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REVIEW

The Etiology of Primary Hyperhidrosis: A Systematic Review

Moshe Hashmonai[1] · Alan E. P. Cameron[2] · Cliff P. Connery[3] · Noel Perin[4] · Peter B. Licht[5]

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Abstract
Purpose Primary hyperhidrosis is a pathological disorder of unknown etiology, affecting 0.6-5% of the population, and causing severe functional and social handicaps. As the etiology is unknown, it is not possible to treat the root cause. Recently some differences between affected and non-affected people have been reported. The aim of this review is to summarize these new etiological data.
Methods Search of the literature was performed in the PubMed/Medline Database and pertinent articles were retrieved and reviewed. Additional publications were obtained from the references of these articles.
Results Some anatomical and pathophysiological characteristics (as well as enzymatic, metabolic, and neurological dysfunctions) have been observed in hyperhidrotic subjects; three main possible etiological factors predominate. A familial trait seems to exist, and genetic loci associated with hyperhidrosis have been identified. Histological differences were observed in sympathetic ganglia of hyperhidrotic subjects: the ganglia were larger and contained a higher number of ganglion cells. A higher expression of acetylcholine and alpha-7 neuronal nicotinic receptor subunit in the sympathetic ganglia of patients with hyperhidrosis has been reported.
Conclusions Despite these accumulated data, the etiology of primary hyperhidrosis remains obscure. Nevertheless, three main lines for future research seem to be delineated: genetics, histological observations, and enzymatic studies.

Keywords Sympathetic System · Primary Hyperhidrosis · Etiology · Epidemiology

Introduction

Primary hyperhidrosis (PH) is a pathological disorder of excessive perspiration, in amounts which exceed the physiological needs of thermoregulation [1]. The anatomical regions most often affected are the palms, axillae, face, and soles of feet [2]. From all sites, oversweating palms represent the major and most disturbing subset of PH. It usually afflicts young people, with a percentage as low as 0.6-1% [3] and as high as almost 5% [4]. A US nationwide survey of the entire population reported an incidence of 2.8% [5]. Palmar hyperhidrosis may lead to severe functional and social handicap, as well as emotional and psychological distress [2]. By definition, a disease is termed "primary" when its etiology is unknown; this applies to PH. However, scrutinizing the literature, some anatomical and physiological characteristics particular to people with PH have been observed. The aim of the present study was to survey the literature and summarize these known characteristics.

On behalf the International Society of Sympathetic Surgery.

✉ Moshe Hashmonai
hasmonai@inter.net.il

[1] Faculty of Medicine, Technion – Israel Institute of Technology (retired), PO Box 359, Zikhron Ya'akov, Haifa, Israel

[2] Department of Surgery, Ipswich Hospital, Ipswich IP4 5PD, UK

[3] Thoracic Surgery, Vassar Brothers Medical Center, Poughkeepsie, NY, USA

[4] Faculty of Neurosurgery, New York University Medical Center, New York, NY, USA

[5] Department of Cardiothoracic Surgery, Odense University Hospital, Odense 5000, Denmark

Methods

Search of the literature was performed in the PubMed/Medline Database (1st September 2016) using the terms "Primary Hyperhidrosis" AND "Etiology" AND one of each of the following words/phrases: Incidence; Epidemiology; Genetics; Anatomy; Histology; Physiology; Pathophysiology; Regulatory Dysfunction; Central Dysfunction; Brain Dysfunction; Neurological Dysfunction; Acetylcholine; Nitric oxide; Oxidants; Catecholamine; Metabolism; Personality. A total of 769 articles were obtained. From this list, according to the titles, 89 relevant articles were retrieved. After excluding the duplicates, 38 articles remained. By examining these publications, other relevant articles were obtained from the lists of references. Thus, a total of 57 articles have been obtained. After being reviewed, 35 ones pertinent to the subject remained, becoming the basis of the present report.

