

Erythropoietic protoporphyria and early onset of cholestasis

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Erythropoietic protoporphyria (EPP) is an inherited defect of mitochondrial ferrochelatase. This defect results in accumulation of protoporphyrin in erythrocytes, plasma, liver, and skin, which causes severe photosensitivity. Liver disease can occur in 1-4% of the patients with EPP, usually after at least a decade of photosensitivity. Herein, we describe a 1.5-year-old child with EPP with severe photosensitivity, heart abnormalities and early onset of cholestatic liver disease, whose clinical condition improved gradually after using ursodeoxycholic acid. It seems that liver disease in EPP patients is not limited to the late phases of the disease and could develop in childhood and early phases of EPP. Awareness among physicians has a major role in the early detection and prevention of mistreatment of EPP in case of its combination with other abnormalities.

Key words: erythropoietic protoporphyria, cholestasis, hepatic failure, ursodeoxycholic acid.

Erythropoietic protoporphyria (EPP) is an inherited defect of the insertion of ferrous iron into protoporphyrin to form heme due to the deficiency in mitochondrial ferrochelatase (FECH). This defect results in accumulation of lipophilic protoporphyrin in erythrocytes, plasma, liver, and skin, which causes severe photosensitivity¹. EPP, as a rare disease, has a prevalence of 1:75,000 to 1:200,000. Painful photosensitivity with erythema as the main manifestation of EPP usually begins in infancy with the first exposures to light. Presence of a neurological syndrome and oral mucosa or eye lesions has also been reported in these patients^{2,3}. The disease may also involve the hepatobiliary system manifesting as cholelithiasis and chronic liver disease⁴.

The lipophilic characteristic of excreted protoporphyrin from the liver has been suggested as a probable reason for the liver damage in these patients¹. It is related to the burden of clearance of excess protoporphyrin by the entero-hepatic circulation⁵. Cholestatic

liver failure as an acute onset and irreversible process is the most serious liver complication in these patients. The liver complications in EPP occur with a low prevalence⁴. Liver disease was reported to develop in 1-4% of the patients with EPP^{4,6}, and presence of cholestasis is said to be even lower⁴. In a cohort of 32 patients with EPP, only one patient had abnormal liver function⁴. Liver disease and liver failure are late presentations of EPP, which usually occur after at least a decade of photosensitivity, and early onset of liver disease in EPP is very rare⁷. The majority of 29 fatal cases of EPP in the literature who died of liver complications were over the age of 30, and the youngest case was an 11-year-old child^{4,8}. Here, we report a patient with EPP who, in addition to heart abnormalities and inguinal hernia, had an early onset of cholestasis.

Case Report

A 15-month-old boy was admitted to the Children's Medical Center, Pediatrics Center



Fig. 1. Erosive and crusted lesions on patient's face and blistering on the dorsum of hands and forearms.

of Excellence in Iran, for evaluation of skin lesions and hepatosplenomegaly. He was the first child of related parents with no family history of dermatological or metabolic diseases. The boy was born with normal delivery at term with good Apgar score and weight of 2900 g. He received complete immunization. At the age of four months, he presented itching and erythema on sun-exposed areas. At eight months of age, in the general hospital, he received prednisone for two months following the suspicion of atopic dermatitis. At the age of 12 months, he developed abdominal distension and hepatosplenomegaly, which was thought to be a side effect of prednisone. Finally, he was referred to our center for further evaluation.

On his physical examination, there were erosive and crusted lesions over his face, ears and hands (Fig. 1). These lesions showed hypertrichosis but without milia or hyperpigmentation. Scleral icterus was seen on ophthalmoscopy. An ejection systolic murmur with a grade of 4/6 was heard along the left sternal border. Abdominal examination revealed hepatomegaly with firm consistency and palpable spleen. Inguinal hernia was present while crying. On the scrotal examination, there was swelling in the scrotum; the testes were not palpable.

Laboratory findings revealed mild microcytic anemia, abnormal liver enzymes and cholestasis markers (Table I). An echocardiography revealed a pulmonary valve stenosis and an abnormal aortic valve. Abdominal ultrasound revealed hepatosplenomegaly and slightly large kidneys and mesenteric lymphadenopathy.

