

Hyperhidrosis: A Brief Review

ABSTRACT

Hyperhidrosis (HH) is a disorder of the eccrine sweat glands causing excessive sweating. It is caused by hyperactivity of the sympathetic nervous system resulting in excessive release of acetylcholine and activation of the sweat glands. Primary essential HH is thought to have a large genetic component, while secondary HH is the result of an underlying condition or medications. HH will often cause excessive sweating in areas with a high density of eccrine sweat glands that include the palms, soles, face, head, or axillae. Diagnosis is largely based on history and physical which can help differentiate between primary and secondary HH. Hyperhidrosis can have a significant impact on quality of life. Management includes identifying and avoiding triggers, the use of topical antiperspirants, and advanced therapies in recalcitrant cases (such as tap water iontophoresis, botulinum toxin injection and surgical options).

KEYWORDS: hyperhidrosis (HH), primary (essential) hyperhidrosis, secondary hyperhidrosis, excessive sweating, eccrine sweat gland



Introduction

Hyperhidrosis (HH) is a disorder of the eccrine sweat gland that results in excessive sweating.^{1,2} Although the cause of HH is poorly understood, it is thought to involve autonomic nervous system dysfunction causing overactivity of normal eccrine sweat glands.² HH can be subdivided into primary (essential) and secondary hyperhidrosis. Primary hyperhidrosis is often idiopathic and has a focal, bilateral, and symmetric distribution. It typically affects the palms, soles, axillae, craniofacial region, and groin.^{1,2} Secondary hyperhidrosis is caused by systemic diseases and/or medications and presents in a more generalized and asymmetrical distribution.^{1,2} Primary HH is more common and represents approximately 93% of all cases.² It often begins between 14 and 25 years of age, while secondary HH often presents after 25 years of age.² Before diagnosing primary HH, secondary causes must be ruled out.^{1,2} HH is not life threatening, but can cause significant patient distress, and can interfere with daily activities, social interactions, and interpersonal relationships.¹⁻³

Epidemiology

Hyperhidrosis is underreported by patients and underdiagnosed by health care professionals.⁴ It affects at least 15.3 million people in the United States, approximately 4.8% of the population, with an incidence between 1% and 20.5% amongst different countries.^{2,5,6} Hyperhidrosis affects women and men equally. However, women are more likely to discuss this as a problem.⁴ Of patients with HH, 93% have primary HH, and 90% of these patients have a typical focal and bilateral distribution affecting the axillae, palms, soles and craniofacial areas.³ The age of onset for primary HH is usually between 14 and 25 years.^{2,3}

When HH presents before puberty, it most commonly affects the plantar or palmar regions and affects the axillary, face, and dorsal and abdominal regions less commonly.² After puberty however, axillary involvement is much more common.² Secondary HH is not as common (7% of total HH patients) and tends to present after 25 years of age.²

Pathophysiology

The pathophysiology of HH is complex and not fully understood. Physiological thermal regulation involves dissipating heat through evaporation of sweat.² Eccrine sweat glands produce

sweat and are abundant in the palms, soles, forehead, axillae, and cheeks.² They are innervated by cholinergic fibers of the sympathetic nervous system and are regulated by the thermoregulatory center of the hypothalamus.⁸ Eccrine sweat production is increased with emotional, gustatory, and physical stimuli.²

