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Varied presentations of progressive familial intrahepatic cholestasis Type 2 in infancy: A report of two cases

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ABSTRACT

Progressive familial intrahepatic cholestasis (PFIC) is a genetic disorder presenting in children with cholestasis. Type 2 known as bile salt export pump (BSEP) deficiency involves ABCB11 gene mutation leading to BSEP defect causing accumulation of bile salts within canaliculi and eventually hepatocellular injury. Disease hallmarks are jaundice, pruritus, and poor growth. We report varied presentations in 10-month old infants. First unusual presentation mimicked viral hepatitis without pruritus and growth failure and second, presenting classically with coagulopathy, pruritus, jaundice, and failure to thrive. Diagnosis of PFIC may be missed in absence of disease hallmark of pruritus and early biopsy with immunohistochemistry can change the outcome.

Key words: *Bile salt export pump, Cholestasis, Coagulopathy pruritus*

Progressive familial intrahepatic cholestasis (PFIC) is a rare heterogeneous autosomal recessive disease with an estimated incidence of about 1/50,000-1/100,000 births [1]. There are three types recognized. Type 2 known as bile salt export pump (BSEP) deficiency involves ABCB11 gene mutation leading to BSEP defect causing accumulation of bile salts within canaliculi and eventually, hepatocellular injury. It typically presents during infancy or early childhood with intractable pruritus, jaundice, failure to thrive, and normal-to-low levels of gamma glutamyl transferase (GGT). Histology reveals canalicular and ductular cholestasis, with minimal inflammation; later, progressing to micronodular or biliary cirrhosis. The first line of treatment is medical management aimed at controlling pruritus along with supportive care. Surgical options include partial internal biliary diversion in non-cirrhotic low GGT PFIC with intractable pruritus [2]. Liver transplantation is indicated in decompensated cirrhosis or in cases of failed diversion with debilitating pruritus.

CASE REPORTS

Case 1

A 10-month-old male child born of non-consanguineous marriage with uneventful antenatal and post-natal course was admitted with complaints of fever for 5 days, 15 days before admission. Fever was followed by yellowish discoloration of eyes and urine for 10 days with one episode of melena for which he received transfusion outside. There was no history of abdominal distension, pruritus, irritability, poor feeding, clay-colored stools, diarrhea, or steatorrhea and no history of jaundice, blood transfusion, or hospital admission in the past.

Child was hemodynamically stable at admission with normal growth pattern. On examination, pallor, icterus, and conjunctival xerosis were present. There was no facial dysmorphism or signs of liver cell failure. His abdomen was distended with firm and enlarged liver (span 11 cm) with splenomegaly of 3 cm below the costal margin. There was no free fluid. Other systemic examination was normal.

Complete hemogram was suggestive of microcytic hypochromic anemia with neutrophilia leukocytosis and normal platelet count. He had total bilirubin of 13.4 mg/dl with direct fraction of 7.4 mg/dl, aminotransferase/AST- 70/283 IU, and international normalized ratio (INR) of 1.4. GGT was 55 IU. We ruled out viral hepatitis, leptospirosis, and infectious mononucleosis. There was evidence of culture positive urinary tract infection (*Escherichia coli*) which was treated with appropriate antibiotics. Metabolic workup, fundus, and G-6PD were normal. Abdominal ultrasonography showed a normal hepatic echotexture and biliary system without any focal lesion. Portal vein size was normal with normal flow seen in portocaval vessels. The patient was treated with antibiotics and vitamin supplements.

During hospital stay, his fever subsided without any features of decompensation. Liver biopsy showed cholestasis pattern with bridging fibrosis suggestive of metabolic liver disease (Fig. 1). This narrowed down our diagnosis to PFIC or bile acid synthetic defects. Further, immunohistochemistry (IHC) depicted the absence of canalicular staining consistent with BSEP deficiency. Fibro scan showed median of 16.3 Kpa suggestive of significant

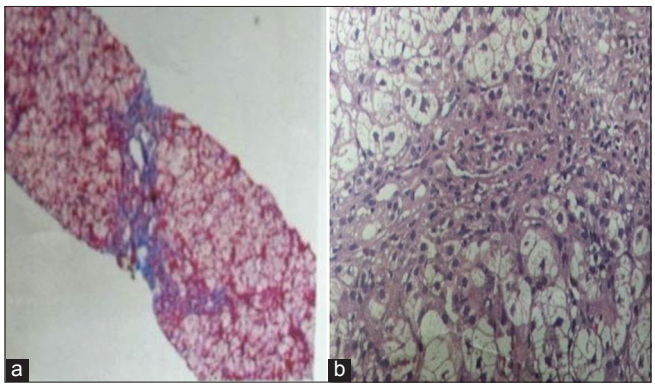

Figure 1: (a and b) Hematoxylin and eosin stained section of liver biopsy shows diffuse intrahepatocytic and focal canalicular cholestasis along with ballooning of hepatocytes and rosette formation with bridging fibrosis with incomplete nodule formation

