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Case Report

Paediatrics Section

The Diagnostic Odyssey of Congenital Bile Acid Synthesis Defect Type 1: A Case Report

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ABSTRACT

Congenital Bile Acid Synthesis Defects (BASDs) are rare, autosomal recessive metabolic conditions defined by defects in primary bile acid synthesis, leading to the accumulation of toxic intermediate sterols, a deficiency of normal primary bile acids (cholic and chenodeoxycholic acid), and subsequent cholestasis and fat-soluble vitamin malabsorption. Early diagnosis and targeted replacement therapy are vital to prevent progressive liver damage and fatal outcomes. This report describes a 6-year and 5-month-old male from a consanguineous marriage in Chennai, presenting late with right arm swelling, gum bleeding, and progressive pallor for one week. He had a significant history of neurodevelopmental delay and a sibling's death from jaundice. Physical examination revealed severe malnutrition, icterus, widespread ecchymoses, ichthyosis, and spastic quadriparesis. Blood investigations confirmed severe microcytic hypochromic anaemia (Hb 1.6 g/dL) and severe coagulopathy {Prothrombin Time (PT)> 100, International Normalised Ratio (INR)>8}. A diagnosis of congenital BASD type 1 was established through abnormal urinary bile acid profiling Fast Atom Bombardment–Mass Spectrometry (FAB-MS) and was confirmed by genetic testing showing biallelic pathogenic variants in the HSD3B7 gene. The child was managed with aggressive supportive care, including blood and Fresh Frozen Plasma (FFP) transfusions and high-dose Vitamin K, alongside targeted therapy with oral cholic acid and fat-soluble vitamins. The child showed dramatic clinical improvement within six days, reinforcing the therapeutic benefit of even delayed intervention, although liver transplantation was advised for the advanced liver disease. This case underscores the challenges of late diagnosis and the life-threatening coagulopathy associated with severe BASD type 1.

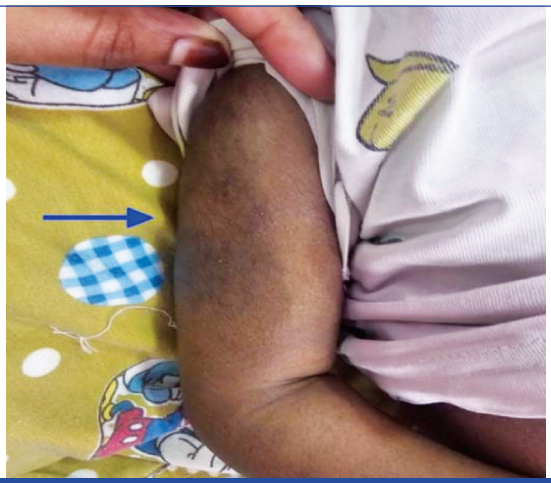
Keywords: Biosynthesis disorders, Blood coagulation disorders, Cholestasis, Cholic acids, Neurodevelopmental delay

CASE REPORT

A 6-year and 5-month-old male child from Chennai, born of a third-degree consanguineous marriage, presented to the paediatric department with a chief complaint of right arm swelling for one week, followed by spontaneous generalised gum bleeding for five days and progressive generalised pallor for the last three days. There was no history of fever or pain associated with the swelling or bleeding episodes. The arm swelling began after a physiotherapy session and quickly progressed to a large area of ecchymosis that extended across his chest.

The child had a history of a neonatal seizure at two months of age, attributed to an intracranial bleed, and subsequently developed global neurodevelopmental delay. He has been undergoing physiotherapy for developmental delay since the age of one year. However, he had never received a formal diagnosis or targeted therapy. He is currently seizure-free but continues to show marked developmental delays. There was no previous history of similar bleeding or swelling episodes. A notable family history included the death of an elder sibling at 1.5 years of age due to jaundice.

