwise there are no restrictions.

Future Perspectives

The benefits of botulinum toxin A treatment are increasingly acknowledged by patients and physicians. As a non-invasive procedure which takes up little time on an out-patient basis, intradermal botulinum toxin A injections may become the treatment of choice for patients suffering from axillary hyperhidrosis unresponsive to topical treatment. This indication – as most other uses of botulinum toxin – is presently 'off-label' (as of November 2000). However, ample clinical evidence for efficacy and safety published in peer-reviewed medical journals, as well as two large multicentre clinical trials on axillary hyperhidrosis which have just been completed will very likely prepare the ground for official approval in the near future.

Even though the majority of hyperhidrotic patients is not suffering from bromhidrosis (malodour), the effect of botulinum toxin A injections on axillary odour awaits further clarification. The perception of smell is highly subjective and therefore difficult to measure. Yet, there are some clues to diminished body odour after axillary botulinum toxin A treatment in a subset of patients in which odorous microbial processes are fostered by the damp milieu of the armpit.

Finally, the reliable effects of anhidrosis produced by botulinum toxin A may be desirable to certain professionals such as dentists, physiotherapists, dancers or actors who are forced by their routine of work to expose their armpits in intimate vicinity to colleagues or clients.

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