Clinical Vignette

Congenital Erythropoietic Porphyria: A Case Report and Approach to Cutaneous Porphyrias

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Abstract

Porphyrias are inherited disorders of the heme biosynthetic pathway characterized by overproduction of precursor metabolites preceding the defective step. Congenital erythropoietic porphyria (CEP) is a rare cutaneous porphyria presenting in childhood. We describe here a child with the classical clinical presentation of CEP, who presented with history of photosensitivity, blisters, and erythrodontia beginning in the 2nd year of life.

Clinical description

A 4-years-3-months old boy, born of non-consanguineous marriage, presented with history of photosensitivity and blisters over the sun-exposed parts for the last two years. The child was born at term with a birth weight of 2.2 kg (small for gestational age), with no antenatal and perinatal complications. He was well until 2 years of age. At two years, parents noticed that the child avoided playing in the sun and would cry excessively when exposed to sunlight. Subsequently, he started developing bullous skin lesions on sun-exposed areas (face, hands and feet). These lesions would heal with scar formation over the next few days. The parents also noticed that the child was passing reddish urine, staining his clothes and diapers. There was no history suggestive of pain while passing urine, oliguria, or swelling of face, eyes and feet. The child was also noted to have reddish-brown teeth. There was no history of acute abdominal pain and seizures. On examination, his anthropometric measurements were normal for age. Hyperpigmentation, hypertrichosis, blisters, multiple scars and ulcers were noted over the entire face. Atrophic scars and hyperpigmentation were also present on the hands and feet. Nails were discolored and periungual hyperkeratosis was present. Teeth were coppery-red in color (erythrodontia) (Figure 1: A,B,C,D). Systemic examination was normal without any hepatosplenomegaly. There was no history of similar illness in any of the family members.

A clinical diagnosis of bullous cutaneous porphyria was made based on the features of severe photosensitivity, blisters, hyperpigmentation, scars, erythrodontia, and coppery- reddish urine. As the onset of illness was in early childhood the possibility of congenital erythropoietic porphyria (CEP) and hepatoerythropoietic porphyria (HEP) were considered first. His complete blood count was suggestive of microcytic hypochromic anemia. Liver function and kidney function tests were normal. Work up for hemolysis was normal with normal urine and plasma hemoglobin. ELISA for HIV was negative.

Urine porphyria screen for δ-aminolevulinic acid (ALA) and porphobilinogen (PBG) was normal. Urinary total porphyrin levels were elevated and urine HPLC for porphyrins was suggestive of elevated uroporphyrins and coproporphyrins with elevated uroporphyrin I and coproporphyrin I isomers (Table 1). Based on the above findings, a diagnosis of CEP was made. Clinical exome sequencing showed a pathogenic homozygous 5′ splice variant c.660+4del A in intron 9 of the *UROS* gene [NM_000375.2], confirming the diagnosis of CEP. This variant has previously been described in patients with CEP (Katugampola et al., 2012; Weiss Y et al., 2019) and is classified as likely pathogenic as per the American College of Medical Genetics and Genomics-Association for Molecular Pathology (ACMG-AMP) criteria (PM2+PP4+PS4) (Richards et al., 2015).

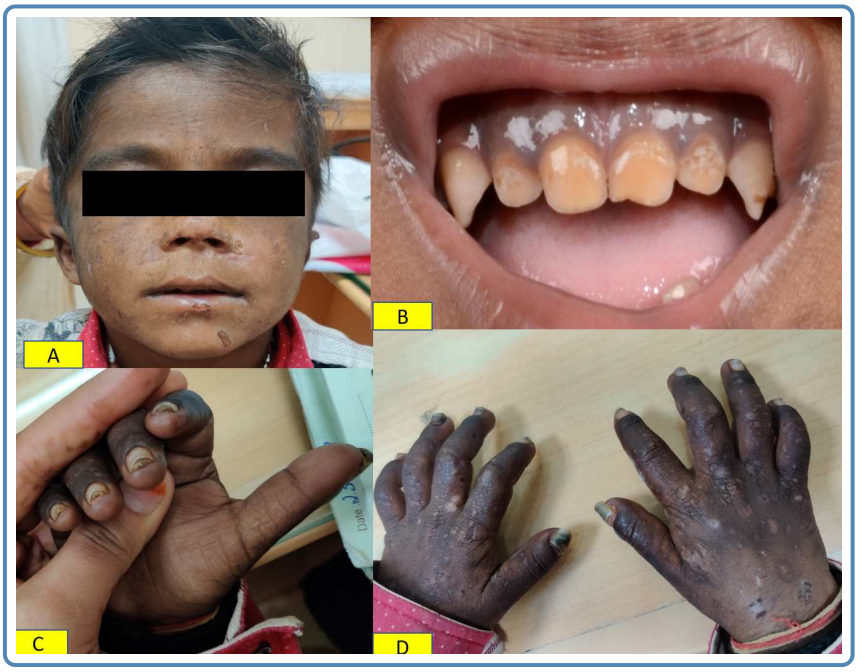

Figure 1 Proband at 4 years 3 months of age showing: A. hyperpigmentation over face along with scars and ulcers. B. erythrodontia. C. periungual hyperkeratosis. D. hyperpigmentation over hands, along with multiple scars and discolored nails.

