Clin Auton Res (2003) 13 : 96–98
DOI 10.1007/s10286-003-0082-x

RESEARCH ARTICLE

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Primary hyperhidrosis

Evidence for autosomal dominant inheritance

Received: 8 November 2002
Accepted: 10 January 2003

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Abstract Primary hyperhidrosis is a neurogenic disorder of unknown cause characterized by excessive sweating in the palmar surface of the hands, armpits, groin and feet. In the course of a therapeutic trial for primary hyperhidrosis, 62 % of patients reported a positive family history. Examination of these pedigrees demonstrated a sibling recurrence risk of $\lambda s = 29–48$ and an offspring recurrence risk of $\lambda o = 41–68$ indicating that hyperhidrosis can be an inherited condition. The pattern of inheritance suggests an autosomal dominant mode of transmission with incomplete disease penetrance.

Key words hyperhidrosis · genetic · inheritance · autosomal dominant

Introduction

Primary hyperhidrosis is a neurogenic disorder of unknown cause characterized by excessive discharge of sympathetic cholinergic sudomotor nerves, most often in the palmar surface of the hands, armpits, groin and feet. Patients sweat excessively in response to thermal and emotional stimuli but also spontaneously with no apparent trigger [4]. Sympathetic cholinergic nerves activate both thermoregulatory and emotional sweating but these stimuli produce sweating in different distribution in the body and are controlled by different neurons in the CNS. Primary hyperhidrosis is likely due to abnormal central control of emotional sweating because it affects the same body areas as emotional rather than thermoregulatory sweating. The disorder frequently begins in early childhood and affects 0.6 to 1 % of the general population [8]. Hyperhidrosis can considerably reduce quality of life and may result in serious emotional and social problems as well as functional impairment. Treatments with topical antiperspirants and systemic anticholinergic drugs are largely ineffective [10], and severe cases only respond to local subcutaneous injections of botulinum toxin [9], which have to be repeated at regular intervals, or surgical sympathectomy which may have severe intra and postoperative side effects [6, 10].

There is some consensus in the field that the disease is often inherited in an apparent autosomal dominant manner and the online database of mendelian inheritance in man (OMIM, http://www.ncbi.nlm.nih.gov/omim/) describes hyperhidrosis as "a clear familial disorder". However, evidence of heredity in primary hyperhidrosis, including the OMIM reference, is based on personal communications or anecdotal evidence with only one recently published report providing substantiation of heredity for this condition [8]. Here we provide

evidence that severe primary hyperhidrosis is an inherited disorder with apparent autosomal dominant transmission and a high level of disease penetrance.

Methods

The study included twenty-one patients (10 males, 11 females) with severe palmar hyperhidrosis (age 30 ± 7 years, mean ± SD) that had sought treatment in an experimental trial with botulinum toxin [9]. All had a history of excessive sweating of the hands for more than three years, confirmed by clinical observation and an iodine-starch test. Exclusion criteria included secondary hyperhidrosis (e.g., hyperthyroidism), neuromuscular disease, and satisfactory therapeutic response to oral anticholinergics or beta-blockers. The Mount Sinai School of Medicine Institutional Review Board approved the project, and all patients signed an informed consent. We questioned 21 patients regarding their family history for hyperhidrosis. Empiric and recurrence risk were calculated to provide an estimate of the increased risk of disease in a sibling or child of an affected family member versus that in the general population. These values were intended to provide a measure of the familial aggregation of hyperhidrosis. This calculation was based on an estimate of population prevalence ranging from 0.6% to 1% [8].

Results

Thirteen of 21 patients reported a positive family history of hyperhidrosis (62%). A total of 45 cases were identified in these kindreds. Males (n = 21) and females (n = 24) were affected equally. In addition to comparable sex distribution, male-to-male transition was observed in two families. Seven of the families fitted a typical autosomal dominant pattern of inheritance, the trait being inherited in every generation (Fig. 1). There were six families in which two or more members were affected but the trait had 'skipped' a generation suggesting either autosomal dominant transmission with reduced disease penetrance or an autosomal recessive disease with a high disease allele frequency.

Examination of these pedigrees demonstrated a sibling recurrence risk of $\lambda s = 29–48$ and an offspring recurrence risk of $\lambda o = 41–68$ (Table 1).

