REVIEW

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The spectrum of nonalcoholic fatty liver disease: From steatosis to nonalcoholic steatohepatitis

ABSTRACT

Nonalcoholic fatty liver disease (NAFL) has been recognized only in the past 20 years. Autopsy studies indicate it is remarkably common, especially among obese persons and patients with type 2 diabetes. Although fatty liver alone is usually benign, an identifiable subset of patients may be at risk of progression to cirrhosis and liver failure. The role of liver biopsy is controversial. No specific, effective therapy as yet exists, although management of weight, lipid levels, and glucose levels is recommended.

KEY POINTS

NAFL spans a spectrum of histologic findings, from steatosis alone, to steatohepatitis and steatonecrosis, to cirrhosis.

In NAFL, the alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels are mildly elevated in more than 90% of cases. In addition, the AST/ALT ratio is usually less than 1. In contrast, in alcoholic liver disease, the AST/ALT ratio is usually greater than 2.

Patients with type 2 diabetes plus hepatocyte necrosis, ballooning, Mallory hyaline, or fibrosis seem to be at risk of progressive liver disease. We therefore consider performing a liver biopsy in patients with type 2 diabetes whose liver enzyme levels remain elevated despite good glycemic control.

The prevalence of NAFL is expected to increase as the US public becomes more overweight; at present as many as 25% of American adults are overweight.

QUESTIONS STILL ABOUND about nonalcoholic fatty liver disease (NAFL), a complex first recognized only about 20 years ago. It is a common cause of elevated liver enzymes, especially among women, persons with type 2 diabetes, and the obese. Although usually benign, it can progress to cirrhosis and liver failure in some groups of patients.

How to diagnose and treat NAFL is not yet clear, but we are beginning to understand which patients with NAFL are at greatest risk of progressive liver disease. Currently, several different medications are being evaluated as potential treatments.

DEFINITIONS

NAFL describes a condition in which the liver undergoes changes identical to those in alcoholic liver disease—except that the patient does not consume alcohol in excess. Other terms for the disease are pseudoalcoholic hepatitis, alcohol-like hepatitis, nonalcoholic Laënnec's disease, fatty liver hepatitis, steatonecrosis, and diabetic hepatitis. The histologic changes can range from simple fat deposition (steatosis) to associated inflammation to necrosis (nonalcoholic steatohepatitis [NASH]) and fibrosis.[1–19]

EPIDEMIOLOGY

Autopsy studies of persons who died in air crashes or motor vehicle accidents indicate that approximately 3% have NAFL. As high as this is, the prevalence is even higher in the presence of several principal risk factors[1–6]:

Pathogenesis of nonalcoholic fatty liver disease: current theories

THEORIES ABOUT the pathogenesis of NAFL include abnormalities of lipid metabolism, increased hepatic lipid peroxidation, and endotoxemia.[1–6,10,13–15]

ABNORMALITIES OF LIPID METABOLISM

Fat can accumulate in the liver as a consequence of aberrations in any of four basic processes:

- Increased free fatty acid delivery to the liver
- Decreased beta-oxidation of fatty acids
- Increased triglyceride synthesis within the liver
- Decreased synthesis or secretion of very-low-density lipoprotein.

This complex process requires a fully functioning protein synthetic capacity in addition to intact mechanisms for exocytosis. Any defect in this process may result in the accumulation of triglycerides within hepatocytes, presenting as fatty liver.

INCREASED HEPATIC LIPID PEROXIDATION

However, steatosis alone is not harmful: a second insult is required for progression to steatonecrosis and fibrosis. Although the mechanism is not clear, abnormal lipid peroxidation may be responsible for this second "hit." It seems plausible that increased oxidative stress leads to peroxidation of membrane lipids, directly damaging the cell. Additionally, it can contribute to the development of toxic by-products such as malondialdehyde and 4-hydroxynanolol. These by-products, in turn, can be proinflammatory and can induce fibrogenesis, both leading to further hepatocyte injury and cirrhosis.

Hyperinsulinemia, seen in obesity and type 2 diabetes, may inhibit free fatty acid oxidation and thereby increase the levels of toxic free fatty acids in the liver. This in turn contributes to worsening oxidative stress, leading to progressive hepatocyte injury and fibrosis.

In addition, a recent theory suggests that mitochondrial uncoupling proteins reduce the cellular energy supply, rendering hepatocytes more vulnerable to any further oxidative stress.

Another potential substrate for oxidative stress is hepatic iron. In a study of the mutation commonly associated with genetic hemochromatosis (*HFE*),[14] the mutation was more commonly found in patients with nonalcoholic steatohepatitis (NASH) and was associated with more fibrosis, indicating the potential role of iron overload in enhancing the progressive form of liver disease. However, in another long-term study of 65 patients with NAFL, significant iron overload (measured by histologic staining and hepatic iron quantitation) was not seen. Iron overload was not associated with any pathologic features or outcome measures of progressive liver disease.[15]

Although patients with both NAFL and iron overload may have a more aggressive course, most patients with NAFL do not have iron overload. The issue of iron and its potential role in the progression of NAFL remains unclear.

