

Diagnosis of palmar hyperhidrosis via questionnaire without physical examination

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Abstract

Objectives In order to determine the reliability of a self-administered instrument to diagnose excessive sweating conditions, including palmar hyperhidrosis (PH), we designed two successive questionnaires and compared responses with physical examination and sweat measurement in normal volunteers and a cohort of patients with documented PH. The reliable diagnosis of PH via questionnaire would enable molecular epidemiological studies without the need for physical examination or direct sweat measurement.

Methods Subjects self identified as either normal or affected by PH. Each completed one or both questionnaires

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and underwent physical examination. Sweat production from the thenar eminence and forehead was measured at rest and following mental/emotional stress. Correlation among sweat measurement, physical examination, and questionnaire score was assessed.

Results Forty-seven subjects enrolled in the study, 29 of whom underwent sweat measurements. The participants' perception of whether they were affected agreed with the examiner's visual and tactile observation of PH in all cases ($P < 0.0005$). The mean peak sweat rate for those participants with PH was 1.59 mg/cm²/min, while that of the normal cohort was 0.37 mg/cm²/min ($P = 0.001$). The mean questionnaire #1 and #2 scores for those participants with PH and the normal cohort was 7.10 versus 0.36 ($P = 0.0005$) and 5.145 versus 0.045 ($P = 0.0005$), respectively. Peak sweat rate correlated with questionnaire score (Pearson correlation coefficient = 0.723).

Interpretation Palmar hyperhidrosis can be accurately diagnosed via questionnaire. Molecular epidemiological studies of PH may be reliably conducted without the need for direct physical examination.

Keywords Hyperhidrosis · Palmar · Diagnosis · Questionnaire · Sweating measurement

Introduction

Hyperhidrosis is commonly defined as sweating in excess of physiologic requirements. Though excessive generalized body and axillary sweating adversely affect the quality of life of a significant portion of the population [9, 28, 29], palmar hyperhidrosis (PH) has proven particularly bothersome, as well as difficult to ameliorate. PH usually begins

in early childhood and is commonly diagnosed by history and physical examination.

The etiology of PH is unknown, though a family history is reported in as many as 65% of patients [12, 23, 24]. Detailed kindred information provided by 49 affected individuals has indicated that the disease allele is present in 5% of the population and that one or two copies of the allele will result in PH in 25% of carriers [24]. Preliminary studies, utilizing linkage analysis, have localized PH-associated genes to chromosomes 14 [10] and 5 [7]. Identification of the gene(s) may aid in elucidating the disease mechanism(s) and devising novel treatments.

Molecular epidemiologic studies of low prevalence diseases require access to patients who may not live within easy commuting range of the investigator. Fortunately, DNA can be reliably obtained from buccal mucosa by the mouthwash method without having the study participant travel to the study site [2, 8]. However, if the subject is not to be examined by the investigators, a reliable instrument is needed to confirm the presence of the disease process under study.

Quality-of-life instruments have been extensively utilized before and after treatment in patients with PH [5, 18]. However, the ability of questionnaires to accurately establish the diagnosis of PH has not been previously documented. In order to determine the reliability of a self-administered instrument to diagnose excessive sweating conditions, including PH, we designed two successive questionnaires and compared responses with physical examination and sweat measurement in normal volunteers and a cohort of patients with documented PH.

Methods

Study design

The current study is part of a larger effort to identify the genetic basis of PH. Following approval by the Institutional Review Board (Montefiore Medical Center) and the Committee on Clinical Investigation (Albert Einstein College of Medicine), normal volunteers and people with PH documented by history and physical examination (SMK) were accrued to the study. Informed signed consent was obtained from all the participants.

The study was divided into two phases. During the first phase, only people who were able to visit the research site were offered participation. All underwent physical examination, completed either one or both of the questionnaires, and donated blood or a buccal sample. Many also had sweat measurement (*vide infra*). During the second phase, accrual was widened to include potential participants who were unable to physically reach the research site.

This report includes only those study participants accrued during the first phase of the investigation.

