367e Genetic, Metabolic, and Infiltrative Diseases Affecting the Liver

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There are a number of disorders of the liver that fit within the categories of genetic, metabolic, and infiltrative disorders (Table 367e-1). Inherited disorders include hemochromatosis, Wilson's disease, α_1 antitrypsin (α_1AT) deficiency, and cystic fibrosis (CF). Hemochromatosis is the most common inherited disorder affecting white populations, with the genetic susceptibility for the disease being identified in 1 in 250 individuals. Over the past 15 years, it has become increasingly apparent that nonalcoholic fatty liver disease (NAFLD) is the most common cause of elevated liver enzymes found in the U.S. population. This disorder is discussed in greater detail in Chap. 364. Infiltrative disorders of the liver are relatively rare.

GENETIC LIVER DISEASES

Hereditary Hemochromatosis Hereditary hemochromatosis (HH) is a common inherited disorder of iron metabolism (Chap. 428). Our knowledge of the disease and its phenotypic expression has changed since 1996, when the gene for HH, called *HFE*, was identified, allowing for genetic testing for the two major mutations (C282Y and H63D) that are responsible for *HFE*-related HH. Subsequently, several additional genes/proteins involved in the regulation of iron homeostasis have been identified, contributing to a better understanding of cellular iron uptake and release and the characterization of additional causes of inherited iron overload (Table 367e-2).

Most patients with HH are asymptomatic; however, when patients present with symptoms, they are frequently nonspecific and include weakness, fatigue, lethargy, and weight loss. Specific, organ-related symptoms include abdominal pain, arthralgias, and symptoms and signs of chronic liver disease. Increasingly, most patients are now identified before they have symptoms, either through family studies or from the performance of screening iron studies. Several prospective population studies have shown that C282Y homozygosity is found in about 1 in 250 individuals of northern European descent, with the heterozygote frequency seen in approximately 1 in 10 individuals. It is important to consider HH in patients who present with the symptoms and signs known to occur in established HH. When confronted with abnormal serum iron studies, clinicians should not wait for typical symptoms or findings of HH to appear before considering the diagnosis. However, once the diagnosis of HH is considered, either by an evaluation of abnormal screening iron studies in the context of family studies, in a patient with an abnormal genetic test, or in the evaluation of a patient with any of the typical symptoms (Table 367e-3) or clinical findings (Table 367e-4), definitive diagnosis is relatively straightforward. Transferrin saturation (serum iron divided by total iron-binding capacity [TIBC] or transferrin, times 100%) and ferritin levels should be obtained. Both of these will be elevated in a symptomatic patient. It must be remembered that ferritin is an acute-phase reactant and can be elevated in a number of other inflammatory disorders, such as rheumatoid arthritis, or in various neoplastic diseases, such as lymphoma or other cancers. Also, serum ferritin is elevated in a majority of patients with nonalcoholic steatohepatitis (NASH), hepatitis C, and alcoholic liver disease in the absence of iron overload.

At present, if patients have an elevated transferrin saturation or ferritin level, genetic testing should be performed; if they are a C282Y homozygote or a compound heterozygote (C282Y/H63D), the diagnosis is confirmed. If liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) are elevated or the ferritin is >1000 μg/L, the patient should be considered for liver biopsy because there is an increased frequency of advanced fibrosis in these individuals. If liver biopsy is performed, iron deposition is found in a periportal distribution with a periportal to pericentral gradient; iron is found predominantly in parenchymal cells, and Kupffer cells are spared.

TABLE 367e-1 GENETIC, METABOLIC, AND INFILTRATIVE DISEASES AFFECTING THE LIVER

Genetic
• Hereditary hemochromatosis
• Wilson's disease
• α_1 Antitrypsin deficiency
• Cystic fibrosis
Metabolic
• Nonalcoholic fatty liver disease
• Lipid storage diseases
• Gaucher's
• Niemann-Pick
• Tangier
• Fabry's
• Porphyrias
• Porphyria cutanea tarda
Infiltrative disorders
• Amyloidosis
• Granulomas
• Sarcoidosis
• Lymphoma

TABLE 367e-2 CLASSIFICATION OF IRON OVERLOAD SYNDROMES

Hereditary Hemochromatosis (HH)
HFE-related (type 1)
C282Y/C282Y
C282Y/H63D
Other *HFE* mutations
Non-*HFE*-related
Juvenile HH
HJV—hemojuvelin (type 2a)
HAMP—hepcidin (type 2b)
TfR2-related HH (type 3)
Ferroportin-related HH (type 4)
African iron overload
Secondary Iron Overload
Iron-loading anemias
Parenteral iron overload
Chronic liver disease
Miscellaneous
Neonatal iron overload
Aceruloplasminemia
Congenital atransferrinemia

Abbreviations: HAMP, hepcidin; HJV, hemojuvelin; TfR2, transferrin receptor 2.

TABLE 367e-3 SYMPTOMS OF HEREDITARY HEMOCHROMATOSIS

Symptom	%
Weakness, lethargy, fatigue	40–85
Apathy, lack of interest	40–85
Abdominal pain	30–60
Weight loss	30–60
Arthralgias	40–60
Loss of libido, impotence	30–60
Amenorrhea	20–60
Congestive heart failure symptoms	0–40