Review Article



# Diagnosis and qualitative identification of hyperhidrosis

**Shiri Nawrocki**

Rutgers-Robert Wood Johnson Medical School, Piscataway Township, Tenafly, NJ, USA

*Correspondence to:* Shiri Nawrocki, BA. Rutgers-Robert Wood Johnson Medical School, 675 Hoes Lane West, Piscataway, NJ 08854, USA. Email: shiri.nawrocki@gmail.com.

**Abstract:** Hyperhidrosis is a dermatologic disease defined as excessive sweating that exceeds thermoregulatory needs, and is estimated to affect at least 4.8% of the population. The condition can be classified as either primary and idiopathic, or secondary due to an underlying medical condition or medication adverse event. Primary hyperhidrosis accounts for 93% of all cases. The diagnosis is partially determined and supported by objective quantitative tools, but is mainly identified by subjective accounts of patients regarding the extent of impact the excessive sweating has on their daily and general quality of life. This article will elaborate on the common and practical tools available for diagnosing hyperhidrosis.

**Keywords:** Hyperhidrosis; primary hyperhidrosis; excessive sweating; sweat gland; quality of life (QoL)

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## Introduction

Hyperhidrosis (HH) is a chronic, autonomic disorder involving excessive sweat secretion beyond the physiological need for thermoregulation. HH can be classified as primary, resulting from an unknown cause (idiopathic), or secondary, resulting from an underlying medical condition or medication consumption (1,2), and may further be classified according to its distribution (1,3). Most often, secondary HH manifests as generalized exaggerated sweating, whereas primary focal idiopathic hyperhidrosis (PFHH) typically presents in a focal, bilateral, and symmetric distribution, commonly affecting the axillae (73%), hands (45.9%), feet (41.1%), and craniofacial regions (22.8%) (1,4-11). In the same patient, more than one area may be affected (8,12). PFHH accounts for 93% of all HH cases and can occur in otherwise healthy individuals without other medical problems (1,4,13). It mostly presents in a phasic manner and usually does not occur at night.

"Excessive sweating" is difficult to define. Instead of quantifying sweat secretion, it refers to the amount of perspiration perceived as limiting activities of daily living, causing physical, emotional, and social discomfort, and impacting quality of life (QoL) (14,15). PFHH may be provoked by thermal stimulations, emotional stress, and physical activity, or no stimuli at all (15,16). It is not considered a psychological disorder (1).

The reported prevalence of PFHH varies due to a lack of a precise definition (5). It is reported that at least 4.8% of the US population develops HH (11,17), but this may be an underestimation as HH is likely under-disclosed by patients and under-detected by healthcare professionals (8). It has previously been reported that only 38% of PFHH patients consult a healthcare provider (8), but with increasing awareness of the condition, the percentage of individuals seeking medical treatment has increased to 51% (11).

PFHH can occur at any age, but the usual onset occurs between 14 and 25 years of age, depending on the area affected (18). Palmar or plantar PFHH usually appears at a prepubertal age, whereas axillary disease emerges more commonly during adolescence (6,8,19,20). The incidence of PFHH in individuals aged 18–39 years has been reported as 8.8%, in contrast to 2.1% in adults aged >65 years and children. The uncommon occurrence of the condition in the elderly suggests its spontaneous regression (21). Both sexes are equally affected, with women seeking treatment more frequently than men (8,10,14).

There is likely a genetic factor involved in PFHH, since 30–65% of patients describe a family history (22-25). A

definitive family history is more common with an earlier age of onset (<20 years) (6). PFHH may have a variable phenotype, partial penetrance, and an autosomal dominant form of transmission (6,22,24-27). Loci for the condition have been mapped on chromosomes 14q11.2-q13 and 2q31.1 (23,27,28).

Approximately 2–4 million sweat glands are found on the human body in varying gland densities: 700/cm$^2$ on the hands, 181/cm$^2$ over the forehead, 64/cm$^2$ on the back, and various other densities on other body surfaces (29,30). Three different recognizable sweat gland types, eccrine, apocrine, and apocrine glands, have been described in humans (31), with the eccrine gland being the most abundant overall and the most numerous in the hands, feet, and axillae (29). Eccrine glands can generate total sweat per day of up to 10 liters under intense physical activity, stress, or extremely hot temperatures (21,29). These glands are considered accountable for PFHH (29,32). However, there is no increase in number or size, or change in microscopic or macroscopic appearance, of these glands in affected patients (21,30,33). Instead, PFHH results from altered kinetics of sweat secretion, with changes in the control mechanism of sweating resulting in the disproportional sweat overproduction.

