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Generalized Hyperhidrosis and Its Systemic Treatment

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Hyperhidrosis may be primary (idiopathic, essential) or secondary to a number of diseases and drugs. Primary hyperhidrosis is a disorder that causes hyperhidrosis of the hands, feet and the axillae. It is estimated that 0.6–1% of the population is suffering from this problem. Primary hyperhidrosis is believed to be inherited and usually has its time of onset in adolescence. The occasional onset in the neonatal period is evidence that primary hyperhidrosis is more than only an emotional disorder. It characteristically does not occur while sleeping. Emotional stimuli and heat both worsen primary hyperhidrosis. It is believed that the hypothalamic sweat centers are more sensitive to emotional stimuli of cerebral origin in patients with primary hyperhidrosis compared to the general population. Emotionally induced sweating tends to be localized to the palms, soles and, not infrequently, the forehead, while axillary hyperhidrosis may be the result of both emotional and thermal stimuli. Palmoplantar hyperhidrosis is frequently observed in patients with a clinical history of chronic abnormal alcohol intake. Sympathetic skin response analysis suggested this to be due to an impairment of central sweat control in these patients [Tugnoli et al., 1999].

Hyperhidrosis may be either localized or generalized (table 1). Conditions associated with localized hyperhidrosis include primary palmoplantar hyperhidrosis, a number of diseases with palmar/palmoplantar keratoderma, including Meleda disease (mal de Meleda) [Bouadjar et al., 1998], idiopathic localized unilateral hyperhidrosis [Kreyden et al., 2001], hyperhidrosis associated with intrathoracic neoplasms, olfactory hyperhidrosis, spinal cord injuries [Andersen et al., 1992], as well as Ross's syndrome and Frey's syndrome. The triad of tonic pupils, areflexia and hypohidrosis/anhidrosis is termed Ross's syndrome [Ross, 1958]. Following surgery of the parotid or submandibular glands, the so-called

Table 1. Causes for localized and generalized hyperhidrosis

Localized hyperhidrosis
Heat
Olfactory
Gustatory: coffee, chocolate, citric acid, peanut butter, spicy foods
Neurological lesions
Primary or essential hyperhidrosis
Generalized
Heat, humidity, exercise
Infections
Neoplasia
Metabolic diseases: thyrotoxicosis, diabetes mellitus, hypoglycemia, gout, pheochromocytoma, hyperpituitarism, menopause
Sympathetic discharge: shock and syncope, pain, alcohol, drug withdrawal
Neurological: Riley-Day syndrome, irritative hypothalamic lesions
Drugs: propranolol, physostigmine, pilocarpine, tricyclic antidepressants

auriculotemporal syndrome – Frey's syndrome – may occur [Bloor, 1958]. Damage to adjacent preganglionic parasympathetic fibers and postganglionic sympathetic fibers may be followed by parasympathetic fibers regrowing into the sympathetic nerves and thereby directly controlling sweat gland function. This occurs on the cheeks or chin (Frey's syndrome) but may also occur on the neck following damage to the sympathetic cervical trunk and the vagus nerve (parasympathetic) at the time of thyroidectomy or after trauma. This reinnervation may then result in gustatory hyperhidrosis even after eating bland foods [Cunliffe and Johnson, 1967]. Furthermore, diabetic autonomic neuropathy, chorda tympani injury, herpes zoster infection and cluster headache may result in gustatory sweating.

In patients with acute hemispherical brain infarction, a significant hyperhidrosis on the paretic side of the body was verified [Korpelainen et al., 1992]. Localized gustatory sweating is seen after intake of coffee, chocolate, citric acid, peanut butter and spicy foods.

Generalized hyperhidrosis is most often caused by heat, humidity and exercise. It is further seen in acute and chronic infections, neoplasia and in a number of metabolic disorders including diabetes mellitus, thyrotoxicosis, hypoglycemia, gout, pheochromocytoma, hyperpituitarism or menopause. It may be induced by sympathetic discharge, i.e. due to shock and syncope, intense pain, alcohol and drug withdrawal. Neurological diseases with generalized hyperhidrosis include the Riley-Day syndrome or familial dysautonomia, a rare autosomal recessive disease occurring in Jews of Ashkenazi descent, with

Table 2. Systemic treatment of hyperhidrosis

Tranquilizers	Diazepam
β-Blockers	Inderal
Spasmolytics	Belladonna
Anticholinergics	Pro-Banthine (propantheline bromide), Robinul (glycopyrrolate), Ditropan (oxybutynin), Cogentin (benztropine mesylate)
NSAIDs	Indomethacin
Calcium channel blockers	Cardizem (diltiazem)

only some 500 recognized cases [Hilz et al., 1999]. Generalized hyperhidrosis may also be found, when irritative hypothalamic lesions are present. Finally, a number of drugs cause generalized hyperhidrosis. They include propranolol, physostigmine, pilocarpine, tricyclic antidepressants and venlafaxine. It is always important to exclude these known causes of hyperhidrosis, before any treatment is considered.