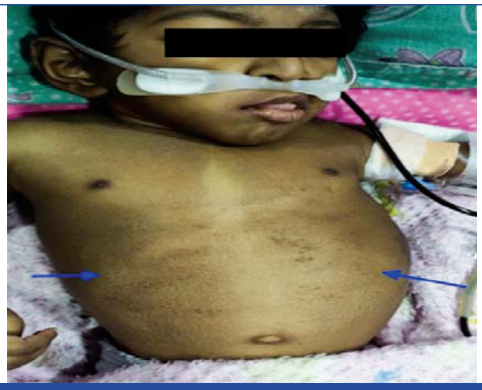
On admission, the child appeared dull and severely malnourished, weighing only 8.1 kg and measuring 77 cm in height, both significantly below the standard deviation for his age. He exhibited generalised pallor, icterus, and spontaneous gum bleeding unrelated to brushing or eating. There was a large haematoma on the right arm, widespread ecchymoses [Table/Fig-1], and the presence of ichthyosis [Table/Fig-2]. Vital signs revealed tachycardia with a heart rate of 160 bpm and tachypnoea with a respiratory rate of 60 per minute. Abdominal examination did not reveal any organomegaly, with both liver and spleen being impalpable. Neurologically, the child had microcephaly, a cortical thumb [Table/Fig-3], hyperreflexia, limb contractures, and signs of increased tone in all four limbs, consistent with spastic quadriparesis [Table/Fig-4].



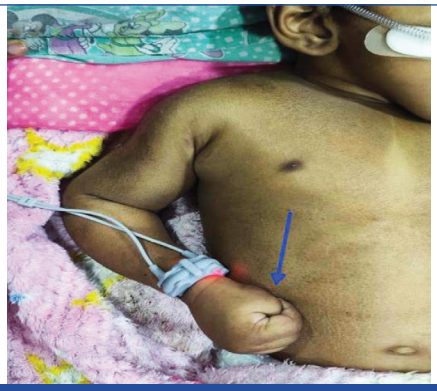
[Table/Fig-1]: Widespread ecchymoses noted on the lateral aspect of the right upper arm.

Laboratory investigations revealed severe microcytic hypochromic anaemia with a haemoglobin level of 1.6 g/dL and a Mean Corpuscular Volume (MCV) of 65 fL. Coagulation studies showed a life-threatening coagulopathy, with a prothrombin time that could not be measured, an undetectable activated partial thromboplastin time, and an undefined international normalised ratio. Liver function tests indicated mild dysfunction, with Aspartate Transaminase (AST) at 98 U/L, Alanine Aminotransferase (ALT) at 76 U/L, total bilirubin at 2.1 mg/dL, conjugated bilirubin at 1.4 mg/dL, and albumin at 2.83 g/dL. Abdominal ultrasound demonstrated altered liver echotexture with coarse and heterogeneous patterns, borderline splenomegaly, and mild ascites [Table/Fig-5]. X-ray imaging showed no evidence of fractures.

The child was managed with oxygen support via High Flow Nasal Cannula (HFNC), daily intramuscular Vitamin K injections (5–10 mg) for four days, multiple transfusions of Packed Red Blood Cells



[Table/Fig-2]: Prominent ichthyosis covering the entire abdomen.



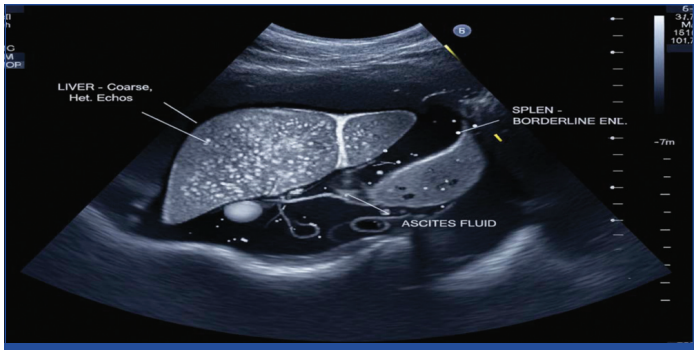
[Table/Fig-3]: Demonstrates the cortical thumb of the right hand.

[Table/Fig-4]: Limb contractures and increased tone noted in all four limbs.

(PRBC), and Fresh Frozen Plasma (FFP) to correct the severe coagulopathy. In view of his malnourished state and potential infection risk, empirical antibiotic therapy with ceftriaxone (80 mg/kg/day) was initiated. Following this intensive supportive care, the child's condition improved significantly. Repeat blood tests showed haemoglobin levels rising to 9.3 g/dL and INR reducing to 1.56.

