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Hyperhidrosis: Pathophysiology and Treatment

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Abstract

Hyperhidrosis is the process of dysregulated sweating beyond homeostatic regulation. It is often classified by aetiology (primary or secondary) and location (focal or generalised). Sweating is essential for thermoregulation but it is thought that failure within the negative-feedback loop, driven by acetylcholine, causes disproportionate sweating. Often this impacts patient's emotional, mental, and physical wellbeing. Personalization of therapy and education is paramount to improving outcomes. Hyperhidrosis can be managed using topical or oral agents, iontophoresis, botulinum toxin injection and with local and endoscopic surgical techniques.

Keywords: Botulinum Toxin, Iontophoresis, Topical Aluminium chloride, Thoracoscopic Sympathectomy

1. Introduction

Hyperhidrosis is a disorder characterised by excessive sweating disproportionate to the homeostatic thermoregulation of the body. Autonomic dysregulation causes hyperstimulation of cholinergic receptors found in eccrine glands in the face, palms, soles, and axillae [1]. Hyperhidrosis is classified by aetiology (primary or secondary) and location (focal or generalised). Primary hyperhidrosis encompasses over 90% of hyperhidrosis and is thought to be idiopathic or related to genetic factors with positive family history in 30-50% of cases [2,3]. It typically follows a focal distribution affecting the axillae, palms, soles, groin, and face whereas generalised and asymmetric pattern is demonstrated in secondary hyperhidrosis. Secondary causes of hyperhidrosis can vary from anxiety, heart failure, endocrine conditions, epilepsy, alcohol, and infection. These must be excluded prior to diagnosis of primary hyperhidrosis [4].

History taking by clinicians should involve location, frequency, duration of sweating episode, age of onset, any triggers, systemic symptoms, sweating during sleep, drug treatments or misuse, psychosocial impact, family history as well as any other comorbidities [5]. Severity of symptoms and disease is assessed by various tools including the validated hyperhidrosis disease severity scale:

• How Would You Rate the Severity of Your Hyperhidrosis?

My sweating is:

1. ...never noticeable and never interferes with my daily activities
2. ...tolerable but sometimes interferes with my daily activities
3. ...barely tolerable and frequently interferes with my daily activities
4. ...intolerable and always interferes with my daily activities (6)

2. Pathophysiology

Apocrine, apoeccrine, and eccrine sweat glands all exist in the axilla. Sweat glands are often concentrated in palms, axillae and soles, and individuals may have up to 2-4 million in total [6]. Eccrine glands function instantly after birth whereas apocrine glands function when stimulated by hormones during puberty. Cholinergic fibres and postganglionic unmyelinated C-fibres innervate eccrine sweat glands to cause sweating in response to thermoregulatory changes in the body during times of physical and psychological stress. The hypothalamus acts as a mediator in this innervation. The negative-feedback loop, which is mainly driven by acetylcholine, fails to supply information to the hypothalamus resulting in deregulated sweating beyond homeostatic control.

Apocrine sweat glands are driven by the norepinephrine neurotransmitter. They are innervated by postganglionic sympathetic nerves and are responsive to emotional sweating. Emotional and thermosensitive stimuli can initiate axillary sweat glands, triggering the sweat centres in the hypothalamus. The cortex controls the centre responsible for emotional sweating. Primary hyperhidrosis is hypothesised to result from atypical central control of emotional sweating [7].

Apoeccrine glands share qualities of both apocrine and eccrine glands. They develop from eccrine glands and are structurally similar with the distal duct excreting directly onto the skin's surface but are confined to the axillary region. They account for 45% of axillary glands by aged 16-18, and development has been linked to puberty [8]. Genetics is also thought to play a role in hyperhidrosis, with some inherited genes leading to overexpression of the sympathetic nerves and hypothesised to affect secretory cell metabolism and cause neuro-hormonal defects. In patient with primary palmar hyperhidrosis, overexpression of neuregulin-1 gene lead to hypermyelination and overexcitability of thoracic sympathetic nerves [9].

3. Current Treatment Options

Hyperhidrosis can be managed medically and surgically. Medical management includes topical aluminium chloride solution, oral anticholinergic agents, iontophoresis, and botulinum type A injections. Surgical management is used in severe cases and can involve direct axillary gland removal and thoracoscopic sympathectomy [3]. Initial management of primary focal hyperhidrosis involves provision of advice related to avoidance of triggers, avoiding tight clothing, to wear white or black clothing to limit signs of sweat, and using footwear that is non-occlusive [10].

For focal hyperhidrosis, NICE guidance states that topical aluminium salt preparations are first line with instructions to apply every 1-2 days before bedtime and remove with water in the morning for up to 6 weeks [4]. Mild potent topical corticosteroid e.g. hydrocortisone 1% cream can also be applied once daily for up to 2 weeks if skin irritation occurs [11]. If treatment is unsuccessful with topical and self-care measures after 6 weeks, referral to dermatology is advised [4]. Topical oxybutynin 3% gel has been found to show higher efficacy and lower recurrence rate for initial management of primary focal hyperhidrosis when applied once daily at night for 4 weeks in a trial which compared it to aluminium chloride 15% lotion [12].

