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Diagnosis and Treatment of Primary Focal Hyperhidrosis in Children and Adolescents

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Primary focal hyperhidrosis is a disorder of excessive sweating that occurs in the axillae, palms, soles, and craniofacial region in amounts greater than needed for thermal regulation. Although the etiology is unknown, this disorder can cause significant emotional and social distress. The focus of this paper is the diagnosis and treatment of primary focal hyperhidrosis in children and adolescents.

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Primary focal hyperhidrosis is a disorder of excessive sweating that occurs in the axillae, palms, soles, and craniofacial region in amounts greater than needed for thermal regulation. Although the cause is unknown, this condition can cause significant emotional and social distress. Axillary hyperhidrosis can produce skin maceration and wet clothing, leading to frequent clothing changes during the day. Palmar hyperhidrosis can interfere with shaking hands when one meets people and also with school work and activities that require dry hands. Plantar and craniofacial hyperhidrosis can cause physical and social discomfort. This disorder is a serious problem that can have a severe impact on daily functioning as well as cause social phobia, anxiety, and depression, as demonstrated by the Hyperhidrosis Disease Severity Scale and the Hyperhidrosis Impact Questionnaire.¹ There also is an increased risk of developing cutaneous infections, such as verruca vulgaris, dermatophytosis, and pitted keratolysis, most likely as the result of increased skin moisture.² Effective treatment of this disorder can decrease suffering and improve quality of life.³ The focus of this paper is the diagnosis and treatment of primary focal hyperhidrosis in children and adolescents.

Epidemiology

Primary focal hyperhidrosis in children and adolescents has probably been underrecognized. A 2004 study reported that up to 1.6% of children and adolescents younger than 18 years of age had primary focal hyperhidrosis.¹ The authors of one

study⁴ reported that a positive family history occurred in 65% of patients. In another study, 58% of those with a positive family history were parent-child cases, whereas 13% had hyperhidrosis occurring in 3 generations.⁵ These studies provide evidence for an autosomal-dominant pattern of inheritance, which suggests a genetic basis for this condition.⁴⁻⁶

Pathogenesis

Sweating helps regulate body temperature by cooling due to the evaporation of sweat from eccrine glands. Normal sweating of the palms and soles starts after birth, whereas axillary sweating does not begin until puberty. Three types of sweat glands have been described in humans—eccrine, apocrine, and apoecrine. Eccrine sweat glands are found primarily in the palms, soles, and axillae but also occur throughout the body, except the external auditory canal, lips, clitoris, and labia minora.⁷ Apocrine and apoecrine glands also are present in the axillae. Eccrine glands are thought to be responsible for primary focal hyperhidrosis, although apoecrine glands may play a role in the axillary form.⁷

The sympathetic nervous system innervates the eccrine glands, and acetylcholine is the primary neurotransmitter. The hypothalamus controls thermal sweating by thermosensitive neurons in the anterior and preoptic areas, whereas the cerebral cortex regulates emotional sweating. In primary focal hyperhidrosis, sweat gland histology and function are normal. Although the cause of this disorder is unknown, one suggestion⁷ is that it could be an abnormal or exaggerated central response to normal emotional stress.

Diagnosis

Primary focal hyperhidrosis can involve the axillae, palms, soles, and craniofacial region.⁸ Sometimes more than one

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Table 1 Focused History and Physical Examination

History	Family History	Review of Systems	Medications Causing Generalized Sweating (Adapted from Smith) ⁹	Physical Examination
Age of onset		Fever	Antidepressants	Glistening axillary vaults, palms or soles, facial
Pattern		Weight loss	Selective serotonin reuptake inhibitors, tricyclic antidepressants	
Duration		Anorexia		
Frequency		Palpitations	Antimigraine	Wet marks on clothing (in the axillae or wet socks)
Volume		Headache	Triptans-serotonin 5-HT (1 b/1 d) agonists	
Areas involved		Vomiting	Antipyretics	Relative symmetry
Symmetry		Abdominal pain	Aspirin	Can be entire palm and sole, including the distal fingertips
Specific triggers			Cholinergic agonists	No sensory deficits
Nocturnal			Pilocarpine	Symmetric lividity of the soles
Impact on daily activities/quality of life. Examples: how many times a day do you have to change your shirt? Can you open a jar? Can you open door knobs? Are you restricted in types of footwear because of sweating?			Hormonal agents: GnRH agonists-leuprolide	Pulse rate
			Hypoglycemic agents	Blood pressure
			Insulin	Weight
			Sympathomimetic agents	
			Beta agonists, phenylephrine	
			Other	
			β -blockers, calcium channel blockers, clozapine, omeprazole, opioids	

