# Progressive familial intrahepatic cholestasis and benign recurrent intrahepatic cholestasis : a review

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## Abstract

**Progressive familial intrahepatic cholestasis (PFIC) and benign recurrent intrahepatic cholestasis (BRIC) are two rare autosomal recessive disorders, characterized by cholestasis. They are related to mutations in hepatocellular transport system genes involved in bile formation. The differentiation between PFIC and BRIC is based on phenotypic presentation : PFIC is a progressive disease, with evolution to end-stage liver disease. BRIC is characterized by intermittent recurrent cholestatic episodes, with irresistible pruritus, mostly without evident liver damage. Between symptomatic periods, patients are completely asymptomatic.**

**In this article, a short overview of the aetiology, the clinical and diagnostic characteristics and the therapy of both PFIC and BRIC are given.** (Acta gastroenterol. belg., **2012**, 75, **405-410**).

**Key words** : progressive familial intrahepatic cholestasis, PFIC, benign recurrent intrahepatic cholestasis, BRIC, pruritus.

## Introduction

Progressive familial intrahepatic cholestasis (PFIC), benign recurrent intrahepatic cholestasis (BRIC), and intrahepatic cholestasis of pregnancy (ICP) represent three different forms of familial intrahepatic cholestasis. Inheritance is autosomal recessive.

Based on the gene mutation, familial cholestasis can be subdivided into three subtypes : ATP8B1 (chromosome 18q21-22) deficiency, ABCB11 (chromosome 2q24) deficiency and ABCB4 ( chromosome 7q21) deficiency. Mutations in these three genes can cause progressive liver disease (respectively PFIC 1, PFIC 2 and PFIC 3), but mutations in ATP8B1 and ABCB11 can also result in the less severe phenotype of episodic cholestasis (respectively BRIC 1 and BRIC 2). Heterozygous mutations in all three genes are associated with ICP (1,2).

The differentiation between PFIC and BRIC is based on phenotypic presentation.

**Progressive familial intrahepatic cholestasis** summarizes a group of three rare inherited cholestatic diseases which starts in infancy or early childhood and may rapidly progress to end-stage liver disease. *PFIC type 1* was initially described in Amish descendants of Jacob Byler, and it was originally named Byler disease (3). It is also know as Greenland familial cholestasis (4). The actual prevalence remains unknown, but the estimated incidence is one per 50 000-100 000 births (5).

**Benign recurrent intrahepatic cholestasis** was first described by Summerskill and Walsch in 1959 (6). Different cases have been described worldwide, with the highest concentration in an extended family from the Netherlands (7). It is characterized by intermittent recurrent cholestatic episodes, with important pruritus. It usually appears later in life and has a more benign recurrent pattern. Each attack, mostly triggered by an (respiratory) infection, last from weeks to months. Between symptomatic periods, patients are completely asymptomatic for months to years (6,8).

## Aetiology

All three genes (ATP8B1, ABCB11 and ABCB4 gene) encode a hepatocanalicular transporter, which is essential for the proper formation of bile (Fig. 1).

The exact *ATP8B1* function is unknown. It is considered to be an aminophospholipid translocator (aminophospholipid-flippase) localized on canalicular membranes in hepatocytes and in cholangiocytes. The asymmetric phospholipid distribution between the outer and inner leaflets of the plasma membrane is necessary for normal flow of bile over the membranes (9). Deficiency of ATP8B1 may result in membrane instability, and reduced function of transmembrane transporters like the bile salt export pump (BSEP). BSEP is the major canalicular bile acid pump. It transports conjugated bile salts into biliary canaliculi against an extreme concentration gradient, thereby generating bile flow. The loss of BSEP function results in severe hepatocellular cholestasis (1). The ATP8B1 gene is also expressed in other organs, including the pancreas and small intestine. This explains the extrahepatic manifestations such as pancreatitis and diarrhea (2,5). Over 50 distinct mutations in ATP8B1 are described (10).

The *ABCB11* gene codes for a BSEP expressed in canalicular membranes of hepatocytes solely (thus not accompanied by extrahepatic symptoms). Deficiency may result in impaired canalicular bile salt excretion and cholestasis (1). Over 100 mutations are identified (2).