The cause of PFHH is unknown. The most reasonable etiology is a hyperexcitability or neurogenic overactivity of the normal eccrine glands' reflex circuits, which is likely associated with a complex dysfunction of the parasympathetic and sympathetic elements of the autonomic nervous system (13). Additionally, the condition may result from a central control anomaly of emotional sweating, since the hands, feet, and axillae are affected in both PFHH and emotional sweating (34,35).

PFHH may have serious consequences on daily life, including emotional and psychological effects resulting in low self-confidence, diminished self-esteem, unhappiness, depression, and even suicidal ideation (14,35); impaired social and interpersonal relationships leading to social interaction avoidance and leisure activity restrictions; and impaired occupational performance and work productivity (5,35-40). One-third to one-half of PFHH individuals find their sweating to be meddling in their daily lives and hardly tolerable (11), and one-half to three-fourths of patients are emotionally affected by their sweating (24,41). The proportion of patients reporting reduced self-confidence is 69–74%, and 54–63% declare feeling unhappy or depressed (24). Moreover, 37–71% complain of feeling severely restrained in social circumstances, such as while socializing, being in public places, and developing personal relationships (8); 54–63% report spending less time for leisure; 63% are seriously restricted at work; and 22% minimize their working time (24). Coping capabilities for the condition do not appear to improve with time (8). In fact, PFHH patients have lower managing-abilities and more psychologic and emotional difficulties than healthy individuals or other dermatologic patients (38). The decline in QoL for PFHH patients is similar to that of other diseases, such as multiple sclerosis, end-stage renal disease, rheumatoid arthritis, and severe psoriasis (39,42-45); however, it exceeds that observed in patients with vitiligo, acne vulgaris, Hailey-Hailey disease, and Darier's disease (42,46,47). The harmful effects of PFHH may be intensified by the lack of awareness of PFHH being a treatable medical disease (35).

## PFHH diagnosis

Early diagnosis and proper treatment of PFHH are essential for minimizing its emotional, psychosocial, and physical effects (48). Secondary HH must be excluded prior to making a diagnosis of PFHH (1,13,14,20,30) (*Table 1*). A complete medical history and physical examination should be performed, which frequently presents all information necessary to differentiate secondary HH from PFHH (49). Laboratory tests are unnecessary in classic PFHH, but should be implemented in atypical PFHH and generalized HH cases (5,14).

PFHH has distinguishable characteristics, allowing its diagnosis to be made solely on the medical history and physical examination (1,5). These characteristics include: healthy young patients with a possible family history; focal, symmetric, and bilateral involvement of the hands, feet, and/or axillae; a possible history of aggravating stimuli (emotional, physical, and/or thermal); and cessation during sleep. The Multi-Specialty Working Group on Hyperhidrosis proposed the following diagnostic criteria for PFHH (5,48): at least 6 months of visible, detectable, focal, exaggerated sweating without any apparent explanation, and two or more of the following typical features: frequent occurrence of at least one incident/week; bilateral and somewhat symmetrical distribution; onset before 25 years of age; a positive family history; lack of focal sweating during sleep; and interference in daily activities. Medical history questions should focus on age of disease onset, family history, HH pattern, impact of HH on a patient's daily life, other associated symptoms, and any medication

**Table 1** Causes of secondary hyperhidrosis

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|---|
| Cardiovascular: congestive heart failure, cardiovascular shock, myocardial infarction, endocarditis |
| Dermatologic: eccrine nevus |
| Drugs/medications: cocaine, heroin, alcohol, antidepressants, antibiotics, antivirals, antipyretics, NSAID's, parasympathomimetic agents, insulin |
| Infectious: tuberculosis, HIV/AIDS, Malaria, Viral/Bacterial infections |
| Malignancy: myeloproliferative disorder, tumor, lymphoma |
| Metabolic: carcinoid syndrome, acromegaly, diabetes, pheochromocytoma, thyrotoxicosis/hyperthyroidism |
| Neurologic: stroke, Frey's syndrome, Parkinson's disease, spinal cord lesion |
| Other: compensatory sweating, menopause, fever, pregnancy, heat |

consumption to exclude secondary causes. Questions assessing further classification of HH are as follows: symptoms, duration, areas affected, symmetry, frequency, amount, distinct triggers, and existence of sweating while asleep. Physical observation should include visible indication of disproportionate sweating in the typical focal areas or signs indicating secondary HH.

