Emotional Eccrine Sweating

A Heritable Disorder

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A family with hereditary emotional hyperhidrosis is described. The inheritance pattern is autosomal dominant. A simple quantitative palmar sweat test was used to objectively confirm historical data. Of two family members tested, both had a marked decrease in palmar sweat secretion during administration of diltiazem, a calcium-channel blocker. Additional studies in a large group of patients are needed to extend this observation. (Arch Dermatol 1987;123:925-929)

Hyperhidrosis, or excessive sweating, may be generalized or localized in its extent. It may be secondary to a systemic disease or occur as a primary idiopathic process. Among the localized forms of idiopathic hyperhidrosis is emotional hyperhidrosis (EH), which is usually restricted to the palms, soles, and/or axillae. Current therapy for EH is not regularly successful, and patients may suffer continued embarrassment and disruption of their school, work, and social lives. It is not uncommon; one study estimated the incidence of EH in Israel to be 0.6% to 1.0%. More than 700 cases have been reported in the surgical literature in the past 15 years.

The diagnosis of this disease is made by clinical observation of dripping palms or large underarm stains on clothing. Although many reports state that EH may be familial, there are no published pedigrees. We describe a family with an autosomal dominant form of EH. A quantitative measurement of palmar sweat secretion was used to objectively verify the clinical history and qualitative observations.

Sato elucidated the central role of calcium flux in eccrine secretion. The movement of extracellular calcium into the secretory cell is an essential event mediating the stimulatory signal and the final active secretion of ions and water by the secretory cell. Sato also showed that prostaglandin E1 has a strong sudorific effect.

Calcium-channel blockers are a relatively recent addition to our therapeutic armamentarium. Prostaglandin inhibitors, although used in the treatment of other disorders for years, have not been thoroughly evaluated for possible beneficial effects in hyperhidrosis, despite anecdotal reports of effectiveness.

The quantitative sweat test was used to evaluate the response of palmar sweating to several medications in two of the family members. During administration of diltiazem, a calcium-channel blocker, there was a marked decrease in sweat secretion. The combination of indomethacin and aspirin was not effective. Calcium-channel-blocking agents, possibly by preventing the essential initial step of calcium influx into the eccrine secretory cell, may be useful in the treatment of hyperhidrosis.

PATIENTS AND METHODS

A 16-year-old man had severe palmar, plantar, and axillary hyperhidrosis, which had been present since birth. There was a strong family history for this condition, and the extended family was studied under a protocol approved by the Walter Reed Human Use Institutional Review Board. A thorough history was obtained from each family member, including complaints referable to hyperhidrosis, duration of symptoms, areas of body affected by increased sweating, and the presence of any history (personal or family) or sensory or motor deficits of the lower extremity and tooth, nail, foot, or hair abnormalities. After written informed consent was obtained, a physical examination was performed, including inspection of hair, teeth, nails, and feet, as well as the performance of a palmar sweat test (defined below). Blood was obtained for typing.

A palmar sweat test was devised as a simple, inexpensive, quantitative determination of palmar sweating. The patients were seated with palms held supine. One 4 × 4-in gauze pad was placed on a previously dried palm and taped to the hand. A surgeon's latex glove (size 8½) was placed over the hand and taped closed at the wrist. By

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weighing the gauze, glove, and tape on an electronic digital scale prior to application and immediately after removal from the hand 20 minutes later, the amount of sweat absorbed by the gauze and retained in the glove could be determined. The palmar sweat reading was then compared with baseline normal data obtained by similarly testing 14 unaffacted controls (aged 26 to 34 years). Neither family members nor controls were taking medication at the time of testing. Any reading greater than 3 SDs from the mean controls was considered objective evidence of hyperhidrosis.

The family study was performed over a three-day period in the fall. Environmental humidity and temperature readings were obtained at each test site (five family homes, all within a three-state area of the northwestern United States).

Two family members, the proband and his mother, were admitted to the hospital for evaluation. The patients underwent a thorough history and physical examination; blood tests consisting of a complete blood cell count, an automated analysis of the serum that included electrolyte values, liver and kidney function tests, fasting serum glucose, and blood fat tests. A thyroid panel screen; a urinalysis; chest, lateral skull, and anterior-posterior knee roentgenograms; electrocardiogram; and echocardiogram were also obtained. During this three-day period of initial evaluation, seven baseline palmar sweat tests were performed for each patient. The patients had taken no medications for five days prior to admission.

During this second inpatient phase of the evaluation, the palmar sweat test was applied to both hands simultaneously and the sweat value used was the mean reading for both hands. All measurements were obtained by the same investigator (W.D.J.), in the same location, under the same environmental conditions (temperature, 22.5°C and 13% humidity) throughout this portion of the study. Blood pressure and heart rate were assessed prior to each test. A different group of 11 normal control subjects who were receiving no medications (aged 26 to 34 years) were tested by the same investigator (W.D.J.) under identical environmental conditions in the same location.

