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ORIGINAL ARTICLE

Botulinum Toxin Type A for the Treatment of Primary Hyperhidrosis: A Prospective Study of 52 Patients

N. Martí,[a,*] D. Ramón,[a] L. Gámez,[a] I. Reig,[a] M.Á. García-Pérez,[b] V. Alonso,[a] and E. Jordá[a]

[a]*Servicio de Dermatología, Hospital Clínico Universitario, Valencia, Spain*
[b]*Fundación para la Investigación, Hospital Clínico Universitario, Valencia, Spain*

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KEYWORDS
Primary hyperhidrosis;
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Abstract
Background and objectives: Primary hyperhidrosis is characterized by excessive sweating in a defined region of the body. It should not be considered a purely cosmetic problem as it has a significant impact on the social and professional relationships of affected individuals. The aim of this study was to determine the clinical profile of patients with primary hyperhidrosis and assess the results obtained with the use of botulinum toxin type A (BTX-A) in clinical practice.
Material and methods: The study included 52 patients (39 women and 13 men) with a diagnosis of primary hyperhidrosis treated for the first time with BTX-A. All patients completed a questionnaire that included the following information: age; sex; profession; age at onset, family history, and site of hyperhidrosis; accompanying signs and symptoms, and previous treatment; time to effect of BTX-A; local or systemic side effects; and severity of hyperhidrosis before and after BTX-A treatment.
Results and conclusions: Primary hyperhidrosis began during puberty in 61.5% of the patients included in the study, 75% were women, and the mean age was 29.9 years. In 36.5% of patients, first-degree relatives also had primary hyperhidrosis. Hyperhidrosis was classified as palmar in 61.5% of cases, plantar in 53.8%, and axillary in 59.6%. Other sites were affected less frequently. The most common accompanying symptoms were facial erythema (32.7%), palpitations (30.7%), muscle tension (28.8%), shivering (23%), and headache (17.3%). Treatment with BTX-A was well tolerated and there was a highly significant reduction in the severity of hyperhidrosis 2 months after performing the treatment ($P<.001$).

*Corresponding author.
E-mail address: nuriamarfa@hotmail.com (N. Martí).

PALABRAS CLAVE
Hiperhidrosis primaria;
Toxina botulínica A;
Escala de severidad de la hiperhidrosis

Toxina Botulínica A en el tratamiento de la hiperhidrosis primaria: estudio prospectivo de 52 pacientes

Resumen

Introducción y objetivos: La hiperhidrosis primaria (HP) consiste en un exceso de sudación de una zona concreta del cuerpo que es clínicamente perceptible. La HP no debe considerarse un simple problema cosmético, pues supone una dificultad muy importante de relación social y laboral para las personas que lo experimentan. Los objetivos de este estudio han sido definir el perfil clínico de los pacientes con HP y evaluar en la práctica clínica los resultados que consigue el tratamiento con Toxina Botulínica A (TB-A).

Material y métodos: La muestra acota un total de 52 pacientes, 39 mujeres y 13 hombres, con diagnóstico de HP tratada por primera vez con TB-A. Todos cumplimentaron una encuesta donde se registraron: edad, sexo, profesión, inicio, antecedentes familiares, localización, signos/síntomas acompañantes y tratamientos previos; inicio del efecto de la TB-A; efectos secundarios locales y/o sistémicos y el grado de severidad de su hiperhidrosis antes del tratamiento y después del mismo.

Resultados y conclusiones: La HP se inicia en la pubertad en el 61,5% de los casos; el 75% son mujeres con una edad media de 29,9 años. El 36,5% de los pacientes tienen familiares de primer grado con HP. La localización de la hipersudación es palmar en el 61,5% de los casos, plantar en el 53,8% y axilar en el 59,6%, siendo menor en otras localizaciones. La clínica acompañante más frecuente es: eritema facial (32,7%), palpitaciones (30,7%), tensión muscular (28,8%), temblor (23%) y cefalea (17,3%). El tratamiento con TB-A es bien tolerado y respecto a la escala de severidad de la hiperhidrosis, se produce una mejoría muy significativa ($p < 1,0 \times 10^{-32}$; potencia estadística = 1) a los dos meses del tratamiento.

