

Pathways and Inborn Errors of Bile Acid Synthesis

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ABSTRACT

Bile acids are synthesized from cholesterol through 17 different enzymes located in different intracellular compartments of hepatocytes. Defects have been identified in the genes encoding the enzymes involved in the bile acid synthesis pathways and nine different diseases have been identified so far. In this review, four different biosynthetic pathways of bile acids together with disorders of bile acid synthesis are described. In inborn errors of bile acid synthesis clinical findings can range from liver failure to cirrhosis in infancy or progressive neuropathy in adolescence / adulthood. Laboratory analysis of urine profiling of bile acids is important in early diagnosis and early treatment.

Key words: Cholesterol, Bile acids, Bile acid synthesis, Synthesis defect

Received: 01 November 2019, Accepted: December 2019,
Published online: 30 December 2019

INTRODUCTION

Bile acids are amphipathic molecules consisting of a 24-carbon steroid core and a carboxyl side chain [1,2]. Beside their role in the cholesterol catabolism, their amphipathic natures make them highly effective detergents in the digestion and absorption of dietary lipids and lipid-soluble vitamins in the small intestine [3].

Primary bile acids are synthesized by multistep enzymatic reactions involving 17 enzymes found in

different intracellular compartments (endoplasmic reticulum, mitochondria, peroxisome, cytosol) of the hepatocytes [4]. Primary bile acids are then conjugated with glycine or taurine prior to secretion into bile [5]. Conjugation increases the water solubility of bile acids and reduces the passive diffusion during passage through the small intestine [6,7]. Conjugated bile acids are actively absorbed in the terminal ileum by specific receptors and enter to the

enterohepatic circulation where they return to the liver for further modification [3].

The synthesis of bile acid is tightly controlled to keep the bile acid concentrations at constant levels, since the accumulation of bile acids in liver and other tissues can be highly toxic [8].

In this review, four different biosynthetic pathways of bile acids together with the disorders of bile acid synthesis are described with the recent studies in the literature.

Chemical Structure and Properties of Bile Acids

Bile acids are amphipathic molecules. Hydroxyl groups are found on only one side of the molecule and give the molecule hydrophilic character. The other face does not contain hydroxyl groups and it is hydrophobic. Due to this amphipathic nature, increased bile acid concentrations decreases the surface tension. When a certain amount of bile acid is present in the water, the hydrophobic groups are clustered together and the hydrophilic groups are positioned towards the aqueous environment. Above a critical bile acid concentration, micelles are formed. This critical bile acid concentration is called critical micelle concentration (CMC). Surface tension remains constant above CMC, but increasing bile acid concentration increases the micelle concentration [9].

The hepatocytes synthesize two primary bile acids: Cholic acid (CA; 3 α , 7 α , 12 α -trihydroxy-5 β -cholanoic acid) and chenodeoxycholic acid (CDCA; 3 α , 7 α -dihydroxy-5 β -cholanoic acid). They are often present as N-aminoacyl conjugates. All of the primary bile acids are α -hydroxylated. This polar hydrophilic group is on one side of the molecule that gives characteristic surface-active properties to bile acids. Deoxycholic acid (DCA; 3 α , 12 α -dihydroxy-5 β -cholanoic acid) and lithocholic acid (LCA; 3 α -monohydroxy-5 β -cholanoic acid) are secondary bile acids, and formed by bacterial 7-dehydroxylation of CA and CDCA. Five percentage of total amount of bile acid is in the form of ursodeoxycholic acid (UDCA; 3 α , 7 β -dihydroxy-5 β -cholanoic acid) which is formed in the liver and intestines [10,11].

Enterohepatic Circulation

The enterohepatic circulation of bile acids between the liver and intestine was first described by Borelli in 1681 [12,13]. Approximately 95% of the bile acids in the pool are recovered by the enterohepatic circulation. It also serves as a feedback mechanism in

which cholesterol 7 α -hydroxylase (CYP7A1) gene transcription and bile acid synthesis are inhibited to maintain bile acid homeostasis in humans [14].