ENDOTOXIN THEORY

In animal models, endotoxins can induce liver damage similar to steatonecrosis. It is postulated that a generalized Kupffer cell dysfunction allows chronic low-grade endotoxemia, which can lead to elevated cytokine production, which in turn can induce steatosis and liver cell damage. This theory may explain the association of NAFL with operations such as gastrointestinal bypass.[4]

- Chronically elevated aminotransferase levels—from 21% to 63%[7–9]
- Type 2 diabetes—as high as 50%
- Obesity—18.5% in one study,[16] compared with 2.7% in lean persons.

In addition to obesity and type 2 diabetes, the following factors and conditions are associated with NAFL:

- Female gender
- Hyperlipidemia
- Jejunoileal bypass or intestinal resection

- Drugs such as amiodarone, perhexiline maleate, glucocorticoids, synthetic estrogens, methotrexate, tamoxifen, and calcium channel blockers.

However, recent studies indicate that some patients with NAFL have none of the above.[5,10–12]

CLINICAL COURSE

Studies have conflicted about the progression of NAFL to cirrhosis. No patient progressed to cirrhosis in a study of 40 patients with steatosis alone,[20] while 5 (18%) of 28 patients progressed to cirrhosis in a pooled analysis with sequential liver biopsies.[17,18] In a recent study of 132 patients with NAFL and at least 10 years of follow-up,[11] those with steatosis alone did not progress to cirrhosis, while 25% of those whose steatosis was accompanied by liver cell damage (ie, hepatocyte necrosis, ballooning, Mallory hyaline, or fibrosis) did progress to cirrhosis. Furthermore, patients with NAFL and type 2 diabetes with evidence of these pathologic features on liver biopsy seem particularly at risk for progressive liver disease.[12]

How do we reconcile these seeming discrepancies? For one thing, different investigators used different pathologic definitions to describe nonalcoholic steatohepatitis. Although some required the presence of hepatocyte necrosis, ballooning, or fibrosis, others only required steatosis and inflammation. In addition, the amount of alcohol required to exclude patients from these studies varied widely, from 20 g/day to 140 g/day. Moreover, superimposed hepatitis C and iron overload were not always excluded. Finally, most studies had short-term follow-up, and few included sequential liver biopsies.

On balance, if strict criteria for pathologic and clinical definition of NAFL and its subtypes are used, a group of patients with NAFL does seem to progress to cirrhosis and end-stage liver disease.

DIAGNOSIS

The clinical presentation varies from patient to patient. Most have no symptoms or minimal symptoms such as vague abdominal discomfort or right upper quadrant pain. Others may present with fatigue and malaise. Most cases occur between the ages of 40 and 60, although NAFL has also been reported in younger persons. Similarly, although NAFL is more common in obese women with type 2 diabetes, it should be considered in all patients with elevated liver enzymes, whether or not these risk factors are present.[1–6,10]

Many cases are discovered incidentally when elevations in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are found on routine testing. ALT and AST levels are elevated in more than 90% of patients with NAFL.[1–9] These elevations are usually mild to modest, usually two to three times the upper limit of normal. The ALT level is more elevated than the AST level: the AST/ALT ratio is usually less than 1. (In contrast, in alcoholic liver disease, the AST/ALT ratio is usually greater than 2.) Other laboratory values including alkaline phosphatase, serum albumin, serum bilirubin, prothrombin time, and gamma-glutamyltransferase are usually normal.

Patients can present with smooth hepatomegaly but no other physical signs.

Most patients with NAFL have no symptoms or only mild ones

It is important to calculate the body mass index and hip-to-waist ratio, given the high prevalence of NAFL in obese persons. Generally, overweight is defined as a body mass index greater than 27.8 kg/m^2 for men and greater than 27.3 kg/m^2 for women. Obesity is defined as a body mass index greater than 30 kg/m^2.[4,19]

Differential diagnosis

Alcoholism. Ruling out excessive alcohol consumption is crucial, and a strict definition should be used: excessive alcohol consumption is defined as more than 20 g/day in women and more than 30–40 g/day in men (10 g is approximately one drink).[4] Although sometimes quite difficult to elicit, a careful history can uncover excessive alcohol consumption. Other indicators of excessive alcohol consumption can be used, such as an elevated AST/ALT ratio and increases in the gamma-glutamyltransferase level, mean corpuscular volume, and, the best single marker,

the ratio of desialylated transferrin to total transferrin.

Drug-related liver disease. All prescription and nonprescription drugs the patient takes should be reviewed. Some medications such as glucocorticoids can cause NAFL.