Table 1 The urinary porphyrin levels in the index patient.

Metabolites	Observed values	Reference Range
Urinary total porphyrin/ Creatinine	3428.13 ug/g creat	<175 ug/g creat
Uroporphyrin total/ Creatinine	2742.58 ug/g creat	<33 ug/g creat
Uroporphyrin I isomers	92%	53-79%
Uroporphyrins III isomers	7.99%	21-47%
Coproporphyrin total/ Creatinine	485.68 ug/g creat	<120 ug/g creat
Coproporphyrin I isomers	96.53%	17-31%
Coproporphyrin III	3.47%	69-83%
Uroporphyrin: coproporphyrin ratio	5.65	0.07-0.65

The child was advised sun protection, protective clothing and sunscreen. Hematopoietic stem cell transplantation is the only curative therapy for CEP at present and the family was counselled about the disorder and further management.

Discussion

CEP also known as 'Günther disease' deriving its name from the physician who first described it, is a rare disorder with approximately 200 patients reported till date (Erwin et al., 2019). It is a severe bullous porphyria characterized by deficiency of the enzyme uroporphyrinogen synthase III (UROS III) which catalyzes the conversion of hydroxymethylbilane into uroporphyrinogen III. In the deficiency of UROSIII, hydroxymethylbilane enters the non-enzymatic pathway and gets converted into uroporphyrinogen I and coproporphyrinogen I and subsequently into uroporphyrin I and coproporphyrin I. These uroporphyrins get deposited in various tissues, bone marrow, plasma, skin and urine. These