After establishing a diagnosis of PFHH, severity is determined (48). Some researchers consider the importance of observing actual perspiration during the physical examination, but since PFHH can be episodic and unpredictable, it may be impossible, and the diagnosis needs to rely on the patient's own assessment of the impact the symptoms have on his or her life.

When sweating is visible during clinical examination, PFHH severity can be classified based on the extent of sweating. Sweat stains on clothing can be useful for axillary involvement: sweat stain diameter <5 cm is considered to be normal; stain diameter of 5–10 cm is considered mild HH; stain diameter of 10–20 cm is defined as moderate HH; and stain diameter >20 cm and approaching the waistline is considered severe HH (50). Regarding palmar HH, the following classifications have been devised: mild involvement—sweaty hands without visible droplets; moderate involvement—hand perspiration reaches the fingertips; severe involvement—sweat drips off the hand and extends to all fingertips (50).

Various quantitative and qualitative methods are available to establish a diagnosis of HH, its severity, and the effect the condition has on a patient's QoL (13).

## Quantitative sweat-production tests

Quantitative measurements for sweat production are not frequently performed in routine clinical practice but may assist in establishing the diagnosis or guiding therapeutic measures (5,13). Currently, a commonly accepted sweat quantity to define HH does not exist. One study characterized normal sweat quantities to be <1 mL/m$^2$/min (29). A threshold for axillary HH was determined to be >100 mg/5 minutes and >50 mg/5 minutes of sweat per axillae for men and women, respectively, or >50 mg/1 minute in men (29,51,52). Additionally, palmar HH may be diagnosed when sweat production is >30–40 mg/min (13,53).

Various quantitative sweat-production measurement tools are available for clinical purposes, with the gravimetry test and starch-iodine (Minor's) test being the most commonly used (5).

Gravimetry (gravimetric testing) is an easy to use and fast procedure for assessing the amount of sweat produced in a certain period of time (51,52,54). After the affected area is thoroughly dried, a pre-weighed filter paper is placed on the HH region for a predetermined period of time. The difference in paper weight before and after the test establishes the amount of sweat produced within that time period, expressed in milligrams/minute. The time required for quantitative measurements varies among authors from 1 (51), 5 (52,55), 10 (56), and 15 minutes (57). This technique has debatable reliability with inter- and intra-patient variability (5,42,51,52).

Gravimetry generates an absolute value, as it does not take into consideration the size of the sweat-secreting area. The Hyperhidrosis Area and Severity Index (HASI) aims to consider the amount of sweat produced in a specific time interval, as well as the size of the sweat-secreting area (56). After performing the gravimetric test, the sweat site is stained using the Minor's starch iodine technique and the area's size is estimated by 'point counting'. After defining

 

the sweat area's size, the amount of sweat secreted can be expressed in mg/cm$^2$/minute (56). HH presumably exists when HASI values are >1 mg/cm$^2$/minute (56).

Another way to standardize gravimetry is to divide the gravimetric test results by the patient's body area, which is calculated using the individual's height [body area (m$^2$) = 0.01667 × height (cm)$^{0.5}$ × mass (kg)$^{0.5}$] (58).

The Minor's starch-iodine test is a simple and inexpensive method for recognizing the presence of perspiration, identifying the affected surface area, and assessing the severity of sweat-overproduction (1,59,60). The technique is mainly useful in mapping areas of focal perspiration before and after treatments (i.e., botulinum toxin injection or surgery) (48,53,55,61,62). The Minor's test is not used to quantify HH severity, but it can identify different perspiration intensities.

