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Letters to the Editor

Clinical variability of mutations in the ABCB11 gene: A case report

Key words: Progressive familial intrahepatic cholestasis. PFIC. Benign recurrent intrahepatic cholestasis. BRIC. ABCB11.

Dear Editor,

Progressive familial intrahepatic cholestasis (PFIC) includes a group of infrequent genetic diseases with autosomal recessive heredity, characterized by intrahepatic cholestasis, usually in childhood and in adolescence. It is caused by defective bile salt secretion and other bile components. The progression leading to liver failure and cirrhosis usually appears in the first few decades of life.

There are three types of PFIC (Table I). PFIC 1, previously called Byler disease, was discovered first, and it is caused by mutations in the ATP8B1 gene (FIC-1); therefore, it is currently called FIC1 deficiency. PFIC 2, previously called Byler syndrome, is due to mutations in the ABCB11 gene, which encodes a protein that works as a canalicular bile salt transporter. Therefore, PFIC 2 is also called BSEP (bile salt export pump) deficiency. Finally, PFIC 3, whose origin resides in the ABCB4 gene, is also called MDR3 (class III multidrug resistance p-glycoprotein) deficiency.

Benign recurrent intrahepatic cholestasis (BRIC) is also a group of diseases related to disorders of the secretion and transportation of bile salt. It differs from PFIC because of its indolent progression, which does not end in cirrhosis. Two types of BRIC have been described, based on the associated genetic defect: BRIC 1 (ATP8B1) and BRIC 2 (ABCB11).

Case report

A 46-year-old woman diagnosed with PFIC when she was 14. She has a brother with PFIC who had a liver transplant because he developed liver cirrhosis.

Table I. Classification of progressive familial intrahepatic cholestasis (PFIC)

	PFIC 1	*PFIC 2*	*PFIC 3*
Functional deficiency	FIC1	BSEP	MDR3
Gene mutation	ATP8B1	ABCB11	ABCB4
Age of onset	Neonatal period	Neonatal period	< 20 years-old
Serum GGT	Normal or low	Normal or low	High
Expression in others organs	cholangiocytes, intestine, pancreas	None	None
Clinical characteristics	Cirrhosis. BRIC 1 Extrahepatic features: malabsorption, pancreatitis	Cirrhosis. BRIC 2 Bile stones ICP, DC, HCC, CCC	Cirrhosis. Bile stones ICP.
Functional defect	Aminophospholipid translocase	Bile acid transport	Phosphatidylcholine translocation

FIC1: familial intrahepatic cholestasis type 1. BSEP: bile salt export pump. MDR3: multidrug resistance protein 3. BRIC: benign recurrent intrahepatic cholestasis. ICP: intrahepatic cholestasis pregnant. DC: drug induced cholestasis. HCC: hepatocelular carcinoma. CCC: cholangiocarcinoma.

In her past medical history, she showed intrahepatic cholestasis of pregnancy (ICP), with disorders in prothrombin activity (which was corrected with vitamin K) and an intrauterine dead fetus within 38 weeks of pregnancy. She had continuous light pruritus that was more intense during ovulation. The most intense episodes of pruritus, which lasted 1 month each and occurred 2 or 3 times per year, were associated with acholia and weight loss.

Currently, she is receiving a treatment of Ursochol® 900 mg per day and is asymptomatic except for occasional self-limited pruritus episodes at night.

Her blood test during pregnancy showed 200 U/L ALT, 800 U/L alkaline phosphatase, 70 U/L AST and a normal gamma-glutamyl transpeptidase (GGT). Currently, she has normal transaminases (AST, ALT, and GGT), 153 U/L alkaline phosphatise, and 1.3 mg/dL total bilirubin.

The last ultrasound showed a liver with a normal size and morphology, regular borders, and a homogeneous pattern. The splenic-portal venous axis and suprahepatic veins were permeable, non-dilated, and had a normal flow. Her gallbladder contained bile stones inside and there was no bile duct dilation.

