

Focal hyperhidrosis: diagnosis and management

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Abstract

HYPERHIDROSIS, A CONDITION CHARACTERIZED by excessive sweating, can be generalized or focal. Generalized hyperhidrosis involves the entire body and is usually part of an underlying condition, most often an infectious, endocrine or neurologic disorder. Focal hyperhidrosis is idiopathic, occurring in otherwise healthy people. It affects 1 or more body areas, most often the palms, armpits, soles or face. Almost 3% of the general population, largely people aged between 25 and 64 years, experience hyperhidrosis. The condition carries a substantial psychological and social burden, since it interferes with daily activities. However, patients rarely seek a physician's help because many are unaware that they have a treatable medical disorder. Early detection and management of hyperhidrosis can significantly improve a patient's quality of life. There are various topical, systemic, surgical and nonsurgical treatments available with efficacy rates greater than 90%–95%.

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Hyperhidrosis, or increased production of sweat, can have a deeply detrimental effect on a patient's quality of life, resulting in dramatic impairments of daily activities, social interactions and occupational activities.^{1,2} It can be generalized, involving the whole body, or focal, involving a limited body area, most often the feet, armpits, hands or face. It is as common a disorder as psoriasis.³ However, patients rarely seek a physician's help because many are unaware that they have a treatable medical disorder. In this article, we review the possible causes, pathophysiology, diagnosis and clinical manifestations of focal hyperhidrosis as well as the wide range of treatment modalities available today.

Epidemiology

A recent large epidemiological survey of 150 000 households in the United States has revealed that focal hyperhidrosis is present in 2.8% of the general population.⁴ The condition affects both men and women equally, and its prevalence was found to be the highest among people aged 25–64 years. The average age of onset is 25 years but depends primarily on the body area affected. Palmar and axillary hyperhidrosis have the earliest average onset, at 13 and 19 years respectively.⁴ As many as

82% of patients with palmar hyperhidrosis have reported onset in childhood.⁵ Focal hyperhidrosis appears to have an onset in childhood; however, people may not seek medical help until early adulthood. Armpits are affected in 51% of patients, feet in 29%, palms in 25% and the face in 20%.^{4,6} No studies have documented the natural course of the disease with increasing age, but in our experience, the severity of sweating seems to decrease in patients older than 50 years.

Pathophysiology

The pathophysiology of focal hyperhidrosis is poorly understood. Sweat is produced by the body's sweat glands: there are up to 4 million sweat glands, of which about 3 million are eccrine sweat glands and the remainder are apocrine glands.⁷ Eccrine sweat glands are innervated by cholinergic fibres from the sympathetic nervous system. Their primary function is the secretion of sweat — an odourless, clear fluid that regulates body temperature — the rate of which is affected by emotional and gustatory stimuli. Eccrine sweat glands, which are responsible for focal hyperhidrosis, are distributed over nearly the entire body surface, although their density is highest in the soles of the feet and the forehead, followed by the palms and cheeks. Apocrine sweat glands are scent glands and are primarily confined to the axillary and urogenital regions. They are not involved in focal hyperhidrosis, and their function is regulated by hormonal processes. There are also mixed sweat glands called apoecrine glands, which are primarily found in axillary and perianal areas. Their role in the pathophysiology of focal hyperhidrosis is unknown, although in some patients they constitute up to 45% of the sweat glands found in the axillary region.⁸

No histopathological changes in the sweat glands have been observed in patients with focal hyperhidrosis, nor do these patients have increased numbers of or larger sweat glands.⁷ Rather, focal hyperhidrosis may represent a complex dysfunction of the autonomic nervous system, involving both the sympathetic and parasympathetic pathways. A genetic predisposition may exist, since 30%–50% of patients have a family history of hyperhidrosis.⁹ In a study by Shih and colleagues,¹⁰ patients with palmoplantar hyperhidrosis showed less reflex bradycardia in response to Valsalva's manoeuvre and a higher degree of vasoconstriction.