The enterohepatic circulation of bile acids mainly consists of biosynthesis, secretion and reabsorption. After their synthesis from cholesterol by a series of enzymatic reactions in the liver, most of the bile acids stored in the gall bladder. By the stimulation of food intake, bile acids are released into the intestines through the bile duct and metabolized to secondary bile acids by intestinal bacterial flora [15]. Unconjugated bile acids are removed by passive diffusion in the jejunum and colon, while the conjugated bile acids are taken up into enterocytes by the apical sodium-dependent bile acid carrier (ASBT). In total, 95% of bile acids are reabsorbed by enterocytes and the remaining is excreted through the feces. This amount (5%) is compensated by de novo bile acid synthesis in the hepatocytes [16].

Pathways of Bile Acid Synthesis

The primary bile acids are synthesized from cholesterol with a complex series of reactions involving 17 different enzymes found in endoplasmic reticulum, mitochondria, cytoplasm and peroxisomes [17]. Recent studies have identified four major biosynthetic pathways of bile acids, named the Classic / Neutral pathway, the Alternative / Acidic pathway, the Yamasaki pathway and the 25-hydroxylation pathway [18,19] (Figure 1).

Cholesterol is a C27-sterol and has a double bond at position C5 (cholest-5-en-3 β -ol). Cholesterol is converted into primary bile acids CA (3 α , 7 α , 12 α -trihydroxy-5 β -cholanoic acid) and CDCA (3 α , 7 α -dihydroxy-5 β -cholanoic acid). One hydroxyl group (at C7 α position) and two hydroxyl groups (at C7 α and C12 α positions) are added for the synthesis of CDCA and CA, respectively. The double bond at the 5-position is reduced; the 3 β -hydroxyl group is converted to a 3 α -hydroxyl group. The aliphatic side chain is oxidized to a carboxyl group and the structure is three carbon atoms shortened resulting in C24-cholanoic acid formation [19].

1. Classical / Neutral Pathway:

The classical or neutral pathway is the most important biosynthetic pathway responsible for the production of 90% of the total amount of bile acids [20]. It is named as neutral pathway because the intermediate metabolites are neutral sterols. This pathway is only in the liver and synthesizes two primary bile

acids, CA (trihydroxy-bile acid with hydroxyl groups at C3, C7 and C12) and CDCA (dihydroxy-bile acid with hydroxyl groups at C3 and C7) [21,22]. CA and CDCA are synthesized at almost equal amounts in this pathway [23,24].

The classical pathway of bile acid synthesis begins with the rate-limiting enzyme cholesterol 7 α -hydroxylase (CYP7A1). The reaction of CYP7A1 produces 7 α -hydroxycholesterol which is converted to 7 α -hydroxy-4-cholesten-3-one. 7 α -hydroxy-4-cholesten-3-one is a common precursor of CA and CDCA which are synthesized in the subsequent reaction steps. It is also called C4 and currently used as a biomarker in determining the rate of bile acid synthesis. CA is formed from C4 by the action of sterol 12 α -hydroxylase (CYP8B1), whereas CDCA is formed in the absence of CYP8B1. The ratio of 12 α -hydroxylated bile acids (CA and DCA) to 12 α -non-hydroxylated bile acids (CDCA and LCA) in the bile acid pool is determined by the CYP8B1. Subsequently, steroid side chain oxidation reactions take place by mitochondrial enzyme sterol 27-hydroxylase (CYP27A1), and followed by the removal of the propionyl group for the formation of C24 bile acids with peroxisomal β -oxidation [14].

2. Alternative / Acidic Pathway:

In the alternative biosynthetic pathway for bile acids, side chain oxidation of cholesterol occurs before steroid ring modification [25,26]. Thus, acidic intermediate metabolites are formed and it is named as acidic pathway [25,27]. It is initiated by mitochondrial enzyme CYP27A1 which is expressed in macrophages and many other tissues [28]. Both pathways can synthesize CA and CDCA, but the alternative / acidic pathway is believed to produce mainly CDCA [29].

CYP27A1 in the inner membrane of mitochondria catalyzes the first hydroxylation reaction to convert cholesterol to 27-hydroxycholesterol (3 β -hydroxy-5-cholestenoic acid) [27,30]. The monohydroxy C-27 bile acid then undergoes hydroxylation at the C-7 position with oxysterol 7 α -hydroxylase (CYP7B1) to form 3 β , 7 α -dihydroxy-5-cholestenoic

acid [27,31]. Subsequently, 3 β -hydroxy-5-C27-steroid oxidoreductase (HSD3B7) initiates sterol nuclear modifications and the same enzymes that are used in the classical pathway complement ring structure modifications [32].

