

Treatment Modalities and the Neuropathology of Palmar Hyperhidrosis

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ABSTRACT

Palmar Hyperhidrosis (PHH) is a largely idiopathic condition that leads to significant dermatological and socio-professional concerns. This article reviews the method of treating PHH and defines the role of the neuropathologist, which is poorly illustrated in current literature. PHH is treated with the stepwise use of aluminum salts, iontophoresis, Botox injections, systemic drugs and finally endoscopic thoracic sympathectomy (ETS). ETS is currently saved for medically refractory PHH and the procedure is being optimized. Currently consideration is being given to whether the T2 vs. the T2 T3 T4 ganglia should be excised or whether they should be reversibly clamped or permanently excised. Although during ETS the surgeon can correctly identify the ganglion, the pathologist still plays a role in studying the histopathology to gain further understanding of the pathophysiology of PHH. Some of the pathohistological changes that may be observed in the PHH ganglia include neuronal cell death, lipofuscin accumulation, and inflammation. At present the relationship of these findings to the clinical presentation and pathogenesis of PHH is unclear, and without an animal model, research will be slow. Thus, the neuropathologist and surgeon should take special note of the clinical picture and correlate the number of pathohistological findings with the degree of clinical symptoms. Finally, the neuropathologist may assess the type of inflammation (i.e. monocytic vs. lymphocytic) via immunohistochemical stains and continue the search for non-documented and undiscovered pathohistologic markers of PHH.

KEYWORDS: hyperhidrosis, sympathectomy, pathology, treatment, ganglia, ganglion

INTRODUCTION

Hyperhidrosis (HH) may be recognized as excessive sweating beyond the quantity needed for temperature control.¹ It affects 2.8% of the general population and can be classified as either generalized or focal. Generalized HH, or HH of a body surface greater than 100 cm², is largely secondary to primary medical conditions (see Table 1).² On the other hand focal HH, or HH of a body surface less than 100 cm², is largely idiopathic and affects the axillae (40%), the hands and feet (40%), and other areas such as the forehead and groin. Given that focal HH is largely idiopathic, this review will not focus on secondary causes. Focal HH may have a serious impact on a patient's psychosocial and professional life – for example, shaking others' hands or holding tools.³ Furthermore, HH left untreated can trigger a variety of dermatological conditions (see Table 2).^{2,4} The purpose of this review is to highlight the current treatment strategy for PHH and to focus on the role of histopathology, which is not well defined in the current literature.

PERIPHERALLY TARGETED TREATMENTS

PHH is predominantly a disorder of the eccrine sweat glands.¹ Sweat glands can be broken down into apocrine and eccrine sweat glands. The apocrine

Table 1. Classifications and etiologies of focal and generalized hyperhidrosis.

Focal HH		Generalized HH
Primary	Secondary	System Etiologies
Armpits	Gustative HH	Biochemical
Hands		Endocrine
Feet		Neoplastic
Forehead		Neurological
Scalp		Night Sweats
Groin		Traumatic
Genitals		Other

Table 2. Dermatological conditions secondary to untreated PHH.

Bacterial infections
Callosity
Candidiasis
Dermatitis
Dyshidrotic eczema
Erythrasma
Friction bubbles
Frostbite
Ingrown nails
Intertrigo
Onychomycosis
Pitted keratolysis
Tinea pedis
Tinea versicolore
Trichomycosis axillaris
Warts

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Progression
of treatment
for refractory
PHH

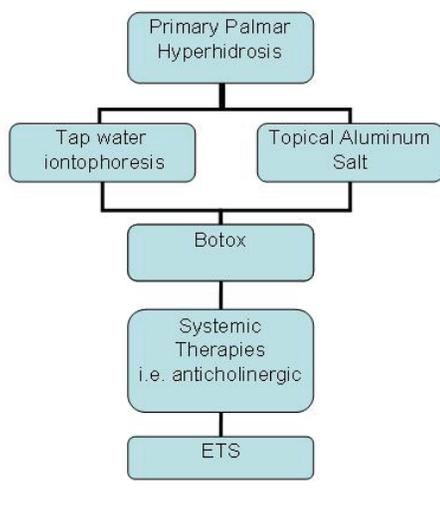


Figure 1. Treatment algorithm for PHH.

