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The eye and the skin in endocrine metabolic diseases

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Abstract The eye and skin may offer critical clues to the diagnosis of a varied spectrum of metabolic diseases from endocrine origin and their different stages of severity, such as diabetes mellitus and Graves disease. On the other hand, such entities may compromise the eye and visual function severely, and awareness of these possible associations is an important step in their diagnosis and management. A large number of less common endocrine diseases may also have significant ocular/visual or skin involvement. Often the etiologic relationship between the endocrine metabolic disease and the ocular compromise is unknown, but diverse pathogenetic mechanisms may act through a common pathologic pathway producing ocular damage, as occur in diabetic retinopathy. This review emphasizes the ocular and skin manifestations of different metabolic diseases of endocrine origin.

Diabetes mellitus

As an emerging pandemic and with its multiple and devastating multisystemic complications, diabetes mellitus is a major concern in public health care, being the leading cause of new cases of blindness among adults 20 to 75 years old. Of 366 million persons that have diabetes worldwide, the majority has type 2 diabetes, and about 30% of them have clinical signs of diabetic retinopathy, with 1 in 10 having vision-threatening complications like macular edema and proliferative retinopathy.[1,2] By the year 2030, the population of diabetic patients is expected to double, impacting tremendously on the prevalence of diabetic complications.[3]

Macrovascular (eg, coronary heart disease, stroke, peripheral arteriopathy) and microvascular (eg, retinopathy, nephropathy, neuropathy) may become progressively worse with the evolution of diabetes.[4]

Diabetic retinopathy is the most common microvascular complication in diabetic patients, and the relative risk of developing retinopathy is higher in patients with type 1 diabetes than in type 2 diabetes patients. Any degree of retinopathy has a predictive value for all-cause mortality and cardiovascular disease events.[5]

Besides retinal microangiopathy, it has been observed that diabetes produces retinal neuronal dysfunction and damage that may precede clinical vascular changes, especially at the level of the photoreceptor layer.[6]

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Diabetic retinopathy is caused by multiple biochemical abnormalities of the underlying metabolic disease, and control of blood glucose and blood pressure and timely identification of coincident nephropathy are important to prevent progression to vision-threatening stages. It has recently been observed that the annual incidence of sight-threatening proliferative retinopathy and macular edema is significantly reduced in groups with timely diabetes diagnosis (in case of type 2 diabetes), intensive control of hyperglycemia, medical treatment of hypertension and dyslipidemia, and increased number of treated patients with photocoagulation.[7,8]

In a recent meta-analysis, the overall prevalence of retinopathy was 35%, the prevalence of vision-threatening forms was 10%, and the prevalence of end-stage proliferative retinopathy (fibrovascular proliferation inside the eye that provoque intravitreous bleeding and tractional retinal detachment) and macular edema was 7%, patients with type 1 diabetes being more prone to retinopathy.[9] Major risk factors were disease duration, metabolic control, and blood pressure.[9] In another study,[10] tobacco smoking and male gender were identified as additional risk factors for any type of retinopathy among type 1 diabetic patients. In type 1 diabetes, albuminuria increases the risk for severe retinopathy by more than fourfold, the risk increasing further with macroalbuminuria.[10]

Macular edema, usually the consequence of focal or diffuse capillary incompetence, is the most common finding in diabetic persons losing visual acuity[11] and may occur at any stage of nonproliferative or proliferative diabetic retinopathy.[12]

Several specific treatments for vision-threatening diabetic retinopathy have been used for the last 60 years, and laser photocoagulation remains as one fundamental means of treatment for macular edema and proliferative retinopathy.[13] As upregulation of vascular endothelial growth factor (VEGF) has been involved in the breakdown of blood–retinal barrier, several anti-VEGF molecules have been used for the treatment of diabetic macular edema.[14–17] Eyes with diabetic macular edema and vitreomacular traction with moderate visual loss may benefit from vitrectomy,[18] often with preceding anti-VEGF administration to reduce the risk of severe intraoperative bleeding.[16,19]

Cataract is more common and presents earlier in diabetic patients.[20] Two distinct types of cataract may occur: Age-related cataract occurs in patients older than 40 years of age, similar to the one observed in nondiabetic patients but classically bilateral and cortical with some vacuoles in the anterior and posterior cortex of the lens. The other type of cataract is rare, occuring more often in young adults with decompensated type 1 diabetes or with a poor glycemic control. It is generally bilateral and develops rapidly, starting with snowflake-like anterior and posterior subcapsular opacities, and initially causing a myopic shift in refraction.[21] It may regress with normalization of the metabolic imbalance or it may become completely opaque and intumescent.[21]

The nonarteritic type of *anterior ischemic optic neuropathy* (AION) occurs more often among diabetic patients than in nondiabetics, and up to 25% of patients with AION have a history of diabetes.[22] *Retrobulbar optic neuropathy* and *diabetic papillopathy* occur rarely, regressing with normalization of glycemia.[23,24]

Ocular motor palsy is not infrequent, affecting 1-14% of diabetic patients, being 7 to 8 times more common in diabetic than in nondiabetic patients; diabetes is associated in 25-30% of patients older than 44 years who develop an acute ocular extrinsic muscle palsy.[25] It starts with a sudden diplopia and affects with decreasing frequency the sixth, third, and fourth cranial nerves. Recovery of muscle function occurs in general within 3 months of onset.[26] They may be of central or, more commonly, peripheral origin.[27]

Chronic open-angle glaucoma, a progressive optic neuropathy associated with changes in the optic disc and visual field deffects, and often with increased intraocular pressure, occurs more often in diabetic patients than in the general population (5% versus 2%, respectively),[28] and the risk is 1.6 to 4.7 times higher in diabetic patients than in nondiabetic people.[29,30] Besides, diabetes is found in aproximatly 12% of patients with chronic glaucoma.[30]

Neovascular glaucoma is an extremely severe complication of advanced proliferative retinopathy and is the consequence of extensive areas of ischemic retina overexpressing VEGF, which promotes new vessel formation on the surface of the iris and trabecular meshwork, blocking the outflow of aqueous humor from the inside of the eye.[31] Timely panretinal photocoagulation treatment in high-risk nonproliferative and proliferative diabetic retinopathy prevents this complication in the majority of cases.[32–34]

Occlusive retinal vasculopathies, in particular *central retinal vein occlusion* (occlusion of the main retinal vein occuring in its path intraoptic nerve) with its severe visual implications and devastating complications such as neovascular glaucoma, are strongly related to complicated diabetes mellitus.[35–37] Diabetes has also been recognized as an important risk factor for *branch retinal vein occlusion* (BRVO, occlusion of a branch of the central retinal vein occuring at the site of a retinal artery/vein crossing).[38]

Ocular surface disorders, such as meibomian gland disfunction and dry eye, are not uncommon in diabetic patients and may cause symptomatic or asymptomatic ocular surface and eyelid ciliary border and eye inflammation.[39,40]

The corneal epithelium appears to be more fragile in diabetic patients with or without retinopathy than in nondiabetic patients, exposing them to corneal epithelial defects and ulceration and higher risk of corneal infection.[41,42] Besides, damage or loss of corneal nerve bundles may cause decreased corneal sensitivity, recurrent corneal erosions, delayed epithelial healing, and persistent epithelial defects.[43,44]

Mucocutaneous manifestations are common in diabetes mellitus and sometimes may mark the onset of the disease. During the course of diabetes at least 30% of patients have some type of mucocutaneous involvement, and in 21.7% it is

the presenting feature of diabetes, affecting equally female and male patients, 79% with type 2 diabetes and 21% with type 1 diabetes.[45]

