Review

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Genetic cholestasis: Clinical and laboratory features

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ABSTRACT

In recent years, access to high-performance genetic techniques has allowed new diagnoses to become evident, allowing us to say today that genetic causes represent more than one-third of the etiologies of cholestasis in newborns and infants. When faced with a pediatric patient with cholestasis, with similar clinical and biochemical findings, an early genetic diagnosis will facilitate specific treatment, delay or exclude invasive diagnostic procedures (for example, liver biopsy), and offer genetic counseling to the family.

We recently published a classification of genetic cholestasis, considering how the molecular defect affects biliary secretion. In this opportunity, we briefly summarize each of them to facilitate their identification by the pediatrician, who is the first professional to detect them and promptly refer them to a high-complexity center.

Keywords: *cholestasis; genetics; testing; diagnosis; clinical course; cirrhosis.*

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INTRODUCTION

Cholestasis in newborns and infants is the consequence of a variety of etiologies, infectious, malformation, immunologic, endocrinologic, toxic, or may be due to genetic defects. In pediatric hospitals, the most frequent causes of cholestasis are hereditary. It is important to note that most of these diseases are typical of pediatric age and are rarely diagnosed in adulthood. Specific characteristics in children with cholestasis will allow the primary care physician to decide whether to refer them to a high-complexity care center for subsequent characterization, administration of the appropriate treatment and required follow-up.[1]

Cholestasis in newborns and infants is evidenced by the appearance of jaundice, which is noticed by the parents or the pediatrician and confirmed by laboratory tests. In addition, from the age of 5-6 months, the appearance of pruritus may be the most important symptom. In some hereditary diseases, the presence of associated malformations can guide the clinical diagnosis; however, their confirmation with the identification of the genetic mutation, in addition to giving certainty, can significantly help parents in cases of future pregnancies.[2]

The following describes the characteristics that will help in the differential diagnosis of progressive cholestasis of genetic origin, remembering that some mutations can cause recurrent cholestasis but with a benign evolution (*Table 1*). In certain circumstances, mutations in a single allele (heterozygous patients) will manifest with cholestasis of pregnancy, and this history in the patient's mother will collaborate with the diagnostic orientation when taking the clinical history. According to the patient's clinical presentation, starting the genetic evaluation with a targeted gene panel (next-generation sequencers) is advisable. If the diagnosis is inconclusive, whole exome or genome sequencing can be performed.[1,3,4]

Recently, we published a classification of the causes of hereditary cholestasis, considering how the molecular defect affects biliary secretion. At this opportunity, it seems appropriate to briefly summarize the clinical features and laboratory tests for different hereditary diseases to facilitate their identification by the pediatrician.[1]

ANOMALIES IN THE TRANSPORT OF BILIS COMPONENTS AT THE APICAL AND BASOLATERAL POLES

Apical pole

ATP8B1/FIC1

This entity, also known as Byler disease, is caused by homozygous mutations or heterozygous components of the *ATP8B1* gene on chromosome 18 (18q21), which encodes the FIC1 (familial intrahepatic cholestasis 1) protein. FIC1 is part of the type 4 subfamily of adenosine P-type triphosphatases, which translocate phospholipids in membranes. This protein, present in the apical membrane of hepatocytes, functions as an aminophospholipid translocase, carrying phospholipids from the outer layer toward the inner layer of the canalicular membrane. The *FIC1* gene is expressed in many extrahepatic epithelia (mainly intestine, pancreas, lung, and inner ear).

Patients may present with diarrhea, pancreatic involvement, pneumonia, abnormal sweat test, hearing loss, and growth retardation. The laboratory is characterized by cholestasis, with moderately elevated transaminases, gamma-glutamyl transferase (GGT), and cholesterol within normal limits.

Hepatic histological findings include hepatic canalicular cholestasis, giant cell transformation, periportal fibrosis, and progression to biliary cirrhosis.[2,5]

ABCB11/BSEP

This disease is caused by bi-allelic mutations in the *ABCB11* gene (chromosomal 2q31), which encodes the bile salt export pump (BSEP). Mutations in BSEP disrupt the bile expulsion from the hepatocyte, causing increased intracellular concentration of bile salts, with consequent damage and predisposition to develop a carcinomatous transformation. Some mutations are associated with a more benign and recurrent course called "benign recurrent intrahepatic cholestasis".

