Motion – All patients with NASH need to have a liver biopsy: Arguments for the motion

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Previously regarded as an obscure disorder, nonalcoholic steatohepatitis (NASH) has recently emerged as an important chronic liver disease. NASH is within a spectrum of disorders characterized by excessive accumulation of fat in the liver, including simple hepatic steatosis (fatty liver), inflammation and necrosis (steatohepatitis), and fibrosis. Collectively, the disorders are called nonalcoholic fatty liver disease (NAFLD). Estimates of the prevalence of these individual conditions are suspect because liver biopsy is required for definitive diagnosis and is not generally performed. Although these conditions have traditionally been thought of as diseases of obese women, and are frequently associated with diabetes mellitus and hypertriglyceridemia, they have also been identified in lean men. Insulin resistance appears to be a common factor. These conditions are difficult to distinguish from each other clinically, and no biochemical or radiological test reliably establishes the diagnosis. A ratio of serum aspartate to alanine aminotransferase levels of less than one can distinguish NAFLD from alcoholic liver disease, but this is a nonspecific finding. Fatty infiltration imparts a diffuse echogenicity to the liver at ultrasonography, but this test cannot easily distinguish fat from fibrous tissue or identify cases of NASH. Only histological examination can establish the diagnosis of NASH, grade its severity, determine the prognosis and guide treatment.

Key Words: Fatty liver; Liver biopsy; Nonalcoholic steatohepatitis

Proposition – Tous les patients atteints de stéatose hépatique non alcoolique doivent subir une biopsie du foie : arguments favorables

Résumé : Autrefois considérée comme une maladie obscure, la stéatose hépatique non alcoolique (SHNA) apparaît depuis peu comme une cause importante de maladie chronique du foie. La SHNA fait partie d'un ensemble de troubles qui se caractérisent par une accumulation excessive de graisses dans le foie, y compris la stéatose hépatique simple, ainsi que par l'inflammation, la nécrose et la fibrose. Ces troubles forment ce qu'on appelle les stéatoses hépatiques non alcooliques. Les évaluations de la prévalence de chacune de ces maladies sont douteuses du fait que le diagnostic définitif nécessite une biopsie et que celle-ci n'est généralement pas pratiquée. Même si ces affections sont traditionnellement considérées comme des maladies de femmes obèses et qu'elles sont souvent associées au diabète sucré et à l'hypertriglycéridémie, elles ont aussi été observées chez des hommes maigres. L'insulinorésistance semble un facteur commun. Ces troubles sont difficiles à distinguer les uns des autres sur le plan clinique, et aucune épreuve biologique ou aucun examen radiologique ne permettent d'établir le diagnostic de façon sûre. Un rapport entre le taux d'aspartate-aminotransférase et le taux de l'alanine-aminotransférase sériques, inférieur à un peut distinguer les SHNA des hépatopathies alcooliques, mais il s'agit là d'un résultat non spécifique. L'infiltration graisseuse donne au foie une échogénicité diffuse à l'échographie, mais l'examen ne permet pas de distinguer facilement le tissu adipeux du tissu fibreux ou de repérer les cas de SHNA. Seul l'examen histologique permet la pose du diagnostic de SHNA, d'évaluer le degré de gravité, de déterminer le pronostic et d'orienter le traitement.

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Nonalcoholic steatohepatitis (NASH) has been increasingly recognized as an important chronic liver disease (1). Initially described by Ludwig et al in 1980 (2), NASH is part of a spectrum of disorders, ranging from simple steatosis to cirrhosis, and collectively known as nonalcoholic fatty liver disease (NAFLD) (3). The exact prevalence of NAFLD and NASH in the general population is unknown, yet estimates range from 10% to 40% and 2% to 7%, respectively (4). Hepatic steatosis has been documented in more than two-thirds of obese people (5) and is more common with increasing age. NAFLD, including NASH, is thought to be present in one of three patients with diabetes mellitus, which represents 7.8% of the American adult population (6). Based on these estimates, it is reasonable to conclude that the prevalence of NASH in the United States is greater than the 1.8% figure associated with chronic hepatitis C infection (7). One factor that has led to the tendency to underestimate the prevalence of NASH has been the misconception that it is predominantly a disease of obese women (8).