Cutaneous infections are the most common dermatologic complication in diabetes, affecting 39.7% of diabetic cases, especially those poorly controlled, followed by acanthosis nigricans (15.3%), xanthelasma (2%), and diabetic ulcers (1.3%) (Figures 1 and 2).[45] *Candida*, *dermatophyte*, and rhinocerebral *mucormycosis* have been found as the most common fungal and yeast infective organisms, followed by gram-positive bacterial infection, particularly *Staphylococcus aureus* and the β-hemolytic group A streptococci.[46–48]

Diabetic dermopathy, characterized by asymptomatic circumscribed, atrophic, slightly depressed, hyperpigmented macules located on the shins, is commonly observed and has an unfavorable association with retinopathy, nephropathy, and neuropathy.[49] Of unknown etiology, its progression is variable, and it may fade slowly leaving a pigmented area without atrophy or may resolve completely, with new lesions developing contiguously (Figures 3 and 4).[50,51]

Scleredema diabeticorum is a rare disorder of unknown origin and is related to long duration of diabetes, poor glucose control, diabetic microangiopathy, obesity, and insulin treatment.[52] It is characterized by an insidous onset of a painless, symmetric, nonpitting induration and thickening of the skin of the neck and posterior back, occasionally extending to the arms and hands due to excessive increase in mucin deposition between the affected collagen fibers (Figures 5, 6, and 7).[53]

Eruptive xanthomas are discrete inflammatory papules of lipid deposits formed mainly from cholesterol esters that are infrequently observed in diabetic patients, usually appearing on the buttocks and elbows.[54]

Diabetic foot ulcers are the consequence of excessive plantar pressure on foot deformities and callous formation (Figures 8 and 9). Diabetic neuropathy and peripheral arterial disease contribute greatly to ulcer formation, soft tissue infection, and osteomyelitis.[55]

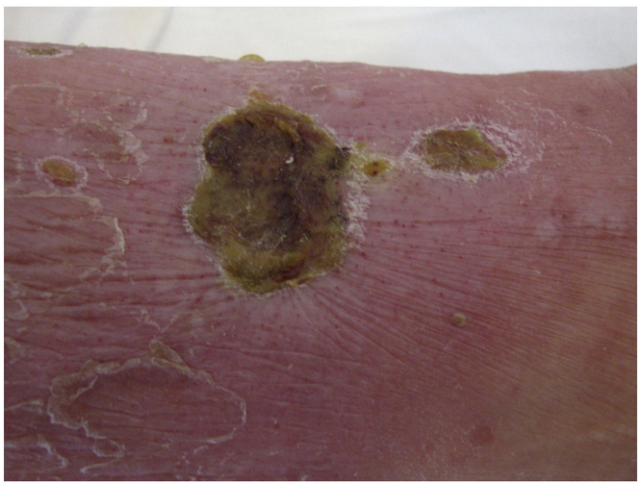

Fig. 1 Diabetic ulcer.

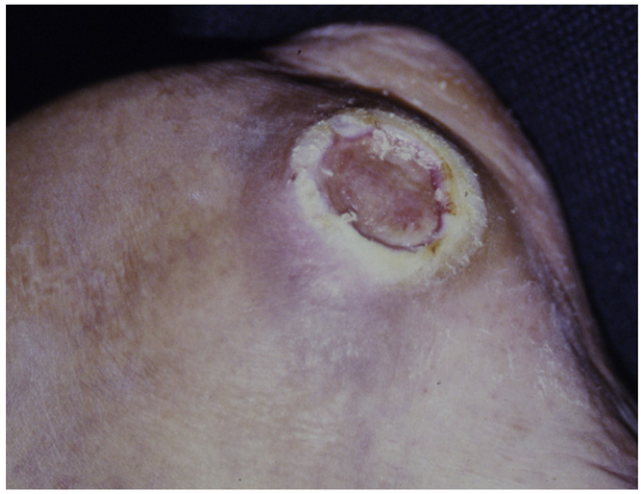

Fig. 2 Charcot ulcer in diabetes.

Necrobiosis lipoidica diabeticorum is a rare, chronic, granulomatous disorder affecting 0.3-1.6% of diabetic patients.[56] It presents clinically as erythematous papules on the shins that may coalesce and form atrophic telangiectatic plaques, with an indolent clinical course (Figure 10) or complicated by painful ulcerations with a difficult healing process (Figure 11).[57]

Diabetic bullosis consists in abrupt, spontaneous, recurrent blisters occasionally developing on the lower extremities of type 1 diabetic patients suffering from peripheral neuropathy. The pathogenesis of diabetic bullosis remains uncertain, although the neuropathy seems to play a prominent role.[58]

Pituitary diseases

Pituitary gland disease may manifest as hyperpituitarism (excessive secretion of trophic hormones), as hypopituitarism (defficient secretion of trophic hormones), and also with local mass efect as the result of expansion of the gland,

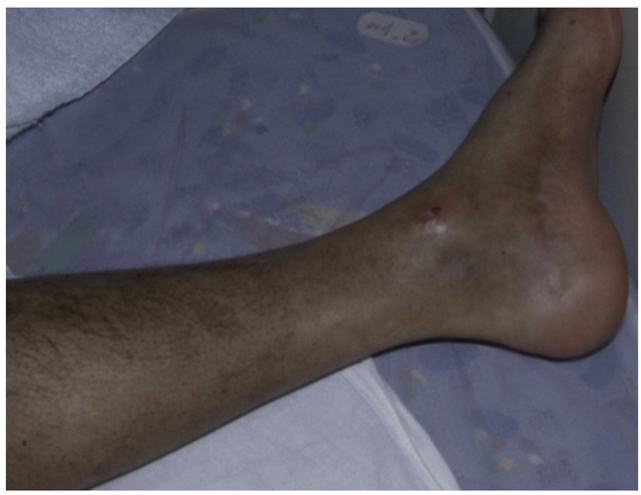

Fig. 3 Diabetic dermopathy of the leg.

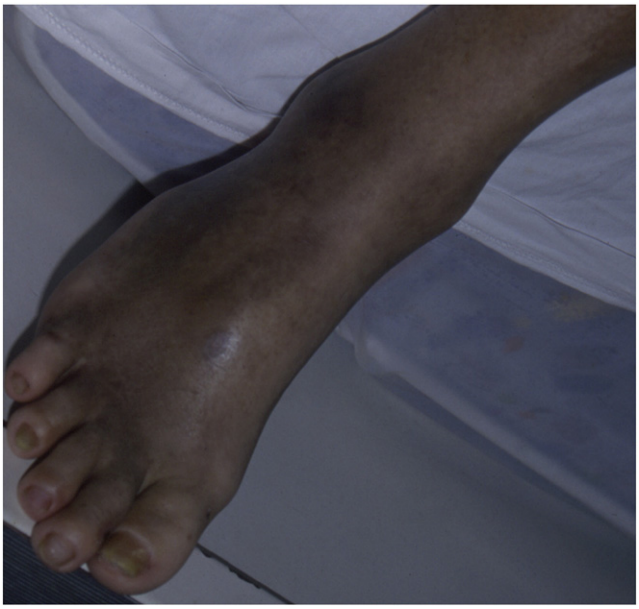

Fig. 4 Diabetic dermopathy of dorsal skin of the foot.

