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Hepatic steatosis and hepatitis C.

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Editorial

Hepatic Steatosis and Hepatitis C

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Hepatic steatosis is increasingly being recognized as a condition that may progress to end-stage liver disease. The clinical implications of fatty liver disease are derived mostly from its common occurrence in the general population and its potential of causing a wide spectrum of liver damage, ranging from simple steatosis to steatohepatitis, advanced fibrosis and cirrhosis.[1]

Hepatic steatosis can occur with the use of alcohol (alcohol-related fatty liver) or in the absence of alcohol (nonalcoholic fatty liver disease).[2] Fatty liver associated with the use of alcohol may occur with as little as 10 oz of alcohol ingested per week. If steatohepatitis is present but a history of alcohol use is not, the condition is termed nonalcoholic steatohepatitis (NASH). Fatty change in the liver results from excessive accumulation of lipids within hepatocytes. It is recognized on liver biopsy specimens and thus is a morphological rather than a clinical diagnosis.[1,2]

Nonalcoholic fatty liver disease (NAFLD) affects 10-25% of the general population in various countries. This prevalence increases to 57-75% in obese individuals. The prevalence of NASH is 2-3%. NASH has been detected in 1.2-8% of patients undergoing routine liver biopsy, although studies have reported rates as high as 7-9%.[2,3]

Fatty liver occurs in all age groups, with a female predominance. It is caused by the accumulation of triglycerides and other lipids in liver cells. In some cases, this may be accompanied by hepatic inflammation and liver cell death, when it is known as steatohepatitis. Potential pathophysiological mechanisms include decreased mitochondrial fatty acid beta-oxidation, increased endogenous fatty acid synthesis or enhanced delivery of fatty acids to the liver and deficient incorporation or export of triglycerides as very-low density lipoprotein from the liver.[2]

Obesity, type 2 diabetes mellitus, and hyperlipidemia are coexisting conditions most commonly associated with (NAFLD), but choline deficiency, obesity, protein-calorie malnutrition, starvation, rapid weight loss and total parenteral nutrition are important metabolic causes. Frequently overlooked causes of NAFLD are medications. Drugs associated with fatty liver include amiodarone, bleomycin, warfarin, estrogens, glucocorticoids, methotrexate and tetracycline.[3]

The diagnosis should be considered in all patients with unexplained elevations in serum aminotransferases. Noninvasive studies such as ultrasound usually identify the presence of a fatty liver. However, imaging techniques cannot distinguish between benign steatosis and steatohepatitis. Benign steatosis may be focal or diffuse, whereas steatohepatitis usually is diffuse. No laboratory studies can help definitively establish a diagnosis of fatty liver or NASH. The only abnormality may be an elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level. These may be elevated as much as 10-fold. However, the AST and ALT may be normal in some patients with fatty liver or NASH.[2]

Before the diagnosis of NASH can be made, viral markers should be tested and viral infection excluded. A liver biopsy and histopathological examination are required to establish the diagnosis. Specific histologic features on biopsy include (1) steatosis, which usually is macrovesicular but may be microvesicular or mixed; (2) inflammation that is mixed neutrophilic and mononuclear cell and (3) Mallory bodies and glycogen nuclei. Fibrosis or cirrhosis may be present in advanced cases.[4]

One of the most important and potentially reversible causes of NAFLD is Hepatitis C infection.[4] The mechanism by which the hepatitis C virus (HCV) causes chronic, progressive liver damage is multifactorial, but factors other than the virus itself have been implicated. Nonalcoholic fatty liver disease (NAFLD) and hepatitis C virus (HCV) related liver disease are common in the general population, but their concurrence is 2 to 3 times higher than would be explainable by chance alone.[5] In patients with chronic HCV infection, steatosis is attributable to a variable combination of the mechanisms considered to play a role in the pathogenesis of NAFLD-insulin resistance, and a direct effect of HCV on hepatic lipid metabolism that leads to triglyceride accumulation through inhibition of export proteins that are required for very low density lipoprotein (VLDL) assembly and secretion.[4,5]

Hepatic steatosis is a common histological finding occurring in more than 50% of patients with chronic hepatitis C.[6] Studies from Pakistan have indicated equally high prevalence rates, of upto 65.7%.[7] In this issue of the journal, Khokhar[8] et al report another series of 109 chronic HCV patients who underwent a liver biopsy and the large majority (62%) were found to have some degree of steatosis, although they could not determine if there was a clear association with inflammation or fibrosis.

Both host and viral factors have been demonstrated to play an important role in the development of steatosis. In

those patients infected with genotype 1, steatosis appears to be due to the co-existence of NASH with HCV and associated with an increased body mass index (BMI).[4] Another possibility is of a direct effect of specific viral sequences on the pathogenesis of lipid accumulation. This is especially true in the case of genotype 3.[9] Furthermore, hepatic steatosis attributed to genotype 3 correlates directly with serum and intra hepatic titters of HCV RNA. The resolution of steatosis after successful antiviral therapy as well as steatosis being a sign of recurrent HCV infection in patients with genotype 3 add convincing evidence that steatosis is viral related. The pathogenic mechanism induced by genotype 3 is speculative, but the correlation between steatosis, intra hepatic HCV RNA and core protein expression suggest a direct effect.[9]

It seems likely that in patients infected with genotype 1, BMI has a role in the pathogenesis of steatosis while in those infected with genotype 3, steatosis may be due to a virus-specific cytopathic effect.[5] Regardless of etiology, it is clear that the presence of steatosis contributes to fibrosis in patients with hepatitis C.[10] The degree of fibrosis has been found to correspond to HCV RNA levels.[11] Even more alarming is the finding that hepatic steatosis may be a risk factor for the development of hepatocellular carcinoma in these patients.[12]

Based on these findings, it is essential that steatosis be diagnosed early, and be treated appropriately. Unfortunately, treatment modalities are few and not highly effective.[1] Hepatitis C should be treated appropriately. Abstinence from alcohol is essential. In patients with diabetes mellitus or hyperlipidemia, good metabolic control is recommended. No medications have been proved to directly reduce or reverse liver damage independently of weight loss. Only small pilot studies lasting one year or less have been reported to date. Gemfibrozil, vitamin E, and metformin have been shown to improve liver-test results. Ursodiol, betaine, vitamin E, and the thiazolidinediones led to improvement in liver-test results as well as histologic findings. These medications deserve further evaluation in carefully controlled clinical trials that have sufficient statistical power.[13]

It is clear that there are many facets of hepatic steatosis that need to be explored. Particular attention should be paid towards preventive strategies, and future therapy should be aimed at exploiting the interactions of HCV with host insulin and lipid metabolism.

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