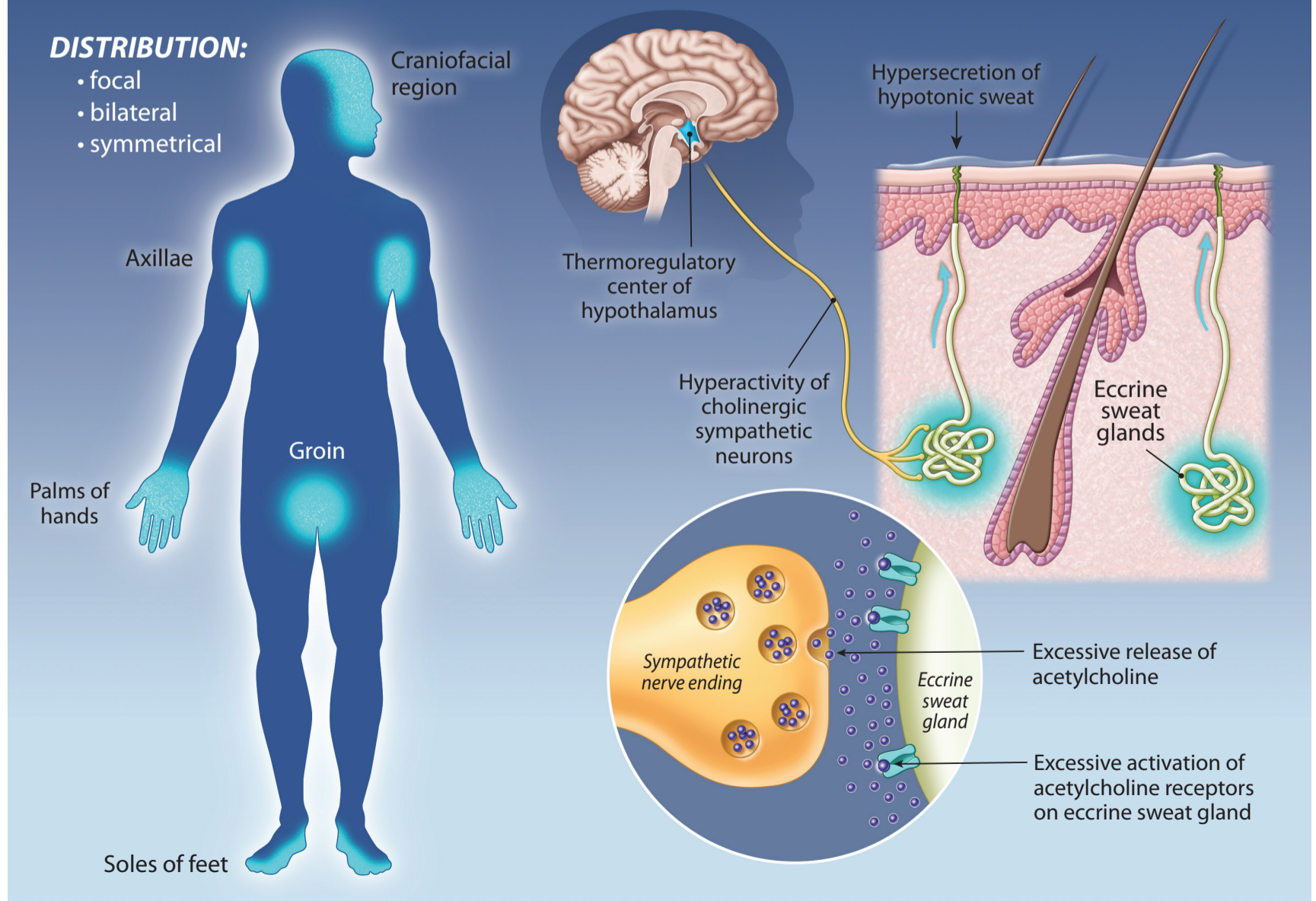
HH involves hyperactivity of the sympathetic nervous system causing excessive release of acetylcholine by the sympathetic neuron leading to excessive activation of the eccrine sweat gland and hypersecretion of hypotonic sweat.⁸ The cause of primary HH is largely unknown. However, genetic factors may be involved, as 35%-65% of cases of primary HH have a positive family history.^{8,9} Primary HH inheritance can show autosomal dominant or recessive inheritance and potential loci have been linked to chromosome 2, 14, and 16. However, a definitive genetic link has not been proven and further research is needed to determine the genetic causes of primary HH.⁸⁻¹⁰ Secondary HH is associated with medications such as dopamine agonists, serotonin reuptake inhibitors (SSRIs), antipsychotics, and systemic illnesses such as diabetes mellitus, hyperthyroidism, and lymphoma.^{2,8-10}

Differential Diagnosis for Hyperhidrosis

It is important to rule out causes of secondary HH before making a diagnosis of primary HH. Secondary causes of hyperhidrosis include:

- Neuropathy
- Hypoglycemia
- Pheochromocytoma
- Menopause
- Lymphoma or other malignancy
- Tuberculosis or other infection
- Alcohol use disorder
- Excessive heat
- Pregnancy
- Diabetes mellitus
- Diabetes insipidus
- Hyperthyroidism
- Acromegaly
- Hyperpituitarism
- Endocarditis
- Congestive heart failure
- Respiratory failure
- Stroke
- Parkinson disease
- Psychiatric disorders
- Drug induced: antidepressants, antipsychotics, SSRIs, antibiotics, antivirals, insulin, glyburide, triptans, antipyretics, NSAIDs, antiemetics, adrenergic agents, cholinergic agents, alcohol, cocaine, heroin, and more

Primary Hyperhidrosis: Common Locations and Pathophysiology



History

A complete history is important to differentiate between primary and secondary causes of HH.^{2,8} Patients with HH will often present with a concern of excessive sweating in areas with a high density of eccrine sweat glands that include the palms, soles, face, head, or axillae.⁸ Primary HH is often seen in younger patients with bilateral involvement. There is often have a positive family history of the disorder.⁸ Secondary HH is usually seen in older patients, and it is critical to rule out medications or systemic illnesses that may be causing symptoms.⁸

Patient history should include pattern of sweating, age of onset, initiating causes, duration of sweating, frequency of sweating, amount of sweating, distribution of sweating, presence of night sweating, family history, and symptoms that suggest secondary causes, such as, fever, night sweats, weight loss, lymphadenopathy, headache, and palpitations.^{2,8,11} A good history should be able to differentiate between primary focal HH and secondary generalized HH.¹¹

Primary focal HH can severely impact quality of life in children and adolescents and the patients should be asked about activities they cannot do or feel uncomfortable doing such as the following:¹²

• Difficulty opening doorknobs (opening doors)
• Writing and using paper (fear of smears/soaking paper)
• Using pencils (constantly need to wipe them)
• Wearing shoes (slipping out of them)
• Raising arm in class
• Removing clothing such as sweaters and jackets despite being too warm
• Socializing (awareness and discomfort)
• Playing sports (handling balls in sports)
• Playing piano and/or guitar (hindered ability)
• Shaking hands with others
• Going to parties (embarrassed)
• Going on dates (embarrassed)

Diagnostic criteria for primary HH include: 6 months of visible focal sweating exceeding thermoregulatory requirements and at least two of the four following: mainly affecting eccrine-dense areas (palms, soles, axillae, craniofacial areas), symmetrical bilateral distribution (sweating on both sides of the body evenly), disturbing daily activities such as causing stress or preventing socializing or work tasks, occurring more than once per week, onset before

25 years of age, positive family history for HH, and lacking nocturnal symptoms (night sweats, disrupted sleep, overheating while sleeping and other changes during sleep).^{1,2,8,13}

The effect of HH on quality of life can be assessed using the Dermatology Life Quality Index (DLQI) and the Hyperhidrosis Disease Severity Scale (HDSS).^{1,13} The Hyperhidrosis Disease Severity Scale (HDSS) is a disease-specific, quick, and easily understood diagnostic tool that provides a qualitative measure of the severity of HH and is made up of four questions answered with a Yes or No: (1) My sweating is never noticeable and never interferes with my daily activities; (2) My sweating is tolerable but sometimes interferes with my daily activities; (3) My sweating is barely tolerable and frequently interferes with my daily activities and (4) My sweating is intolerable and always interferes with my daily activities.¹⁷ A positive answer is scored with 1 point with a maximum of 4 points.

A score of 3 or 4 indicates severe hyperhidrosis. A score of 1 or 2 indicates mild or moderate hyperhidrosis. The HDSS can also be used to assess the effect of treatment. Post-A 1-point improvement in HDSS score has been associated with a 50% reduction in sweat production and a 2-point improvement with an 80% reduction.¹⁷

Physical Examination

The physical examination is important to differentiate between primary and secondary HH and for looking for complications of HH.^{1,8,13} The physical examination should include inspection of the effected areas for excessive moisture and for complications of hyperhidrosis such as tinea pedis.^{1,13}

Investigations

The starch-iodine test is a test that can map out the areas of sweating.^{1,8} This is performed by painting an iodine solution (such as povidone-iodine or Betadine®) to the skin where the sweating occurs. After the skin is dry, starch is dusted onto the skin and the combination results in a dark blue colour in areas of excessive sweating. Supplementary laboratory testing may be useful if secondary HH¹³ is suspected, and these include a complete blood count, basic metabolic panel, thyroid-stimulating hormone, erythrocyte sedimentation rate, antinuclear antibody, hemoglobin A1C, and chest x-ray.⁸ Ultimately, the history and physical examination will guide the direction of additional diagnostic testing.

