LABORATORY FINDINGS

Suspicion of NASH is usually prompted by abnormal serum chemistries. Typically, these laboratory test abnormalities are noted during "routine" testing or when patients seek attention for other illnesses. Increased aminotransferase activities are the predominant laboratory abnormality reported in patients with NASH. Usually, ALT and/or AST are only mildly to moderately increased in NASH. Unlike hospitalized patients with alcohol-induced steatohepatitis, who typically manifest disproportionate increases in AST relative to ALT, patients with NASH usually have AST/ALT ratios of less than 1. Increased levels of serum alkaline phosphatase and y-glutamyl transpeptidase are not uncommon in NASH patients. However, hyperbilirubinemia, prolonged prothrombin time, and hypoalbuminemia are infrequently noted in most series. Abnormal serum lipid profiles (e.g., hypercholesterolemia, hypertriglyceridemia) and/or elevated serum glucose concentrations are also common and have been reported in 25 to 75% of patients with NASH. A recent series from Australia reported that elevated serum ferritin, iron, and/or decreased transferring saturation were common findings in NASH. Further characterization of these patients revealed that about one third of NASH patients had either one or two copies of the Cys282Tyr mutation in the HFe gene (the genetic defect believed to cause hemochromatosis). However, not all homozygotes for this mutation had elevated liver iron stores, and some patients with increased serum iron parameters were neither homozygous nor heterozygous for the hemochromatosis mutation. The authors noted a trend toward more severe hepatic fibrosis in NASH patients with a genetic basis for hepatic iron overload but acknowledged that hepatic iron overload occurred in only a minority of their NASH patients. These results do not permit firm recommendations about the wisdom of genetic testing for hemochromatosis or phlebotomy therapy in patients with NASH.

A diagnosis of NASH can only be established in patients who do not consume significant amounts of alcohol. There is reasonably good evidence that incidence of alcohol-induced liver disease only begins to increase after certain "threshold" levels of alcohol consumption (i.e., 20 g ethanol/day in women and 80 g ethanol/day in men) are exceeded habitually. Thus, alcohol is not incriminated as the cause of liver disease in individuals who report alcohol intakes that consistently fall below these threshold doses. However, it is conceivable that alcohol may contribute to liver disease in some individuals with NASH who are unusually sensitive to alcohol-mediated hepatotoxicity. In addition, there has long been skepticism about the validity of self-reporting as a measure of alcohol consumption. This has prompted cynicism by some physicians who doubt that the histologic features of alcoholic liver disease can ever occur in the absence of alcohol consumption.

The latter arguments are difficult to refute, since there is no perfect test to identify alcohol use, particularly within the context of underlying liver disease. Indeed, some commonly used tests to identify habitual alcohol use (e.g., abnormally elevated aminotransferases y-glutamyl transpeptidase, or mean corpuscular volume (MCV)) are increased by liver disease per se and, hence, may overestimate alcohol use in the setting. For that reason, the diagnostic utility of these markers to differentiate NASH from alcohol-induced liver disease is limited.

Recently, other biochemical markers, partially desialylated transferring (dTf) and the mitochondrial isozyme of aspartate aminotransferase (mAST), have been advocated as tests for active alcohol use in patients with liver disease. The ratio of desialylated transferring (dTf) to total transferring (dTf/Tf) appears to be the best single marker of chronic excessive alcohol consumption in this setting. In one study, which included patients with liver disease, a dTf/Tf ration of 1.3% or greater was a reliable indicator of excessive chronic alcohol consumption, with a sensitivity of 81% and a specificity of 98%. By contrast, the ratio of mitochondrial AST to total AST was not useful in distinguishing patients with NASH from alcoholic subjects. Despite early promising results with dTf testing, it is premature to conclude that the test is required to establish the diagnosis of NASH.

