REVIEW

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Primary Pediatric Hyperhidrosis: A Review of Current Treatment Options

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Abstract: **Hyperhidrosis is a disorder of excessive sweating beyond what is physiologically necessary for thermoregulation. Primary hyperhidrosis is localized; it can affect the axillae, palms, soles, face, and other areas and is idiopathic. The prevalence of hyperhidrosis in the United States is estimated to be 2.8% of the population, with about one-half (1.4%) of these individuals having the axillary form. Hyperhidrosis occurs in both children and adults, with the average age of onset of primary hyperhidrosis being 14–25 years. This disorder can be detrimental to a patient's social, professional, psychological, and physical well-being. Early detection and management can significantly improve a patient's quality of life, yet hyperhidrosis remains widely under diagnosed and under treated, particularly among pediatric patients. The purpose of this article is to review the treatment of pediatric hyperhidrosis, and to increase awareness and inspire further research on this important and often overlooked medical problem.**

Hyperhidrosis is a disorder of excessive sweating beyond what is physiologically necessary for thermoregulation. Primary hyperhidrosis is localized; it can affect the axillae, palms, soles, face, and other areas and is idiopathic. Secondary hyperhidrosis can be focal or generalized and is usually the result of an underlying condition, most often an infectious, endocrine, or neurologic disorder. A detailed history and physical examination are necessary before ruling out secondary hyperhidrosis. A national survey by Strutton et al in 2004 estimated the prevalence of hyperhidrosis in the United States to be 2.8% of the population, with about one-half (1.4%) of these individuals having the axillary form (1).

Hyperhidrosis occurs in both children and adults, with the average age of onset of primary hyperhidrosis being 14–25 years (1–3). Patients with disease onset before the age of 20 are more likely to have at least one affected family member (3). Isolated palmoplantar hyperhidrosis is more common in patients with prepubertal onset of disease (3). Although data documenting the course of the disease are scarce, some authors have noted that symptom severity often declines in patients over the age of 50 (4).

This disorder can be detrimental to a patient's social, professional, psychological, and physical well-being. In Strutton's survey, one-sixth of responders reported sweating that was either "barely tolerable and frequently interfered," or was "intolerable and always interfered" with their daily activities. However, many patients do not realize they have a treatable medical condition, and according to the survey, only 38% of patients had

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discussed their sweating with a health care professional (1). Early detection and management can significantly improve a patient's quality of life, yet hyperhidrosis remains widely under diagnosed and under treated, particularly among pediatric patients. The purpose of this article is to review the treatment of pediatric hyperhidrosis, and to increase awareness and inspire further research on this important and often overlooked medical problem.

TOPICAL THERAPY

Treatment of hyperhidrosis often begins with the use of topical agents (Table 1). Aluminum salts are the most common active ingredient in antiperspirants today. Aluminum chloride is the partially neutralized form used in over-the-counter antiperspirants, whereas aluminum chloride hexahydrate is the more effective compound found in prescription preparations (5). The mechanism of action of topical aluminum chloride compounds is thought to involve mechanical obstruction of eccrine sweat gland pores and atrophy of the secretory cells (6).

Several studies support the use of aluminum chloride hexahydrate in alcohol solution as the first-line treatment for axillary hyperhidrosis. In 1975, Shelley and Hurley concluded that 25% aluminum chloride hexahydrate in absolute ethyl alcohol, used under occlusion overnight, was the most effective of the topical antiperspirant agents for axillary hyperhidrosis (7). A few years later, Scholes et al treated 65 patients aged 14–51 with 20% aluminum chloride hexahydrate in alcohol, of which all but one reported excellent control of sweating. Patients used the solution nightly for 1 week and then as needed, with most patients needing to reapply only once every 7–21 days for adequate control. They found that an occlusive dressing was actually unnecessary, making the treatment less cumbersome and more acceptable to patients. Axillary irritation was the only side effect reported, and most patients experienced relief of this with 1% hydrocortisone cream applied in the morning after each treatment (8).

