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CASE REPORT
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Benign recurrent intrahepatic cholestasis type 2 in a child: A case report and novel mutation

Ulaş Emre Akbulut[1], Nadide Cemre Randa[2], İshak Abdurrahman Işık[1], Atike Atalay[1]

[1]Department of Pediatric Gastroenterology Hepatology and Nutrition, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkey
[2]Department of Medical Genetics, University of Health Sciences, Antalya Training and Research Hospital, Antalya, Turkey

What is already known on this topic?

Benign recurrent intrahepatic cholestasis is characterized by intermittent episodes of cholestasis without progression to liver failure. Benign recurrent intrahepatic cholestasis type 2 is an autosomal recessive disorder caused by ABCB11 mutations.

What this study adds on this topic?j

The novel mutation in ABCB11 (c.3083_3084delCAinsTG) was first detected in a patient with benign recurrent intrahepatic cholestasis.

ABSTRACT

Benign recurrent intrahepatic cholestasis is a rare disorder characterized by recurrent episodes of cholestatic jaundice without liver damage. A mutation in the ABCB11 gene encoding bile salt export pump protein causes the disease. A 16-year-old boy with severe jaundice is presented here. His laboratory tests were consistent with intrahepatic cholestasis despite having normal gamma-glutamyl transpeptidase levels. Acute and chronic liver diseases with viral, metabolic, and autoimmune etiology were excluded. Magnetic resonance imaging revealed normal intra- and extrahepatic bile ducts. A liver biopsy showed cholestasis in the centrilobular and intermediate zones and sinusoidal dilatation. Genetic testing revealed a homozygous c.3083_3084delCAinsTG (Ala1028Val) mutation in the ABCB11 gene. The patient was treated with ursodeoxycholic acid 20 mg/kg/day and cholestyramine 4 g twice daily, and total bilirubin decreased to normal ranges after two months of therapy. This mutation (c.3083_3084delCAinsTG) in the ABCB11 gene is the first reported in a patient with benign recurrent intrahepatic cholestasis type 2.

Keywords: ABCB11, bile salt export pump, child, cholestatic jaundice, mutation, pruritus

Introduction

Benign recurrent intrahepatic cholestasis (BRIC) is an autosomal recessive disease characterized by recurrent attacks of jaundice and pruritus. These self-limiting attacks may recur lifelong at intervals ranging from a few weeks to several months. Onset of disease can occur at any age, in the majority of the cases, the first symptoms appear in early adolescence. Normal or mildly elevated gamma-glutamyl transpeptidase (GGT) but significantly high serum bilirubin and alkaline phosphatase (ALP) levels are detected during attacks. Patients are asymptomatic with normal levels of biochemical parameters between attacks (1). A mutation in ATP8B11, the gene encoding hepatocanalicular flippase for phosphatidylserine; a mutation in ABCB11, the gene encoding the hepatocellular bile salt export pump (BSEP); and a mutation in ABCB4, the gene encoding the multidrug resistance protein 3 (MDR3) result in BRIC type 1, 2, and 3 respectively (2). Here, we report a novel BSEP mutation in a child with BRIC type 2.

Case Presentations

A 16-year-old boy was referred with symptoms of jaundice and pruritus for two weeks. He had no fever, skin rash, history of drug use, and family history of liver disease. After his first attack at age 8 years lasting about two weeks, he had 2-3 attacks per year. He also had jaundice during his last attack a year before. He was asymptomatic between attacks. On physical examination, there was widespread icterus without signs of liver failure. The liver was palpable just below the costal margin on the midclavicular line. There were scratches on the skin caused by itching.

Corresponding Author:
Ulaş Emre Akbulut
✉ulasemre@hotmail.com
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turkarchpediatr.org

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In the laboratory evaluation, full blood count, urinalysis, serum electrolytes, cholesterol, and lipid levels were normal. His liver functions were as follows: alanine aminotransferase (ALT) 57 U/L, aspartate aminotransferase (AST) 56 U/L, total serum bilirubin 9.6 mg/dL and the direct fraction 5.4 mg/dL, alkaline phosphatase (AP) 535 U/L, gamma-glutamyl transpeptidase (GGT) 11 U/L, serum albumin 4.1 g/dL, prothrombin time 12.5 s, and international normalised ratio (INR) 1.2. The serum total bile salt level was 250 (normal range 0-10) µmol/L. Virologic studies were negative for hepatitis A, B, and C viruses, cytomegalovirus, Epstein-Barr virus, herpes simplex virus, and rubella. Antinuclear antibodies, antimitochondrial antibodies, anti-smooth muscle antibodies, anti–liver-kidney microsomal antibodies and serum ceruloplasmin levels were also normal. An ultrasonographic examination revealed mild hepatomegaly with normal echotexture. Magnetic resonance cholangiopancreatography showed a normal intra- and extrahepatic biliary tree and pancreatic ductal system. Cholestasis in the centrilobular and intermediate zones and sinusoidal dilatation was detected in the pathologic examination of the liver biopsy.

We performed ATP8B1 and ABCB11 gene sequencing due to recurrent intrahepatic cholestasis. Genetic testing revealed that our patient had a homozygous c.3083_3084delCAinsTG (p.A1028V) variant in the ABCB11 gene, and there was no genetic abnormality in the ATP8B1 gene. The A1028V variant has not been reported in the literature.