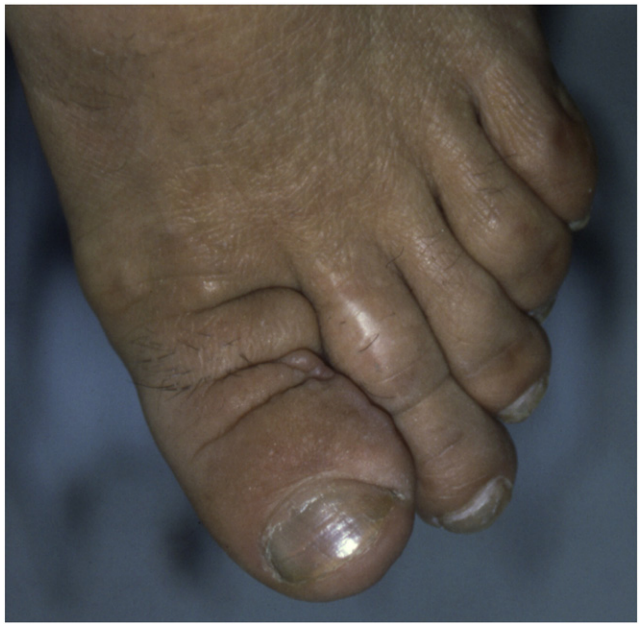

Fig. 6 Scleroderma diabeticorum in the toes area.

producing compression effects to the surrounding structures (optic chiasm, sella turcica, and cavernous sinus) and intracranial hypertension.[59] The most common cause of hyperpituitarism is an adenoma in the anterior lobe affecting predominantly adults, with a peak incidence between 35 to 60 years of age.[60]

Pituitary adenomas may be functional or secreting (excessive hormone production with corresponding clinical manifestations) and nonfunctional or nonsecreting (without hormonal clinical manifestations), the latter being the most commonly observed and now recognized as of gonadotroph origin.[61] Less commonly, other causes of hyperpituitarism are represented by hypophysial carcinoma and hypothalamic disorders.[61]

Visual symptoms and visual field defects are typical, linked to the anatomic relationship between the pituitary gland, the optic nerves, and optic chiasm, and the most common type of visual

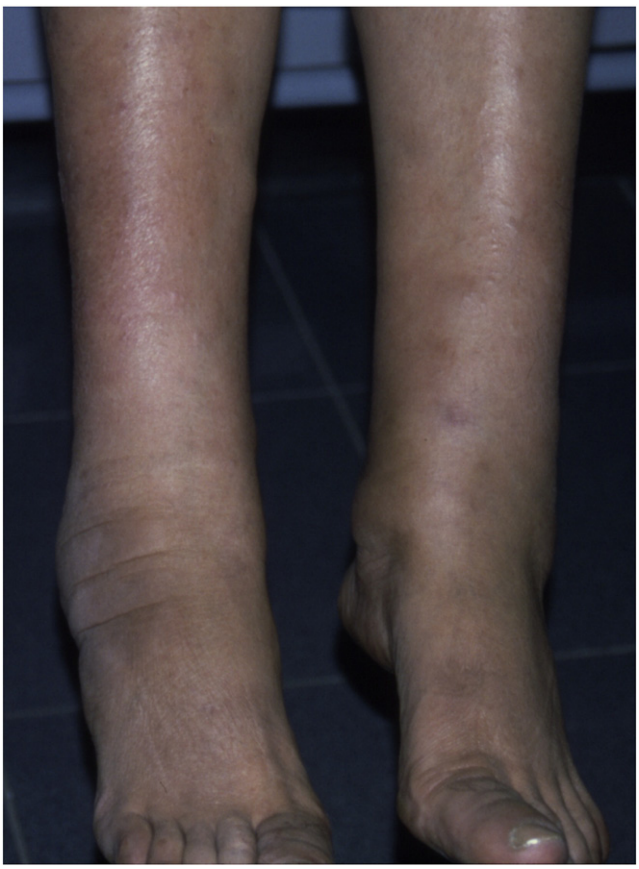

Fig. 5 Scleroderma diabeticorum in ankles.

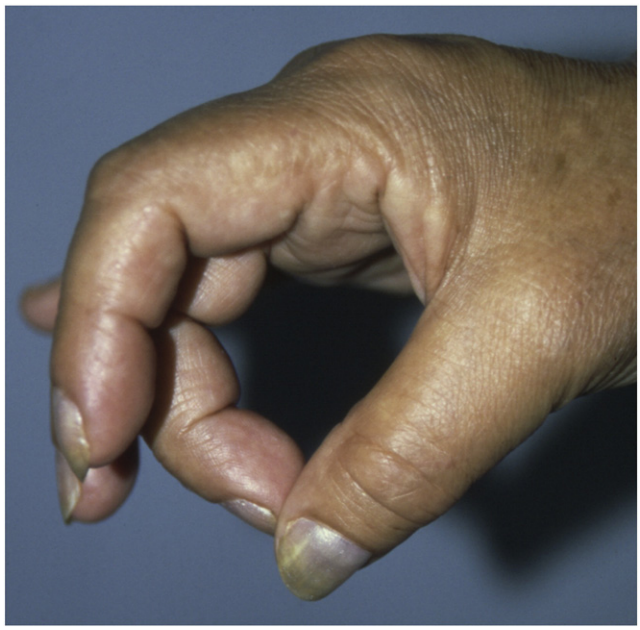

Fig. 7 Scleroderma diabeticorum in fingers.

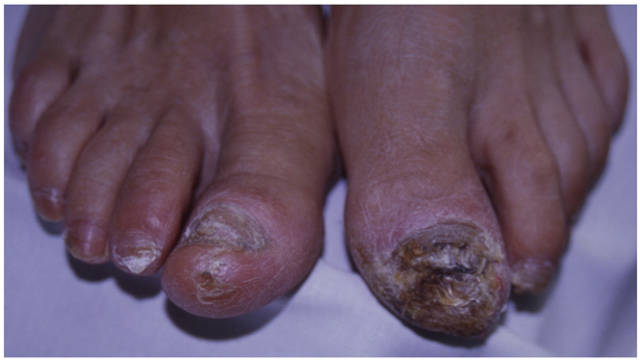

Fig. 8 Diabetic foot.

field defect is bitemporal hemianopsia.[62] Macroadenomas generally extend suprasellary, causing clinically evident visual function impairment that is slowly progressive, whereas microadenomas may have no effect on the visual pathway.[63] Nonfunctional pituitary adenomas cause more damage to vision than functional adenomas, the latter becoming symptomatic earlier due to systemic effects of increased hormone secretion.[64] As nonfunctional macroadenomas grow silently until they may become symptomatic, visual field defects are detected in up to 69% at the time of diagnosis in these cases, but only in 2% of ACTH-secreting tumors that are generally highly symptomatic.[65]

In general, early visual field defects are observed in the upper temporal quadrant (due to inferior chiasmal compression), unilateral or bilateral but often with asymetrical presentation[66]; however, atypical visual field defects may be observed as the consequence of the different anatomic positions of the chiasm, in the case of empty sella syndrome, or associated vascular or inflammatory phenomena.[66]

Extrasellar pituitary tumor growth may expand laterally into the cavernous sinus, compressing most commonly the oculomotor nerve and manifesting with diplopia.[66]

Visual acuity remains normal during long time in pituitary adenomas and may be affected when the tumor extends anteriorly and compresses the optic nerve. Sudden visual loss can occur in complicated adenomas (pituitary apoplexy; see later).

