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The eye and the skin in nonendocrine metabolic disorders

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Abstract As metabolism is controlled by the input of genes and the environment, metabolic disorders result from some disturbance in the interaction between genes and environmental factors. Many metabolic disorders consist in congenital enzyme deficiencies, also known as "inborn errors of metabolism," that may be disabling or cause severe illness and death and are predominantly inherited in an autosomal recessive fashion. The deposit in cells and tissues of storage substances from errors in metabolic processes may produce a wide variety of disorders affecting different organs and functions, with different degrees of severity, and often present around the time of birth or early childhood. Distinctive ocular and skin manifestations accompany many metabolic diseases and may provide clues for their diagnosis and evolution.

Uric acid metabolism disorders

Gout

Gout is one of the most common causes of arthritis. It is a disease of uric acid metabolism, characterized by the rise of serum urate, intraarticular and connective tissues (tophi) deposition of monosodium urate crystal, urate urolithiasis, and, rarely, gouty nephropathy.[1] The first acute manifestation of gout is preceded by asymptomatic hyperuricemia for many years (up to 20 years) in the absence of gout or uric acid nephrolithiasis, and it usually occurs between the ages of 40 and 60 in men and after age 65 in women.[2] Onset in young adulthood is often related to an inherited defect in purine metabolism or renal urate transport.[2,3]

In acute gouty arthritis, more than 50% of initial episodes present as oligoarticular podagra, an acute inflammation of the first metatarsophalangeal joint; the ankles, knees, and feet can also be affected.[4] The joint is usually very tender and swollen, and the attack may last a few days, relapsing from

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time to time.[4] The chronic stage of gout is represented by tophi formation that usually occurs 10 or more years after the onset of the disease.[4] Tophi, a pathognomonic feature of gout, are yellowish and nontender nodules ranging in size from 1 mm to 7 cm, observed mainly in articular, periarticular, bursal, bone, auricular, and cutaneous tissues.[4] Tophi themselves are generally painless, but they can trigger local inflammation.[5] Without treatment, joint destruction and large tophi deposition can result in grotesque deformities as a result of the chronic surrounding inflammation.[5]

Although infrequent, ophthalmologic manifestations of gout are varied and generally observed in longstanding disease. Urate crystals may be found in eyelids, tarsal plates, extraocular muscle tendons, conjunctiva, cornea, sclera, iris, and lens. They appear as irregular, flake-like white crystals. Other findings consisting of tortuous conjunctival and episcleral blood vessels, some of them spiral shaped, and transparent conjunctival vesicles with metal-like shine have been observed.[6–15]

Lesch-Nyhan disease

Lesch-Nyhan disease and its variants are X-linked inborn errors of metabolism of the uric acid that are caused by a defect in the hypoxanthine-guanine phosphoribosyltransferase gene.[16] Congenital deficiency of the enzyme hypoxanthine-guanine phosphoribosyltransferase results in marked overproduction of uric acid, severe motor handicap resembling dystonic cerebral palsy, intellectual disability, and recurrent self-injurious behaviors such as biting of lips, tongue, and fingers, and head banging.[17]

One of the first signs of the disease may be the observation of orange crystals in the diapers or crystalluria with obstruction of the urinary tract. Other uncommon forms of presentation include renal failure or acidosis with repeated vomiting.[17] Psychomotor delay, when present, becomes evident within 3 to 6 months.[17]

All characteristic findings associated with gout may be present in these patients: acute arthritis, tophi, nephrolithiasis or urolithiasis, and renal disease. If the diagnosis and treatment are delayed, tophi and renal failure may appear.[17]

Patients with severe enzyme deficiency may present with mild blepharospasm and abnormal eye movements, such as unwanted and voluntary ocular saccades, the latter being preceded by an initial head movement and/or eyeblink.[18] These abnormal eye movements are consistent with a dysfunction of the basal ganglia or their connections with ocular motor centers in the prefrontal cortex or midbrain.[18]

Porphyrias

Porphyrias are a group of inherited metabolic disorders of heme biosynthesis and metabolism, each one resulting from a specific enzymatic alteration in its biosynthesis pathway. Porphyrias are often classified as hepatic or erythropoietic, according to the organ in which heme precursors accumulate. Classification based on clinical presentation as acute porphyrias, cutaneous porphyrias, and rare recessive porphyrias is directly related to a simple biological diagnosis strategy and is more practical.[19]

Porphyria cutanea tarda, erythropoietic protoporphyria, and congenital erythropoietic porphyria have predominantly cutaneous manifestations. Hereditary coproporphyria and variegate porphyria are classified as mixed because they may have both cutaneous and neuropsychiatric features.[19]

Porphyrin molecules absorb visible light, generating excited states with consequent lipid peroxidation and protein crosslinking leading to cell membrane damage and death.[19]

Porphyria cutanea tarda (PCT) type 1 (sporadic) is the most common type worldwide, accounting for 80%-90% of all cases of PCT, and presents predominantly with skin symptoms.[20] Possible etiologic factors include alcohol, estrogens, iron, chemicals (eg, hexachlorobenzene), and hepatitis C and HIV infection.[21] Type 2 (familial) PCT, an autosomal dominant disease with incomplete penetrance, is heterozygous for *UROD* mutations, and asymptomatic patients have approximately half-normal enzyme activity systemically.[22] Many of the risk factors related to type 1 PCT may contribute to the expression of type 2 disease.[22]

PCT usually presents in adults and is characterized by blistering skin lesions that appear most commonly on the backs of the hands.[21] These blisters rupture and crust over, leaving areas of atrophy and scarring (Figures 1 and 2).[22] Lesions may also occur on the forearms, face (Figure 3), legs, and feet.[23] Skin friability and small white papules termed milia are common, especially on the back of the hands and fingers.[23] Hypertrichosis (Figure 4) and hyperpigmentation (Figure 5), particularly on the face, are especially troublesome in women.[24] Occasionally, in sun-exposed areas the skin becomes severely thickened with scarring and calcification, which resembles systemic sclerosis.[25] Neurologic features are absent.[23]

Erythropoietic protoporphyria, the most common erythropoietic porphyria and the most common porphyria in children, is essentially an autosomal dominant disorder due to an inherited partial deficiency of ferrochelatase, the last enzyme in the heme biosynthetic pathway.[26] The erythropoietic protoporphyria phenotype is characterized by acute,

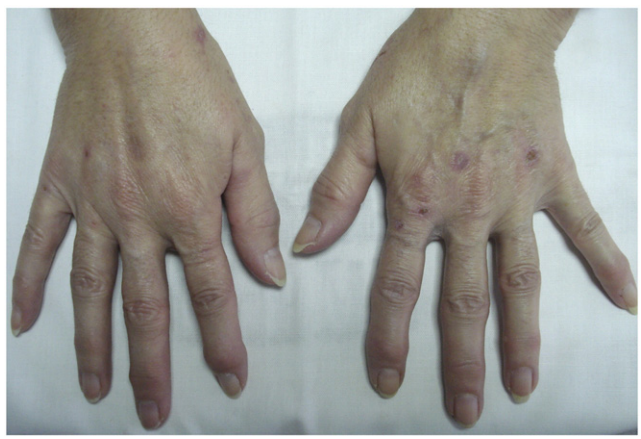

Fig. 1 Porfiria cutanea tarda—scars of blistering lesions on hands.