Primary hyperhidrosis – pathogenesis

Primary Hyperhidrosis (PHH) is a disease of genetic origin, characterized by excessive secretion of eccrine sweat, mainly within palms, armpits and feet (1, 2, 3). Having onset in early childhood or adolescence, according to correspondence research the disease concerns circa 0.6-1% of the Caucasian population (4, 5) and is associated with significant reduction of life quality resulting from impairment of daily activities, social interactions and professional activities (6, 7). The disease is more common in females than males, with a predominance of females 65: 35 (1, 8).

A reliable evaluation of hyperhidrosis prevalence in the population is not easy. Correspondence research, which constitutes the majority of PHH epidemiological analyses, are burdened with interpretation error made by respondent. As demonstrated in papers of our team, the subjective evaluation of hyperhidrosis prevalence in population often significantly differs from actual data obtained with objective methods (9, 10, 11). On the basis of research conducted by our team on 253 students it has been demonstrated that primary palmar hyperhidrosis may occur even from 4.7% of people (subjective declaration) to 7.1% (gravimetric screening method), whereas axillary hyperhidrosis from 11% (subjective declaration) to 16.2% (gravimetric assessment) (10).

The pathophysiology of primary hyperhidrosis is not fully understood. Front cortex of a part of cingulate gyrus is presumably responsible for excessive sweating which occurs in response to sensory or emotional stimuli (5). Research conducted by Sato et al. (2) has not revealed the presence of histopathological changes in the sweat glands or their increased number in patients with diagnosed primary hyperhidrosis. Cholinergic sympathetic nerve overactivity (12) or disorder of the sympathetic nervous system (13), which lead to the production of excessive amounts of sweat and reduce cutaneous blood flow, are considered to be the cause of the symptoms. The most common form of focal hyperhidrosis is excessive sweating localized mainly on the surface of palms or feet. In circa 50% of cases, excessive sweating in axillary area additionally coexists with that types of localization. The least frequently occurring type of primary hyperhidrosis is isolated craniofacial hyperhidrosis (5). Maceration is not a rare ailment occurring in people who excessively sweat in axillary area. Moreover, skin inflammation with general irritation or contact allergies may occur as a result of too frequent use of soap and antiperspirant (14). Sweat drops are often visible to the naked eye, especially often they appear on the sides or even on the backs of the fingers. Patients complain of high discomfort which they experience in everyday life such as constant staining of documents and other objects made of paper as well as that items made of metal touched by people affected by the disease are often subject to corrosion (14). Thus, the disease has a significant impact on the life quality of patients, leading to withdrawal from social functioning and avoidance of interpersonal relationships (7). Young people do not take the effort to achieve a higher level of edu-
cation, resign from occupations which require working with people, documents, food or is burdened with considerable stress (6, 7). PHH also affects in a significant way the emotional and sexual lives of patients, impairing the possibility of establishing relationship with another person (6, 7).

Family history of the disease has been proved by many authors (15, 16) – 40-65% of patients have a positive family history and, as mentioned above, an autosomal dominant influence of incomplete gene penetrance seems to be the most likely inheritance model. According to Higashimoto et al. (3) one of the loci responsible for the formation of primary palmar hyperhidrosis is located between genes D14S1070 and D14S990 in region 14q11.2-q13 (3). Genetic screening has also revealed the connection with genetic syndrome referred to as nail-patella syndrome (region 9q34.1) (17).

Diagnosis of primary hyperhidrosis

Natural hyperhidrosis occurs when adapting to a new, more humid and warmer climate. Obese people being in high temperature or working hard are affected by excessive sweating. Sweating with facial flushing during menopause is quite common. Numerous medical conditions also cause an increase in perspiration, but this case is referred to as secondary hyperhidrosis (tab. 1). Patients consider emotional or idiopathic sweating having no obvious cause to be the most disturbing (14).

In the diagnosis of primary hyperhidrosis it is primarily important to exclude secondary causes of excessive sweating, which include various types of infections, tumours, drugs as well as neurological and endocrine diseases (tab. 1).

Walling describes over 40 causes of hyperhidrosis both local and generalized. According to this author unilateral, asymmetric, generalized prevalence of hyperhidrosis is strongly linked to its secondary cause. In contrast, the diagnosis of primary hyperhidrosis may be supported by primary involvement of armpits, hands, feet or face, bilateral and relatively symmetrical prevalence of the lesions, frequency of at least one episode per week, cessation of sweating during sleep, onset before

<table>
<thead>
<tr>
<th>Focal</th>
<th>Generalized</th>
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<tbody>
<tr>
<td>Nerve damage (central/peripheral)</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>Frey’s syndrome</td>
<td>spinal cord injuries</td>
</tr>
<tr>
<td>Compensatory hyperhidrosis (after sympathectomy)</td>
<td>meningioma</td>
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<tr>
<td>Arnold–Chiari malformation</td>
<td>intracranial abscess</td>
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<tr>
<td>Neuropathies</td>
<td>stroke</td>
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<td>Complex Regional Pain syndrome</td>
<td>neuromyotonia</td>
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<td>Raynaud’s disease</td>
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<tr>
<td>Tumours</td>
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<tr>
<td>Mesothelioma</td>
<td>carcinoïd syndrome</td>
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<td>Lung cancer</td>
<td>pheochromocytoma</td>
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<td>Chondroblastoma</td>
<td>lymphomas</td>
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<td>Thymoma</td>
<td>thymoma</td>
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<td>Hodgkin’s lymphoma</td>
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<tr>
<td>Genetic syndromes</td>
<td></td>
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<tr>
<td>Epidermolysis bullosa</td>
<td>phakomatosis pigmentokeratotica</td>
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<tr>
<td>Pachyonychia congenital</td>
<td>ectodermal dysplasia</td>
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<tr>
<td>Palmoplantar keratoderma</td>
<td>familial dysautonomia (Riley-Day syndrome)</td>
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<tr>
<td>Autonomic eccrine glands disorders (e.g. eccrine nevus)</td>
<td>congenital endochromatosis</td>
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<td>Klippel-Trénaunay syndrome</td>
<td></td>
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<tr>
<td>Endocrine and metabolic diseases</td>
<td></td>
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<tr>
<td>Has not been described</td>
<td>diabetes</td>
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<td></td>
<td>hyperthyroidism</td>
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<td>hyperpituitarism</td>
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<td>acromegaly</td>
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<td>pregnancy</td>
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<td></td>
<td>porphyria</td>
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<td></td>
<td>phenylketonuria</td>
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</table>
Diagnosis and treatment of primary hyperhidrosis

