Case Report

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Erythropoietic Protoporphyria: The Real Culprit Of Unexplained Liver Dysfunction

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1. Abstract

Erythropoietic protoporphyria (EPP) is an inborn error in heme biosynthesis caused by a pathogenic variant encoding the mitochondrial enzyme ferrous chelatase (FECH). Patients with EPP commonly present with lifelong cutaneous photosensitivity and potential liver disease. Here, we reported a clinical case of EPP in a Chinese patient who only exhibited abnormal liver enzyme, but no photosensitivity manifestations. The results of whole-exome next-generation sequencing in the patient indicated a homozygous intronic mutation in the FECH gene: c.315-48T>C, which confirmed the diagnosis of EPP.

2. Keywords:
Liver Dysfunction; Erythropoietic Protoporphyria; Diagnosis

3. Introduction

Erythropoietic protoporphyria (EPP, OMIM: 177000) is a rare disease of inborn disorder of porphyrin metabolism with estimated prevalence from 1 in 75,000 to 1 in 200,000 worldwide [1]. The pathogenesis of EPP is associated with complete or partial genetic deficient mutation of ferrous chelatase (FECH) located at the chromosome 18q21.32 region [2]. FECH functions as the terminal enzyme in the heme biosynthesis to catalyze the transformation of protoporphyrin IX into heme for the entrapment of ferrous molecules. In the pathological condition, the activity of FECH is markedly decreased or even absent due to the abnormality of gene regulation, which causes excessive accumulation of protoporphyrin in erythrocytes, plasma, skin and liver, leading to the corresponding clinical symptoms [3]. Painful skin-photosensitive erythema is the main symptom of EPP, which commonly appears in early childhood. Another manifestation of EPP is the damage of hepatobiliary system, displaying chronic liver disease such as cholestasis, or even liver failure [4]. However, the incidence of EPP concurrent with liver disease is rarer, only occupying 1-5% of EPP patients. Here, we reported a case of a Chinese patient with EPP involved in liver lesion, which was confirmed by consulting repeated history, screening for causes of abnormal liver function, and performing whole-exome next-generation sequencing.

4. Case presentation

A 43-year-old male presented to the hepatology clinic with recurrent abnormal liver enzymes: alanine aminotransferase (ALT) 105 U/L (normal 9-50 U/L), alkaline phosphatase (ALP) 171 U/L (normal 45-125 U/L), γ-glutamyl transpeptidase (GGT) 890 U/L (normal 10-60 U/L). Blood lipid test showed total cholesterol 7.58 mmol/L (normal <5.81 mmol/L), triglyceride 4.12 mmol/L (normal <1.70 mmol/L), low-density lipoprotein cholesterol 4.64 mmol/L (normal <3.37 mmol/L), high-density lipoprotein cholesterol 0.92 mmol/L (normal 1.16-1.42 mmol/L). Test results of blood routine, urine routine, stool routine, iron, transferrin, 25-OH-vitamin D, thyroid and coagulation function were basically normal. An extensive etiological examination was performed for common causes of liver disease. Serological tests for viral markers, autoimmune markers, ceruloplasmin, and humoral immune markers were all negative. Fatty liver was indicated by ultrasonic examination. Abdominal magnetic resonance cholangiopancreatography did not reveal any biliary abnormalities. Liver magnetic resonance elastography showed increased liver stiffness, with an elastic value of about 2.76kPa, and the stage of liver fibrosis was F2. Liver biopsy demonstrated clear lobular structure, partial loosening of hepatocytes in the lobule, scattered focal necrosis, occasional cholestasis, fatty degeneration of some hepatocytes (mixed type, accounting for about 40% of the sample size); mild chronic inflammatory cell infiltration in the portal area, no abnormalities in the small bile ducts and small blood vessels, fibrous tissue hyperplasia, some extending into the lobules, fibrosis stage S1-2 (Figure 1A-C). Masson staining further indicated the deposition of collagen fibers (Figure 1D).