A genetic study was done, which detected two heterozygotic mutations in the ABCB11 gene. The first mutation was found in exon 8 (change T>C in nucleotide 698), meaning the substitution of leucine 233 for serine (L233S) took place. The second was in exon 27 (change C>A in nucleotide 3933) which entailed the substitution of tyrosine 1311 for a stop codon (Y1311X). This data was compatible with a BSEP deficiency.

A genetic analysis of her children and her brother, who had had a transplant, was suggested to the patient, due to the lack of clinical and genetic correlation between her family history and initial diagnosis. However, the patient rejected this suggestion.

Discussion

PFIC 2 is caused by a deficiency of BSEP, an ATP-dependent transporter of bile salt across the canalicular membrane of hepatocytes. It is due to mutations in ABCB11, which is located on chromosome 2q24-31. About 80 mutations have been described in patients diagnosed with PFIC 2. This transporter is selectively expressed in hepatocytes; therefore, there is no expression of the disease in other organs like there is in PFIC 1, in which diarrhea, acute pancreatitis, and pneumonia can appear.

PFIC 2 usually occurs during the neonatal period or in childhood, progresses quickly to liver cirrhosis, and in most cases, requires a liver transplant.

Clinical symptoms are mainly jaundice and intense pruritus. As in PFIC 1, and despite cholestasis, GGT is usually normal or low; however, there are higher ALT levels (up to 5 times the upper normal limit) and normal alpha-fetoprotein.

There is an increased risk of developing a hepatocellular carcinoma or cholangiocarcinoma (15%), so it is recommended to perform periodic evaluations to come to an early diagnosis.

Mutations in ABCB11 (BSEP) are also linked with benign recurrent intrahepatic cholestasis (BRIC), and due to this genetic association, it is called BRIC 2 (1). This illness involves episodes of jaundice, pruritus, weight loss, malabsortion, malaise, and cholestasis, but does not end in severe liver damage. These episodes last weeks or months and they are monitored for clinical and analytical normalization. It is also associated with intrahepatic cholestasis of pregnancy (ICP) and oral contraceptive-induced cholestasis (CC). These patients usually present cholelithiasis.

Therapy with ursodeoxycholic acid (UDCA) is considered during the initial therapeutic management of children with all types of PFIC. In MDR3 deficiency, chronic administration of UDCA normalizes liver function tests and improves clinical symptoms, so UDCA should be first choice in the initial management of these patients. Some patients with PFIC1 or PFIC2 may also benefit from surgical biliary diversion to interrupt the enterohepatic circulation of bile acids. Although UDCA therapy has advantages, especially for PFIC3, the progression to liver cirrhosis in PFIC patients still requires liver transplantation as a definitive therapy. In patients with episodic cholestasis, medical treatment with rifampicin or cholestyramine can be attempted (2,3).

The identification of the genes that are responsible for the three types of PFIC and BRIC has revealed the complexity of intrahepatic cholestasis diseases. Despite the fact they are monogenic diseases with Mendelian patterns of heredity, these illnesses present difficulties with their differential diagnoses because of their phenotypic heterogeneity and their incomplete genetic penetrance. The most recent revisions tended to call these gene alterations FIC 1, BSEP and MDR3 deficiency, instead of PFIC 1, 2 and 3, which had followed the old nomenclature. The phenotypic variability of the genetic heterogeneity in ABCB11 is also supported by a recent association of ABCB11 variants with other less severe cholestasic syndromes, like intrahepatic cholestasis of pregnancy (ICP) and drug-induced cholestasis (DC), as well as the association with BRIC, as was mentioned previously (4).

On the other hand, a recent study identified some mutations in BSEP deficiency, like D482G , that cause the illness to assume a more indolent path, with less progression of liver disease and better chances of survival (5).

In our patient's case, a woman initially diagnosed with PFIC 2, it is possible that she actually shows a better clinical and developmental correlation with benign recurrent intrahepatic cholestasis type 2 (BRIC 2), considering the results of the genetic analysis. However, due to her family history (a brother diagnosed with PFIC 2 who had had a liver transplant), it is also possible that she could have presented a BSEP deficiency or PFIC 2 with a less aggressive progression.

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