Sweat measurement

Subjects were given a standardized sweat test utilizing the SKD-2000 skin moisture meter (Skins Co., Ltd., Japan) [26]. Moisture evaporation from the skin is measured utilizing the ventilation capsule method. Briefly, a 1 cm² cup captures the moisture from the skin and directs it to the measurement electronics [22]. The total moisture in the capsule, which is the sum of ambient humidity and the perspired water, is subtracted from the ambient humidity. This differential method readily accounts for environmental variations. Results are reported as mg/cm²/minute and are recorded digitally.

Sweat production was measured on the thenar eminence and forehead (control). Baseline measurements were taken after the subject was asked to recount a pleasant experience. Next, subjects were subjected to mental and emotional stress utilizing the Stroop test [25] which requires the subject to correctly identify the color of a word that is itself the name of a color. The word may be printed in a color that does not correspond to its true meaning. For instance, “red” could appear in yellow. The successful subject would enter “red.” Words appear sequentially on a computer screen with increasing rapidity.

Questionnaires

The initial questionnaire was designed as a hyperhidrosis scale (Appendix 1) to measure the severity of palmar, axillary, and plantar sweating in patients who were evaluated by a physician (SMK) for possible therapeutic intervention and to assess the effect of treatment, if surgery was performed. The 15 questions reflected the common physical symptoms and social stigmata associated with PH. Responses were graded between 0 (mild) and 10 (severe). Individual analysis of the hyperhidrosis scale questions revealed strong reliability (Cronbach’s Alpha = 0.89) [14]. Pedigree and medical information were collected separately.

Upon initiation of the remote patient accrual and sample collection phase of the current study, a revised questionnaire (Appendix 2 of electronic supplementary material) incorporating the hyperhidrosis scale, family history information, and medical history was designed. The questions from the first questionnaire were incorporated into the later version; however, the response scale was altered. The second questionnaire was completed not only by remote study participants, but also by those participants who were able to be present at the

study location. For purposes of this report, only the questionnaires of those patients available for physical examination were included. A subgroup of participants completed both questionnaires.

Statistics

The net sweating rate was computed by subtracting the forehead sweating rate (control) from the palmar sweating rate. The peak sweat rate under stress conditions of the normal and affected groups was compared with an independent sample's *t* test.

The effectiveness of questionnaire #1 to distinguish between those subjects with and without PH (as objectively determined by physical examination and the sweat test) was assessed by creating a summary score which was computed by adding the numeric score on the 15 questions. Because every question was not answered by every patient, the score was normalized by dividing by the number of questions completed. The normalized score ranged between 0 and 10. In order to determine the optimal cutoff score so as to maximize sensitivity and specificity, an ROC analysis was performed.

The effectiveness of questionnaire #2 to distinguish between those subjects with and without PH was assessed by creating a summary score which was computed by adding the numeric score of 27 questions relating to the physical and quality of life features (questions 1, 3, 4, 5, 6, 7, 11, 12, 13, 13a, 14, 14a, 15, 15a, 16, 16a, 17, 17a, 18, 18a, 19, 19a, 20, 20a, 21, 21a, 22, 22a, 23, 23a, 24.2, 24.2a, 25, and 25a). "No" answers were counted as 0. If participants responded "Yes", the score assigned was 1. If there was a part "a" to the question the score of part "a" was assigned to that pair of questions (e.g., 14/14a). Answers of "Not sure" were assigned 0.5. In order to account for the fact that not every question was answered by every participant, the score was normalized by dividing by the number of possible points on the questions answered. The normalized score, which ranged between 0 and 1, was multiplied by a factor of 10.

Correlation between the two questionnaires was examined with a scatter plot of the normalized scores of both questionnaires plotted against each other. The Pearson's correlation coefficient was calculated.

All statistics were performed using SPSS 15 (SPSS Inc., Chicago, IL, USA). Histograms were constructed using automatic binning. Continuous variables were compared using Student's *t* test. The Welch *t* test was used in cases of unequal variances between the two groups. Optimal cutoff values were selected as the value at which sensitivity and specificity were equal. Best fit lines were determined using linear regression. *P* values less than 0.05 were considered significant.

Results

Forty-seven participants were accrued to the first phase of the study, 22 (47%) of whom stated that they had PH. The patients' perception of whether they were affected agreed with the examiner's visual and tactile observation of PH in all cases ($P < 0.0005$).