Box 1: Causes of generalized¹² and focal hyperhidrosis¹³**Focal hyperhidrosis**

Primary idiopathic hyperhidrosis
 Gustatory sweating (Frey's syndrome)
 Neurologic
 Neuropathies
 Spinal injury

Generalized hyperhidrosis

Endocrine	Infection
Hyperthyroidism	Cardiovascular
Hyperpituitarism	Shock
Diabetes mellitus	Heart failure
Menopause	Respiratory failure
Pregnancy	Drugs
Pheochromocytoma	Fluoxetine
Carcinoid syndrome	Venlafaxine
Acromegaly	Doxepin
Neurologic	Toxicity
Parkinson's disease	Alcoholism
Spinal cord injury	Substance abuse
Cerebrovascular accident	
Malignant disease	
Myeloproliferative disorders	
Hodgkin's disease	

tion in response to finger immersion in cold water. Such an increased sympathetic activity through the T2–T3 ganglia could cause palmar hyperhidrosis. Excessive palmar and plantar sweating could thus result in a vicious cycle, as evaporative cooling of the skin increases sympathetic outflow through reflex action, which in turn increases sweat output. Parasympathetic dysfunction was implicated in a study that compared heart rate variability in patients with focal hyperhidrosis with that of healthy control subjects.¹¹ The authors found that, although sympathetic activity seemed to be similar, patients with focal hyperhidrosis exhibited heart rate patterns suggesting parasympathetic dysfunction.

Diagnosis and clinical presentation

The first step in the evaluation of hyperhidrosis is to differentiate between generalized and focal hyperhidrosis. Generalized hyperhidrosis is usually part of some other underlying condition, such as infective or malignant disease or a hormonal disorder,¹² and focal or primary idiopathic hyperhidrosis occurs in otherwise healthy people (Box 1). It usually peaks in the second or third decade of life and manifests as bilateral excessive sweat production confined to the armpits, soles of the feet, palms of the hands, face or other specific sites. Gustatory sweating (Frey's syndrome) is also a form of focal hyperhidrosis. A positive family history is evident in

30%–50% of patients.⁹ Furthermore, patients with focal hyperhidrosis generally do not sweat during sleep. Thus, a medical history focusing on location of excessive sweating, duration of the presentation, family history, age at onset and the absence of any apparent cause allows one to easily differentiate focal from generalized hyperhidrosis (Box 2). Although there is no standard definition of focal hyperhidrosis, less than 1 mL/m² of sweat production per minute by eccrine glands at rest and at room temperature is considered normal.⁸ Alternatively, sweat rates of discrete anatomic areas (e.g., palm, axilla) may be measured for research purposes (e.g., normal sweat rates for the axilla are < 20 mg/min).¹³ For practical clinical purposes, any degree of sweating that interferes with the activities of daily living should be viewed as abnormal.

Diagnosis of focal hyperhidrosis does not require laboratory investigations. A starch iodine test can be used to outline the area of excessive sweating (Fig. 1). Iodine solution (1%–5%) is applied to a dry surface, and after a few seconds

starch is sprinkled over this area. The starch and iodine interact in the presence of sweat, leaving a purplish sediment. This purple area identifies the duct of the sweat gland. Although the starch iodine test is not necessary for diagnosis, it allows the qualitative identification of areas of excessive sweating, which can be recorded by pictures taken before and after treatment.

Psychosocial impairment is a significant aspect of focal hyperhidrosis (Box 3). In a US survey, one-third of patients with axillary hyperhidrosis reported their sweating as being barely tolerable or intolerable and as frequently interfering with activities of daily living; 35% of patients reported a decrease in leisure activity time due to exces-

Box 2: Diagnostic criteria for primary focal idiopathic hyperhidrosis¹³

Focal, visible, excessive sweating of at least 6 mo duration without apparent cause with at least 2 of the following characteristics:

- Bilateral and relatively symmetric sweating
- Frequency of at least 1 episode per wk
- Impairment of daily activities
- Age at onset < 25 yr
- Positive family history
- Cessation of sweating during sleep

sive sweating.⁴ Many patients with focal hyperhidrosis go to considerable lengths to hide their condition,¹ and social interactions are significantly impaired, since patients experience feelings of humiliation and embarrassment. Simple aspects of socialization, such as shaking hands or hugging, become awkward. Focal hyperhidrosis also has a profound impact on occupational activities. Despite this, only one-third of the survey participants had consulted a physician about their problem. Clearly, primary care physicians can be instrumental in the initial diagnosis and assessment of this condition.