location is involved. In 2004, the Multi-Specialty Working Group on the Recognition, Diagnosis, and Treatment of Primary Focal Hyperhidrosis recommended criteria for the diagnosis of primary focal hyperhidrosis—focal, visible, excessive sweating of at least 6-months duration without apparent cause, plus at least 2 of the following characteristics: (1) a distribution that is bilateral and relatively symmetric; (2) impairment of daily activities; (3) at least 1 episode per week; (4) onset before 25 years of age; (5) family history of primary focal hyperhidrosis; or (6) focal sweating that ceases during sleep.⁶

The presence of generalized sweating suggests a disorder other than primary focal hyperhidrosis. Excessive heat is the most common cause of generalized sweating. Other causes include systemic diseases and medications, with sweating

often continuing during sleep. A focused history and physical examination (Table 1)⁹ can screen for many of the causes of secondary sweating, which are listed in Table 2.⁶ Suspicion for pheochromocytoma is heightened if sweating is seen in conjunction with any of the following conditions: neurofibromatosis, von Hippel–Lindau disease, multiple endocrine neoplasia syndromes, tuberous sclerosis, Sturge–Weber syndrome, or ataxia-telangiectasia.

The diagnosis of primary focal hyperhidrosis is clinical. Tests used to quantify sweat production are not generally needed in clinical practice.⁶ Minor's starch iodine test¹⁰ or the quinizarin test¹¹ can be used to map areas of excessive sweating, which can be useful in planning before botulinum toxin A injections or local surgical ablation.⁶

Table 2 Principal Causes of Secondary Hyperhidrosis in Children and Adolescents (Adapted in part from Hornberger)⁶

Physiologic		
Increased environmental temperature		
Exercise		
Severe pain		
Anxiety		
During defervescence		
Ingestion of foods (most common: spicy, citrus, alcohol)		
Obesity		
Pregnancy		
Pathologic		
Generalized	Regional	Focal
Infectious: tuberculosis, malaria, brucellosis	Compensatory: spinal cord lesion (trauma, syringomyelia), neuropathy	Frey syndrome
Neoplastic: lymphoma	Reflex sympathetic dystrophy	Chorda tympani syndrome
Endocrinologic: hyperthyroidism, hypoglycemia, pheochromocytoma		Gustatory sweating
Neurologic: familial dysautonomia		Eccrine angiomatoid nevus
Other: medications, substance abuse		

Treatment

Most of the research concerning treatment of primary focal hyperhidrosis has been performed in the adult population. Only a few studies have involved children and adolescents. Patients and their parents should be counseled about possible treatment options but also about limitations and complications of each therapeutic modality, which include topical therapy, systemic medications, iontophoresis, botulinum toxin A, and surgery.

Axillary Hyperhidrosis

Topical Therapy

Topical therapy with antiperspirants can be effective in the treatment of axillary hyperhidrosis. Antiperspirants are often combined with deodorants. Metallic salts (usually aluminum chloride) are the active ingredients, with concentrations ranging from 6.25% to 25%. The mechanism of action is thought to be physical blockage of the eccrine sweat gland leading to structural and functional degeneration of the sweat glands.¹² Over-the-counter Certain Dri® (DSE Healthcare Solutions, Edison, NJ) contains 12% aluminum chloride, whereas newer over-the-counter products, such as degree and Dove (both manufactured by Unilever, Englewood Cliffs, NJ), and Secret Clinical Strength products (Proctor and Gamble, Cincinnati, OH) contain 20% aluminum zirconium tetrachlorohydrate glycine. Twenty percent aluminum chloride requires a prescription and often causes a significant irritant dermatitis, to a degree that patients often cannot tolerate the medication.¹³ Although lower concentrations may minimize skin irritation, they often are not as effective as the greater-concentration products.¹⁴