Introduction

Primary or idiopathic hyperhidrosis is a benign condition of unknown etiology, although most authors agree that it is linked to dysfunction of the autonomic control mechanism mediated by postganglionic cholinergic fibers.[1] It involves clinically apparent excessive sweating in a specific area of the body (focal hyperhidrosis).[1,2]

Although it can affect any of the body's eccrine glands (which receive nerve impulses via acetylcholine), it is usually associated with the palms of the hands, soles of the feet, axillas, or, occasionally, the face and scalp. It is a common condition that can affect up to 1% of the population.[3-6]

Focal idiopathic hyperhidrosis should not be considered only a cosmetic problem, since it has a substantial impact upon social and workplace relationships in affected individuals. Until recently, treatment options were largely ineffective (eg, topical aluminium salts or glutaraldehyde), awkward (eg, iontophoresis), or extremely invasive (eg, excision of the axillary sweat glands).[7,8] Other approaches have included the use of systemic drugs (sometimes with side effects), psychotherapy, thoracic sympathectomy, and botulinum toxin.

Botulinum toxin is a potent neurotoxin produced by the gram-positive bacterium *Clostridium botulinum*, which is responsible for botulism. Its mechanism of action involves blocking the release of acetylcholine from peripheral cholinergic synapses. When synaptic transmission is blocked, neurogenesis is stimulated and new terminals sprout from the end of the axon, leading to recovery of neurotransmission within weeks or months.[9-14] The 7 botulinum toxin serotypes (A, B, C1, D, E, F, and G) differ in their biosynthesis, size, and mechanism of action. Botulinum toxin type A (BTX-A) is used for the treatment of primary hyperhidrosis.

The aims of this study were to define the clinical profile of patients with primary palmar or axillary hyperhidrosis who attended the Department of Dermatology at Hospital Clínico Universitario de Valencia, in Valencia, Spain, to be assessed for treatment with BTX-A and to assess the results, tolerance profile, and duration of remission following BTX-A treatment in clinical practice.

Material and Methods

We undertook a prospective, descriptive, observational study of patients treated for the first time with BTX-A for primary palmar or axillary hyperhidrosis between September 2006 and April 2008 in the dermatology department at Hospital Clínico Universitario de Valencia.

Patients

The sample comprised 52 patients (39 women and 13 men) with a diagnosis of primary hyperhidrosis treated for the first time with BTX-A. The inclusion criteria were completion of a questionnaire, prepared by us, after 2 months and to have been examined and interviewed at least 12 months after treatment.

Twenty patients were treated with BTX-A for axillary hyperhidrosis, 22 for palmar hyperhidrosis, and 10 for combined axillary and palmar hyperhidrosis. In total, 60 axillas and 64 palms were treated.

Methods

All patients underwent a pretreatment evaluation (to rule out secondary hyperhidrosis and contraindications for the use of BTX-A), objective identification of the area of hyperhidrosis (Minor test), and photographic documentation of the affected area. All patients provided signed informed consent, including consent to compassionate use of BTX-A (in the case of palmar hyperhidrosis) for the treatment of primary hyperhidrosis.

They were also given a questionnaire to be completed after 2 months and additional data were collected at subsequent follow-up appointments.

For the treatment of axillary hyperhidrosis, a vial of BTX-A (Botox, Allergan, Irvine, California, USA) containing 100 mouse units (MU) was diluted in 4 mL of saline to obtain a concentration of 25 MU/mL. Twenty points were marked in the previously identified area of each axilla and 0.1 mL was injected at each point to introduce a total of 50 MU in each axilla (Figure 1). No anesthesia was required since injection in the axilla is usually well tolerated.

For the treatment of palmar hyperhidrosis, a vial of BTX-A was diluted in 5 mL of saline to obtain a concentration of 20 MU/mL. Thirty points were marked on each palm, sparing the thenar eminence, and 20 on the palmar surface of the fingers (1 in each proximal and medial phalanx and 2 in the distal phalanges) and 0.1 mL was injected at each point, to introduce a total of 100 MU in each palm (Figure 2). In all cases of palmar hyperhidrosis, injections were performed after locoregional anesthesia had been provided.

