Commentary: Discerning the porhyrias!

Porphyrias are the group of disorders involving heme biosynthesis caused by hereditary or acquired deficiencies of one of the eight intracellular enzymes in porphyrin pathways. Specific enzyme deficiencies lead to the accumulation of photosensitive, toxic intermediates in various body organs, including the skin, eye, and neural tissue.[1]

Physiologically, porphyrias are classified into hepatic and erythropoietic porphyrias based on the sites of accumulation of porphyrins, namely the liver or erythrocytes and bone marrow, respectively. Congenital erythropoietic porphyria (CEP) is caused by the deficiency of the fourth enzyme in heme pathway namely uroporphyrinogen 3 cosynthase (synonyms: uroporphyrinogen HI synthase, uroporphyrinogen 3 isomerase, hydroxymethyl bilane hydrolase) caused by mutation in the *UROS* gene on chromosome 10 q 25.2-26. This enzyme specifically converts the linear molecule, hydroxymethyl bilane (HMB), to a cyclic tetrapyrrole called uroporphtrinogen. The problems in CEP stem in not from the deficiency of heme (needed for the formation of hemoglobin, myoglobin, catalase, peroxidase, cytochrome P450 enzymes) but from the accumulation of its precursors that are toxic to the cells. This is because most heme synthesis enzymes, including the dysfunctional ones, have enough residual activity to assist in heme synthesis.

In CEP, the enzyme deficiency causes the HMB to spontaneously condense to 85% inactive isomer called uroporphrinogen 1 and 15% to physiologic isomer 3 called uroporphyrinogen 3. These porphyrin metabolites are deposited in skin causing oxygen-dependent type 2 blisters. The *sine quo non* factors needed for skin damage are increased amounts of porphyrins with an intact cutaneous circulation along with molecular oxygen to induce phototoxic reaction.

To discretely prove CEP, simultaneous determination of porphyrins in erythrocytes, urine, and feces with differentiation between isomers 1 and 3 is recommended. In particular, the absence of isocoproporphyrin in urine and stool and a normal value of uroporphyrinogen decarboxylase activity have to be demonstrated to disprove hepatoerythropoietic porphyria. However, in the developing world, when facilities for high-performance liquid chromatography (HPMC) are not available, qualitative tests over quantitative methods correlated with protean clinical features[2] could well be considered by an astute clinician.[3]

Ocular manifestations[1] includes blepharitis, cicatricial ectropion, conjunctivitis, and complete loss of eyelashes and eyebrows. Scleral inflammation initially starts with interpalpepbral fissures in perilimbal sclera due to porphyrin deposition on the collagen that is proven by pink fluorescence in the Wood's light. It can potentially progress to scleromalacia, corneal scarring, and blindness if not correctly diagnosed. The other ocular features include pterygium, decreased corneal sensitivity, retinal hemorrhages, and optic atrophy. The exact ocular pathogenesis is not clear. The proposed causes include photic damage, ischemia, and secondary inflammation. The pointers to the diagnosis of porphyrias are readily evident in the systemic manifestations.

The cardinal dermatological manifestations of CEP is the photosensitivity reactions that start in the sun exposed to the nonexposed areas in the late stages. Central to the pathogenesis is the increased formation of collagenase induced by uroporphrin with UVA rays.[1] The photosensitive reactions in CEP are severe enough to manifest as second or third-degree burns. They manifest as vesicles, bullae, and ulcers with secondary infections. In the end stages, they progress to mutilation of fingers, hands, and face. The deformities extend to nails and fingers with hypertrichosis, and pigmentary changes (hyperpigmentation/depigmentation) in the unexposed areas.

The skeletal changes manifest as severe osteolysis with mutilations. Bone marrow hypertrophy, osteopenia, and coarse bone trabecular meshwork are secondary to hemolysis and hypersplenism. In particular, vitamin D deficiencies due to sun avoidance leads to acro-osteolysis, secondary hyperparathyroidism, and mineralization defects. Dental changes such as the red-colored tooth with fluorescence in wood's light merits attention.

Delineating the different porphyrias clinically before ordering for the specific enzymes is a daunting task. CEP differs from erythropoietic protoporphyria (EPP) by dermatological features,[3] namely bullae formation and lack of paraesthesia typically experienced in CEP under sunlight. In particular, in the neonatal period, hepatoerythropoietic porphyria (HEP) presents with similar symptoms with lack of isocoproporphyrin in urine or feces. Porphyria cutanea tarda (PCT) is the most common porphyria of adult onset with an acquired defect in uroporphryinogen decarboxylase (UROD). Its association with hepatitis C virus and HIV infection needs practical application during treatment.

Ocular treatment consists of lubricants, bandage contact lenses to prevent and treat dry eye. Scleral patch graft, and keratoprosthesis[4] in advanced cases appears promising. Agarwal *et al.* compiled the ocular literature review of the cases of porphyrias of varied severity.[5] The treatment needs to be individualized with the heterogeneous nature of the disease severity with multidisciplinary care.

In CEP, with no definitive proven modalities, sunlight exposure as a preventive measure assumes significance. Porphyrin binders like charcoal, cholestetyramine, and metabolic alkalinization have been considered. Free radical quenchers like ascorbic acid, and alpha tocopherol are helpful. To reduce the synthesis of porphyrins, frequent blood transfusions were considered. The benefit of glucocorticosteroids is not definitive to suggest as a plan of treatment. However, bone marrow transplantation and gene therapy appears promising.[1] Proteosome inhibitors, such as bortezomib,[6] and melanocortin stimulating analogue, such as afamelanotide,[6] are in the pipeline.

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