Clinically, these patients present at an early age with jaundice, hepatomegaly, and growth retardation. Laboratory findings include increased bilirubin, normal GGT, high transaminases, and elevated alpha-fetoprotein. The disease can progress rapidly, with debilitating pruritus from 4 to 6 months, liver failure, and hepatocellular carcinoma. The information provided by an international registry made it possible to categorize these patients according to the

Table 1. Clinical characteristics of patients with neonatal cholestasis of genetic origin

Classification	Genes	GGT	Extrahepatic compromise	RBIC	ICP
Transport anomalies in the canalicular and basolateral membranes	*ATP8B1*	N	Diarrhea, hearing impairment. pancreatitis.	Yes	Yes
	ABCB11	N		Yes	Yes
	ABCB4	E		Yes	Yes
	ABCC2	E			
	SLC10A1	N			
	SLC01B1	N			
	SLC51A-SLC51B	E	Congenital diarrhea.		
Transit disturbances intracellular vesicles	*VIPAs39* *VPS33B* *VPS33B* and *VIPAR*	N N N	Arthrogryposis, renal dysfunction, ichthyosis.		
	VPS50	N	Developmental delay, microcephaly, hypoplasia of the corpus callosum, seizures.		
	MYO5B	N	Microvillus inclusion disease, diarrhea.		
	UNC45A	N	Congenital diarrhea, hearing impairment, bone fragility.		
Increased paracellular permeability	*CLDN1*	E	Ichthyosis, alopecia.		
	TJP2	N	Hearing impairment or deafness, neurological and respiratory compromise, renal tubular involvement, hypomyelination.	Yes	
	USP53	N	Hearing impairment.	Yes	
	LSR	N	Intellectual disability.		
	PLEC	N			
Defect in the production of nuclear receptors	*NR1H4*	N			Yes
Cholangiopathies with bile ducts paucity	*KIF12*	E	Hypothyroidism, short stature.		
	HNF1B	E	Renal and urinary tract abnormalities, diabetes, exocrine pancreatic insufficiency, hypomagnesemia, hyperuricemia, cognitive impairment.		
	ABCC12	N			
	JAG1-NOTCH2 (Alagile syndrome))	E	Cardiovascular malformation, posterior embryotoxon, defects of the vertebral arches, cerebrovascular anomalies.		
Cholangiopathies secondary to ciliary anomalies	*DCDC2*	E	Renal disease, hearing impairment.		
	ZFYVE19	E			
	INVS, NEK8 y *NPHP9*	E	Nephropthosis.		
	CC2D2A, MKS1 y *TMEM216* (Meckel-Joubert syndrome)	E			
	PKD1L1		Splenic and cardiac malformations.		
Transport in cholangiocytes	*CFTR* (fibrocystic disease)	E	Pancreatic insufficiency.		
Disturbance of hepatocellular function	*SERPINA1* (alpha-1-antitrypsin deficiency)	E			
	GALT	E			
	EHHAD	E	Fanconi´s syndrome.		
Errors in bile acids metabolism	*HSD3B7*	N			
	AKR1D1	N			
	CYP27A1 (cerebrotendinous xantomatosis)	N	Neurological involvement, diarrhea.		
	BAAT	N			

GGT: gamma-glutamyl transferase; N: normal; E: elevated. RBIC: Recurrent benign intrahepatic cholestasis; ICP: intrahepatic cholestasis of pregnancy.

severity of the genetic defect, allowing us to predict more remarkable survival with native liver, the risk of hepatocellular carcinoma, and the response to treatment. Exceptionally, they may present cholangiocarcinoma or pancreatic adenocarcinoma.

Hepatic histology is characterized by giant cell transformation, chronic hepatitis with lobular inflammation, and progressive fibrosis.[2,4,6]

ABCB4/MDR3

The disease is caused by biallelic mutations in the *ABCB4* gene (chromosome 7q21), which encodes p-glycoprotein 3 (multidrug-resistant protein 3, MDR3). This protein confers multidrug resistance and is the primary phospholipid transporter to bile. Elevated GGT characterizes this disease in response to injury of the biliary epithelium by hydrophobic bile salts in the absence of phospholipids.