the age of 25, positive family history and impairment of daily activities. According to Walling, the presence of 4 out of 7 of the above mentioned symptoms is related to 99% sensitivity and 82% specificity in the diagnosis of primary hyperhidrosis (18) (tab. 2).

Research conducted by our team has, however, revealed that restriction of qualification to surgical procedure only to history data assessment may be insufficient (9, 19). Subjective assessment allows in fact for diagnosis of primary hyperhidrosis, however, in the context of reported serious side effects of thoracic sympathectomy described below it is not sufficient to qualify a patient for this form of treatment. Therefore, objective assessment of disease progression is required.

The methods of objective assessment of hyperhidrosis include gravimetry, vapometry and skin resistance measurements. Gravimetry is a short and simple test that measures the amount of sweat per unit of time (20). Gravimetric test is performed in patients after 15-minute rest at room temperature 21 to 25 degrees Celsius. Initially, cotton swabs are weighed on a laboratory scale with high precision (requires an accuracy of ±0.1–0.5 mg). Patients collect sweat with 1-3 swabs during 1 minute. Afterwards, the swabs are weighed again. Net weight of secreted sweat is calculated as the difference between the gross weight (swab weight after the test) and tare (swab weight before the test). The result is divided by the total surface of the subject’s body in order to minimize the impact of the body build on the result (11, 20). Reference values for the different areas of the body have been determined in the study conducted by our team on over 400 volunteers (11). They amount to 16 mg/min/m² for the face and

<table>
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<th>Focal</th>
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<tr>
<td>Primary</td>
<td>Common</td>
</tr>
<tr>
<td>Medications</td>
<td>has not been described</td>
</tr>
<tr>
<td>Infections</td>
<td>has not been described</td>
</tr>
<tr>
<td>Cardiovascular/ respiratory diseases</td>
<td>has not been described</td>
</tr>
</tbody>
</table>

Table 2. Differential diagnosis of hyperhidrosis

<table>
<thead>
<tr>
<th>Primary hyperhidrosis</th>
<th>Secondary hyperhidrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>– Primary involvement of armpits, hands, feet or face</td>
<td>– Generalized occurrence of hyperhidrosis</td>
</tr>
<tr>
<td>– Bilateral and relatively symmetrical sweating</td>
<td>– Unilateral or asymmetric sweating</td>
</tr>
<tr>
<td>– Frequency of at least once a week</td>
<td>– Onset after the age of 25</td>
</tr>
<tr>
<td>– Cessation of symptoms during sleep</td>
<td>–</td>
</tr>
<tr>
<td>– Onset before the age of 25</td>
<td>–</td>
</tr>
<tr>
<td>– Positive family history</td>
<td>–</td>
</tr>
<tr>
<td>– Impairment of daily activities</td>
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</table>
palms, 40 mg/min/m² for axillary region and 13.5 mg/min/m² for abdominolumbar region. Thus, qualification values for thoracic sympathectomy (defined as mean + two standard deviations) have been determined. They amount respectively to 55 mg/min/m² for face and palms and 125 mg/min/m² for axillary region (9).

Vapometric test is based on the assessment of transepidermal water loss performed in open diffusion chamber in which gradient of vapour pressure measured in g/h/m² according to Fick’s law is being assessed (21). Assessment is performed by portable device called Vapometer (Delfin Technologies Ltd., Kuopio, Finland) (22). The chamber is adjacent to skin with a surface of 1 cm diagonal, whereas the test lasts from 8 to 10 seconds. The result is presented as grams of evaporated water per unit of surface area per hour (g/m²/h) (21). This method is a simple, yet sensitive and able to assess the level of hyperhidrosis (23). The study of 75 patients (50 patients with primary hyperhidrosis of palms and feet and 25 healthy volunteers) (24) has revealed that transepidermal water loss on palms and feet for the first group amounted to respectively 133.6 ±51 g/m²/h and 71.8 ±40.3 g/m²/h, while these values amounted respectively to 37.9 ±18.4 g/m²/h and 27.6 ±14.3 g/m²/h in the second group. Similarly, the results of the axillary hyperhidrosis assessment with gravimetric method amounted to 473 g/m²/h (within the range of 98–998) in a group tested before the treatment and 58 g/m²/h (within the range of 21-227) after the treatment and 23.7 mg/m²/h (in the range of 18–31) in a control group (25). The use of this method in patients with primary hyperhidrosis is limited by: high variability in transepidermal water loss in these patients and episodic nature of the symptoms (26), relatively high cost of the device as well as the fact that it is impossible to quickly assess several localizations or patients during the test with a group stress provocation component.

