Palmar hyperhidrosis: Evidence of genetic transmission

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Background: Primary palmar hyperhidrosis is a condition marked by excessive perspiration and is reported to have an incidence of 1% in the Western population. It is a potentially disabling disorder that interferes with social, psychological, and professional activities. Over the past several years, several investigators have reported a positive family history in their patients treated for hyperhidrosis. To date, the cause is unknown; furthermore, epidemiologic data are scarce and inadequate.

Methods: To characterize the genetic contribution to hyperhidrosis, we conducted a prospective study of 58 consecutive patients with palmar, plantar, or axillary hyperhidrosis treated with thoracoscopic sympathectomy from September 1993 to July 1999. Forty-nine of the 58 probands volunteered family history data for these analyses (84% response rate). A standardized questionnaire was administered during the postoperative visit or by phone interview, and a detailed family history was obtained. The same questionnaire was also administered to a set of 20 control patients. The familial aggregation of hyperhidrosis has been quantified by estimating the recurrence risks to the offspring, parents, siblings, aunts, uncles, and cousins of 49 probands and 20 controls. We estimated the penetrance by use of a genetic analysis program.

Results: Thirty-two of 49 (65%) reported a positive family history in our hyperhidrosis group, and 0% reported a positive family history in our control group. A recurrence risk of 0.28 in the offspring of probands compared with frequency of 0.01 in the general population provides strong evidence for vertical transmission of this disorder in pedigrees and is further supported by the 0.14 risk to the parents of the probands. The results indicate that the disease allele is present in about 5% of the population and that one or two copies of the allele will result in hyperhidrosis 25% of the time, whereas the normal allele will result in hyperhidrosis less than 1% of the time.

Conclusions: We conclude that primary palmar hyperhidrosis is a hereditary disorder, with variable penetrance and no proof of sex-linked transmission. However, this does not exclude other possible causes, and we anticipate that genetic confirmation of this disorder may lead to earlier diagnoses and advances in medical and psychosocial interventions. (J Vasc Surg 2002;35:382-6.)

Primary palmar hyperhidrosis is a condition marked by excessive perspiration beyond physiological need and is reported to have an incidence of 0.6% to 1.0% in the Western population.[1,2] The excessive sweating often begins in childhood and is primarily of the upper extremities but may involve the plantar surfaces and axillae as well. The degree of sweating is variable, ranging in severity from moderate moisture to severe dripping, and it can be aggravated during periods of stress and anxiety. Although the pathophysiology of the condition is uncertain, it is believed that the overactivity of the sympathetic cholinergic fibers passing through the upper dorsal sympathetic ganglia at T2-T3 causes abnormal innervation of the eccrine glands responsible for sweat secretion resulting in subsequent vasoconstriction and cooling of skin.[3] In a study conducted by Lin and Fang,[4] abnormal sympathetic skin responses have been shown in patients with hyperhidrosis and may be due to regulatory dysfunction, as well as sympathetic hyperactivity. It has also been postulated that the center in the hypothalamus that controls sweating of the palms and soles is regulated by cortical input and thus differs from the other hypothalamic sweat centers.[5] Further evidence has also revealed that on challenge with hyperventilation, patients with hyperhidrosis show abnormal wave bursts on electroencephalography and possible hyperperfusion of the frontal cortex.[6]

Although considered a benign condition, the psychologic, social, and professional burden to those afflicted with hyperhidrosis can be disabling. There are numerous conservative therapies used in the treatment of hyperhidrosis, including antiperspirants, tap water iontophoresis, botulin toxin A, anticholinergic drugs, and psychotherapy[7-13]; however, most patients seldomly find permanent relief from conservative management because the palliative effects are usually transient and successful only for mild cases. Thoracoscopic sympathectomy is now primarily performed for treatment of palmar hyperhidrosis by resecting the sympathetic chain and ganglia in the upper thoracic region (T2-T3) to increase blood flow through the cutaneous