sweat glands are predominantly located in the axillae and the groin and have a role in production of body odor. On the other hand, the eccrine sweat glands are primarily involved in thermoregulation and are located throughout the body. The eccrine sweat gland is made of a spiral duct called the acrosyringium, which opens up to the skin and is located within the epidermis. It also has a straight dermal portion and a coiled secretory part called the acinar portion located within the dermis or hypodermis.⁵

Patients with PHH can be treated via a stepwise approach based on the severity of their symptoms (see Figure 1).³ Current literature recommends the use of a 40% aluminum chloride hexahydrate (ACH) in salicylic acid gel (SAG) as a first line agent. The patient should wait a period of one month to assess the effectiveness of treatment. If excessive dryness develops, the clinician may lower the concentration of ACH to 30%. If the initial ACH treatment is ineffective, the clinician may increase the concentration of ACH to 55%.^{3,6} ACH reduces sweat by destroying luminal epithelium, causing mechanical obstruction of the eccrine duct at the level of the acrosyringium.^{7,8}

As a second line therapy, the clinician can consider tap-water iontophoresis.³ Iontophoresis is a non-invasive method of propelling bioactive ionically-charged substances transdermally by using an electromotive force generated from small electric charge interactions.⁹ Some PHH authorities speculate that the electric charge generated causes the stratum corneum to thicken and subsequently block the sweat glands.^{10,11}

Failure of both ACH and iontophoresis should lead the clinician to consider botulinum toxin type A injections (Botox).³ Although Botox is easier to use for axillary HH as there is no anesthesia required, it can also be used for palmar and sole HH with anesthesia. Botox works by inhibiting the release of acetylcholine from the nerve terminal, thus preventing transmission of the signal to the M3 receptor of the sweat gland. Botox injections do present with some potential complications.^{11,12} First is the issue of the local anesthesia prior to palmar nerve block as repeated needle

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Focal HH may have a serious impact on a patient's psychosocial and professional life...

injections do risk damaging the nerve. Second, repeated Botox injections are costly and can also lead to immuno-resistance. Third, Botox can periodically lead to transient paralysis of the hand.¹³

Some literature also describes the use of anticholinergics to inhibit the sweat gland's M3 receptor. There is a randomized, placebo-controlled, double blinded study showing a positive effect of methanethelinium bromide for axillary HH but not palmar HH.¹⁴ However the use of anti-cholinergics has been limited due to their side effects such as dry mouth, accommodation disorders, urinary retention, constipation, and memory impairment. The successful use of benzodiazepines, antidepressants, and calcium channel blockers has also been described in case studies.⁵

SYMPATHETIC SYSTEM TARGETED TREATMENTS

The eccrine gland-targeted nerve signal can stem from either the peripheral or the central nervous system.¹⁵ Central mechanisms of sweating stem from the hypothalamus where all of the thermosensory afferents are integrated.¹⁶ As the core body temperature increases, the hypothalamus acts to decrease this temperature by cutaneous vasodilation and sweating.^{17,20} Hormones, oxygen saturation, and emotions also all influence sweating through various neurological centers including the amygdala, prefrontal cortex, insular cortex, and cingulum.^{5,21}

Peripherally, the sweat glands are innervated by the sympathetic nervous system, which can be broken down into the adrenergic preganglionic fibres and the postganglionic fibers. The postganglionic sympathetic C fibers, which release acetylcholine onto the M3 receptors of the eccrine glands, are the targets for PHH treatment directed at the sympathetic nervous system.²²

Over the last several decades, sympathectomy has been employed as a treatment for medically refractory PHH.⁵ During the 1990s, advancement in endoscopic techniques allowed the surgeon to approach the sympathetic chain through a small incision. The endoscopic thoracic sympathectomy (ETS) of T2 T3 is successful at reducing PHH in almost 98% of all cases.²³ All patients will experience compensatory sweating, as there is decreased sympathetic tone to the head, which triggers an increase in total body sweat to regulate temperature at a new set point. The amount of compensatory sweating depends on the patient, the damage that the white rami communicans incurs, and the amount of cell body reorganization in the spinal cord after surgery.²⁴ Studies have shown that the number of patients experiencing compensatory sweating can be further decreased in two ways: first, by reversibly clamping the sympathetic chain as opposed to destroying or cutting it and second, by clamping at the T2 level only instead of clamping at the T2 T3 T4 level.^{23,25,26} Other potential complications include inadequate resection of the

ganglia, gustatory sweating, pneumothorax, cardiac dysfunction, post-operative pain, and finally Horner's syndrome secondary to resection of the stellate ganglion.²⁷

