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Case Report

Biochemistry Section

Congenital Defect in Primary Bile Acid Biosynthesis: A Case Study of Clinical Spectrum and Long-term Prognosis

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ABSTRACT

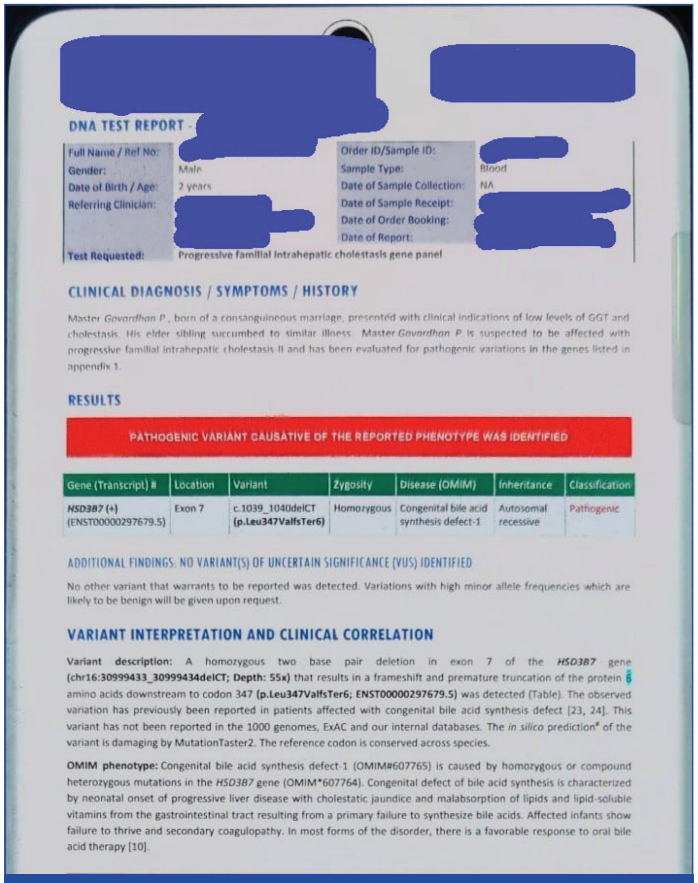
Congenital Bile Acid Synthesis defect type 1 (CBAS1), caused by pathogenic variants in *HSD3B7 gene*, is the most common inborn error of primary bile acid synthesis. Deficiency of 3β-hydroxy-Δ-C-steroid oxidoreductase results in accumulation of hepatotoxic intermediates and near absence of Cholic Acid (CA) and Chenodeoxycholic Acid (CDCA). Clinically, infants typically present with cholestasis, fat-soluble vitamin deficiency, coagulopathy, and developmental delay. Importantly, CBAS1 is a treatable disorder; early initiation of oral bile acid therapy can restore bile flow and prevent progression to end-stage liver disease. A six-year-old boy with genetically confirmed CBAS1 (homozygous exon 7 *HSD3B7* deletion), presented with limb swellings, mucosal bleeding, ecchymoses, and profound pallor. The clinical spectrum included global developmental delay, seizure disorder, and multiple hospitalisations for complications associated with cholestasis. His laboratory evaluation showed hyperbilirubinaemia, hypoalbuminaemia, prolonged coagulation profile, and severe microcytic hypochromic anaemia (haemoglobin ~1.6 g/dL), a finding rarely reported in CBAS1. Child was managed with blood transfusion, vitamin K, fat-soluble vitamin supplementation, antibiotics, and supportive care. CBAS1 is a rare but treatable disorder. Early recognition, newborn screening in high-risk families, and timely CA therapy are essential to improve survival, preserve native liver function, and reduce transplant burden.