In a study of 7 adults who had previously experienced skin irritation, burning, or pruritus with 12% or 20% aluminum chloride solutions, the authors administered 15% aluminum chloride hexahydrate with 2% salicylic acid in a gel base without any side effects.¹³ This product is available as a physician-dispensed product in the United States. One treatment regimen for topical antiperspirants is to apply nightly for 1 week, and then as needed to control sweating.^{13,14} Reapplication may be needed only once every 1 to 3 weeks for adequate control.¹⁴ The use of occlusion with antiperspirants does not improve the effectiveness of therapy.¹⁴

Botulinum Toxin A

If topical therapy fails to control excessive axillary sweating, botulinum toxin A can be used.¹⁵ Intradermal injections of this toxin can decrease eccrine sweat production. Although the mechanism of action is unknown, this toxin is thought to produce functional denervation of the sweat glands.¹⁶ OnabotulinumtoxinA (BOTOX®, Allergan, Irvine, CA) is currently the only form of botulinum toxin A approved by the Food and Drug Administration (FDA) for use in patients with axillary hyperhidrosis who are older than 18 years of age. It also has been approved for blepharospasm and strabismus in patients older than 12 years of age and for cervical dystonia in those older than 16 years of age. AbobotulinumtoxinA (Dysport, IPSEN, Brisbane, CA) is another form of botulinum

toxin A that has been used with success outside the United States for the treatment of primary focal hyperhidrosis.¹⁷ The FDA has approved abobotulinumtoxinA (Dysport, IPSEN, Brisbane, CA) for treatment of cervical dystonia and glabellar lines in adults.

The first reported successful use of botulinum toxin A in the pediatric population was in a 14-year-old female patient who had a 2-year history of excessive axillary sweating.¹⁷ The treatment is usually well tolerated in the office setting with the use of a topical anesthetic.¹⁸ A 30-gauge needle on a 1-mL syringe is often used and should be inserted approximately 2 mm and at a 45-degree angle with the bevel side up into the dermis.¹⁹ The entire volume is divided into 0.1- to 0.2-mL aliquots and distributed among 15 to 30 sites, which are 1 to 2 cm apart. The package insert from Allergan recommends 50 U per axilla¹⁹; however, dosages used to treat this disorder range from 50 to 200 U per axilla.²⁰ Before the injection is made, it is often helpful to perform Minor's starch iodine test to visualize the affected area and then to mark the planned injection sites using a marking pen, so that it is easy to track which sites have already been injected.

The primary disadvantage of this form of therapy is that the effect wears off in approximately 6 to 12 months,²¹ so that retreatment is necessary. In some individuals the effect may last up to 24 months.²¹ Greater initial doses may extend the inhibition.²⁰ Antibodies can also develop to the toxin, eventually rendering it ineffective.²² In 2009, the FDA added a black box warning of generalized muscle weakness and respiratory difficulty, which can occur hours to weeks after injection. Informed consent is essential before botulinum toxin A usage.

There is considerable interest in topical botulinum toxin A. A 2007 report showed efficacy in 10 adults with axillary hyperhidrosis, but trials are still ongoing.^{23,24} This product has not yet been approved for use in the United States. If topical botulinum toxin A is proven safe and effective, it will be useful in children and adolescents who prefer not to receive injections.

Surgery

If topical therapy and botulinum A toxin injections have not been effective, surgery can be offered with local destruction of sweat glands or endoscopic thoracic sympathectomy. Disruption of the sweat glands is accomplished via suction curettage and/or tumescent liposuction techniques and is often performed by a dermatologist skilled in this type of procedure or a plastic surgeon. These procedures can decrease sweating in 70% to 90% of patients.²⁵ The risk of complications, such as lymphedema, diminished sensation, or decreased arm mobility, is low. Compensatory hyperhidrosis does not occur with these local procedures.