Palmar hyperhidrosis is less responsive to aluminum chloride therapy but may show some effect. Goh found that aluminum chloride 20% helps reduce palmar hyperhidrosis within 48 hours after application; however, its effect wears off within 48 hours after stopping treatment. The major limitation of this treatment is itching and burning after application and ongoing skin irritation (9).

In a more recent study, 4% salicylic acid in a hydroalcoholic gel base was used as the vehicle for aluminum chloride hexahydrate in 238 patients with hyperhidrosis of the axillae, hands, and feet. Salicylic acid was chosen because it is thought to enhance the absorption of aluminum chloride, act as an adjuvant via its own antiperspirant properties, and help minimize skin dryness and irritation. Excellent-to-good results were reported in 94%, 60%, and 84% of patients with axillary, palmar, and plantar disease, respectively. Patients who had previously failed to respond to aluminum chloride in absolute alcohol, or could not tolerate the side effects, showed marked improvement with this new formulation (10).

Astringent topical agents including formaldehyde, glutaraldehyde, and tannic acid have also been shown to effectively reduce hyperhidrosis, but are rarely used as they often cause allergic contact dermatitis and skin staining (11).

Although few studies have evaluated the efficacy and safety of topical aluminum chloride in the pediatric population, most practitioners utilize this treatment as a first-line therapy for hyperhidrosis in children. The advantages of topical aluminum chloride therapy include its favorable safety profile and the noninvasive nature of the treatment. However, the benefits are short-lived, and side effects include burning, stinging, and skin irritation. Application can be messy and time-consuming, and may lead to decreased compliance, particularly in the pediatric population. In addition, many cases of hyperhidrosis remain refractory to topical therapy.

ANTICHOLINERGICS

The ability of anticholinergic medications to improve hyperhidrosis was discovered accidentally when patients given elixirs from atropine plants noted decreased sweating (12). Although acetylcholine is typically thought of as a parasympathetic neurotransmitter, sweat glands are innervated by sympathetic cholinergic nerve fibers. Anticholinergic drugs block sweat secretion by acting as competitive antagonists of acetylcholine at the muscarinic receptor (13).

Topical anticholinergics have been considered in the treatment of hyperhidrosis, but large randomized studies are lacking, and reported cases are limited to the adult population. There have been several case reports of patients successfully treated with topical glycopyrrolate for craniofacial hyperhidrosis with minimal side effects (dry mouth) (14,15). Topical glycopyrrolate has also been used with some success in the treatment of diabetic gustatory sweating (5,16) The use of anticholinergics in iontophoresis treatment is discussed in the next section.

Oral anticholinergics have also been used in the treatment of hyperhidrosis. Glycopyrrolate and propantheline bromide are the most commonly used systemic agents to treat hyperhidrosis. Unfortunately, the doses required to reduce sweating often lead to

TABLE 1. *Treatment Options for Primary Hyperhidrosis*

Treatment	Treatment type	Common sites of use	Side effects	Studies including children
Topical therapy	Aluminum salts (±4% salicylic acid) Topical anticholinergics: glycopyrrolate (topical or with iontophoresis) Other (rarely used): tannic acid, formaldehyde, glutaraldehyde	Axilla, palms, soles	Burning, itching, erythema, irritation Skin staining may be seen with aldehydes and tannic acid	Scholes et al
Oral anticholinergics	Glycopyrrolate Propantheline bromide Oxybutynin	Axilla, palms, soles, face	Dry mouth, blurred vision, tachycardia, urinary retention, constipation	No studies specifically analyzing treatment in children with hyperhidrosis. Several studies evaluate use in children with other conditions (Ayan et al, Jongerius et al)
Other systemic treatments	Calcium-channel blockers (diltiazem) Clonidine Alpha-adrenoceptor antagonists Benzodiazepines	Axilla, palms, soles, face	Treatment dependent	No studies specifically analyzing treatment in children with hyperhidrosis
Iontophoresis	Tap water iontophoresis, with or without anticholinergic drugs (glycopyrrolate)	Palms, soles	Stinging, burning, occasional reports of blister formation	Dolianitis et al Karakoc et al
Botulinum toxin	Botulinum toxin A (Botox®, Dysport®) Botulinum toxin B (Myobloc®)	Axilla, palms, soles	Muscle weakness Pain at injection site	Farrugia et al Bhakta et al Vazquez-Lopez et al
Surgery	Curettage Liposuction Thoracic sympathectomy (via either "open" or "minimally invasive" approach)	Axilla, palms	All treatment modalities: wound infection, scar Sympathectomy: compensatory hyperhidrosis in surrounding areas, hemothorax, pneumothorax, atelectasis, subcutaneous emphysema, Horner's syndrome	Steiner et al Cohen et al