Considering these congenital heart problems, hepatosplenomegaly, scleral icterus, and skin manifestations, we approached this patient suspecting Alagille syndrome.

On skin histopathology, no bacteria or white blood cells (WBC) were seen. Wound culture was negative for bacteria. Microscopy revealed a large crust over a mild spongiotic epithelium associated with chronic dermal inflammation. No epithelial bullae, perivascular or papillary, periodic acid-Schiff (PAS)-positive deposition, or papillary neutrophilic infiltrations were seen. Direct immunofluorescence (DIF) test of skin was nonspecific.

The tests for viral hepatitis were all negative. Autoimmune hepatitis markers such as antinuclear antibodies (ANA) and antibodies to liver kidney microsome (anti-LKM), anti-

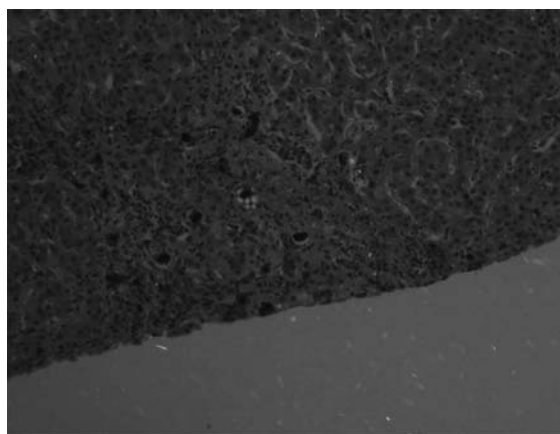


Fig. 2. A view of red birefringence with a Maltese cross configuration in brown pigment.

Table I. Laboratory Findings of the Patient

	Patient	Normal range
CBC		
White blood cell (WBC) count	11200/ μ l	6200–14500/ μ l
Platelet	319* 10^3	219–452* 10^3
Red blood cell (RBC) count	4.62* 10^6 / μ l	3.7–4.9* 10^6 / μ l
Hematocrit	27.2%	33–38%
Hemoglobin	10.2 g/dl	10.5–13 g/dl
Mean cell volume (MCV)	68.6 μ m ³	80.0–100.0 μ m ³
Red blood cell distribution width (RDW)	22.9	<16
Mean corpuscular hemoglobin (MCH)	22.5 pg	26.0–34.0 pg
Erythrocyte sedimentation rate (ESR)	65 mm/hr	0–20 mm/hr
Hepatic markers		
Aspartate aminotransferase (AST)	182 U/L	10–60 U/L
Alanine aminotransferase (ALT)	166 U/L	5–45 U/L
Alkaline phosphatase (ALP)	288 U/L	130–560 U/L
γ - glutamyl transferase (GGT)	177 U/L	0 to 50 U/L
Total bilirubin	5.2 mg/dl	0.6–1.4 mg/dl
Conjugated bilirubin	2.8 mg/dl	0–0.5 mg/dl
Partial thromboplastin time (PTT)	34 seconds	25.0–38.0 seconds
Prothrombin time (PT)	13.3 seconds	10–12 seconds
Lactate dehydrogenase (LDH)	573 units/L	290–501 units/L
α -fetoprotein	8.5 ng/ml	0.6–5.6 ng/ml

CBC: Complete blood count.

mitochondrial antibodies (AMA), anti-ds DNA, and anti-smooth muscle antibody (ASMA) were also negative. The laboratory work-up for other causes of cholestasis such as galactosemia, tyrosinemia and α -antitrypsin deficiency were all done and were within normal ranges. The liver biopsy revealed presence of dark brown pigments in canaliculi and liver cells. Bile duct proliferation and dark bile plugs in the canaliculi were also seen, but there was no evidence of bile duct paucity. Under polarized light, birefringent crystalline structures with a Maltese cross shape were seen (Fig. 2).

Considering photosensitivity, liver and skin biopsy findings, Alagille syndrome was ruled out as a differential diagnosis. Instead, blood, stool and urine were evaluated to detect porphyrins to consider another probable disease, porphyria. Porphyrins were detected in stool and blood but not in the urine.

