

Hyperhidrosis: A Review of a Medical Condition

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Abstract: Sweating is a normal and important mechanism of thermoregulation which is essential for survival. When sweating becomes excessive, the resulting condition is called hyperhidrosis. While hyperhidrosis is not a fatal condition, it can greatly affect one's quality of life due to its psychological and social impact. To understand this condition, it is necessary to explore the biology of sweat glands including the eccrine, apocrine, and apoeccrine sweat glands. It is also vital to understand the physiological significance of sweat to maintain the human body temperature in order for it to function properly. Hyperhidrosis can be divided into a primary and secondary condition and it is also associated with a wide variety of other conditions. Many treatments exist to alleviate this disorder including aluminum compounds, aldehydes, anticholinergic agents like glycopyrrolate, benztropine and oxybutynin, botulinum toxin A, antiperspirants, sympathectomy, iontophoresis, and sweat gland suction. Ultimately, knowledge of this disorder and its methods of treatment and management are imperative to optimize treatment for patients suffering from hyperhidrosis.

Hyperhidrosis is defined as sweating greater than is necessary for the maintenance of normal body thermoregulation. While hyperhidrosis is not a fatal condition, it can greatly affect one's quality of life due to its psychological and social impact. Hyperhidrosis can also render the skin susceptible to infection because of the continuous dampness of the skin. It is thus important to understand this condition and its complications in order to better manage and treat patients.

In order to understand the disorder of hyperhidrosis, it is first necessary to explore the biology of sweat glands. There are three major types of sweat glands: eccrine, apocrine, and apoeccrine. Eccrine sweat glands are the most numerous of all glands and can be found throughout the body surface except for the lips and the glans penis. Eccrine sweat glands consist of a ductal portion and a secretory portion. The major function of the ductal portion is to reabsorb ions from the primary sweat to create an isotonic sodium chloride solution. The major function of the secretory portion is as its name suggests: secretion. Eccrine sweat is composed primarily of water in addition to other ions such as sodium, chloride, potassium, and calcium. Eccrine sweat glands are innervated by postganglionic sympathetic fibers and the major neurotransmitter is acetylcholine. Many different types of muscarinic acetylcholine receptors can be found on eccrine sweat glands and thus these receptors can be blocked by antimuscarinic agents. Apoeccrine glands can be found on the hairy areas of the body like the axilla, mammary, perineal, and genital regions. Apoeccrine sweat is oily, lacks an odor, and is rich in proteins, lipids, and steroids. Apoeccrine glands receive sympathetic innervation and the major neurotransmitters are epinephrine and norepinephrine. These glands are mixed glands found in the hairy regions of

the body that develop during puberty from eccrine glands as the number of eccrine glands decrease with age. Apoeccrine glands secrete a watery solution similar to that of eccrine sweat. These glands receive cholinergic, alpha adrenergic, and beta adrenergic innervations [1].

It is vital that an individual's core body temperature remain within physiological range in order for the body to function normally. The major function of sweating is to decrease the core body temperature when environmental temperatures exceed the normal physiological "set point" established by the hypothalamus [2]. This is carried out by the evaporation of water from the skin and the release of heat energy. The body's ability to sweat up to 1.8 liters per hour allows survival in a wide range of temperatures [3]. When temperatures consistently remain above forty degrees Celsius, protein denaturation and cell death result [1]. The sweating pathway starts in the preoptic area in the anterior hypothalamus and descends to the lateral funiculus of the brainstem and synapses in the intermediolateral region of the spinal cord [2].

Hyperhidrosis is the excessive production of sweat by the eccrine sweat glands due to overactive cholinergic innervation of these glands. Histologically, though, the eccrine sweat glands are morphologically and functionally normal. It can affect any region of the body. Currently, one percent of the population suffers from this condition. It can be primary (idiopathic/essential) or secondary to another condition. Secondary hyperhidrosis can be further classified as generalized, local, or emotionally induced. Emotionally-induced hyperhidrosis, like from fear or anxiety, targets the palms, soles, and axillae. Generalized hyperhidrosis can be due to autonomic dysregulation or it can arise secondary to an underlying condition like a malignancy, diabetes mellitus, thyrotoxicosis, diabetes insipidus, anxiety, menopause, and carcinoid syndrome among many other conditions [2]. Localized hyperhidrosis results from the abnormal regeneration of sympathetic nerves following

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injury, from a defect in the number of or distribution of eccrine sweat glands, or from a vascular defect. Primary (idiopathic/essential) hyperhidrosis affects the eccrine sweat glands and is due to excessive sympathetic activity. It does not affect the vascular endothelium [4]. Patients with essential hyperhidrosis constantly sweat from the skin surfaces which can be so severe as to make these individuals embarrassed and ashamed to shake their hands with others [2].