On the other hand, testing to exclude viral hepatitis has become prerequisite for the diagnosis of NASH. While studies of NASH typically exclude individuals infected with hepatitis A or B, early reports of NASH were published before routine testing for hepatitis C infection was available. Results of more recent studies

suggest that HCV is not involved in the pathogenesis of NASH, since markers of hepatitis C infections are negative in the great majority of NASH patients. Similarly, there is no evidence that the prevalence of hepatitis G infection is increased in patients with NASH.

Several noninvasive imaging techniques, including ultrasonography, computed tomography (CT), and magnetic resonance imaging (MRI), can identify hepatic steatosis and have been advocated as noninvasive diagnostic tests for NASH. Of these, phase-contrast MRI appears to be the most promising because its results correlate well with the degree of histologic steatosis. Unfortunately, none of these imaging techniques is sufficiently sensitive to detect hepatic inflammation. Similarly, these tests can only suggest the presence of hepatic fibrosis after cirrhosis has progressed to the stage at which extrahepatic manifestations of portal hypertension are evident. Thus, currently available imaging modalities are relatively insensitive and nonspecific and can neither definitively establish a diagnosis of NASH nor reliably grade its severity. This implies that liver biopsy remains the best diagnostic test for confirming clinical suspicions of NASH.

HISTOLOGICAL FEATURES

The major histologic features of NASH resemble those of alcohol-induced liver disease: steatosis (fatty liver), hepatitis (parenchymal inflammation with or without accompanying focal necrosis), and variable degrees of fibrosis (including cirrhosis). The histologic stages are presented in Table 2. As in alcoholic liver disease, steatosis in NASH is predominantly macrovesicular and more or less diffusely distributed throughout the liver lobule, although prominent microvesicular or zone 3 (perivenular) steatosis have been reported occasionally. In NASH, lobular infiltration with both acute and chronic inflammatory cells and Mallory body formation resembles that noted in some patients with alcoholic liver disease. Patients with NASH can also develop perivenular and sinusoidal fibrosis, reminiscent of that observed in alcohol-induced liver disease. As in patients with alcohol-induced fibrosis, fibrosis can progress to cirrhosis in NASH. Indeed, NASH is indistinguishable from alcohol-induced liver disease on histologic grounds. Given the similarities between the histologic features of NASH and alcohol-induced liver pathology, it is likely that the two diseases have a similar natural history. If true, steatosis is the principal finding early in NASH, but episodes of steatohepatitis can punctuate the course, and cirrhosis will eventually develop in some patients with NASH. Failure to appreciate time-dependent variations in the histologic features of NASH may explain some of the confusion about its prognosis. This is compounded by the general dearth of long-term epidemiologic studies in NASH patients.

TABLE 2. HISTOLOGIC STAGES OF NASH

Steatosis
Steatohepatitis
Cirrhosis

ROLE OF LIVER BIOPSY AS A DIAGNOSTIC TEST

The combination of history, physical examination, noninvasive blood tests and imaging studies is very useful for excluding other diseases as an explanation for abnormal LFT's. Thus, liver biopsy is seldom necessary simply to diagnose NASH, which is currently a diagnosis made by excluding other causes of chronic hepatitis in patients with fatty liver. On the other hand, liver biopsy is the only diagnostic test that can reliably identify and quantify hepatic necrosis, inflammation and fibrosis. Thus, liver biopsy is the most sensitive and specific means to stage patients with NASH. As discussed below, histologic features do provide important prognostic information about NASH. This may guide management recommendations concerning the advisability of other diagnostic testing (e.g., screening endoscopy for varices or screening α-fetoprotein with or without ultrasonography in patients with unsuspected cirrhosis), as well as providing a justification for aggressive treatment strategies and/or follow-up visits. However, because so little is known about the natural history of untreated or treated NASH, it is impossible to justify liver biopsy on the

grounds that it will permit the identification of patients whose natural history would be altered beneficially by any change in management recommendations.

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Tomorrow we will pick up with Prognosis.