The diagnosis of NASH should be suspected in people who have asymptomatic elevations of liver enzymes, increased liver echogenicity at ultrasound or unexplained hepatomegaly, and any combination of increased body mass index (BMI), type 2 diabetes mellitus and dyslipidemia (8-11). The fact that these findings are distributed across the spectrum of NAFLD limits their diagnostic value as noninvasive markers for NASH.

Uncomplicated hepatic steatosis (in the absence of alcohol abuse, inflammation or fibrosis) rarely progresses to more advanced fibrosis or cirrhosis (12). On the other hand, advanced fibrosis (septal or bridging) and cirrhosis have been found in 25% and 15%, respectively, of patients with NASH at the time of initial liver biopsy (2,3,8-13). It is important to recognize NASH, especially if it is accompanied by extensive fibrosis, because this condition may lead to end stage liver disease (14) and can even recur after liver transplantation (15,16).

INDICATIONS FOR LIVER BIOPSY IN NAFLD

Histological assessment is the gold standard for the diagnosis of NASH, but whether it should be undertaken in all suspected cases is controversial. The diagnosis of NAFLD can be missed in patients who do not undergo liver biopsy, even if other chronic liver diseases are excluded by appropriate laboratory tests. In a biopsy study of 90 patients with chronically elevated serum liver enzymes, the prebiopsy diagnosis of NAFLD had a positive predictive value of only 56% (17). Another study involved 81 adults with chronically elevated transaminase levels and no serum markers of infectious, metabolic, autoimmune or hereditary liver disease, no history of alcohol abuse or hepatotoxic drug use, and no signs of chronic liver disease (18). Liver biopsies revealed uncomplicated hepatic steatosis in 41 cases (51%) and NASH in 26 (32%). The presence of excessive hepatic fat was not correlated with obesity, diabetes mellitus or hyperlipidemia in this study.

While of limited additional value in the diagnosis of NAFLD, a liver biopsy that shows abnormalities consistent with NASH can avoid the error of assuming that an individual patient has uncomplicated benign steatosis. In addition, liver biopsy material can identify the presence of significant hepatic fibrosis or cirrhosis, which cannot be detected noninvasively. In reported series of patients with NASH, the initial (diagnostic) liver biopsy revealed hepatic fibrosis in 67% of cases, septal or bridging fibrosis in 25% and overt cirrhosis in 14% (2,3,8-13). There is no agreement, however, about how to determine which patients are at the greatest risks for NASH and advanced fibrosis.

PREDICTION OF NASH BY NONINVASIVE TEST STRATEGIES

Serum transaminases

A ratio of serum aspartate to alanine aminotransferase (AST:ALT) levels of less than one has been proposed as a noninvasive marker for NASH. In a comparison of 70 NASH patients with 70 age- and sex-matched individuals with alcoholic liver disease (all confirmed histologically), the mean AST:ALT ratios were 0.9 and 2.6, respectively (19). Among the NASH patients, the AST:ALT ratios were 0.7, 0.9 and 1.4 when there was no fibrosis, mild fibrosis and cirrhosis, respectively. While an AST:ALT ratio of less than one can help to distinguish between NASH and alcoholic liver disease, many other chronic liver diseases also exhibit this low ratio and, thus, this index is not diagnostic (20).

Ultrasonography

Hepatic ultrasonography has been employed in determining the presence and extent of fatty infiltration in NAFLD. Case series and population studies using this technique have estimated that the prevalence of hepatic steatosis is between 16% and 58% (21,22). The low negative predictive value of sonography in detecting fatty infiltration (14% to 42.5%) limits its usefulness because more than one in three cases of NAFLD are missed (22). Moreover, fatty and fibrous tissues are not easily distinguished because sonography has a sensitivity of 49% to 77% and specificity of 60% to 89% for the detection of fibrosis (22,23). However, it is somewhat more accurate in cases of severe fibrosis or cirrhosis (23).

