Secondary Hyperhidrosis: Endocrinopathies and Hyperhidrosis

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Menopause

Menopause has as a landmark the definitive cessation of spontaneous menses. In this way, the onset of menopause can only be considered after 1 year following the last menstrual flow, because in this period, called climacteric, occasional menstruation may still occur. The climacteric represents the passage from the reproductive to the non-reproductive phase, with progressive reduction of the production of estrogens and progesterone.

The age of onset of menopause is variable, usually occurring between 45 and 55 years. If it occurs before the age of 45 years, it is called early menopause and, although it may be physiological, is often linked to pathophysiological processes, such as autoimmune oophoritis, drugs, surgical or radiotherapy iatrogenesis, and pituitary diseases such as hyperprolactinemia/prolactinomas and clinically non-secretory macroadenomas.

The symptomatology includes, in addition to menstrual absence, hot flashes, reduction of libido, vaginal dryness, changes in body composition, insomnia, reduced memory, increased cardiovascular risk, and loss of bone mass.

The hot flashes are present in about 80% of menopausal women, and may already be present during the climacteric period. They are characterized by an intense sudden and transitory sensation of heat, usually beginning in the face and chest, accompanied by the activation of mechanisms of heat loss, which include cutaneous vasodilation and sweating. The duration is minutes, and hyperhidrosis can be associated with palpitations and tremors. Hot flashes can occur several times a day and also at night, leading to sleep disorders. In untreated women, the hot flashes usually last for 5–6 years, with decreasing intensity and frequency, but in some cases they may persist for longer.

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M. P. Loureiro et al. (eds.), *Hyperhidrosis*,
https://doi.org/10.1007/978-3-319-89527-7_2

It is assumed that the pathophysiology of hot flashes is associated with estrogen-modulated hypothalamic body temperature control dysfunction, which presents a marked decline in menopause. Some studies have shown that hot flashes occur simultaneously with the release of luteinizing hormone (LH), but patients with central cause hypogonadism and those with pituitary tumors also have hot flashes despite low LH levels.

Laboratory diagnosis of menopause is made by the low levels of estrogens and progesterone, accompanied by elevation of gonadotrophins (follicle-stimulating hormone [FSH] and LH). When gonadotrophin levels are normal or low, we should think of hypothalamic–pituitary causes as responsible for amenorrhea.

The treatment of choice is estrogen replacement, since, besides improvement of the hot flashes, the other clinical aspects of the menopause also benefit. For those women with a contraindication to estrogen therapy, due to personal or familial history of gynecological neoplasia or coagulation disorders, other therapies are available. These include use of phytoestrogens such as isoflavones, and medications such as the selective serotonin reuptake inhibitors, clonidine, and gabapentin.

Men who have hypogonadism or undergo anti-androgen therapy for prostate cancer may also present hot flashes, with a high incidence in the latter. Psychotherapy and the use of progestagens, gabapentin, and serotonin reuptake inhibitors are measures that may ease the discomfort of these patients.

Hyperthyroidism

Hyperthyroidism is the most prevalent dysfunction in hyperhidrosis secondary to endocrine causes. It consists of a syndrome that results from excessive exposure to thyroid hormones, with a classic clinical picture, usually accompanying adrenergic manifestations: palpitations, tachycardia, tremors of extremities, and sweating, in addition to heat intolerance and diarrhea. Its most common cause, toxic diffuse goiter (Graves' disease) may or may not be accompanied by ocular manifestations such as exophthalmos (Fig. 2.1).There are, however, other causes of hyperthyroidism, often with less exuberant clinical manifestations. This is the case of toxic

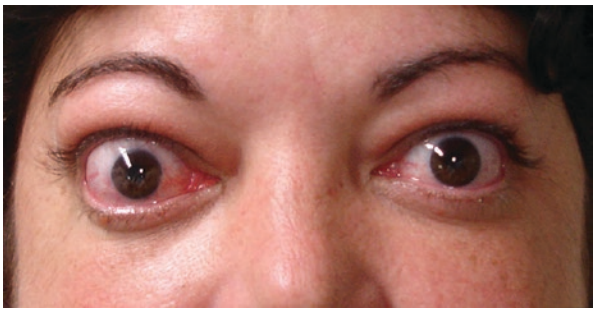

Fig. 2.1 Bilateral proptosis and eyelid retraction in a patient with Graves' orbitopathy

uni- or multinodular goiter, which usually affects older patients. Treatment of hyperthyroidism is performed with thyroid-blocking drugs, radioiodine therapy, or surgery, depending on the case. Blocking drug therapy with thioureas, such as tapazole and propylthiouracil, is used as the initial treatment, especially in more severe cases, such as preparation for surgery or radioiodine therapy. In the case of Graves' disease with small goiter and no ocular signs, there is a good chance of remission of hyperthyroidism without the need for other procedures. The indication of radioiodine therapy or subtotal thyroidectomy will depend on the volume of the goiter and the presence or absence of exophthalmos.

