The porphyrias – part II

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Abstract

CEP is an AR porphyria that results from deficient activity of URO-synthase and results in the accumulation of Uroporphyrin I and Coproporphyrin I isomers. The skin areas overexposed to sunlight are friable and blisters and vesicles are prone to rupture and infection. Skin thickening, focal hypo- and hyperpigmentation and hyperthricosis of the face and extremities are characteristic. The diagnosis is confirmed by the demonstration of significantly deficient URO-synthase activity or the identification of specific mutations of the UROS-gene.
The knowledge of these advances is relevant for hematologists because they administer the hematin infusions to treat the acute attacks in patients with acute hepatic porphiryas, perform the chronic phlebotomies to reduce iron overload, clear the dermatologic lessions in PCT, diagnose and treat the erithropoietic porphiryas, including chronic erythrocyte transfusions, B.M. or SCT transplants and experimental pharmacologic chaperone and stem cell gene therapies for CEP. These developments are relevant to update hematologists on the latest advances in these diverse disorders.

ERYTHROPOIETIC PORPHYRIAS

Classification

- Congenital Erythropoietic Porphyria (CEP);
- Erythropoietic Porphyria (EPP);
- X-Linked Porphyria (XLP)

Type	Deficient enzyme	Inheritance	Enzyme activity, % of normal	Increased porphyrin / porphyrin precursors		
				Erythrocytes	Urine	Stool
Erythropoietic porphyrias						
CEP	URO-synthase	AR	1-5%	Uroporphyrin I Coproporphyrin I	Uroporphyrin I Coproporphyrin I	Coproporphyrin
EPP	Ferrochelatase	AR	20 – 30 %	-Primarily free proporphyrin	-	Proporphyrin
XLP	ALA-synthase 2	XL	> 100%	Zn- and free proto-porphyrin	-	Proporphyrin

CONGENITAL ERYTHROPOIETIC PORPHYRIA (CEP)

- CEP is an AR disorder;
- The activity of URO-synthase is deficient and the result is an accumulation of uroporphyrin I and coproporphyrin I isomers;
- Uroporphyrinogen I is metabolised by uro-decarboxylase in coproporphyrinogen I, but the latter is not a substrate for copro-oxydase;
- CEP is associated with hemolytic anemia and severe cutanate photosensibility;
- The porphyrins in excess are also deposited in teeth and bones (1).

CLINICAL MANIFESTATIONS

- Severe cutaneous sensibility in early infancy;
- Hydrops fetalis, through a non-immune mechanism, is not uncommon;
- Skin overexposed to sunglight is red, friable and the blisters and vesicles are prone to rupture and infection;
- Healing is slow and the skin presents hypo and hyperpygmentatio areas, hypertrichosis of the face and extremities are chracteristic;
- Secondary infection and bone resorbtion may lead to