Treatment

There is a wide range of nonsurgical (e.g., topical, systemic) and surgical treatments available for patients with focal hyperhidrosis. These treatment modalities vary in



Fig. 1: A starch iodine test is used to outline the area of excessive sweating. Iodine solution (1%–5%) is applied to a dry surface, followed by a sprinkling of starch (top). The iodine and starch interact in the presence of sweat, leaving a purplish sediment (bottom).

their therapeutic efficacy, duration of effect, side effects and cost, as well as in the scientific evidence of their efficacy (Tables 1 and 2).

Topical treatments

Aluminum salts are the most common ingredient in over-the-counter antiperspirants used to treat focal hyperhidrosis. It has been postulated that the mechanism of their action is related to mechanical obstruction of the eccrine gland duct or to atrophy of the secretory cells.²⁷ The concentrations of aluminum salts in most commercial antiperspirants is 1%–2%; however, aluminum chloride solutions are available in 20%–25% concentrations. Repeated applications are often necessary every 24–48 hours. Improvement can be seen in mild cases within 3 weeks of treatment. The major limitation of aluminum chloride products is localized burning, stinging and irritation. To minimize irritation, these products can be applied to the affected area at bedtime and washed off after 6–8 hours. According to the literature, 25% aluminum chloride is an effective first-line treatment for mild axillary hyperhidrosis.²⁸ Aluminum chloride 20% can reduce palmar hyperhidrosis within 48 hours after application, but the effect diminishes within 48 hours after the end of treatment.¹⁴ Aluminum chloride 20% in alcohol can be effective in as many as 98% of cases of mild axillary hyperhidrosis.¹⁵

Topical aldehyde agents, such as formaldehyde and glutaraldehyde, have limited use in the treatment of focal hyperhidrosis because they can cause allergic sensitization and localized skin irritation.²⁹

Iontophoresis

Iontophoresis is defined as the introduction of ions into the skin by means of an electrical current. The mode of action is not yet clear, but it is postulated that a charged particle obstructs the duct or the electrical

Box 3: Burden of disease in hyperhidrosis

- Severe embarrassment associated with soaked clothing and wet palms
- Change of clothing required 2 or more times per day
- Handshaking avoided when possible
- Frustration with activities of daily living
- Impairment of performance and productivity at work
- Change in the type of leisure activities pursued
- Missed social gatherings with friends and family
- Depression and lack of confidence
- Skin maceration from constant wetness can lead to bacterial and fungal infections
- Difficulty with social and intimate relationships

change disrupts eccrine gland secretion.³⁰ The procedure entails placing the hands or feet in a shallow basin filled with water, through which an electric current is passed. Iontophoresis is primarily used for focal palmoplantar hyperhidrosis, since the hands and feet are the easiest body parts to submerge in water.

Iontophoresis has not been studied in large randomized controlled trials, but it has been reported to be 80%–100% effective in uncontrolled trials.^{16–18,31} However,

long-term maintenance therapy is generally required. The limitation of this treatment is that it causes skin irritation, dryness and peeling. It is also time consuming, as it may require 30–40 minutes per treatment site daily for at least 4 days a week. Normal sweating is generally achieved after 6–10 treatments. Overall, iontophoresis is considered a second-line treatment for focal palmoplantar hyperhidrosis and is contraindicated in patients who are pregnant or who have a pacemaker.

