

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

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 that~~ 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 These gene defects~~ are ~~found-detected~~ in both genders in the same ~~distributionrate~~. Early diagnosis is very important to introduce a bile acid replacement therapy as soon as possible as the treatment of choice to date. ~~The d~~Diagnosis ~~will-must~~ be confirmed by molecular ~~trstingtesting~~, 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 CRISPR 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 uncommon genetic disorders that can manifest as neonatal cholestasis, neurological problems, or deficiencies in fat-soluble vitamins. There are nine recognized defects in bile acid synthesis, including deficiencies in oxysterol 7 α -hydroxylase, Δ 4-3-oxosteroid-5 β -reductase, 3 β -hydroxy- Δ 5-C27-steroid dehydrogenase, cerebrotendinous xanthomatosis (sterol 27-hydroxylase deficiency), α -methylacyl-CoA racemase, and Zellweger syndrome (cerebrohepato-renal syndrome). These conditions are characterized by ~~the inability-failure~~ 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 present with the characteristic features ~~of-such as~~ normal or low serum bile acid levels, normal γ -glutamyl transpeptidase levels, and the absence of itching. Failure to diagnose any of these conditions can lead to liver failure or progressive chronic liver disease. If identified early, many patients can have a significant clinical improvement with oral bile acid therapy. Inborn ~~errors-defects~~ of bile acid synthesis are rare genetic disorders that account for up to 1–2% of cases of neonatal cholestasis, a condition characterized by the development of conjugated or direct hyperbilirubinemia within the first few months of life. Most patients with inborn ~~errors-defects~~ 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 classic 'neutral' pathway is the main route for bile acid synthesis and produces both cholic acid and chenodeoxycholic acid in roughly equal amounts. The rate-limiting step in this pathway is the modification of the steroid nucleus, which occurs in hepatic microsomes and is catalyzed by cholesterol 7 α -hydroxylase, the product of the CYP7A1 gene. The farnesoid X receptor (FXR) plays a crucial role in regulating CYP7A1 through bile acids. FXR is a member of the superfamily of ligand-activated transcription factors that acts on target genes as both a monomer and as a heterodimer with the retinoid X receptor (RXR). Bile acids are natural ligands for FXR, with chenodeoxycholic acid being the most potent activator of human FXR. FXR activation by primary bile acids leads to the upregulation of the atypical nuclear receptor small heterodimer protein (SHP), which interacts with liver receptor homolog 1 (LRH-1) and inhibits LRH-1's ability to activate CYP7A1. LRH-1 is also crucial for SHP gene expression, as the SHP–LRH-1 complex reduces SHP expression, thereby decreasing the negative feedback signal. An alternative 'acidic' pathway has also been identified, in which the initial step is C27-hydroxylation of cholesterol by sterol 27-hydroxylase, followed by C7 α -hydroxylation by oxysterol 7 α -hydroxylase. This pathway ~~results in the ends up with~~ production of primarily chenodeoxycholic acid. In both the classic and alternative pathways, side-chain modification occurs after steroid nucleus modification and is initiated in other organelles: C27-hydroxylation takes place in mitochondria, but further side-chain modification requires functioning peroxisomes. The final step in primary bile acid synthesis is the conjugation of cholic acid and chenodeoxycholic acid to taurine or glycine. In the past 20 years, ~~deficiencies-many defects~~ have been ~~found-detected~~ in the genes encoding the multiple enzymes involved in the bile acid synthesis pathways. These defects are thought to cause liver disease ~~in-by~~ two ways. First, impaired hepatocyte production of primary bile acids reduces canalicular bile acid secretion, thereby hindering bile acid dependent bile flow. Second, potentially hepatotoxic atypical bile acid precursors accumulate in hepatocytes and cause cellular injury. These disruptions most commonly present in infants as cholestasis that can resemble other neonatal liver diseases, including biliary atresia.