Chronic viral hepatitis. Serologic tests for hepatitis B and C should be performed.

Hereditary hemochromatosis. Approximately 10% of persons of northern European descent carry the gene for genetic hemochromatosis, an autosomal recessive disorder marked by chronic iron overload. Iron levels are helpful but not specific.[4] Although carrying a mutation for hereditary hemochromatosis was proposed as a reason for progression of NAFL,[14] iron overload does not seem to be the explanation for most cases of progressive NAFL.[15] Diagnosis of iron overload is made by hepatic iron (hepatic iron index > 1.9).

Wilson disease, another autosomal recessive disorder that can masquerade as fatty liver, is marked by copper toxicosis. A serum ceruloplasmin evaluation and a slit-lamp examination should be performed, especially if the patient is young.

Autoimmune hepatitis. Tests for autoimmune markers (antinuclear antibodies, antimitochondrial antibodies, and anti-smooth muscle antibodies) should be performed, especially in middle-aged women with chronically elevated liver enzyme levels.

Imaging studies cannot distinguish between steatosis and steatohepatitis

Imaging studies

The role of imaging studies in establishing the diagnosis of NAFL is unclear. Ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) can show increased fat accumulation (ie, steatosis) as a hyperechoic texture or a bright liver. However, these imaging studies cannot distinguish between steatosis alone and NASH. Although it is unclear which imaging study is most appropriate or accurate, ultrasonography is attractive because it is relatively inexpensive and noninvasive.[1–6,10,21]

The role of liver biopsy and histology

Whether a liver biopsy should be performed in every person suspected of having NAFL remains controversial. On one hand, since no established therapy for NAFL exists, one could argue that biopsy merely exposes the patient to an invasive test, and one should concentrate on helping the patient manage his or her weight, lipid levels, and glucose levels if these are high.

On the other hand, since clinical data alone cannot predict the course of NAFL, histological findings on the liver biopsy may be important to distinguish different subtypes of NAFL and the stage of the disease. For example, some asymptomatic patients may have histologically advanced disease. In these patients, liver biopsy remains the gold standard not only for establishing the diagnosis of NAFL, but also for distinguishing among the various histologic types of NAFL with potentially important prognostic implications.

Therefore, we consider biopsy in patients with persistent elevation of liver enzymes (despite attempts to treat the underlying cause), especially if the patient is young or has type 2 diabetes.

But once a biopsy specimen is obtained, what pathologic features are required for the diagnosis of NAFL and its subtypes? Over the last 2 decades, experts have disagreed. Although the term NASH has received the widest acceptance, it is important to remember that steatohepatitis (literally, fat accumulation plus inflammation) is quite different from the clinicopathologic entity described as NASH, since NASH requires not only the presence of increased fatty accumulation but also hepatocyte ballooning, necrosis with or without fibrosis, or Mallory hyaline.[3,4]

In a recent study[22] that evaluated the intraobserver and interobserver variability of each pathologic feature associated with NAFL, six features had the best concordance:

- Extent of steatosis
- Grade of fibrosis
- Presence of sinusoidal fibrosis
- Perivenular fibrosis
- Vacuolated nuclei
- Ballooning degeneration.

Conversely, observers' ratings of inflammation were variable and therefore not useful. This indicates that if features with the highest concordance are grouped as a single overall diag-

nosis, the high concordance is retained. These six features are important for establishing the diagnosis of the progressive form of NAFL or NASH.[22]

Since NAFL represents a pathologic spectrum, a pathologist familiar with the strict definition of NASH and other forms of NAFL can offer input that would assist the diagnosis and management of these patients.

MANAGEMENT OF NAFL

In general, the goal of management in NAFL is to prevent progression to fibrosis and cirrhosis. Although no established therapy for NAFL exists, obese patients with NAFL should undertake a program of gradual weight reduction in which they try to lose 10% of their body weight over 6 months. After this, they should strive to maintain their ideal body weight. Optimal management of hyperlipidemia and diabetes mellitus are also important.[1–6,10,23–26]

Role of medication

Few studies have evaluated the potential role of medication. Ursodeoxycholic acid and clofibrate were both evaluated in a small pilot study by Laurin and colleagues.[27] In this study, 24 patients who received ursodeoxycholic acid for 12 months showed significant improvement in liver enzyme levels and a reduction in hepatic steatosis, but patients taking clofibrate had no clear benefit. The potential benefit of ursodeoxycholic acid therapy in patients with NAFL is being investigated in a randomized, controlled clinical trial.

Antioxidants such as vitamin E are also being evaluated. Liver enzyme levels returned to normal in five children with obesity-induced steatohepatitis receiving 400 to 1,200 IU of vitamin E orally for 4 to 10 months.[28] However, the echogenicity of the liver did not change, and liver enzyme levels returned to abnormal levels after therapy was stopped. The role of these agents in the management of NAFL remains investigational.

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