The questionnaire comprised an initial section containing questions on epidemiological and clinical variables: age, sex, profession, age at onset of hyperhidrosis, family history of hyperhidrosis, involvement of areas other than the treated region, accompanying signs and symptoms, and previous treatments. A second part contained questions on the onset of effect of BTX-A and local or systemic side effects, and a third part comprised questions on the severity of hyperhidrosis before treatment and 2 months after treatment on the Hyperhidrosis Disease Severity Scale:

- *Score of 1: My sweating is never noticeable and never interferes with my daily activities.*
- *Score of 2: My sweating is tolerable but sometimes interferes with my daily activities.*
- *Score of 3: My sweating is barely tolerable and frequently interferes with my daily activities.*
- *Score of 4: My sweating is intolerable and always interferes with my daily activities.*

The Hyperhidrosis Disease Severity Scale is easily understood and can be answered quickly. It provides a qualitative measure of the severity of the condition based on the extent to which it affects the patient's daily life. A score of 3 or 4 indicates severe hyperhidrosis. A score of 1 or 2 indicates mild or moderate hyperhidrosis.

Furthermore, the scale can be used as a measure of treatment efficacy and patient satisfaction.

A 1-point improvement has been associated with a 50% reduction in the production of sweat and a 2-point improvement with an 80% reduction.[15,16]

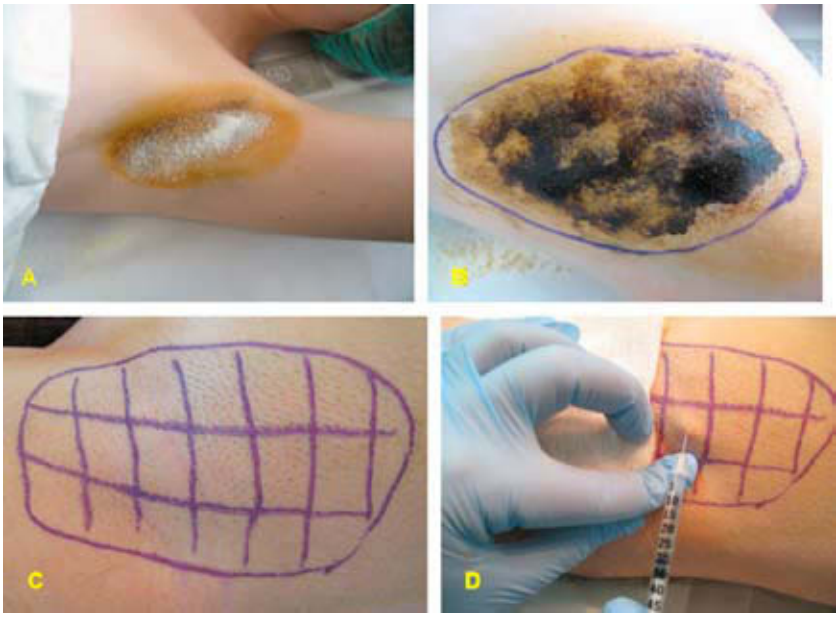

Figure 1 A and B, Minor test. C, A 1-cm grid drawn with a surgical marker pen on the area to be injected. D, Injection of toxin with a 29-guage needle at the marked points.

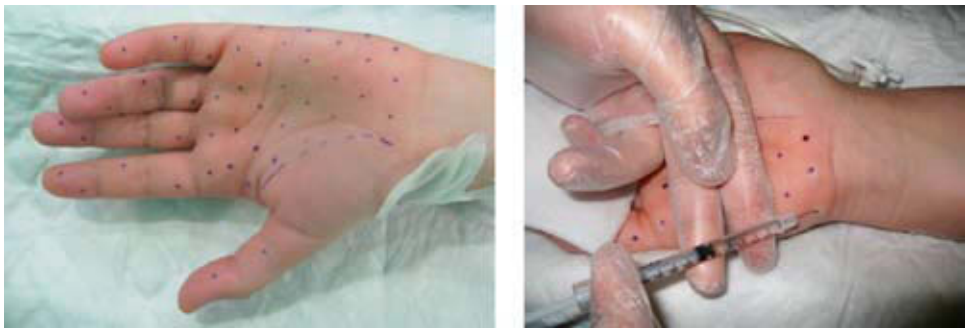

Figure 2 A, Injection points marked on the palms and palmar surface of the fingers (sparing the thenar eminence). B, The injection must be parallel to the skin surface in order to avoid depositing the toxin in the muscles.