Table 1: Evidence for medical treatments of focal hyperhidrosis

Trial	No. of patients	Study design	Intervention; affected area	Outcome measure	Result	<i>p</i> value	Follow-up period	Comment
Goh et al ¹⁴	12	Controlled, single blind; within patient comparison	Aluminum chloride 20%; palms	Rate of skin vapour loss (g/m ² per hour)	Treated: 51.4 g/m ² (SD 16.5) Control: 72.7 g/m ² (SD 17.0)	0.004	4 wk	Skin irritation in 4/12 (33%)
Scholes et al ¹⁵	65	Prospective, uncontrolled	Aluminum chloride 20%; axillae	Self-reported improvement	64/65 (98%) reported excellent control of sweating	NA	12 mo	Skin irritation in 29/65 (45%)
Karakoc et al ¹⁶	112	Prospective, uncontrolled	Iontophoresis; palms, soles	No recurrence of symptoms 20 d after end of treatment	91/112 (81%)	NA	20 d	Vesicles 8/112 (7%) Erythema 10/112 (9%) Discomfort 16/112 (14%)
Reinauer et al ¹⁷	25	Controlled, single blind	Iontophoresis (comparison of DC, AC, and AC with DC offset); palms, soles	Gravimetric sweat rate (mg/min)	No change with AC alone; both DC and AC with DC offset resulted in normal sweat rates (< 20 mg/min) after 11 sessions	NA	3 wk	Acrocyanosis, edema (rates not provided)
Holzle et al ¹⁸	71	Prospective, uncontrolled	Iontophoresis; palms, soles	Gravimetric sweat rate (mg/min)	Palmar: mean 52 mg/min at baseline to < 20 mg/min Plantar: mean 43 mg/min at baseline to < 15 mg/min	None provided	14 mo	Burning, tingling, erythema, vesicles in short term; none in long term
Heckmann et al ¹⁹	145	Randomized, double blind; within patient comparison of intervention v. placebo	Botulinum toxin; axillae	Gravimetric sweat rate (mg/min)	Treatment: 24 ± 27 mg/min Placebo: 144 ± 113 mg/min Mean difference: 111 mg/min; 95% CI 91–132 mg/min	< 0.001	24 wk	Compensatory hyperhidrosis (< 1%) Axillary itching (< 1%) Shoulder muscle soreness (< 1%)
Naumann et al ²⁰	320	Randomized, double blind, placebo controlled*	Botulinum toxin; axillae	≥ 50% reduction in gravimetric sweat rate (mg/5 min)	Treatment: 198/320 (82%) Placebo: 16/78 (21%)	< 0.001	16 wk	Compensatory hyperhidrosis (5%)
Lowe et al ²¹	17	Randomized double blind; within patient comparison of intervention v. placebo*	Botulinum toxin; palms	Patient satisfaction	Treatment: 17/17 (100%) Placebo: 2/17 (12%)	< 0.001	4 wk	Transient intrinsic muscle weakness (< 1%)
Schnider et al ²²	11	Randomized, double blind; within patient comparison of intervention v. placebo	Botulinum toxin; palms	Mean reduction in sweating measured by triketohydrindene hydrate sweat test	Treatment: 31% (95% CI 20%–42%) Placebo: 0.2%–1.2%	< 0.001 Not significant	13 wk	Transient intrinsic muscle weakness (< 1%) Self-reported improvement in 8/11 (73%) of patients at end of study

Note: SD = standard deviation, NA = not available, DC = direct current, AC = alternating current, CI = confidence interval.

*Study used a normal level of sweating of < 20 mg/min.

Botulinum toxin A

Botulinum toxin A is the best-studied treatment to date for focal hyperhidrosis. It is a neurotoxin produced by the anaerobic bacterium *Clostridium botulinum*;³² 7 serotypes of toxin exist, of which type A is the most potent. When used to treat focal hyperhidrosis, botulinum toxin is injected intradermally and acts to inhibit the release of acetylcholine at the neuromuscular junction and from sympathetic nerves that innervate eccrine sweat glands, which results in loss of sweating (Figs. 2 and 3).³⁴

Botulinum toxin has been evaluated as a treatment for axillary hyperhidrosis in 2 large randomized controlled trials.^{19,20} A significant improvement was reached in 95% of patients at 1 week, and the average duration of effect was 7 months. For palmar hyperhidrosis, the response rate was greater than 90%;^{21,22} the duration of effect was generally 4–6 months. The major limitation of this treatment is that the injections are painful and require a nerve block for anesthesia. However, patient satisfaction in randomized controlled trials with botulinum toxin was nearly 100%. Excellent response rates to botulinum toxin application in plantar hyperhidrosis have also been reported^{135–37} but still need to be confirmed by controlled studies.