The clinical presentation is highly variable, ranging from severe neonatal cholestasis to chronic cholestasis or cirrhosis in older children or adults. In addition, it may be associated with cholelithiasis, intrahepatic cholestasis during pregnancy, drug-induced cholestasis (such as contraceptive oral), and primary sclerosing cholangitis of small ducts.

Histological findings are also variable. In neonates, the proliferation of bile ducts, inflammatory infiltration, and portal and periportal fibrosis evolving into cirrhosis are observed.

In the follow-up of 38 patients with MDR3 deficiency, 50% of 26 patients diagnosed during childhood needed liver transplantation, compared to none of those diagnosed as adults. Hepatocellular carcinoma and cholangiocarcinoma have been associated with this chronic cholestasis.[2,4,7]

ABCC2/MRP2

Known as Dubin-Johnson syndrome (nowadays, once the genetic defect is known, it is called Dubin-Johnson disease), it is an autosomal recessive genetic disease more frequent in Spanish Jews. It is associated with mutations in the *ABCC2* gene (74 mutations have been described), which leads to a functional defect of the MPR2 protein, which is responsible for transporting conjugated bilirubin from the hepatocytes to the bile ducts for excretion.

Patients present persistent or intermittent conjugated hyperbilirubinemia during the neonatal period or later. Progressive liver involvement has not been observed. Most of the publications consist of case reports.[2,8]

Basolateral pole

SLC10A1/NTCP

Sodium-taurocholate cotransporter polypeptide deficiency (NTCP) is an inherited disease first described in 2015. NTCP is involved in transporting bile acids from the blood to the hepatocytes (enterohepatic circuit), and its deficiency leads to an elevated level of circulating bile acids. Patients also present with hyperbilirubinemia and a mild increase in aspartate aminotransferase (AST).[9]

SLC01B1/OATP1B1 and *1B3*

Referred to as Rotor disease, it is a rare, benign, autosomal recessive, inherited disease characterized by conjugated hyperbilirubinemia. Mutations in the *SLCO1B1* and *SLCO1B3* genes result in simultaneous and complete deficiency of the organic anion transporting polypeptides OATP1B1 and OATP1B3. Like Dubin-Johnson disease, mild jaundice begins after birth or during childhood.[10]

SLC51A-SLC51B/OSTα-OSTβ

Rare deficiencies of these sinusoidal or basolateral membrane proteins are characterized by cholestasis, fibrosis/cirrhosis, and congenital diarrhea.[11,12]

INTRACELLULAR VESICLE TRANSIT ANOMALIES *VIPAS39/SPE39; VPS33B/VPS33B and VIPAR/VIPAR*

They are autosomal recessive multisystemic diseases that manifest with neurogenic arthrogryposis, renal tubular dysfunction, ichthyosis, cholestasis, bile duct hypoplasia, and decreased GGT. They are frequently associated with platelet dysfunction. Patients die within the first year of life.[13]

VPS50/subunit *of* EARP/GARP11 complex

The disease is characterized by severe developmental delay, microcephaly, hypoplasia of the corpus callosum, seizures, transient neonatal cholestasis, and growth arrest.[14]

MYO5B/myosin Vb

Bi-allelic mutations of the *MYO5B* gene are identified in most patients diagnosed with villous inclusion disease. They present with intractable early-onset infantile diarrhea requiring

prolonged parenteral nutrition or intestinal transplantation. Up to 54% of patients develop persistent cholestasis with normal GGT and progressive liver disease that may require liver transplantation during childhood. Some cases show similarity to BSEP deficiency, with mild and transient cholestasis. In addition, patients with cholestasis, without intestinal involvement, have been described.[2,4,15]

UNC45A/UNC45A associated with myosin

It is a rare genetic disease with syndromic manifestations that include cholestasis, congenital diarrhea, hearing impairment, and bone fragility.[16]

INCREASED PARACELLULAR PERMEABILITY

CLDN1/claudin-1

It manifests during the neonatal period with ichthyosis, sclerosing cholangitis, alopecia, and portal hypertension. The laboratory shows increased alanine aminotransferase (ALT) and GGT. Liver histology shows hepatocellular and canalicular cholestasis with biliary plugs, portal fibrosis, steatosis, ductal proliferation, and ductopenia. Hepatic transplantation does not usually resolve the extrahepatic manifestations.[17,18]