Following the initial evaluation, several different oral medications were given to the patients in a single-blind manner, and sweat tests were performed to determine a response or no response. The first medication tested was propantheline. On day 4, two doses (15 mg and 30 mg) were administered at an interval of six hours. Sweat tests were performed immediately before and one hour after administration of propantheline, as was done on all subsequent challenges. A washout period of 36 hours followed the 30-mg propantheline dose.

On day 6, 50 mg of indomethacin and 650 mg of aspirin were given together three times at nine-hour intervals. This was followed by another 36-hour washout period.

On day 8, lactose-containing placebo was administered twice at six-hour intervals. The following day, treatment with the calcium-channel blocker, diltiazem, was initiated; it was administered every six hours for three days. On the first day of treatment, each dose of diltiazem was 30 mg; on the final two days, each dose was 60 mg. Sweat testing was done in the morning, afternoon, and evening of the first two days and in the morning and afternoon of the third day. Electrocardiograms were obtained daily during this last three-day period.

RESULTS

The clinical history of the proband reveals that the onset of hyperhidrosis was noted by the mother in the newborn nursery, when the baby's cloth shoes were soaked soon after she put them on his feet. The older sister had the same history and age of onset. The family suffered from problems in the social, school, and occupational spheres. Sweating was minimal during sleep and on awakening. During waking hours, sweat secretion was high and any type of social interaction provided a strong stimulus to maximally sweat. All affected family members except one suffered from increased sweating of the palms, soles, and axillae. The proband's 51-year-old aunt complained only of abnormal plantar sweating, relating that she had to change her shoes several times a day due to moisture accumulation.

Through history and physical examination, hereditary syndromes associated with hyperhidrosis were eliminated. There were no abnormalities in the family related to early graying of the hair, nail dystrophy of any type, high arched feet, or dental changes. There were no sensory or motor changes of the lower extremities, and no one in the family had required leg braces because of deficits in this regard.

The data from the sweat tests are included in the pedigree. The mean amount of measured sweat for the control group (N = 14) was 0.100 g (SD, 0.045). The mean for the six members of the family with palmar hyperhidrosis was 0.775 ± 0.620 g (SD, 1). This difference was significant by Student's t test (P = .001). The tests were obtained at an average temperature of 29.5°C (range, 18°C to 21°C) and an average humidity of 48% (range, 34% to 58%).

Blood typing was done to determine if linkage between EH and ABO blood type could be demonstrated. Linkage to the ABO locus was not confirmed, but could not be rejected by the data obtained.

All inpatient initial baseline laboratory test results of the mother and son were normal. The 16-year-old boy had severe hyperhidrosis as evidenced by his medical history, examination, and palmar sweat test readings. During the baseline testing, it was difficult for him to put on the gloves because of the moisture accumulated on them during the few seconds required to tape the gauze in place. By the end of the 20-minute test, the gauze and gloves were grossly wet. His inpatient baseline mean sweat weight (SW) was 0.454 g, compared with the control group, whose mean was 0.172 g (range, 0.09 to 0.23 g). In the control group, the gloves were often not perceptibly moist by the end of testing.

Propantheline, an effective medication on an outpatient basis, did show an objective decrease in SW after propantheline administration. Sweat tests performed with regard to propantheline disclosed the following SWs: before administration of a 15-mg dose the patient's SW was 0.355 g; after administration, 0.185 g; before administration of a 30-mg dose, 0.456 g; after administration, 0.25 g.

Indomethacin and aspirin did not prevent sweating (mean three postdose readings, 0.485 g). Placebo readings were elevated from the baseline values, with the mean being 0.690 g.
Graves' disease, acromegaly, pheochromocytoma, hypoglycemia, salicylism, and lymphoma. In the idiopathic localized form, emotional stimuli will exacerbate the condition. While often viewed as a condition causing only social embarrassment, schoolwork, and job performance may be negatively affected. The simple task of writing on paper is often impossible due to the excessive moisture dripping onto the paper.

Several authors have suggested that EH may be familial. Cloward reported that 19 (23%) of his 82 patients with EH had one or more relatives with EH. Adar et al. stated that 58 of 100 patients had some family history of hyperhidrosis, 21 of whom had a strong family history of severe palmar hyperhidrosis in first-degree relatives. In four families, several siblings were affected. In the series reported by Shih and Wang, 61 of 264 patients had a strong family history of severe hyperhidrosis in first-degree relatives. Although Solomons' studied 12 families with hyperhidrosis and stated that it was transmitted by an autosomal-dominant gene, this work was apparently published only in abstract form. No pedigrees of this condition could be found in the indexed medical literature; thus, a familial form is not mentioned by the authors of several major textbooks.