Given the combination of progressive liver dysfunction, coagulopathy likely due to vitamin K deficiency secondary to chronic fat malabsorption, ichthyosis, neurodevelopmental delay, consanguinity, and a family history suggestive of a hereditary disorder, a metabolic liver disease was strongly suspected. An urgent metabolic workup was initiated. The provisional diagnosis was a metabolic liver disorder, most likely a congenital bile acid synthesis defect or another inborn error of metabolism leading to cholestasis and coagulopathy.

Differential diagnoses considered were congenital Bile Acid Synthesis Defects (BASDs), particularly type 1 (HSD3B7 deficiency) or type 2 (AKR1D1 deficiency), with the low or normal Gamma-Glutamyl Transferase (GGT) level supporting BASD over other causes of cholestasis. Progressive Familial Intrahepatic Cholestasis (PFIC), especially types 1 or 2 with low GGT, was also a possibility, though distinguishable by the absence of toxic bile acid precursors characteristic of BASD. Other differentials included alpha-1



[Table/Fig-5]: Abdominal ultrasound demonstrated altered liver echotexture (coarse and heterogeneous), borderline splenomegaly, and mild ascites.

antitrypsin deficiency, which often presents with cholestasis or cirrhosis, and biliary atresia, which was considered unlikely due to the low/normal GGT levels and chronic non-surgical presentation. Cystic Fibrosis (CF)–related liver disease was also unlikely in the absence of classical CF features.

BASD type 1 emerged as the most probable diagnosis based on the triad of cholestatic liver disease, features of fat-soluble vitamin deficiency (manifested as severe coagulopathy, ichthyosis, and rickets-like changes), and neurological symptoms including spasticity and global developmental delay, in the context of consanguinity and sibling death due to suspected liver disease. This diagnosis was confirmed through urinary bile acid analysis using Fast Atom Bombardment–Mass Spectrometry (FAB-MS), which revealed elevated levels of specific abnormal bile acid metabolites, pathognomonic for BASD type 1. Genetic testing further established the diagnosis by identifying biallelic pathogenic variants in the HSD3B7 gene, consistent with autosomal recessive congenital bile acid synthesis defect type 1.

The genetic analysis revealed a pathogenic variant in the HSD3B7 gene, located in exon 7, consistent with a diagnosis of congenital bile acid synthesis defect type 1.

Over a six-day hospital course, the child showed marked clinical improvement. His vitals stabilised, haematologic parameters improved, and respiratory distress resolved. A paediatric hepatologist was consulted, and the child was discharged with a plan for follow-up care, including supportive therapy and initiation of oral cholic acid (10 mg/kg/day) and therapeutic supplementation of fat-soluble vitamins A, D, E, and K. Due to the advanced stage of liver disease, suspected cirrhosis or extensive fibrosis based on clinical and ultrasound findings, liver transplantation was advised as the definitive treatment.

At the three-month follow-up, the child continued oral cholic acid and fat-soluble vitamins. His weight had improved (specific value not recorded), his activity levels had increased, and his coagulation parameters had normalised with an INR of 1.1. Liver enzyme levels had decreased (AST 55 U/L, ALT 42 U/L), and there had been no recurrence of bleeding or seizures. Planning for liver transplantation was ongoing, although feasibility remained a significant concern given the limitations of low-resource settings.

DISCUSSION

Congenital Bile Acid Synthesis Defects (CBASDs) are a rare group of inborn errors of metabolism with an estimated prevalence of fewer than 1 per million people, accounting for a significant proportion of unexplained neonatal cholestasis [1]. CBASD type 1, caused by mutations in the HSD3B7 gene, is the most reported subtype [2]. The defective enzyme, 3β-hydroxy-Δ^5-C27-steroid oxidoreductase, encoded by HSD3B7, impairs the second step in bile acid synthesis, resulting in the accumulation of hepatotoxic intermediates and the absence of primary bile acids such as cholic acid and chenodeoxycholic acid [3].