PREDICTION OF NASH BY CLINICAL RISK FACTOR ASSESSMENT

Obesity

There appears to be a direct correlation between the degree of obesity and the prevalence of NASH (24). Autopsy reports have noted steatohepatitis and severe hepatic fibrosis in 18.5% and 13.8%, respectively, of markedly obese patients (4). Among patients with morbid obesity who are referred for gastric stapling surgery, the prevalences of NASH and significant fibrosis are even higher than those in markedly obese patients, at 24% to 36% and 8% to 26%, respectively (25,26). The presence of diabetes mellitus

appears to increase the likelihood of advanced forms of NAFLD among severely obese patients as well (24-26). For individuals with moderate to severe obesity (BMI of 25 to 30 kg/m²), however, the predictive ability of the BMI alone to distinguish between NASH and hepatic steatosis is quite limited (8,10-13).

Insulin resistance

Insulin resistance is a key feature of conditions associated with NAFLD, including obesity, type 2 diabetes mellitus and dyslipidemia (26-28). A number of animal and human studies have also supported the association between insulin resistance and NAFLD, even in some lean individuals who lack obvious clinical risk factors (27). The relationship between NAFLD and hepatic iron overload in subjects who are not homozygous for the C282Y gene (which is associated with genetic hemochromatosis) has also been explained by the presence of insulin resistance (28). It has been reported that insulin resistance is an independent risk factor for the development of NASH (29), but this finding has not yet been confirmed. Elevated levels of triglycerides, but not of cholesterol, have been associated with sonographic findings of fatty liver (30).

Prognostic models

The ability to predict the existence of advanced or progressive forms of NAFLD may assist in the selection of patients for liver biopsy and, possibly, for specific types of treatment. Older age, obesity, diabetes mellitus and a serum AST:ALT ratio of greater than one were significant predictors of advanced liver fibrosis among 144 patients with NASH (11). BMI was the only independent predictor of the degree of fatty infiltration when adjusted for age and the presence of diabetes mellitus. The severity of steatosis was not associated to the same degree as BMI with the presence of fibrosis.

Age greater than 50 years, BMI of 28 kg/m² or higher, serum triglyceride levels of 1.7 mmol/L or more and ALT levels greater than two times the upper limit of normal have been associated with septal fibrosis in a study of 93 subjects with moderate to severe obesity (BMI 25 to 35 kg/m²) (13). These factors yielded a 100% negative predictive value, but a specificity of only 47% in the detection of septal fibrosis. Advanced fibrosis has also been correlated with the male sex, diabetes mellitus and hyper-

tension among severely obese patients (BMI of 35 kg/m² or greater) (29).

NATURAL HISTORY OF NASH

Fifty-four of 257 patients with NAFLD, reported in five different case series (8-13), have undergone serial liver biopsies during an average follow-up interval of 3.5 to 11 years. Of these patients, 28 exhibited progression of liver damage, 59% remained essentially unchanged, and 13% showed either resolution or improvement of histological findings. In several cases, progression along the stages of NAFLD from steatosis to steatohepatitis to advanced fibrosis or cirrhosis was documented. A total of 26 patients in these series have died, of whom one died from hepatocellular carcinoma and one died from a liver-related disorder. The finding of uncomplicated steatosis on the initial liver biopsy is associated with a more favourable prognosis than either steatohepatitis or advanced fibrosis.

It has been suggested that necroinflammatory activity on liver biopsy is associated with an increased risk of progression to advanced fibrosis (3), but this remains to be confirmed. Larger prospective studies of unselected patients with NASH are required to better define its prognosis. It appears that liver biopsy assessment would be required to reach these goals.

CONCLUSIONS

Based on the absence of noninvasive markers with acceptable predictive and discriminative value, histological assessment is required to make the definitive diagnosis of NASH. It is also the most sensitive and specific means of providing important prognostic information. The unexpected finding of cirrhosis is beneficial to individual patients in that the treating physician can initiate a program of screening for hepatocellular carcinoma and treatable complications of portal hypertension, such as esophageal variceal hemorrhage. Opponents contend that liver biopsies are unjustified because there is no compelling evidence of frequent progression to end stage liver disease, nor is there an identified effective medical therapy. Nevertheless, the provision of information about the natural history of disease and the risk of advanced fibrosis in NASH from liver biopsy is invaluable. In addition, the patients who might derive the most benefit from emerging therapeutic trials for NASH can currently be identified only by histological assessment.

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