The following data were then collected for each patient: timing of reinitiation of sweating and presence of long-term local or systemic side effects.

Statistical Analysis and Data Interpretation

Database management, processing, and statistical analysis were performed using SPSS version 15. To assess treatment effectiveness, the results for the severity scale were compared before and after initiation of treatment by repeated measures analysis of variance (ANOVA). To assess the effect of confounders, we analyzed data on efficacy in terms of the age of the patient at the time of treatment, sex, site of treatment (axilla or palms), and age at onset of hyperhidrosis, which were the covariables in multivariate repeated measures ANOVA models. When we detected a significant interaction with a covariable, we re-analyzed for sex (male or female) or site (axilla or palms) to clarify the cause of the interaction. Finally, we defined a new variable (response) as the difference in score on the severity scale before and after treatment. In this case, we analyzed the results by simple ANOVA using sex and site of treatment as the independent variables and response as the dependent variable. All analyses were 2-tailed and the results were shown as mean (SD). The cutoff for statistical significance was set at $P<.05$.

Results

The mean age of the patients was 29.8 (9.5) years and the median, 29 years (range, 15-53 years). The group included 39 (75%) women (mean age, 29.9 years) and 13 (25%) men (mean age, 31.9 years).

Overall, 26.9% of patients worked in administration; 21.1% were students; 13.5% worked in construction, industry, or transport; 11.5% were freelance professionals; 9.6% worked in retail; 7.6% in health care; 3.8% in the restaurant and catering industry; and 5.8% were unemployed.

Two patients had been diagnosed with hypothyroidism and 1 with hypertension; all were receiving treatment for their condition.

Table 1 Distribution of Primary Hyperhidrosis

Body region	No. of Patients	Percentage
Facial area	6	11.5
Axilla	31	59.6
Chest	4	7.7
Back	5	9.6
Hands	32	61.5
Abdomen	3	5.8
Groin	8	15.4
Feet	28	53.8

Nineteen patients (36.5%) had a first-degree relative with primary hyperhidrosis; the sites and severity of hyperhidrosis in those relatives were variable.

The mean age at onset was 11.38 (4.6) years, with a median age of 10 years (range, 5-30 years). Onset occurred during puberty in 61.5% of patients (n=32), in childhood in 35%, and only after puberty in 3.5%.

The site of hyperhidrosis was palmar in 22 patients (42.3%), axillary in 20 patients (38.5%), and mixed in 10 patients (19.2%). Patients who consulted for sweating in a specific area also reported sweating in other regions of the body: hands (32 patients, 61.5%), feet (53.8%), axillas (59.6%), groin (15.4%), face (11.5%), back (9.6%), chest (7.7%), and abdomen (5.8%) (Table 1).

Among the patients with palmar hyperhidrosis, 71.8% had cold hands and 81.2% erythema. In 34.3% of those patients, accompanying cutaneous lesions were present in the form of nail disease, pruritus, or scaling (Table 2).

Primary hyperhidrosis was accompanied by facial erythema in 32.7% of patients, palpitations in 30.7%, muscle tension in 28.8%, shivering in 23%, headache in 17.3%, gastric discomfort or nonspecific epigastric pain in 15.4%, and dry mouth in 13.5% (Table 3).

All patients had received prior medical treatment without success. All patients had used a topical treatment and 3 patients (5.77%) had received systemic drugs. Iontophoresis had been applied in 1 case (1.9%).

Seventeen patients (85%) treated for axillary hyperhidrosis had a score of 3 on the Hyperhidrosis Disease Severity Scale

prior to treatment and 3 patients (15%) had a score of 4. Two months after treatment, all 20 patients (100%) had achieved a score of 1 (Figure 3).

Of the patients treated only for palmar hyperhidrosis, 5 (22.72%) had a score of 3 and 17 (77.27%) had a score of 4 prior to treatment with BTX-A. Two months after treatment, 16 patients (72.72%) achieved a score of 1, 2 patients (9.09%) moved from a score of 4 to a score of 2, and 2 patients (9.09%) had a score of 3 after treatment (1 patient with a baseline score of 4 moved only to a score of 3 due to persistent sweating on the finger pads and sides of the fingers and the other patient did not show improvement on the severity scale because the effect of BTX-A only lasted 1 month). Finally, 2 patients (9.09%) showed no improvement from an initial score of 4; in 1 patient the treatment was ineffective and in the other the effect lasted only 1.5 months (Figure 4).