Another, less frequently used method to measure the amount of sweating is skin resistance measurement. The basic idea of this method is the fact that the better moisturized the skin, the better it conducts electrical impulses, so its resistance it will be smaller in comparison with the resistance of dry skin. Universal multimeter Metex Me-31, equipped with two gold electrodes placed in a standard distance from each other being 1 cm, is used in the measurements. Changes in skin resistance are observed for 10 s in each observed point. The average result of 10 measurements is used for statistical analysis (27).

Diagnostics of primary hyperhidrosis in our centre is based on: (i) the history of disease (presence of symptoms since childhood or adolescence, limitation of hyperhidrosis to trigger points, absence of generalized hyperhidrosis in response to stress or temperature), (ii) endocrine consultation in order to exclude endocrine diseases that may lead to hyperhidrosis, (iii) gravimetric assessment (28). Gravimetric test has qualitative and quantitative nature, as it allows for the assessment of sweating type (isolated increase in trigger points, i.e. palms, armpits and feet, and no increase in other regions i.e. face, torso) and it indicates possibilities and limitations of treatment i.e. the choice of treatment method depending on the severity of the symptoms.

Treatment

The primary hyperhidrosis treatments include oral or topical medications, iontophoresis, subcutaneous injections of botulinum toxin and surgical treatment involving retrodermal curettage and sympathectomy (tab. 3) (4, 5).

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Palmar</th>
<th>Axillary</th>
<th>Therapeutic options</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>0-20 mg/m²/min</td>
<td>0-40 mg/m²/min</td>
<td>topical treatment, conservative treatment, iontophoresis, botulinum therapy</td>
</tr>
<tr>
<td>Mild</td>
<td>20-55 mg/m²/min</td>
<td>40-125 mg/m²/min</td>
<td></td>
</tr>
<tr>
<td>Mediocre</td>
<td>55-150 mg/m²/min</td>
<td>125-200 mg/m²/min</td>
<td>iontophoresis, botulinum therapy</td>
</tr>
<tr>
<td>Severe</td>
<td>over 150 mg/m²/min</td>
<td>over 200 mg/m²/min</td>
<td>retrodermal axillary curettage, sympathectomy</td>
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</table>

Table 3. Available treatment methods depending on the severity of primary hyperhidrosis
Conservative treatment

The main groups of drugs used in conservative treatment of PHH are anticholinergics (Oxybutilin), beta-blockers (Inderal), sedative drugs (Relanium), topically applied aluminium chloride (Etiaxil, Antidral, Driclor) and preparations containing formaldehyde (Uro) as well as plant preparations containing extracts of sage, perilla frutescens, oak or birch rind. The advantages of conservative methods include relatively small price, simplicity of therapy and lack of side effect in the form of compensatory hyperhidrosis occurring after treatment with other methods. Unfortunately, their effectiveness is limited and side effects of therapeutic doses of medicines acting generally often prevent their long-term use.

Sedatives cause numerous side effects such as reduced motivation or drowsiness. Young and active people may consider it to be a significant inconvenience, therefore it is not recommended to use this treatment method in the above mentioned group of patients. Anticholinergics are the most commonly used drugs in conservative treatment of PHH. Mechanism of their action is based on direct influence on sweat glands by inhibiting their secretive function. Side effects of this drugs result from their systemic effects and include xerostomia, tachycardia, constipation, painful or difficult defecation or urination, indigestion, dizziness, and headache. This method should not be applied to patients suffering from cataracts or urological diseases.

Topical treatment with preparations containing aluminium chloride or formaldehyde results in a decrease in perspiration in the area where it was applied. However, side effects such as skin irritations, burning sensation are present, especially if there is no possibility to apply the preparation on completely dry skin. In addition, the effectiveness of preparations in relation to PHH with a medium and a high intensity is insufficient (29).

Swaile et al. have evaluated the effectiveness of medicines available without prescription containing aluminium preparations and used in hyperhidrosis treatment with gravimetric method. They have demonstrated that in 85% of respondents the intensity of sweating has decreased by at least 50%, while products without the aluminium content decreased sweating intensity at an average of 34%. The authors have however emphasised that products with no aluminium caused skin irritation in considerably less extent (30).

Invasive treatment

Iontophoresis

Iontophoretic treatment is based on cutaneous introduction of ionophore i.e. an agent with charged particles with the use of galvanic, direct current. This method has been used in the treatment of palmar and plantar hyperhidrosis. It can be used as therapeutic in hyperhidrosis with mild or moderate intensity, as a method preceding the use of invasive treatment or to treat compensatory hyperhidrosis (20). The mechanism of iontophoresis is based on distracting the communication between the nerve end and eccrine sweat gland, or on disturbing the functioning on the gland itself (31). It is not required to use any ionophores, as interaction of ions present in tap water is sufficient. Side effects are mild and include excessive hand dryness and tendency of skin to rupture. Application of moisturizing creams or lowering the frequency of the treatment results in decrease in the number of side effects. Erythaema or less frequently skin blisters can be easily reduced with application of 1% hydrocortisone in cream. In the case of burns or epithelium damage due to other reasons, it is recommended to cover the lesions with thick layer of insulating substance (e.g. vaseline) during the treatment. Treatment of burns caused by iontophoresis is rather long-lasting. Argosulfan 2% is a recommended drug. Usually the treatment is started with series of 20 initial sessions, after which patient may attempt to gradually extend the interval between treatments. Compensatory hyperhidrosis does not occur after iontophoretic treatment due to lack of damage to the gangliated cord. This treatment is not used in facial or axillary hyperhidrosis treatment because of troublesome application of electrodes (32). Iontophoresis is promising for the treatment of compensatory hyperhidrosis (20). This form of treatment is possible with the use of self-adhesive gel electrodes, similar to those used as passive electrodes in surgery.
Botulinum toxin therapy