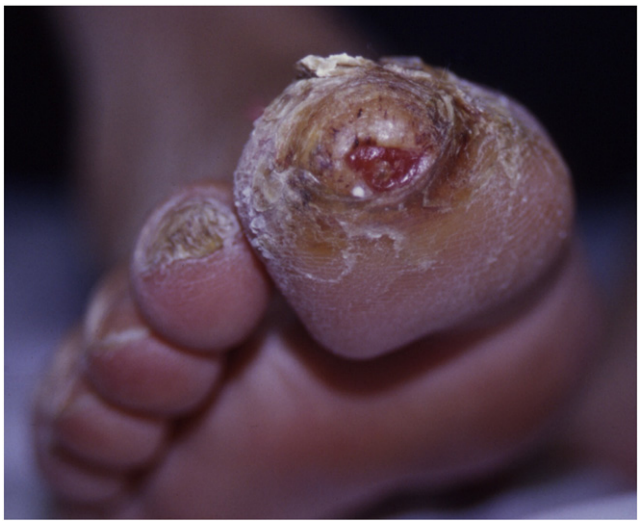

Fig. 9 Toe diabetic ulcer.

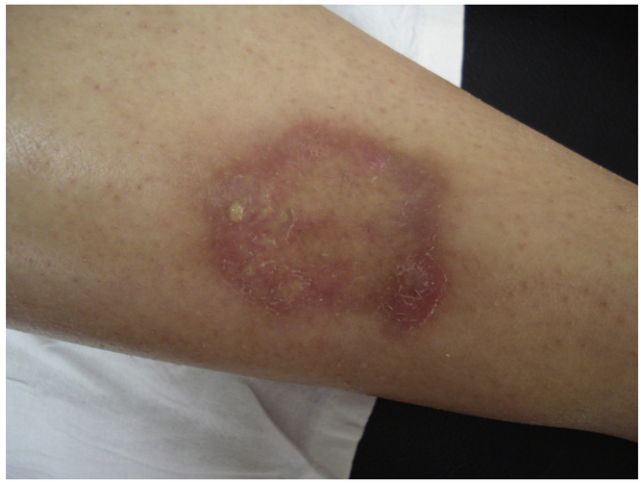

Fig. 10 Plaque of necrobiolisis lipoidica diabeticorum in middle shin.

Prolactinoma

The most common functional pituitary adenomas are those secreting prolactin (30% of clinical recognized cases), and they range from microadenomas (< 1 cm) to large tumors that also produce a mass effect. Prolactin secretion and its serum concentration are generally proportional to tumor size. Functional symptoms are more evident in middle-aged women than in men and older women, and hence allowing adenomas to reach considerable size before being diagnosed.[59]

No particular skin changes are observed and visual field defects may be observed in large prolactinomas.

Acromegaly

The second most common functional pituitary adenomas are those secreting growth hormone, and they are usually

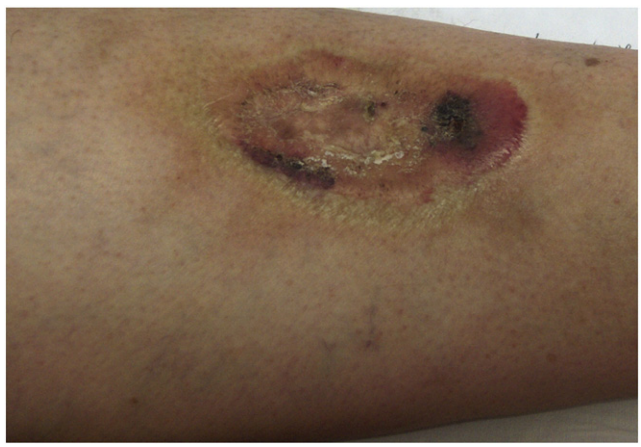

Fig. 11 Ulcerated area of necrobiolisis lipoidica diabeticorum in middle shin.

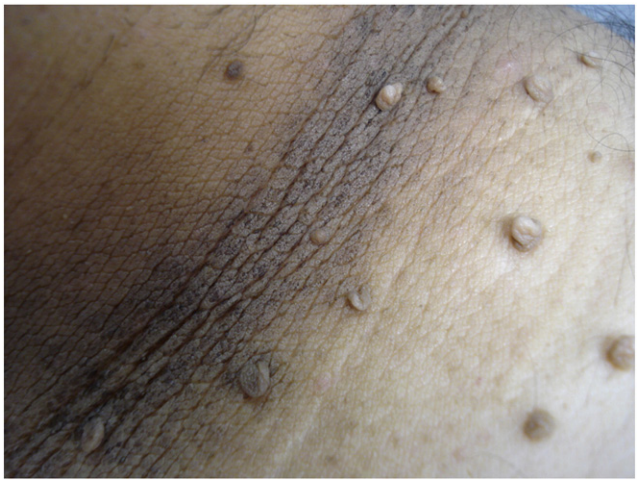

Fig. 12 Acanthosis nigricans base of the neck in acromegalia.

large.[59] Macroadenomas are observed in 71% of acromegalic patients, and 28% present suprasellar extensions, with a positive correlation between size of the adenoma and levels of growth hormone.[66]

If the adenoma appears in infancy (before the epyphyseal closure), it will produce gigantism. If it occurs in adulthood, it will produce acromegaly, characterized by pronounced growth of skin; thyroid; liver; heart; adrenal glands; and bones of face, hands, and feet. Other alterations may accompany, such as hyperostosis in spine and hips, generalized muscle weakness, diabetes mellitus, arterial hypertension, gonadal dysfunction, increased risk of gastrointestinal cancers, and arthritis.[59] Acromegaly is a slow progressive disease, with an increased risk in mortality rate due to cardiovascular disease, respiratory complications, and malignancies.[67]

The skin is thickened, with accentuation of nasolabial folds and forehead creases that contribute to the coarseness of facial features and somber expression.[68] Thickened eyelids, enlarged lower lip, and macroglossia are also characteristic.[68] Most patients have oily skin with large pores and hypertrichosis, and excess sweating is prominent in a great number of patients.[69] Acanthosis nigricans (Figures 12 and 13) may be observed in up to one third of patients with severe acromegaly.[69] Nails become thick and hard, and hair growth increases.[70]

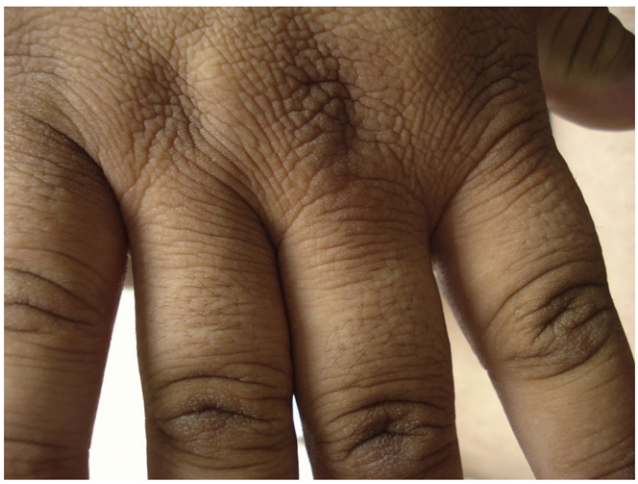

Fig. 13 Acanthosis nigricans of the hand in acromegalia.