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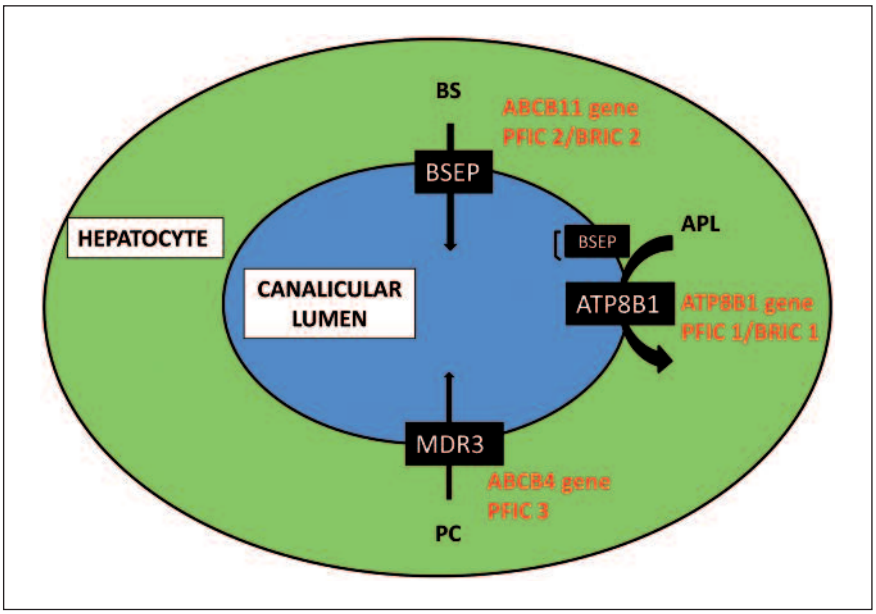


BS : bile salts ; BSEP : bile salt export pump ; APL : aminophospholipids ; PC : phosphatidylcholine ; MDR3 : class III multidrug resistance P-glycoprotein.
ATP8B1 gene, ABCB11 gene and ABCB4 gene encode a hepatocanalicular transporter. *ATP8B1* is considered to be an aminophospholipid translocator (aminophospholipid-flippase). The asymmetric phospholipid distribution between the outer and inner leaflets of the plasma membrane is necessary for normal flow of bile over the membranes. Deficiency of ATP8B1 may also reduced the function of transmembrane transporters like BSEP. The *ABCB11* gene codes for a BSEP expressed in canalicular membranes of hepatocytes. BSEP is the major canalicular bile acid pump. The *ABCB4* gene codes for MDR3, a phospholipid transporter (phosphatidylcholine-floppase) that translocates phosphatidylcholine across the canalicular membrane.

Fig. 1. — Aetiology of PFIC and BRIC : Transport defects

Patients with this genotype have a high risk of developing gallstones (11).

While the ATP8B1 deficiency and ABCB11 deficiency involve a defect in bile acid secretion, the ABCB 4 deficiency involves a defect in phospholipid secretion.

The *ABCB4* gene codes for the class III multidrug resistance P-glycoprotein (MDR3), which is a phospholipid transporter (phosphatidylcholine-floppase) that translocates phosphatidylcholine across the canalicular membrane. ABCB4 deficiency results in deficient biliary phospholipid secretion. The lack of phospholipids produces unstable micelles that have a toxic effect on the bile ducts, leading to bile duct plugs and biliary obstruction (1,12).

## Clinical and diagnostic characteristics (Table 1)

*ATP8B1 deficiency*

ATP8B1 deficiency can appear as persistent (PFIC 1) or episodic (BRIC 1) cholestasis.

*PFIC type 1* typically presents within the neonatal period with jaundice and growth failure. Fat malabsorption results often in fat-soluble vitamin deficiency. The patients often develop end-stage liver disease requiring liver transplantation at ages usually ranging from infancy to adolescence (2,13).

*BRIC 1* is characterized by episodes of cholestasis, with irresistible pruritus. The first symptoms usually appear in childhood and early adolescence, but presentation in infancy or late middle age is also described. Each cholestatic attack last from weeks to months. Between symptomatic periods, patients are completely asymptomatic for months to years. Attacks seem to be associated with a viral infection (6,8). There is generally a reduction in the frequency of cholestatic attacks at an older age (14).

In addition to cholestasis, patients with ATP8B1 deficiency may also suffer from extrahepatic symptoms, such as diarrhea, pancreatitis, hearing problems, and elevated sweat chloride concentrations (15).