3. Yamasaki Pathway:

C24 bile acids and 3 β -hydroxy-5-cholestenoic acid in the Yamasaki pathway are formed in a similar way as in the alternative / acidic way. After this step, the hydroxylation reaction carried out by the enzyme 7 α -hydroxylase in humans produces 3 β , 7 α -dihydroxy-5-choleonoic acid. It is the CDCA precursor, and at the last step of the reactions CDCA occurs [33]. CDCA is thought to be the main product of the Yamasaki pathway in humans. The exact contribution of the Yamasaki pathway to the bile acid pool in humans has not been fully established. However, the presence of monohydroxy bile acids in fetal bile and the relatively high levels of these bile acids in meconium and amniotic fluid suggest that this pathway is at least important during development [34].

4. 25-hydroxylation Pathway:

After completion of the ring structure modifications, C24-carboxylic acid is obtained by 25-hydroxylation instead of sterol 27-hydroxylation reactions and peroxisomal β -oxidation. The formation of 3 α , 7 α , 12 α -trihydroxy-25-cholestane-5 β -24-one is catalyzed by the microsomal sterol 25-hydroxylase (CH25H). Subsequent dehydroxylation reactions producing 24-oxo-petroleum reduced to CA and acetone [33].

Bile Acid Conjugation

Primary bile acids synthesized by the enzymatic reactions in the liver, are conjugated with glycine and taurine with amidation reactions at carboxyl groups. The conjugation reaction is mediated by two enzymes: Bile acid coenzyme A synthase (BACS) and bile acid CoA-amino acid N-acyltransferase (BAAT) [12]. (Figure 1)