When treatment of hyperhidrosis is considered, botulinum toxin should not be the first choice, despite its excellent action. It is therefore important for the physician to know the alternatives of botulinum toxin treatment in hyperhydrosis, and the advantages and side effects should be discussed with the patient.

Among the systemic drugs considered in the treatment of hyperhidrosis, anticholinergics are the most widely used. They block neuroglandular transmission due to competitive inhibition of synaptic acetylcholine.

Systemic treatment may be considered in patients whose hyperhidrosis is related to anxiety-producing events, and, in this condition, anticholinergic drugs may be helpful. Unfortunately, the doses required to achieve a good anhidrotic effect also result in side effects like xerostomia, mydriasis, cycloplegia or bowel and bladder dysfunction [LeWitt, 1988]. Among the anticholinergic drugs used are oxybutynin (Ditropan, Hoechst Marion Roussel, Kansas City, Mo., USA), propantheline or benztropine [Garber and Gregory, 1997]. Other systemic drugs described to be beneficial in hyperhidrosis are tranquilizers like diazepam (5–20 mg/day recommended), β-blockers like Inderal (3 × 40 mg/day recommended), spasmolytic agents such as belladonna, diltiazem, a calcium channel blocker [James et al., 1987], indomethacin, a nonsteroid anti-inflammatory agent [Tkach, 1982], clonidine, a centrally active α-adrenergic autoreceptor stimulant [Feder, 1995], and fludrocortisone acetate [Khurana, 1987]. However, many of the reports of therapeutic efficacy of different drugs are anecdotal and carry the risk of side effects. If considered in the treatment of generalized hyperhidrosis (table 2), they should be used with care.

References

Andersen LS, Biering-Sorensen F, Muller PG, et al: The prevalence of hyperhidrosis in patients with spinal cord injuries and an evaluation of the effect of dextroproxyphene hydrochloride therapy. Paraplegia 1992;30:184–191.

Bloor K: Post-parotidectomy gustatory sweating. Br Med J 1958;ii:1295.

Bouadjar B, Heilig R, et al: Genetic linkage of Meleda disease to chromosome 8_{9}ter. Eur J Hum Genet 1998;6:542–547.

Cunliffe WJ, Johnson CE: Gustatory hyperhidrosis: A complication of thyroidectomy. Br J Dermatol 1967;79:519–526.

Feder R: Clonidine treatment of excessive sweating. J Clin Psychiatry 1995;56:35.

Garber A, Gregory R: Benztropine in the treatment of venlafaxine-induced sweating. J Clin Psychiatry 1997;58:4176–4177.

Hilz MJ, Stemper B, Sauer P, et al: Cold face test demonstrated parasympathetic cardiac dysfunction in familial dysautonomia. Am J Physiol 1999;276:1833–1839.

James WD, Schoomaker MC, Rodman MC: Emotional eccrine sweating. Arch Dermatol 1987;123: 925–929.

Khurana RK: Orthostatic hypotension-induced autonomic dysreflexia. Neurology 1987;37:1221–1224.

Korpelainen JT, Sotaniemi KA, Myllyla VV: Hyperhidrosis as a reflection of autonomic failure in patients with acute hemispherical brain infarction: An evaporimetric study. Stroke 1992;23: 1271–1275.

Kreyden OP, Schmid-Grendelmeier P, Burg G: Idiopathic localized unilateral hyperhidrosis – case report at successful treatment with botulinum toxin – and review of the literature. Arch Dermatol 2001;137:1622–1625.

LeWitt P: Hyperhidrosis and hyperthermia response to oxybutynin. Neurology 1988;38:506–507.

Ross AT: Progressive selective sudomotor denervation. Neurology 1958;8:809–817.

Tkach JR: Indomethacin treatment of generalized hyperhidrosis. J Am Acad Dermatol 1982;6:545.

Tugnoli V, Eleopra R, De Grandis D: Hyperhidrosis and sympathetic skin response in chronic alcoholic patients. Clin Auton Res 1999;9:17–22.

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