On the basis of these findings and absence

of urinary porphyrins, the diagnosis of EPP was established in the patient^{9–11}. After establishment of the EPP diagnosis, the parents were advised to avoid the patient's exposure to the sun, even through window glass. Zinc oxide ointment was applied several times a day acting both as a physical sunscreen and a repairing cream. Ursodeoxycholic acid (UDCA), vitamins A, K, D and E, zinc, and folic acid were also prescribed to manage the liver disease. Regarding the heart abnormalities, prophylaxis antibiotics were given to prevent bacterial endocarditis.

Within one month, the erosive and bullous lesions had cleared completely, but post-lesional scars remained. After five months, with regular hepatic evaluations every month, the hepatic status was stable except for some exacerbations that were managed with supportive care.

Discussion

Patients with EPP are prone to hepatobiliary disease due to the retention of protoporphyrin in the liver¹². Liver damage in these patients has been explained by two main mechanisms. Deposition and accumulation of insoluble protoporphyrin in bile canaliculi can cause cholestatic phenomena in these patients. The second mechanism is protoporphyrin-induced oxidative stress due to the interaction of unmetabolized protoporphyrin with the hepatocellular membrane¹⁰. This hepatobiliary disease in these patients has several degrees and different manifestations, such as cholelithiasis, mild parenchymal liver disease, progressive hepatocellular disease and end-stage liver disease⁴. Progressive hepatocellular disease usually presents with upper abdominal pain and jaundice and is characterized by cholestasis. In our patient, the scleral icterus and abdominal tenderness were associated with these phenomena. The precipitation of excess protoporphyrin in bile canaliculi causes cholestasis. The cholestasis initiates a vicious cycle that can rapidly deteriorate both hepatic symptoms and photosensitivity due to a further reduction in biliary protoporphyrin excretion¹³. In this condition, hemolysis due to the increased levels of porphyrins will rapidly cause a decrease in hematocrit and deteriorate the usual microcytic anemia in these patients¹³. This mechanism was the reason for the reduction of hematocrit in our patient. Our patient had the characteristic birefringent pigment deposits due to the presence of protoporphyrin crystals reported in older EPP patients with liver disease⁴. Cardiac abnormalities such as ventricular septal defect and aortic stenosis and regurgitation were reported in patients with EPP, who subsequently underwent cardiac surgery^{14,15}.

Progressive hepatocellular disease usually develops after at least a decade of EPP¹³, and it is rare as the initial presentation^{10,13}. The early onset of liver disease in our patient may be due to the effect of prednisone as an inducer of P450 isoenzymes on his liver¹⁶. Inducers of P450 isoenzymes are known to exacerbate the porphyric state¹⁷. Furthermore, several unknown host factors may increase the susceptibility of patients with EPP to protoporphyrin-induced liver damage⁴. Therefore, other underlying gene defects responsible for his heart abnormalities and inguinal hernia probably influenced the

course of his liver disease.

These abnormalities, besides accelerating the progression of liver disease, also complicated the diagnosis. At first, Alagille syndrome seemed to be a probable cause for his mixed presentation. Presentations like congenital heart problems, scleral icterus and liver disease, kidney enlargement, inguinal hernia, itching, and skin problems are also seen in this syndrome¹⁸. As the severity of symptoms in this syndrome are quite variable and some characteristic facial features may not be obvious during early childhood, some characteristic symptoms like broadened forehead, pointed chin, elongated nose with bulbous tip, butterfly hemivertebrae, and xanthomas would not yet be noticeable¹⁸.

Early diagnosis of these patients is of importance to establish monitoring for hepatic involvement at an early stage, since hepatic complications are the major determinant in the prognosis of the disease^{1,10,19}. In addition, delayed diagnosis with a false diagnosis and treatment may exacerbate the course of the disease, like the effect of mistreatment with prednisone in our patient. Our patient was firstly misdiagnosed as atopic dermatitis regarding the skin manifestations. Awareness of general practitioners plays a major role in the accurate diagnosis of EPP among possible differential diagnoses such as light-sensitive atopic dermatitis^{1,20}. In a cohort of 233 patients with EPP, the median age at diagnosis was 12 years. This study showed that unawareness by the physician is an obstacle in the early diagnosis of these patients⁶.

