

## Bullous skin lesions in a jaundiced infant after phototherapy: a case of congenital erythropoietic porphyria

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Congenital erythropoietic porphyria is a rare autosomal recessive disorder of porphyrin metabolism in which the genetic defect is the deficiency of uroporphyrinogen III cosynthase (UROS). Deficiency of this enzyme results in an accumulation of high amounts of uroporphyrin I in all tissues, leading to hemolytic anemia, splenomegaly, erythrodontia, bone fragility, exquisite photosensitivity, and mutilating skin lesions.

We discuss a female infantile case who was admitted for jaundice; bullous lesions appeared on her trunk during phototherapy in the neonatal period. The skin biopsy findings were consistent with epidermolysis bullosa. Due to persistent hepatosplenomegaly and cholestasis, metabolic tests and liver biopsy were performed. During the follow-up, hemolytic anemia and red urine were detected. The levels of porphyrin metabolites were determined at high concentrations in plasma, stool and urine analysis, which were suggestive of congenital erythropoietic porphyria.

*Key words:* congenital erythropoietic porphyria, cholestasis, skin lesions, neonatal period.

The porphyrias are a group of metabolic disorders that result from enzyme defects of heme biosynthesis. Congenital erythropoietic porphyria (CEP; Gunther disease) is a rare autosomal recessive disorder caused by a deficiency of uroporphyrinogen III synthase (UROS)<sup>1</sup>. This disease usually manifests in infancy or early childhood, although it can be diagnosed later in life<sup>2</sup>. It is the rarest of bullous porphyrias, and many clinicians may not have seen even one case of porphyria during their professional life. The consequence of the enzyme defect is the accumulation of type I porphyrins, which leads to severe cutaneous photosensitivity with mutilating skin lesions, erythrodontia, chronic hemolysis, splenomegaly, and massive porphyrinuria. The prognosis is poor in severely affected patients because of severe scarring and destruction of subcutaneous tissues<sup>1</sup>. Here, we report an infantile case with bullous skin lesions, hemolytic anemia and cholestasis.

### Case Report

A girl born of a nonconsanguineous marriage who was full-term was admitted to the hospital with jaundice, fatigue and fever on the first day of life. Phototherapy and antibiotherapy were started after the diagnosis of hyperbilirubinemia and sepsis (total/direct bilirubin; T. Bil: 20 mg/dl, D. Bil: 1.8 mg/dl). A couple of blisters appeared on her body during phototherapy. A skin biopsy was performed and the result was consistent with epidermolysis bullosa. In two weeks, the cutaneous lesions healed with hypopigmented scars after discontinuation of phototherapy. On the 47<sup>th</sup> day of life, the patient was referred to our clinic due to ongoing cholestasis and hepatosplenomegaly. On the physical examination, her length was 50 cm (<3p, SDS: -2.791) and weight: 3550 g (3p, SDS: -2.258). Hypopigmented scars were present on her trunk (Fig. 1). The liver and spleen were palpable 3 cm below the respective costal margins. Central nervous system and respiratory system assessments were normal.



Fig. 1. Hypopigmented scars on the body surface due to phototherapy at 6 months of age.

Laboratory investigations were as follows: hemoglobin: 6.9 g/dl, hematocrit: 21.3%, mean corpuscular volume (MCV): 69.4 fL, red cell distribution width (RDW): 16.7%, white blood cells (WBC): 7200/mm<sup>3</sup>, platelets (Plt): 144000 mm<sup>3</sup>, prothrombin time (PT): 12 sc, activated partial thromboplastin time (aPTT): 26 sc, international normalized ratio (INR): 1.1, urine microscopy: 3-4 erythrocytes, 1-2 leukocytes, blood glucose: 84 mg/dl, aspartate aminotransferase (AST): 105 IU/dl, alanine aminotransferase (ALT): 72 IU/dl, T. Bil: 4.8 mg/dl, D. Bil: 3.4 mg/dl, gamma glutamyl transpeptidase (GGT): 412 IU/L, alkaline phosphatase (ALP): 310 IU/L, and lactate dehydrogenase (LDH): 412 IU/L. Peripheral blood smear examination revealed microcytic, hypochromic red blood cells (RBC) with anisopoikilocytosis. Direct Coombs test and hemoglobin electrophoresis were normal. Metabolic tests including urine reducing substances, blood-urine amino acids, thyroid function tests, alpha-1-antitrypsin, and alpha-fetoprotein levels were normal. Serological investigations for hepatotropic agents (hepatitis B virus [HBV], Epstein-Barr virus [EBV], cytomegalovirus [CMV], hepatitis C virus [HCV], parvovirus, and toxoplasmosis) were all normal. Ophthalmological examination was normal. Histological examination of bone marrow did not reveal any storage cell. In the 3<sup>rd</sup> month of life, a liver biopsy was performed, and the histology showed nonspecific intrahepatic cholestasis with hemosiderin storage in portal and periportal areas and hepatocytes with granular form. Family history revealed that the patient's grandfather had reddish-brown colored