The family described by us has subjective and objective evidence of palmar hyperhidrosis in several family members. The mode of transmission is autosomal dominant with incomplete penetrance. The previously described aunt with only hyperhidrosis of the soles is suggestive of variable expressivity as well (Figure). Several other hereditary conditions are known to have hyperhidrosis as an associated feature. These include Böök's syndrome, Charcot-Marie-Tooth syndrome, the nail-patella syndrome, pachydermoperiostosis, familial dysautonomia, and dyskeratosis congenita. Evidence for these concurrent inherited diseases was looked for and none was found. In fact, all family members are remarkably healthy.

To investigate if inheritance of hyperhidrosis was linked to the ABO blood group determinant, ABO blood typing was performed. A large family study demonstrating the association of the nail-patella syndrome (known to be linked to the ABO blood group allele) and palmar-plantar hyperhidrosis prompted us to address this question. Unfortunately, the family size and preponderance of type O blood does not permit us to either refute or accept the hypothesis of linkage.

Medical therapy for this condition is often ineffectual. Some patients may respond adequately to topical formaldehyde, glutaraldehyde, scopolamine, or aluminum chloride, or to iontophoresis or systemic anticholinergics, such as propantheline. However, the fact that over 700 cases have been reported in the surgical literature since 1969,17 attesting to the good results obtained by thoracic sympathectomy, indicates that less invasive approaches have their limitations. The drawbacks to current medical ther-

**COMMENT**

Hyperhidrosis may occur as an idiopathic primary disease or secondary to other conditions, such as...
apies for this condition include not only their ineffectiveness, but the incidental risk of contact sensitization, irritation, and the toxic side effects of anticholinergic therapy. The cost and potential morbidity of a neurosurgical procedure for this condition adds to the desirability of introducing a medical therapy that would be effective, nontoxic, and available on an outpatient basis.

The patients described in this article have been difficult to treat, having failed on numerous topical agents. Probanthine is usually effective if taken in doses between 15 and 45 mg. However, there have been side effects of dry mouth and blurred vision, and repeated doses are needed if an effect is desired for a four-hour period.

Calcium flux plays a central and essential role in the stimulation of active sweat secretion. Influx of calcium from the extracellular compartment to the intracellular compartment has been shown by Sato to be required for eccrine gland secretion to occur. Calcium-channel blockers act selectively by inhibiting calcium influx through the cell membrane. These facts suggested the possible usefulness of calcium-channel blockers in hyperhidrosis.

Although a present these agents are approved for use only in angina, reports of their effectiveness in other diseases such as hypertensive, urticaria pigmentosa, migrain headaches, and Raynaud's phenomenon continue to appear. Also, inhibition of secretion from endocrine organ cells, such as pancreatic $\beta$ cells and anterior pituitary cells, is a published action of these medications. Side effects are usually minimal and protocols dealing with their use in non-cardiac diseases have been accomplished on an outpatient basis. Diltiazem has the least incidence of overall adverse reactions and was chosen for use because of this. Our patients experienced no adverse reactions at the doses given.

The palmar sweat test used in this study was designed to provide a simple and accurate objective measure of relative sweat secretion over a period of time. This was deemed preferable to observation of gross sweating in corroborating clinical history during the genetic study. It can be seen that in the involved family members, tests ranged from three to 17 times the normal SW. There was generally good correlation between the clinical severity of hyperhidrosis and the sweat test results (i.e., the subject most severely involved clinically, the proband, had the highest sweat test reading). It proved useful in documenting response to the proposed therapies.

Other authors have used differing methods to objectively measure palmar sweating. Both Randall and Shelley and Horvath used colorimetric indicators to judge sweat response by measuring size and number of sweat puctas after various interventions. Peterson et al. used a specially designed developing paper, which estimated the amount of sweating present through a graded scaling system. Gorden and Mailbach used an electrical system for sensing water vapor pressure over the skin to indirectly express the amount of sweat secretion. In 1950, Cohen used a method similar to ours, where blotter paper was applied to the palm for one minute and the change in weight was recorded as palmar sweat secretion. His study primarily evaluated neurocirculatory asthenia, but there is great similarity between his results and ours. He measured one patient with hyperhidrosis incidental to his primary study; that patient had a reading 3.5 times the control group mean. Cohen studied the effect of variable humidity (range, 33% to 77%) and temperature (range, 22°C to 27°C) and found no correlation between amount of palmar secretion and temperature or humidity. Because of this, and the fact that our readings were done under environmental conditions that showed little variability, we believe that these factors do not explain the markedly abnormal palmar sweat secretion observed among affected family members in the initial phase of the study.

This study documents that hyperhidrosis may occur as an autosomal dominant trait. It describes a simple, direct quantitative test for determining palmar sweat secretion, which may be of use in further clinical studies. Also reported is the effect of diltiazem in decreasing palmar sweat secretion in two patients with familial emotional hyperhidrosis. These patients were in a nonstressful environment. Additional studies are indicated and should be directed at a larger series of patients and done in an outpatient setting. These will then help to determine if the effect observed here is clinically useful in the treatment of hyperhidrosis.

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