Subacute thyroiditis also leads to thyrotoxicosis by releasing thyroid hormones stored in the glandular colloid. It is usually accompanied by cervical pain and evening fever, but it can be painless (silent thyroiditis) and its diagnosis is often confused with classic hyperthyroidism. The treatment for subacute thyroiditis, usually lasting 2–3 months, is with non-hormonal anti-inflammatories or glucocorticoids and β-blockers. There are extremely rare conditions associated with thyrotoxicosis, such as pituitary tumors producing thyroid-stimulating hormone (TSH), pituitary resistance to thyroid hormone, hydatidiform mole, and struma ovarii. Finally, we must remember factitious thyrotoxicosis, a condition resulting from the ingestion of high doses of thyroid hormone for the general purpose of weight loss. This is a deplorable practice that must be fought.

Pheochromocytoma

Hyperhidrosis is one of the clinical manifestations of pheochromocytomas. These tumors originate from chromaffin cells of the sympathetic nervous system, which release norepinephrine and/or epinephrine and, more rarely, dopamine and other active peptides, and account for about 0.1% of the causes of arterial hypertension. All ages and both sexes are affected, although they are more common in the fourth and fifth decades. Although paroxysmal episodes of hypertension are typical of pheochromocytoma, about half of the cases exhibit maintained hypertension. The triad of headache, diffuse sweating, and pallor in the presence of hypertension is classic and highly suggestive of pheochromocytoma. The location of pheochromocytomas is almost always abdominal (95% of cases) and 85% are in the adrenal glands; 5% are extra-abdominal (e.g., in the mediastinum). Laboratory diagnosis is made by serum or urinary catecholamines or their metabolites, such as metanephrines and vanilmandelic acid. In cases where a laboratory diagnosis is not confirmed, so-called provocative tests, such as the clonidine or glucagon test, are indicated. Diagnosis by magnetic resonance imaging (MRI) is now considered the gold standard: the presence of hyperintense signal in T2 is highly suggestive of pheochromocytoma. Computed tomography is also useful, as is scintigraphy with metaiodobenzylguanidine, which is a more functional assessment because it is based on the uptake of a catecholamine precursor. The treatment of pheochromocytoma is surgical, and requires preparation to avoid serious pressure accidents. This preparation is usually done only with α-adrenergic blockers, in combination with

β-adrenergics in cases with tachyarrhythmias. Patients with pheochromocytomas may be carriers of type 2 multiple endocrine neoplasia, in which case these tumors are associated with hyperparathyroidism and with medullary thyroid carcinoma or neurofibromatosis.

Hypoglycemia

Hypoglycemic syndrome has several causes and usually presents the Whipple triad as a clinical feature: (1) adrenergic manifestations, such as tachycardia and generalized hyperhidrosis, and neuroglycopenic symptoms, such as changes in behavior and loss of consciousness; (2) low plasma levels of glucose; and (3) clinical reversibility with glucose administration. The manifestations usually occur with blood glucose lower than 50 mg/dL, but if the fall is rapid they can occur with higher blood glucose levels. Its causes are several, the main ones being (1) tumors of the pancreatic islets, insulinomas, whose most important manifestations usually occur in prolonged fasting—insulinomas may be associated with multiple endocrine neoplasia type 1, which is also characterized by the presence of hyperparathyroidism and pituitary tumors; (2) reactive hypoglycemia, occurring postprandially; (3) iatrogenic hypoglycemia, especially in diabetic patients taking insulin or oral hypoglycemic agents, particularly chlorpropamide; and (4) hypoglycemia linked to specific conditions, such as alcohol abuse, liver failure, or adrenal insufficiency.

Acromegaly

Acromegaly is a rare disease, with an estimated prevalence of 60 cases per million. It is caused in 99% of cases by a growth hormone (GH)-producing pituitary adenoma, leading to the hypersecretion of this hormone, which in turn induces excessive production of insulin-like growth factor-1 (IGF-1), which leads to facial and extremities deformities and visceromegaly. In addition to somatic changes, which generally make the clinical diagnosis quite clear, patients with acromegaly have a high prevalence of co-morbidities such as high blood pressure, heart disease, and diabetes mellitus, which reduce their life expectancy by about 10 years. Acromegalic patients are hypermetabolic, with hyperhidrosis, mainly palmar and plantar, being a common manifestation of this disorder. Clinical diagnosis is confirmed by baseline GH (elevated), glucose tolerance test (non-suppressible), and IGF-1 (elevated). MRI of the sellar region almost invariably shows the presence of a pituitary tumor, usually macroadenoma. The most commonly used initial treatment is pituitary surgery via the transsphenoidal approach. Alternatively, for non-cured cases, those with a low possibility of surgical cure, or with contraindications for general anesthesia, drug treatment with somatostatin analogs, dopaminergic agonists, or GH receptor antagonists plays an important role. Finally, conventional or stereotaxic radiotherapy is indicated for cases of resistance to or impossibility of drug treatment. Hyperhidrosis yields rapidly in efficiently treated cases.

Carcinoid Syndrome

Carcinoid syndrome, a relatively rare condition, is caused by hypersecretion of serotonin, usually by neuroendocrine tumors that may be located in various regions, such as the lung, pancreas, intestine, appendix, and so on. Although it is associated with hyperhidrosis, sweating in patients with carcinoid syndrome is generally relatively modest compared with other symptoms such as flushing, diarrhea, and bronchoconstriction. The main screening test is the determination of 5-hydroxyindolacetic acid. This assay is very affected by food, requiring a fundamental preparatory diet guided by the laboratory. The treatment can be surgical and/or clinical with somatostatin analogs, and should be individualized.

Suggested Reading

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