Primary bile acid disorders: A largely unknown group of rare genetic diseases in newborns

MINIREVIEW

Abstract
Primary bile acid disorders (BASD) in newborns are rarely found with a prevalence of 1-9/1,000,000 and include 1-2 % of all cases with neonatal cholestasis. Causes are different gene defects, which lead to liver enzyme defects, which play a major role in both cholic acid pathways, the classical with production of cholic acid and the alternative one with chenodeoxycholic acid. They are found in both genders in the same distribution. Early diagnosis is very important to introduce a bile acid replacement therapy as soon as possible as the treatment of choice to date. Diagnosis will be confirmed by molecular trsting, liver biopsy and different forms of mass spectrometry methods. Differential diagnosis includes progressive familial intrahepatic cholestasis, neonatal hepatitis and biliary atresia. Further gene therapy approaches must be developed, like CRISP Cas9 technology, to repair the spontaneous point mutations on DNA of these patients to cure and not to treat them the whole life finally.

Keywords
BASD-children-cholestasis-bile acid

Introduction
Inherited defects in bile acid synthesis are rare genetic disorders that can manifest as neonatal cholestasis, neurological issues, or deficiencies in fat-soluble vitamins (1-67). There are nine recognized defects in bile acid synthesis, including deficiencies in oxysterol 7α-hydroxylase, Δ4-3-oxosteroid-5β-reductase, 3β-hydroxy-Δ5-C27-steroid dehydrogenase, cerebrotendinousxanthomatosis (sterol 27-hydroxylase deficiency), α-methylacyl-CoA racemase, and Zellweger syndrome (cerebrohepatorenal syndrome). These conditions are characterized by the inability to produce normal bile acids and an accumulation of abnormal bile acids and bile acid intermediates. Individuals with inherited defects in bile acid synthesis typically have normal or low serum bile acid levels, normal γ-glutamyl transpeptidase levels, and no itching. Failure to diagnose these conditions can lead to liver failure or chronic liver disease. Early identification can lead to significant clinical improvement with oral bile acid therapy. Inborn errors of bile acid synthesis are rare genetic disorders that account for 1–2% of neonatal cholestasis cases, characterized by conjugated or direct hyperbilirubinemia in early infancy. Most patients with inborn errors of bile acid synthesis respond well to oral bile acid therapy. Cholic acid and chenodeoxycholic acid, the primary bile acids, are produced through a series of enzymatic modifications to cholesterol involving at least 14 enzymes, multiple subcellular compartments, and two complementary chemical pathways. The main route for bile acid synthesis is the classic 'neutral' pathway, which produces both cholic acid and chenodeoxycholic acid in equal amounts. The rate-limiting step in this pathway is the modification of the steroid nucleus, catalyzed by cholesterol 7α-hydroxylase. The farnesoid X receptor (FXR) regulates CYP7A1 through bile acids. FXR is a ligand-activated transcription factor that acts on target genes as a monomer or heterodimer with RXR. Bile acids are natural ligands for FXR, with chenodeoxycholic acid being the most potent activator. FXR activation leads to upregulation of SHP, which inhibits LRH-1's ability to activate CYP7A1. An alternative 'acidic' pathway involves C27-hydroxylation of cholesterol followed by C7α-hydroxylation. Side-chain modification occurs after steroid nucleus modification in mitochondria and peroxisomes. The final step is the conjugation of cholic acid and chenodeoxycholic acid to taurine or glycine. Deficiencies in genes encoding enzymes involved in bile acid synthesis pathways can cause liver disease by reducing canalicular bile acid secretion and accumulating potentially hepatotoxic bile acid precursors. These disruptions typically present as cholestasis in infants, resembling other neonatal liver diseases like biliary atresia.

Classical and alternative bile acid pathways

Bile acid synthesis involves two pathways: the classic 'neutral' pathway and the alternative 'acidic' pathway. In the classic pathway, cholesterol is converted to 7α-hydroxycholesterol by cholesterol 7α-hydroxylase, which is the rate-limiting step. Enzymes like HSD3B7, sterol 12a-hydroxylase, AKR1D1, and 3α-hydroxysteroid dehydrogenase then modify the steroid nucleus and side chain to produce cholic acid and chenodeoxycholic acid. In the alternative pathway, cholesterol is converted to 3β-hydroxy-5-cholestanoic acid by CYP27A1, followed by conversion to 3β, 7α-dihydroxy-5-cholestenoic acid by CYP7B.