TJP2/protein 2 of tight junctions

Patients present with severe cholestasis, low or normal serum GGT, and extrahepatic manifestations, including hearing impairment or sensorineural deafness, neurological and respiratory compromise, renal tubular involvement, hypomyelination, and myopia. Hepatic involvement may progress to severe liver disease, cirrhosis, and liver cancer in adolescents or adults. Extrahepatic involvement is not severe enough to contraindicate liver transplantation. In its heterozygous form, it can be responsible for benign recurrent cholestasis. A genotype-phenotype correlation capable of predicting the clinical course of the disease has been described. Patients carrying a truncated mutation in both alleles presented a more aggressive disease.[19-21]

USP53/ubiquitin-specific 53

He presents cholestasis with normal GGT and hearing impairment. The *USP53* gene interacts with *TJP2* and participates in the tight junction structures, presenting a phenotype similar to that associated with the *TJP2* gene mutation but milder.[4,22,23]

LSR/lipoprotein receptor stimulated by lipolysis

Transient neonatal cholestasis, intellectual disability.[22,24]

PLEC/plectin

The plectin that binds the cytoskeleton of the hepatocyte protects it from cholestatic injury. Cholestasis is described at 2 months with progression to cirrhosis and the need for transplantation at 2 years of age.[25]

DEFECT IN THE PRODUCTION OF NUCLEAR RECEPTORS

NR1H4/Farsenoid X-receptor

It is characterized by early, progressive cholestasis, with normal GGT and early death or need for liver transplantation.[26,27]

CHOLANGIOPATHIES ASSOCIATED WITH BILE DUCTS PAUCITY

KIF12/kinesin family member 12

It is associated with sclerosing cholangitis, low stature, and hypothyroidism.[22,28]

HNF1B/HNF1 homeobox B

It is characterized by the presence of ciliary defects in the cholangiocytes. Clinically, it manifests cholestasis with elevated GGT or asymptomatic increase in transaminases. In addition, it is associated with renal and urinary tract abnormalities, diabetes, pancreatic exocrine insufficiency, hypomagnesemia, hyperuricemia, cognitive impairment, and hepatocellular carcinoma in pediatric patients.[2,4,29]

ABCC12/ATP-binding cassette subfamily C, member 12

This gene is a member of the ATP-binding cassette (ABC) transporter superfamily; the encoded protein contains two ATP-binding domains and 12 transmembrane regions. Loss of function is associated with cholestasis, decreased GGT, and bile ducts paucity.[30]

JAG1-NOTCH2/Jagged1 and its receptor - Notch2

Autosomal dominant disease, with variable penetrance, is known as Alagille syndrome, presenting progressive cholestasis with elevated GGT, peculiar facies, pruritus, butterfly wing vertebrae, xanthomas, posterior embryotoxic, vascular anomalies, and renal involvement. Patients linked to the *NOTCH2* mutation do not

usually present with the characteristic facies, which often guide us to the diagnosis.[31-33]

CHOLANGIOPATHIES SECONDARY CILIARY ANOMALIES

Ciliopathies are rare causes of genetic cholestasis linked to the development of the bile ducts. The genes responsible for ciliary anomalies generate abnormal biliary structures, bile duct cysts, or ductopenia. One example is fibrocystic liver disease, which encompasses a diverse range of biliary conditions resulting from abnormalities in ductal plate remodeling. These conditions frequently involve the liver and kidneys.[2,4]

HNF1B/HNF1 "homeobox B"

It is already described among the cholangiopathies associated with bile ducts paucity.

DCDC2/double-curtain Z-domain

Neonatal sclerosing cholangitis, cholestasis with elevated GGT, renal disease, and hearing impairment.[34]

ZFYVE19/"Zinc finger" *FYVE-19*

Bile duct epithelial pyelopathy, cholestasis with elevated GGT, and phenotype of neonatal sclerosing cholangitis and congenital hepatic fibrosis.[35]

INVS/inversin, *NEK8/NIMA* kinase-8, and *NPHP9*/nephrocystin

Cholestasis, ciliopathy, bile ducts paucity, renal disease, congenital hepatic fibrosis.[36]

CC2D2A/"Coled-coil" C2 domain 2ª, *MKS1/MKS* complex and *TMEM216*/transmembrane protein 216

Ciliopathy, cholestasis, Meckel-Joubert syndrome.[37]

PKD1L1/polycystin 1

Ciliopathy, biliary atresia with splenic malformations, cardiac malformations.[38]

