



Is still hyperhidrosis a worthy of investigation issue?—primary hyperhidrosis and its treatment: state of the art

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Introduction

Hyperhidrosis is an excessive sweating compared to physiological body thermoregulation. It is a benign disease much more common than anyone thinks. Hyperhidrosis is not life-threatening but severely affects individual's social, mental and working life leading to a lower QoL.

Therapy involves different medical specialists ranging from dermatologists to thoracic surgeons and is not standardized at the moment. Common guidelines edited by the main medical societies should be welcomed but unfortunately, they are missing, therefore, only International Hyperhidrosis Society recommendations for clinicians are available at present.

That is way, an all-round review of this issue is strongly needed. Our aim is to introduce point by point all main topics regarding this disease and to highlight items to be developed.

Etiology

Hyperhidrosis can be primary or secondary. It is called secondary when consequence of other different underlying health conditions or diseases; for example, obesity, gout, menopause, tumor, mercury poisoning, diabetes mellitus, or hyperthyroidism. Secondary hyperhidrosis is never treated by surgical intervention since it is cured by systemic treatments for each specific underlying disease. Instead, primary hyperhidrosis (PH) is idiopathic, that means “of unknown cause”, and may require surgery. PH arises by any affection of the sweating pathway comprising different neurological structures originating from hypothalamic sympathetic centers and descending through the sudomotor chain to the sweat glands. These affections are supposed

to be responsible of a great discrepancy between normal stimuli and sweating response so much that sweating could be even triggered by any motivation.

Physiologists have sought to identify the anatomical and physiological characteristics of patients affected by PH (1). The most interesting suggestions can be summarized as follows:

- (I) PH familial history ranges between 34% to 50% of patients;
- (II) A disease allele has been found in 5% of patients. It is supposed to give hyperhidrosis in 25% of times when present;
- (III) Higher number of ganglion cells and apoptotic cells in the ganglia that result larger in size have been found. Moreover, thicker myelin sheath of axons has also been reported (2);
- (IV) Assuming that neural tissue is exposed to an improved functional stimulation, a higher expression of acetylcholine receptors and an oxidative damage in the sympathetic ganglia have been found (3);
- (V) Some personality disorders or traits such as character affect biological systems.

Conclusions: unfortunately, all of these etiologic assumptions are still hypothesis since most of findings must be confirmed. Thereby, PH is in fact an idiopathic disease and its true etiology need to be better addressed.

Diagnosis

PH presents with specific clinical features. It is usually focal and bilateral affecting hands (palms), axillae and/or foot

(plants). Craniofacial hyperhidrosis may also be associated with facial blushing, but is infrequent. It arises during the first decade of life (childhood) usually with palmar hyperhidrosis. During adolescence, symptoms become very disturbing and badly affecting QoL. Family history is often positive.

Symptoms should be not conditioned by atmospheric events but, at least, excessively affected. On the contrary, mental or emotive stimuli significantly improve sweating. Sweating rarely arises during sleep.

Therefore, diagnosis is easily reached by mere careful clinical history recording and by routine clinical evaluation based on assessment of the sweat stains of clothes or palmar sweating extension. However, some instruments that quantitatively assess sweating amount are available. These are the gravimetric measurement, the vaporimetry, the Minor test and a variety of tools or questionnaires at clinician's disposal for quantifying patient's discomfort or QoL (4,5).

Once excessive sweating has been argued, secondary hyperhidrosis must be excluded researching signs and symptoms of possible underlying diseases. Above clinical and pharmacological history, these exams are mandatory: thyroid function, metabolic panel, 24 h urine collection for catecholamines, metanephrines and normetanephrines, serum free metanephrines and normetanephrines, urine 5-hydroxyindolacetic acid.

Conclusions: despite PH suspicion is quite simple, the challenge is to correctly quantify patient's affliction in order to point out the best therapy. The questions are (I) does exist a measurable cutoff for excessive sweating or it is a subjective discomfort different for each patient? (II) which is the role of surveys? More recommendations about this issue are needed especially when surgical approach has to be considered.

PH management

PH is managed by a step-therapy model which firstly provides medical or non-invasive therapies. Then, more invasive procedures are usually considered until it gets to surgery. However, surgery could be also initially proposed after that advantages and disadvantages of non-surgical approaches have been discussed. We present an all-around update on every treatment focusing on more deserving items.

Topical and systemic therapies

Medical PH treatment is based on topical and systemic

drugs. Unfortunately, these are affected by similar disadvantages which consist in short term results and nasty adverse events (6).