teeth, scars and crusted lesions on his limbs, which had resulted in mutilating deformities of the fingers that were characteristic for porphyria.

Family history and clinical findings were highly suggestive of a porphyria. During the follow-up, red-colored urine was detected. On screening with a spectrophotometer, urinary total porphyrin was 5850 nmol/mmol of creatinine (normal <35 nmol/mmol). Twenty-four hour urinary level of uroporphyrin was 64520 µg/day (normal <25 µg/day) and of coproporphyrin was 14940 µg/day (normal <25µg/day). The urinary porphyrin fractions were: uroporphyrin-I 71% and coproporphyrin-I 17%, and the stool porphyrin level was 908 nmol/g (normal <200 nmol/g). Total plasma porphyrin level was 530 nmol/L (normal <10 nmol/L). We diagnosed the child as CEP, and the genetic analysis revealed a homozygous mutation in the UROS gene, the missense mutation c562G>A (p.G188R).

## Discussion

Congenital erythropoietic porphyria (CEP) is an extremely rare inborn error of porphyrin-heme synthesis, and until recent times, less than 200 cases had been reported in the world literature<sup>3,4</sup>. In patients with this autosomal recessive disease, the clinical manifestations are markedly heterogeneous, ranging from nonimmune hydrops fetalis to milder forms that have only cutaneous lesions in adult life<sup>5,6</sup>.

The patient was suspected of an inborn error of metabolism due to massive hepatosplenomegaly and cholestasis. Blood-urine amino acids chromatography and endocrine tests were normal. No storage cells were found in bone marrow aspiration, and the neurologic examination was normal. Moreover, the liver biopsy revealed nonspecific intrahepatic cholestasis with hemosiderin storage. Therefore, we excluded the lipid storage diseases such as Niemann-Pick and Gaucher disease.

Excess plasma porphyrins, which probably originate from the bone marrow and circulating red cells, are mostly uroporphyrin, coproporphyrin, and protoporphyrin in CEP. These porphyrins are also found in the spleen and to a lesser extent in the liver<sup>2</sup>. It is known that protoporphyrin is a lipophilic molecule that is excreted by the liver, and

increased accumulating protoporphyrin has a hepatotoxic effect and strains the excretory function of the liver<sup>7</sup>. There is no direct data about the hepatotoxic effect of coproporphyrin. However, experimental studies in rats have suggested a possible role of a Multidrug-Resistance Protein (MRP) system in hepatocyte excretion of coproporphyrin, and alteration in this system causes abnormal accumulation of coproporphyrin in the liver<sup>8</sup>. We were unable to analyze MRPs in our case. In this case, we hypothesized that the reason for the cholestasis was the toxic effect and accumulation of protoporphyrin and maybe coproporphyrin in the liver, arising from chronic hemolysis in CEP.

Hereditary epidermolysis bullosa is in the differential diagnosis of the vesicles in the newborn period. However, the patient's skin biopsy was reported as epidermolysis bullosa. The lesions of epidermolysis bullosa appear on the extremities, but lesions in our case were observed on the trunk. The three types of hereditary epidermolysis bullosa are simplex, dystrophic and junctional. In hereditary epidermolysis bullosa, the disease also appears at birth or soon after birth. The skin lesions heal without residual scarring in simplex and dystrophic types. In junctional epidermolysis bullosa, bullae and erosions usually form on the trauma site on hands and feet resulting in atrophic scars. In our case, the bullous lesions emerged during phototherapy. The common features of bullous porphyrias are vesicobullous lesions on photo-exposed parts, atrophic scars and hypopigmentation, like in this case<sup>9,10</sup>. We may propose that blistering under phototherapy is a significant clue for the diagnosis of CEP.