Keywords: Anaemia, Cholestasis, Cholic acid, Congenital disorders, Developmental delay, Hyperbilirubinaemia

CASE REPORT

A six-year-old boy presented in paediatric department with progressive limb swelling, mucosal bleeding, and profound pallor. The child had global developmental delay and was unable to sit even with support since six months of age. The milestone of standing was also not achieved at 12 months of age. Due to persistent motor delay, physiotherapy was started, and the child continued to receive regular rehabilitation therapy. A seizure disorder was diagnosed at three months following evaluation for incessant crying, which revealed an intracranial haemorrhage, and the child has been on antiepileptic therapy since then and had no episodes lately.

The history also includes pyelonephritis, circumcision with left inguinal herniotomy, and multiple hospitalisations due to complications of neonatal cholestasis. Antenatal history was uneventful and mother has no co-morbidity. The diagnosis of CBAS1 was established at age two during family evaluation after a sibling's death at two years of age from cholestatic liver disease and as history of consanguinity in parent was noted. [Table/Fig-1] presents the DNA test report of the child at 2 years of age.



DNA TEST REPORT

Full Name / Ref No:	[redacted]	Order ID/Sample ID:	[redacted]
Gender:	Male	Sample Type:	Blood
Date of Birth / Age:	2 years	Date of Sample Collection:	NA
Referring Clinician:	[redacted]	Date of Sample Receipt:	
		Date of Order Booking:	[redacted]
		Date of Report:	
Test Requested:	Progressive familial intrahepatic cholestasis gene panel		

CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

Master *Govardhan P.*, born of a consanguineous marriage, presented with clinical indications of low levels of GGT and cholestasis. His elder sibling succumbed to similar illness. Master *Govardhan P.* is suspected to be affected with progressive familial intrahepatic cholestasis II and has been evaluated for pathogenic variations in the genes listed in appendix 1.

RESULTS

PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS IDENTIFIED

Gene (Transcript) #	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
HSD3B7 (+) (ENST00000297679.5)	Exon 7	c.1039_1040delCT (p.Leu347ValfsTer6)	Homozygous	Congenital bile acid synthesis defect-1	Autosomal recessive	Pathogenic

ADDITIONAL FINDINGS: NO VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

No other variant that warrants to be reported was detected. Variations with high minor allele frequencies which are likely to be benign will be given upon request.

VARIANT INTERPRETATION AND CLINICAL CORRELATION

Variant description: A homozygous two base pair deletion in exon 7 of the *HSD3B7* gene **(chr16:30999433_30999434delCT; Depth: 55x)** that results in a frameshift and premature truncation of the protein 6 amino acids downstream to codon 347 **(p.Leu347ValfsTer6; ENST00000297679.5)** was detected (Table). The observed variation has previously been reported in patients affected with congenital bile acid synthesis defect [23, 24]. This variant has not been reported in the 1000 genomes, ExAC and our internal databases. The *in silico* prediction# of the variant is damaging by MutationTaster2. The reference codon is conserved across species.

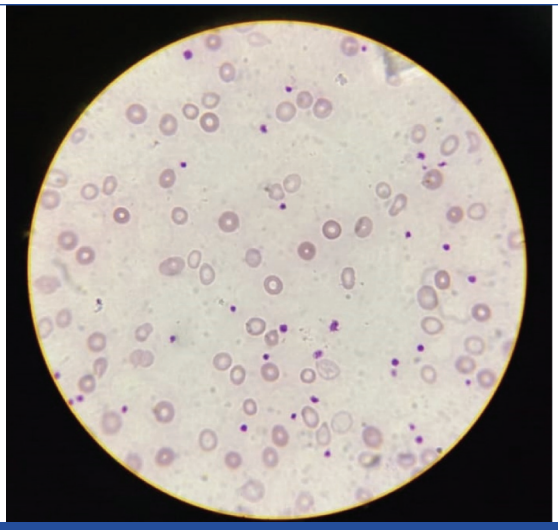
OMIM phenotype: Congenital bile acid synthesis defect-1 (OMIM#607765) is caused by homozygous or compound heterozygous mutations in the *HSD3B7* gene (OMIM*607764). Congenital defect of bile acid synthesis is characterized by neonatal onset of progressive liver disease with cholestatic jaundice and malabsorption of lipids and lipid-soluble vitamins from the gastrointestinal tract resulting from a primary failure to synthesize bile acids. Affected infants show failure to thrive and secondary coagulopathy. In most forms of the disorder, there is a favorable response to oral bile acid therapy [10].