Another method of hyperhidrosis treatment is treatment with botulinum toxin type A (TB-A). It is a neurotoxin produced by anaerobic bacterium Clostridium botulinum (33). This form of treatment acts by inhibiting acetylcholine release in neuromuscular junction and, more importantly, in postganglionic sympathetic fibres that innervate the sweat glands what leads to the secretion of local anhydrase (34, 35). The use of botulinum toxin type A seems to be an effective, safe and well-tolerated method of primary hyperhidrosis treatment. The effectiveness of this method is estimated at 95% in the treatment of axillary hyperhidrosis and over 90% in palmar hyperhidrosis treatment. The effects lasts approximately 4 to 7 months (36-39). Unfortunately, according to the experience of our team, it seems that application of botulinum therapy is ineffective in treatment of PHH with severe symptoms (20). Side effects include pain related to injections and slight hand muscle weakness after palmar injections (40). Counter indications of botulinum toxin therapy include neuromuscular disorders such as myasthenia gravis, pregnancy, lactation, organic causes of excessive sweating and the treatments that may affect motor end plate (41).

Among the complications in patients treated with this method, appearance of antibodies against the toxin should be mentioned what implies significant reduction of the effectiveness of treatment during subsequent therapeutical sessions as well as pain particularly due to TB-A palmar injection which often require local blockage of the ulnar and intermediate nerve. Moreover, penetration of nearby motor palmar muscles by TB-A may result in impairment of ability to perform precise movement of fingers (5). Other complications include also indigestion and pyrosis (42).

Therapeutic effects of injections are observed after circa 2–4 days, whereas full effect is achieved around day 14 after the first injection (5). Talarico-Filho et al. (43) have conducted research on the percentage of people whose treatment was successful. Reduction by 50% of secreted sweat after the treatment in comparison to measurements performed before botulinum toxin type A has been treated as objective success. Both first and second measurements have been made by gravimetric test. After a month, 100% of patients have presented satisfactory results on both sides of armpits, whereas after three months two patients showed decline in treatment effectiveness below 50% in objective assessment arising from gravimetric measurement. Data on permanence of the effects are rather divergent in the literature but fall in the range of 7 to over 12 months after which the sweat glands activity is gradually restored and the treatment must be performed again (14, 43).

Montaser-Koushari et al. have performed a comparison of effectiveness of treatment of isolated axillary hyperhidrosis with botulinum toxin and ionophoresis. Observations have been made after one week, one month and six months. They have revealed the superiority of botulinum treatment in all measured points (respectively 84%, 76% and 50% vs 73%, 22%, and 32%). Short observation period may be considered to be disadvantage of their research (44).

Retrodermal courettage

Retrodermal courettage is a surgical procedure consisting of mechanical removal of axillary sweat glands located on the inner surface of the dermis. Treatments may be divided into three main groups: 1) removal of subcutaneous tissue without cutting the skin, 2) removal of axillary skin along with adjacent subcutaneous tissue, 3) partial excision of the axillary skin with the removal of subcutaneous tissue (45).

First attempts of eccrine glands excision were performed in the sixties and were significantly disfiguring. Currently, the development of technology and medicine has improved the method which allows for surgical excision of eccrine and apocrine glands located in axillary region in people suffering from hyperhidrosis. There are two types of treatments: liposuction and courettage, which are conducted under local anaesthesia.

The aim of treatment is to remove sweat glands which are located between the subcutaneous adipose tissue and the dermis. Usually qualification for treatment procedure consists of performing Minor test only. In our centre, it is recommended to perform gravimetric tests as well.

Treatment results indicate that 80-90% of people affected by hyperhidrosis, who have
benefited from a local excision of sweat glands in axillary area, experience satisfaction of the procedure and have noticed significant reduction in sweating (5). Researchers variously report the permanence of treatments effects to last from 6 weeks to 28 months, but agree on the fact that treatment effectiveness declines with the elapse of time (5, 46, 47, 48).

The big advantage of courettage is not only a relatively long time of permanence of treatment effects but also avoiding the risk of compensatory hyperhidrosis, which in the case of thoracic sympathectomy is very high (46). It should be noted that this method is also burdened with the risk of complications such as infections, bruising, pain or scars and can only treat excessive sweating in axillary region (5, 46). However, some studies have revealed subjective increase of trunkal sweating after courettage treatment (49). Heidemann and Licht have observed prevalence of gustatory hyperhidrosis in 25% of the patients, while compensatory hyperhidrosis in 26% of patients after axillary retrodermal courettage (49).

West et al. have compared the effectiveness botulinum toxin therapy and courettage in axillary hyperhidrosis treatment. They have revealed that botulinum toxin caused decrease in sweating measured gravimetrically by 72.1% compared to a reduction of 60.4% observed after courettage treatment in relation to rest sweating and one induced by physical activity what led to more significant improvement of life quality after botulinum toxin therapy. Unfortunately, the study has been limited to 6 months after the treatment what significantly affects its generalization. After a longer period the regression of therapeutic effect of botulinum toxin therapy would most likely disappear (50).

