advanced disease (i.e., bridging fibrosis, cirrhosis) on histologic examination.

Liver biopsy is the "gold standard" for diagnosis of NASH. The procedure is invasive and costly and can cause complications including a small mortality risk (0.01% to 0.1%). Radiologic imaging studies are neither sensitive nor able to distinguish simple steatosis from steatohepatitis. Noninvasive biomarkers are currently under active investigation. The NAFLD Activity Score has been developed and represents the sum of scores for steatosis, lobular inflammation, and hepatocyte ballooning. It ranges from 0 to 8, with a scores of 5 or higher considered diagnostic of NASH.

Currently, no generally accepted medical treatment is available for NASH. However, weight loss and regular exercise are associated with biochemical and histologic improvement and are important components of therapy. Vitamin E and pioglitazone have recently been shown to improve hepatic inflammation in nondiabetic patients with NASH, but they are not routinely recommended because of questions regarding long-term safety.

Genetic and Metabolic Hepatitis

Hemochromatosis is an autosomal recessive genetic disorder that causes defective sensing of iron stores and leads to excessive absorption of iron from the digestive tract. In the United States, about 5 of every 1000 white people have the condition. Elevated ferritin and transferrin saturation values are typically used to screen patients with evidence of chronic liver disease and guide the need for further genetic testing. Most patients with hemochromatosis are homozygous for the C282Y mutation in the *HFE* gene, and a subset of individuals who are heterozygous for both C282Y and the H63D mutation may also develop iron overload. Iron overload is very uncommon among those who are homozygous for the H63D mutation. Genetic mutations in a number of other proteins involving in iron sensing have also been associated with iron overload but are not routinely tested in clinical practice. Hemochromatosis is a systemic disease that can cause skin discoloration, liver cirrhosis and cancer, heart failure, diabetes mellitus, hypogonadism, and arthralgias due to iron deposition in various organs. A high index of suspicion is required to detect the disorder in early stages. The standard treatment for hemochromatosis is therapeutic phlebotomy. For patients who cannot undergo phlebotomy, chelation therapy may be offered.

Wilson's disease is an autosomal recessive genetic disorder that results from mutations in the *ATP7B* gene located on chromosome 13. These mutations result in excessive accumulation of copper in a number of organs, most notably the liver, cornea, and brain. The prevalence of the disease is approximately 1 in 30,000 live births in most populations. Wilson's disease can occur at any age. Measurement of the 24-hour urine copper excretion, slit lamp examination of corneas for Kayser-Fleischer rings, and direct measurement of hepatic copper confirm the diagnosis. Patients should receive lifelong chelation treatment with either penicillamine or trientine. Zinc may be used to maintain stable copper levels in the body.

α_1-Antitrypsin deficiency is an autosomal recessive genetic disorder of chromosome 14 that causes retention of α_1-antitrypsin in the liver, resulting in liver damage. The normal gene product is designated as PiM, and the deficiency variants are PiS (50% to 60%) and PiZ (10% to 20%). The most common carrier phenotypes are PiMS and PiMZ, and the disease phenotypes are PiZZ, PiSS, and PiSZ. A low serum α_1-antitrypsin level and diastase-positive staining of hepatocellular α_1-antitrypsin inclusions on liver biopsy support the diagnosis. Phenotypic testing in the serum has been the traditional gold standard for the diagnosis. However, genotypic testing is now available and widely used. Lung disease results from a loss of protective effects in patients with low levels of circulating α_1-antitrypsin. α_1-Antitrypsin replacement therapy is an option for those with lung disease but is not useful for patients with liver disease.

For a deeper discussion on this topic, please see Chapters 148, "Acute Viral Hepatitis," and 149, "Chronic Viral and Autoimmune Hepatitis," in Goldman-Cecil Medicine, *25th Edition.*

SUGGESTED READINGS

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