NEUROPATHOLOGY

In ETS, the T2 ganglion is adequately and precisely visualized and excised from the sympathetic chain by the surgeon. However, to aid current research efforts in trying to understand the pathophysiology of PHH, the tissue should still be examined by a neuropathologist. To examine the ganglion's neuropathology one does need to be familiar with the normal anatomy and histology of the sympathetic nervous system. The sympathetic ganglia can be separated into two different groups: the paravertebral (next to the vertebrae) and the prevertebral (in front of the vertebrae). The prevertebral ganglia provide sympathetic innervation to the internal organs whereas the paravertebral ganglia provide innervation to the skin surface and the eccrine glands. The paravertebral ganglia lie bilaterally along the dorsal wall of the thorax from C1 to S2 with one pair of ganglia per spinal cord level.²⁸

A sympathetic efferent pathway typically consists of two networked neurons. The first neuron, the cholinergic preganglionic neuron, is in the intermediolateral cell column of the spinal cord grey matter. It sends its axon to synapse with a multipolar neuron, typically an adrenergic postganglionic neuron in a paravertebral ganglion. In the case of a sweat gland, the postganglionic neuron is cholinergic and innervates the M3 receptor in the gland. The postganglionic axons leave the ganglion via the ventral roots through the white rami communicans at varying spinal levels where they travel to their target organ, in this case the eccrine glands.²⁸

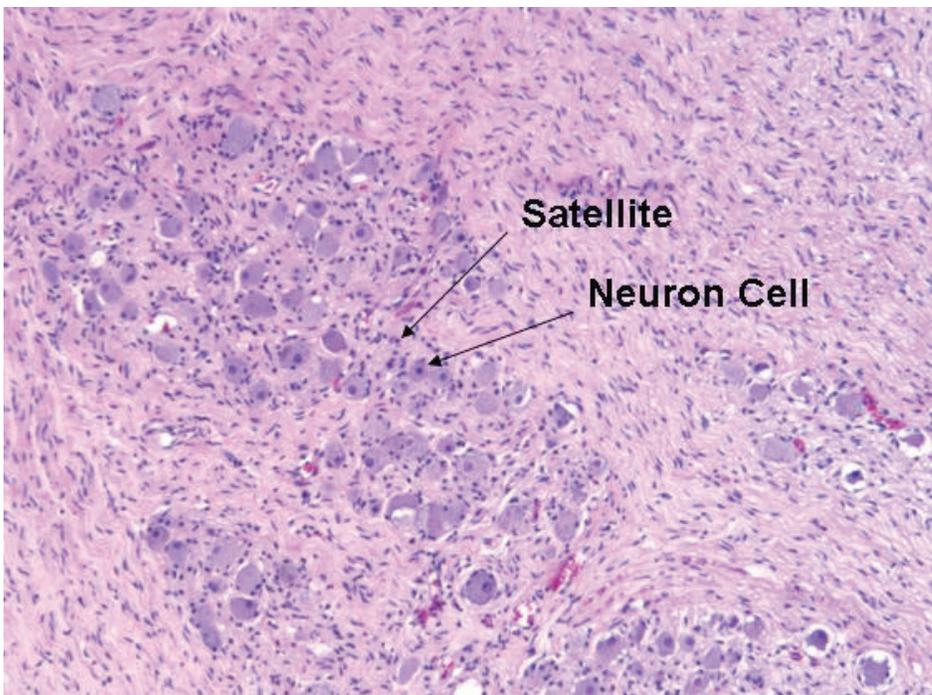


Figure 2. Histological appearance of a normal ganglion stained with hematoxylin and eosin. Neuron cell bodies and satellite cells are indicated. Note the size and quantity of satellite cells vs. neurons. Given the poor understanding of PHH and lack of photos of PHH-related ganglia only a normal photo is included in this article.

