Article published online: 2020-10-09

A Novel Compound Heterozygous Mutation in *ABCB4* Gene Leading to Cholelithiasis, Progressive Familial Intrahepatic Cholestasis (Type 3), and Cirrhosis in a Child

Nida Mirza[1] Smita Malhotra[1] Anupam Sibal[1]

[1] Indraprastha Apollo Hospital, New Delhi, India

Address for correspondence Nida Mirza, MBBS, MD, 279 South Ex., Part 2, Delhi 110049, India (e-mail: nydamirza.1@gmail.com).

J Child Sci 2020;10:e134–e136.

Abstract

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of autosomal recessive disorders of childhood which presents with intermittent or progressive episodes of cholestasis, with jaundice and pruritus as most common presenting symptoms. PFIC type 3 occurs due to mutations in the *ABCB4* gene, mutation in this gene has wide spectrum of features which include intrahepatic stones, cholelithiasis, PFIC type 3, and intrahepatic cholestasis of pregnancy. Here, we are reporting a peculiar case of young male adolescent with novel variant compound heterozygote missense mutation in *ABCB4* gene who had gall stone as initial symptom, followed by symptoms of PFIC and eventually decompensated chronic liver disease.

Keywords
- gallstone
- novel mutation
- liver cirrhosis

Introduction

Progressive familial intrahepatic cholestasis (PFIC) is a group of autosomal recessive disorders which presents with intermittent or progressive episodes of cholestasis, clinically most common presenting symptoms are jaundice and pruritus. Three types of PFIC (types1, 2, and 3) are extensively studied; however, recently many other types are also identified. PFIC types 1 and 2 are usually presents in early infancy, whereas onset of PFIC3 may occur in late infancy, childhood, or even during young adulthood. Most PFIC patients develops fibrosis and end-stage liver disease in variable time course. Serum gamma-glutamyl transferase (GGT) level is normal or low in PFIC1 and PFIC2 patients, while it is high in PFIC3 patients. Mutation in *ABCB4* gene, results in wide spectrum of features which include intrahepatic stones, cholelithiasis PFIC type 3 and intrahepatic cholestasis of pregnancy.[1] Here, we have described a young male adolescent who had gallstones at the age of 9 years, followed by features of PFIC and decompensated cirrhosis at the age of 14 years found to have novel compound heterozygous mutation in *ABCB4* gene.

Case Report

A 14-year-old previously asymptomatic male presented with complains of progressive jaundice associated with moderate-to-severe pruritus since 1 month. He was apparently alright till the age of 9 years when he had acute onset of jaundice and abdominal pain; investigations revealed multiple gall stones for which cholecystectomy was performed at that time and he improved symptomatically. He remained asymptomatic for next 5 years except with mild intermittent episodes of pruritus, in this duration, he was growing well and had no episodes of jaundice, bleeding from any site, abdominal distension, or altered sensorium. He was the only child, born full term to a nonconsanguineous marriage. His maternal grandmother had history of gall stones at the age of 35 years and maternal aunt had on and off self-limiting pruritus, the etiology of which is not known. Physical examination showed mild pallor, generalized icterus, scratch marks on skin, mild distended abdomen, palpable left lobe of liver, and mild-to-moderate splenomegaly. There was no clubbing, cyanosis, or generalized body edema. His weight was 38 kg (3rd percentile) and

received
July 1, 2020
accepted
August 22, 2020

DOI https://doi.org/10.1055/s-0040-1717106.
ISSN 2474-5871.

height was 165 cm (43 percentile). Investigations revealed deranged liver function test; alanine aminotransaminase 85 U/L, (N: 10–49 U/L) and aspartate aminotransaminase 110 U/L (N: < 34 U/L), alkaline phosphatase 216 U/L (N: <500 U/L), GGT 280 UI/L (N: <38 U/L), total bilirubin (16.9 mg/dL, N: 0.3–1 mg/dL), conjugated bilirubin (9.4 mg/dL, N: 0.1– 0.4 mg/dL), and low albumin 2.8 g/dL (N: 3.5–5.2 g/dL). Prothrombin Time Iinternational Normalized Ratio (PT INR) was elevated (1.48), which, however, got corrected to normal by vitamin K. Features of hypersplenism with 90,000 platelets/cubic mm, 5,000 leukocytes/cubic mm and hemoglobin of 9.5 g/dL were seen. Ultrasound abdomen showed ascites, dark coarse liver parenchyma, absent gall bladder, and splenomegaly, liver biopsy showed cirrhotic changes with ductular proliferation. Viral markers for hepatitis A, B, C, and E were negative, ceruloplasmin levels were normal, and antibody panel for autoimmune hepatitis were negative ruling out viral, autoimmune, and Wilson's disease. Upper gastrointestinal (GI) endoscopy showed grade-1 varices and mild portal gastropathy. In view of cholelithiasis in childhood, pruritus and progressive jaundice with high GGT we kept a possibility of PFIC type 3. Exome sequencing identified two heterozygous missense variants c.1529A > G in exon 13 and c.370G > C in exon 6 of the *ABCB4* gene that results in the amino acid substitution from Asparagine to Serine at codon 510 (p.Asn510Ser) and from glycine to arginine at codon 124 (p.Gly124Arg), respectively. Both of these variants in *ABCB4* gene were not reported previously. Thus, we made a final diagnosis of type 3 PFIC in this patient. He was discharged on regular follow-up with ursodeoxycholic acid (UDCA), vitamin supplementation, β blocker, and diuretics. His family was counselled regarding the need for liver transplantation in future.

