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TJP2 Deficiency Presenting as High γ-Glutamyl Transferase (GGT) Neonatal Cholestasis and Mimicking Biliary Atresia: A Case Report

*Aashay Abhay Shah, MD, *Shivani Deswal, MBBS, DNB, *Neelam Mohan, DNB, and †Amit Nath Rastogi, MS, DNB

INTRODUCTION

Progressive familial intrahepatic cholestasis (PFIC) is a group of autosomal recessive genetic disorders associated with a defect in bile acid secretion or transport. The estimated incidence varies from 1 per 50 000 to 1 per 10 0000 births (1). It accounts for 10%–15% of cases of cholestasis requiring liver transplant (2). Till date, there have been reports of at least 7 variants of PFIC and tight junction protein 2 (TJP2) disease is one of them. It is linked to mutation of genes encoding *TJP2* and has been reported with low levels of γ-glutamyl transferase (GGT) in children. Here, we report a case of a 2 month old baby presenting as neonatal cholestasis with high GGT and carrying the homozygous pathogenic *TJP2* mutation.

CASE REPORT

A 40-day-old male baby, a resident of Nepal, was referred to us with a diagnosis of cholestatic jaundice since the first week of life. He was born at term by normal vaginal delivery, with a birth weight of 3 kg. There was no antenatal history of jaundice or pruritis. On day 3 of life, he was admitted to the neonatal intensive care unit for fever with jaundice. A diagnosis of sepsis was made and he received intravenous antibiotics for 5 days. There was no history of administration of total parenteral nutrition. At discharge, his total bilirubin was 8.5 mg/dL with a direct component of 5.7 mg/dL. He was referred to us at 2 months of age for persistent jaundice with dark urine and clay-colored stools. On examination, the baby was jaundiced with no dysmorphic features; the liver span was 7 cm and spleen 2 cm below the left costal margin. The rest of the systemic examination was normal. His direct bilirubin was 7.7 mg/dL (131.6 mmol/L). Table 1 shows the trend of liver function tests.

Fasting ultrasound examination was suggestive of a small gall bladder and technetium-99m radionuclide scan following phenobarbitone priming was nonexcretory. Liver biopsy performed at day 50 of life was suggestive of bile duct proliferation, cholestasis with bile plugs, and Ishak staging of 3/6 fibrosis. There was no evidence of Periodic acid - Schiff stain-positive diastase-resistant globules. A diagnostic possibility of biliary atresia was kept and peroperative cholangiogram performed on day 51 of life, which confirmed patent extrahepatic and intrahepatic ducts. This excluded the diagnosis of biliary atresia (Fig. 1). Blood tandem mass spectrometry, urine gas chromatography-mass spectrometry, urinary nonglucose reducing substances, urinary succinylacetone, galactose-1-phosphate uridylyltransferase enzyme assay, and α-fetoprotein, were all within the normal range. Treatment included ursodeoxycholic acid (15 mg/kg/day), both fat and water-soluble vitamin supplements along high medium-chain triglycerides-based milk formula. Considering the possibility of PFIC type 3, the whole exome sequencing was sent to Centogene laboratory in Germany. The genetic report suggested a homozygous frameshift pathogenic mutation [c.2473del p.Thr825Leufs*8] in the *TJP2* gene confirming autosomal recessive PFIC type 4. A probable need for liver transplantation was suggested at 8 months of age in view of persistent jaundice with hepatosplenomegaly and coagulopathy (international normalized ratio 1.6) along with hypoalbuminemia.

Parents are aware of the case report and have given their consent.

DISCUSSION

PFIC is a spectrum of heterogeneous disorders presenting in early infancy, childhood, or adolescent age with fluctuating jaundice, pruritus, and malabsorption. Most cases of PFIC are characterized by low or near normal GGT cholestasis with increased serum bile acid levels, except PFIC type 3. Recently, newer variants of PFIC like *TJP2*, Farnesoid X receptor, MYO5b, and ABCC12 diseases are being reported with varied presentations (3).

