Bile Acid Conjugation Defect in an Infant

Bile acid conjugation defect 1 (BACD) is a rare autosomal recessive disorder caused by homozygous or compound heterozygous mutation in *bile acid-CoA: amino acid N-acyltransferase* (*BAAT*) gene located on chromosome 9q31 [1]. In BACD, low levels of intraluminal bile acids in the intestine result in steatorrhoea, failure to thrive and malabsorption of fat-soluble vitamins. Symptoms usually respond to treatment with ursodeoxycholic acid (UDCA) [2]. We report a 9-month-old girl with BACD who mani-fested with steatorrhoea, pruritus and vitamin K deficiency without jaundice.

The child was first born to a non-consanguineously married couple with birth weight of 2.4 kg. At 5 months of age, there was a history of fever with watery loose stools lasting for two days. Following which she developed ecchymotic patches over the chest and abdomen. The child was evaluated in another medical facility. Pro-thrombin time (PT) was 180 s with an International normalized ratio (INR) of 12, and activated tissue thromboplastin time (aPTT) was 120 s (control 30sec). Hemoglobin was 8.6 g/dL, platelet count was 3.9×10^9/L. The child was administered vitamin K injection 5 mg intravenously. Following vitamin K injection, PT/INR and aPTT tests normalized, suggesting vitamin K deficiency.

At 9 months of age, the child presented to our hospital with history of steatorrhea and pruritus for two months. The child's weight was 7.5 kg and length of 68 cm, which were appropriate for age. Examination showed scratch marks due to pruritus. The child had no ecchymotic patches or any features of rickets. Similar to previous hospitalization, the child had prolonged PT/INR, which normalized after parenteral vitamin K. Liver function tests were normal with total bilirubin 0.3 mg/dL, aspartate transaminase (AST) 60 IU/L, alanine transaminase (ALT) 41 IU/L, alkaline phosphatase (ALP) 783 IU/L, gamma-glutamyl transferase (GGT) 5 IU/L, total protein 6.8 g/dL, and serum albumin 4.2 g/dL. Serum bile acid level was high (134 µmol/L, reference range 0.5-10 µmol/L). Clinical exome sequencing showed homozygous missense variation in exome 4 of *BAAT* gene (chr9:g. 101362505C >T; Depth L: 240x) that results in amino acid substitution of threonine for alanine at codon 394 (p.ala394Thr; ENST00000259407.7) consistent with diagnosis of BACD. This variant has not been reported previously. Silico predictions of the variant are probably damaging by PolyPhen2 (HumDiy) and damaging by SIFT, and LRT. This variant was classified as a variant of unknown significance as per the American College of medical genetics and genomics criteria [3]. The child was started on ursodeoxycholic acid (UDCA) orally, 30 mg/kg/day in three divided doses along with supplementation of vitamin K 5 mg parenterally every 3 weeks and other fat-soluble vitamins orally and also medium-chain triglycerides. The child showed improvement in pruritus, no steatorrhea and normal PT/INR at the last follow-up at 14 months of age. Her growth was normal with weight of 8.9 kg and height 80 cm.

Steatorrhea, fat-soluble vitamin deficiency and pruritus with normal GGT in infancy can be due to bile acid transporter defects, bile acid conjugation disorders and bile acid synthesis defect (pruritus being rare). With the absence of jaundice, possibility of bile acid transporter defects was unlikely. High serum bile acid levels ruled out bile acid synthesis defects. Steatorrhea and fat-soluble vitamin deficiency can also occur in intestinal malabsorption, but pruritus is not seen in that disorder.

In a previous case series of BACD [2], the age at diagnosis was 3 months - 14 years, and one child had progressive liver disease with decompensation requiring a liver transplant. Mild to moderate cholestatic liver disease in BACD is presumably because cholic acid is synthesized at normal rate and its efficient intestinal absorption leads to a recycling pool of bile acids that can generate bile flow. Thus, BACD patients can develop variable liver disease in later age that needs follow up [2]. Thus our patient will require follow up to look for progression of liver disease.

UDCA displaces endogenous hepatotoxic bile by hydrophilic bile acid pool [4]. Alteration of the bile acid pool might help increasing the intestinal concentration of hydrophilic bile acids in this disorder. In a previous case series [5], children treated with glycocholic acid (conjugated bile acid with glycine) showed improvement in fat soluble vitamin absorption and growth. However, it is not yet available in Indian market. BACD cases are rare, but once diagnosed effective medical treatment with a good outcome is possible with simple medical management. However, these children need to be maintained on UDCA to control the disease.

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