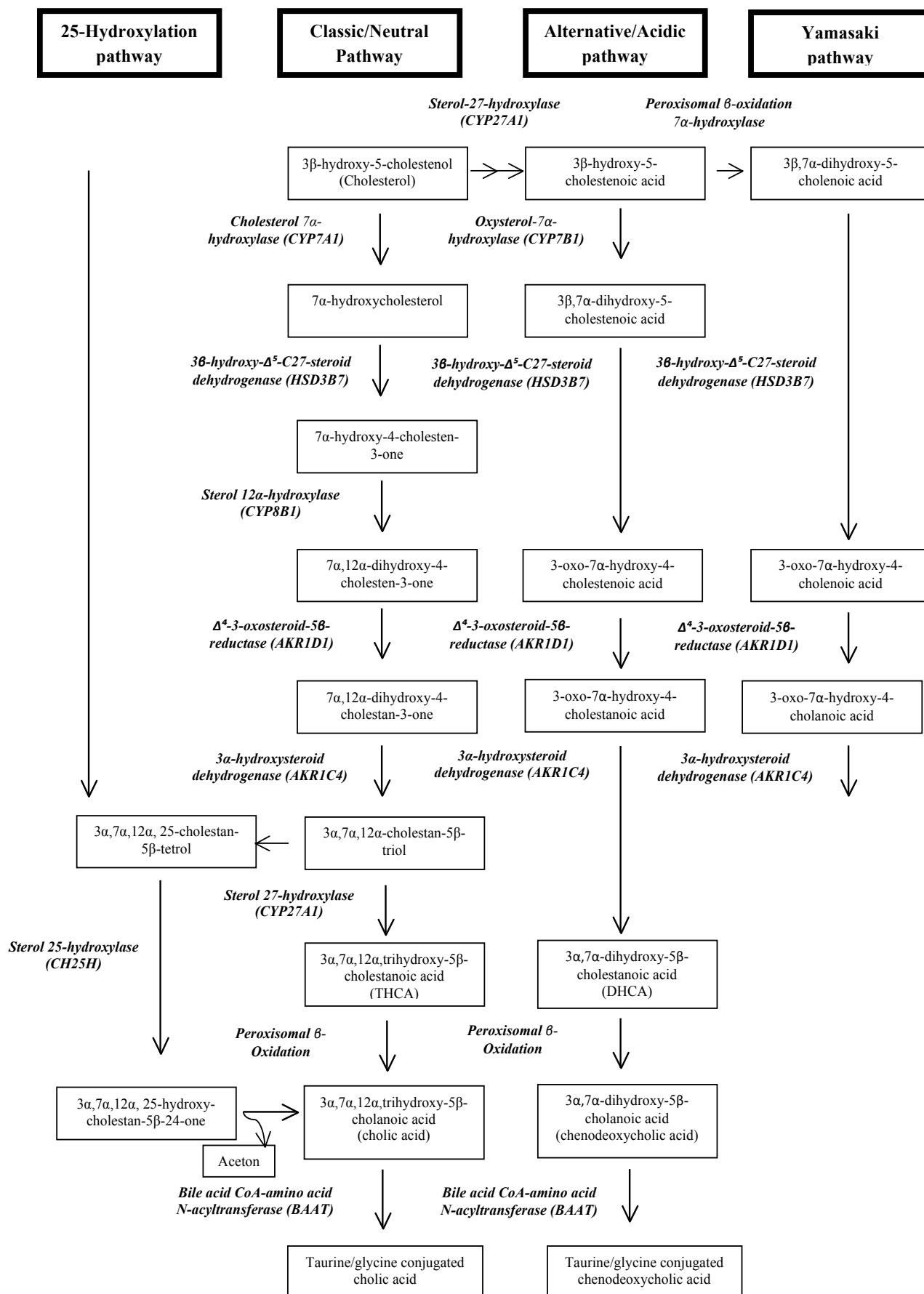


Figure 1. Biosynthetic pathways of bile acids.

Conjugation with amino acids significantly increases the polarity of the molecule [21]. Unconjugated bile acids have about 5 pKa. Conjugation reduces pKa of bile acids, increases water solubility, and reduces their ability to cross lipid membranes [10].

Defects of Bile Acid Synthesis

Inborn errors of bile acid synthesis (IEBAS) are rare genetic disorders of liver metabolism that cause chronic liver disease and fat-soluble vitamin deficiencies in childhood [35,36]. These defects are characterized by the inability to produce normal bile acids. There is accumulation of unusual bile acid and bile acid intermediates due to enzyme defects in the bile acid biosynthetic pathways from cholesterol [37,38]. Although 17 enzymes are present in the bile acid biosynthetic pathway, only 9 types of IEBAS have been identified to date [39] (Table 1).

Table 1. Inborn Errors of Bile Acid Synthesis

Disorder	OMIM	Gene	Abbreviation	Alternative name	Affected Protein
3 β -Hydroxy- Δ 5-C27-steroid dehydrogenase/isomerase deficiency	607764	HSD3B7	C27-3 β -HSD	3 β -Dehydrogenase deficiency	3 β -Hydroxy- Δ 5-C27-steroid dehydrogenase/isomerase
Δ 4-3-Oxosteroid-5 β -reductase deficiency	604741	AKR1D1	SRD5B1	5 β -Reductase deficiency	Delta(4)-3-oxosteroid-5 β -reductase
Oxysterol 7 α -hydroxylase deficiency	603711	CYP7B1	CYP7B1	Spastic Paraplegia 5A	Oxysterol 7 α -hydroxylase
Cholesterol 7 α -hydroxylase deficiency	118455	CYP7A1	CYP7A1		Cholesterol 7 α -hydroxylase
Sterol 27-hydroxylase deficiency	213700	CYP27A1	CTX	Cerebrotendinous Xanthomatosis	Sterol 27-hydroxylase
α -Methylacyl-CoA racemase deficiency	604489	AMACR	AMACR	AMACR deficiency	α -Methylacyl-CoA racemase
Bile acid-CoA: amino acid N-acyltransferase deficiency	602938	BAAT	BAAT	Bile acid amidation defect	Bile acid-CoA: amino acid N-acyltransferase
Bile acid-CoA ligase deficiency	603314	SLC27A5	BA CoA LD		Bile acid-CoA ligase
ATP8B1 deficiency	211600	ATP8B1	PFIC1	Progressive familial intrahepatic cholestasis type 1	ATP8B1 (type 4 P-type ATPase)

Long-term jaundice in the neonatal period is one of the main findings of IEBAS. In cases of obstructive jaundice with normal levels of total cholesterol and gamma-glutamyl transpeptidase (GGT); hepatic dysfunction or cirrhosis with an unknown cause; family history of hepatic dysfunction; no improvement with the treatments after a diagnosis of neonatal hepatitis; clinical symptoms similar to tyrosinemia;

no itching despite cholestasis; recurrent diarrhea or steatorrhea; symptoms of fat-soluble vitamin deficiency (intracranial hemorrhage, rickets, hypocalcemic seizures, etc.), IEBAS should be considered. To date, 9 types of IEBAS have been discovered. Urine bile acid profiling is an important tool in the diagnosis of IEBAS (Table 2).