Routine laboratory tests may not provide a clue for CEP. History, physical examination, the presence of hemolytic anemia findings on the peripheral blood smear, and red color in the macroscopic examination of urine are important predictors for pre-diagnosis. The diagnosis was confirmed by the increase of the porphyrin fractions in plasma, urine, and stool and genetic analysis.

Some correlation exists between genotype and phenotype, and severe transfusion-dependent cases are usually associated with a C73R mutation, the most frequent mutation found in CEP<sup>1</sup>. Our patient was homoallelic for a mutation of the UROS gene, the missense

mutation c562G>A (p.G188R). This mutation was described in a Turkish patient in homoallelic state who also had a severe form of CEP with hepatosplenomegaly and transfusion-dependent anemia<sup>11</sup>.

Congenital erythropoietic porphyria (CEP) has severe symptoms in early childhood, and its management is particularly critical. A better understanding of the molecular genetic basis of CEP is extremely significant since there is no causal therapy for this disease. Prevention and symptomatic therapy includes avoidance of ultraviolet and sunlight exposure, the use of sunscreens, and avoidance of mechanical trauma. If hemolytic anemia occurs, patients may require blood transfusion therapy. At this moment, the only curative therapeutic attempt consists of bone marrow transplantation<sup>9,11</sup>. Allogeneic bone marrow transplantation is also planned for our patient.

In conclusion, CEP is a rare disease, but diagnosis of this disorder is vitally important for affected children. Severe cases like ours present with hemolytic anemia during the neonatal period, and we postulated that this hemolysis caused protoporphyrin storage in hepatocytes and intrahepatic bile ducts. CEP should be considered in neonates with bullae and vesicles on the areas exposed to phototherapy light in the presence of hemolytic anemia, hepatosplenomegaly and cholestasis.

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## REFERENCES

1. Dupuis-Girod S, Akkari V, Ged C, et al. Successful match-unrelated donor bone marrow transplantation for congenital erythropoietic porphyria (Günther disease). *Eur J Pediatr* 2005; 164: 104–107.
2. Shaw PH, Mancini AJ, McConnell JP, Brown D, Kletzel M. Treatment of congenital erythropoietic porphyria in children by allogeneic stem cell transplantation: a case report and review of the literature. *Bone Marrow Transplant* 2001; 27: 101–105.
3. Gross U, Hoffmann GF, Doss MO. Erythropoietic and hepatic porphyrias. *J Inher Metab Dis* 2000; 23: 641–661.
4. Koley S, Saoji V. Congenital erythropoietic porphyria: two case reports. *Indian J Dermatol* 2011; 56: 94–97.
5. Desnick RJ, Astrin KH. Congenital erythropoietic porphyria: advances in pathogenesis and treatment. *Br J Haematol* 2002; 117: 779–795.
6. Aoki V, Sousa JX Jr, Fukumori LM, Périgo AM, Freitas EL, Oliveira ZN. Direct and indirect immunofluorescence. *An Bras Dermatol* 2010; 85: 490–500.
7. Doss MO, Frank M, Seig I. Cholestatic erythrohepatic protoporphyria: porphyrin metabolism before and after liver transplantation. *Z Gastroenterol* 1993; 31: 85–89.
8. Moriondo V, Marchini S, Di Gangi P, et al. Role of Multidrug-Resistance Protein 2 in coproporphyrin transport: results from experimental studies in bile fistula rat models. *Cell Mol Biol (Noisy-le-grand)* 2009; 55: 70–78.
9. Koley S, Saoji V. Congenital erythropoietic porphyria: two case reports. *Indian J Dermatol* 2011; 56: 94–97.
10. Fine JD, McGrath J, Eady RA. Inherited epidermolysis bullosa comes into the new millennium: a revised classification system based on current knowledge of pathogenetic mechanisms and the clinical, laboratory, and epidemiologic findings of large, well-defined patient cohorts. *J Am Acad Dermatol* 2000; 43: 135–137.
11. Tezcan I, Xu W, Gürgey A, et al. Congenital erythropoietic porphyria successfully treated by allogeneic bone marrow transplantation. *Blood* 1998; 92: 4053–4058.