Visual field defects are observed in 20.2% of acromegalic patients, and the vast majority (87%) of abnormal visual fields are detected at the time of diagnosis of the disease.[66] Indicators for risk of visual field defects are young age at onset, high levels of growth hormone at the time of diagnosis, and greater volume of adenoma.[66]

Besides visual pathway compressive compromise, mean intraocular pressure has been found to be significantly higher in acromegalic patients, irrespective of central corneal thickness values.[71]

Cushing syndrome

Cushing syndrome may be exogenous or iatrogenic (administration of corticosteroids), accounting for the majority of cases of this syndrome, and endogenous. *Endogenous Cushing syndrome* refers to the manifestations of increased cortisol secretion by the adrenal glands or as the consequence of ectopic secretion of adrenocorticotropic hormone (ACTH), and it may be ACTH dependent (Cushing disease) or ACTH independent (specific adrenal disease, mainly adenoma).[72]

The classic clinical manifestations of Cushing syndrome include upper body obesity with thin arms and legs due to muscle wasting (rhizomelic amyotrophia) and typical facial plethora (moon face), observed in 95% of cases.[73] In children, a slow growth rate is also observed.[74,75]

The skin becomes dry and thin, and wide purple to red cutaneous striae are observed in the abdomen, flanks, breasts, hips, and axillae, with easy bruising and slow healing. Impaired immune defense mechanisms increase the rate of infections. Pigmented facial hypertrichosis, androgenic alopecia, and hirsutism may be also be present.[76]

Ophthalmologic manifestations include ocular hypertension and exophthalmos.[77] Cataract may complicate a long-standing exogenous administration of glucocorticosteroids, and they are typically posterior subcapsular. In exogenous iatrogenic Cushing syndrome, a clinical picture simulating thyroid orbitopathy has been observed, presumbably due to fat deposition within the orbit, but with normal orbital muscles.[78] Also, retinal vascular changes similar to those of diabetic retinopathy,[79] hypertensive retinopathy with optic disc edema, multiple focal retinal pigment epithelium detachments, or central serous chorioretinopathy have been described.[80–83]

Luteinizing hormone–producing and follicle-stimulating hormone–producing adenomas

Gonadotrophic adenomas are inefficient secreting tumors, and they usually do not produce functional symptoms, but they may become symptomatic when they become large

tumors, causing impaired vision, diplopia, headaches, symptoms of pituitary apoplexy, or symptoms of impaired secretion of luteinizing hormone.[59]

Other anterior pituitary tumors

Thyroid-stimulating hormone–producing adenomas are rare (1% of all pituitary adenomas), and they are a rare cause of hyperthyroidism.[59]

Nonfunctioning pituitary adenomas, previously named "silent variants" or "null-cell adenomas," constitute 25%-30% of all pituitary tumors. They manifest as the consequence of their mass effect or hypopituitarism.[59]

Pituitary carcinomas are very rare, and they constitute less than 1% of all pituitary tumors. The majority of them are secreting tumors, often of ACTH and prolactin, and they metastasize late in the course of the disease, after multiple local recurrences.[59]

Posterior pituitary syndromes

Inappropriate antidiuretic hormone (ADH) secretion syndrome is the consequence of excess ADH secretion that causes increased resorption of free water, and the hallmark is hyponatremia. This syndrome is related to ectopic ADH secretion by malignant tumors (eg, lung small-cell carcinoma), increased ADH secretion by drugs, and diverse nervous system disorders such as trauma and infections.[84]

Deficient production of ADH, either spontaneous or caused by head trauma, inflammatory disorders, surgical procedures involving the pituitary gland and hypothalamus, or tumors, causes *diabetes insipidus* (central type).[59]

Hypopituitarism and posterior pituitary ectopia have been observed in association with one case of optic nerve aplasia[85] and another case of morning glory disc anomaly.[86] No specific skin manifestations have been described in association with posterior pituitary syndromes.

Pituitary apoplexy

Pituitary apoplexy is defined as the intratumoral hemorrhage and hemorrhagic infarction of a pituitary tumor complicating principally macroadenomas, presumably due to a sudden loss of pituitary gland's blood supply.[87,88] Rapid expansion of the enlarged adenomatous infarcted and hemorrhagic pituitary gland into the cavernous sinus produces sudden-onset symptoms like headache, nausea, vomiting, hormonal dysfunction, and ophthalmic symptoms, especially oculomotor nerve palsy.[89]

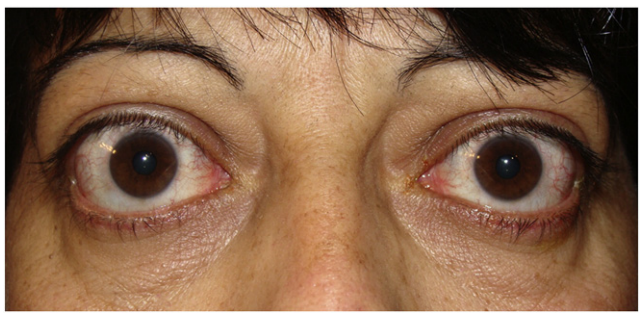

Fig. 14 Upper eyelid retraction and proptosis in dysthyroid ophthalmopathy.

Thyroid metabolic disease

Hyperthyroidism

Hyperthyroidism is a form of thyrotoxicosis due to an inappropriately high synthesis and secretion of thyroid hormone(s) by the thyroid.[90] In the United States, the prevalence of hyperthyroidism is approximately 1.2% (0.5% overt and 0.7% subclinical); the most common causes of hyperthyroidism are Graves disease, toxic multinodular goiter, and toxic adenoma.[91]

The complications of untreated thyrotoxicosis include loss of weight, osteoporosis, atrial fibrillation, embolic events, and even cardiovascular collapse and death.[92,93]

The severity of *Graves ophthalmopathy*, the inflammatory disease that develops in the orbit in association with autoimmune thyroid disorders, may be discordant with the degree of hyperthyroidism or hyperthyroid symptoms.[90] Despite evidence of an immune-mediated cause, the precise pathophysiologic mechanisms of thyroid eye disease remain unknown.[94] The minority of patients with Graves disease have clinical eye involvement, and it may develop even after the diagnosis and treatment of hyperthyroidism.[95] Eye symptoms include excess tearing, photophobia, and a feeling of grittiness. Also, diplopia, eye pain, and a decrease of visual acuity may be referred.[95] Physical findings may include lid lag on down gaze (von Graefe sign), upper eyelid retraction (Dalrymple sign) (Figure 14), incomplete and infrequent blinking (Stellwag sign), lack of convergence (Moebius sign), difficulty in maintaining gaze fixation in extremes (Suker sign), paralysis of one or more extraocular muscles (Ballet sign), spasmodic retraction of the upper eyelid during fixation (Kocher sign), conjunctival injection and suffusion (chemosis), proptosis (either unilateral or bilateral) (Figure 14), periorbital edema (Enroth sign), tremor of the eyelids when keeping them closed without force (Rosenbach sign), mobility jerking, spasmodic or gear upper eyelid and directing gaze downward (Boston sign), difficulty in upper eyelid eversion (Gifford sign), upper eyelid pigmentation (Jellinek sign), delay of lower eyelid in up gaze (Griffith sign), congestion surrounding cornea (Topolansky sign), horizontal nystagmus (Sainton sign), lack of contraction to look up front (Jeffroy sign), and emergence or intensification of congestion on the lateral rectus insertion (Dunphy sign).[95]

Exposure keratitis may occur when the patient is unable to close the eyelids completely. When eye disease occurs in patients with known hyperthyroidism, no specific laboratory tests are required to confirm the diagnosis.[95]

Therapy for Graves eye disease is directed toward restoring thyroid function to normal, as well as treating the eye symptoms. Management of patients with more than mild symptoms and signs should be carried out in conjunction with an ophthalmologist. Sunglasses (to decrease photophobia) and artificial tears (for lubrication) may be helpful. For periorbital edema, elevation of the head of the bed while sleeping may be useful, as well as the judicious use of diuretics. Systemic glucocorticoids have been used by some physicians in patients with active ophthalmopathy, in an effort to prevent its progression, particularly after 131-I therapy, but their efficacy is not fully established.[96]

Ophthalmoplegia, proptosis, diplopia, eyelid swelling, and retraction may be improved by using subconjunctival triamcinolone injections.[97] Proptosis, exposure of the globe, optic neuropathy, and intraocular pressure may be significantly reduced by decompression surgery.[98]