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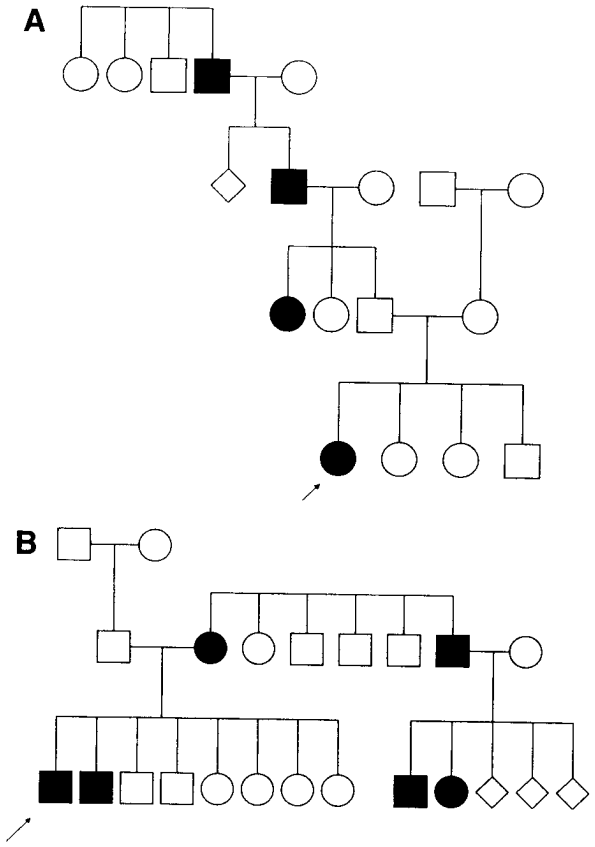
Table I. Patient characteristics

Total patients	58
Average age	31.7 y (range 16-66 y)
Males	62%
Hyperhidrosis type	
Palmar only	45% (26)
Palmar and plantar	50% (29)
Palmar and axillae	3.4% (2)
Palmar, plantar, and axillae	1.7% (1)
Questionnaire response rate	84%
Positive family history	65%

Table II. Ethnicity of patients with hyperhidrosis

White	53% (31)
Asian/Pacific Islander	31% (18)
Hispanic	6.9% (4)
Middle Eastern	6.9% (4)
Black	1.7% (1)



Pedigree shows strong degree of familiarity.

arteriovenous fistula and decrease sweating in the ipsilateral hand. Application of this technique has been fueled by impressive technical and patient satisfaction rates, with success rates ranging from 71% to 100%.[14] Possible short-term complications include pneumothorax, hemothorax, subcutaneous emphysema, pleural effusion, and segmental atelectasis. Incomplete reinflation of the collapsed apical lobe will result in postoperative complications from atelectasis and pneumothorax. Rare complications include false aneurysm of the intercostal artery and inferior brachial plexus injury. Long-term complications include compensatory sweating in the trunk or lower extremities, intercostal neuralgia, and Horner's syndrome. Compensatory hyperhidrosis is the most common and unpredictable side effect and is reported in 0% to 74.5% of cases, with anecdotal evidence suggesting that the sweating subsides over time.[14]

To date, the cause of hyperhidrosis is unknown; furthermore, epidemiologic data are scarce and inadequate. Over the past several years, different investigators have reported positive family histories in their patients treated for hyperhidrosis, ranging from 5% to 50%; however, no further empirical data have been offered.[15-20] To characterize the genetic contribution to hyperhidrosis, we conducted a prospective study of 58 consecutive patients with palmar, plantar, and axillary hyperhidrosis treated with thoracoscopic sympathectomy from September 1993 to July 1999.