Twenty-nine participants underwent sweat rate measurements. Thirteen said they had PH and all were found to be affected by physical examination. The mean peak sweat rate for those participants with PH was 1.59 mg/cm²/min, while that of the normal cohort was 0.37 mg/cm²/min ($P = 0.001$) (Table 1; Fig. 1).

Thirty-four participants answered questionnaire #1 of whom 20 (59%) were found to be affected by physical examination. The mean score for those participants with PH was 7.10, while that of the normal cohort was 0.36

Table 1 Mean peak sweat rate (mg/cm²/minute)

	Exam	N	Mean	Std. deviation	Std. error mean
Sweat rate	Affected	13	1.591	0.9550	0.2649
	Control	16	0.366	0.3891	0.0973

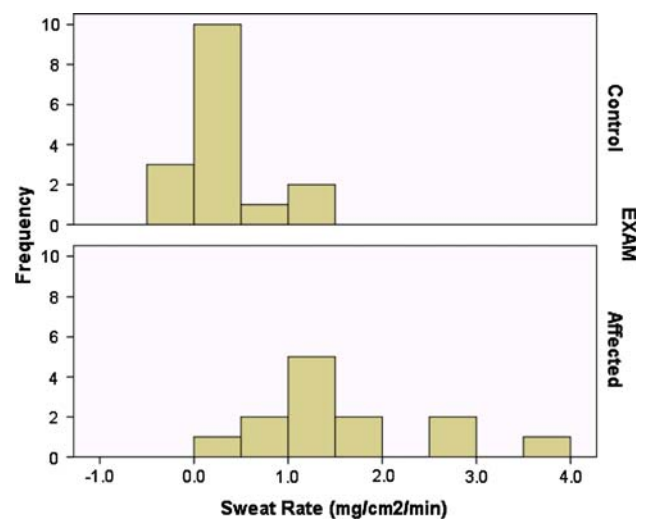


Fig. 1 Peak sweat rate histogram. Sweat rate was measured on the thenar eminence using the SKD-2000 skin moisture meter as described in the "Methods". Sweat rate is expressed in mg/cm²/min. Physical examination was used to evaluate whether the palms were moist or dry. The Y-axis represents the number of individuals with a determined sweat rate on the X-axis. There was substantial overlap of peak sweating rates between the two groups. Some members of the affected cohort (all of whom were determined to be affected by physical examination) had peak sweat rates similar to some members of the control group

Table 2 Normalized numeric scores of questionnaire #1

Cohort	<i>N</i>	Mean	Std. deviation	Std. error mean
Affected	20	7.1005	1.68195	0.37610
Control	14	0.3571	0.63008	0.16840

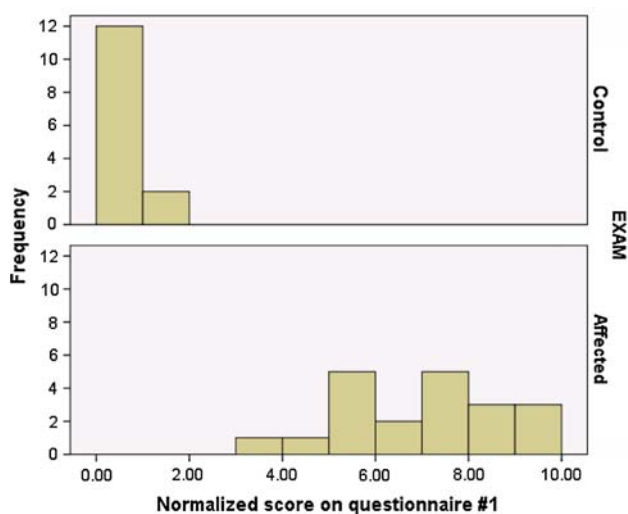


Fig. 2 Normalized questionnaire #1 score histogram. The normalized scores from questionnaire #1 were determined as described in the “Methods” and are present on the *X*-axis. Wet or dry palmar surface was determined by physical exam and the scores of individuals are displayed in the *top* and *bottom panels*, respectively. The number of individuals with specific normalized questionnaire scores is listed on the *Y*-axis. The scores of the affected and control groups did not overlap

($P = 0.0005$) (Table 2; Fig. 2). ROC analysis demonstrated that a cutoff value ≥ 2.7 resulted in a sensitivity and specificity of 100% for the diagnosis of PH.

