Metabolic disorders of the liver

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Abstract

Metabolic diseases could be inherited as inborn errors of metabolism or acquired. In this review we discuss some of the metabolic disorders likely to present in the adult population and in which liver biopsy could be indicated as part of diagnosis or treatment. These include iron overload/hemochromatosis, Wilson's disease, alpha-1-antitrypsin deficiency, Niemann—Pick's disease and Gaucher's disease with emphasis on characteristic or helpful histopathologic features. In this era of molecular and other non-invasive analyses, the role of liver biopsy for primary diagnosis has decreased but is still an important tool for supplementing clinical/molecular diagnosis, staging disease and as a guide to management. In addition to qualitative assessment, quantitative measurements of iron and copper per unit dry weight of liver tissue can be performed on paraffin-embedded blocks and should be considered in patients being treated for iron overload or being worked up for possible Wilson's disease respectively. Gaucher's disease and Niemann—Pick's disease are examples of lysosomal storage diseases that could present outside of the pediatric population; these diseases have fairly distinguishing features that could be used to triage which patients need additional enzyme or other assays for definitive diagnoses. While non-alcoholic steatohepatitis remains the commonest metabolic liver disease in adult population, the pathologist should also be aware of these other entities discussed in this review.

Keywords alpha-1-antitrypsin deficiency; Gaucher's disease; hemochromatosis; iron overload; metabolic liver diseases; Niemann—Pick's disease; Wilson's disease

Introduction

Metabolic diseases could be inherited as inborn errors of metabolism or acquired. In many of these disorders, the liver is one of the major organs affected. Historically liver biopsy along with clinical and laboratory findings has played a big role in diagnosis and management of these diseases. In the new era of molecular analysis and development of increasingly more accurate non-invasive methods, liver biopsy has continued to play some, but not as prominent a role as in the past, at least in making initial diagnoses in many cases of metabolic disorders. Liver biopsy however remains an important tool for supplementing clinical and molecular diagnosis, as well as defining prognosis, staging disease and serving as a guide to management.[1—3]

The list of metabolic disorders with liver involvement is quite long and includes **alpha-1-antitrypsin deficiency**, cystic fibrosis, erythropoietic protoporphyria, familial apolipoprotein A-I amyloidosis, galactosemia, **Gaucher's disease**, glycogen storage diseases (various types), GM2 gangliosidosis, heme oxygenase-1 deficiency, **iron overload/hemochromatosis**, hereditary fructose intolerance, hereditary hepatic coproporphyria, hereditary tyrosinemia, mucopolysaccharidoses, **Niemann—Pick's disease**, **non-alcoholic steatohepatitis**, primary hyperoxaluria, and **Wilson's disease**. This review addresses the common metabolic diseases presenting in the adult population (in bold letters above), with the exception of non-alcoholic steatohepatitis, which is reviewed separately in this series.

Iron overload in the liver

Iron overload is a condition in which there is excessive iron accumulation in the liver and other organs. Abnormal accumulation of iron could be primary, (due to an inherited abnormality of iron metabolism) or secondary/acquired (as a result of increased iron load beyond the body's ability to utilize iron); excessive unutilized iron is therefore forced to be stored within macrophages and parenchymal organs including the liver.

Inherited causes of iron overload: mutations in several genes involved in iron absorption, transport and other metabolic activities have been implicated as a cause of iron overload. The largest is the hemochromatosis (HH) group, of which four types (HH1—HH4) are described (Table 1). HH1, in which the *HFE* gene is mutated, is by far the commonest of all variants, accounting for 85—90% of patients who have inherited forms of iron metabolic abnormalities and overload. The main disease-causing genotype is the homozygous C282Y point mutation in this gene or compound heterozygosity with one allele carrying the C282Y mutation and the other allele with the H63D or some other less common mutation. The remaining 10—15% of patients with inherited forms of iron overload have mutations in one of the other genes involved in iron homeostasis.[4—6] A summary of genes linked to inherited iron overload syndromes is shown in Table 1.[6,7]

Ferroportin disease (HH4) is one example of the other types of inherited iron overload conditions that differ from the rest in having an autosomal dominant (rather than autosomal recessive) pattern of inheritance[6] (Table 1). It can show a great deal of phenotypic variability. It is caused by a defect in *SLC40A1* gene, which encodes ferroportin, a protein that modulates iron efflux by macrophages and enterocytes. Its pattern of histologic findings will be discussed later but also differs from HH1 in having a primarily macrophage (Kupffer cells) site of accumulation.