Results

Several characteristics were reported on patients with PH

Epidemiology

A familial trait has been observed in most epidemiological studies. Park et al [6] found in their study that 34.1 % of patients had a family history of hyperhidrosis. A similar figure (35.9%) was observed by Yamashita et al [7]. A higher amount (45%) was reported by Lima et al [8], and a family history in 50.2% was described by Karimian-Teherani et al [9]. Kaufmann et al [10] identified a familial history of PH in 62% of their patients and Ro et al [11] stated an even higher figure (65%).

Genetics

Based on their study, Ro et al [10] considered that there was evidence of genetic transmission. They calculated that the disease allele was present in 5% of the population and that one or two alleles would result in hyperhidrosis in 25% of the time, whereas the normal allele would result in hyperhidrosis in less than 1% of the time. Similarly, Kaufman et al [11] concluded that there was evidence of genetic autosomal dominant inheritance with a sibling recurrence risk of λs = 29-48 and an offspring recurrence risk of λo = 41-60. Two studies in Chinese and Japanese populations, respectively, located loci for focal hyperhidrosis; one on chromosome 2q31.1 [12] and the other on chromosome 14q11/2-q13 [13].

Anatomical/Histological Characteristics

Structural and histochemical changes have been observed in the sympathetic ganglia. De Oliveira et al [14] compared the histology of the third thoracic sympathetic ganglion of patients with primary palmar hyperhidrosis with the same ganglion obtained from "deceased heart-beating organ donators". They identified a significantly higher number of ganglion cells in the ganglia of the study group, as well as a higher number of cells in apoptosis. Hyperhidrotic patients were found to have less collagen in the sympathetic ganglia, but the difference was short of statistical significance. In a further similar study by the same group [15], the size of the ganglion was found to be statistically larger compared to the same ganglion in controls.

Another study compared the third thoracic ganglia of primary palmar hyperhidrotic subjects with those obtained during pleurectomy of non-hyperhidrotic patients [16]. Electron micrographs showed that patients with primary palmar hyperhidrosis had sympathetic ganglia with a significantly greater average axonal myelin thickness, probably due to a significantly higher relative expression of Nrg-1 mRNA, than controls.

Physiological/Pathophysiological Characteristics

Moya et al [17] examined the presence of inflammation, chromatolysis, and lipofuscin accumulation. Their results suggested neuronal death not due to apoptosis as expressed by an elevated chromatolysis, and functional hyperstimulation/functional overload of the neural tissue, as expressed by lipofuscin accumulation.

Enzymatic or Metabolic Dysfunctions

de Moura Jr et al [15] observed a higher expression of acetylcholine and alpha-7 neuronal nicotinic receptor subunit in the sympathetic ganglia of patients with hyperhidrosis compared to controls. In another controlled study [18], Karaca et al assessed the activities of antioxidant enzymes and lipid peroxidation end product levels in erythrocytes of hyperhidrotic patients and healthy controls. Their results support the hypothesis that oxidative damage, resulting from increased reactive oxygen species production along with insufficient capacity of antioxidant mechanisms may be involved in the pathogenesis of PH. In a further study, the same group [19] identified significantly increased plasma nitric oxide (NO) levels in hyperhidrotic patients in comparison with the control group.

Neurological Dysfunction

In a study by de Marinis et al. [20] qualitative and quantitative (skin conductance) sweat tests were performed in a group of hyperhidrotic patients compared to a control group. Cardiovascular autonomic function tests, orthostatism, tilt to 65°, cold pressor test, deep breathing, Valsalva maneuver, and hyperventilation, were performed. According to their results, the authors concluded that PH seems to be a complex dysfunction that involves autonomic pathways beyond those related to sweating. Similar results were reported by Birner et al [21]. Based on sympathetic skin response to excitatory stimulation tests in hyperhidrotic subjects and controls, before and after T_2-T_3 sympathectomy, Lin et al [22], hypothesized that PH may be due to a regulatory dysfunction, rather than to purely overfunction. In another neurological study of the foot, Iwase et al [23] compared simultaneous skin sympathetic nerve activities from the tibial and peroneal nerves in patients with primary palmoplantar hyperhidrosis and in controls. They observed an excessive response to both mental and thermal stimuli of the skin sympathetic activity to the soles (tibial nerve) in the hyperhidrotic patients as compared to controls. However, only a slight change was recorded in the peroneal nerves, which innervate the dorsum of the foot (not hyperhidrotic area). Based on their results, they concluded that an excessive response in sympathetic nerve activity to the palmar and plantar skin to both mental and thermal stimuli may be responsible for the profuse sweating. Another study on patients with PH [24], showed perceptual abnormalities and exaggerated sudomotor reactions to thermoalgesic stimulation, consistent with central sensitization of sympathetic circuits. Sympathectomy was found to reduce the sympathetic outflow and induce normalization of sensory perception, but it did not modify the abnormal control of efferent sudomotor activity, thus confirming the central neurological dysfunction in patients with PH. A further study by Manca et al [25], demonstrated enhancement of the sudomotor skin response recovery curve in patients with PH, suggesting hyperexcitability of the somatosympathetic polysynaptic pathway involved in sweating.