Table 2. Urine bile acid profiling in IEBAS

Disorder	Urine cholanoic (bile acid and alcohol) profile
3 β -Hydroxy- Δ 5-C27-steroid dehydrogenase/ isomerase deficiency	Sulphate/glycine-conjugated di/trihydroxy-5-cholenoic acids
Δ 4-3-Oxosteroid-5 β -reductase deficiency	7 α -hydroxy-3-oxo and 7 α ,12 α -dihydroxy-3-oxo-4-cholenoic acids
Oxysterol 7 α -hydroxylase deficiency	3 β -hydroxy-5-cholenoic acids
Cholesterol 7 α -hydroxylase deficiency	Normal
Sterol 27-hydroxylase deficiency	Cholestane pentol glucuronides
α -Methylacyl-CoA racemase deficiency	Taurotetra-(tri/penta)-hydroxycholestanoic acids
Bile acid-CoA: amino acid N-acyltransferase deficiency	Unamidated bile acids
Bile acid-CoA ligase deficiency	Unamidated bile acids
ATP8B1 deficiency	Normal

1.3 β -Hydroxy- Δ 5-C27-steroid dehydrogenase / isomerase deficiency: 3 β -hydroxy- Δ 5-C27-steroid dehydrogenase (HSD3B7) is the first discovered disorder of bile acid synthesis [40]. It is also the most common defect in bile acid synthesis [41,42]. The estimated prevalence in Europe is 0.99 per 10 million [43] and only 53 cases have been reported to date [44]. Although clinical symptoms (cholestasis, bleeding tendency, rickets, developmental disorder, etc.) vary in patients, GGT and total bile acid (TBA) concentrations are generally within normal limits [42]. High levels of sulfated 3 β , 7 α -dihydroxy-5-cholenoic acid and 3 β , 7 α -trihydroxy-5-cholenoic acid are determined in the urine or blood [45]. Serum liver enzymes may be normal in the early stages of the disorder, but then show gradual increases [46].

2. Δ 4-3-Oxosteroid-5 β -reductase deficiency: This deficiency in bile acid synthesis is due to a defect in the aldo-ketoreductase family 1 member D1 (AKR1D1) gene, which encodes the key enzyme Δ 4-oxosteroid 5 β -reductase [47]. This enzyme catalyzes the reduction of Δ 4-3-ketosteroid AB to form the cis ring structure AB [48]. The deficiency of this cytosolic enzyme results in misreduction of the double bond between the C-4 and C-5 of the sterol A-ring, which is the basic step in major bile acid synthesis. Thus, there is a misconversion of the 3-oxo intermediates to the corresponding 3 α -hydroxyl products. This deficiency results in significantly reduced primary bile acid synthesis

and deposition of 3-oxo- Δ 4 and allo (5 α -H) - bile acids [32,49]. Accumulated unsaturated C27-3-oxo- Δ 4 steroids are converted to the corresponding C24-bile acids and can be detected in both blood and urine [19]. The main findings in 5 β -reductase deficiency are normal or slightly elevated TBA and GGT in blood; high levels of conjugated bilirubin and alanine aminotransferase (ALT), and steatorrhea.

3.Oxysterol 7 α -hydroxylase deficiency: Oxysterol 7 α -hydroxylase deficiency is caused by mutations in the CYP7B1 gene encoded by 6 exons on chromosome 8q21.3 [50]. Oxysterol 7 α -hydroxylase converts 3 β -hydroxy-5-cholestenoic acid to 3 β , 7 α -dihydroxy-5-cholestenoic acid, particularly an important step in the acidic pathway in the first year of life [51]. This deficiency has the lowest prevalence in known IEBAS [52]. Only 4 cases have been reported to date and clinical signs or prognosis have not been clearly clarified [39].