The sympathetic innervation of the axilla is less predictable compared with that for the palms, therefore some procedures have not been successful in the past.²⁶ However, 2 studies in which the authors used endoscopic thoracic sympathectomy of the T4 and/or T5 ganglion for treatment of axillary hyperhidrosis report success rates of at least 96%.^{27,28} Compensatory hyperhidrosis is reported in approximately 75% of

treated patients.²⁷ The risk of complications is low and includes pneumothorax, Horner's syndrome, and hypotension.²⁹

Iontophoresis and Systemic Medications

There is no convincing evidence for the use of iontophoresis or systemic medications in the treatment of axillary hyperhidrosis. Iontophoresis is difficult to administer in this location. Systemic medications, including anticholinergics,³⁰ calcium channel blockers (diltiazem),³¹ clonidine,³² and benzodiazepines³³ can decrease sweating, but high doses are required and these dosages usually cause undesirable side effects.³⁴ Therefore, they have not often been recommended in children and adolescents.

Palmar and Plantar Hyperhidrosis

Topical Therapy

Topical antiperspirants (as outlined previously) used on the palms and soles can be effective, but this therapy may not control sweating to an acceptable degree, even when applied twice daily.

Iontophoresis

Iontophoresis is a method in which an electric current is passed through tissue. It was initially used in the 1950s for treatment of palmar hyperhidrosis.³⁵ Direct current through tap water is most often used and the mechanism of action is thought to result from an accumulation of hydrogen ions, generated by hydrolysis of water in the anodal bath, which may lead to destructive changes of the sweat glands.³⁶ Because a tingling sensation often occurs with direct current, alternating current may be better tolerated.³⁷

For tap water iontophoresis, the hands or feet are placed in 2 separate reservoirs of tap water and an electrical current is directed through the water to the skin. After approximately 10 minutes, the polarity is switched and another 10 minutes of treatment are given. This method is labor-intensive and usually requires 2 to 3 treatments per week for 20 to 30 minutes at each session. One advantage is that this can be done at home. In a study of tap water iontophoresis, which included children as young as 8 years old, palmar hyperhidrosis was controlled after 8 treatments, while plantar hyperhidrosis improved in 65% of the patients whose hands only were treated.³⁸

Iontophoresis using anticholinergic medications, such as glycopyrrolate 0.05% solution also is effective with longer periods of dry palms or soles in children and adults due to both local and systemic effects.³⁹ The risks of systemic absorption in children are likely greater than in adults, due to a larger body surface area-to-volume ratio.

A new "dry type" iontophoretic device, which avoids the need for reservoirs of water, has also been shown to be effective in adults with palmar hyperhidrosis.⁴⁰ No studies have been reported in the pediatric population.

Botulinum Toxin A

Botulinum toxin A injections have been used successfully to treat palmar hyperhidrosis in adults^{41,42} and children.^{43,44} The largest case series in the pediatric age group included 9 children with an age range from 6.5 to 15 years.⁴⁵ These

children received palmar injections of BOTOX® after ulnar and median nerve blocks. This treatment was effective in all the children, as measured by gravimetry, severity and frequency scales, and the Questionnaire of Quality of Life. After a single treatment with BOTOX® injections, one child required no further treatment for 3 years.⁴⁵ Decreased sweating is usually noticed within 4 to 5 days after treatment, with maximum improvement occurring by 1 month. Transient weakness of the hand muscles can occur with botulinum toxin A injections because of diffusion from the dermis to the underlying muscles. With repeated injections, atrophy of the thenar and hypothenar eminences may develop and weakness can become irreversible.

Injections of the palms and soles are painful. Topical lidocaine 2.5% and prilocaine 2.5% cream (EMLA Cream, APP Pharmaceuticals, LLC, Schaumburg, IL), ice packs, ethyl chloride spray, and iced water have been used successfully in adults;⁴⁶ however, children are less likely to tolerate injections with these methods.⁸ The MED-JET device, a needleless method of administering anesthesia before injection of botulinum toxin A to the palms, may be helpful; however, this device has not yet been approved by the FDA.⁴⁷

Nerve blocks of the wrists or ankles are usually required to inject safely with minimal pain. The risk associated with administering nerve blocks is low, but complex regional pain syndrome has developed after bilateral median and ulnar nerve blocks were performed before botulinum toxin A injections in an adult.⁴⁸ For children who cannot tolerate nerve block placement, general anesthesia is often necessary to inject successfully.