In ATP8B1 deficiency, but also in ABCB11 deficiency, there is a characteristic combination of **profound cholestasis** (with elevated serum bile salts, bilirubin, and transaminase levels) and **low gamma-glutamyltransferase (GGT) levels**. Histologically, there is canalicular cholestasis with coarse granular bile. In PFIC 1 there is eventually fibrosis and cirrhosis (2,15). In BRIC 1, there is cholestasis, without signs of fibrosis, and between the attacks liver biopsy is normal.

PFIC 1 and BRIC 1 represent a continuum in which PFIC 1 is the severe end of the spectrum and BRIC1 the milder form. Patients who initially were diagnosed as having BRIC may occasionally develop a continuous and progressive form of cholestasis (14).

Table 1. – **Characteristics of PFIC and BRIC**

| Deficiency | Disease | Cholestasis | Other clinical characteristics | Diagnostic features |
|---|---|---|---|---|
| ATP8B1 gene | PFIC 1<br>BRIC 1 | Progressive<br>Recurrent | Extrahepatic symptoms possible (diarrhea, pancreatitis, hearing problems) | Elevated serum bile salts<br>Normal serum GGT<br>Liver biopsy : Coarse granular bile |
| ABCB11 gene | PFIC 2<br>BRIC 2 | Progressive<br>Recurrent | Risk of cholelithiasis<br>Risk of hepatobiliary cancer | Elevated serum bile salts<br>Normal serum GGT<br>Liver biopsy : Amorphous filamentous bile |
| ABCB4 gene | PFIC 3 | Progressive | | Elevated serum bile salts<br>Elevated serum GGT<br>Liver biopsy : Bile duct proliferation |

PFIC : progressive familial intrahepatic cholestasis, BRIC : benign recurrent intrahepatic cholestasis, GGT : gamma-glutamyl transpeptidase.

*ABCB11 deficiency*

*PFIC type 2* presents like PFIC type 1 in early childhood with permanent cholestasis, with clinical and biochemical signs and symptoms of progressive liver disease and fat-soluble vitamins deficiency. It mainly occurs in the Middle East and Europe. Patients also can present with episodic cholestasis (*BRIC 2*), although the episodic cholestasis is more frequent in ATP8B1 deficiency (2,16). Extrahepatic symptoms are not seen. In up to one third of the patients, cholelithiasis is observed. ABCB11 deficiency is a risk factor for the development of hepatocellular carcinoma or cholangiocarcinoma (17,18).

There is **profound cholestasis**, with increased serum bile salt and transaminase activities, contrasted by **low levels of GGT**. Histology reveals portal inflammation and giant cell hepatitis. The bile seen in this condition is amorphous and filamentous (2,15).

*ABCB4 deficiency*

Age of first symptoms and clinical presentation of *PFIC type 3* vary considerably, ranging from neonatal cholestasis to cirrhosis of adulthood. PFIC type 3 rarely presents with cholestatic jaundice in the neonatal period, but typically later in infancy, in the first years of childhood, and even in young adulthood, with progressive cholestasis. Untreated, the persistent cholestasis usually progresses to hepatic failure before adulthood. *ABCB4* deficiency should also be considered in young adults with unexplained biliary cirrhosis and may be involved in other adult liver diseases (19,20). No extrahepatic symptoms or malignancies are described (2).

In contrast to PFIC 1 and PFIC 2, there is a characteristic **high serum GGT** activity. Liver histology reveals fibrosis with portal inflammation, progressing into a typical picture of biliary cirrhosis. In contrast to the other forms of PFIC, there is strong bile duct proliferation in the early stages despite patency of intrahepatic and extrahepatic bile ducts (15,20).

The absence of bile salts in the bile ducts in ATP8B1 deficiency and ABCB11 deficiency, and their presence in the bile ducts in ABCB4 deficiency accounts for the difference in biochemical tests. In ABCB4 deficiency (as in most cholestatic diseases), prolonged exposure of the duct cell membranes to bile salts results in solubilization of GGT, absorption of the enzyme into the circulation, and elevated GGT levels on serum tests. In contrast, in ATP8B1 deficiency and ABCB11 deficiency there are low levels of biliary bile salts, the GGT is never solubilized, and the serum GGT is normal (3).