Of the 10 patients treated for combined palmar and axillary hyperhidrosis, 7 (70%) had a score of 3 and 3 (30%) had a score of 4 for axillary hyperhidrosis; all 10 patients (100%) had a score of 4 for palmar hyperhidrosis.

Two months later, all patients had achieved a score of 1 for axillary hyperhidrosis and the following scores were obtained for palmar hyperhidrosis: 7 patients (70%) achieved a score of 1, 1 patient (10%) went from a score of 4 to a score of 3 as a result of sustained excessive sweating on the finger pads and thenar eminence, and 2 patients (20%) went from a score of 4 to 2.

The mean time to onset of effect of BTX-A injection in the 30 patients treated for axillary hyperhidrosis was 3.8 (3.5) days, with a median of 2 days (range, 1-14 days).

BTX-A injection was performed for palmar hyperhidrosis in 32 patients but in one of them the treatment was ineffective. The mean time to onset of effect in the remaining 31 patients was 3.6 (3.4) days, with a median time to onset of 2 days (range, 1-15 days).

The 30 patients treated for axillary hyperhidrosis had a mean time to reoccurrence of sweating of 6.6 (2.3) months, with a median of 6 months (range, 1-12 months).

The duration of effect in the 31 patients in whom treatment of palmar hyperhidrosis was effective was 4.9 (1.9) months, with a median effect duration of 5 months (range, 1-9 months).

In terms of short-term side effects, 5 of the 30 patients with axillary hyperhidrosis (16.6%) reported local irritation lasting less than 24 hours and 2 patients out of 32 treated for palmar hyperhidrosis (6.25%) had hematomas following treatment. Sixteen out of 32 patients treated for palmar hyperhidrosis (50%) displayed transient weakness in the hands that affected pinching between the thumb and index finger and lasted a mean of 2 (0.8) weeks.

No long-term local effects (minimum follow-up of 12 months from the first treatment session) or systemic side effects were observed in any of the 52 patients studied.

The improvement on the Hyperhidrosis Disease Severity Scale at 2 months was highly significant ($P<1.0^{-32}$; statistical power = 1) when the data were considered together without adjusting for sex or site of hyperhidrosis. Furthermore, treatment was effective irrespective of patient age, since including age as a covariable revealed no significant interaction between age and treatment. The same was

Table 2 Concomitant Cutaneous Symptoms in the Hands

Local Symptom	No. of Patients	Percentage
Cold	23	71.8
Erythema	26	81.2
Other lesions	11	34.3

Table 3 Symptoms Accompanying Hyperhidrosis

Symptom	No. of Patients	Percentage
Headache	9	17.3
Facial erythema	17	32.7
Dry mouth	7	13.5
Epigastric pain/ gastric discomfort	8	15.4
Muscle tension	15	28.8
Shivering	12	23
Palpitations	16	30.7

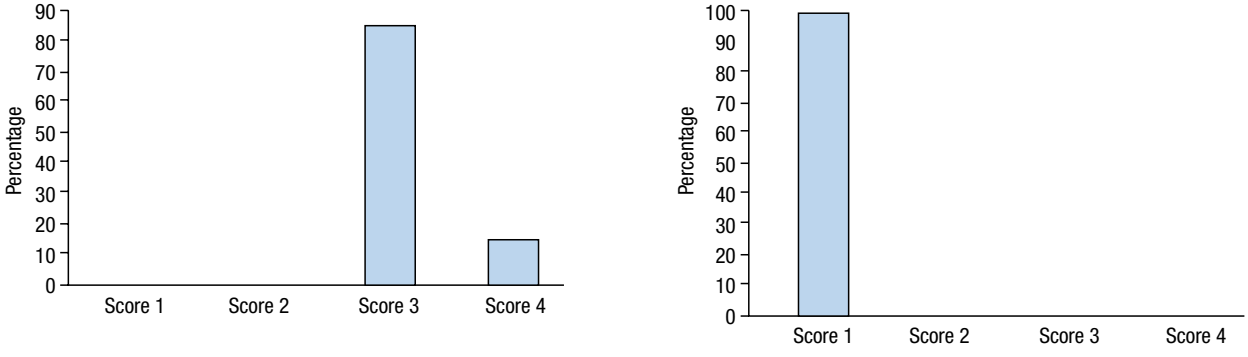

Figure 3 Hyperhidrosis Disease Severity Scale before treatment of axillary hyperhidrosis with botulinum toxin type A (left) and 2 months later (right) (n=20).