Thoracic sympathectomy

The most common method of surgical treatment of primary hyperhidrosis is endoscopic thoracic sympathectomy (ETS), consisting of discontinuing the gangliated cord by excision, ablation or clamping sympathetic ganglia. Stem damage level depends on the location of the primary symptoms and should be determined according to the level of the ribs (R). Recent reports indicate that the best results in treatment of palmar hyperhidrosis are obtained if gangliated cord is damaged at the level of upper edge of R3 or R4 rib (51). In the case of axillary or axillary-palmar hyperhidrosis it is recommended to discontinue gangliated cord at the level of R4 and R5 (51). R2 level is recommended in facial hyperhidrosis treatment (51). Literature, however, does not provide any data on differences concerning the effectiveness of treatment between various techniques of gangliated cord discontinuation (51).

The majority of medical centres perform the procedure from anterior approach. Patient is positioned in a sitting position with arms abducted upwards, while trocars are entered in the axilla adjacent to lateral edge of pectoralis major and slightly lower in posterior axillary line. Some centres, especially connected with cardiothoracic surgery, prefer lateral approach. The disadvantage of this approach is the need to turn the patient during bilateral procedure – isolated intubation of one bronchus may cause problems related to endotracheal tube displacement. Centre in Gdańsk, thanks to the experience gained during videothoracoscopic splanchnicectomy (52), perform the procedure from posterior approach with endotracheal intubation with reinforced tube. Patient is placed on the abdomen. Trocars are placed 2 cm medially from scapula angle or in posterior axillary line in fourth or third intercostal space (fig. 1). This position enables to perform simultaneous bilateral procedure with no need to turn the patient and change surgical draping (28).
There are some interesting reports on the order of sympathectomy performance. Ibrahim et al. have revealed that performing two-stage procedure leads to smaller intensity of compensatory hyperhidrosis (53) (14% vs 19%), although this paper has met with strong methodological criticism, mainly due to vague definition of compensatory hyperhidrosis.

Heinemann and Licht have presented the comparison of axillary hyperhidrosis treatment with R2-4 or R3-4 sympathectomy and retrodermal courettage of the axillae (49). During nine years of observatory research they have noted that incidence of symptom recurrence occurred more often after courettage procedure (51%) than after sympathectomy (5%), nevertheless the intensity of recurrence was minor and did not require another surgery. As it was mentioned above, side effects after sympathectomy have been more severe. The authors have emphasized in the conclusions that application of topical treatment to isolated axillary hyperhidrosis should become a preferred method mainly due to minor side effects (49).

Lumbar sympathectomy

Treatment of palmar-plantar primary hyperhidrosis may be complemented with lumbar sympathectomy. In Gdańsk centre, it is recommended to perform second phase of treatment after a break lasting for at least 12 months when the intensity of compensatory hyperhidrosis is determined. In the case of minor severity of this side effect, lumbar sympathectomy is recommended. If compensatory hyperhidrosis is severe, plantar iontophoretic treatment is suggested.

Rieger et al. describes the procedure of endoscopic lumbar sympathectomy (ELS) to eliminate plantar symptoms. The procedure consists of creating endoscopic approach to retroperitoneal space at the level of L2 and L3 vertebra and afterwards discontinuation of gangliated cord. Rieger et al. perform the procedure from anterolateral approach with flank elevation. In the case of ELS, the procedure comprises excision of various ganglia depending on patient’s sex: in female patients excision involves L2, L3 and L4 ganglia, while in men sympathectomy should be limited to third or fourth ganglia in order to avoid ejaculation disorders. Excision level is determined by surgical location of umbiculus which corresponds to L4 level (54).

In Gdańsk, posterior approach is preferred what results from prior experiences with retroperitoneal adrenalectomy (55). Performing the procedure while patient is lying on stomach allows for single-stage bilateral approach, however it should be mentioned that lumbar sympathectomy is more challenging in terms of anatomy for a surgeon than thoracic sympathectomy (56). Thus, bilateral procedure is performed in our centre only in case if unilateral sympathectomy is finished during first 45 minutes of the procedure. In other case the procedure is performed unilaterally and subsequent intervention is planned after one month break.

Lumbar sympathectomy requires an external positioning of the direction what is achieved by Rieger et al. by pre-operative radiological evaluation of the location of each lumbar vertebrae (54). In Gdańsk, first trocar (for vision) is placed midway between the costal arch and anterior superior iliac spine circa 10 cm laterally from the spine. The other two manipulative trocars are placed 2 cm ventrally downward and upward from the optical trocar (fig. 2). In the first phase of the procedure, optical trocar is directed vertically downwards with viewing angle from the bottom. Afterwards, viewing angle becomes flattened. During the entire procedure high pressure of carbon dioxide oedema (circa 22 mm Hg) is maintained on the same level. The cooperation with anaes-

Fig. 2. Location of trocars for endoscopic retroperitoneal lumbar sympathectomy from posterior approach.
Identification of gangliated cord as well as the location of the transection are important elements of the procedure. They are obtained by constant maintenance of the right angle between optical and spine axis. Methods confirming correct level of damage are additionally applied. It may be achieved by constant temperature evaluation, even though the readings are not always clear what has been revealed in previous report of our team (56). Currently, in Gdańsk we use laser evaluation of capillary flow (Doppler laser). This method seems to be very promising.

Treatment results – surgical context

Numerous studies indicate that the treatment of primary hyperhidrosis with thoracic sympathectomy is a safe and effective method (4, 20, 28, 49, 51, 57-63). Treatment results depend on the centre which performs the procedure, but the percentage of complete symptoms relief remains usually at 95% (51, 57-63). The most serious intraoperative problems include: the presence of pleural adhesions (incidence <3%), hindered visualization of gangliated cord due to excessive adipose tissue (ca. 1%), blood vessels obscuring gangliated cord (<1%) and bleeding into the pleural cavity (1–5%) (59). No perioperative mortality has been observed in any major study. The most common complication is postoperative pain that occurs in 30–90% of patients (51, 57-63). Other early complications such as pneumothorax with required drainage, neurological disorders of upper limbs are encountered rarely, with a frequency not exceeding 5% (51, 57-63). Horner’s syndrome, significant bleeding, subcutaneous oedema, chylothorax, rupture of subclavian artery, intracostal neuralgia are encountered even less frequently, below 1% of patients subjected to thoracic sympathectomy (4, 20, 28, 49, 51, 57-63).