unpleasant side effects such as dry mouth, blurred vision, tachycardia, urinary retention, and constipation (4,11). A retrospective analysis of 24 patients treated with oral glycopyrrolate for hyperhidrosis noted response in 79% of patients who were evaluated in follow-up. The authors note, however, that treatment was limited by side effects. This study only included adult subjects, with an age range of 19–62 years (13). Although the use of oral anticholinergics in children with hyperhidrosis has not been studied, these drugs have been used with some success for the treatment of children with other disorders, such as drooling and urinary voiding dysfunction. Further research is needed to determine the safety and benefit of this treatment in the pediatric population (17,18).

A case report of successful treatment of hyperhidrosis with the anticholinergic drug oxybutynin is also available. A woman with a history of hyperhidrosis was treated with oxybutynin for urge incontinence and noticed resolution of her hyperhidrosis that continued through a 6-month follow-up period (12).

OTHER TREATMENTS

Isolated case reports also exist citing the use of other systemic agents such as calcium-channel blockers (i.e., diltiazem), alpha-adrenoceptor antagonists, and clonidine as effective treatments for hyperhidrosis; however, randomized controlled studies are needed to further evaluate their safety and efficacy for this purpose (19).

Benzodiazepines may be useful in patients with anxiety or emotionally induced hyperhidrosis; however, long-term use may lead to dependency or side effects such as sedation, which are particularly problematic in a pediatric population (4,11).

Psychotherapy has also been suggested as a treatment for hyperhidrosis. In 1980, Duller and Gentry demonstrated clinical improvement in sweating in 11 of 14 patients following biofeedback training. The authors suggest that relaxation resulting from biofeedback may lead to symptom improvement in patients with hyperhidrosis. Further studies are needed to determine the efficacy of this treatment modality (20).

IONTOPHORESIS

Iontophoresis introduces ions into cutaneous tissues using electric current. This technique has been used for the treatment of hyperhidrosis since the 1930s, and iontophoresis devices have been available for home use since 1984 (19). Iontophoresis most commonly utilizes tap water, either alone or with anticholinergic drugs. Despite its relatively long history of use in the treatment of hyperhidrosis, the mechanism of action of iontophoresis still remains unclear. Initially, iontophoresis was thought to lead to hyperkeratinization and plugging of the orifice of eccrine ducts (21,22); more recently, alterations in electrochemical gradients have been suggested as the basis for the effect of iontophoresis on sweat production. One commonly held theory proposes that selective targeting of sweat glands occurs due to the high concentration of electrolytes, and the current causes protein coagulation and disruption of the eccrine gland function. An alternative theory holds that the electric current interferes with transmission of the stimulus that signals sweat secretion (21).

Although iontophoresis has been shown to be effective in the treatment of palmar and plantar hyperhidrosis, it requires long-term use in order to maintain its effect. Most patients experience a recurrence of symptoms within weeks of treatment cessation (11). In addition, frequent treatments are required, and the anatomy of the axilla makes iontophoresis an impractical treatment for hyperhidrosis in this area. Side effects are typically minimal, and include stinging, erythema, and vesicles or papules at the treatment site. When anticholinergics are added, side effects may include mild systemic effects such as sore or dry throat (21).

Although most of the studies evaluating iontophoresis are small and have not specifically examined this treatment in the pediatric population, they do often include children in their cohorts. A single-blinded, right left comparison study of 20 patients between the ages of 12 and 50 years with moderate to severe hyperhidrosis compared the efficacy of tap water iontophoresis with iontophoresis with glycopyrrolate. Iontophoresis with glycopyrrolate was more effective than tap water iontophoresis, and bilateral glycopyrrolate was more effective than unilateral glycopyrrolate iontophoresis. Increased duration of symptom relief with bilateral glycopyrrolate treatment led the authors to conclude that the effectiveness of glycopyrrolate iontophoresis on hyperhidrosis was due to both local and systemic effects. Patients demonstrated only mild side effects, with eight patients reporting a dry or sore throat (21).