The observation that affected participants have higher net peak sweat rates and higher normalized scores on questionnaire #1 suggest that there is a positive correlation between these two measurements. Sweat measurements were available for 26 of the 34 participants who answered questionnaire #1. A scatter plot of peak sweat rate versus normalized questionnaire #1 score demonstrates that the affected and control groups are well separated (Fig. 3). As was previously seen in the peak sweat rate analysis, some affected participants had low peak sweat rates but none of the control participants had a high peak sweat rate.

Twenty participants answered questionnaire #2 of whom 8 (40%) were found to be affected by physical examination. The mean normalized score for those participants with PH was 5.145, while that of the normal cohort was 0.045 ($P = 0.0005$) (Table 3). ROC analysis demonstrated that a cutoff value ≥ 1.964 resulted in a sensitivity and specificity of 100% for the diagnosis of PH. A histogram of the

normalized scores demonstrated complete separation of the two groups (Fig. 4).

The correlation between physical findings and normalized questionnaire #2 scores was examined. Sweat measurements were available for 5 of the 20 patients who answered questionnaire #2. A scatter plot of peak sweat rate versus normalized questionnaire #2 scores demonstrated that the groups were well separated (not shown). Due to the small number of patients available, no further correlation analysis was performed.

Correlation between the two questionnaires was examined. Seven participants answered both questionnaires, only one of whom did not have PH. A scatter plot (not shown) revealed a significant correlation (Pearson coefficient 0.82, $P = 0.024$).

Discussion

A survey of 150,000 US households yielded an overall hyperhidrosis prevalence of 2.8% [28]. Based on a survey of 13,000 college and high school students, investigators from Asia reported a PH prevalence of 4.6% [29]. The prevalence of PH was estimated as 0.6–1% in a study of Israeli army recruits [1]. Among patients who were evaluated at American and Canadian Dermatology Clinics for the diagnosis and treatment of hyperhidrosis, 46% had PH [19]. Sweating is usually worse during the summer months and occurs both at times of apparent calm and obvious stress [16]. Our questionnaires, as well as those of others [5, 9, 18], demonstrate a significant social morbidity. Hyperhidrosis adversely affects a significant portion of the population and merits further study.

In order to investigate a disease process a precise definition of the necessary symptoms, physical findings, and objective measurements is required. Currently, there are no uniformly accepted criteria for the diagnosis of hyperhidrosis. One group of clinicians defined hyperhidrosis as focal sweating of greater than 6 months duration that fulfills at least two of the following criteria: bilateral and symmetric, impairs daily activities, occurs at least weekly, age of onset <25 years, family history, and cessation of focal sweating during sleep [11]. This definition has been utilized in combination with a hyperhidrosis disease severity index to make treatment recommendation [27].

An objective definition of hyperhidrosis remains even more elusive because sweating has proven difficult to reliably quantify. The established and simple gravimetric method entails wearing a vinyl glove containing one pre-weighed filter paper. After a specified length of time the glove is removed and the filter paper reweighed [21]. Reproducibility and accuracy have not been established. More recently, the ventilation capsule method has been