He was treated with ursodeoxycholic acid 20 mg/kg/day and cholestyramine 4 g twice daily. He was advised to take a low-fat diet and supplied with fat-soluble vitamins during attacks. His bilirubin and transaminase levels were decreased to normal ranges after two months of therapy. The patient was followed up for six months and he developed one episode without jaundice. This case report was written after obtaining the parents' written informed consent.

Discussion

Familial intrahepatic cholestasis is a group of heterogeneous autosomal recessive liver disorders characterized by intrahepatic cholestasis that can be divided into three groups: progressive familial intrahepatic cholestasis (PFIC), BRIC, and intrahepatic cholestasis of pregnancy. PFIC and BRIC can also be divided into three types by the causing genes: BRIC type 1/PFIC type 1, mutations in ATP8B1 and a low/normal GGT level; BRIC type 2/PFIC type 2, mutations in ABCB11 and a low/normal GGT level; BRIC type 3/PFIC type 3, mutations in ABCB4 and a high GGT level (2). BRIC is characterized by recurrent cholestasis attacks, without liver damage, and cirrhosis. PFIC is progressive and can lead to end-stage liver disease. Different types of mutations lead to different clinical phenotypes. Mutations that cause PFIC are usually found in conserved regions of genes encoding conserved functional domains of corresponding proteins, and mutations in BRIC only partially affect protein function and expression (3).

The diagnostic criteria of BRIC are at least two attacks with asymptomatic periods lasting months or years; laboratory tests compatible with intrahepatic cholestasis; severe ichtiosis causing by cholestasis; normal intra- and extrahepatic bile tree cholangiographically; liver biopsy showing centrilobular cholestasis, and exclusion of other cause of cholestasis (4). In addition, a gene test can be performed to confirm the diagnosis of BRIC type 2. Our 16-year-old male patient with cholestasis and low levels of GGT fulfilled all of the diagnostic criteria. A homozygotic mutation of c.3083_3084delCAinsTG (p.A1028V) was also detected in secans analysis of ABCB11 gene (https://varsome.com/about/acmg-implementation). This is a novel mutation causing BRIC.

The synthesized and recycled bile acids are transported from hepatocytes across the canalicular membranes against a concentration gradient by an ATP-dependent pump. The ABCB11 gene, located on chromosome 2q24, encodes an ATP-binding cassette transporter, known as BSEP in the human liver. A mutation of ABCB11 can result in the impairment of canalicular bile salt excretion and bile flow, leading to intrahepatic cholestasis (1).

Different ABCB11 gene mutations have been reported in different regions of the world. Although E297G and D482G are common mutations reported in the European population, they have not been detected in the Asian population. A c.1331T > C p.V444A (rs2287622) variant, known as a single nucleotide polymorphism (SNP) in familial intrahepatic cholestasis, is found at a rate of 74.5%. Another SNP variant c.3084A> G p.A1028A (rs497692) is 67.2% in familial intrahepatic cholestasis (5). rs497692 has also been associated with patients with BRIC type 2, patients with PFIC type 2, and primary intrahepatic stones (6). It could promote exon skipping and disrupt gene splicing, resulting in impaired function of BSEP.

In our case, the patient carried a homozygous missense mutation in ABCB11, namely p.A1028V. Replacement of alanine with valine resulted in a mutation that caused the impaired function of the ABCB11 protein, which has not been previously reported. We classified this variant as likely pathogenic by using the ACMG criteria (PM1, PM2, PP3, PP4_strong) (7). To determine the segregation of the p.Ala1028Val variant, we performed genetic testing to the patient's healthy parents, which showed that both parents were heterozygous. Finally, ACMG criteria were updated to PM1, PM2, PP1, PP3, PP4_strong with the segregation analysis results, and we classified the p.A1028V variant as pathogenic for BRIC type 2.

There is no specific treatment of BRIC. The goal of treatment is to shorten the duration of attacks, prevent recurrence, and decrease the severity of symptoms. It is believed that bile acid retention within the body causes pruritus in these patients. Cholestyramine decreases its level by binding to bile acids and increasing excretion in feces (8). Rifampin competes with the hepatic uptake of bile acid, thus lowering hepatocyte bile concentrations and reducing pruritus (9). Also, it has been shown that phenylbutyrate partially corrected BSEP canalicular expression detected by immune staining in patients with PFIC type 2. By the way, biliary bile acid secretion is increased, and cholestasis is decreased (10). Our patient improved with cholestyramine and ursodeoxycholic acid therapy.

In conclusion, we report a Turkish child with clinically proven BRIC type 2, and we detected a novel mutation in the ABCB11 gene. The novel mutation in ABCB11 (c.3083_3084delCAinsTG) was detected for the first time and could help further the understanding of the mechanism of BRIC type 2. Inherited disorders should be considered in patients with cholestasis and normal serum GGT levels. BRIC-associated genetic mutations can be detected easily with the widespread use of molecular

techniques. Accordingly, genetic tests should be performed on patients suspected of having BRIC.

Informed Consent: This case report was written after obtaining the parents' written informed consent.

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