Contraindications to botulinum toxin therapy include neuromuscular disorders such as myasthenia gravis, pregnancy and lactation, organic causes of hyperhidrosis, and medications that may interfere with neuromuscular transmission. For this treatment, patients should be referred to

physicians specialized in the administration of botulinum toxin. It must be noted, however, that the cost of the drug is a limitation to its wider use.

Surgical treatments

Surgical treatments include endoscopic thoracic sympathectomy, which destroys the sympathetic ganglia by excision, clamping, transection or ablation with cautery or laser. Several retrospective studies and uncontrolled clinical trials have demonstrated that endoscopic thoracic sympathectomy is effective in eliminating axillary, palmar and facial hyperhidrosis in 68%–100% of cases.^{5,23–25} Plantar hyperhidrosis was reduced in 58%–85% of patients. The main limitation of this procedure is a high incidence of mild to severe compensatory hyperhidrosis, usually involving the trunk and lower limbs, in up to 86% of patients.³⁴ Other adverse effects include gustatory sweating, phantom sweating (the sensation of impending hyperhidrosis in the absence of sweating), neuralgia, Horner's syndrome and the risk of hemothorax or pneumothorax.³⁴ Furthermore, lumbar sympathectomy for plantar hyperhidrosis is associated with sexual dysfunction.¹³ Other surgical procedures with reported efficacy include excision of axillary tissue and subcutaneous axillary curettage and liposuction.^{26,38,39} Surgical options for focal hyperhidrosis are associated with high efficacy rates, but they should be reserved for patients for whom other treatments have been ineffective and who appreciate the risks associated with the procedure and potential complications.

Table 2: Evidence for surgical treatments of focal hyperhidrosis

Trial	No. of patients	Study design	Intervention; affected area	Outcome measure	Result	p value	Follow-up period	Side effects
Doolabh et al ²³	180	Retrospective	Endoscopic sympathectomy (cauterization); axillae, palms, soles, face	Self-reported improvement	Satisfied patients: axillae 54/55 (99%) palms 140/140 (100%) soles 72/125 (58%) face 37/39 (95%)	NA	17 mo	Compensatory hyperhidrosis (78%) Horner's syndrome (1%) Hemothorax (2%)
Reisfeld et al ²⁴	1312	Retrospective	Endoscopic sympathectomy clamping v. cauterization; palms, face	Self-reported improvement	Satisfied patients: clamping 98% cauterization 95%	< 0.025	23 mo	Compensatory hyperhidrosis (> 90%) Pneumothorax (< 1%)
Lin et al ⁵	1360	Retrospective	Endoscopic sympathectomy (cauterization); palms	Self-reported improvement	Resolution of symptoms in 99% of patients immediately and at follow-up	NA	28 mo	Compensatory hyperhidrosis (84%) Pneumothorax (< 1%)
Zacherl et al ²⁵	369	Retrospective	Endoscopic sympathectomy with v. without video assistance (cauterization); palms	Self-reported improvement	With video assistance 27/30 (90%) had dry limbs; without video assistance 239/293 (91%) had dry limbs	None provided	36 mo	Compensatory hyperhidrosis (69%) Horner's syndrome (2%)
Proebstle et al ²⁶	38	Prospective, uncontrolled before–after comparison	Subcorial curettage; axillae	Gravimetric sweat rate (mg/min)	Mean sweat rate before curettage 48.4 mg/min; after curettage 18.1 mg/min	< 0.001	8 wk	Scars (53%) Paresthesia (33%) Pigmentation (33%) Partial alopecia (44%)

Systemic treatments

The main systemic agents used to treat focal hyperhidrosis are anticholinergic agents. By inhibiting synaptic acetylcholine, they interfere with neuroglandular signalling.³⁴ The main limitation of these drugs is that the doses required to achieve reduced sweating may also result in adverse effects such as dry mouth, blurred vision, urinary retention, constipation and tachycardia. Glycopyrrolate, an anticholinergic drug, at initial doses of 1 mg twice daily may improve hyperhidrosis, but the eventual dosage required usually results in unacceptable side effects.³⁴ Other systemic agents include amitriptyline, clonazepam, β -blockers (e.g., propranolol) and calcium-channel blockers (e.g., diltiazem), gabapentin and indomethacin.^{34,40-42} However, these drugs have been used mostly by patients with generalized hyperhidrosis; their role in the treatment of focal hyperhidrosis remains to be established.