The ganglion containing the postganglionic cell body histologically consists of neuron cell bodies, satellite cells, and axons (see Figure 2). The ganglion cells generally have a diameter of 10 to 50 μm and are multipolar with multiple dendrites and a long axon that exits the ganglion. The multipolar cell dendrites are of variable length and periodically form “dendritic glomeruli” with adjacent cells. Surrounding the neurons is a multitude of satellite cells that form a contiguous sheath with the Schwann cells of the peripheral nervous system.²⁹

In a review of the literature of the histopathological changes of postganglionic cells in individuals with PHH, one article was found. In a study of 55 post-sympathectomy ganglia of 35 individuals with a mean age of 29 years, researchers found an increase in neuronal death and lipofuscin accumulation as compared to expected levels (i.e. 60% of biopsies contained significant lipofuscin accumulation and chromatolysis).³⁰ These results were acquired by assigning a value to the fraction of the biopsy affected (i.e. where 75% of a biopsy containing lipofuscin or neuronal death was considered significant and assigned a value of 2; a biopsy with 25%-75% was assigned a value of 1; and a biopsy with less than 25% was insignificant and assigned a value of 0). The value was then compared to literature descriptions of normal sympathetic ganglia in mice, rats, and rabbits as there is no known normal value in humans. Further, only 5.5% of the biopsies contained any inflammation in the form of swelling, and no further marker of inflammation was assessed. Thus, chromatolysis and lipofuscin were independent of inflammation in 32.1% of cases.

From the results of this article and the young age of the patients affected by PHH, the authors postulated that the neuronal changes could be secondary to neuronal hyperstimulation.³⁰ It was noted that patients who received a sequential bilateral sympathectomy separated by a period of months experienced a decrease in the number of ganglia exhibiting significant neuron death from 71% in the first surgery to 42% in the second. Thus, a unilateral sympathectomy of T2 T3 provided protection, through an unknown mechanism, to the contralateral ganglion's neurons. This same study noted that the larger the body area de-innervated by ETS, the higher the incidence of compensatory hyperhidrosis.³⁰ Removal of bilateral ganglia would result in upward of 79% of patients suffering from compensatory hyperhidrosis vs. 56% for a unilateral ETS.

A second research group described the role of histopathology in the sympathectomy to verify that two ganglia and an interconnecting peripheral nerve were excised.³¹ Thus the histopathology confirmed that the surgeon alone could excise the ganglion with a success rate of surgery at 98%. Additionally this article noted that excision of the lower third of the stellate ganglia – as identified surgically – increased the rate of Horner's syndrome.³²

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CONCLUSION

PHH is a medical condition leading to a wide range of dermatological conditions and socio-professional issues. In medically refractory PHH, the surgeon identifies and diagnoses the ganglion during ETS and then excises it intraoperatively with a success rate of 98%. The pathologist confirms that the removed tissue is a ganglion, but this is not required for the diagnosis. The main role of histopathology in ETS is to further the current knowledge of the pathophysiology of PHH.

At this point very little research exists on the relationship of the histopathology of ganglia in PHH to its pathophysiology, but the existing literature does raise its own questions. As noted, individuals begin to suffer from PHH at a mean age of 29, which is considered very young for disease states. This begs the question, is there hyperstimulation of the sympathetic ganglion leading to cell death? At present there is no research, but animal models could be employed to test whether an increase in the frequency, duration, or volume of stimulation over time has any effect on the sympathetic ganglia. Furthermore, animal models could also be employed to investigate why a unilateral sympathectomy for PHH is protective to the contralateral side's neurons, which was excised at a later date after a second ETS. Unfortunately, as there is no animal model of PHH, these hypotheses may be difficult to test. Without an active animal model for PHH, research into this field will continue to rely on case reports and histopathology with related clinical correlations.

The role of the neuropathologist is to document carefully the amount of lipofuscin, neuronal death, and inflammation observed in addition to any findings not previously reported as correlating to PHH. In recording the degree of inflammation the pathologist may use immunohistochemical stains to further illustrate the type of inflammation, namely whether it is lymphocytic or monocytic. Furthermore, the neuropathologist and surgeon should take special note of the clinical picture and correlate the number of pathohistological findings with the degree of clinical symptoms. Appropriately documenting these correlations will assist future researchers in correlating more findings and generating a greater understanding of PHH. 

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