Histology of Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis in Adults and Children

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KEYWORDS

• Steatohepatitis • Liver biopsy • Steatosis • Histology • Scoring • Staging

KEY POINTS

- Nonalcoholic fatty liver disease (NAFLD) is a histologically complex disease with the potential to progress to cirrhosis.
- Nonalcoholic steatohepatitis is a specific progressive subtype of NAFLD, characterized by ballooning hepatocellular injury in zone 3, steatosis, inflammation, and often fibrosis.
- NAFLD in preadolescent children has an acinar zone 1 pattern of steatosis, inflammation, and fibrosis that usually lacks ballooning but may progress to advanced fibrosis.
- Liver biopsy remains the gold standard for confirmation of the diagnosis and definition of the severity of histologic findings.
- Paired biopsy-based natural history studies suggest that over the short term there may be fluctuation in disease severity and fibrosis.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) and its more severe subtype, nonalcoholic steatohepatitis (NASH), are steatotic liver diseases that develop in the absence of significant alcohol use. NAFLD is most often associated with obesity, specifically central obesity; insulin resistance and other insulin resistance syndromes; type II diabetes; and hyperlipidemia. Because of these associations, NAFLD is now recognized as

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the hepatic manifestation of the metabolic syndrome. It shows a spectrum of liver disease characterized by the accumulation of lipid, mainly in the form of macrovesicular steatosis. The histologic manifestations range from mild steatosis in only 5% of hepatocytes to more severe forms with lobular and/or portal inflammation, ballooning hepatocyte injury, and fibrosis in varying patterns of distribution to the end stage of cirrhosis.[1] As with other chronic liver diseases, patients are at risk to develop hepatocellular or other primary liver carcinomas.[2]

There is a growing recognition of NAFLD as a serious disease. Even with the most conservative estimates, NAFLD is very common in the United States (it is probably more common than hepatitis C and alcoholic liver disease [ALD]) and is significantly more prevalent in patients who are obese or diabetics. The prevalence of NAFLD is higher than was previously estimated and is 5-fold to 6-fold higher than the estimated prevalence of chronic hepatitis C.[3,4] The prevalence of NAFLD has been estimated to range from 2.8% to 46% throughout the world depending on the study population and the diagnostic tool used to verify NAFLD (eg, serology, imaging, liver biopsy).[4,5]

Prevalence studies of NASH, the most clinically relevant subtype of NAFLD, depend on histologic evaluation. In an autopsy study from the late 1980s, the prevalence of steatohepatitis was significantly different between the markedly obese patients (18.5%) and the lean patients (2.7%).[6] In Marchesini and colleagues'[7] study of well-characterized NAFLD, 163 of 304 patients underwent liver biopsy and, of those, 74% had NASH. More recently, Dr Stephen Harrison and his team evaluated the prevalence of NAFLD and NASH in healthy US adults via ultrasonography followed by liver biopsy.[4] Of 328 patients who completed an ultrasonography and questionnaire, 156 (48%) had at least 5% steatosis on ultrasonography. In addition, nearly 30% of patients with NAFLD had NASH on histologic review. Moreover, 9 (3%) of the patients with NASH had significant fibrosis (more than stage 1). These patients were more insulin resistant than those with mild fibrosis.[4]

Nonetheless, it remains challenging to estimate the prevalence of a disease for which there are no serologic confirmatory tests and a liver biopsy is required for definite diagnosis.

IMPORTANCE OF LIVER BIOPSY IN NONALCOHOLIC FATTY LIVER DISEASE

The presumptive diagnosis of NAFLD is often made in the setting of persistently increased serum aminotransferase levels with a positive imaging study (often ultrasonography), no history of significant alcohol use, and absence of other congenital or chronic liver diseases. However, 4% to 5% of patients with other chronic liver diseases may have NASH[8] and autoantibodies may be present in significant titers in 20% of patients with NAFLD.[9,10] In order to correctly classify the liver disease and exclude other coincident liver diseases, a liver biopsy is required.[1,11,12] Although a liver biopsy can provide a wealth of information about the state of the liver, is it not practical to try to distinguish NAFLD from ALD by histopathologic examination only.[13]

Several retrospective and prospective studies have suggested that simple steatosis without inflammation carries a benign prognosis, whereas those with the lesions of NASH are more likely to progress to advanced fibrosis and cirrhosis.[14,15] NASH has also been the focus of clinical trials.[1] It is therefore important to try to distinguish those with steatosis alone from those with NASH. Steatosis can be detected by imaging, using ultrasonography, computed tomography, or MRI. Modern MRI methods can detect a fat fraction as low as 5%, making it useful for detecting clinically relevant steatosis.[16] However, the distinction between steatosis and steatohepatitis cannot be made by current imaging methods, nor can imaging detect the lobular arrangement