Discussion

PFIC type 3 occurs due to mutations in the *ABCB4* gene, characterized by high serum GGT, later onset of symptoms, and liver histology which shows ductular proliferation and portal inflammation.[1] ABCB4 mutation have been associated with several biliary disorders which include transient neonatal cholestasis, low phospholipid-associated cholelithiasis syndrome, intrahepatic cholestasis of pregnancy, drug-induced liver injury, adult biliary fibrosis, or cirrhosis and intrahepatic cholangiocarcinoma.[2,3] *ABCB4* gene encodes the hepatobiliary phosphatidylcholine floppase, which is expressed at the canalicular membrane of the hepatocytes, and transports phosphatidylcholine for excretion into the canalicular bile lumen along with bile acids and cholesterol to form phospholipid and bile acid vesicles that protect the hepatocytes and bile duct epithelial cells from bile acid and cholesterol crystal induced injury (cholangitis and cholestasis). Mutation in *ABCB4* gene causes low-phospholipid content in bile, causing a decreased rate of biliary phosphatidylcholine excretion, leading to the formation of extra and intrahepatic crystals and gallstones.[4] Initially homozygous mutation in the *ABCB4* gene leading to PFIC type 3 in children were detected.[5] Later heterozygous mutations in the *ABCB4* gene in adult patients were found associated with intrahepatic sludge, gallbladder cholesterol gallstones, and intrahepatic cholestasis of pregnancy, it is considered that female sex hormones may reduce the expression of the normal allele during pregnancy resulting in clinical cholestasis in the heterozygous.[5,6] Here in this case two different missense mutation (compound heterozygote) in *ABCB4* gene resulted in the three different clinical features gall stone, PFIC type 3, and biliary cirrhosis, ultimately leading to decompensated chronic liver disease within 5 years of first symptom. Both of these mutations are not reported before. A novel compound heterozygote mutation in *ABCB4* gene at exons 6 and 17 was previously reported in a 17-year-old female who had intrahepatic cholestasis and fibrosis.[7] It is earlier reported that complete abolition of protein expression occurs nonsense mutation, whereas residual function of the transporter may persist with missense mutation.[8,9] If the child has been diagnosed before, he may not have developed decompensated cirrhosis so early as treatment with UDCA was found effective in *ABCB4* gene mutation associated with adult-onset liver disease.[10] There have been case reports with both gallstone and cirrhosis but mostly the interval between gall stone and cirrhosis is higher, while in our case, decompensated liver disease developed at an earlier age.[11,12]

Conclusion

In conclusion, we describe a novel compound heterozygous missense mutation which lead to juvenile cholelithiasis and biliary cirrhosis at adolescent age; however, further pathogenicity of this mutation will be proven with identification of similar mutations in other patients. This case shows that *ABCB4* gene defect should be suspected in children with gallstones and pruritus and a close follow-up to be done.

Conflict of Interest
None declared.

References

1 Davit-Spraul A, Gonzales E, Baussan C, Jacquemin E. Progressive familial intrahepatic cholestasis. Orphanet J Rare Dis 2009;4:1
2 de Vree JM, Jacquemin E, Sturm E, et al. Mutations in the *MDR3* gene cause progressive familial intrahepatic cholestasis. Proc Natl Acad Sci USA 1998;95(01):282–287
3 Wadsworth CA, Dixon PH, Wong JH, et al. Genetic factors in the pathogenesis of cholangiocarcinoma. Dig Dis 2011;29(01):93–97
4 Lammert F, Wang DQ, Hillebrandt S, et al. Spontaneous cholecysto- and hepatolithiasis in Mdr2-/- mice: a model for low phospholipid-associated cholelithiasis. Hepatology 2004;39 (01):117–128
5 Jacquemin E, Cresteil D, Manouvrier S, Boute O, Hadchouel M. Heterozygous non-sense mutation of the *MDR3* gene in familial intrahepatic cholestasis of pregnancy. Lancet 1999;353(9148): 210–211
6 Rosmorduc O, Hermelin B, Poupon R. *MDR3* gene defect in adults with symptomatic intrahepatic and gallbladder cholesterol cholelithiasis. Gastroenterology 2001;120(06):1459–1467
7 Wu Z, Zhang S, Zhang L, Li M. Novel ABCB4 mutation in a Chinese female patient with progressive familial intrahepatic cholestasis type 3: a case report. Diagn Pathol 2020;15(01):39

8 Jacquemin E. Role of multidrug resistance 3 deficiency in pediatric and adult liver disease: one gene for three diseases. Semin Liver Dis 2001;21(04):551–562
9 Jacquemin E, De Vree JM, Cresteil D, et al. The wide spectrum of multidrug resistance 3 deficiency: from neonatal cholestasis to cirrhosis of adulthood. Gastroenterology 2001;120(06): 1448–1458
10 Pasmant E, Goussard P, Baranes L, et al. First description of *ABCB4* gene deletions in familial low phospholipid-associated cholelithiasis and oral contraceptives-induced cholestasis. Eur J Hum Genet 2012;20(03):277–282
11 Lucena JF, Herrero JI, Quiroga J, et al. A multidrug resistance 3 gene mutation causing cholelithiasis, cholestasis of pregnancy, and adulthood biliary cirrhosis. Gastroenterology 2003;124(04): 1037–1042
12 Francis FF, Frye R, Hashash JG. Cholelithiasis and biliary cirrhosis in a 28-year-old man. Clin Gastroenterol Hepatol 2017;15(05): A31–A32