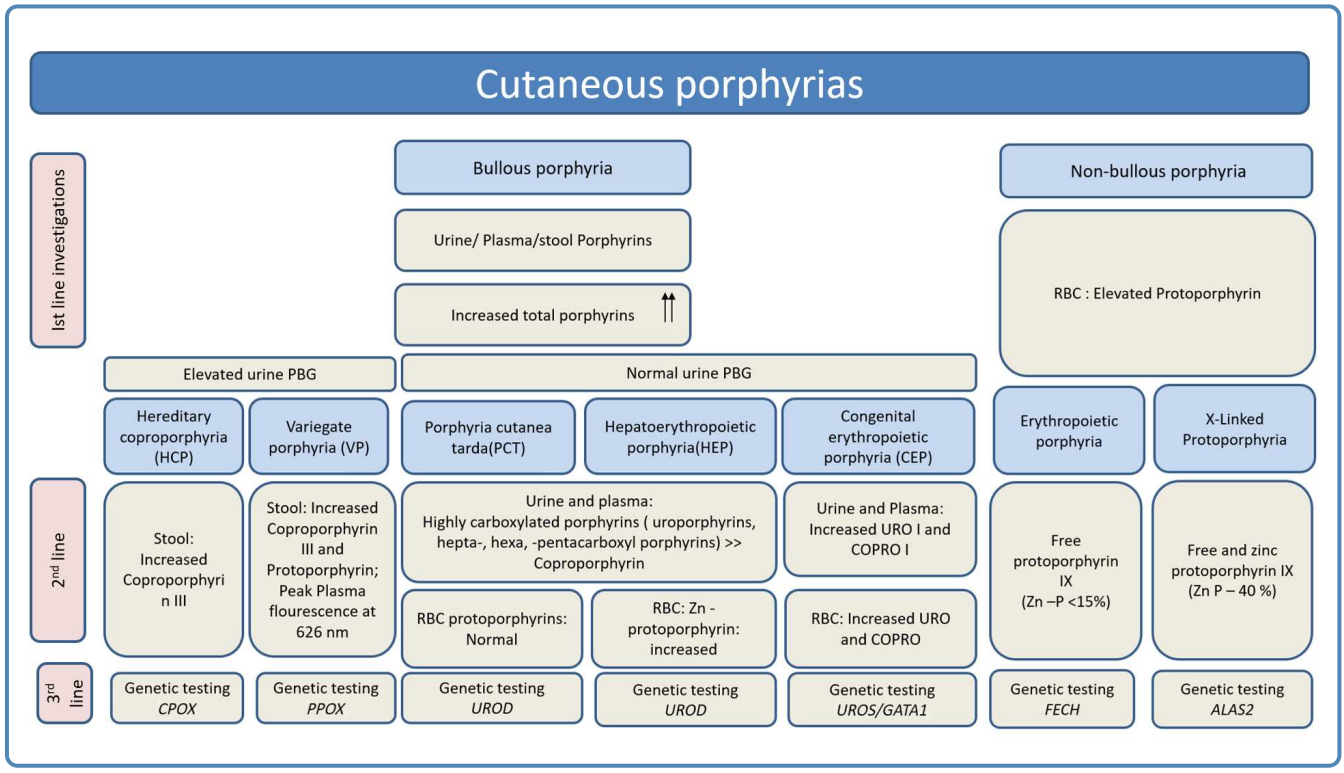

Figure 2 Stepwise diagnostic approach to cutaneous porphyrias.

compounds are photocatalytic and on exposure to long-wavelength ultraviolet (UV) light result in blister and vesicle formation and increased skin fragility as seen in our patient. In erythrocytes and bone marrow these result in hemolysis and subsequent ineffective erythropoiesis and erythroid hyperplasia (Erwin et al., 2019).

The clinical phenotype of CEP is quite variable ranging from in-utero presentation to mild adult phenotype. The most common clinical presentation is photosensitivity with the formation of bullous lesions which heals with scarring and hyperpigmentation. In severe cases, the loss of digits of hands and feet, also known as photo-mutilation, has been reported. Other features include corneal scars, ulcers, red or dark colored urine, erythrodontia and hemolytic anemia. Earliest sign in infancy is red staining of diapers with urine due to accumulated porphyrins (Erwin et al., 2019).

Other differentials which need to be considered include other bullous porphyrias and photocutaneous disorders like pseudoporphyria, and epidermolysis bullosa. The other bullous porphyrias which need to be considered include HEP, PCT, VP and HCP (Figure 2). HEP, caused by biallelic variants in *UROD* has a childhood-onset with similar phenotype whereas PCT, caused by heterozygous variant in *UROD*, has an adult-onset and a milder presentation. Both are differentiated through urine and plasma porphyrin analysis. Pseudoporphyria is a drug-induced bullous disorder seen in children with juvenile rheumatoid arthritis who are on nonsteroidal anti-inflammatory drugs (NSAIDs). In pseudoporphyria, levels of porphyrins in the urine, plasma, and stool are in the normal range. Patients with epidermolysis bullosa have bullous lesions, which usually present in the neonatal period or early infancy and the bullae usually heal without scar formation.

For bullous cutaneous porphyrias, the first-line investigations include measurement of total porphyrins in urine, plasma or stool, followed by high-performance liquid chromatography (HPLC) for typing the porphyria based on the quantity of porphyrins elevated in urine (Figure 2). CEP is characterized by the accumulation of uroporphyrin I and coproporphyrin I as seen in our patient. Initial screening can also be done with spectrofluorometer which gives specific plasma fluorescence emission peaks for VP and CEP at 626

nm and 615-618 nm respectively (Rigor et al., 2019). Further confirmation can be done with molecular testing.

CEP is caused by either biallelic pathogenic variants in the *UROS* gene in 98% of the cases or on rare occasions, by hemizygous pathogenic variants in the *GATA1* gene (1%). Variants including missense, nonsense, frameshift and splice site variants as well as intragenic deletions/duplications have been reported in the *UROS* gene. The most common *UROS* pathogenic variant reported in literature is p.Cys73Arg, observed in 30-40% of the cases. The clinical phenotype is largely determined by the amount of residual enzyme activity (Erwin et al., 2016; 2019).

The treatment is predominantly supportive and consists of avoidance of exposure to sunlight and artificial sources of UV light, and red blood cell transfusions for hemolytic anemia. The only curative therapy is hematopoietic stem cell transplantation, but this is also associated with significant morbidity and hence is performed only in transfusion-dependent patients or those with very severe skin manifestations. Other therapies are experimental including gene therapy, proteasome inhibitor (Bortezomib) and chaperone therapy (Ciclopirox) (Urquiza et al., 2018).

Conclusions

A meticulous clinical and laboratory approach is the key to early diagnosis of congenital erythropoietic porphyria, to halt further disease progression and open ways for future treatment options. Molecular testing is confirmatory and is necessary for family counseling and management and prevention of recurrence in future pregnancies.

References

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