disfiguration of the face and hands;
- Retraction of the alar parts of the nose, of the eyelids, eyebrows, pavilions of the ear, resulting in a monstruos appearance of the patient;
- Hypertrichosis and hirsurtism results in a lion or simian-like appearance of the patient;
- The teeth are reddish brown and in UV light emanate a reddish-crimson fluorescence due to the erythrodontia which appears mainly because of the protoporphyrin crystals accumulated in the dentine;
- Hematological myeloid malignancies and especially secondary MDS without any connections to the apparition of UROS or GATA 1 mutatios (2) ;
HEMATOLOGIC MANIFESTATIONS
- Moderate-hemolytic anemia due to the excess of porphyrins in erythrocytes;
- Clinical: splenomegaly;
- On exposure to U.V., the erythrocytes, normoblasts and reticulocytes from the perypheral blood and bone marrow present fluorescences;
RENAL MANIFESTATIONS
- Urine is reddish-brown, alkaptonuria, urine that taints the lingerie;
- Uro and coproporphyrin >500 mg/24 hours;
LABORATORY DIAGNOSIS
-Uroporphyrin and coproporphyrin (type I isomers)accumulate in the bone-marrow, circulating erythtrocytes, plasma,urine and faeces;
- The diagnosis is confirmed by demonstrating the deficient URO-syntase activity or by identifying specific mutations of the UROS-gene;
- The disease can be detected antenatally by measuring porphyrins in the amniotic fluid and URO-syntase activity in cultured amniotic cells or chorioral villi;
- More than 35 UROS-mutations have been identified, including four in its erythroid specific promoter and genotype/phenotype corrrelations in patients with severe manifestations;
TREATMENT
- Chronic transfusions of red cell mass can be started antenatally;
- Protection from sunlight is essential, superinfections or traumatisms should be avoided;
- Bone marrow and cord blood transplant have proven effective in several transfusion-dependent patients;
- Modern treatment for the UROS-mutation (C73R) with chaperone and/or protease inhibitor was reported;
ERYTHROPOIETIC PORPHYRIA (EPP) and X-LINKED PORPHYRIA (XLP);
- EPP is an AR disorder, resulting from mutations in the FECH-gene, with heavy reduction of the activity of the enzyme;
- It is the most common porphyria in adults and children;
-XLP, a clinically distinguishable form of EPP only by demonstrating the presence of mutations in the last exon of ALAS 2-gene (3).
CLINICAL MANIFESTATIONS
- Cutaneous photosensibility usually beginning in early childhood, redness, itchting that lasts for hours, diffuse oedema, vesicles and blisters persisting for hours or days, manifestations occuring within minutes of sunlight exposure;
- Electric light, heat, traumatisms can trigger the symptoms;
- Purpura, oedema, agitation, shivers or even collapse;
CLINICAL MANIFESTATIONS
- Permanent sequelae which can persist on the exposed regions (nose, cheekbones, forehead, the back of the hands and fingers);
- Hyperkeratosis, scars, vesicles and blisters;
- Other clinical symptoms: biliary colic (pigmentary lithiasis in women), intrahepatic cholestasis, (lethal) liver failure;
BIOLOGICAL DIAGNOSIS
- The primary source of excess of protophorphirin in EPP and XLP in the B. M. reticulocytes and erythrocytes will exhibit red fluorescence when examined by fluorescence emission microscopy at 620 nm with excitation at 405 nm;
- Demonstrating increased protoporphyrin - in EPP, erythrocyte protoporphyrin is mostly bound to Hb and not complexed with Zn (as in XLP);
- Normal urinary levels of Urinary levels of porphyrins and porphyrin precursors;
- Mutational analysis confirms mutations of the FECH and ALAS 2-genes;
- IVS 3-48T>C (25% of transcripts normal FECH) in cys, followed by a low expression of the allel in trans, but with a normal activity of FECH;
PATHOGENESIS
- Protoporphyrin accumulates primarly in B.M. reticulocytes during Hb synthesis and then appears in plasma, is transported to the liver and excreted in bile and faeces. Protoporphyrin can be deposited in the skin and blood vessels and can be activated by light, causing cutaneous photosensivity.
- Protoporphyrin is insoluble at neutral pH, due to an excess, form crystalline structures in liver cells and can decrease hepatic bile flow in bile fistula rats, causing progressive liver disease in EPP due to a constant accumulation of protoporphyrins in the liver, erythrocytes, plasma and causing photosensitivity;
- Hepatic complications appear especially in AR forms of EPP because of 2-FECH mutations and in XLP.
TREATMENT
- Solar light protection;
- Beta-carotene (oral), 120-180 mg/dl, causing carotenodermia that improves tolerance to sunlight;
- Treatment with alpha-MSH-analogue which darkens the skin and can increase tolerance to sunlight exposure;

- Plasmapheresis;
- Treatment with intravenous HEMIN;
- Liver transplant and administration of intravenous HEMINE and sessions of plasmapheresis;
- Treatment of hepatic complications: Cholestyramine, activated Charcoal (may interrupt the enterohepatic circulation of protophorphyrins and promote their fecal excretion);
- Treatment with MSH (melanocyto-stimulating-hormone) because the darkening of the skin may be followed by a painless tolerance to sunlight exposure;

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