Rituximab, a biological agent, has been found efficacious in a heterogeneous cohort of patients with thyroid-associated orbitopathy.[99]

Thyrotoxic skin is described as the texture of an infant's skin: Warm, moist, and smooth. Although the smooth skin is an epidermal finding, the warmth is caused by increased cutaneous blood flow, and the moisture is a reflection of the underlying metabolic state. Increased blood flow in the skin along with peripheral vasodilation may be responsible for facial flushing and palmar erythema. The hair is often fine and soft, and nail changes may also occur, characterized by a concave contour accompanied by distal onycholysis (Plummer nails).[100] The thyrotoxic patient may suffer generalized hyperhydrosis, usually more prominent on the palms and soles.[101]

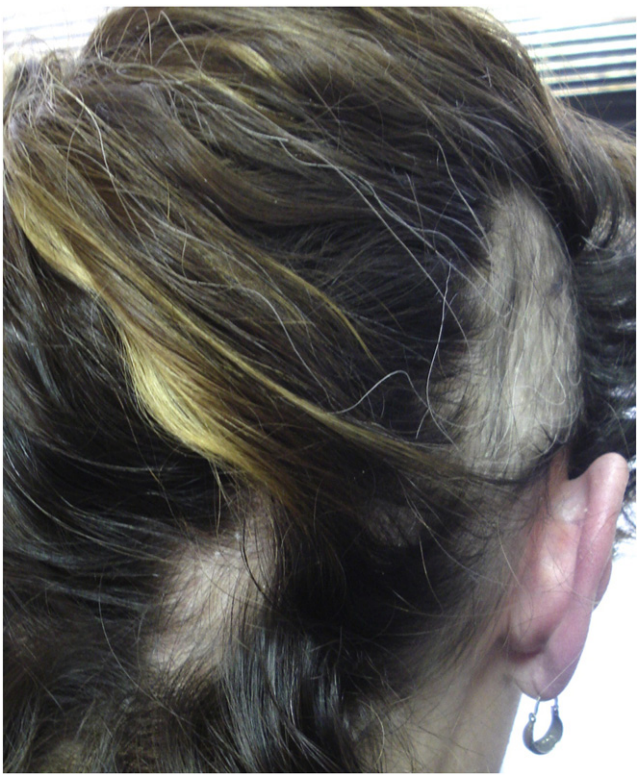

Fig. 15 Alopecia areata in hypothyroidism.

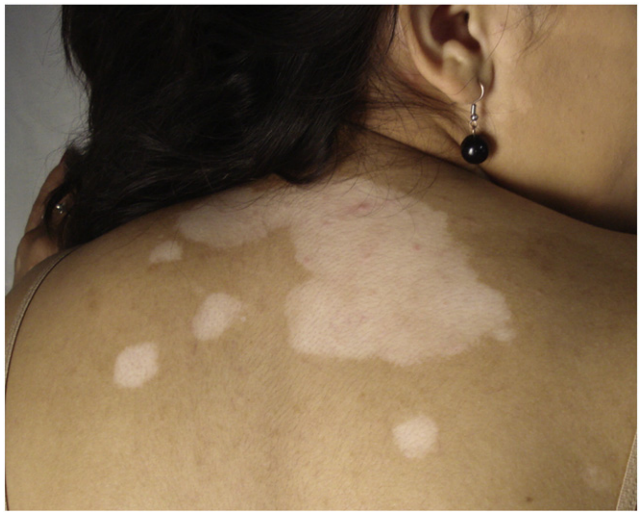

Fig. 16 Vitiligo in hypothyroidism.

Thyroid dermopathy, formerly termed "pretibial myxedema," is noted in 0.5%-4% of patients with Graves disease.[102] It may manifest as a localized skin thickening identical to that seen in hypothyroidism, and it has been named "pretibial myxedema" for many years due to its common identification in the pretibial area.[102] Rarely, it may present with overlying hyperhidrosis or hypertrichosis.[103] The most common form of dermopathy is the nonpitting type; the nodular and plaque-like forms are less common.[102] The polypoid and elaphantiasic types are rare, presenting in less than 1% of cases.[104,105] Thyroid dermopathy is almost always associated with ophthalmopathy.[102,106]

Acropachy is observed in approximately 1% of patients and typically manifests in the presence of both ophthalmopathy and dermopathy.[107] It consists in digital clubbing, soft-tissue swelling of the hands and feet, and periosteal new bone formation.[108]

Hypothyroidism

Hypothyroidism is a clinical syndrome resulting from a deficiency of thyroid hormones. It may be congenital

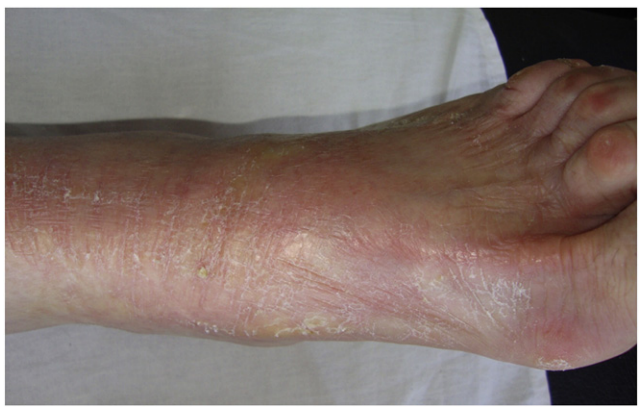

Fig. 17 Sclerodermia in hypothyroidism.

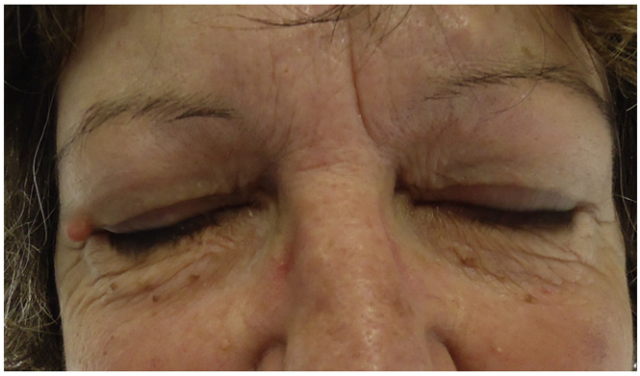

Fig. 18 Myxedema in hypothyroidism.

(endemic dietary deficiency of iodine), acquired (most commonly by the treatment of Graves disease), or autoimmune (Hashimoto thyroiditis). Other causes include alterations in the hypothalamic-pituitary axis, resulting in hypopituitarism, and congenital chemical defects, resulting in decreased thyroid hormone secretion.[109] The skin in hypothyroidism becomes cool, xerotic, and pale and is covered with fine scales resembling ichthyosis.[110] Hypohidrosis, possibly accompanied by diminished epidermal sterol biosynthesis, may lead to acquired palmoplantar keratoderma.[111,112] A yellowish hue may be imparted to the skin, particularly on the palms, soles, and nasolabial folds, as a result of carotenemia observed in hypothyroidism.[101] Hair changes manifest as dry, coarse, brittle hair, with a tendency to fall out, resulting in diffuse, partial alopecia.[100] Eyebrows often disappear, with loss usually originating laterally (madarosis).[113] Nails are thin, striated, brittle, and grow slowly. Onycholysis has also been reported.[114] Hypothyroidism may be associated with a number of different cutaneous and/or systemic diseases. The cutaneous diseases associated with hypothyroidism include alopecia areata (Figure 15),[115] chronic urticaria,[116,117] vitiligo (Figure 16),[118] and scleroderma (Figure 17).[119]