4.Cholesterol 7 α -hydroxylase deficiency: Cholesterol 7 α -hydroxylase is found in the endoplasmic reticulum and expressed only in the liver. It is the rate-limiting step of bile acid synthesis [21]. It is located in the classical pathway, the main bile acid biosynthetic pathway in adults. Since the alternative pathway can still produce bile acids via oxysterol 7 α -hydroxylase, CYP7A1 defect does not cause deficiency in bile acids [53].

5. Sterol 27-hydroxylase deficiency: Cerebrotendinous Xanthomatosis (CTX) is a lipid storage disease that affects many organs and systems. It is characterized by abnormal accumulation of cholesterol and cholestanol resulting in neurological dysfunction (dementia, spinal cord paresis and cerebellar ataxia), peritendinous xanthomas, early atherosclerosis and cataracts [54]. It is caused by mutations in the CYP27A1 gene encoding sterol 27-hydroxylase. The defect blocks the initial modification of the cholesterol side chain, which leads to a reduction in the synthesis of primary bile acids together with the production and excretion of bile alcohols [55]. As a result of CYP27A1 deficiency, 5 α -cholestanol (a 5 α -dihydro cholesterol derivative) is accumulated in the tissues. Intense accumulation of 5 α -cholestanol in the brain results in severe neurological dysfunction [56]. The increase in 5 α -cholestan-3 β -ol in the nervous system and high levels of this sterol in blood are unique features of CTX patients [57,58].

6. α -Methylacyl-CoA racemase deficiency: 2-methylacyl-CoA racemase (AMACR) is an enzyme of the β -oxidation system in both peroxisome and mitochondria. AMACR deficiency is caused by mutations in the AMACR [59]. A deficiency in this enzyme disturbs bile acid side chain oxidation, which leads to high concentrations of (25R) -taurohydrocholic acid (THCA) in urine, bile and blood [60]. Therefore, AMACR deficiency causes accumulation of (25R) -pyrystanic acid, (25R) -THCA and (25R) -dihydrocholic acid (DHCA) in blood, cells and tissues [59]. This enzyme deficiency has profound effects on both bile acid and fatty acid pathways [60].

7. Bile acid-CoA: amino acid N-acyltransferase deficiency: Conjugation of CA and CDCA with an amide bond to C-24 of an amino acid (taurine or glycine) is the final step in primary bile acid synthesis [61]. BAAT deficiency is caused by mutations in the BAAT gene encoding the liver-specific bile acid-CoA: amino acid N-acyltransferase (a peroxisomal enzyme), which converts CoA esters of bile acids into taurine or glycine conjugates [38].

8. Bile acid-CoA ligase deficiency: The final step in bile acid synthesis involves conjugation with amino acid glycine and taurine [62]. The two enzymes catalyze reactions that lead to amidation of bile acids. First, a CoA thioester is formed by the rate-limiting enzyme bile acid-CoA ligase, followed by the combination of glycine or taurine in a reaction catalyzed by a cytosolic BAAT [52]. BACS is the first enzyme required for amidation of primary bile acids and converts C24-bile acids into their corresponding bile acyl-CoAs [63]. CoA is then replaced by BAAT with taurine or glycine. BACS is a liver-specific enzyme found in the endoplasmic reticulum and is required for the conjugation of bile acids deconjugated by enterohepatic circulating intestinal bacteria [64]. Due to a homozygous mutation in SLC27A5, only two siblings were identified with BACS deficiency [65].

9. ATP8B1 deficiency: Progressive familial intrahepatic cholestasis (PFIC) is a bile acid deficiency that accounts for approximately 10% to 15% of cholestatic liver disease in children [66]. The estimated prevalence of PFICs is 1 / 50,000 to 1 / 100,000 [66,67]. Three subtypes of PFIC (PFIC1, PFIC2, PFIC3) have been identified [68]. PFIC is caused by mutations in the ATP8B1 gene on the chromosome 18q21-q22 encoding type 1 FIC1 protein [69]. The main clinical features of PFIC are cholestasis, jaundice and pruritus. These clinical features typically occur during infancy or early childhood [68].

CONCLUSION

In IEBAS clinical findings can range from liver failure to cirrhosis in infancy or progressive neuropathy in adolescence or adulthood. Early diagnosis is important for early treatment and crucial to prevent fatal outcomes in which urine bile acid profiling is an important tool [38,39].

CONFLICT of INTEREST

There is no conflict of interest.

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