Another study evaluated the effectiveness of eight treatments with direct current on 112 patients aged 8–32 years with hyperhidrosis. A significant reduction in sweat intensity was observed, and 81.2% of patients were satisfied with their treatment. Side effects included erythema, local burning, and vesicle formation. Interestingly, although only the palms were treated, 65 of the patients also noted improvement in plantar sweating following treatment. The authors hypothesized that a biofeedback mechanism may be involved in the mechanism of action of iontophoresis (22).

BOTULINUM TOXIN

Botulinum toxin is a neurotoxin produced by the anaerobic bacterium *Clostridium botulinum*. Intradermal injection of botulinum toxin decreases sweat production by inhibiting acetylcholine release from the sympathetic cholinergic nerve terminals that innervate sweat glands. Animal studies in the 1950s first demonstrated botulinum toxin's ability to block these nerves. However, the first report of the toxin's anhydrous effect on humans was not until 1994, when patients treated for hemifacial spasm experienced sweating cessation in the treatment area. Botulinum toxins A and B are two of the seven antigenically distinct serotypes of toxin produced by *C. botulinum*. All seven types exert their effects at the neuromuscular junction by cleaving specific receptor proteins necessary for fusion of acetylcholine vesicles with the presynaptic membrane. The target of botulinum toxin A is SNAP-25, while the target of botulinum toxin B is synaptobrevin. By cleavage of theses proteins, both botulinum toxins A and B inhibit the release of acetylcholine from the nerve terminal. Studies have shown that botulinum toxins A and B have equal efficacy in the treatment of axillary hyperhidrosis; however, there appears to be a greater incidence of pain at the injection site and autonomic side effects with botulinum toxin B (23,24). In 2004, the FDA approved botulinum toxin A (Botox®: Allergan, Irvine, CA; Dysport®: Ipsen Biopharm, Wrexham, UK) for use in adults with primary axillary hyperhidrosis. Botulinum toxin B (Myobloc®; Solstice Neurosciences, Malvern, PA, USA) is FDA approved only for treatment of cervical dystonia; however, it has been reported to be used "off label" for hyperhidrosis (5).

Repeated intradermal injections of botulinum toxin A have been shown to be safe and effective treatment for patients with severe primary axillary hyperhidrosis. In a 1-year, randomized, placebo-controlled trial of 193 patients aged 18–75, and a subsequent 3-year open-label extension of 186 patients, botulinum toxin A injections were given for the treatment of axillary hyperhidrosis. The timing for retreatment was based on their self-reported Hyperhidrosis Disease Severity Scores (HDSS) and on gravimetric sweat measurements. Only one to two treatments were necessary per year, and HDSS indicated that impairment caused by hyperhidrosis was eliminated or substantially reduced in at least 80% of patients 4 weeks after injections. Treatment also resulted in a $>75\%$ reduction in sweat production in $>78\%$ of patients at week 4, based on gravimetric sweat measurements. No serious adverse reactions were reported (25).

Botulinum A has previously been used in the treatment of numerous other conditions in children including spastic and rigid cerebral palsy, involuntary movements, dystonia, muscle spasm, strabismus, spasmodic torticollis, blepharospasm, and hemifacial spasm. Studies have also been conducted to evaluate the safety of botulinum toxin A in children with muscle spasticity. A prospective, multicenter trial was performed in 207 children with cerebral palsy to determine the long-term safety and efficacy of repeated intramuscular injection of botulinum toxin A. Adverse events occurred in 1–11% of subjects and included increased stumbling, leg cramps, leg weakness, and calf atrophy. No serious treatment-related side effects were reported. A retrospective study of the safety profile and efficacy of Dysport® (Ipsen Biopharm) for muscle spasticity in 758 children (mean age, 7.2 years) showed the highest rate of adverse effects to be with doses exceeding 1,000 U of Dysport® (Ipsen Biopharm) per treatment session (26).