Horner’s syndrome is associated with too high transection of gangliated cord during the procedure. Risk of this complication can be minimized by performing the procedures below the second rib (R2) as well as by avoiding of direct contact between electrocoagulation and gangliated cord. Nevertheless, it is worth to mention that presence of rare anatomic variants of location of stellate ganglion below third rib (more often on the left). The incidence of this complications decreases together with experience of the centre. Bleedings and postsurgical pain may be minimized by careful introduction of trocars, use of 5 mm optics and trocar, injecting point of entry port of local anaesthetics, such as bupivacaine. Incidence of pneumothorax is minimized by avoiding to damage lung parenchyma during the initial placement of the port (57-63).

Temporary bradycardia is noted in a small percentage of patients (0.13%) after ETS (59), while permanent bradycardia requiring pacemaker implantation is casuistically described (64). Studies with the use of Holter monitoring have demonstrated that thoracic sympathectomy results in statistically but not clinically significant decreases in the average heart rate (77±8 vs 67.8±6.5). The treatment has not affected other parameters of electric heart rate apart from tendency indicating shortening of the QTc interval (65). In contrast to anatomic studies, dominance of the right sympathetic system has not been demonstrated in clinical conditions (65). The influence of order of bilateral sympathectomy (left side at first vs. right side at first) on hemodynamic parameters has been compared (66). There was a significant decrease in systolic blood pressure in group ‘left side first’. Moreover, 7 patients (35%) in this group have presented temporary intraoperative bradycardia in comparison to its absence in the group ‘right side first’. Authors have recommended to start the procedure from sympathectomy on the right side (66).

The issue of decrease in average heart rate or even bradycardia must be discussed with patients who have resting heart rate lower than 55 or 50 beats per minute. The issue of bradycardia may also have relevance for those working in professions where it is necessary to pass fitness tests that require the preset heart rate limits. After ETS achieving this limit may become impossible.

Treatment results – psychological context

As it was mentioned above primary hyperhidrosis is a chronic disease with a positive feedback, which means that any attempt to hide it almost always leads to greater symptom severity. Moreover, patients are not able to
influence symptoms severity with behavioural factors (diet, activity limitations, less stimulants, etc.). This mechanism of helplessness in facing the disease leads to significant impairment of sense of efficacy and value as well as certainty of own body and thus self-confidence. All those factors significantly influence life quality impairing it in all dimensions of this generic construct. The strongest impairment is observed in emotional and functional component, then social (60, 67).

Undoubtedly, primary hyperhidrosis is a chronic disease which diagnosis forces the patient to face new area of psychological and social balance. Emotional adaptation plays significant role on how a person affected by hyperhidrosis adapts to the disease. The results of studies conducted by Naumann et al. (47) indicate that 90% of people affected by hyperhidrosis have confirmed its significant impact on their emotional and functional state. Over 70% of respondents have reported the need to change their clothes even more often than twice a day. Over 50% of patients have low self-confidence level, 38% of respondents suffer from frustration during daily activities, 34% have identified themselves as unhappy, while 20% as depressed (47). Before treatment the majority of respondents reported feeling stigmatized by the disease, lack of self-confidence (94%) or lower self-confidence as a result of hyperhidrosis. During daily activities, even 64% of respondents feel frustration related to their skin condition. Before treatment, patients also reported limitations in maintaining relationships, both in establishing new ones and in friend or family relationships. Excessive sweating had negative impact on sexual activity of over half of the respondents (48, 67).

The most commonly used tools to assess the psychological impact of the disease on the patient’s functioning are tools assessing the quality of life associated with dermatological disorders (DLQI and Hyperhidrosis Disease Severity Scale HDSS) (69, 70). A very simple scale HDSS (tab. 4) consisting of one question: ‘How do you rate the severity of your hyperhidrosis?’ deserves special attention. Patient chooses one of four answers obtaining the result from 1 (lowest severity) to 4 (highest severity) points. Very high correlation of the results obtained with DLQI and gravimetric results has been demonstrated (69-70). Moreover, it has been proved that improvement by 1 point corresponds to 50% decrease in sweating while by 2 points to 80% decrease in sweating (69, 70).

Generic tools (e.g. FACIT or ST-36) are also commonly used. Their goal is to assess the disease impact on life quality in general what allows for drawing the comparison between disease impact on hyperhidrosis patients to impact on patients with other diseases, or to healthy people (66, 71).

The research conducted by team from Gdańsk has revealed a significant impact of surgical treatment on life quality of people suffering from primary hyperhidrosis (66). Improvement of life quality has been observed immediately after the procedure, while favourable results of the treatment have been maintained during the entire observation period. The exception comprised patients who suffered severe compensatory hyperhidrosis leading to life quality impairment as well as dissatisfaction from treatment.