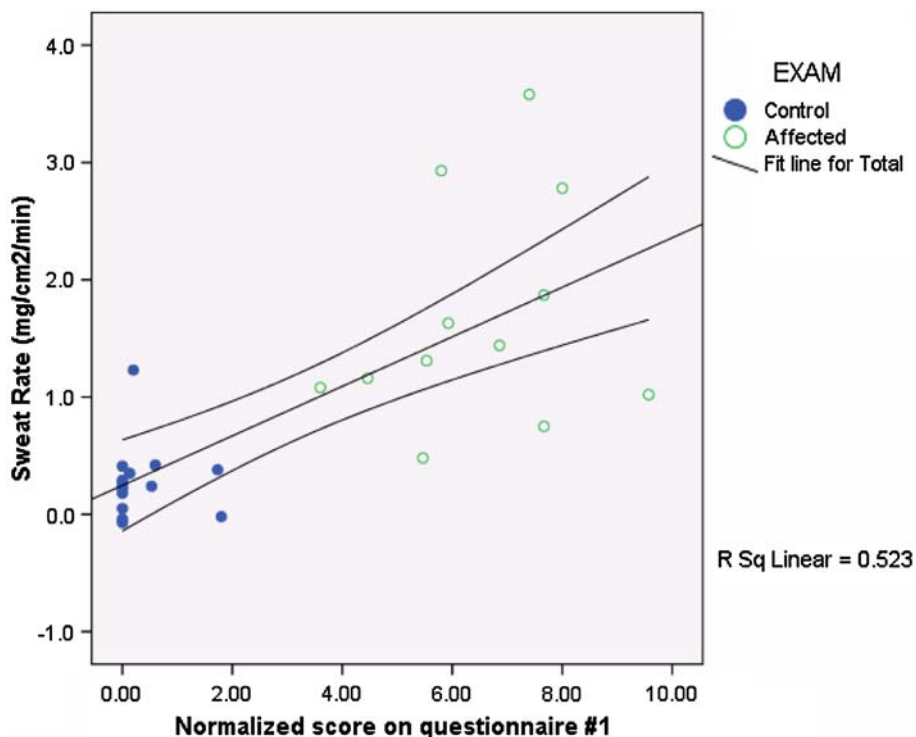


Fig. 3 Scatter plot of peak sweat rate and normalized questionnaire #1 score. The sweat rate of individuals was determined by direct measurement as described in the “Methods” and is indicated on the Y-axis. Wet or dry palmar surface was determined by physical exam and is represented by circles and squares, respectively. Normalized scores from questionnaire #1 were determined as described in the

“Methods”. The straight line is a best fit line and the two curved lines are the 95% confidence interval for the best fit line. The Pearson correlation coefficient (r) was 0.723 and this was significantly different from zero ($P < 0.0005$). r^2 was 0.523, indicating that 52% of the variability in the normalized score on questionnaire #1 can be explained by the variability in mean peak sweat rate

Table 3 Normalized numeric scores of questionnaire #2

Cohort	<i>N</i>	Mean	Std. deviation	Std. error mean
Affected	8	5.145	1.4491	0.5123
Control	12	0.045	0.1110	0.0320

employed by a number of investigators with promising results [6, 15, 30]. Our study demonstrates a mean peak sweating rate of 1.59 mg/cm²/min on the thenar eminence is present in patients with PH. This is in agreement with the results of Yamashita (1.15 mg/cm²/min) [30], Bonde (0.88 mg/cm²/min) [6] and Krogstad (2.1 mg/m²/min) [17].

In addition to direct sweat measurement, a number of physiologic differences between people with PH and normal volunteers have been demonstrated. The absence of a decrease in mean heart rate with controlled respiration in 12 subjects with PH when compared to 20 normal volunteers, in conjunction with the absence of statistically significant differences in heart rate variability parameters, was interpreted as representing a complex autonomic dysfunction involving both the sympathetic and parasympathetic systems [13].

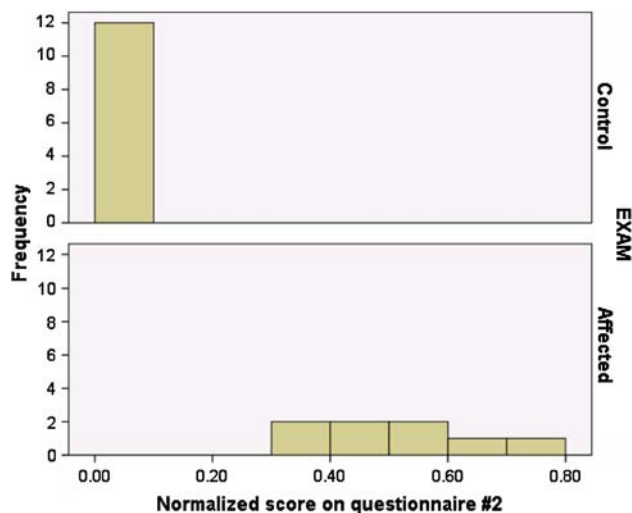


Fig. 4 Normalized questionnaire #2 score histogram. The normalized scores from questionnaire #2 were determined as described in the “Methods” and are present on the X-axis. Wet or dry palmar surface was determined by physical examination and the scores of individuals are displayed in the top and bottom panels, respectively. The number of individuals with specific normalized questionnaire scores is listed on the Y-axis. The scores of the affected and control groups did not overlap

