

Severe Neonatal Presentation of Progressive Familial Intrahepatic Cholestasis Type 4 in an Omani Infant

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ABSTRACT: Progressive familial intrahepatic cholestasis type 4 (PFIC4) is a relatively newly described autosomal recessive disorder caused by biallelic mutations in the gene encoding tight junction protein 2 (*TJP2*) which is located in chromosome 9q21. PFIC4 is characterised by cholestasis with or without other extrahepatic manifestations. Bleeding tendency due to vitamin K deficiency is a well-known complication of cholestasis. We present a neonate who presented to the Emergency Department at a tertiary care hospital in 2021 with cholestasis and multiple intracranial bleeds. He was found to have severe coagulopathy and his genetic work up revealed a homozygous variant mutation in *TJP2* gene causing PFIC4. He had persistent cholestasis that necessitated an internal biliary diversion with some clinical improvement.

Keywords: Jaundice; Intracranial haemorrhage; Progressive Familial Intrahepatic Cholestasis type 4; Case Report; Oman.

HEREDITARY CHOLESTASIS IS A GROUP OF rare autosomal recessive liver disorders, which are caused by defects in genes related to the secretion and transport of bile salts and lipids. It is characterised by intrahepatic cholestasis, pruritus, jaundice and malabsorption.¹ Progressive familial intrahepatic cholestasis (PFIC) is one of the phenotypic manifestations of hereditary cholestasis with onset in early infancy that can progress to end-stage liver disease. It accounts for 10–15% of the causes of cholestasis in pediatric patients and is the cause of 10–15% of liver transplants in this population.^{1,2} PFIC types 1 and 2 usually present in infancy as infantile cholestasis characterised by low to normal gamma-glutamyl transferase (GGT). However, PFIC type 3 presents in older children and it is associated with high GGT.³ With advancement and increasing availability of genetic testing technologies rare types of PFIC are becoming recognised over the past decade.⁴ PFIC type 4 is a newly described clinical entity caused by biallelic mutations in *TJP2*. The clinical spectrum of this condition has not been fully elucidated. We report a neonate who presented with jaundice and severe coagulopathy at the age of 3 weeks and was found to have a homozygous NM_004817.3:c.2417G>A, p.Trp806Ter, pathogenic variant in the *TJP2* gene.

Case Report

A one-month-old boy presented to the Emergency Department at a tertiary care hospital in 2021 with

one-week history of progressive jaundice, poor feeding, dark discoloration of the urine and 2 days history of irritability. There was no history of acholic stools, vomiting, fever or any drug/herbal medicine intake. The patient was born to apparently healthy parents related as first cousins. He was delivered at 36 weeks of gestation via normal vaginal delivery with birth weight of 1.9 kg (<3rd percentile), length of 47 cm and head circumference of 31 cm (<3rd percentile). The mother had gestational diabetes mellitus (GDM). The patient has 2 healthy older siblings [Figure 1]. There was no family history of unexplained death, liver disease, bleeding disorders, or malignancy.

Physical examination revealed an irritable, pale infant with generalised icterus. His growth parameters were below the third percentile (weight = 2.5 kg, Z-score = -2.9, length = 48 cm, Z-score = -2.8). He had no dysmorphic features. His anterior fontanelle was full and pulsatile. His pupils were equal and reactive to light. He had no focal neurological deficit. His abdominal examination revealed a firm palpable liver 2 cm below the right costal margin. There was no clinical splenomegaly or ascites. He had no cutaneous findings suggestive of bleeding tendency.

Investigations revealed severe anaemia with haemoglobin 3.8 g/dL (10–14), high reticulocytes 5% (0.2–2) and low haematocrit of 0.12 L/L (0.33–0.39). Lactate dehydrogenase (LDH) was elevated at 782 U/L (120–300). Coagulation profile showed markedly prolonged PT and APTT with high INR of >17.4 (0.9–1.12). Liver chemistry demonstrated conjugated

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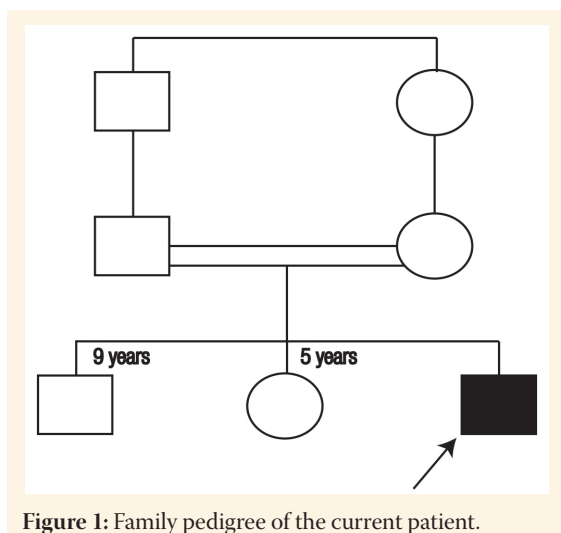