Discussion

The data described here provides evidence that severe primary hyperhidrosis is most frequently a hereditary disorder. Because male-to-male transmission was seen in two families, X-linked inheritance is unlikely. Mitochondrial transmission is not likely either, as the trait was not passed through women only, and was not inherited by all children of affected females. Seven of the families fitted a typical autosomal dominant pattern of inheritance. There were six families in which two or more members were affected but the trait had 'skipped' a generation, thus reduced penetrance is likely but this may also be a result of under-reporting by some family mem-

Table 1 Recurrence risk for siblings and offspring. To simplify analysis, pedigrees were broken into small nuclear families. Recurrence risk was calculated using an estimate of disease occurrence ranging from 0.6–1 % (2)

Relationship	Unaffected	Affected	Empiric Risk	Recurrence Risk
Sibling	32	13	0.29	λs 29–48
Offspring	33	23	0.41	λo 41–68

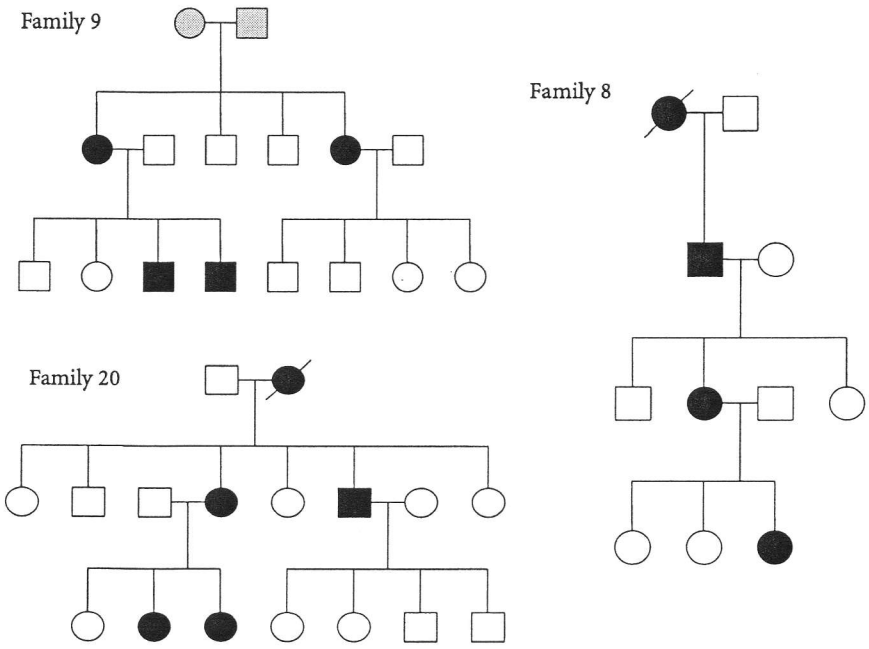

Fig. 1 Sample pedigrees demonstrating clustering of disease suggestive of autosomal dominant inheritance. Black symbols represent affected, gray unknown

bers. Autosomal recessive inheritance combined with high disease allele frequency remains a possibility but the presence of families with disease in three generations makes this unlikely. A third possibility is that primary hyperhidrosis is a genetically heterogeneous disease and may be transmitted by various modes of inheritance. Calculation of empiric and recurrence risk (Table 1) clearly demonstrate that this disorder possesses a familial component although sampling bias may indicate that the inheritance pattern observed here is only representative of the most severe cases. Family history was taken by proband questionnaire but the hyperhidrosis observed in these patients was severe and disease status was unequivocal upon examination. Thus, false positive scoring of relatives by the proband is unlikely.

Ro et al. reported a similar incidence of positive family history, 65 %, in a sample of 49 patients with hyperhidrosis that had undergone thoracoscopic sympathectomy [8].

Hyperhidrosis has been associated with other genetic autosomal dominant conditions such as nail patella syndrome [7], Weaver syndrome [3], pachyonychia congenita [1], and Book syndrome [2], and autosomal recessive conditions such as Mal de Meleda [11]. In these disorders, however, sweating is only one feature of complex hereditary dermatologic syndromes (genodermatoses). Isolated hyperhidrosis triggered by emotions has been reported as a hereditary entity in one case report [5].

In summary, although our sample ascertainment may bias towards the most severe cases, our study suggests that primary hyperhidrosis is a genetic disorder with an autosomal dominant mode of inheritance exhibiting either reduced penetrance or variable expressivity. Sample ascertainment followed by a systematic genome screen should lead to localization of the disease gene and ultimately to the identification of the causal defect(s).

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