METHODS

Study population. The University of California at Los Angeles (UCLA) Center for Health Science Study on hyperhidrosis is a prospective study consisting of 58 patients who received treatment at the UCLA Medical Center from September 1993 to July 1999. Patient characteristics are shown in Tables I and II. Four additional patients were evaluated for hyperhidrosis but were not included in this study because these patients did not receive treatment at our institution, and follow-up data were unattainable after their initial visit. Indication for surgery was severe and debilitating primary palmar hyperhidrosis with failed conservative management with psychosocial sequelae. The population consisted of 35 white or Middle Eastern persons, 18 of Asian/Pacific Island origin, 4 Hispanics, and 1 black person (36 males and 22 females), with a mean age at operation of 31.7 years (range 16 to 66 years). All 58 patients were ruled out for hypermetabolic states by history, thyroid function test results, and physical examination and were found to be otherwise healthy with no other significant medical condition. The senior author personally observed profuse, nonphysiological sweating in each patient; in each case, it was quite obvious, and starch iodine and other tests for sweat chloride were not performed. However, the first author did not grade the degree of sweating in each patient, and thus no association between this and family history was made. Various tools have been devised to support the diagnosis of palmar hyperhidrosis, including metal corrosion tests and starch-iodine tests; however, such quantitative assessments are now considered obsolete as the excessive perspiration is visually obvious and an accurate diagnosis can be made by careful history and physical examination.[2] Furthermore, reported symptoms were unanimously socially or professionally disabling, with most patients undergoing extensive failed medical therapy before surgical intervention.

Table III. Recurrence risks for each class of relatives in 49 hyperhidrosis pedigrees

Class	*No. relatives*	*No. of affected relatives*	*Empiric risk*
Offspring	32	9	0.28
Parents	98	14	0.14
Siblings	148	10	0.07
Aunt/Uncle	224	9	0.04
Niece/Nephew	93	5	0.05

These 58 patients underwent minimally invasive thoracoscopic sympathectomy by use of the techniques previously described by Ahn et al.[21] Of those patients treated at the UCLA Medical Center to date, the success rate has been 100% with no recurrence of symptoms. All patients had an excellent immediate sympatholytic response, further confirming their preoperative diagnosis.

We also obtained 20 control subjects who were seen by the senior author at the UCLA Medical Center for treatment of thoracic outlet syndrome. The control patients were chosen randomly from a group of patients with thoracic outlet syndrome and with demographics similar to our study population (87% response rate, 30% males, mean age 35 years, range 16 to 59 years); they were then administered the same questionnaire as our affected group. The controls consisted of 16 white persons, 2 Asians, and 2 individuals of Middle-Eastern descent. Patients in both the hyperhidrosis and control groups were otherwise healthy.

Measurements. Forty-nine of the 58 probands volunteered family history data for these analyses (84% response rate). Each of the 49 families in the study was ascertained through a proband with clinically validated hyperhidrosis. A standardized questionnaire was administered during the postoperative visit or by phone interview, and a detailed family history was obtained. The proband was queried with regard to the structure of his or her pedigree, and first- and second-degree relatives of the proband were identified. Patients were asked age, sex, ethnicity, medical history, marital status, number of children, number of aunts and uncles, number of siblings, and the number of siblings' children. The proband was then asked to individually identify the affected and nonaffected family members. Forty-nine pedigrees with 32 offspring, 98 parents, 148 siblings, 224 aunts and uncles, and 93 nieces and nephews have been analyzed. Hyperhidrosis status was ascertained in the relatives of the proband by the proband, who were all personally knowledgeable and familiar with the diagnosis of hyperhidrosis. If the proband was uncertain of the hyperhidrosis state of specific family members, these relatives were considered unaffected.

Method of analysis. The familial aggregation of hyperhidrosis has been quantified by estimating the recurrence risks to the offspring, parents, siblings, aunts, uncles, and cousins of 49 probands. The estimates have been made without regard to ethnic group or sex, because we found no evidence of ethnic variation in our series. Because most of the pedigrees with multiple affected members show transmission from generation to generation, we have postulated that the susceptibility for development of hyperhidrosis may result from the effects of a major gene. However, a recurrence risk of 50% in the first-degree relatives, which is consistent with dominant inheritance, has not been observed, indicating that this major gene may not be fully penetrant or others may have been affected but not identified. We have estimated the penetrance, or the likelihood for development of hyperhidrosis, given the postulated predisposing major gene, by use of the MENDEL package of genetic analysis programs.[22] The disease allele frequency and penetrance of the homozygotic and heterozygotic disease genotypes and normal genotype were estimated by maximizing the likelihood of the observed pattern of inheritance in the pedigrees, and the standard errors of the estimates have been calculated numerically.