Supporting this conclusion was the documentation of a significantly lower power in the very-low-frequency band in short-term frequency domain power cardiac spectral analysis [4]. Other investigators demonstrated abnormal sensory processing [20]. Though intriguing, these physiologic abnormalities are not diagnostic of PH.

Physical measurements, though preferred, are not useful if the potential study participants are not available or interested in a face-to-face examination. Moreover, because of the social stigmata associated with excessive sweating, many affected individuals are emotionally unable to participate in person, but find home participation acceptable. A reliable instrument that can be self-administered is required. We have documented that it is possible to accurately diagnose PH by questionnaire alone. Therefore, investigations into the genetics of this disorder may be conducted without direct access to the subjects under study with the knowledge that PH is truly present. However, utilization of this questionnaire in a population-based survey might underestimate the prevalence of PH, as it is likely that not all affected individuals regard PH as distressing.

Most non-operative therapies for PH (20% solution of aluminum chloride hexahydrate, iontophoresis, anticholinergic medication) have not been evaluated in a rigorous fashion and when critically examined do not demonstrate effectiveness [3]. Botox injection, which has been subjected to controlled trials is effective, but requires multiple (>15) biannual palmar injections. Thoracoscopic sympathectomy is effective, but involves general anesthesia and is associated with a substantial incidence of compensatory sweating that may be, in a small percentage of patients, as troublesome as the initial disease [23]. Novel therapy, that is both effective and free from unwanted side effects, will only be developed when the disease mechanism is thoroughly understood.

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Appendix

Hyperhidrosis scale

Questions about distress caused by sweating of the hands.

How much distress do you experience when you:

1. Shake hands with others?
(None) 0 1 2 3 4 5 6 7 8 9 10 (worst)

2. Hold hands with a boyfriend/girlfriend/spouse?
(None) 0 1 2 3 4 5 6 7 8 9 10 (worst)
3. Writing (by hand) on paper to complete examinations, applications or other important documents?
(None) 0 1 2 3 4 5 6 7 8 9 10 (worst)
4. Grasp heavy objects and/or tools?
(None) 0 1 2 3 4 5 6 7 8 9 10 (worst)
5. Attempt to initiate intimate contact?
(None) 0 1 2 3 4 5 6 7 8 9 10 (worst)
6. Turn knobs or faucets?
(None) 0 1 2 3 4 5 6 7 8 9 10 (worst)
7. Drive a car?
(None) 0 1 2 3 4 5 6 7 8 9 10 (worst)
8. Eat with forks, knives, or spoons?
(None) 0 1 2 3 4 5 6 7 8 9 10 (worst)
9. Wear fabric, leather or rubber gloves?
(None) 0 1 2 3 4 5 6 7 8 9 10 (worst)

Questions related to sweating of your feet

10. Put on socks or stockings?
(None) 0 1 2 3 4 5 6 7 8 9 10 (worst)
11. Walk barefoot?
(None) 0 1 2 3 4 5 6 7 8 9 10 (worst)
12. Wear sandals?
(None) 0 1 2 3 4 5 6 7 8 9 10 (worst)
13. Wear high-heel shoes?
(None) 0 1 2 3 4 5 6 7 8 9 10 (worst)

Questions related to sweating from areas of the body other than the hands and feet

14. Sweat from your axilla (underarms)?
(None) 0 1 2 3 4 5 6 7 8 9 10 (worst)
15. Sweat from other parts of the body other than hands and axilla?
(None) 0 1 2 3 4 5 6 7 8 9 10 (worst)
Is yes, where (please describe)

©Hyperhidrosis scale, 1998. Keller, Sekons, Scher, Bookbinder, Portenoy (HYPERQUE).

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