Management

Initial treatment should include reasonable avoidance of identifiable triggers such as crowded areas, emotional provocations, spicy food, alcohol, tight clothing, man-made



SUMMARY OF KEY POINTS

- Hyperhidrosis is common and affects about 5% of the population
- A simple measure of the severity of hyperhidrosis can be done with the 4-question hyperhidrosis disease severity score
- Secondary hyperhidrosis should be ruled out with a good history and physical exam
- Patients who fail treatment with topical antiperspirants can be treated with tap-water iontophoresis, botulinum toxin injections, oral anticholinergics and surgical options.

synthetic fabrics, and occlusive footwear.¹⁵ Masking sweat using under-arm liners or dress shields, frequent sock and shoe changes, leather shoes, absorbent shoe insoles, foot powder, and cotton or wool socks may also help.¹⁵ Beyond these conservative measures, other targeted therapies, and medications may be used.

Topical antiperspirants (prescription or OTC) which include aluminum chloride hexahydrate (ACH) or topical glycopyrrolate applied at bedtime for 6 to 8 hours are first-line therapy for primary focal HH and provide significant benefit in many patients.^{1,15} If this fails to achieve an acceptable level of sweat reduction, tap water iontophoresis 3 to 4 times per week for 20 to 30 minutes can be used. This involves using a galvanic current transferred via tap water to undamaged palmar, plantar, and axillary skin.¹⁵ Four devices are approved by the FDA, and these include RA Fischer, Hidrex USA (both prescription-based), Dri-onic (OTC) and Dermadry which is also approved by Health Canada.^{1,15} Another treatment for refractory HH consists of botulinum toxin injections administered at the dermal-

subcutaneous junction 1 to 2 times annually.^{1,15} Although a great treatment option, botulinum toxin injections can be expensive for the patient and can cause pain and discomfort making it less suitable for the pediatric population.^{1,3,15} Oral systemic medications may be used for treatment-resistant cases or generalized HH and typically involve oral anticholinergics (e.g., oxybutynin and glycopyrrolate). Other systemic oral agents include oral beta-blockers, clonidine, indomethacin, calcium channel blockers, and benzodiazepines.^{1,15} Energy-delivering devices which include lasers (non-invasive and subdermal), ultrasound technology, microwave thermolysis, and fractional microneedle radiofrequency may also be used especially in cases of focal sweating.¹⁵ When conservative treatments fail, local surgical techniques may be used and include excision, curettage, liposuction, or a combination of these for axillary HH.¹⁵ A last-resort treatment is sympathectomy and may be done after accepting secondary compensatory HH as a potential complication.¹⁵ In many cases, treatment of generalized HH only includes oral

medications but patients may elect to use topical therapy for their most bothersome areas.¹⁵

Therapeutic selection is dependent on many factors and patient age and affected site are very important in determining the type of treatment modality used.^{3,15} Younger children often prefer topical therapies due to ease of administration and minimizing negative side effects of systemic therapies.³ In children, topical therapies are first-line treatment with oral anticholinergics, iontophoresis, and botulinum toxin injection therapy as second-line treatment.³ Overall, it is important to consider many factors which should consider patient preferences as the forefront of the decision-making process.