Figure 1: Family pedigree of the current patient.

hyperbilirubinaemia with raised transaminases and normal gamma-glutamyl transferase (GGT). Total bilirubin was 237 $\mu\text{mol/L}$ (0–17) and 84% of it was conjugated, alanine aminotransferase (ALT) 79 U/L (normal: <40), aspartate aminotransferase (AST) 261 U/L (normal: <41), and GGT 36 U/L (normal: <200) [Table 1]. Metabolic workup including, newborn metabolic screen, urine reducing substances, ammonia and CK level were all normal. Investigations for infective and endocrine causes were all negative. Brain magnetic resonant imaging (MRI) showed intracranial bleed with multiple parenchymal, intraventricular and extra-axial haemorrhages. The liver appeared of normal size and echotexture on ultrasound examination of the abdomen, and remained so on follow-up examination during the neonatal period.

The patient was intubated and mechanically ventilated and kept on brain protective measures. He received packed red blood cells and fresh frozen

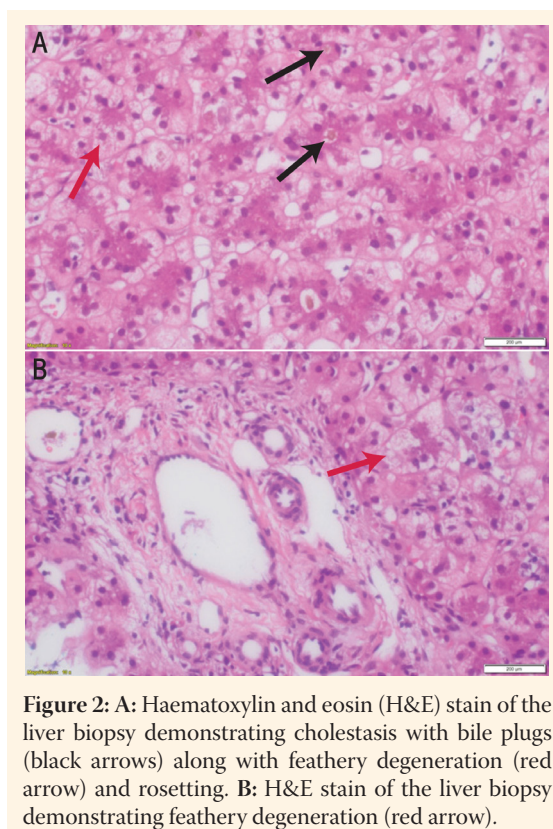


Figure 2: A: Haematoxylin and eosin (H&E) stain of the liver biopsy demonstrating cholestasis with bile plugs (black arrows) along with feathery degeneration (red arrow) and rosetting. B: H&E stain of the liver biopsy demonstrating feathery degeneration (red arrow).

plasma. He was also commenced on intravenous vitamin K. Cefotaxime and ampicillin were initiated to cover the possibility of infections. He developed a generalised tonic-clonic seizure and was started on phenobarbital. He did not require any surgical intervention. His coagulation profile improved the following day and he was extubated after 2 days. The intracranial bleeding was clinically attributed to a late onset vitamin K deficiency with superimposed cholestatic liver disease. As the patient had normal GGT and the initial work up for neonatal cholestasis

Table 1: The patient blood tests over an 11-month period

Biochemical parameter	Reference value	At admission	Age 2 months	Age 3 months	Age 4 months	Age 8 months	Age 11 months
Total bilirubin in $\mu\text{mol/L}$	0–17	269	23	132	110	302	58
Direct bilirubin	0–4	237	203	122	99	81	56
ALT in U/L	0–41	79	488	111	63	207	102
AST in U/L	0–40	261	768	130	86	309	164
GGT in U/L	<203	36	47	35	36	27	31
INR	0.9–1.1	17.4	1.1	1.06	1.06	1.17	1.2
AFP in KIU/L	0–7	1934	ND	ND	ND	116	20
Albumin in g/L	38–54	28	32	39	42	39	33
Haemoglobin in g/L	10–14	3.8	9.1	10.6	11.7	11.3	10.9

ALT = alanine transaminase; AST = aspartate transaminase; GGT = Gamma glutamyl transferase; INR = international normalised ratio; AFP = Alpha-fetoprotein; ND = not done.

were negative, PFIC and bile acid synthetic defects were the main differential diagnosis. He underwent ultrasound guided liver biopsy, and the histopathology revealed marked cholestasis with bile plugs along with feathery degeneration and rosetting [Figure 2]. Whole exome sequencing revealed a homozygous NM_004817.3:c.2417G>A, p.Trp806Ter pathogenic variant in the *TJP2* gene, consistent with a diagnosis of PFIC 4. He was also found to have a heterozygous likely pathogenic c.1642G>T (p.Glu548Ter) variant in *ITGB3* gene (NM_000212.3). Parental heterozygosity for the variant in *TJP2* was confirmed. The variant in *ITGB3* was proven to be paternally inherited. Biallelic pathogenic variants in this gene are related to autosomal recessive Glanzmann thrombasthenia type 2.