RESULTS

Thirty-two of 49 patients (65%) reported a positive family history. Several of the 17 patients with no known family history had a limited recall of the structure of their extended family, one patient was adopted, and another was born to a mother who herself was adopted. There was no reported consanguinity.

The Figure shows pedigrees that illustrate a particularly strong degree of familial aggregation. Included in the Figure are affected individuals in generations beyond those used in the analyses. The recurrence risks for each of the classes of relatives studied in these analyses are reported in Table III. These data provide ample evidence that primary hyperhidrosis is familial. A recurrence risk of 0.28 in the offspring of probands compared with a frequency of 0.01 in the general population provides strong evidence for vertical transmission of this disorder in pedigrees and is further supported by the 0.14 risk to the parents of the probands. This estimate is attributed to the fact that one half of the parents of the probands will probably not carry the major gene contributing to hyperhidrosis so that the risk to parents in the adjusted sample is 0.28, the same risk as that of the offspring. The risk to siblings is 0.07, which is quite low compared with the other first-degree relatives. The relatively low risk to siblings may be explained if the proband has only limited recall of his/her family or is unaware of the hyperhidrosis status of his or her siblings. Aunts, uncles, nieces,

and nephews, all having the same degree of relationship to the proband, have a similar recurrence risk (0.04 vs 0.05). These individuals share 0.25 of their genes with the proband, so a penetrance of 0.25 estimated by the pedigree analysis should result in an empiric risk of 0.06, which is fairly consistent with the estimated risk.

Our estimated penetrance of 0.25 for hyperhidrosis can be compared with those of known familial disorders such as breast cancer (*BRCA1* gene), schizophrenia, and idiopathic torsion dystonia (*DYT1* gene), which have been estimated at 0.7 (by age 70), 0.31 to 0.51 (dominant inheritance), and 0.46, respectively.[23-25] Although the penetrance value in our study population is less than with these familial disorders, it is suggestive of a familial aggregation with a possible multigenic mechanism.

Among the 20 control families ascertained for hyperhidrosis, there were 40 parents, 45 siblings, 18 offspring, and 47 nieces and nephews. Each control proband was questioned about hyperhidrosis in similar fashion to those families ascertained for the disorder. No one reported a relative with hyperhidrosis, indicating that the risk to relatives in the general population is low compared with that in the families with hyperhidrosis. These data indicate that the frequency of hyperhidrosis of first degree relatives in the general population is at most 3% with 95% confidence, and may even be considerably lower. The fact that no one in our control group had this condition may be attributed to sampling variability or underreporting. The risk in our sample of first degree relatives of hyperhidrosis patients is clearly much higher at 12%.

Table IV delineates the penetrance estimates of the disease gene for the possible genotypes. The result of this analysis indicates that the disease allele is present in about 5% of the population and that one or two copies of the allele will result in hyperhidrosis 25% of the time, whereas the normal allele will result in hyperhidrosis less than 1% of the time.

Table IV. Estimated allele frequency and genotype penetrance of major susceptible gene

Genotype	*Estimate*	*Standard error*
Dx allele frequency	0.048	0.036
Dx/dx penetrance	0.2543	0.59
Dx/nl penetrance	0.2540	0.083
Nl/nl penetrance	0.0049	0.006

Dx, Diseased; *nl*, normal.

DISCUSSION

In McKusick's *Mendelian Inheritance in Man*,[26] palmar and plantar hyperhidrosis (144110) is identified as a "clear familial disorder" with implications of an autosomal dominant origin. Additional studies have also suggested a genetic cause.[15-20] As far back as 1967, Mailander[27] reported a case of hereditary gustatory hyperhidrosis in a three-generation pedigree with five affected individuals; furthermore, the author reported an instance of a skipped generation with no proof of sex-linked transmission. However, this conclusion was drawn solely on the basis of anecdotal evidence; the absence of sound empirical evidence or data has made such suggestions inconclusive.