Conclusion

Hyperhidrosis is perspiration exceeding the physiological requirements of thermoregulation in the eccrine sweat glands that often results in a decreased quality of life and patient distress. It can be subdivided into primary which is idiopathic and bilateral, focal, or multifocal, or secondary

which results from an underlying cause such as a systemic illness or medication and presents as a generalized sweating. It is important to rule out secondary HH before diagnosing primary HH. HH can affect all ages, however, primary HH is more common in those younger than age 25 including children, while secondary HH is more common in older ages. The sites most affected in primary HH include the axillae, craniofacial region, palms, and soles. A thorough history and physical examination are usually enough to sufficiently diagnose primary or secondary HH, but tests such as the starch-iodine test to assess sweating severity, and the DLQI or HDSS may be used to understand the impact of HH and monitor treatment progression. Treatments for HH are dependent on many factors such as sweating location and patient age, and include topical antiperspirants, iontophoresis, botulinum toxin injections, oral medications, energy-delivering medical devices, local surgical procedures and as a last resort, sympathectomy.



CLINICAL PEARLS

Hyperhidrosis is excessive sweating that can be most commonly primary but can have secondary causes

Patients with hyperhidrosis can experience significant impairment on quality of life and this should be explored

First-line treatment consists of topical antiperspirants

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Hyperhidrosis Key Points for the Practitioner

History (key points to cover)

- Background information (age of onset, location, unilateral or bilateral involvement)
- Features of secondary hyperhidrosis (fever, hyperthyroid symptoms, generalized hyperhidrosis)
- Family history of hyperhidrosis
- Severity of hyperhidrosis (can use hyperhidrosis disease severity score)
- Impact of hyperhidrosis

Physical Examination (key features to note)

- Examine for complications such as tinea pedis



Hyperhidrosis Information for the Patient and Family

What is hyperhidrosis?

The purpose of sweating is to keep a constant body temperature around 37°C through evaporation. Hyperhidrosis happens when the body makes too much sweat. This can affect the armpits, palms, soles and rarely over the face. It affects up to 5% of the general population. This means over 8 million people in the USA and 800,000 in Canada sweat too much.

People suffering from hyperhidrosis are often embarrassed to reveal their problem even to their closest friends. However, there are ways to reduce the amount of sweat that is produced.

What can be done?

1. Aluminum chloride/chlorhydrate (over-the-counter)

- This is found in most antiperspirants available over the counter. Its concentration is higher in antiperspirants than in deodorants. Among the aluminum salts, aluminum chloride is the most effective followed by aluminum chlorhydrate / zinc compounds and finally aluminum chlorhydrate used alone.

2. Aluminum chloride hexahydrate in an alcoholic solution (over-the-counter)

- This is available as a 20% alcoholic solution Drysol®. (Lower concentrations are available at 12% and 6.25%). The armpits, hands and feet must be washed and dried before putting this on. The solution is applied under occlusion. Gloves may be used for the hands and plastic bags or plastic wrap for the feet. The cover is kept on overnight and repeated 2 to 3 nights per week. Stinging and burning sensation are common at the beginning but get better with time. This can be treated with over-the-counter hydrocortisone.

3. Topical or oral glycopyrrolate

- This is available online as a prescription from pharmacy.ca as a 4% solution or as 1 mg pills. The pills are taken once in the morning (1 mg). Every week, the amount can be increased by 1 mg (by adding 1 mg at morning or at night) to a maximum of 4 mg twice a day.



4. Oral oxybutynin (2.5 mg pill)

- Oral oxybutynin is a second-line treatment for hyperhidrosis. When taking this medication, you will find that the sweating gets better within a few hours and comes back about a day after stopping. The most common side-effects are dry mouth (25%) and dry eyes (10%) and are related to the dose. The starting dose is 2.5 mg once a day. Every 3-4 days, the dose can go up by 2.5 mg (you can take the extra dose at night) until the sweating is under control. The maximum dose is 5 mg twice a day.

5. Other treatments

- Iontophoresis (Drionic, Fisher, i2m, Dermadry): This involves using a machine that generates a low intensity electrical current to the hands, armpits and/or feet that are sitting in tap water baths or tap water-soaked electrodes.
- Botox: Botox injections can be done to decrease sweating of the armpits and/or for the hands and feet. The amounts and frequency in injections can be determined by the treating doctor.
- Surgery: Surgery can be done to cut out the sweat glands in the armpits (excision of axillary eccrine glands) or to cut the nerves that control sweating of the palms.