Several studies have been published on the use of botulinum toxin type A for the treatment of hyperhidrosis in adults; however, fewer studies have focused on its use in children with hyperhidrosis. In 2002, the effective use of botulinum toxin type A was reported in a 13-year-old girl with refractory palmar hyperhidrosis. The patient's palmar sweating was socially embarrassing and interfered with her ability to do her schoolwork. The patient was treated with 20 U of Dysport® (Ipsen Biopharm), injected into the finger tips and over the hypothenar and thenar eminences. The patient reported decreased palmar sweating within 1 week, allowing her to do her school work; however, she experienced a slight decrease in grip strength lasting 3 weeks. Four months later, the patient required repeat injections, which were given to the fingertips only with no adverse effect on grip strength. She received a total of four courses of treatment over 2 years with good results (27).

The first documented use of botulinum A toxin in a pediatric patient with axillary hyperhidrosis was in 2005. A 14-year-old girl had a 2-year history of excessive sweating that had prevented her from participating in sports and had caused her to develop bad posture to conceal her perspiration. Previous topical and systemic therapies were ineffective. The patient was treated with injection of 250 U of Dysport® (Ipsen Biopharm) in each axilla. Significant improvement was noted at 3 months follow-up, allowing the child to gain confidence in social settings and to revert back to her normal posture (26).

Botulinum toxin A injections were used to treat a 13-year-old boy with palmar hyperhidrosis who had failed treatment with both aluminum chloride and tap water iontophoresis. Following median and ulnar nerve blocks at the wrists, 2 U of lyophilized botulinum toxin type A (Botox®; Allergan) were injected at 15 mm intervals, with a total of 50 injections per palm. The

patient reported improvement at day 2 postinjection with an 80% decrease in sweat production, as well as a significant improvement in quality of life indices. No complications occurred and repeat treatment was not required for another 8 months (28).

The main disadvantage of botulinum toxin A is pain during injections. Cryotreatment and application of anesthetizing cream are considered mildly effective or ineffective. Intravenous regional anesthesia (Bier's block) is effective but requires cardiac monitoring, and carries the risks of cardiovascular and central nervous system toxicity (28). Median and ulnar nerve blocks are a safe technique, but may result in moderate palsy of the hand muscles for 1–2 hours after injection, and may cause paresthesias when injecting into the nerve rather than near it. Refrigerant sprays with dichlorotetrafluoroethane have been used with some success (28). Other side effects from injection may include small hematomas, dry skin, and transient weakness of small hand muscles for up to 2 weeks because of diffusion of the toxin. Injections in the thenar eminence may be avoided if they lead to reduction in finger grip strength. Injecting the toxin as superficially as possible may also aid in decreasing the risk of muscle weakness (28).

SURGICAL TREATMENT

Surgical treatment of hyperhidrosis should be reserved for cases of hyperhidrosis unresponsive to any other treatments. Local procedures such as curettage or liposuction of adipose tissue can be used to remove sweat glands from the axilla. Although this treatment provides long-term relief from excessive sweating and does not result in the compensatory sweating that is often seen with sympathectomy, it does place patients at risk of complications such as wound infections, contractures, and scarring (29).

Thoracic sympathectomy involves the transection of the sympathetic chain by either a "minimally invasive" or "open" approach, with the aim of eliminating the transmission of nerve signals to the cholinergic fibers responsible for sweat secretion. This procedure should be reserved for cases of hyperhidrosis unresponsive to any other treatments. Complications include wound infection, scar, compensatory hyperhidrosis in surrounding areas, pneumothorax, hemothorax, atelectasis, subcutaneous emphysema, and Horner's syndrome (29,30).