Classical and alternative bile acid pathways

Bile acid synthesis occurs through two pathways: the classic 'neutral' pathway and the alternative 'acidic' pathway. In the classic 'neutral' pathway, the rate-limiting step in bile acid formation is the conversion of cholesterol to 7 α -hydroxycholesterol by cholesterol 7 α -hydroxylase. Multiple sequential steps modify both the steroid nucleus and the side chain to produce cholic acid and chenodeoxycholic acid. The main enzymes involved in this process include cholesterol 7 α -hydroxylase, 3 β -hydroxy- Δ^5 -C27-steroid dehydrogenase (encoded by HSD3B7), sterol 12 α -hydroxylase, Δ^4 -3-oxosteroid-5 β -reductase (encoded by AKR1D1 [previously known as SRD5B1]), and 3 α -hydroxysteroid dehydrogenase. A series of side-chain modifications then occurs to yield cholic and chenodeoxycholic acid. Alternatively, in the alternative 'acidic' pathway, cholesterol is converted to 3 β -hydroxy-5-cholestanic acid by sterol 27-hydroxylase (encoded by CYP27A1). This is followed by conversion to 3 β , 7 α -dihydroxy-5-cholestenic acid by oxysterol 7 α -hydroxylase (encoded by CYP7B).

| Enzyme defect | Gene encoding the affected enzyme (reference) | Urine bile acid profile | serum bile acid profile | Clinical features |
|--|--|---|---|---|
| Oxysterol 7 α -hydroxylase deficiency | <i>CYP7B1</i> | ↑ Sulfate and glycosulfate conjugates of 3 β -5 α -monohydroxy bile acids Absence of primary bile acids | Extremely high levels of bile acids, primarily 3 β -5 α -monohydroxy bile acids | Neonatal hepatitis (single reported case; unrecognized cases could be due to prenatal or early postnatal death) |
| Δ^4 -3-oxosteroid-5 β -reductase deficiency | <i>AKR1D1</i> (<i>SRD5B1</i>) | ↑ 3-oxo- β 4 bile acids ↑ Allo bile acids ↓ Primary bile acids | ↑ 3-oxo- β 4 bile acids ↑ Allo bile acids ↓ Primary bile acids | Neonatal hepatitis with rapid progression to liver failure Neonatal hemochromatosis |
| 3 β -hydroxy- Δ^5 -C27-steroid dehydrogenase deficiency | <i>HSD3B7</i> | ↑ Dihydroxy & trihydroxy cholenoic acids ↓ Primary bile acids | ↓ or absence of primary bile acids | Neonatal hepatitis Late-onset liver disease Malabsorption |
| Cerebrotendinous xanthomatosis (sterol 27-hydroxylase deficiency) | <i>CYP27A1</i> | ↑ Plasma cholestanol: cholesterol ratio | ↑ Bile alcohol glucuronides | Progressive neurologic dysfunction in 2 nd -3 rd decade of life Chronic diarrhea Bilateral juvenile cataracts Neonatal cholestasis |
| Alpha methylacyl-CoA racemase deficiency | <i>AMACR</i> gene on chromosome 5p13.2-q11.1 ²¹ | ↑ C27 trihydroxycholestanic and pristanic acid ↓ Primary bile acids | ↑ C27 trihydroxycholestanic 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 (cerebrohepato-renal syndrome) | 12 <i>PEX</i> gene mutations; <i>PEX1</i> mutations are the most common. | Atypical monohydroxy, dihydroxy and trihydroxy C27 bile acids ↓ Primary bile acids | ↑ Long-chain fatty acids ↑ Cholestanic and piperolic 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 overall prevalence of BAS defects is unknown, but estimated prevalence may be around 1-9/1,000,000, excluding cerebrotendinous xanthomatosis (1-67). Inborn **errors-defects** in BAS likely account for 1-2% of cases of unexplained liver disease in infants, children, and adolescents (1-67). The age at diagnosis varies (3,6,7,12,24). Presentation may occur in infancy with liver cholestasis, in childhood with unexplained liver disease, or in adulthood with neurologic disease (1-68). Infants and children may present with complications secondary to fat malabsorption and fat-soluble vitamin deficiency, including rickets, bleeding diathesis, neuroaxonal dystrophy, and night blindness (23,34,50,55). The seven inborn **errors-defects** of BAS leading to liver cholestasis include: 3-beta-hydroxy-C27-steroid oxidoreductase deficiency (BAS defect type 1), delta4-3-oxosteroid-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), trihydroxycholestanic acid (THCA) CoA oxidase deficiency, bile acid CoA ligase deficiency, and defective amidation, and cerebrotendinous xanthomatosis (1-67). Cholesterol 7alpha-hydroxylase deficiency leads to hypercholesterolemia without liver cholestasis. A reported defect in side chain oxidation in the alternate 25-hydroxylation pathway needs further confirmation. Diagnosis is based on serum hepatic enzyme and bilirubin profile, and analysis of urine, serum, and bile using liquid secondary ionization mass spectrometry (LSIMS) and gas chromatography-mass spectrometry (GC-MS) (1-67). The spectrum of differential diagnoses is large and includes neonatal cholestasis, unexplained fat-soluble vitamin deficiency in infancy and childhood, unexplained liver disease in infancy, childhood, and adolescence, and unexplained neurologic disease in adults (1-6, 17,34,48). Most defects can be diagnosed antenatally from embryonic tissue when there has been a previously affected sibling. Urine from suspected cases may be screened by LSIMS in the first neonatal days, and therapy initiated before significant morbidity develops. The clinical presentation, liver histopathology, diagnostic procedures, and response to therapy of each of the nine known bile acid