In homozygous *TJP2* deficiency, there is a remarkably low claudin-1 expression which disrupts the compactness of tight junctions leading to leakage of toxic bile contents into the liver parenchyma and subsequently cholestatic disease (4). Heterozygous individuals may remain unaffected or have intrahepatic cholestasis of pregnancy. In a large case series of *TJP2* disease comprising 12 babies, the mean age of presentation was 2 months of age with cholestatic jaundice and low GGT activity. Nine of 12 babies required liver transplantation while 1 died at 13 months of age (5). A case report of *TJP2* disease from China and another from south India recognized the association of hepatocellular carcinoma with *TJP2* deficiency (6). Rarely, pathogenic variants of *TJP2* have been associated with deafness, respiratory problems, and duodenitis.

Our case was unique in having a high GGT cholestasis. The infant did not have any other systemic involvement. However, the future risk of hepatocellular carcinoma cannot be undermined.

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From the *Department of Pediatric Gastroenterology, Hepatology and Liver Transplantation, Medanta – The Medicity and †Liver Transplantation and HPB Surgery, Medanta – The Medicity, Gurugram, Delhi-NCR, India.
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A.S. worked up the case, reviewed the literature, and drafted the case report. S.D. reviewed the literature and drafted the case report. N.M. worked up and followed up the case, facilitated molecular diagnosis, and critically analyzed the article. A.R. operated the case and facilitated diagnosis. N.M. is the guarantor.
Correspondence: Neelam Mohan, DNB, Department of Pediatric Gastroenterology, Hepatology and Liver Transplantation, Medanta, The Medicity Hospital, Sector 38, Gurugram, Haryana-122001, India. E-mail: drneelam@yahoo.com

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TABLE 1. Trend of liver function tests with age

Day of life	Total Bilirubin (mg/dL)	Direct Bilirubin (mg/dL)	Aspartate Aminotransferase (IU/mL)	Alanine Aminotransferase (IU/mL)	Gamma Glutamyl Transferase (IU/mL)	Alkaline Phosphatase (IU/mL)	Albumin (g/dL)
Day 3	8.5	5.7					
Day 40	9.6	7.7	188	155	202	590	3.2
Day 43	8.2	6.5	310	192	197	631	3
Day 45	8.3	7.1	278	210	213	761	3.2
Day 150	8.4	4.3	234	254	154	836	3.6
Day 240	10.2	5.6	250	420	158	1130	3.3

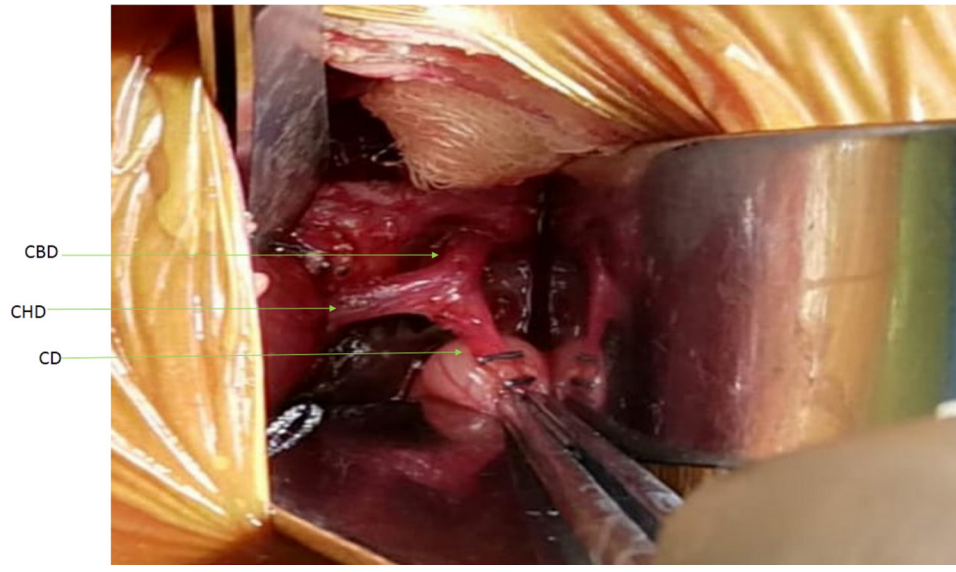

FIGURE 1. Intraoperative image showing clamped cystic duct (CD), common hepatic duct (CHD), and common bile duct (CBD).

CONCLUSION

This report from Asia suggests that the *TJP2* variant of PFIC can present in the neonatal age with high GGT levels. Genetic testing is a valuable tool for the definitive diagnosis of idiopathic cholestatic disorders.

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