PFIC should be suspected in children with a clinical history of cholestasis of unknown origin after exclusion of other main causes of cholestasis. Diagnosis is based on the clinical manifestations, laboratory findings and liver histology (described in the previous paragraphs). Only genetic investigation of the corresponding genes can confirm the diagnosis. Genetic testing for ABCB4 deficiency should be performed when there is a history of chronic cholestatic liver disease of unknown origin, associated with persistently increased serum GGT activity, with ductular proliferation and patency of the biliary tree ; and after exclusion of other main causes of cholestasis and liver diseases (including sclerosing cholangitis, alfa1-antitrypsin deficiency, cystic fibrosis, autoimmune hepatitis, Wilson disease, chronic hepatitis C and B, and inborn errors in bile acid synthesis) (5,20).

There are diagnostic tools as liver immunostaining and biliary lipid analysis. Commercially available BSEP and MDR3 antibodies allow liver immunostaining to be performed. Normal staining does not exclude a gene defect as a mutation may induce a loss of function but normal synthesis and addressing. Biliary lipid analysis is performed on gallbladder bile or on bile collected by duodenal aspiration. The biliary bile salt concentration is dramatically decreased in PFIC2 patients and only mildly decreased in PFIC1 patients. In PFIC3 patients, the biliary bile salt concentration is normal, but the biliary phospholipid level is dramatically decreased (5,21).

BRIC diagnosis should be kept in mind in patients with recurrent cholestatic attacks with at least 2 episodes of jaundice and severe pruritus separated by a symptom-free interval lasting several months to years. Laboratory values have to be consistent with profound intrahepatic cholestasis with normal GGT. Other factors associated with cholestasis (such as gallstones, extrahepatic cholestasis, primary biliary cirrhosis, primary sclerosing cholangitis, drugs and pregnancy) should be excluded.

Exclusion of other causes of liver disease such as toxic, viral, and autoimmune hepatitis, hepatic sarcoidosis and malignant liver disease is necessary. Finally, the diagnosis can be confirmed by genetic testing for the presence of mutation in ATP8B1 or ABCB11 gene (1).

## Therapy

The therapeutic strategies for cholestasis due to canalicular transport defects may target bile composition, bile salt toxicity and the secretion of bile salts (9). Unfortunately, most forms of medical therapy for the described deficiencies are of limited effectiveness, and invasive therapies as biliary diversion and liver transplantation are inevitable in most patients. BRIC resolves spontaneously, treatment of the condition is purely symptomatic.

Supplementation with medium chain triglycerides and fat-soluble vitamins is generally recommended in children.

## Treatment of pruritus

– *Ursodeoxycholic acid* (UDCA) protects hepatocytes and cholangiocytes by replacing endogenous, cytotoxic bile salts. UDCA also stimulates the hepatobiliary secretion of bile acids (1,9). In ABCB4 deficiency (PFIC 3) half of the patients seem to respond to UDCA treatment (9,22,23). In patients with ATP8B1 or ABCB11 deficiency, the results of UDCA treatment are disappointing (9,24,25). In patients with BRIC, UDCA seems not to prevent or to abort cholestatic attacks (9,14,26).

– *Rifampicin* competes with bile acids for hepatic uptake, thereby lowering hepatocyte bile salt concentration. It also promotes the elimination of bile salts. Starting dose is 150 mg daily. If well tolerated, the dose can be increased to a maximum of 600 mg daily. In case series, drug-induced hepatitis and significant liver dysfunction after two to three months of therapy have been reported in up to 12% of cholestatic patients (27). In PFIC patients, the effect is limited. For patients with BRIC, it can be helpful in shortening episodes (2,28,29).

– *Cholestyramine* binds bile salts, preventing their reabsorption in the enterohepatic circulation. Administration of 4 g up to four times daily is advised. Poor tolerance due to the taste can be a problem. When both cholestyramine and ursodeoxycholic acid are used, administration should be spaced a minimum of four hours apart to prevent binding and loss of efficacy (16). To prevent interactions, some medications (as digitalis glycosides, vitamin K antagonists, fibrates, statins) should be given at least one hour before or four hours after the administration of cholestyramine. It does not seem to be effective in patients with PFIC. For patients with BRIC the results are variable from shortening of the cholestatic episodes to no effect at all (9,14,29,30).