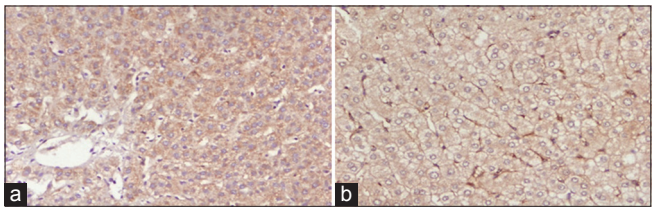

Figure 2: Immunohistochemistry for bile salt export pump shows absence of canalicular staining in (a) as against brown canalicular staining in control (b)

fibrosis. MCT-based diet with ursodeoxycholic acid (UDCA) was prescribed. He was immunized for Hepatitis B and discharged in stable condition without any signs of decompensation. Parents were counseled for the need of liver transplantation as the definitive treatment. At 2-month follow-up showed increase in weight, decrease in pruritus, and no evidence of vitamin deficiency. Total bilirubin was 1.4 mg/dl with INR-1 and serum albumin-3.8 g/dl.

Case 2

A 10-month-old female child born of non-consanguineous marriage with uneventful post-natal course presented with pruritus for 3 months, bluish patches over the body for 45 days and yellowish discoloration of eyes and urine for 15 days. She also had an episode of melena 1 month back. There was no history of clay-colored stools, steatorrhea, abdominal distension, or drug intake. Child was being managed on outpatient basis and had received injection Vitamin K and antihistaminic for pruritus. There was no past or family history of jaundice.

On examination, her height and weight were between −2 and −3 Z score indicating failure to thrive. Pallor and icterus along with scratch marks were present. There were no signs of liver cell failure or rickets. Firm non-tender hepatomegaly 3 cm below costal margin (Span-7.5 cm) with firm splenomegaly of 2 cm was present. Rest of the systemic examination was normal. Clinical possibility of PFIC 1 or 2, Alagille syndrome and secondary sclerosing cholangitis were considered. Her liver function test showed a total bilirubin of 2.6 mg/dl (direct fraction: 2 mg/dl). Serum glutamic oxaloacetic transaminase/serum glutamic pyruvic transaminase was 86/42 IU with GGT of 27 IU which was low. She had an albumin of 3.8 g/dl with INR - 1. Complete hemogram was suggestive of iron deficiency anemia. Her liver biopsy showed distorted acinar architecture, focal bridging fibrosis with cellular, and canalicular cholestasis. IHC showed absence of canalicular staining confirming BSEP deficiency (Fig. 2). Genetic analysis could not be done. Her pruritus was managed with UDCA and subsequently rifampicin was added on follow-up. Parents refused the option of biliary diversion. Parents were counseled about autosomal recessive inheritance and risk in next child.

DISCUSSION

Case 1 is an atypical presentation as there was no pruritus and growth failure in the infant despite advanced stage of cholestatic liver disease. His presentation simulated viral hepatitis but conjunctival xerosis (sign of Vitamin A deficiency) and a firm hepatomegaly guided us to investigate for chronic liver disease. This could possibly be explained on the basis of genetic polymorphism associated with the disease and varied phenotypes [3,4]. Both infants showed signs of fat soluble vitamin deficiency. Case 1 presented with xeropthalmia due to Vitamin A deficiency while case 2 had ecchymosis secondary to Vitamin K deficiency. Thus, highlighting the need to look for subtle signs of fat soluble vitamin deficiencies and treat them early to avoid life-threatening complications of coagulopathy and blindness.

In a recent study of 24 PFIC patients in Indian children, a time lag of 13 months in diagnosis was seen and familial clustering was seen in 12 of 24 cases [5]. Both our cases were first born and parents had no history of consanguinity. At 10 months, they had advanced fibrosis on liver biopsy. This highlights the importance of IHC and GGT in early diagnosis to prevent lethal consequences of the disease and improve the outcomes of such children. The gold standard for the diagnosis is genetic testing using DNA sequencing of the 27 coding exons and their splice junctions. Patients with normal BSEP staining should be tested for ATP8B1 and with negative BSEP staining should be first looked for ABCB11. Genetic analysis in parents may help us in prenatal diagnosis [6].

CONCLUSIONS

It is important that diagnosis of PFIC be kept in mind even in the absence of disease hallmarks such as jaundice, pruritus, and poor growth. Subtle signs of fat soluble vitamin deficiency should prompt us to search deeper into the cause. Importance of GGT and liver biopsy with IHC cannot be undermined in diagnosing rare cases of intrahepatic cholestasis at early stages.

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