TRANSPORT IN CHOLANGIOCYTES

CFTR/chlorine channel

Cystic fibrosis: variable phenotypes that may include increased transaminases, neonatal cholestasis, portal hypertension (biliary cirrhosis), and pancreatic insufficiency.[39]

DISTURBANCE OF HEPATOCELLULAR FUNCTION

SERPINA1/alpha-1-antitrypsin

Cholestasis and cirrhosis in childhood; emphysema in adults.[40]

GALT/galactose-1-phosphate uridyltransferase

Galactosemia, cholestasis, and hepatic insufficiency.[41]

CYP27A1/27-hydroxylase

It is a disorder of bile acid synthesis presenting with cerebrotendinous xanthomatosis, neonatal cholestasis without pruritus, neurological involvement, and diarrhea.[42]

EHHADH/enoyl-CoA hydratase and 3-hydroaxyl CoA dehydrogenase

Cholestasis, peroxisome disease, Fanconi syndrome.[43]

ERRORS OF BILE ACID METABOLISM

These are rare, autosomal recessive diseases caused by deficiencies of the enzymes involved in synthesizing or conjugating primary bile acids. They are the consequence of intracellular accumulation of atypical, hepatotoxic bile acids. They are clinically characterized by cholestasis without pruritus, GGT at the normal and normal or decreased serum bile acid level. They differ from progressive genetic cholestasis, which is also associated with normal GGT but with pruritus and increased serum bile acids.[2,4]

HSD3B7/3β-hydroxy-C27-steroid dehydrogenase

Neonatal or later cholestasis, growth retardation, hepatosplenomegaly. Normal GGT, decreased serum bile acids. It responds to treatment with cholic acid, which, by producing CYP7A1 enzyme inhibition, reduces the production and excretion of toxic intermediates. Administration of ursodeoxycholic acid may lead to partial improvement; however, the absence of enzyme inhibition does not interrupt the synthesis of toxic intermediates.[44-46]

AKR1D1/4-3 oxosteroid 5β reductase

Neonatal cholestasis, growth retardation, hepatosplenomegaly, normal GGT, decreased bile acids. It responds to treatment with cholic acid.[45-47]

CYP27A1/27-hydroxylase

It has already been described as a hepatocellular disease caused by disturbances in the function of intracellular organelles or metabolic errors.

BAAT/amino amidation N-acetyltransferase

Neonatal cholestasis, growth retardation, hepatomegaly. Hepatic failure has been reported. Liver transplantation in severe cases. It responds to treatment with glycolic acid.[48]

DISCUSSION

In recent years, access to high-throughput genetic techniques has allowed a notable increase in the diagnosis of genetic cholestasis, incorporating new entities and progressively reducing the so-called "idiopathic" cholestasis group. The incorporation and diffusion of next-generation sequencing (NGS), which allowed the simultaneous analysis of multiple genes, resulted in broader availability and reduced the cost and time to obtain the results. However, we must insist on the importance of clinical suspicion to avoid the overuse of these diagnostic studies.

In the presence of a neonate with cholestasis, with clinical and biochemical findings that evoke some of the diseases described, the performance of an early targeted gene panel will be instrumental in obtaining a definitive diagnosis to act accordingly.[2,4]

A series of pediatric patients with cholestasis, etiologically characterized with next-generation sequencers, have been published in the last few years. Two multicenter studies, which included 603 and 2,171 patients, are worth mentioning. The first was conducted in France, and the second was in the United States, Canada, and the United Kingdom, with a 28% and 12% diagnosis rate, respectively. The most frequent pathologies were associated with the following mutated genes: *JAG1/NOTCH2* (Alagille syndrome), *ABCB4* and *ABCB11* (bile transport abnormalities in the biliary canaliculus), *SERPINA1* (alpha-1-antitrypsin deficiency), *TJP2* (increased paracellular permeability), *MYO5B* and *VPS33B* (vesicle intracellular transit abnormalities), and *DCDC2* (cholangiopathy secondary to ciliary abnormalities).[49,50]

In conclusion, it is necessary to become familiar with the diagnostic complexity of genetic cholestasis in childhood, understanding that this is a constant change and evolution subject. Patients without a diagnosis today may achieve it shortly. Finally, as in all genetic diseases, epigenetic and environmental factors may be involved and should be investigated. ■

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