– *Oral opiate antagonists* (Naltrexone 50 mg daily) can also be used against the pruritus (31). Studies have demonstrated that endogenous opioids in the central nervous system may have an important role in pathogenesis of the pruritus. It has been suggested that opioids bind to the μ-opioid receptor and presumably induce pruritus centrally. The usefulness of opoid antagonists was first documented in the late 1970s ; administration of the opioid receptor antagonist naloxone led to the dramatic amelioration of otherwise intractable pruritus in a patient with cholestatic liver disease (32). It should be considered as a third-line treatment, after proven lack of efficacy of cholestyramine and rifampicin. The most frequent side effects of short- and long-term administration are dizziness, nausea and vomiting (33). Treatment should be started at a low dose (25 mg) to prevent an opiate withdrawal-like reaction on initiation such as agitation, anxiety, muscle aches, insomnia etc. (29).

– *Sertraline* (75-100 mg daily) may be considered as a fourth-line treatment for pruritus, although the mechanism of its action remains unclear (29,34).

– No topical agents have demonstrated efficacy against pruritus (29).

– The use of antihistamines, ondansetron and phenobarbitone is not recommended for reasons of lack of efficacy and excessieve side-effects respectively (29).

– By using *plasmapheresis or Molecular Adsorbent Recycling System (MARS*), circulating cholestatogenic factors and bilirubin are reduced. If performed early enough, it can shorten the duration of the cholestatic attack in BRIC (35-37).

Often more invasive therapies such as biliary diversion or liver transplantation is necessary.

– *Biliary diversion* reduces the accumulation of toxic bile salts by interruption of the enterohepatic circulation, decreasing re-uptake. Partial biliary diversion can be extern (gallbladder connected to the abdominal skin) or intern (to the colon). In ileal bypass the terminal ileum is skipped by an ileocolonic anastomosis (2,25,30). Biliary diversion often successfully reduces pruritus and jaundice (30,38,39). The diversion procedure might slow the progression of the liver disease (40).

Recent studies show good long-term outcome in patients with partial external biliary diversion, if performed early enough, before liver cirrhosis has developed. Liver transplantation, which is limited by organ availability and may be associated with significant morbidity and mortality, can be postponed. The presence of liver cirrhosis at the time of partial external biliary diversion indicate an unfavorable outcome (41,42).

– For patients with BRIC, biliary diversion is less advisable because of its permanent character in an episodic disease. When medication is not able to abort the cholestatic episode, a temporary *nasobiliary drain* can be endoscopically introduced to interrupt the enterohepatic circulation. In most of the patients, the pruritus is resolved within a few days (39).

– *Orthotopic liver transplantation* is an important option for patients with end-stage liver disease due to PFIC, and for some patients with pruritus that is

unresponsive to other treatments (24). It usually gives complete correction of the phenotype in patients with ABCB11 and ABCB4 deficiency (19). Patients with ATP8B1 deficiency however may have ongoing disease due to the extrahepatic expression of the gene, and the extrahepatic symptomatology as pancreatitis and diarrhea is not corrected by liver transplantation (26).

Future therapies such as hepatocyte transplantation, specific targeted and mutation-specific pharmacological therapies are still under investigation (43-45).

## Conclusion

ATP8B1 gene, ABCB11 gene and ABCB4 gene are hepatocellular transport system genes involved in bile formation. Mutations in these genes can cause progressive liver disease (respectively PFIC 1, PFIC 2 and PFIC 3), but mutations in ATP8B1 and ABCB11 can also result in the less severe phenotype of episodic cholestasis (respectively BRIC 1 and BRIC 2).

ATP8B1 deficiency and ABCB11 deficiency have few clinical differences, and are both characterized by low GGT levels. GGT is only elevated in ABCB4 deficiency. Extrahepatic symptoms are only seen in ATP8B1 deficiency, while cholelithiasis and hepatobiliary malignancies are associated with ABCB11 deficiency.

Patients with progressive forms of ATP8B1 or ABCB11 deficiency should be treated with biliary diversion, or liver transplantation when this fails. In patients with ABCB4 deficiency, UDCA treatment should be given. If not successful, liver transplantation should be performed. In patients with BRIC, rifampicin with or without cholestyramine should be given at the start of an attack. If the pruritus does not improve, nasobiliary drainage can be performed. In BRIC patients with very frequent attacks, a partial biliary diversion can be considered.

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