Before the test, the skin area to be evaluated needs to be thoroughly cleaned and dried. A 1–5% iodine in alcohol solution is applied over the field. The Modified starch-iodine test utilizes BetadineTM solution. After the solution is thoroughly dried, a starch powder (e.g., cooking corn starch) is lightly dusted on the skin area using a cotton ball, brush, sifter, or loose gauze. Paper saturated with starch-iodine placed over the sweat area works similarly. The sweat moisture dissolves the iodine and starch, resulting in a polyiodide chain via a chemical reaction, which turns the light brown iodine color into a dark purple color (61). The purple area marks the sweat gland orifices, which appear as small dots. Alizarin or ponceau red dye and starch, instead of iodine solution, may be used for iodine-sensitive patients and result in the sweat area turning pink (63). False positives, appearing as streaks or smears of dark pigments, occur if the skin has not been thoroughly dried of sweat or if the iodine solution is not thoroughly dried prior to starch application. False negatives may occur if the starch is applied too heavily. Digital photography taken from the hyperhidrotic areas aids in documentation and comparison pre- and post-treatment.

Although the Minor's test does not determine HH severity (48), it can categorize different perspiration intensities by using the Intensity Visual Scale. Applying a 6-grade visual scale, the final color from the Minor's test is classified as follows: 0, no sweating; 1, initial; 2, mild; 3, moderate; 4, intense; and 5, excess sweating (64). Regions with great sweating will appear homogenous and highly pigmented (scores 3–5), whereas areas with less sweating will appear heterogeneous and speckled (scores 0–2) (64).

Other less frequently used objective quantitative tests for HH measurements are presented below.

The ninhydrin test is a quantification method that relies on the chemical reaction between ninhydrin and amino acids in the sweat. Ninhydrin is sprayed on a paper, which is placed over the sweat area (65). The image produced on the paper can assess the sweat production via a digital analysis.

Dynamic quantitative sudometry is a technique that quantifies the amount of moisture absorbed into a dried gas flowing through a chamber that is placed over the examined area (66,67).

Evaporimetry is a quantitative test that measures the amount of evaporated sweat produced using a vapor pressure gradient. It represents an indirect transepidermal water loss (TEWL) measurement through the skin (68). Different methods for measuring TEWL include the open-chamber, ventilated-chamber, and unventilated-chamber (closed) methods (69). In closed-chamber devices, TEWL is measured by calculating the evaporation rate (evaporimetry) based on the increased relative humidity in the closed chamber. The resultant calculation is expressed in weighed amount of water (g)/area of evaporation (m$^2$)/time (hours) (70). Various evaporimetry measurement devices have been reported.

## Qualitative sweat-production tests

HH is commonly determined in qualitative terms. Any amount that substantially interferes with an individual's QoL and affects his/her daily life is determined to be abnormal sweating (13). In other words, the individual's subjective perception of the impact his/her perspiration has on daily activities is the focus in diagnosing PFHH. As a result, it is imperative to qualitatively measure the effects of PFHH on a patient's QoL, and any resultant daily life impairments (47). These data can be collected through history taking, specifically-designed questionnaires, or self-rated patient evaluations (47).

The scoring systems used in questionnaires are subjective, reflecting a bias in data collection (71). Patients from different cultures may place varying importance on the diverse aspects of impairment included in a questionnaire (71), which can explain the wide variability of PFHH prevalence rates obtained in various countries. Although 4.8% is the most widely cited population prevalence estimation of HH in the United States (11,17,72,73), prevalence rates of 12.3–17% for HH from other countries [12.3% in Vancouver, Canada (74); 12.8% in Japan (75); 14.5% in Shanghai, China (74); 16.3% in Germany (76); and 16.7% in Poland (77)] have also been

reported.

Impact on QoL has evolved to be the most valuable and essential evaluation modality for PFHH (35). QoL has different interpretations and traits. It acknowledges various factors, such as medical health, emotional, mental, and physical welfare, cultural background, and education level. QoL involves the individual's environment, including occupation, family, and friends. Furthermore, QoL must be interpreted in the context of the patient's social and cultural environment, standards, and values.