The patient was commenced on ursodeoxycholic acid and fat-soluble vitamin supplements. After discharge, he continued taking ursodeoxycholic acid, fat-soluble vitamin supplements and phenobarbital. He was kept on breastfeeds and medium-chain triglyceride-based formula. He remains seizure free and the repeated electroencephalogram (EEG) was normal. At the age of 9 months he underwent internal biliary diversion. When he was last assessed at the age of 11 months, he was able to cruise around objects, but still unable then to stand alone. He was able to drink from a cup. He had monosyllables, and he recognised his siblings by their names. He had no seizures. He remained clinically jaundiced with no pruritus. His weight was 5.4 kg (Z-score = -5), length was 64 cm (Z-score = -3). His liver chemistry has improved gradually [Table 1]. The family consented for publication of this case report.

Discussion

PFIC4 is among the most recently described forms of PFIC, and it is caused by mutations in the tight junction protein-2 (*TJP2*) gene.⁵ So far, a few cases of PFIC4 have been reported worldwide.^{4,6} To the best of the authors' knowledge, this is the first report of an Arab patient with severe neonatal presentation of PFIC4.

Truncating variants, as seen in the patient we describe, are known to be causative of *TJP2*-related PFIC4.⁷ A total of 15 nonsense variants have been described in *TJP2* so far.^{4,8} Patients with PFIC4 present with severe progressive cholestasis during infancy or early childhood. They are also at a higher risk of acquiring hepatocellular carcinoma.⁸ Serum GGT activity is typically normal or low. In addition to cholestasis, extrahepatic features have been identified in PFIC4 patients, including respiratory and

neurological disorders.⁶ The mechanism of cholestasis in PFIC 4 is due inappropriate function of the tight junction's protein at the hepatocytes. That results in leakage of cytotoxic bile salts into the paracellular space, causing damage to the surrounding liver cells.⁹ The purpose of the biliary diversion surgery is to bypass the enterohepatic circulation, thereby lowering the amount of bile salts that are reabsorbed by the terminal ileum. These surgeries sometimes have led to improvement in some PFIC patients.⁹ The patient we report so far has no extra-hepatic manifestations, and although the AFP and ultrasonographic appearance of the liver are not suggestive of malignancy at present, the concern about future development of hepatocellular carcinoma (HCC) in this child cannot be excluded. Despite the small number of patients with disorder reported so far, age-dependent penetrance of some mutations and notable clinical variabilities in some families have already been recognised.¹⁰

The patient in this report had a severe neonatal presentation with coagulopathy and multiple intracranial bleeds. This maybe explained on the basis of cholestatic liver disease and vitamin K deficiency, particularly owing to the drastic improvement in coagulopathy with the supportive therapy and vitamin K administration. However, the possible contribution of the heterozygous likely pathogenic variant identified in the *ITGB3* gene to the severity of coagulopathy arguably has some legitimate ground. Both dominant and recessive phenotypes associated with coagulopathy have been described in relation to this gene.¹¹⁻¹³ Although the variant identified was inherited from an asymptomatic parent the possibility of this variant being dominant with variable penetrance cannot be excluded.

Given the poorly defined risk of hepatocellular carcinoma and lack of reliable clinical predictors of this complication among patients with PFIC4, the patient is under close follow-up and monitoring with low threshold for consideration of liver transplantation when clinically merited.

Conclusion

The current patient is the first reported patient with PFIC4 in the Arab population. This case reports highlights some important points. First, for any neonate with normal GGT cholestasis, PFIC is a potential differential diagnosis and PFIC4 is among the most recently described forms of PFIC. Secondly, late onset vitamin K deficiency bleeding can be secondary to fat-soluble vitamin malabsorption due to neonatal cholestasis. Thirdly, *TJP2* gene mutation have

been reported to be associated with hepatocellular carcinoma, hence it is important to closely monitor PFIC4 patients from this perspective.

AUTHORS' CONTRIBUTION

SH, KA-T, DR, YW and YR wrote the first draft of this manuscript. KA-T, YW and YR were involve in revising the manuscript. All authors approved the final version of the manuscript.

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