Progressive Familial Intrahepatic Cholestasis

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Progressive familial intrahepatic cholestasis (PFIC) is a group of rare disorders which are caused by defect in bile secretion and present with intrahepatic cholestasis, usually in infancy and childhood. These are autosomal recessive in inheritance. The estimated incidence is about 1 per 50,000 to 1 per 100,000 births, although exact prevalence is not known. These diseases affect both the genders equally and have been reported from all geographical areas. Based on clinical presentation, laboratory findings, liver histology and genetic defect, these are broadly divided into three types—PFIC type 1, PFIC type 2 and PFIC type 3. The defect is in ATP8B1 gene encoding the FIC1 protein, ABCB 11 gene encoding BSEP protein and ABCB4 gene encoding MDR3 protein in PFIC1, 2 and 3 respectively. The basic defect is impaired bile salt secretion in PFIC1/2 whereas in PFIC3, it is reduced biliary phospholipid secretion. The main clinical presentation is in the form of cholestatic jaundice and pruritus. Serum gamma glutamyl transpeptidase (GGT) is normal in patients with PFIC1/2 while it is raised in patients with PFIC3. Treatment includes nutritional support (adequate calories, supplementation of fat soluble vitamins and medium chain triglycerides) and use of medications to relieve pruritus as initial therapy followed by biliary diversion procedures in selected patients. Ultimately liver transplantation is needed in most patients as they develop progressive liver fibrosis, cirrhosis and end stage liver disease. Due to the high risk of developing liver tumors in PFIC2 patients, monitoring is recommended from infancy. Mutation targeted pharmacotherapy, gene therapy and hepatocyte transplantation are being explored as future therapeutic options. (J Clin Exp Hepatol 2014;4:25–36)

Progressive familial intrahepatic cholestasis (PFIC) is a heterogeneous group of liver disorders of autosomal recessive inheritance, presenting as intrahepatic cholestasis in infancy or early childhood and resulting in end stage liver disease (ESLD) and death or liver transplantation in infancy to adulthood.[1–3] Clayton et al first described this disease in 1965 as Byler disease in a population of Amish kindred.[4] The disease has been classified into three types (types 1, 2 and 3) based on the genetic defect involved in bile transport.

PFIC accounts for 10–15% cases of neonatal cholestasis syndrome[2,3] and 10–15% of children requiring liver transplantation.[2,3] It is a rare disease with an estimated incidence of 1 per 50,000 to 1 per 100,000 births although the exact prevalence is not known. The disease affects both genders equally and has been reported from around the world.[5–9]

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All the three types of PFIC are caused by defects in bile secretion from hepatocyte to canaliculi (Figure 1). The defects are in form of penetrant mutations in genes encoding proteins associated with hepatocellular transport system.

PFIC1: It is also known as Byler disease and is associated with defects in ATP8B1 gene on chromosome 18 (18q21-22) which encodes for familial intrahepatic cholestasis 1 (FIC1) protein.[10–12] FIC1 protein is a member of the type 4 subfamily of P type adenosine triphosphatase (ATPase). Type 4 ATPases are multispan transmembrane proteins that are involved in phospholipid translocation (flippase activity) from the exoplasmic (outer) to the cytoplasmic (inner) leaflet of the biological bilayer membrane.[13] FIC1 is located on canalicular membrane of hepatocytes. It acts as a flippase for aminophospholipid transport and leads to movement of phosphatidylserine and phosphatidylethanolamine from the outer to inner leaflet of plasma membrane of hepatocyte. This flippase activity of FIC1