[Table/Fig-1]: DNA test report of the child at 2 years of age.

On admission, child was drowsy but afebrile. Parents noted multiple spontaneous bluish skin patches increasing in size and number in the arm. A gradually enlarging, tender swelling of the right arm developed over a few days, restricting limb movement, suggestive of a haematoma. There were no episodes of gum bleeding during feeding, epistaxis, haematemesis, or melena. Appetite was poor with recent weight loss. Systemic examination revealed pedal oedema. Abdomen was soft with hepatosplenomegaly. Cardiovascular and respiratory examinations were unremarkable. Neurological examination showed reduced tone in both the limbs of both sides without focal neurological deficits. He was formula fed because of cow's milk protein allergy and had incomplete immunisations.

Laboratory investigations revealed elevated total bilirubin (8.6 mg/dL) with predominantly direct hyperbilirubinaemia (direct bilirubin 6.1 mg/dL), hypoalbuminaemia (2.4 g/dL), and low globulin levels (1.9 g/dL) [Table/Fig-2]. Coagulation parameters were prolonged {Prothrombin Time (PT) 21.8 seconds; International Normalised Ratio (INR) 1.9}, indicating impaired hepatic synthetic function. Renal function tests were within normal limits.

Haematological evaluation showed severe microcytic hypochromic anaemia (haemoglobin≈1.6 g/dL), along with neutrophilic leukocytosis and packed cell volume of 6.2% (reference: 30-



[Table/Fig-2]: Microcytic hypochromic anaemia- (Leishman stain – oil immersion magnification-haematological picture).

40%). The RBC count was 1.0 million/cumm (reference: 3.5-5.0 million/cumm). Total leucocyte count was elevated at 19.45×10^3/cumm (reference: 4-11×10^3/cumm), with differential count showing neutrophils 62.5% (reference: 40-70%), lymphocytes 32% (reference: 20-40%), monocytes 0.8% (reference: 2-8%), and eosinophils 0.1% (reference: 1-4%). Platelet count was 2.33×10^3/cumm (reference: 1.5-4.5×10^5/cumm). Red cell indices were suggestive of microcytic hypochromic anaemia, with Mean Corpuscular Volume (MCV) 61.5 fL (reference: 75-95 fL), Mean Corpuscular Hemoglobin (MCH) 15.7 pg (reference: 24-30 pg), and Mean Corpuscular Hemoglobin Concentration (MCHC) 25.8% (reference: 32-36%). Given the severity of anaemia, further evaluation was undertaken. Haemolysis was assessed with reticulocyte count 13,000/µL (reference: 25,000-75,000/µL), indirect bilirubin fraction 2.5 mg/dL; findings were not suggestive of active haemolysis. Iron studies demonstrated reduced serum iron of 32 µg/dL (reference: 50-120 µg/dL) and serum ferritin of 26 ng/mL (reference: 12-200 ng/mL). The Total Iron-Binding Capacity (TIBC) was elevated at 224 µg/dL (reference: 250-400 µg/dL), with a transferrin saturation of 4.28% (reference: 20-45%). Nutritional assessment was also undertaken to evaluate possible micronutrient deficiencies as the child was underweight 8.1 kg and emaciated and was advised high calorie and protein rich diet.

The overall biochemical profile of conjugated hyperbilirubinaemia, coagulopathy, and impaired hepatic synthesis, along with confirmatory metabolic and genetic evaluation, supported the diagnosis of CBAS1, also known as HSD3B7 deficiency.