Focal hyperhidrosis was first treated by sympathectomy in the 1920s and 1930s in European countries. An "open" method was used, requiring a large thoracic incision and rib separation to allow identification of the sympathetic chain. Endoscopic techniques began to replace the open method in the 1940s (31). Currently, video-assisted thoracoscopic sympathectomy is the most common technique used, and requires only two to three small incisions (5–10 mm) below the axilla. The patient's lung is deflated to allow visualization of the sympathetic chain and for the introduction of a telescopic camera and surgical instruments. Specific sympathetic ganglia are then destroyed via electrocautery or laser (32). Palmar hyperhidrosis is treated by the destruction of the T2, and often the T3 ganglia. Axillary hyperhidrosis is treated by the destruction of the T2, T3, and often T4 ganglia. A sympathotomy is a slightly modified version of the sympathectomy in which the sympathetic chain is interrupted instead of destroying the ganglia (19). The goal of surgery is to prevent the transmission of nerve signals from sympathetic ganglia to fibers innervating the areas producing excessive sweating.

Several studies have shown that endoscopic thoracic sympathectomy (ETS) is an effective treatment for primary hyperhidrosis, with the majority of patients reporting improvement in quality of life and overall satisfaction following surgery. Endoscopic thoracic sympathectomy is most commonly used for palmar hyperhidrosis, with cure rates $>98\%$. Success rates for axillary hyperhidrosis have been $>96\%$, and some patients may even report improvement in plantar hyperhidrosis (5,23,33).

Even with minimally invasive methods, surgical complications include wound infection, scar, pneumothorax, hemothorax, atelectasis, subcutaneous emphysema, Horner's syndrome, and compensatory sweating in other regions. Compensatory sweating is seen in $>70\%$ of patients, and although it is often mild, it was reported as severe in as many as 40% of patients treated with ETS (5). Patients treated with sympathotomy are less likely to report severe compensatory hyperhidrosis than those treated with sympathectomy (19,29,30). Interestingly, a recent study found that children (defined as $\leq$14 years of age) actually tolerated compensatory sweating better than adolescents and adults and therefore had higher postoperative satisfaction rates (34).

A report by Cohen et al in the *Journal of Pediatric Surgery* from 1995 describes 23 minimally invasive thorascopic sympathectomies performed on children aged 9–17 with primary palmar hyperhidrosis. Seventeen of the patients (90%) also complained of excessive plantar sweating and 11 (56%) complained of axillary hyperhidrosis. The intraoperative time was 12–25 minutes, and no intraoperative complications occurred. Eighteen patients had an uneventful postoperative course and were discharged the following day. One patient had a subsequent pneumothorax requiring intercostal drainage and was sent home postoperative day 3; however, all patients returned to school and full activity within

3–5 days after the operation. At follow-up (1–13 months postoperatively), 17 of the patients (90%) were completely satisfied with their outcome. One patient was unsatisfied, claiming very minimal improvement, and one was moderately satisfied complaining of excessive dryness of the palm. Two children complained of moderate compensatory sweating. Three patients reported some improvement in the plantar sweating after the surgery (32).

Following their initial study, Cohen et al compiled an even larger case series of 179 thoracoscopic sympathectomies performed from 1992 to 1995 on children and adolescents aged 5.5–18 years with severe primary palmar hyperhidrosis. Ninety-four patients (98%) had immediate and permanent relief of palmar sweating. Although most patients experienced uneventful postoperative courses, two had residual pneumothoraces requiring intercostal drainage. Compared with the older "open" transaxillary approach, the minimally invasive thoracopic approach results in less pain, earlier discharge, quicker return to normal activity, and smaller, less conspicuous scarring. The authors of the above studies emphasize the benefits of early surgery for children with severe palmar hyperhidrosis to avoid the many years of psychological, social, and physical suffering during adolescence; however, surgery is not without risks and complications, so it is still strongly recommended that patients try more conservative management first and be fully informed of the risks before undergoing a surgical procedure (35).

CONCLUSION

Primary hyperhidrosis is a condition that can interfere with daily activities and is often psychologically and socially debilitating. The disease prevalence is estimated to be 2.8% of the population, and onset is often in childhood or adolescence. Despite being relatively common, this condition is under diagnosed and undertreated, particularly in children. With a focus on the pediatric population, we have reviewed the current available treatment options for hyperhidrosis, including topical and systemic therapies, iontophoresis, botulinum toxin injection, and surgical interventions. Although many treatment options exist, further research is warranted to determine the interventions which are most beneficial for the pediatric patient with hyperhidrosis.

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