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Abbreviations: ABC: ATP binding cassette; ASBT: apical sodium bile salt transporter; ATP: adenosine triphosphate; ATPase: adenosine triphosphatase; BRIC: benign recurrent intrahepatic cholestasis; BSEP: bile salt exporter protein; CFTR: cystic fibrosis transmembrane conductance regulator; CYP: cytochrome P; DNA: deoxyribonucleic acid; ERAD: endoplasmic reticulum associated degradation; ESLD: end stage liver disease; FIC1: familial intrahepatic cholestasis protein 1; FXR: farnesoid X receptor; HCC: hepatocellular carcinoma; IB: ileal bypass; ICP: intrahepatic cholestasis of pregnancy; LT: liver transplant; MARS: Molecular Adsorbent Recirculating System; MDR: multidrug resistance protein; MRCP: magnetic resonance cholangiopancreaticography; mRNA: messenger ribonucleic acid; PBD: partial biliary drainage; PEBD: partial external biliary drainage; PFIC: progressive familial intrahepatic cholestasis; PIBD: partial internal biliary drainage; pGp: p-glycoprotein; PPAR: peroxisome proliferator activator receptor; UDCA: ursodeoxycholic acid
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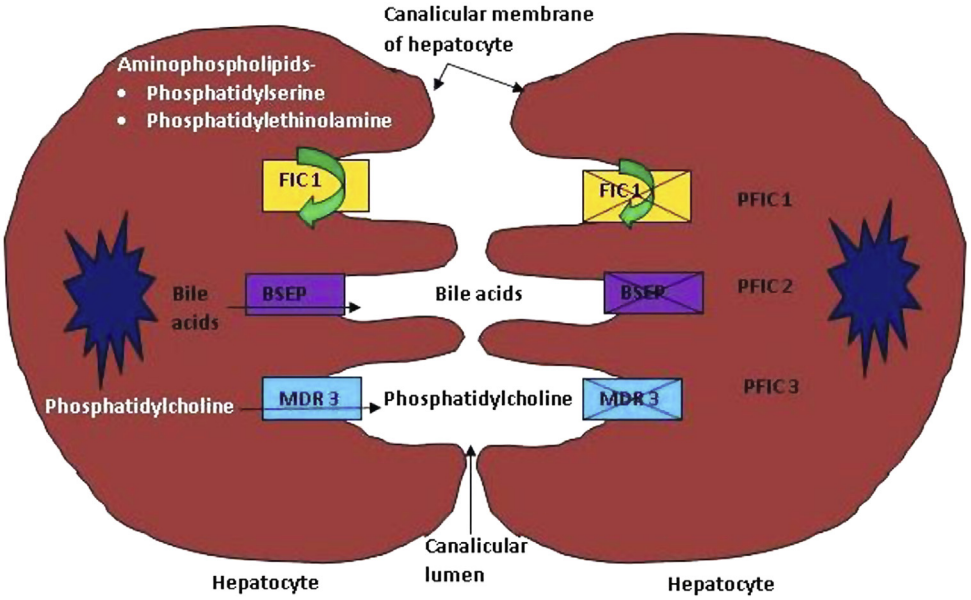

Figure 1 Etiopathogenesis of PFIC (PFIC: progressive familial intrahepatic cholestasis; FIC1: familial intrahepatic cholestasis protein 1; BSEP: bile salt exporter pump; MDR3: multidrug resistance protein 3).

helps in maintaining asymmetric distribution of phospholipids in the membrane bilayer (higher concentration of phosphatidylserine and phosphatidylethanolamine in inner layer) which helps to protect the membrane from high bile salt concentration in canalicular lumen[14–16] and maintain its integrity.[17–19]

Exact mechanism of cholestasis and other symptoms in PFIC1 is not fully elucidated. The proposed mechanisms include:

- Overload of bile acid in hepatocyte due to reduced bile salt secretion and increased ileal bile salt reabsorption. Disturbed biliary secretion of bile salts occurs due to downregulation of farnesoid X receptor (FXR), a nuclear receptor related to regulation of metabolism of bile acids.[1,2] This in turn results in downregulation of bile salt exporter pump (BSEP) protein and upregulation of synthesis of bile acid in the hepatocytes. There is also an upregulation of apical sodium bile salt transporter (ASBT) in microvilli of small intestine[20–25] which increases the intestinal uptake. It is not clear if downregulation of FXR is primarily due to gene defect or is secondary to increased bile salt concentration.[26]
- Increased secretion of cholesterol from apical (canalicular) membrane of hepatocyte in atp8b1 (capital letters denote human gene while small letters denote mouse gene) deficient mice has been shown.[27] Cholesterol content of the membrane is an essential determinant of BSEP activity. Impaired BSEP activity leads to cholestasis as explained in pathogenesis of PFIC2.
- Down regulation of cystic fibrosis transmembrane conductance regulator (CFTR) in cholangiocytes of patients with PFIC1 has been described which may explain extrahepatic features of the disease as well as contribute to the impaired bile secretion.[1]
- ATP8B1 is also expressed in the membrane of cells of small intestine, kidney and pancreas.[1,2] This might explain extrahepatic manifestations of PFIC1 viz. pancreatic insufficiency, sweat electrolyte abnormalities and diarrhea. FIC1 probably also has a general biological cell function and therefore results in features like short stature, and sensorineural deafness.[1]

Genotype–phenotype associations are complicated in patients with ATP8B1 mutations as these mutations are also present in patients with milder presentations like benign recurrent intrahepatic cholestasis 1 (BRIC1), transient neonatal cholestasis and intrahepatic cholestasis of pregnancy 1 (ICP1).[28] These diseases are taken as continuum of FIC1 deficiency and the protein function is only partially impaired in them. In approximately 10% patients with PFIC1, only one mutated allele or no mutation is seen. In these patients, possible disease mechanisms include either the presence of mutations in regulatory sequences of the gene, or in the other genes involved in the transcription of PFIC1 gene or control of protein trafficking of FIC1 protein.[29]

PFIC2: This disease was previously known as Byler's syndrome[6] and is a result of mutation in the ABCB 11 (ATP binding cassette [ABC] family B, member 11)[30] gene encoding BSEP, located on chromosome 2 (2q24).

BSEP is a transporter protein, expressed at the canalicular membrane of hepatocyte.[31] It is the main exporter of bile acids from hepatocyte to canaliculi against a concentration gradient.[1] Genetic mutations (insertion, deletion, nonsense and splicing) result in either premature