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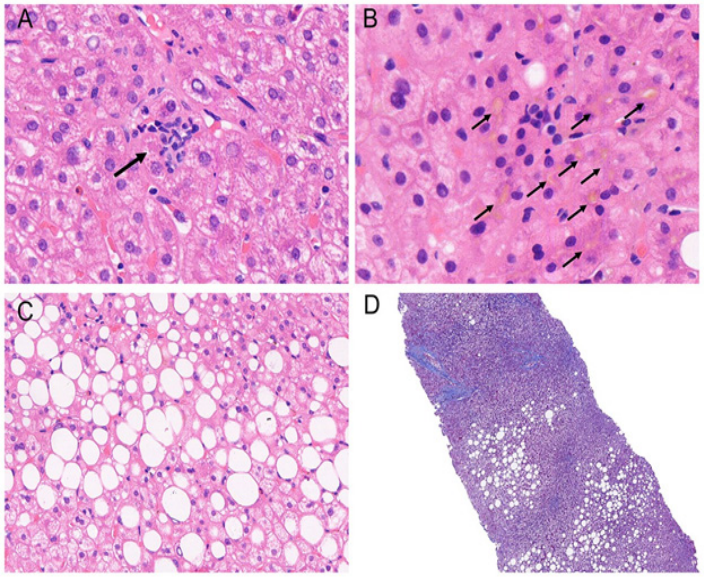

Figure 1: Microphotographs showing (A) focal necrosis (black arrow; 400×); (B) cholestasis (black arrows; 400×); (C) fatty degeneration of hepatocytes (200×); (D) Masson stain positive (4×).

The patient stated that abnormal liver function had been found 16 years ago, but had no other clinical symptoms. During this period, he presented to many hospitals for treatment, but the cause was still not clear. Despite long-term liver protection and enzyme-lowering treatment, liver enzymes were always higher than normal. Genetic variation analysis was performed on the patient's whole exome and adjacent splicing regions, and it was finally found that the subject carried a homozygous intronic variation in the FECH gene: c.315-48T>C. The verification results of next-generation sequencing and first-generation sequencing showed that the above-mentioned variations were true and reliable, confirming the diagnosis of EPP (Figure 2). The family members of the proband had no sign of EPP. We recommended that other relatives of the patient undergo pedigree verification and receive genetic counseling.

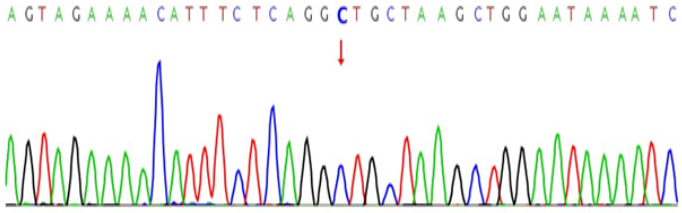

Figure 2: First-generation sequencing peak map. The peak marked with an arrow indicates the homozygous nucleotide variant c.315-48T>C.

The patient was treated with ursodeoxycholic acid (promoting biliary secretion of protoporphyrin), as well as liver protection and lipid-lowering treatments, with partial improvement in symptoms and liver function tests (Figure 3).

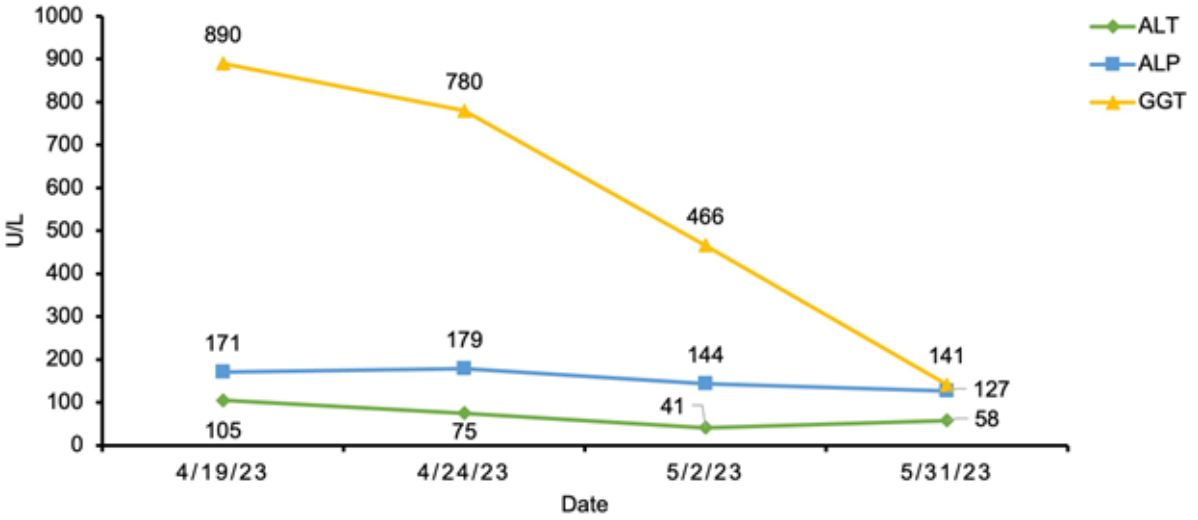

Figure 3: Liver function test results.