Hyperhidrosis can accompany other diseases such as peripheral neuropathy, unilateral circumscribed idiopathic hyperhidrosis, spinal cord disease, thoracic tumors, cerebrovascular disease, and cutaneous disease. It can also be stimulated by the presence of food in the mouth also known as gustatory hyperhidrosis. Peripheral neuropathies are characterized by pain, tingling, burning, and numbness primarily in the foot and hand region. Compensatory hyperhidrosis often occurs with peripheral neuropathies mainly in the proximal regions like the head and trunk. Patients can also experience distal sweating due to spontaneous firing from the injured neurons [2]. Riley-Day syndrome is an inherited sensory and autonomic neuropathy characterized by episodic hyperhidrosis that affects the development and function of nerves which results from a splice defect in the *IKBKAP* gene [5]. Unilateral circumscribed idiopathic hyperhidrosis is characterized by excessive sweating from a well-demarcated area of skin that is surrounded by dry skin primarily in the face and arms [2]. Autonomic dysreflexia is a syndrome due to imbalanced sympathetic discharge that affects patients with an injury above the sympathetic outflow at the T6 level (thoracic 6 level or sixth vertebrae of the thoracic region of the spinal cord) [6]. This condition can be stimulated by bowel and bladder distension, urinary tract infection, hemorrhoids, deep vein thrombosis, and visceral stimulation among others. Thoracic tumors can present with hyperhidrosis. Malignancies such as mesothelioma, myeloma, osteoma, and cervical rib can compress the sympathetic chain ganglion resulting in unilateral hyperhidrosis of the face, neck, and thorax. Infarction in the cerebral hemispheres, brain stem, or hypothalamus can result in short lived hemihyperhidrosis due to disruption of the crossed sympathoinhibitory pathway thereby resulting in copious sweating on one side of the body. Hyperhidrosis can occur with a variety of skin disorders like nevus sebaceous, eccrine nevus, eccrine pilar angiomatous hamartomas, glomus tumors, and blue rubber bleb nevus. Gustatory sweating can result from the consumption of spicy food. Frey syndrome is characterized by asymmetrical facial gustatory sweating due to injury to the autonomic nerves that innervate the parotid gland and sweat glands. In diabetes mellitus, herpes zoster, and cluster headaches, patients have reported facial hyperhidrosis during salivation [2].

There are a variety of drugs that can induce hyperhidrosis by acting on the hypothalamus, the spinal thermoregulatory centers, the sympathetic ganglia, or the eccrine-neuroeffector junction. These drugs include cholinesterase inhibitors, selective serotonin reuptake inhibitors, opioids, and tricyclic antidepressants. This can be managed by reducing the drug dosage or substituting the drug for another [7].

Many treatments exist to treat hyperhidrosis. Aluminum compounds are antiperspirants used to treat hyperhidrosis. According to a prior theory, aluminum was thought to physically occlude the sweat gland orifice. Evidence gathered recently explores a different mechanism by which aluminum possibly alters the flow from eccrine sweat glands [8]. Aluminum has anticholinergic effects by acting on choline transport in the presynaptic nerve terminals. It regulates the activity of the Na^+/K^+ ATPase enzyme located in the plasma membrane which is necessary for maintaining an appropriate cell potential and cell volume. It also affects cell membrane structures, intracellular calcium homeostasis, and transport of ions within the secretory cells of the gland. Aluminum chloride causes degeneration of eccrine sweat glands after long term application. More specifically, this new theory presents the idea that aluminum affects the secretion of sweat by constricting the lumen of the dermal duct. This is accomplished by its direct actions on the structure and function of the ductal membranes or by its anticholinergic effects [8].

Aldehydes are another treatment option that denature the keratin in the skin and occlude the pores of the sweat glands to reduce sweating. They are particularly effective in the palms and soles but not the axillae. Acetylcholine is the major neurotransmitter that mediates sweat secretion. Therefore, drugs that inhibit the binding of acetylcholine, called anticholinergic agents, can be used to treat hyperhidrosis. Glycopyrrolate is an anticholinergic agent that blocks the muscarinic acetylcholine receptors in the smooth muscle, central nervous system, and secretory glands. Benztropine is another anticholinergic agent that may be useful in the treatment of hyperhidrosis. Oxybutynin inhibits smooth muscle spasms primarily by blocking the action of acetylcholine and can also be used to treat hyperhidrosis. Neuromuscular blocking drugs such as botulinum toxin-A can treat hyperhidrosis by inhibiting synaptic vesicle fusion and release of acetylcholine into the synaptic cleft which prevents acetylcholine action at the post-synaptic receptors and prevents sweating [4]. Antiperspirants decrease the amount of sweat that is secreted by the eccrine sweat glands. Metal salt antiperspirants function by blocking the eccrine ducts with plugs composed of metal salts and keratin fibrils [9]. Surgical removal of the sympathetic chain, which is called sympathectomy, is another approach to treat hyperhidrosis. It is effective in treating palmar, axillary, and facial hyperhidrosis. Complications of sympathectomy include compensatory and gustatory hyperhidrosis, Horner's syndrome, and neuralgia. Iontophoresis is another treatment that involves soaking the skin in a solution and applying low intensity electrical current which introduces charged ions into the skin and inhibits the function of the sweat glands in that area [10]. Sweat gland suction is a new surgical technique in which local anesthesia is applied and the sweat glands are carefully removed. This process is similar to liposuction [11].

Sweating is a normal and important mechanism of thermoregulation which is essential for survival. When sweating becomes excessive, the resulting condition is called hyperhidrosis. Hyperhidrosis greatly impacts individuals and it can accompany other disorders as well. Exploration of this disorder and knowledge of available treatment and methods of management are imperative to care for such patients, who

may feel vulnerable and embarrassed, in order to improve their quality of life.

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