Pathologic Features of Hereditary Cholestatic Diseases

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KEYWORDS

• Liver pathology • Neonatal cholestasis • Bile canalicular transporter disorders • Alagille syndrome

Key points

- An obstructive appearance with ductular reaction can occur in cystic fibrosis, ATP-binding cassette B4 (ABCB4) deficiency, and, uncommonly, in alpha-1-antitrypsin (A1AT) deficiency and Alagille syndrome (early in the disease course).
- In neonates, A1AT deficiency often does not have typical globules in the hepatocytes and instead shows cholestasis and, in some cases, duct loss.
- As well as progressive biliary cirrhosis in children, bile canalicular transporter deficiency can have a milder disease phenotype that includes recurrent cholestasis, intrahepatic cholestasis of pregnancy, chronic cholestatic liver function tests with a mild ductular reaction on biopsy, low phospholipid-associated cholelithiasis with early gallstones, or unexplained late biliary cirrhosis in adults. In severe disease, the level of the γ–glutamyl transferase and the histologic pattern helps to distinguish the likely transporter deficiency.

ABSTRACT

The inherited diseases causing conjugated hyperbilirubinemia are diverse, with variability in clinical severity, histologic appearance, and time of onset. The liver biopsy appearances can also vary depending on whether the initial presentation is in the neonatal period or later. Although many of the disorders have specific histologic features in fully developed and classic cases, biopsies taken early in the disease course may be nonspecific, showing either cholestatic hepatitis or an obstructive pattern of injury requiring close correlation with the laboratory and clinical findings to reach the correct diagnosis. Additionally, increased understanding of the range of hepatic changes occurring in mild deficiencies of bile canalicular transporter proteins suggest that these disorders, particularly ABCB4 deficiency, may be more common than previously recognized; improved awareness should prompt further investigation.

OVERVIEW

Inherited cholestatic diseases are a group of disorders that commonly present early in life and are characterized clinically by conjugated hyperbilirubinemia. Although most have one or more pathognomonic histopathologic features in classic cases, the initial biopsy may not demonstrate these; therefore, the diseases need to be actively considered in a differential diagnosis and the biopsies correlated with the clinical, laboratory, and genetic data. Particularly in the neonate and infant, there are a limited number of reaction patterns. An obstructive appearance with ductular reaction, portal inflammation, edema, and cholestasis can occur not only in biliary but also in metabolic disorders, such as alpha-1-antitrypsin

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Abbreviations

A1AT	Alpha-1-antitrypsin
ABCB4	ATP-binding cassette B4
ABCB11	ATP-binding cassette B11
BRIC	Benign recurrent intrahepatic cholestasis
BSEP	Bile pump export pump
CF	Cystic fibrosis
CFTR	Cystic fibrosis transmembrane conductance regulator
DR	Ductular reaction
FXR	Farnesoid X receptor
HCC	Hepatocellular carcinoma
LPAC	Low phospholipid-associated cholelithiasis
MDR3	Multidrug resistance P-glycoprotein 3
PC	Phosphatidylcholine
PFIC	Progressive familial intrahepatic cholestasis
Pi	Protease inhibitor
γ-GT	γ-Glutamyl transferase

(A1AT) deficiency. Other diseases present as neonatal hepatitis with hepatocyte swelling, giant cell transformation and inflammation, and parenchymal cholestasis.

The histologic patterns may vary between neonates, children, and adults because of several factors. Early clinical manifestations often lead to biopsy before the disease pattern has fully manifested itself, such as A1AT deficiency causing cholestatic changes before characteristic globules develop after 3 months. The maturity of the liver also plays a role particularly in the very young; neonatal factors, such as narrow bile ducts, an incompletely developed biliary tree, slow bile flow, immaturity of bile acid profile, and variable maturity of hepatocytes and cholangiocytes, can exacerbate cholestasis at this time.[1] Duct loss and portal fibrosis can be early changes and may develop quickly in the very young.[1,2] Finally, factors such as the severity of the genetic anomaly and age-associated variation in response to injury modify the biopsy appearances.[1]

It has become clear in recent years that bile acids play an important role in many cholestatic liver disorders and their transporters may be affected by several inherited conditions.[3] The hydrophobic bile acids are osmotically active and have a key role in bile drainage in the canaliculi and proximal bile ductules. They are also toxic, so dysregulation of their secretion or failure to be incorporated into protective micelles in the bile can lead to direct hepatocellular or biliary injury. Mild manifestations of abnormal canalicular biliary transporters can be clinically silent or very slowly progressive, precipitated by external factors, such as hormones, drugs, or inflammation. It is probable that many of these patients remain undiagnosed, but increased awareness and access to genetic testing could see an increase in recognition. A bicarbonate barrier or umbrella at the luminal surface of the cholangiocytes, maintained particularly by the cystic fibrosis (CF) transmembrane conductance regulator (CFTR) chloride channel, is also important for cholangiocyte protection.[4]

CYSTIC FIBROSIS

CF is a common multi-organ hereditary disease affecting mainly lung and pancreatic function and occurring in about 1 in 3000 births.[5] It is caused by mutation in the gene encoding CTFR, an ATP-dependent chloride channel promoting chloride/bicarbonate exchange. Although almost 2000 mutations are described, about two-thirds are due to a phenylalanine deletion (F508del).[6,7]

The mutations in CF result in clinical manifestations of variable severity.[6] Defective function of the CTFR channel causes altered biliary transport of bile acids and also affects the bicarbonate umbrella at the cholangiocyte surface.[4] This results in duct plugging by inspissated secretions and also toxicity to cholangiocytes and hepatocytes, leading to inflammation, ductular proliferation and activation of myofibroblasts to produce fibrosis.[8,9]

Improved therapy and, thus, life span has seen an increase in the number of cases of adult CF liver disease, particularly when revised diagnostic criteria are used[10,11]; it is now seen in about a third of patients,[6,11] although causes only 2.5% of deaths. In those developing significant liver disease it occurs relatively early, with initial manifestations generally developing before 18 years of age and most presenting before the age of 10.[5,12] Neonatal hepatitis can also occur.[13] Advanced cases are characterized by portal hypertension more often than synthetic failure[8]; it was suggested recently that portal venous obliterative lesions possibly caused by gut inflammation[14] could be playing a role, discussed further later. A primary sclerosing cholangitis-like appearance may be seen on imaging (magnetic resonance cholangiopancreatography [MRCP]) with intrahepatic and extrahepatic strictures and beading.[15]

PATHOLOGY

Liver biopsy has a role in CF management but is used variably and is more commonly performed