Enzyme defect	Gene encoding the affected enzyme (reference)	Urine bileacidprofile	serumbileacidprofile	Clinical features
Oxysterol 7α-hydroxylasedeficiency	*CYP7B*[84]	↑ Sulfate and glycosulfate conjugates of 3β-δ5-monohydroxy bile acids Absence of primary bile acids	Extremely high levels of bile acids, primarily 3β-δ5-monohydroxy bile acids	Neonatal hepatitis (single reported case; unrecognized cases could be due to prenatal or early-postnatal death)
Δ^4-3-oxosteroid-5β-reductase deficiency	*AKR1D1(SRD5B1)*	↑ 3-oxo-δ4 bile acids ↑ Allo bile acids ↓ Primary bile acids	↑ 3-oxo-δ4 bile acids ↑ Allo bile acids ↓ Primary bile acids	Neonatal hepatitis with rapid progression to liver failure Neonatal hemochromatosis
3β-hydroxy-Δ^5-C_{27}-steroid dehydrogenase deficiency	*HSD3B7*	↑ Dihydroxy & trihydroxy cholenoic acids ↓ Primary bile acids	↓ or absence of primary bile acids	Neonatal hepatitis Late-onset liver disease Malabsorption
Cerebrotendinousxanthomatosis (sterol 27-hydroxylase deficiency)	*CYP27A1*	↑ Plasma cholestanol: cholesterolratio	↑ Bilealcoholglucuronides	Progressive neurologic dysfunction in 2nd–3rddecade of life Chronic diarrhea Bilateral juvenile cataracts Neonatal cholestasis
Alpha methylacyl-CoA racemase deficiency	*AMACR* gene on chromosome 5p13.2-q11.1[71]	↑ C27 trihydroxycholestanoic and pristanic acid ↓ Primary bile acids	↑ C27 trihydroxycholestanoic and pristanic acid ↓ Primary bile acids Normal long-chain fatty acids and phytanic acid	Adult onset peripheral neuropathy Neonatal cholestasis with considerable fat-soluble-vitamin deficiency
Zellweger syndrome (cerebrohepatorenalsyndrome)	12 *PEX* gene mutations; *PEX1* mutations are the most common.	Atypical monohydroxy, dihydroxy and trihydroxy C27 bile acids ↓ Primary bile acids	↑ Long-chain fatty acids ↑ Cholestanoic and pipecolic acid ↑ C29 dicarboxylic acid ↓ Primary bile acids	Craniofacial abnormalities Neuronal migration defects Polycystic kidneys

Table 1

Genetic, biochemical and clinical features of bile acid synthesis defects in the newborn

Discussion

The prevalence of bile acid synthesis (BAS) defects is estimated to be around 1-9 per 1,000,000, excluding cerebrotendinousxanthomatosis (1-67). Inborn errors in BAS likely contribute to 1-2% of unexplained liver diseases in infants, children, and adolescents (3,7,9,11,23). The age at diagnosis varies, with presentations in infancy, childhood, or adulthood. Infants and children may experience complications due to fat malabsorption and vitamin deficiencies, leading to conditions like rickets, bleeding diathesis, neuroaxonal dystrophy, and night blindness (1,5,7,9,14,24).There are seven known inborn errors of BAS causing liver cholestasis, including 3-beta-hydroxy-C27-steroid oxidoreductase deficiency (BAS defect type 1), delta4-3-oxosteriod-5-beta reductase deficiency (BAS defect type 2), oxysterol 7alpha-hydroxylase deficiency (BAS defect type 3), 2-methylacyl-CoA racemase deficiency (BAS defect type 4), trihydroxycholestanoic acid (THCA) CoA oxidase deficiency, bile acid CoA ligase deficiency, and defective amidation, along with cerebrotendinousxanthomatosis (16,23,24,37,68). Cholesterol 7alpha-hydroxylase deficiency leads to hypercholesterolemia without liver cholestasis.Diagnosis is based on hepatic enzyme and bilirubin profiles, along with urine, serum, and bile analysis using liquid secondary ionization mass spectrometry (LSIMS) and gas chromatography-mass spectrometry (GC-MS) (1-67). Differential diagnoses include neonatal cholestasis, unexplained vitamin deficiencies, liver diseases, and neurologic conditions. Early diagnosis is crucial for initiating therapy before significant morbidity occurs.BAS defects share key clinical features, including normal or low total serum bile acid concentrations, minimally elevated γ-glutamyl transpeptidase (GGTP) levels, and absence of pruritus. A high index of suspicion is necessary to prevent overlooking these rare disorders, as they can mimic other liver conditions (75,76). Early recognition and treatment offer an excellent prognosis, as many BAS defects are treatable.Treatment involves primary bile acid therapy, with cholic acid, ursodeoxycholic acid (UDCA), and glycocholic acid being used based on the specific defect (23,33,41,42). Prognosis varies depending on the type of defect, with untreated cases leading to progressive liver disease or serious complications (34,37,43,67). Early treatment can lead to long-term survival and clinical improvement (23,55,61).

Conclusion

BAS defects represent a rare significant group of liver disorders withsimilar presentations to other liver diseases, emphasizing the need for a high level of suspicion for accurate diagnosis. Early detection and treatment are essential for favorable outcomes in these rare conditions.

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