The presented case of a 6.5-year-old boy reflects the severe and late-stage complications of untreated CBASD type 1. Typically,

this disorder presents in infancy with cholestasis, jaundice, hepatosplenomegaly, and failure to thrive, features that may have been seen in the deceased sibling. In contrast, late presentation, as in this case, may manifest with decompensated liver disease, neurological deficits, and life-threatening consequences of chronic fat-soluble vitamin deficiency—especially vitamin K deficiency leading to severe coagulopathy [4].

The differential diagnosis for cholestasis with coagulopathy and neurological findings includes other bile acid synthesis defects (e.g., AKR1D1 deficiency), Progressive Familial Intrahepatic Cholestasis (PFIC), and metabolic disorders such as tyrosinaemia type 1 [5]. A key diagnostic feature of BASD types 1 and 2 is a normal or low Gamma-Glutamyl Transferase (GGT) level in the presence of cholestasis, which helps distinguish them from conditions like biliary atresia, PFIC type 3, and Alagille syndrome that typically present with elevated GGT [6]. A definitive diagnosis requires urinary bile acid profiling using mass spectrometry (such as fast atom bombardment or gas chromatography methods) to identify abnormal bile acid metabolites, followed by genetic confirmation of HSD3B7 mutations [7].

The correlation between impaired bile acid synthesis and progressive liver disease was first demonstrated by Setchell KDR and Heubi JE [1]. Later, Clayton PT emphasised the efficacy of primary bile acid replacement therapy, including oral cholic acid, in restoring liver function, preventing disease progression, and improving the absorption of fat-soluble vitamins [2]. Subramaniam P et al., further supported the benefits of early intervention [3]. In a larger study, long-term cholic acid therapy was shown to be both safe and effective in children with HSD3B7 deficiency, often avoiding the need for liver transplantation when started early [8].

Although the child in this report had advanced disease at presentation, the rapid improvement in coagulation status and overall clinical recovery following supportive care and the initiation of cholic acid therapy highlights the therapeutic value of even delayed intervention. However, likely established cirrhosis and neurological impairment necessitate consideration of liver transplantation as definitive treatment [9].

The clinical presentation of $HSD3B7$ deficiency (CBASD type 1) is highly heterogeneous, often leading to significant diagnostic delays, a challenge mirrored by the index case. Several recent reports highlight this variability, particularly in older children, where the findings deviate from classic neonatal cholestasis. Late presentation with severe coagulopathy and multi-organ involvement is a recurring theme. For instance, Morrissey M and Krada P described an 11-year-old male with $HSD3B7$ deficiency who initially presented to the haematology service with recurrent epistaxis and prolonged INR/Partial Thromboplastin Time (PTT) due to severe vitamin K deficiency, with the underlying liver enzyme abnormalities only pursued after coagulation normalised [10]. Similarly, Elham Mahjoub et al. (2023) documented a 7-year-old girl whose late diagnosis was secured via genetic sequencing after years of non-specific complaints, including failure to thrive, muscle weakness, renal microcalculi, and nosebleeds, all complications stemming from prolonged fat-soluble vitamin malabsorption [11]. These cases underscore that severe, extra-hepatic complications can be the primary presentation, often leading to extensive misguided workups.

Furthermore, the disease can manifest as acute or recurrent decompensation. Yaja C et al., reported a young child with an $HSD3B7$ mutation presenting with recurrent episodes of acute liver failure, where the metabolic etiology was initially missed during the first presentation despite supportive care successfully resolving the coagulopathy and encephalopathy [12]. This demonstrates the necessity of a low threshold for metabolic screening in any child with unexplained recurrent liver failure. Lastly, some of the most atypical reports show that the hallmark of the disease, cholestasis, may be absent. Bossi G et al., described a child with $HSD3B7$ deficiency presenting with failure to thrive and hepatomegaly but lacking any biochemical evidence of cholestasis [13]. This highlights a crucial diagnostic pitfall, emphasising that advanced metabolic screening (e.g., urinary bile acid profiling) is paramount in children with compatible systemic features, even when traditional cholestatic markers are absent.

This case also underscores the diagnostic challenges in low-resource settings, where metabolic investigations and access to specific therapies such as bile acid supplementation and liver transplantation may be limited.

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