Higher concentrations of aluminium salts (up to 50%), topical glutaraldehyde or formaldehyde may be used [4]. Topical glycopyrronium tosylate is an additional agent with mild side effects which has demonstrated improvement in symptoms by 25-30% after 4 weeks of daily treatment [5]. Oral antimuscarinics such as oxybutynin may be used as adjuncts to decrease sweat secretion by competing to inhibit acetylcholine at the muscarinic receptors near eccrine glands [13]. Side effects related to these agents include dry eyes, blurry vision, constipation, and urinary retention, however using a modified release product can support with tolerance. Additionally, topical combined agents such as

THVD-102, an agent containing oxybutynin and pilocarpine, have shown fewer reported side effects with similar performance profiles to the use of oxybutynin alone for treating primary focal hyperhidrosis [14].

For the axillae, craniofacial and palmar hyperhidrosis, botulinum toxin injection has demonstrated significant improvement and can be considered first or second line for treatment in these areas, with lidocaine sometimes combined with botulinum toxin [15,16]. Some common side effects include pain, transient muscle weakness and compensatory sweating. The high costs associated with this treatment must be considered as repeat treatments are often required due to symptom relief lasting only 6-9 months [7]. Another treatment option is iontophoresis. This involves usage of local electrical current which passes through skin soaked in water, 0.9% saline or an anticholinergic solution. It has been beneficial for the axillae, palmar hyperhidrosis and at the soles of the feet and carries a limited side effect profile including paraesthesia, dermatitis, and erythema [17].

Surgical interventions are considered the last stage of management. These include local excision of eccrine glands, liposuction, and curettage. High risk of relapse commonly begins 6 to 12 months following surgery; thus, these techniques offer limited short-term benefits [4]. Invasive sympathectomy has also been used in severe hyperhidrosis, where cutting or clipping of sympathetic nerves results in decreased sweating. However, compensatory hyperhidrosis, thought to be related to reduced surface area for body cooling, results in sweating from the abdomen, gluteal and gustatory region. There are also risks of infection, pneumothorax, atelectasis, and substantial bleeding [2].

4. Alternative Treatments and Findings

Anecdotal sources have claimed that cannabis was effective in the management of hyperhidrosis [18]. A case report followed a 28-year-old male with generalised hyperhidrosis in the forehead, chest and neck region which was refractory to treatment (topical and oral treatments, iontophoresis and botulinum toxin). The patient used DLQI, EQ-5D-3L, EQ-VAS, Hyperhidrosis Disease Severity Scale, and Hyperhidrosis Quality of Life Index, assessed weekly for 3 months. Results highlighted both subjective and objective improvement in symptoms, with DLQI reduced by 55.6% and decreased measured sweat during the therapy, with almost cessation in the forehead, and 80-90% decrease in other areas. While research is limited and there is a lack of clinical evidence to validate the use of cannabinoids, it is important to reflect on the subjective improvement in the patient's quality of life. Further qualification of these findings through substantive clinical trials may prove fruitful.

In another case report, a 34-year-old female patient developed nocturnal generalised hyperhidrosis secondary to clozapine for treatment-resistant schizophrenia [19]. Clozapine has an unclear association with sweating. The mechanism is suggested to be due to clozapine's partially agonistic effect at the muscarinic receptors M1 and M3 which increases acetylcholine release and stimulates a sweat response [20]. Secondary hyperhidrosis is

often managed with oral anticholinergic medications however in this case clozapine provided an existing anti-cholinergic burden. Therefore beta blockers, clonidine or an alpha-2 agonist are alternatives [1]. The patient was unable to use topical or oral agents due to background constipation, which would be worsened by an anticholinergic, and a beta blocker would have worsened her pre-existing asthma so diltiazem, a calcium channel blocker, was used. Diltiazem was effective in reducing clozapine induced hyperhidrosis and had a limited side effect profile when given together.

5. Conclusion

The pathophysiology of hyperhidrosis is linked to dysregulated sympathetic stimulation and can be augmented by physiological, emotional, and physical behaviours of a patient. Studying genetic patterns in those with hyperhidrosis can aid in understanding the mechanism of the condition and guide potential management strategies. Treatment with topical, oral, injection and surgical agents has shown benefit in the management of the condition. When managing patients with secondary hyperhidrosis, it is important to consider medical interactions and offending agents causing hyperhidrosis. Management of the symptoms can rely on anticholinergics or antimuscarinic agents.

There is space for further research in the use of alternative agents such as cannabinoids which may have a role in the improvement of mental status, and thus result in overall improvement of the condition.

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