A common denominator in HH types 1—4 is Hepcidin which is a key protein in the regulation of iron absorption from the intestine. In HH1 for example the C282Y mutation in the *HFE* gene prevents the protein from reaching the cell surface of enterocytes and interacting with, and thereby modulating, Hepcidin synthesis and function. This loss of interaction leads to reduced synthesis of Hepcidin and ultimately uncontrolled absorption of iron from the intestine.[6]

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Genetic abnormalities of iron metabolism: list of mutated genes with respective affected protein products, inheritance patterns, and disease phenotypes

Gene	Protein	Also known as	Inheritance	Onset	Primary site of iron deposition
HFE	HFE	HH type 1	AR	Late	Hepatocyte
HJV	Hemojuvelin	JH type 2A	AR	Early	Hepatocyte
HAMP	Hepcidin antimicrobial peptide	JH type 2B; HH type 2	AR	Early	Hepatocyte
TFR2	Transferrin receptor	HH type 3	AR	Late	*Hepatocyte*
SCL 11A2 (DMT-1)	DMT1	None yet	AR	Early	*Hepatocyte*
SCL 40A	Ferroportin	Ferroportin disease type B; HH type 4	AD	Late	Kupffer cells
TF	Transferrin	Hypotransferrinemia	AR	Early	Kupffer cells
CP	Ceruloplasmin	Hypoceruloplasminemia	AR	Late	Kupffer cells

AR: autosomal recessive; AD: autosomal dominant; JH: juvenile hemochromatosis; HH: hereditary hemochromatosis; DMT1: divalent metal transporter 1.

Table 1

African iron overload — previously considered as a dietary iron overload, which occurs mostly in sub-Saharan Africa is now considered to be due to a non-HFE-related genetic abnormality which could be exacerbated by consumption of an iron-rich fermented beverage.[5,8]

Secondary causes of iron overload: the most common causes of secondary iron overload are ineffective erythropoiesis, parenteral iron overload, and chronic liver disease.[9,10] Except for individuals with genetic predisposition or ineffective erythropoiesis, oral iron intake usually does not cause iron overload.[10]

Clinical features

With an incidence of 1/250, HH1 is one of the most common genetic disorders in Caucasians.[6,10] The presenting signs and symptoms vary depending on the stage of the disease when diagnosis is made. This could range from no symptoms to signs and symptoms of tissue damage due to iron overload in many organs, including abdominal pain, arthralgias (usually involving metacarpophalangeal joints), chondrocalcinosis, decreased libido, skin pigmentation and symptoms of heart failure, diabetes, and liver insufficiency. In the early stages of the disease the liver involvement presents as hepatomegaly with only mild changes in liver enzymes and in the later stages as ascites, portal hypertension and encephalopathy.[5,10]

Mechanism of liver injury

Iron is a direct hepatotoxin. Based on multiple experimental models of iron overload, it is shown that iron-induced oxidative damage leads to rapid lipid peroxidation of hepatocytes, mitochondrial and lysosomal membranes. This ultimately leads to hepatocyte death, activation of Kupffer cells and release of cytokines causing stellate cell activation and collagen production, resulting in micro- and eventually macro-nodular cirrhosis.[5,10–14] Following development of advanced fibrosis, the risk for hepatocellular carcinoma increases, with an annual incidence of about 3–4% and a relative risk compared to normal population of about 20.[5,15]

Role of liver biopsy

Before the availability of molecular analysis, liver biopsy played an essential role in diagnosis of hereditary hemochromatosis.[3,10] Currently its primary role is in assessing the degree of iron overload, fibrosis and presence or absence of cirrhosis in these patients, as well as identifying other concurrent liver diseases overlapping with iron overload.[10,16] Also, up to 50% of patients with other liver diseases such as alcoholic liver disease, NAFLD or chronic viral hepatitis demonstrate abnormal serum iron studies.[5,17] Liver biopsy therefore provides prognostic and diagnostic benefits in patients, including those with iron overload but having equivocal biochemical results and/or no known genetic alteration.[10,16]

The following recommendations for evaluating patients with HH and other instances of iron overload with liver biopsy, were published in 2011 by the *American Association for the Study of Liver Diseases*:[5]

- To stage the degree of liver disease in C282Y homozygotes or compound heterozygotes if liver enzymes (ALT, AST) are elevated or if ferritin is >1000 μg/L.
- For diagnosis and prognosis in patients with phenotypic markers of iron overload who are not C282Y homozygotes or compound heterozygotes.
- In patients with non-HFE-related HH, data on hepatic iron concentration is useful, along with histopathologic iron staining, to determine the degree and cellular distribution of iron.

Histopathologic findings

Routine histopathologic assessment of liver biopsy includes hematoxylin and eosin stain (H&E), Masson's trichrome stain for evaluation of fibrosis as well as Perls' Prussian blue stain for assessment of the degree and distribution of iron deposition. However histological findings lack the specificity to determine a cause of iron overload, including the ability to determine primary versus secondary as considerable overlap of pathologic findings exists. In HH, iron deposits of golden brown hemosiderin granules are dispersed evenly, beginning in the cytoplasm of periportal hepatocytes and can be identified even on H&E stain (Figure 1a). Pearls' Prussian blue stain is a histochemical stain that converts iron from the ferric state into an insoluble blue compound that could be easily seen histologically (Figure 1b–d).[18] Presence of a blue blush in all hepatocytes is one of the major pitfalls in interpretation of Perls' stain (Figure 1c). This