Hepatic Neoplasia and Metabolic Diseases in Children

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KEYWORDS

• Cirrhosis • Tyrosinemia • α_1-Antitrypsin • Hemochromatosis
• Reversion • NTBC • Hepatocellular cancer

Hepatic involvement in metabolic diseases is a natural corollary to the central and pivotal role of the liver in metabolism. Most childhood metabolic liver diseases are classical mendelian single-gene disorders affecting key enzymes and proteins in diverse metabolic pathways.[1,2] Other disorders, such as the metabolic syndrome and its hepatic manifestation, nonalcoholic fatty liver disease, are multifactorial (genetic dyslipidemias, insulin resistance, and diet),[3–5] and increasingly prevalent in the pediatric age group in association with childhood obesity.[6] Yet others (eg, idiopathic copper toxicosis and Indian childhood cirrhosis) are postulated to be multifactorial, with contribution from as yet unresolved genetic and environmental risk factors.[7–9]

Metabolic liver disease is often studied within the paradigm of "toxic metabolite" accumulation and chronic injury. In this model of pathogenesis, metabolic disorders initially present with characteristic histologic and ultrastructural patterns on liver biopsy,[10,11] but chronic injury over months or years leads to cirrhosis or hepatic neoplasia. Prototypes of such a model are the endoplasmic reticulum retention of α_1-antitrypsin (AAT) in AAT deficiency, increased levels of succinylacetone in hereditary tyrosinemia, and increased glycogen in glycogen storage disease (GSD). Accordingly, the most frequently diagnosed hepatic neoplasm in children with inherited metabolic disorders is hepatocellular carcinoma (HCC),[10,12] a tumor otherwise rare in the pediatric population[13] but the most common to arise in a cirrhotic liver. Cholangiocarcinoma, combined cholangio-hepatocellular carcinoma, hepatic adenoma, and focal nodular hyperplasia are less frequently encountered (**Table 1**). In contrast, hepatoblastoma, the most common pediatric liver malignancy, is not usually associated with cirrhosis or metabolic disease but rather with other heritable defects.[10,12]

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Table 1
List of metabolic disorders associated with hepatocellular carcinoma

Disorder	Gene	Inheritance	Neoplasia	Background Cirrhosis	RR
Hereditary tyrosinemia	*FAH*	AR	HCC	++	ND
AAT deficiency	*SERPINA1*	ACoD	HCC, CC, CHCC	±	5
Hereditary hemochromatosis	*HFE*	AR	HCC	++	20
Wilson disease	*ATP7B*	AR	HCC, CC	+	ND
Acute intermittent porphyria	*HMBS*	AD	HCC	+	>30
PFIC-2	*ABCB11* (*MDR3*)	AR	HCC, CC, CHCC	±	ND
Mitochondrial ETC disorders	Multiple	AR	HCC	+	ND
GSD-I	*G6PC*, *G6PT*	AR	HA, HCC	-	ND
GSD-III	*AGL*	AR	HCC, HA	+	ND
GSD-IV	*GBE1*	AR	HCC	+	ND
NASH	Multiple	Complex	HCC	+	ND

Abbreviations: AAT, α_1-antitrypsin; ABCB11, ATP-binding cassette, subfamily B, member 11; ACoD, autosomal codominant; AD, autosomal dominant; AGL, amylo-1,6-glucosidase, 4-α-glucanotransferase (glycogen debrancher enzyme); AR, autosomal recessive; ATP7B, ATPase, Cu++ transporting, beta polypeptide; CC, cholangiocarcinoma; CHCC, mixed cholangio-hepatocellular carcinoma; FAH, fumarylacetoacetate hydrolase; G6PC, glucose-6-phosphatase, catalytic subunit; G6PT, glucose-6-phosphatase transporter; GBE1, glucan (1,4-α-), branching enzyme 1 (glycogen branching enzyme); GSD, glycogen storage disease; HCC, hepatocellular carcinoma; HFE, hemochromatosis; HMBS, hydroxymethylbilane synthase; NASH, nonalcoholic steatohepatitis; ND, not determined; PFIC, progressive familial intrahepatic cholestasis; RR, relative risk; SERPINA1, serine protease inhibitor, alpha 1.