Contemporary Evaluation of the Pediatric Liver Biopsy

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KEYWORDS

• Liver • Biopsy • Pediatric • Metabolic • Cholestatic

KEY POINTS

- Main histologic patterns of liver injury in children include cholestatic, storage, steatotic, hepatitic, cirrhotic, and neoplastic patterns.
- Ultrastructural examination may be essential for diagnosis in some pediatric liver diseases.
- Hepatic neoplasia may occur in children with metabolic diseases, so investigation for an underlying metabolic disease may be warranted for patient and family.

INTRODUCTION

Liver disease in the pediatric patient encompasses a vast range of disorders that include neonatal cholestasis, disorders of metabolism, drug-induced liver injury, viral diseases, immunologic disorders, nonalcoholic fatty liver disease (NAFLD), and issues affecting the transplanted liver. The liver biopsy is an essential component in the workup of most of these diseases. The most frequent indication for liver biopsy in the native livers of infants is persistent jaundice, whereas in older children hepatomegaly, splenomegaly with gastrointestinal bleeding, incidental discovery of a mass, and elevated serum transaminases are more common indications. Workup in most of these cases typically includes biochemical, genetic, and imaging analysis. Liver biopsies also are performed for prognosis, or monitoring disease progression or response to treatment.[1]

The first percutaneous liver biopsy was performed by Paul Ehrlich in Germany in 1883 but was not widely used until Menghini developed a safer and quicker technique in 1958, leading to widespread use of the liver biopsy in practice.[2,3] This article provides a brief overview of current biopsy procedures and the range of histopathology

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in the more common liver diseases affecting the neonatal/pediatric population. NAFLD, autoimmune disorders with their overlap syndromes, and drug-induced liver disease are discussed elsewhere in this issue.

Surgical pathologists are integral players in the evaluation of liver diseases, and their participation begins when the liver biopsy is received in the laboratory. They must have a working knowledge of the patient's history so tissue can be triaged appropriately. Tissue is routinely processed for light microscopy and ultrastructural examination. Tissue can then be set aside for additional studies based on the patient's clinical history and laboratory tests. Portions can be snap frozen in liquid nitrogen for "special" stains, such as Oil Red O for fat and immunofluorescence, reference laboratory assays, direct assessment of enzyme activities (ie, glycogen storage disease type I), specific chemical assays (ie, copper quantification), viral polymerase chain reaction (PCR), and molecular analyses (ie, mitochondriopathies and tumors).[4] Typically two 2.0-cm-long core biopsies are recommended for there to be enough tissue for all required tests.

Neonatal Cholestasis

Neonatal cholestasis can be caused by a heterogeneous group of disorders that present with jaundice and can also include hypocholic/acholic stools, dark urine, and hypoglycemia.[1] The incidence of neonatal liver disease with clinical or biochemical evidence of cholestasis is approximately 1 in 2500 livebirths.[5] Neonatal cholestasis can be divided into cholestatic, which includes extrahepatic biliary atresia, bile duct paucity, cystic fibrosis, and neonatal sclerosing cholangitis, and intrahepatic cholestasis, which includes viruses, bacteria, genetic causes such as alpha-1-antitrypsin (α1AT) deficiency, tyrosinemia, progressive familial intrahepatic cholestasis (PFIC), and Alagille syndrome (ALGS), and total parenteral nutrition (TPN) cholestasis.[5,6] Many of these disorders demonstrate overlap in clinical history and serum liver chemistries, so the clinical evaluation begins with liver function tests, which include aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase, and levels of direct and conjugated bilirubin, but often require biochemical, genetic, and imaging analyses (**Table 1**).

Biliary atresia (BA) is a congenital fibro-inflammatory obstructive cholangiopathy of the extrahepatic biliary tree and the most common cause of pathologic direct hyperbilirubinemia, with an incidence of 1 in 8000 to 18,000 livebirths.[6,7] It is also the most common cause of progressive liver disease, with approximately 80% of children with BA requiring liver transplantation over the course of their lifetime.[6,8] The underlying pathogenesis of BA remains unclear and may be due to an initial hit by viral infection, such as rotavirus, reovirus-2/3, or cytomegalovirus with a subsequent autoimmune disorder causing the second hit.[9,10] Other hypotheses are based on the role of T, B, and natural killer cells in the destruction of extrahepatic bile ducts mediated by interferon-γ, interleukin (IL)-2, tumor necrosis factor-α, and IL-12.[11] Recently, maternal chimeric $CD8^+$ T cells were discovered in BA infant livers, suggesting graft-versus-host interaction by engrafted maternal effector T cells as the initiating hit.[12,13] The typical biopsy histology consists of a triad of expanded portal ducts with bile plugs, acute pericholangitis and direct cholangitis, and bile ductule proliferation. Portal tract edema is a prominent feature as well, but may be seen in other extrahepatic obstructive conditions. BA may show multinucleated "giant" hepatocytes containing bile, which are not uncommon in all forms of neonatal cholestasis and provide a challenge to the pathologist. Fibrosis develops quickly with rapid progression to cirrhosis, so early recognition and diagnosis are essential. Early intervention with a hepatoportoenterostomy (HPE), initially described by Morio Kasai[3] to redirect the flow of bile directly into the duodenum, provided the basis for survival, and patients who receive an HPE