Hepatic complications of our patient were stabilized using UDCA to increase the excretion of protoporphyrin into bile and vitamin E to reverse oxidative stress caused by protoporphyrins¹⁰. UDCA is known to stimulate biliary secretion and to protect hepatocytes against hydrophobic bile acids and bile acid-induced apoptosis, although its use in EPP is controversial²¹. However, several case reports have described biochemical and clinical improvement of severe EPP-related liver disease resulting from this treatment^{19,22,23}. Liver transplantation does not correct the underlying FECH enzyme deficiency in bone marrow as the main site of protoporphyrin production, so the risk of developing EPP-related liver disease

in the transplanted liver is high²⁴. As our patient was young, he will need several liver transplantations during his life. Furthermore, high circulating protoporphyrin levels due to delayed function of a transplanted liver²⁵ might permanently influence the brain functions, as our patient was at the age of brain development. There have been reports of severe neurological dysfunction after liver transplantation due to the increased levels of plasma protoporphyrin and use of immunosuppressive drugs^{26,27}.

Patients with EPP have some limitations to undergoing major surgeries²⁸. Long exposure to operating lamps or other light-conducting devices in laparoscopy and endoscopy can cause life-threatening phototoxic abdominal burns, especially in patients with cholestatic liver disease with high levels of protoporphyrin^{1,4,29}. Blood loss during surgery through positive feedback increases erythropoiesis resulting in an increase in protoporphyrin production; thus, it can be a life-threatening condition as preoperative autologous donation of blood cannot be done in these patients²⁸. In addition to surgery, many drugs have been associated with porphyrin crisis in these patients³⁰. These considerations influenced the treatment of the other complications like heart abnormalities and inguinal hernia. In addition to these general considerations, the effect of cardiopulmonary bypass and hypothermia is unknown in these patients³¹.

In conclusion, liver disease in EPP patients is not limited to the late phases of the disease and can develop in childhood and early phases of EPP. Awareness of physicians has a major role in the early detection and prevention of mistreatment of EPP in the case of its combination with other abnormalities.