The differential diagnosis of CBAS1 includes other inborn errors of bile acid synthesis, progressive familial intrahepatic cholestasis (PFIC types 1 and 2), and bile acid transport defects. Additional considerations include Alagille syndrome, metabolic disorders such as galactosaemia, tyrosinaemia, and α-1 antitrypsin deficiency, as well as endocrine and infectious causes of neonatal cholestasis. Viral serology was negative for HAV IgM, HEV IgM, HBsAg, and anti-HCV, effectively ruling out viral hepatitis.

The child was started on intravenous fluids, and subsequently, two units of whole blood were transfused, along with administration of vitamin K and comprehensive supplementation of fat-soluble vitamins (A, D, E, and K). The child was treated with intravenous ceftriaxone (50 mg/kg/day) for seven days and paracetamol (10-15 mg/kg/dose every 6 hours as needed). Orthopaedic consultation advised conservative management, as no fracture, compartment syndrome, or neurovascular compromise was identified. The affected limb was immobilised and elevated, with appropriate analgesia and local supportive measures, while intramuscular interventions were avoided. Ongoing monitoring and correction of coagulopathy and nutritional deficiencies were undertaken to facilitate resolution. Antiepileptic therapy with levetiracetam (20 mg/kg/day in two divided doses) was continued, along with nutritional support, including a high-calorie diet and fat-soluble vitamin supplementation, throughout hospitalisation. Importantly, the child was not on CA therapy despite a confirmed diagnosis of CBAS1. The absence of bile acid replacement likely contributed to persistent cholestasis, progressive hepatic dysfunction, fat-soluble vitamin deficiency, coagulopathy, growth failure, and severe malnutrition. Early initiation of CA is known to suppress the synthesis of hepatotoxic bile acid intermediates and improve bile flow; therefore, delayed or absent treatment may result in worsening liver injury and systemic complications.

On follow-up, the six-year-old child with CBAS1 due to pathogenic variants in *HSD3B7* demonstrated partial clinical improvement with nutritional optimisation and supportive care, including an increase in haemoglobin from 1.6 g/dL at presentation to 7.3 g/dL on follow-up. Following supportive management with vitamin K, blood transfusion, and fat-soluble vitamin supplementation, the child showed gradual clinical improvement. For the developmental delay the child is undergoing regular physiotherapy but the milestones have not yet been achieved.

Sensorium improved, and the right arm haematoma decreased in size and tenderness. Pedal oedema subsided and appetite improved. Serial laboratory parameters showed a decline in total bilirubin from 8.6 to 3.2 mg/dL (direct bilirubin from 6.1 to 2.0 mg/dL), rise in serum albumin from 2.4 to 3.3 g/dL, correction of PT from 21.8 to 13.9 seconds with INR improving from 1.9 to 1.2 , indicating recovery of hepatic synthetic function and stabilisation of bleeding manifestations, emphasising the need for close long-term monitoring to assess disease progression and prevent complications.

DISCUSSION

HSD3B7 deficiency, or CBAS1, is a rare autosomal-recessive disorder of the classic bile acid synthetic pathway that disrupts hepatic and systemic metabolic homeostasis. Bile acids, the end products of cholesterol metabolism, are essential for bile flow, lipid digestion, absorption of fat-soluble vitamins (A, D, E, K), and metabolic regulation through nuclear receptors such as FXR. Loss of 3β-hydroxy-Δ-C27-steroid oxidoreductase (3β-HSD7) activity results in deficiency of the primary bile acids, CA and CDCA, with accumulation of hepatotoxic intermediates. This leads to cholestasis, impaired bile flow, coagulopathy, rickets, growth failure, and progressive liver injury [1].