Aluminum chloride is probably the most widespread topic agent labelled for axillary and palmar hyperhidrosis. It acts as an antiperspirant by obstructing eccrine sweat glands and destroying secretory cells. Unfortunately, results are disparate, not permanent and skin irritation afflicts many patients.

Other topic treatments which acts with an anticholinergic effect are available. These are glycopyrronium tosylate, propantheline and oxybutynin.

Glycopyrronium tosylate has been approved only for axillary hyperhidrosis and is related to adverse effects as dry mouth, erythema and burning that enhance its discontinue use.

Propantheline is an off label treatment for axillary and plantar hyperhidrosis. Its results are modest and adverse effects absent.

Oxybutynin is a muscarinic antagonist used for overactive bladder. It is also used as off label anticholinergic for PH. When administered orally it provides good results but also severe adverse effects such as dry mouth, constipation, urinary retention, tachycardia, blurry vision and drowsiness. Transdermal patch seems to guarantee same results but less adverse effects.

Oral therapy is based on anticholinergic effects provided by glycopyrrolate or oxybutynin. Both give interesting results but also typical severe adverse effects. Moreover, geriatrics patients or people with gastrointestinal disorders, urinary retention or glaucoma should avoid this treatment.

Conclusions: topical therapies for hyperhidrosis are often off label medicine providing disparate results and invalidating adverse effects. Moreover, improved symptoms came to an end when therapy is interrupted. Oral anticholinergics usually help to manage excessive sweating for some hours or in short term situations and are rarely used as long term therapy. Based on these considerations it follows that medical approach is still first-line treatment to be considered; however, disparate results and adverse effects often make patients unsatisfied and lead to quit treatments that rarely are long-term therapy but rather a temporary solution. Therefore, further studies are needed to better define treatment dose range or introduce new molecules.

Non-invasive therapy

Iontophoresis

Iontophoresis provides local effects on eccrine sweat glands

due to ionized water passage through the skin via direct electrical current. Therapeutic mechanism is still unclear, however results are encouraging. Unfortunately, this can be applied almost only to palmar and plantar regions. Adverse effects are mild (erythema, paresthesia, vesiculation) and usually treated by local steroids (7).

However, it requires a medical device and each treatment last about half an hour. Sessions should be repeated several times a week especially at the beginning. This is why patients usually quit therapy looking for a definitive cure.

Conclusions: modern equipments are expected to guarantee more effective and sustainable sessions.

Injectable agents

Botulinum toxin

Botulin toxin A is used for every types of local hyperhidrosis. Injected under the skin in the areas affected by excessive sweating, it reduces discomfort reversely blocking autonomic cholinergic sympathetic nerve fibers. Results are very satisfying and last for several months, therefore usually two sessions per year are needed (8).

This is an effective but not a definitive cure. Moreover, each session consists of several injections often requiring local anesthesia. Pain is indeed the only reported adverse effect. However, these points sometimes adversely affect patients' opinion. Furthermore, there is also a central economic aspect.

Conclusions: despite botulinum toxin A therapy has probably been the most studied non-surgical treatment for hyperhidrosis, new trials have been engaged to compare different existing products and investigate new therapy options.

Medical devices

Another option is to reduce the severity of sweating by sweat glands destruction with application of heat in the dermis. The aim is to provide long lasting results and few adverse effects compared to the other non-surgical treatments. Due to their non-selective effect, skin and nerve damages are possible. This procedure can be applied only for axillary hyperhidrosis; therefore cases of palmar and plantar excessive sweating must be excluded. There are many devices adopting different techniques to produce thermal glands destruction. They are classified as nonsurgical treatments. We introduce the most common.

Microwaves

This is a painful procedure obtained positioning device

antennas at the skin-adipose interface. Dielectric heating causes sweat glands thermolysis. Usually 10–40 applications are need per session. Session duration is about 30 min per axilla. Two sessions in two weeks are required. Besides temporary pain, usually managed by local anesthesia, adverse effects are due to local inflammation and last few weeks (9).

Radiofrequency

This procedure uses bipolar radiofrequency delivered into the skin by multiple micro needles. Local anesthesia and multiple sessions are required. Data showed good results in 80% of patients but are limited and long-term studies are still lacking (10).

Laser

Some Authors have proposed laser energy to destroy sweat glands. Despite laser therapy has been already and successfully adopted for other treatments, its application for hyperhidrosis is still in its early days (11).

Ultrasound

This is another technique to reduce sweat glands numbers by local heating. Its use is about anecdotal (12).