Various QoL evaluation questionnaires are available for PFHH patients (35,36). They can be HH disease-specific [such as the Hyperhidrosis Disease Severity Scale (HDSS) or The Hyperhidrosis Impact Questionnaire (HHIQ)], dermatology-related (such as The Dermatology Life Quality Index (DLQI) or Skindex), or general [such as the Short Form questionnaire-36 items (SF-36)] health-related assessments of QoL. HDSS, DLQI, and Hyperhidrosis Quality of Life Questionnaire (HQLQ) are the most commonly used questionnaires in the literature for QoL evaluation in HH patients. It is common to find two or more questionnaires (such as DLQI and HDSS) being used concurrently. These tests have shown substantial QoL decline in various aspects of daily living in PFHH patients (42).

The Hyperhidrosis Disease Severity Scale (HDSS) is disease-specific, simple, and the most commonly used method for measuring QoL in HH patients. It consists of a single-item questionnaire for patients to grade their responses using a four-point scale (48,78). The tolerability and interference that perspiration causes in daily life is graded as follows: tolerable/never interferes =1 (lack of HH); tolerable/sometimes interferes =2 (moderate HH); hardly tolerable/repeatedly interferes =3 (severe HH); and intolerable/constantly interferes =4 (severe HH) (48,79). The greater the score, the more negative impact PFHH has on the patient's QoL (39,48,80).

The Canadian Hyperhidrosis Advisory Committee used HDSS as an important tool in outlining treatment recommendations based on the severity of PFHH (48). HDSS scores show good correlation with gravimetric results (78). Treatment success is interpreted as HDSS score improvement from 4 or 3 to 2 or 1, or from 2 to 1, reflecting improvement in QoL. Failed therapy is defined as absence of a HDSS score change at 1-month post-treatment, or unbearable treatment (35). Two-point improvement in HDSS score was correlated with 80% decrease in sweat production, whereas one-point improvement was associated with a 50% reduction (13,78,81).

The Dermatology Life Quality Index (DLQI) is a validated, sensitive questionnaire that assesses the effects of chronic dermatologic diseases on QoL (71,82). It consists of ten questions related to activities of daily living, occupation, school, leisure, intimate contacts, disease manifestations, and treatment. Each question has the following four graded-responses: no impact or not relevant = '0'; little effect = '1'; a lot of influence = '2'; and very significant disturbance = '3'. All ten scores are added up, resulting in a sum ranging from 0 to 30, with higher scores indicating worse QoL. For PFHH patients, the average combined DLQI result was found to be 9.2, with the highest influence revealed in the daily life category (24). Since DLQI is a dermatology-related questionnaire, it is often considered too general for recognition of hyperhidrosis-specific concerns.

The Hyperhidrosis Quality of Life Questionnaire (HQLQ) is a questionnaire consisting of one comprehensive question regarding the general decline in a patient's QoL, and 20 additional specific questions concerning the outcomes in four domains: social activities and function; limitations with partners; emotional damage; and restrictions in specific circumstances, such as hot environments, occupational activities or stressful situations (such as speaking in public or in an important meeting, or taking an examination) (36,38). Each question has five graded-responses from 1 (excellent) to 5 (very poor). Adding the scored responses results in a cumulative score between 20 and 100, which corresponds to one of five QoL categories: 20–35, excellent QoL; 36–51, very good; 52–67, good; 68–83, poor; and 84–100, very poor. HQLQ was constructed specifically for QoL evaluation following surgical intervention.

The 36-item Short Form Health Survey (SF-36), along with its alternative, abbreviated variant, the 12-item Short Form Health Survey (SF-12), is a reliable and widely utilized questionnaire designed to assess basic, daily functioning and emotional status, and is not a disease-specific QoL evaluation (83,84). The SF-36 includes questions comprising eight health categories, including energy, pain, sense of overall health, physical and mental well-being, and physical, emotional, and social performance conditions. Answers are expressed in 2 major measurements, namely the Mental Component Summary (MCS) and Physical Component Summary (PCS) scores. Summed scores range from 0 to 100, with higher scores indicating better QoL. The SF-36 questionnaire has revealed that PFHH patients have inferior MCS and PCS scores

compared to healthy individuals (85) and improved SF-36 scores after endoscopic thoracic sympathectomy (ETS) (86-89). The SF-12 tool is a shorter version of the SF-36 form, reducing the time needed to complete the questionnaire to approximately two minutes but still preserving the certainty of the SF-36 survey results (90).