Importantly, CBAS1 is a treatable condition; early bile acid replacement suppresses toxic metabolites, restores enterohepatic circulation, and prevents progression to cirrhosis [2,3]. Clinically, CBAS1 presents in infancy with prolonged jaundice, hepatomegaly, steatorrhoea, and fat-soluble vitamin deficiencies, predisposing to bleeding diathesis and bone disease. Untreated disease progresses to fibrosis, cirrhosis, and early mortality. With an estimated global incidence of 1-9 per million, it is the most common CBAS defect [2,4]. Early recognition and therapy are therefore critical. Our patient, homozygous for an exon 7 *HSD3B7* deletion, demonstrated features of untreated or late-recognised CBAS1, including chronic cholestasis, hypoalbuminaemia, prolonged coagulation, growth retardation, neurodevelopmental delay, and multisystem involvement. A notable and unusual feature was profound microcytic iron-deficiency anaemia (Hb 1.6 g/dL, MCV 52 fL, MCH 14 pg), which is rarely described in CBAS1 [4,5]. Likely contributors include malnutrition, impaired nutrient absorption, chronic inflammation, and blood loss from vitamin K–related coagulopathy. This finding expands the recognised systemic nutritional impact of advanced cholestatic disease.

Diagnosis relies on biochemical and molecular testing. Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) bile acid profiling demonstrates markedly reduced Cholic Acid (CA) and Chenodeoxycholic Acid (CDCA) with elevated atypical intermediates

characteristic of HSD3B7 deficiency. Definitive confirmation is achieved through genetic testing using targeted next-generation sequencing with copy-number analysis. In resource-limited settings, clinical red flags-neonatal cholestasis with fat-soluble vitamin deficiency and coagulopathy-should prompt early empiric CA therapy while awaiting confirmation [4,5].

Management includes both acute stabilisation and long-term metabolic correction. Immediate priorities are treatment of coagulopathy (vitamin K±plasma), transfusion for severe anaemia, and nutritional rehabilitation with energy-dense feeds and aggressive fat-soluble vitamin supplementation. Disease-specific therapy consists of oral CA (6-13 mg/kg/day), titrated to clinical and biochemical response. CA is preferred due to effective FXR activation and a favourable safety profile, while CDCA is used cautiously because of potential hepatotoxicity. Regular monitoring includes liver function, coagulation parameters, vitamin status, growth, and neurodevelopment [6].

Outcomes depend strongly on early diagnosis. Treatment initiated in infancy can normalise liver biochemistry and prevent fibrosis, whereas delayed diagnosis- as in this case- permits only partial recovery and carries a higher risk of progressive liver disease. This case highlights three lessons: CBAS1 is a treatable metabolic liver disease; prolonged untreated cholestasis leads to multisystem and haematologic complications; and improved access to bile acid profiling, genetic testing, and early screening can reduce diagnostic delay and improve prognosis [7].

Another case report describes an infant with HSD3B7-related bile acid synthesis defect in whom early CA therapy led to normalisation of clinical features and liver function over follow-up [8]. In a recent case report of HSD3B7 mutation presenting with recurrent liver failure, liver function initially improved with supportive care, but without early targeted bile acid therapy the child experienced repeated decompensation episodes before genetic diagnosis was made. Although the report does not specifically document long-term outcomes without treatment, it highlights that late or absent bile acid therapy is detrimental to disease control and overall prognosis [9]. A large study of 39 genetically confirmed HSD3B7-deficient patients found that those treated with primary bile acids (CA or CDCA) had improved liver biomarkers and decreased toxic bile acid metabolites, while untreated patients often developed more severe liver disease, fibrosis, or required transplantation, indicating bile acid replacement drastically alters the disease course [9].

CONCLUSION(S)

The CBAS1 is a rare but treatable inherited metabolic liver disorder caused by pathogenic variants in *HSD3B7*. This case illustrates the severe multisystem consequences of delayed diagnosis-progressive cholestasis, coagulopathy, fat-soluble vitamin deficiency, neurodevelopmental impairment and profound microcytic anaemia. Timely initiation of oral CA can transform the disease course: it restores bile flow, corrects nutritional deficiencies, prevents progression to cirrhosis and substantially reduces the need for liver transplantation. These outcomes highlight the urgency of greater clinical awareness, improved access to bile-acid profiling and genetic testing, and consideration of newborn or targeted family screening in high-risk populations to enable early, life-saving therapy.

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