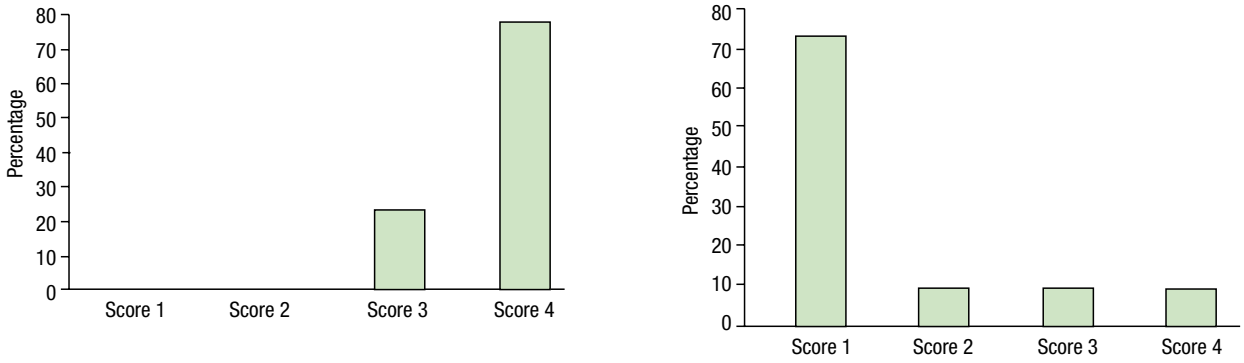

Figure 4 Hyperhidrosis Disease Severity Scale before treatment of palmar hyperhidrosis with botulinum toxin type A (left) and 2 months later (right) (n=22).