The Keller scale includes three blocks with five questions each, concerning social and physical limitations experienced from excessive axillary, palmar, and plantar sweating, respectively (91,92). This questionnaire scales the impact on QoL from mild to severe (0 to 10). This scale has revealed the benefits of ETS in treating palmar and plantar PFHH (93-95).

The Hyperhidrosis Impact Questionnaire (HHIQ) assesses the effect of PFHH on daily activities and monitors treatment response (13). It appraises typical disease features, various daily activities, work productivity, and emotional and psychological health (96). The test combines two related components: 41 questions for measuring the baseline impact of the disease and 10 items for follow-up assessment.

The Skindex test is a questionnaire used to evaluate the impact of a dermatologic disease on a patient's QoL (97). It includes 61 components, which are divided into 8 domains (physical limitations and discomfort, embarrassment, fear, anger, depression, and cognitive and social effects), within three categories: symptoms, functioning, and emotions. The test utilizes five graded responses never, rarely, sometimes, often, all the time. The summed results are standardized to a scale of 0–100, with 100 indicating the maximum impact on a patient's QoL. The original 61-item questionnaire has been shortened to sequential versions of 29-item (Skindex-29) (98), 17-item (Skindex-17) (99), and 16-item (Skindex-16) questionnaires to minimize the time required to complete the form (100), while still maintaining comparable tests.

The disease-specific health-related questionnaire for hyperhidrosis by Amir *et al.* is a 35-item questionnaire with a 7-point scale for each answer, divided into five domains (38). Score levels are as follows: 1–2 (high QoL); 3–5 (medium QoL); and 6–7 (significantly low QoL). The results for PFHH patients have shown that women's QoL is more affected than men's, various aspects of QoL are affected, and that lower QoL occurs when the disease begins in childhood (101). This questionnaire has also demonstrated the effectiveness of surgical interventions for PFHH patients (102).

The Hyperhidrosis Quality of Life Index (HidroQoL) is a newly developed disease-specific QoL measurement tool (103). Its final version contains 18 items, categorized into two domains: activities of daily living (6 questions) and psychosocial impact (12 questions). Patient responses are rated in a 6-point scale: not at all = '1'; little = '2'; somewhat = '3'; quite a bit = '4'; very much = '5'; and not relevant = '6'. The results are summed up to either a sub-score (Q1–Q6 activities of daily living score, or Q7–Q18 psychosocial impact score), or overall score.

The Hyperhidrosis Questionnaire is a disease-specific tool that includes 29 questions combining five domains: physical, functional, social, psychological, and affective (104).

The Illness Intrusive Rating Scale (IIRS) is a non-disease-specific questionnaire designed to appraise the intrusion impact of either a disease, its therapy, or both, on a patient's daily activity (43,105). IIRS utilizes 13 QoL domains, which are scored using seven scaled responses from not very much to very much (1 to 7). The questionnaire may be used as one, 13-item scale, or may be separated into three individual subsets of personal, family or social relationship development; intimacy; and influential (such as work) applications. Even though IIRS is too general for QoL assessment of PFHH patients, patients have shown dramatically improved scores after surgery using this questionnaire (43).

Other less frequently used measurement tools for reviewing QoL of HH patients, which are mostly mentioned in single literature articles, include The Everyday Life Questionnaire (106), Patient Benefit Index (107), Hyperhidrosis Disease Severity Measure-Axillary (108), The State–Trait Anxiety Inventory (109), VQ-Dermato scale: a French-language scoring instrument validated for chronic skin diseases (110,111), Freiburg Life Quality Assessment (112), EuroQol-5 Dimensions (113), The Leibowitz Social Anxiety Scale (114), The University of California, Los Angeles, Loneliness Scale (115), The Nottingham Health Profile (116), and Quality of Life survey adaptation from the Caregiver Questionnaire (117).

## Conclusions

HH is a debilitating disease affecting patients in almost every aspect of daily living. Early diagnosis and proper treatment may prevent devastating consequences on QoL. Although the diagnosis of HH is commonly based on subjective testimonies from HH patients, various quantitative and qualitative measurement tools are available to identify the disease, grade its severity, and provide appropriate and prompt treatment.

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