Personality Dysfunction

There are few studies which have examined the possibility of a personality traits as an etiological factor for PH and only one (26) raised this possibility. Ak et al [26] compared the temperament and characteristics of hyperhidrotic patients to a group of healthy individuals. Their results suggested a difference between the two groups. They concluded that the results indirectly raise the possibility that personality traits may underlie biological mechanisms. However, other reports either refuted it [27, 28] or considered the psychological differences to be the result of hyperhidrosis and not its cause [29].

Discussion

Sweat is produced by glands in the skin distributed all over the entire body. They are most numerous on the soles, forehead, axillae, palms, and cheek (30). Their total number is considered to be between two to four million, of which only 5% are active at the same time [30]. There are two main types of sweat glands: eccrine and apocrine. The eccrine glands are distributed on almost the entire body and are the only glands to be found on the hands [31]. These glands produce a watery secretion into the skin surface in response to stimuli such as heat, exercise, or emotional stress [31]. The apocrine glands are found less widely, mainly in the axilla, breasts, vermilion border of the lips, perineum, and occasionally the face, but never on the hands [31]. They produce small volumes of viscid fluid into the hair follicle rather than the skin surface [31]. A third type of glands, apo-eccrine, was described to constitute 45% of the axillary sweat glands [31]. However, a later study examining serial sections of axillary skin [32], found no evidence of their existence. It is, therefore, the eccrine sweat glands that are the source of overperspiration.

Emotional stimuli, mental activity, and heat activate the hypothalamic sympathetic center, provoking sweat production. The sweating pathway originating from this center descends uncrossed through the medial portion of the lateral funiculus of the brain stem to synapse upon preganglionic neurons in the intermediolateral column of the spinal cord [33]. Ipsilateral cholinergic axons from these neurons activate the paravertebral sympathetic ganglion cells, ultimately triggering the sympathetic cholinergic sudomotor axons terminating in the sweat glands [14]. These anatomical structures make up the sudomotor chain. Accordingly, sudomotor disorders may involve the frontal operculum, hypothalamus, brain stem, spinal cord, sympathetic chain ganglia, peripheral nerves, or eccrine sweat glands [33]. The etiology of PH should therefore be sought in changes along these structures.

The data provided by the studies compiled in the present review are preliminary, but clearly point to possible histoanatomical and physiological differences, as well as possible metabolic-enzymatic and neurological dysfunctions present in subjects with hyperhidrosis compared to persons with normal perspiration. These differences may be classified in three major groups:

a. A hereditary-genetic trait with identified pathological foci-alleles in some chromosomes, which may be the underlying cause of these anomalies.
b. A larger number of ganglion cells in the ganglia of hyperhidrotic subjects, also found to be larger than in controls, and a thicker myelin sheath of involved axons.
c. A higher expression of acetylcholine receptor subunits in the sympathetic ganglia of subjects with hyperhidrosis

The data do not support personality traits as an etiological factor. The presence of certain traits may be a result and not a cause of PH.

The etiology of PH is still obscure. However, the data so far accumulated have elucidated some paths in which further studies are required to clarify the role of the anatomical and enzymatic characteristics in patients with primary hyperhidrosis, which may provide a better method of treatment in future.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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