In further support of a possible genetic cause, some investigators have estimated a higher incidence of hyperhidrosis among specific populations, especially among Asians. McKusick[26] claims there may be an unusually high frequency among the Chinese, and Cloward[28] reported a greater development of hyperhidrosis in Japanese-American persons living in Hawaii compared with non-Japanese Hawaiian residents. There is no evidence to suggest there is a higher prevalence among men versus women.

Several other diseases and syndromes have been associated with hyperhidrosis. Noppen and Vincken[20] described two patients with Turner's syndrome who also were diagnosed with palmar hyperhidrosis. Although they acknowledge the possibility that the two patients affected (of the 150 patients with Turner syndrome studied) may be coincidental, the apparent rarity of both disorders suggests that this association may be more common than previously reported. Several genetic disorders are also associated with the manifestation of hyperhidrosis including pachydermoperiostosis, pachyonychia congenita, inflammatory familial palmoplantar keratoderma, ectodermal dysplasia, Book syndrome, Meleda disease, and nail patella syndrome.[29-34] Most recently, Stromme et al[35] in their description of the localization of the cross-linked mental retardation disease gene *Xp11.4-Xp22.11* found that 12 of the 13 patients examined had a history of hyperhidrosis. A pedigree analysis suggested that the disorder segregated independently as an autosomal dominant trait and was not inherited as a cross-linked trait.

Hyperhidrotic disorders are associated with previous spinal cord injuries such as posttraumatic syringomyelia, autonomic dysreflexia, and peripheral neuropathies, including familial dysautonoma.[5,36] Systemic illness, brain lesions, or intrathoracic neoplasms are also known to cause generalized hyperhidrosis.[5] All 58 patients in our study were otherwise healthy and had idiopathic primary hyperhidrosis not caused by another disease or pathologic state.

If hyperhidrosis is truly a condition caused by hyperactivity of the sympathetic nervous system, the peripheral catecholamine levels in patients with hyperhidrosis should exceed normal levels. In another recent study, Noppen et al[37] measured plasma catecholamine level in patients with primary hyperhidrosis before and after thoracoscopic sympathectomy and found the levels of norepinephrine to be markedly reduced, whereas that of epinephrine were unchanged. The authors concluded that primary hyperhidrosis is not related to general sympathetic overactivity but results from a localized overactivity of the upper dorsal ganglia.

This preliminary study has several limitations. The hyperhidrotic status of the family members was limited to the recall of our proband. We were unable to determine a definitive clinical diagnosis of the family members reported positive for hyperhidrosis. We did not contact the relatives of the proband given that many of them were deceased,

lived outside of the United States, or had been out of contact with their relatives. Because of the embarrassing nature of this condition, affected individuals have historically been reluctant to discuss this condition with others and often deny having any abnormal sweating. As a consequence, our data may have been affected by recall bias and nonresponse bias by those who did not answer our questionnaire, and the true penetrance of the disorder might be underestimated. Consideration must also be given to the potential for ascertainment bias, with subjects admitted for surgical intervention of hyperhidrosis potentially more likely to provide information of a positive family history when queried. Nonetheless, our data should reflect an accurate prevalence of familial hyperhidrosis given a response rate of 84% and a prevalence of hyperhidrosis of 0% in our control population. Many affected individuals are hesitant to seek treatment; therefore the prevalence of 1% reported in the current literature may be a gross underestimation. Our observed penetrance of 25% and allele frequency of 5% suggest a higher true prevalence of the condition.

With increasing awareness among physicians and patients of treatment options, we expect the identification of individuals with hyperhidrosis to increase substantially and future studies to become more reliable. We believe the data help support the theory that hyperhidrosis is indeed a real clinical disorder with a physiological basis, not a disorder of behavioral origin. Surgical treatment has provided long-lasting effects in all our patients, further sustaining a biologic basis of the disorder. We anticipate that this study will help remove some of the stigma associated with primary hyperhidrosis, enable patients and physicians to accept the disorder as a medically validated condition, and encourage patients to seek treatment.

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