5. Discussion

EPP is a rare genetic disorder with an autosomal recessive (very rare) and autosomal dominant incomplete penetrance pattern of inheritance [5]. EPP is typically characterized by cutaneous photosensitivity (usually beginning in childhood) with burning, tingling, and itching within minutes of sun or UV exposure, followed later by erythema and swelling [6]. Many patients have chronic anemia, iron deficiency, and low vitamin D levels. Liver complications only occur in a very small number of patients. Protoporphyrin liver disease may cause severe abdominal pain, especially in the upper right quadrant, and jaundice. Because protoporphyrin is fat-soluble, it needs to be excreted from the liver to the intestinal tract through bile. When it accumulates in excess in the liver, it will cause bile excretion disorder, intrahepatic protoporphyrin mixed with cholestasis, and micro biliary plug formation. Pathological examination showed

that a large number of brown-yellow to brown granular deposits were deposited in hepatocytes, Kuffer cells, hepatic sinusoids, and micro biliary ducts, accompanied by the formation of micro biliary plugs; polarizing microscopy showed characteristic red birefringence and Maltese crosses [7]. EPP induces different degrees of liver damage, including mild swelling and degeneration of liver cells, progressive liver disease, and even end-stage liver diseases such as liver fibrosis and cirrhosis. Approximately 2-5% of affected individuals may develop advanced liver disease, most notably cholestatic liver failure [8]. Our patient had liver dysfunction (especially GGT) as the only clinical characteristic, without abdominal pain, cutaneous photosensitivity, and hematological manifestations. The patient's liver biopsy did not reveal the presence of protoporphyrin deposits in hepatocytes either. The patient's diagnosis was delayed for 16 years due to lack of specific symptoms and typical indicators. Fortunately, genetic testing has now confirmed the diagnosis for us.

FECH gene mutations causing EPP are highly heterogeneous and mostly show family specificity [9]. Many different FECH gene mutations have been identified, most of which are null allelic mutations and a few are missense mutations. Minder et al. described a significant genotype-phenotype association between "null allele" mutations and liver complications in EPP [10]. However, as more evidence accumulates, these mutations by themselves do not account for the severe liver disease phenotype, as the same mutations were reported both in asymptomatic family members of patients with liver disease and in patients who did not develop liver disease [11]. The mutation c.315-48T>C (also known as IVS3-48T>C), a known hypomorphic allele located within intron 3, results in residual ferrochelatase activity and is a necessary but insufficient pathogenic variant to cause overt clinical symptoms [12,13], which partially explains the manifestation of abnormal liver enzymes but without typical skin photosensitivity in our patient.

As a rare genetic metabolic disease, there is currently no effective cure for EPP. First of all, measures should be based on the prevention of risk factors, such as avoiding light, drinking, and smoking. Recommendations include annual monitoring of liver function, blood count, erythrocyte protoporphyrin levels, iron profile, and vitamin D. For patients with hepatic involvement, therapy with ursodeoxycholic acid (induce bile flow), cholestyramine and other porphyrin absorbers (interrupt enterohepatic circulation of protoporphyrins), heme and red blood cell transfusions (reduce protoporphyrin production), and plasmapheresis (reduce circulating levels of protoporphyrin) may provide some benefit. Patients with advanced liver disease should also be evaluated for indications for liver transplantation [14]. However, liver transplantation can only improve liver function and cannot reduce the source of protoporphyrin in bone marrow. If necessary, liver transplantation combined with bone marrow transplantation can be used for sequential treatment [15,16]. In conclusion, we report a rare case of a Chinese EPP patient with only liver involvement. Our study provides a direction for the diagnosis of clinically unexplained liver function abnormalities and enriches the clinical features of EPP in different ethnic groups.

6. Funding

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7. Ethical statement

The study was performed in accordance with the ethical standards of the institutions to which we are affiliated and with the Declaration of Helsinki (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report.

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