Alternative treatments

Biofeedback training, hypnosis and different types of relaxation techniques have been used to treat hyperhidrosis,^{43,44} but research data on their efficacy are still scarce to nonexistent. The lack of well-designed trials and long-term follow-up limits their use.



Fig. 2: Intradermal botulinum toxin injections for the treatment of axillary hyperhidrosis. Focal axillary hyperhidrosis is treated with 50–200 units of botulinum toxin A per axilla. The usual starting dose is 50 units per axilla. The drug is injected intradermally using a 13-mm-long 30-gauge needle. Injections are done in a grid-like pattern in order to cover the entire affected area, with injection sites generally 1–2 cm apart. There is no difference in efficacy of botulinum toxin A in the treatment of axillary hyperhidrosis when administered by subcutaneous or intradermal injection, but intradermal injections are reported to be more painful.³³ The subcutaneous injection technique requires further study for validation of the results.

Conclusion

Various treatments of focal hyperhidrosis are available. Aluminum chloride-based topical treatments can be used as first-line treatment of axillary hyperhidrosis, which is the most frequent form of focal hyperhidrosis, as well as of palmar hyperhidrosis. Iontophoresis can be used as second-line treatment of palmar and plantar hyperhidrosis. Botulinum toxin seems the most effective treatment, but it is painful and costly. Surgical thoracic sympathectomy may be the only solution for patients with severe hyperhidrosis in whom other treatments have not produced satisfactory results. The role of alternative and systemic treatments in focal hyperhidrosis remains to be established. Given that effective treatment can result in dramatic improvements to a patient's quality of life, physicians can play an instrumental role in the diagnosis and management of this distressing condition.

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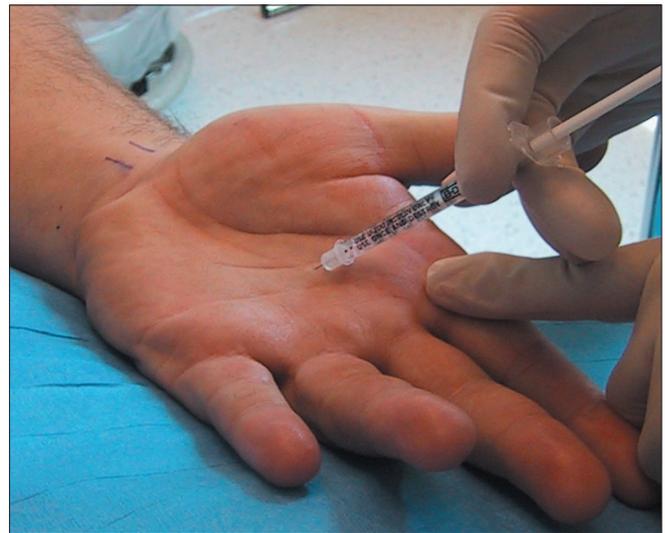


Fig. 3: Intradermal botulinum toxin injections for the treatment of palmar hyperhidrosis. For palmar hyperhidrosis, intradermal injections spaced about 1–2 cm apart seem to give the best results. About 2 units of botulinum toxin A are injected per site as required, with a total dose of 100 units for each palm. The main limitation is that most patients find the injections painful and may require regional anesthesia via median, ulnar and radial nerve blocks at the wrist level. A similar technique and dosage of botulinum toxin A is used for the treatment of plantar hyperhidrosis, requiring regional nerve blocks of posterior tibial and sural nerves for anesthesia. Other methods of reducing the pain of injections have included high-intensity vibration devices, cool packs and liquid nitrogen spray, all with variable results.¹³

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