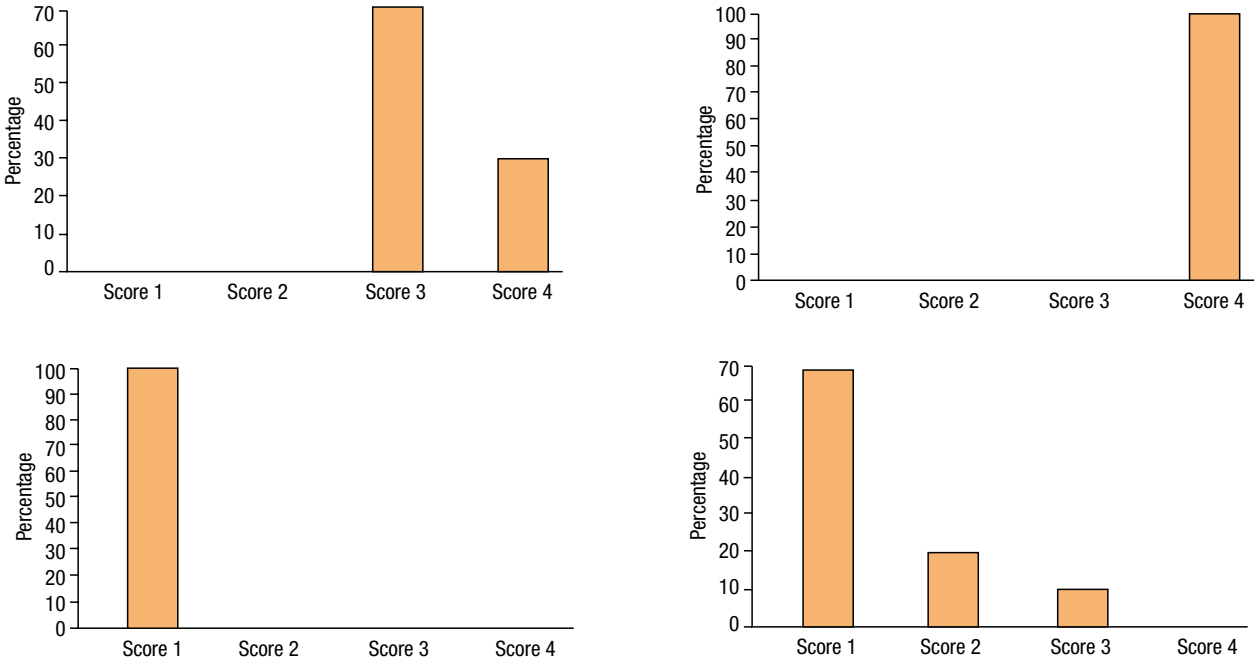

Figure 5 Hyperhidrosis Disease Severity Scale before treatment with botulinum toxin type A in the axilla (upper left) or palms (upper right) and 2 months later in the axilla (lower left) or palms (lower right) (n=10).

observed for age at onset of hyperhidrosis and treatment site. However, there was a significant interaction between treatment effectiveness and sex (P=.019). We therefore assessed the effect of sex separately for the 2 sites of hyperhidrosis.

That analysis showed that treatment response (difference between the score on the severity scale from baseline to 2 months) was not significantly different between the treatment sites but confirmed that response did differ between sexes (Figure 5).

Comparison of the response obtained at the 2 sites showed that there was no difference between the sexes in those treated for palmar hyperhidrosis but there were differences between the sexes in the case of axillary hyperhidrosis (Figures 6 and 7).

Discussion

Primary hyperhidrosis is characterized in most cases by sympathetic hyperactivity, although it is unclear whether this is generalized or restricted to the sympathetic ganglia responsible for sudomotor innervation of the upper limbs.[17,18]

Efforts have been made to identify treatments for the condition, not because of its clinical consequences but

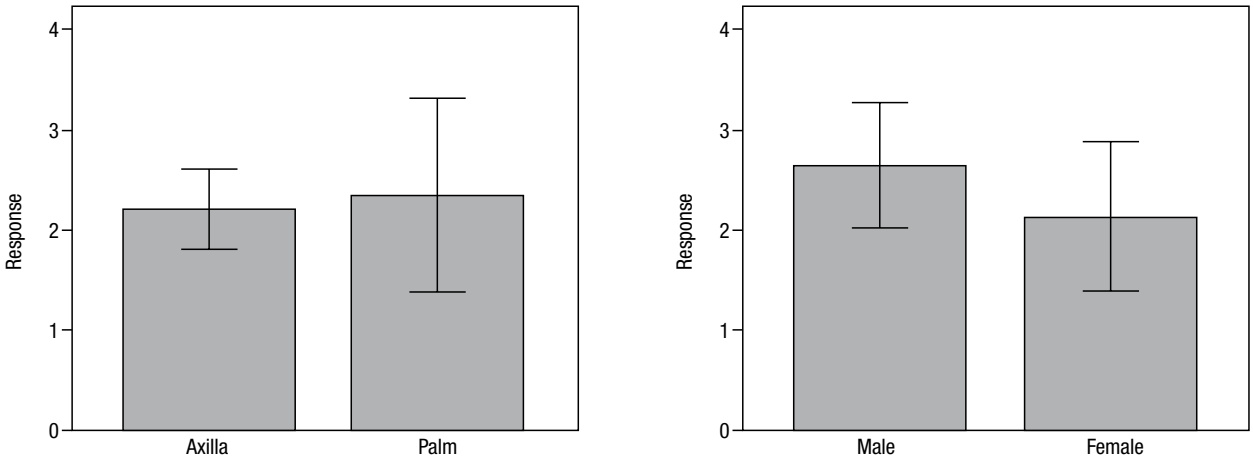

Figure 6 No significant difference in response was observed between the axilla and palms (P=.455) but significant differences were observed between sexes (P=.019).