Myxedema is caused by an accumulation of water-binding mucopolysaccharides in the dermis. Manifestations of myxedema range from unnoticeably mild to markedly severe.[109] The facial skin has puffy features with increased skin creases, and patients may have a flat, expressionless facies (Figure 18). The tongue is large, red, smooth, and clumsy.[109]

Eye disease of hyperthyroidism is also observed in hypothyroidism state, with same demographics, clinical characteristics, and severity and activity scores.[120] Dry eye symptoms of patients appear to be attributable to an underlying ocular surface inflammation rather than to dryness, showing improvement of their ocular surface disease with topical antiinflammatory and immunomodulating therapy.[121] Individuals with hypothyroidism seem to have an increased frequency of age-related macular degeneration, but further studies are needed to support this hypothesis.[122]

Loss of eyelashes and eyebrows, especially on the temporal side, eyelids myxedema, ocular irritation, corneal changes, and cataract are common clinical signs that accompany hypothyroidism.[123]

Ascher syndrome

Ascher syndrome, a rare entity of unknown etiology, is characterized by a double upper lip due to maldevelopment, bilateral blepharochalasis (present in more than 80% of cases), and nontoxic thyroid enlargement (present in less than 50% of cases).[124] Blepharochalasis starts in puberty as a painless swelling of lids and represents a form of localized angioedema with decreased dermal elastin (first stage).[124] Progressively, an atonic ptosis is installed as the consequence of dehiscence of levator aponeurosis or an overhanging redundant fold of lax and thin skin over the lid margin (second stage), and lately the atrophy of the medial fat pad, orbital fat prolapse, and lacrimal gland prolapse (third stage).[124] Corrective surgical treatment is indicated if visual acuity disturbances or ocular complications occur and should be deferred for at least 1 year from previous attack of eyelid edema.[124]

Parathyroid diseases

Parathyroid glands control concentrations of calcium in the blood and bones and concentrations of serum phosphate by means of the parathormone.

Hyperparathyroidism

Hyperparathyroidism is divided into primary, secondary, and tertiary. Primary hyperparathyroidism is the spontaneous overproduction of parathormone and is principally related to parathyroid adenoma (85%-95%), primary diffuse or nodular hyperplasia (5%-10%), and parathyroid carcinoma (1%). Secondary hyperparathyroidism is most commonly caused by chronic renal insufficiency, in which serum phosphate levels stimulate the kidneys to excrete calcium along with the phosphate-inducing parathormone hypersecretion to replace the lost calcium, resulting in bone resorption and cyst formation.[59,125–127]

Primary hyperparathyroidism may be asymptomatic (hypercalcemia found in a routine laboratory workup) or symptomatic, characterized by painful and weakened bones, bone fractures secondary to osteoporosis or osteitis fibrosa cystica, renal lithiasis (20%), gastrointestinal disorders (nausea, constipation, peptic ulcer, gallstones, and pancreatitis), central nervous system and neuromuscular alterations (depression, lethargy, seizures, weakness, fatigue), and cardiovascular disorders (aortic and/or mitral valve calcifications).[59]

In *secondary hyperparathyroidism*, clinical manifestations are dominated by manifestations of renal insufficiency, which is by far the most common cause of secondary

hyperparathyroidism.[59] *Calciphylaxis*, known as a small-vessel calcification vasculopathy, involves mural calcification with intimal proliferation, fibrosis, and thrombosis.[128] The most commonly affected tissues are the dermis and the subcutaneous fat, but the vasculopathy may also occur in visceral organs and skeletal muscle.[128]

Tertiary hyperparathyroidism refers to an excessive secretion of parathormone after longstanding secondary hyperparathyroidism and occurs both in men and women with chronic renal disease, usually after kidney transplantation.[129] Metastatic calcifications characteristically form grossly visible nodules in the dermis and subcutaneous tissue and may also appear at periarticular sites, the lesions regressing as calcium and phosphate serum levels normalize.[130] Benign nodular calcification is defined as calcification of the cutaneous and subcutaneous tissue without tissue necrosis, as seen in calciphylaxis, and may coexist with calciphylaxis.[131]

Skin manifestations of hyperparathyroidism present as painful, violaceous, mottled to reticulated skin lesions resembling *livedo reticularis* that may become plaque-like or nodular.[132] The lesions often progress to nonhealing ulcers with significant tenderness and ischemic pain and usually become gangrenous.[132,133] Characteristically, the ulcers are deep and stellate or wedge shaped, and they are often multiple, being located on the lower limbs in 90% of patients.[133] In addition, the digits, penis, and internal organs may be affected by calciphylaxis.[132,133] Proximal involvement (lesions on trunk or proximal to the knees and elbows) has been associated with a poorer prognosis.[133] Ulcerations may be a starting point for septic complications that are associated with a mortality rate of 50%-80%.[134]

Ocular manifestations of hyperparathyroidism are generally observed in the context of an already diagnosed hyperparathyroidism, and rarely as the initial clinical manifestation of the disease.[135] They include asymptomatic conjunctival calcifications, conjunctivitis, and intraepithelial corneal calcification in the area of the interpalpebral fissure (band keratopathy).[77] Sclerochoroidal calcifications have also been described, being generally asymptomatic and found in occasion of an ocular fundus examination or an orbital computed tomography scan,[136,137] but with the potential of producing late choroidal neovascularization with subretinal exudation.[138] Extensive ocular calcifications have been observed in a case of secondary uremic hyperparathyroidism that had bilateral attenuated and calcified retinal arterioles, calcifications of the bulbar conjunctiva, and unilateral band keratopathy and limbal calcifications.[139] Orbital involvement as part of craniofacial brown tumors has been observed in primary and secondary hyperparathyroidism, and the lesions may regress after the control of hyperparathyroidism.[140]

McCune-Albright syndrome is a rare disease with an estimated prevalence of 1/100,000 to 1/1,000,000, characterized by the triad of fibrous dysplasia of bone (single or multiple skeletal sites), café-au-lait skin spots (neonatal period), and precocious puberty, with ovary, thyroid, adrenals, and pituitary and parathyroid glands involved.[141] Visual field defects, decreased visual acuity, diminished color vision, and optic atrophy may be observed as the consequences of optic nerve compression by craniofacial fibrous dysplasia compromising the optic canal.[142] Ocular manifestations of hyperparathyroidism such as band keratopathy, asymptomatic conjunctival calcification, and scleritis may be observed as part of this syndrome.[77]

Hypoparathyroidism

Hypoparathyroidism is much less common than hyperparathyroidism, and its clinical hallmark is hypocalcemia. There are several genetic and congenital causes of hypoparathyroidism, such as autosomal-dominant hypoparathyroidism, familial isolated hypoparathyroidism, and congenital absence of parathyroid glands (occuring in conjunction with thymic aplasia and cardiovascular defects, or as a component of the DiGeorge/22 q11 deletion syndrome), but acquired hypoparathyroidism is almost always the consequence of inadvertent thyroid surgery or radical neck dissection. Autoimmune hypoparathyroidism is associated with primary adrenal insufficiency (as part of the *autoimmune polyendocrine syndrome type I*, a rare autosomal recessive disease that presents in childhood; see later) and chronic mucocutaneous candidiasis.[59,143]

Tetany is the hallmark of hypoparathyroidism, and classic findings of neuromuscular compromise include *Chvostek sign* (contraction of periocular, mouth, or nose muscles when tapping along the course of the facial nerve) and *Trousseau sign* (carpal spasms produced by circulatory occlusion of the forearm and hand with a blood pressure cuff). Mental disturbances (emotional instability, anxiety, depression, confusional state, hallucinations, and psychosis), neurologic manifestations (Parkinsonian-like movements, increased intracranial pressure and papilledema, and calcification of the basal ganglia), cardiovascular disorders (conduction defects), and dental abnormalities occuring during early development (dental hypoplasia, defective enamel and root formation, and carious teeth) are associated.[59]