It should be noted that the team from Gdańsk as one of the few in the world conducts continuous study on the dynamics of changes in life quality of people suffering from primary hyperhidrosis obtaining the results in several points of the observation period, which allows them to assess an impact of factors with no

<table>
<thead>
<tr>
<th>Table 4. Hyperhidrosis Disease Severity Score (HDSS)</th>
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<tr>
<td><strong>English version</strong></td>
</tr>
<tr>
<td>My sweating is never noticeable and never interferes with my daily activities</td>
</tr>
<tr>
<td>My sweating is tolerable but sometimes interferes with my daily activities</td>
</tr>
<tr>
<td>My sweating is barely tolerable and frequently interferes with my daily activities</td>
</tr>
<tr>
<td>My sweating is intolerable and always interferes with my daily activities</td>
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influence of factors independent from surgery (71, 72).

Conducting postoperative meetings (follow up visits at place where the procedure has been performed) allows for direct support of the patients as well as objective verification of treatment results and perception of these results by patients (19). It is particularly important for patients whose satisfaction of treatment is not high due to compensatory hyperhidrosis. Mandatory follow up visits in Gdańsk centre allow for precise defining of frequency and severity of side effects felt by patients and adjustment of eventual additional therapy, such as plantar or trunkal iontophoresis.

In many cases, it turns out that problems only occur as a result of stimulation by physical activities or thermal stimuli what happens less frequently than several times during the week, only in the summer. However, the exacerbation of the disease is then considerable, especially in comparison to very small sweating of the torso that was typical for patients before surgery.

In unpublished studies of our team it has been revealed that participation in follow up visits with gravimetric measurement leads to change in perception of scale of the problem related to compensatory hyperhidrosis in 32% of patients. Lack of direct contact with the physician during the assessment of long-term result may therefore lead to overestimation of people indicating strong discomfort related to compensatory hyperhidrosis. Unfortunately, the disadvantage of the approach related to direct follow up visit is decreasing the number of people fully participating in this meeting, especially if they live in remote regions in the country or abroad. The percentage of people participating in follow up visits in Gdańsk amounts to 51% to 81% depending on the time from procedure. For comparison, the response rate obtained by correspondence may reach even 91-95% (49, 62).

Treatment results – side effects

Despite undoubted therapeutic success in surgical treatment of primary hyperhidrosis using sympathectomy procedure, some patients who have undergone this form of treatment suffer from long-term side effects (73, 74, 75). This is particularly important in the light of the fact that the goal of hyperhidrosis treatment is improvement of life quality. Thus, impact on patient’s life other than planned should be reduced to minimum.

The most common and significant adverse effect of sympathectomy is compensatory sweating (CS). It occurs in 0-95% of patients (20, 51, 62, 63, 73, 74, 75). Large discrepancy in the results is related to lack of precise definition of compensatory sweating. On one hand, any increase in trunkal sweating as a result of sympathectomy (maximalistic definition), on the other hand, only constant and not periodic or episodic increase in trunkal sweating above population standards (reductionist definition). Excessive sweating of torso in response to thermal stimuli and/or related to physical activity does not meet the reductionist definition of compensatory sweating. This side effect of thoracic sympathectomy can be divided into mild, moderate and severe (74, 75).

Estimation methods determining the number of days with no need for changing clothes or percentage of time with excessive sweating of torso induced by thermal stimuli or physical activity in comparison to period of time with no CS are used in more insightful analyses. As indicated by our research team, compensatory sweating is significantly more common in patients treated with ETS due to axillary and facial hyperhidrosis than isolated palmar hyperhidrosis (20). Compensatory sweating depends also on height of sympathectomy (and thus sympathectomy Th2, considered for many years to be golden standard of palmar hyperhidrosis treatment, causes more severe compensatory hyperhidrosis than Th3 or Th4, which are comparably effective).

Impact of lumbar sympathectomy performed as the second stage of treatment of compensatory hyperhidrosis is controversial (76). According to studies conducted by Loueiro in half of patients this procedure leads to escalation of the disease, while in other half to its decrease (76). Another interesting technical aspect is the extent of sympathectomy. There are still no clear data whether excision of more sympathetic ganglions leads to greater severity of compensatory sweating (51).

One of the methods of severity assessment of compensatory sweating is chemical sympathectomy test with bupivacaine hydrochloride which causes reversible blockage of gangli-
ated cord (77). In this case if symptoms of truncal hyperhidrosis are not inconvenient, patient should be qualified for ETS. Unfortunately, this method has a number of shortcomings. First of all, it requires hospitalisation and performance of chemical aortal sympathectomy which bear large possibility of risk and complications (77). Secondly, the efficiency of chemical sympathectomy is limited, hence it would not always reflect the situation which would occur after surgical sympathectomy.

In order to limit the impact of compensatory hyperhidrosis on the life of patients after ETS, numerous treatment methods have been proposed including (i) behavioural comprising body weight control, proper selection of clothes or avoiding visits in countries with hot and humid climate, (ii) medical comprising topically acting agents (aluminium chloride, botulinum toxin (78) or oxybutynin treatment (79).

Appeasement of compensatory hyperhidrosis, in case if no behavioural and medical treatment is possible, may be obtained using two methods: by removing clamps if they were placed during the procedure and using post-operative trunkal iontophoresis, so called RALI (regional abdomino-lumbar iontophoresis) (20). Clamping of intraganglionic connections instead of ablative methods or excision allows for their extraction in the case of occurrence of significant compensatory sweating. However the phenomenon of compensatory hyperhidrosis is long-lasting, usually lasting even to 24 months and its resolution is not always complete (77). Moreover, clamps removal results in recurrence of primary symptoms (77). Alternative technique consists of implantation of nerve graft taken from sural or intracostal nerves. The procedure is performed with classically, laparoscopically or with the use of surgical robot (80, 81). In study conducted by Telaranta, compensative hyperhidrosis has been reduced after such intervention in 81% of patients, while 29% of patients have reported complete resolution of CS as well as recurrence of primary hyperhidrosis symptoms (81).