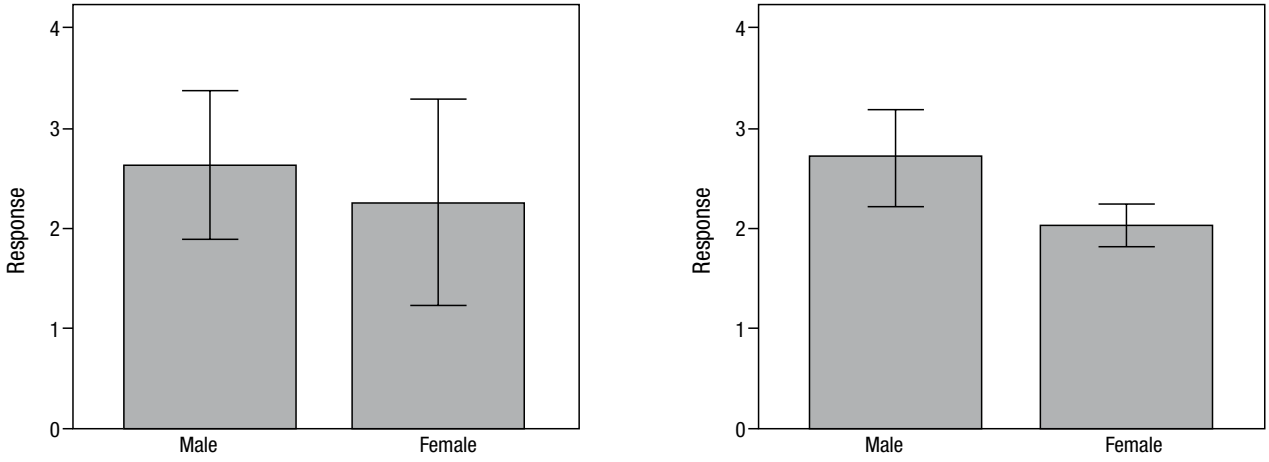

Figure 7 There was no significant difference between the sexes in the response to treatment of the palms (left, P=.352), whereas there was a significant difference in the axilla (right, P<.001).

rather to alleviate the problems it generates for daily life in affected individuals or because it may be a symptom of other diseases.[19] The results obtained in our study allow us to define the usual clinical characteristics of patients with hyperhidrosis in our setting.

In our study, onset of symptoms was generally during puberty, as is usually the case[1,20]; some, however, have described onset in childhood[19] (as was observed in 18 patients from our study). The patients generally have few associated conditions, possibly due to the low mean age of the group.

In our study, 36.5% of patients had first-degree relatives with hyperhidrosis. Based on similar findings, other authors have suggested that, empirically, the etiology corresponds to an autosomal dominant hereditary condition[21] or a hereditary, non-sex-related disease with incomplete penetrance.[22] However, primary hyperhidrosis cannot be described as a hereditary condition, since other causes must have been excluded.

Excessive sweating is not restricted to a single area but rather extends to other parts of the body. This suggests that focal hyperhidrosis could be the predominant sign of sympathetic hyperactivity that is more or less generalized but that may manifest to differing degrees. Nevertheless, this hypothesis cannot be confirmed by the results of our study.

Many patients display accompanying symptoms that could be a cause or an effect of hyperhidrosis. Some studies have reported primary hyperhidrosis as a symptom of psychiatric disorders such as social phobia[23] or high levels of anxiety.[6] Some authors who have analyzed psychopathology in patients with hyperhidrosis, however, find that symptoms of anxiety and depression are reactive rather than causal.[24]

Patients report discomfort and high levels of anxiety associated with work situations that require physical contact as well as in social situations.

We observed a statistically significant improvement on the Hyperhidrosis Disease Severity Scale, and the effect

observed in patients treated for axillary hyperhidrosis was greater in men than women. Further studies will be required to confirm this observation, as this study was not designed to investigate such an effect.

Although higher doses of BTX-A (200 MU Botox in each axilla) have been reported to achieve more prolonged axillary anhidrosis,[25,26] their use could increase the risk of side effects and the formation of neutralizing antibodies.

In conclusion, the results of our study indicate that focal hyperhidrosis usually manifests during puberty. Patients have few concomitant diseases and the local dermatologic repercussions are mild. The condition may have a genetic basis, given the proportion of family members who are also affected. It is characterized by excessive sweating in multiple areas of the body and can also have accompanying symptoms.

Since primary hyperhidrosis is a common condition with a substantial impact on the daily life of affected individuals, infiltration of BTX-A may be a valid treatment option before resorting to surgery in patients who have not responded to topical treatments.

It is a simple treatment with minimal side effects and is well tolerated during application. Its use is limited, however, by its cost and the transient therapeutic effect.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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