Skin manifestations in aquired hypoparathyroidism include dry and keratotic skin, brittle and ridged nails, onycholysis, loss of axilarry or pubic hair, coarse hair, alopecia areata, pellagra-like pigmentation, and pustular psoriasis.[144]

Ocular manifestations of hypoparathyroidism are common, and cataract is present in 50%-60% of cases. It is bilateral and characterized by thin cortical opacities associated with posterior and anterior cortical polychrome crystals. Cataract of zonular or subcapsular type is observed early in familial forms of the disease and may sometimes be stabilized or even reversed with phosphocalcic normalization.[59,145]

In *autoimmune polyendocrine syndrome I*, caused by mutations in the autoimmune regulator gene with

progressive multiple organ–specific autoimmunity of endocrine and nonendocrine tissues, hypoparathyroidism and Addison disease are the most common disease components.[146] Several ocular complications, such as dry eye, chronic keratitis (the most common), iridocyclitis, cataract, retinal detachment, and optic atrophy, have been described.[147] Alopecia and vitiligo may also be observed in some patients.[148]

Adrenal diseases

The adrenal glands present two distinct regions that differ in their development, structure, and function: the cortex, which secretes three different types of steroids (glucocorticosteroids, mainly cortisol; mineralocorticosteroids, mainly aldosterone; and sexual steroids), and the medulla, which secretes catecholamines (mainly epinephrine).[149]

Adrenal cortex diseases

Adrenocortical hypofunction

Adrenocortical hypofunction or insufficiency may be primary or secondary.[59]

Primary acute adrenocortical insufficiency may be the consequence of any form of stress demanding a sudden increase in steroid output, in the context of a chronic adrenocortical insufficiency, with a gland completely unable to respond to such demand. It also may occur in patients with longstanding corticosteroid treatments that are abruptly withdrawn or failure to increase the dose in response to an acute stress. Lastly, it may be produced by a massive adrenal hemorrhage, as seen in newborns after prolonged delivery with trauma and hypoxia due to their often deficient prothrombin in the first days after birth, in patients undergoing anticoagulant therapy, and in patients with disseminated intravascular coagulation.[59]

Acute hemorrhagic adrenal necrosis *(Waterhouse-Friderichsen syndrome)* is an infrequent but devastating and often fatal bacterial disease that may occur at any age but is seen more commonly in children. It is classically produced by *Neisseria meningitidis* and also by *Pseudomonas* species, pneumococci, *Haemophilus influenza*, or staphylococci and is a rapidly progressive, leading to hypotension and shock, disseminated intravascular coagulation, and acute adrenocortical insufficiency.[59]

Primary chronic adrenocortical insufficiency (Addison disease) is a rare endocrine condition caused by a deficiency of aldosterone and cortisol. The most common cause of primary adrenal insufficiency in developed countries is autoimmune adrenalitis, which may be isolated or associated with other autoimmune endocrinopathies.[150,151] One of the hallmark signs of Addison disease is cutaneous and mucosal hyperpigmentation related to ACTH melanogenic action.[152] Pigmentation can be homogeneous or blotchy and may involve skin, oral cavity, conjunctiva, and genitalia.[153] Brown patches of gingival, vermillion border of the lips, oral mucosa, palate, and tongue may represent the first signs of Addison disease.[153]

Ophthalmologic manifestations are rare in Addison disease and include ptosis, blepharitis, blepharospasm, keratoconjuncitivits, corneal ulcers, episcleritis, lens opacities, and papilledema (if associated with intracranial hypertension).[77]

Secondary adrenocortical insufficiency is produced by a reduced production of ACTH secondary to a disorder of the pituitary gland (metastatic tumor, infection, infarction, or irradiation) or longstanding administration of corticosteroids.[154] Clinically it has many similarities to Addison disease, also with deficient cortisol and androgen output, but aldosterone synthesis is near normal ranges, and classical hyperpigmentation is lacking.[154]

Triple A syndrome (Allgrove syndrome) is a rare, autosomal recessive disorder characterized by ACTH-resistant adrenal insufficiency, alacrimia, achalasia, progressive neurologic degeneration, dwarfism, microcephaly, autonomic dysfunction, and chronic symptomatic neutropenia.[155,156] Ophthalmologic manifestations are prominent, and they include alacrimia and keratoconjunctivitis sicca, lacrimal gland atrophy, pupillary abnormalities (sluggish or tonic pupils), accomodative disturbances, amblyopia, and optic atrophy.[157] Areas of buccal and gums mucosal hyperpigmentation have been observed, and skin pigmentation is common but variable and often missed. Hyperkeratosis and fissuring of palms of hands and soles represent unique features of this syndrome.[158,159]

Adrenocortical hyperfunction diseases (hyperadrenalism)

Depending on the type of hypersecreted corticosteroid, hyperadrenalism may consist of: (1) excess of cortisol (Cushing syndrome; see Pituitary Diseases), (2) excess of aldosterone (hyperaldosteronism), and (3) excess of androgens (adrenogenital or virilizing syndromes).[59]

Ocular complications of primary or secondary hyperaldosteronism are due to arterial hypertension and are represented by retinal and choroidal vasculopathy, similar to those observed in primary hypertension or other severe causes of hypertension like eclampsia.[160]

Androgenetic alopecia has been observed to be related to hyperaldosteronism.[161]

Adrenogenital syndromes occur as the consequence of adrenal androgen excees secretion (1) by adrenocortical virilizing tumors (more often carcinomas than adenomas), (2) as a component of Cushing disease, and (3) in the context of congenital adrenal hyperplasia (autosomal recessive, associated with cortisol deficiency and sometimes aldosterone deficiency).[59] Congenital adrenal hyperplasia, an inherited autosomal recessive disease with an incidence of 1:12,099 to 1:23,044, occurs as the consequence of a defect in one of the five enzymatic steps of cortisol biosynthesis from cholesterol.[162,163] It can be divided into two groups: the classical form (severe, salt wasting, born with virilized external genitalia,

potentially lethal if undiagnosed) and the nonclassical form (less severe, late onset, non–salt wasting).[162] In the latter form, clinical signs are characterized by premature pubarche, tall sature, advanced bone age, menstrual disturbances, infertility, and skin manifestations such as progressive hirsutism and acne, occuring later in childhood and after puberty or adolescence.[162] No specific ocular manifestations have been described in association with this disease.

Adrenal medulla diseases

Adrenal medulla is the major source of catecholamines (epinephrine and norepinephrine). Diseases of the adrenal medulla are principally neoplastic, some of them originating from chromaffin cells (pheochromocytoma) and others from neuroendocrine cells (neuroblastoma).[59] Ocular manifestations of pheochromocytoma are related to those of hypertensive retinopathy (arteriolar narrowing/sclerosis, abnormal arteriovenous crossings, optic disc edema) and choroidopathy (triangular syndromes, patchy atrophy of the pigment epithelium). In pheochromocytoma associated with multiple endocrine neoplasia type 2 (thyroid medullar neoplasia, pheochromocytoma, parathyroid adenoma), ophthalmologic manifestations are prominent and consist of hypertrophic corneal nerves (constant finding), bulbar conjunctival (87%) and lid neuromatosis (80%),[164,165] and dry eye (67%).[166,167]

Addisonian-like hyperpigmentation has been reported in pheochromocytoma and is probably due to ectopic ACTH and melanocyte-stimulating hormone production by the tumor.[168]

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