Recent studies have demonstrated some success in the treatment of palmar hyperhidrosis by using botulinum toxin A iontophoresis. Eight patients had decreased sweating as measured by gravimetry; an obvious reduction in density and extent of Minor's starch iodine test and a significant reduction in the Dermatology Life Quality Index.⁴⁹⁻⁵¹ Compensatory hyperhidrosis and decreased grip strength did not occur.⁴⁹ Maximal benefit with commercially available iontophoresis units is difficult because the volume is so small and the toxin is likely binding to the sponge, pad or glove (Kavanagh GM, personal communication, 2009). If this treatment is proven safe and effective, it would be a valuable addition to the treatment options of palmar and plantar hyperhidrosis, because injections of botulinum toxin A could be avoided, as well as the need for nerve blocks or general anesthesia.

Surgery

Surgical treatment of palmar and plantar hyperhidrosis is another therapeutic option for patients who have tried other treatments without success or who desire a more permanent solution. No local surgeries are feasible; however, endoscopic thoracic sympathectomy can be effective for both palmar and plantar hyperhidrosis.^{26,52} The youngest reported patient treated with thoracic sympathectomy for palmar hyperhidrosis was an 11-year-old girl.⁵³ Thoracic sympathectomy is performed at the T2-3 level for palmar hyperhidrosis.²⁶ Although results have been variable with lumbar sympathectomy at the L3

and/or L4 level for plantar hyperhidrosis, a recent study reported a 97% anhidrotic rate in adults.^{26,54} Compensatory hyperhidrosis almost always occurs and is usually thermal and truncal.^{55,56}

Although sympathectomy can produce longer lasting improvement, some patients report that the compensatory hyperhidrosis is so unacceptable that they would rather not have undergone the procedure.⁵⁶ Because children and adolescents seem to tolerate compensatory hyperhidrosis better than adults, some physicians recommend that surgery should be performed before adulthood.⁵⁶

Craniofacial Hyperhidrosis

Few studies have been published concerning the treatment of craniofacial hyperhidrosis. The avoidance of triggers, particularly foods, is the first step. Some patients are affected by spicy foods; however, other types of foods, including citrus and condiments can elicit a response. Topical aluminum chloride solutions are anecdotally reported to decrease sweating. Glycopyrrolate topically administered with a pad applicator can be effective in compensatory gustatory hyperhidrosis.⁵⁷

Botulinum toxin A injections have been successful in the treatment of frontal^{58,59} and gustatory hyperhidrosis.⁶⁰⁻⁶² Successful surgical treatment via thoracic sympathectomy of the T2 and/or T3 ganglion also has been reported, but sparse data exists.^{63,64} Ptosis is the main complication with sympathectomy for craniofacial hyperhidrosis.

Multiple-Site Hyperhidrosis

Treatment of multiple-site hyperhidrosis deserves special mention. Multiple-site hyperhidrosis, in which more than one area is involved, occurs in approximately one half of patients with primary focal hyperhidrosis. Palm and sole involvement is the most common combination (28%) in 1 study, followed by axillary and palmoplantar (6%). Axillary and palmar involvement alone is rare (2%).² Craniofacial hyperhidrosis almost always occurs in isolation. Expectations should be reviewed for treatment with the patient and parents and the most distressing site addressed first. Sometimes it is possible to treat 2 areas at the same time; however, botulinum toxin A dosing limitations, as well as the fact that iontophoresis does not work for axillary hyperhidrosis, may hinder combination therapy. Sympathectomy must be performed at the correct level; however, some patients with palmar hyperhidrosis who improve with a T2-3 sympathectomy also may experience improvement of plantar hyperhidrosis.⁵⁵ Tailoring treatment to each patient provides optimal management.

Conclusions

Primary focal hyperhidrosis can be a life-altering condition. The diagnosis is clinical. If primary focal hyperhidrosis is untreated, it will continue unabated. Several effective treatment options are available and should be offered to patients. A profound difference in the lives of children and adolescents

affected by hyperhidrosis can be made with proper diagnosis and treatment.

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