synthesis defects have been characterized. Bile acid synthesis defects share three important clinical features that should raise clinical suspicion for these disorders (34,56,64). First, while other cholestatic liver diseases are associated with elevated total serum bile acid concentrations, levels are generally normal or low in infants with bile acid synthesis defects. Second, the serum level of γ -glutamyl transpeptidase (GGTP), which is often elevated in patients with other cholestatic liver diseases, is characteristically normal or minimally elevated in those with inborn errors of bile acid synthesis. Third, pruritus, which is a common and distressing feature of chronic cholestasis, is usually absent in infants with bile acid synthesis defects. A high index of suspicion is required to prevent the diagnosis of a bile acid synthesis defect being overlooked, as the clinical presentations of these rare disorders can be similar to those of other causes of neonatal liver failure, neonatal cholestasis, and chronic liver disease. Importantly, many bile acid synthesis defects are readily treatable and therefore have an excellent prognosis if [recognized-diagnosed](#) and treated early in life. Moreover, these disorders represent 'accidents of nature' that have led to a more thorough understanding of basic biochemistry and biology, which can be applied to normal liver physiology and the pathophysiology of other diseases. In this Review, the current state of our understanding of bile acid synthesis defects is characterized, with emphasis on the translational and clinical investigations that have led to the emergence of this relatively new field within hepatology. It should be noted that because of the rarity of these diseases, many of the treatment recommendations mentioned are based on expert opinion rather than on firm data. Disorders in bile acid synthesis are a growing group of significant liver problems. These conditions have similar clinical presentations to other causes of neonatal cholestasis and chronic liver disease, so a high level of suspicion is necessary for diagnosis. Early detection is crucial because most of these disorders can be effectively treated with bile acid replacement therapy (1-67). The current gold standard for definitive diagnosis, FAB-MS and GC-MS analyses of serum and urine, is technically challenging and only available in a few specialized referral laboratories (2,3,8,18). Our improved understanding of these disorders demonstrates the success of combining modern biochemical and molecular techniques to uncover the causes of rare liver diseases.

Treatment is based on primary bile acid therapy (1-67). Cholic acid creates a bile acid pool that stimulates bile flow and fat absorption. It does not appear to be effective for type 3. Ursodeoxycholic acid (UDCA) therapy creates a bile acid pool but does not suppress production of toxic intermediates and is not very effective at facilitating fat absorption. Glycocholic acid therapy is the treatment of choice for bile acid CoA ligase deficiency and defective amidation, improving fat absorption and growth (24,54,55,57). Prognosis depends on the type of defect (1-68). In all defects that affect the steroid nucleus of the bile acid molecule, if untreated, progressive liver disease may develop, or reduced intestinal bile acid concentrations may lead to serious morbidity or mortality. Long-term survival and clinical improvement are possible with early treatment. In those defects that affect the side chain, liver disease is milder, and neurological disease may predominate.

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