Prospects for the development of treatment methods of primary hyperhidrosis

Due to relatively frequent prevalence of the disease, its significant impact on functioning from the childhood and development of information media, it seems that new methods of primary hyperhidrosis treatment will be developed. Development directions will presumably lead to minimization of the invasiveness of procedures, greater selectiveness, what will allow for lowering side effects, and even to development of conservative treatment method of PHH.

Selective postganglionic transsection of rami communicantes seems promising in lowering the frequency of compensatory hyperhidrosis prevalence. So far, the procedure has been performed mainly with the use of robot. Coverialrs et al. (82, 83) have evaluated the benefits of using the Da Vinci robot to perform postganglionic sympathectomy of rami communicantes in order to reduce the percentage of patients with compensatory hyperhidrosis. The robot primarily allowed for precise dissection of postganglionic fibres and selective transsection of rami communicantes. The procedure has been performed in 55 patients resulting in complete resolution of the disease in 96% of cases, and compensatory hyperhidrosis occurred in only 7.2% of cases (82, 83).

Other application of the robot include procedures of restoring continuity of gangliated cord in patients after resective sympathectomy, who presented with very severe compensatory hyperhidrosis. Latif et al. (80) have conducted series of studies on application of a graft drew from intracostal nerve to restore continuity of gangliated cord in an animal model. Procedures have been performed with da Vinci robot. Nerve implants have been sewed with nylon sutures 10-0 affixed to the epineurium. Authors have concluded that even though the procedure is technically possible and with the use of robot relatively easy, there is no evidence for clinical efficacy of this form of treatment (80).

Considerable attention has been paid to studies on application of microwave technology and lasers in axillary hyperhidrosis treatment. The idea behind the studies was to minimize surgical trauma and even reduction of sweating as side effect of laser depilation in axillary region. Hong et al. have evaluated the effectiveness of a device using microwave technology in axillary hyperhidrosis treatment (84). They have revealed that 12 months after the treatment over 90% had at least 50% decrease in axillary sweating, while 85% at least
5-point decrease of symptoms severity in DLQI scale (84). Similar results have been presented by Glaser et al (85), who have emphasized the stability of the result during observation, after finishing of observation, 12 months after treatment reduction of axillary sweating still amounted to 68%.

Bechara et al. have evaluated the effectiveness of axillary treatment with 800 nm diode laser (86). Five therapeutic cycles have been performed yielding improvement of average perspiration from 89 to 48 mg/min in comparison to change from 75 to 65 mg/min in non-treated condition. The authors have concluded that observed effect is rather related to placebo phenomenon than actual therapeutic reduction (86). On the other hand, Letada et al (87) have evaluated the influence of laser depilation of armpits on symptoms severity in this region. They have used Nd:YAG 1,064 nm laser, studied 6 patients who were subjected to the procedure performed only at one side, while the other has been left as control area. They have observed improvement both in life quality test i.e. Global Assessment Questionnaire (GAQ) and objectivised iodine-starch test (87). Unfortunately, small test group and lack of quantitative methods indicate the need of in-depth studies on application of this minimally invasive therapeutic method.

Interesting finding concerning application of oxybutynin (in Poland Ditropan and Driptane are available) has been made. Oxybutynin has directly relaxant effect on smooth muscles by blocking calcium channels and simultaneously competitively inhibits muscarinic acetylcholine receptor. It also exhibits poor properties as local anaesthetics and antihistamine. It is currently used in treatment of overactive bladder with urgent symptoms and/or urinary incontinence as well as other neurogenic bladder diseases resulting in urinary incontinence, nocturnal and diurnal enuresis or sudden need to urinate. Dosage regimen starting from 2.5 mg once a day during first week, afterwards 2.5 mg twice a day from day 8 to 42, and 5 mg twice a day from day 43 is used in hyperhidrosis treatment (88-93). The effectiveness of this medicine has been evaluated in treatment of facial, palmar and axillary hyperhidrosis noting reduction of severity (partial or substantial) in 60–70% of patients (91-93). Main side effects was dryness in the mouth that affected approximately 60% of patients (89-90). Therapeutic effect was independent of body weight (89). The same team has evaluated the influence of oxybutynin on plantar hyperhidrosis noting reduction of symptoms in 70% of patients, while 76.7% have reported side effect in the form dry mouth (88).

Studies have also been conducted on children aged 7-14, who due to immaturity of sympathetic system and lack of knowledge about potential procedure effects in such young age are not qualified for surgical treatment (93). Over 85% of children have presented with moderate to substantial reduction of symptoms. Mainly dryness of mouth (55.5% of subjects) has been reported as side effect associated with the treatment. One patient has reported neurological symptoms, i.e. drowsiness (93).

Oxybutynin is also applied in treatment of secondary hyperhidrosis resulting from the use of antidepressants (94, 95) and hyperhidrosis occurring during menopause (96). It should be, however, noted that studies on effectiveness of this drug on healthy volunteers in relation to sweating induced by physical activity have revealed no differences in comparison to placebo group (97).

Summary

Primary hyperhidrosis is a common disease that significantly impairs social functioning of people affected. Available methods of treatment are either relatively ineffective or linked with uncomfortable side effects. Methodology of reversing or mitigating the effects is difficult and expensive, and moreover not always effective. Thus, proper classification for procedure and availability of wide range of therapeutic alternatives, which allow for adjustment of treatment form to characteristics and needs of the patients during pre- and postoperative period, is extremely important.
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