REFERENCES

1. Lecha M, Puy H, Deybach JC. Erythropoietic protoporphyria. *Orphanet J Rare Dis* 2009; 4: 19.
2. Muley SA, Midani HA, Rank JM, Carithers R, Parry GJ. Neuropathy in erythropoietic protoporphyrias. *Neurology* 1998; 51: 262-265.
3. Tsuboi H, Yonemoto K, Katsuoka K. Erythropoietic protoporphyria with eye complications. *J Dermatol* 2007; 34: 790-794.
4. Anstey AV, Hift RJ. Liver disease in erythropoietic protoporphyria: insights and implications for management. *Postgrad Med J* 2007; 83: 739-748.
5. Todd DJ. Erythropoietic protoporphyria. *Br J Dermatol* 1994; 131: 751-766.
6. Holme SA, Anstey AV, Finlay AY, Elder GH, Badminton MN. Erythropoietic protoporphyria in the U.K.: clinical features and effect on quality of life. *Br J Dermatol* 2006; 155: 574-581.
7. Meerman L. Erythropoietic protoporphyria. An overview with emphasis on the liver. *Scand J Gastroenterol Suppl* 2000; 79-85.
8. Mooyaart BR, de Jong GM, van der Veen S, et al. Hepatic disease in erythropoietic protoporphyria. *Dermatologica* 1986; 173: 120-130.
9. Thadani H, Deacon A, Peters T. Diagnosis and management of porphyria. *BMJ* 2000; 320: 1647-1651.
10. Casanova-Gonzalez MJ, Trapero-Marugan M, Jones EA, Moreno-Otero R. Liver disease and erythropoietic protoporphyria: a concise review. *World J Gastroenterol* 2010; 16: 4526-4531.
11. Sassa S. Modern diagnosis and management of the porphyrias. *Br J Haematol* 2006; 135: 281-292.
12. Holme SA, Worwood M, Anstey AV, Elder GH, Badminton MN. Erythropoiesis and iron metabolism in dominant erythropoietic protoporphyria. *Blood* 2007; 110: 4108-4110.
13. Reisenauer AK, Soon SL, Lee KK, Hanifin JM. Erythropoietic protoporphyria presenting with liver failure in adulthood. *Dermatology* 2005; 210: 72-73.
14. Asokumar B, Kierney C, James TW, Amato J, Tumanmd KJ. Anaesthetic management of a patient with erythropoietic protoporphyria for ventricular septal defect closure. *Paediatr Anaesth* 1999; 9: 356-358.
15. Akinci E, Erentug V, Bozbuga N, Polat A, Mansuroglu D, Yakut C. Combined valve and coronary surgery in a patient with erythropoietic protoporphyria. *J Card Surg* 2005; 20: 267-268.
16. Pichard L, Fabre I, Daujat M, Domergue J, Joyeux H, Maurel P. Effect of corticosteroids on the expression of cytochromes P450 and on cyclosporin A oxidase activity in primary cultures of human hepatocytes. *Mol Pharmacol* 1992; 41: 1047-1055.
17. Uejima E, Takahashi K, Morisaki T, et al. Microsomal enzyme induction and clinical aggravation of porphyria: the evaluation of human urinary 6beta-hydroxycortisol/cortisol ratio as the index of hepatic CYP3A4 activity. *J Clin Pharmacol* 2002; 42: 1374-1379.
18. Emerick KM, Rand EB, Goldmuntz E, Krantz ID, Spinner NB, Piccoli DA. Features of Alagille syndrome in 92 patients: frequency and relation to prognosis. *Hepatology* 1999; 29: 822-829.
19. Doss MO, Frank M. Hepatobiliary implications and complications in protoporphyria, a 20-year study. *Clin Biochem* 1989; 22: 223-229.
20. Gross U, Frank M, Doss MO. Hepatic complications of erythropoietic protoporphyria. *Photodermatol Photoimmunol Photomed* 1998; 14: 52-57.
21. Paumgartner G, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. *Hepatology* 2002; 36: 525-531.

22. Komatsu H, Ishii K, Imamura K, et al. A case of erythropoietic protoporphyria with liver cirrhosis suggesting a therapeutic value of supplementation with alpha-tocopherol. *Hepato Res* 2000; 18: 298-309.
23. Pirlich M, Lochs H, Schmidt HH. Liver cirrhosis in erythropoietic protoporphyria: improvement of liver function with ursodeoxycholic acid. *Am J Gastroenterol* 2001; 96: 3468-3469.
24. Bloomer JR, Rank JM, Payne WD, et al. Follow-up after liver transplantation for protoporphyric liver disease. *Liver Transpl Surg* 1996; 2: 269-275.
25. Anstey AV, Hift RJ. Liver disease in erythropoietic protoporphyria: insights and implications for management. *Gut* 2007; 56: 1009-1018.
26. Murphy GM. The cutaneous porphyrias: a review. The British Photodermatology Group. *Br J Dermatol* 1999; 140: 573-581.
27. Lock G, Holstege A, Mueller AR, et al. Liver failure in erythropoietic protoporphyria associated with choledocholithiasis and severe post-transplantation polyneuropathy. *Liver* 1996; 16: 211-217.
28. Yotsumoto G, Masuda H, Iguro Y, Kinjo T, Matsumoto H, Sakata R. Aortic valve replacement in a patient with erythropoietic protoporphyria. *Ann Thorac Surg* 2003; 75: 1003-1005.
29. Meerman L, Verwer R, Slooff MJ, et al. Perioperative measures during liver transplantation for erythropoietic protoporphyria. *Transplantation* 1994; 57: 155-158.
30. Wright YG, Parvata CP. Anesthetic considerations of porphyria. *AANA J* 1981; 49: 55-58.
31. Stevens JJ, Kneeshaw JD. Mitral valve replacement in a patient with acute intermittent porphyria. *Anesth Analg* 1996; 82: 416-418.