Conclusions: unfortunately, there are few strong evidences in favor of these minimally invasive procedures especially if compared with Botulin toxin A. This is why few trials, with small population and short follow-up, are available, except for radiofrequency. Therefore, since beginning results on sweating management are encouraging, further trials should be promoted.

Surgical therapy

Surgery for hyperhidrosis consists of endoscopic thoracic sympathectomy (ETS) or underarms surgery.

Local surgery

Underarms surgery provides sweat glands reduction in number so that they can no longer produce sweating. It is typical for axillary hyperhidrosis. Its advantages are absence of compensatory sweating and limited invasiveness. However, adverse effects are frequent and very disturbing. Different techniques have been proposed but all are barely widespread. They are office procedures with awake patient, ranging from radical excision of the axillary skin to subcutaneous procedures performed by curettage, suction curettage or laser-assisted suction curettage. Outcomes in

sweating reduction are interesting but often associated with scar tissue, wound healing, skin necrosis, fistulas, cysts or hematoma. Recurrences have been described (13).

Conclusions: unfortunately, there is a lack of prospective or comparative studies about underarms surgery for hyperhidrosis. Therefore, further trials should be encouraged with the aim to obtain comprehensive recommendations.

ETS

ETS is a surgical procedure consisting of sympathetic chain disruption. It is usually known as sympathectomy. With VATS advent, the removal of part of the nerve has been abandoned but the name sympathectomy is still common. Nowadays, chain interruption is obtained by a simple resection and is named sympathicotomy or sympathectomy.

Nerve interruption is usually bilateral for palmar, axillary or facial PH. Endoscopic surgery is the gold-standard, however there are many different approaches and techniques. Biportal technique is the most widespread, but uniportal VATS introduction has been welcomed for ETS as well.

VATS sympathectomy is the most diffuse surgical therapy. It is safe and permanently successful but associated with an undesired effect called compensatory hyperhidrosis (CH) (14).

Remission of the target body area excessive sweating is the main purpose of surgery. Results are clear just at patient's awakening and consolidate in the first 30 days.

ETS success rate depends on symptoms localization and surgical approach. Palmar sweating management, for instance, is more effective than cranium-facial. As concerning technique, nerve disruption level is probably the most important factor conditioning results, in terms of both sweating remission and CH occurrence. Surgical strategy is based on the statements that high level and multiple nerve chain disruption more likely guarantee dry skin whereas low resection prevent CH occurrence.

Several papers have been already published showing outcomes for each symptoms location according to nerve interruption level and related CH onset rate. Unfortunately, these series are hardly comparable because of heterogenous data and therefore, thoracic surgeons still perform denervation at different levels with different techniques (transection or clipping).

Only an expert consensus for surgical management of PH, edited by STS in 2011, is available. It provides many recommendations about interruption level of the

sympathetic chain in order to obtain the best outcomes concerning sweating reduction and CH occurrence for each affected body area (15).

Conclusions: we are conscious that target level of interruption should be always chosen weighting benefits and adverse effects by agreement with patient will, however the lack of endorsed guidelines is a gap that should be filled. With regard to technical aspect, new trials should be encouraged to find out which is the best approach (biportal *vs.* uniportal) and the best way to interrupt sympathetic chain (clipping, harmonic devices, electrocautery, etc.).

CH management

CH is excessive sweating arising in another body area after sympathectomy; it often affects thorax, back or thighs. It is an adverse effect rather than a real complication. However, CH sometimes severely makes patient's QoL worsen. Its mechanism is unclear; the most likely assumption is that dorsal sweating compensates for the lack from the denervated areas to maintain thermoregulation. Many therapeutic options include treatments which have been already considered for PH itself. They are topical agents, botulinum toxin, systemic anticholinergics. When nerve trunk interruption has been performed by clipping, clip removal may be considered (16). Some Authors have also proposed sympathetic chain reconstruction but its efficacy is not well-established (17). Some series of nerve grafting have been reported and nerve regeneration was successful in many cases. However, follow-up was short.

Conclusions: more data are needed to find out efficacy and factors contributing to successful nerve reconstruction to manage CH after sympathectomy.

Conclusions

PH has been already investigated by different specialists in order to definitively determine its etiology and the best diagnostic and therapeutic pathway. Several data have been already collected and different options are now available for its treatment. However, many meaningful points still lack of evidence and definitive guidelines are expected. Based on this need, we have listed the most interesting topics that will be investigated by a team of specialists in the next chapters.

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