

The role of liver biopsy in the management of patients with liver disease

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The role of liver biopsy in the diagnosis and management of liver disease is a controversial issue even among hepatologists. Although most causes of elevated liver enzymes can be determined, or at least suspected, on the basis of a careful history and laboratory tests, histological assessment remains the gold standard for most liver diseases. Histological evaluation can either confirm or refute clinical diagnoses and can provide information about the severity and stage of disease. Occasionally, the liver biopsy also provides an additional diagnosis. The spectrum of nonalcoholic fatty liver disease accounts for a substantial proportion of cases of chronically elevated liver enzymes and can be reliably diagnosed only by liver biopsy. Prognostic information can be obtained in patients with this disorder, as well as in those with alcoholic liver disease and viral hepatitis, and liver biopsy can be used as a guide to their management.

Key Words: *Alcoholic liver disease; Liver biopsy; Nonalcoholic steatohepatitis; Viral hepatitis*

Although there are many causes of liver disease (Table 1), recent advances in diagnostic techniques have led many physicians to question the need for liver biopsy (1-5). For example, alcoholic liver disease can often be diagnosed with a reliable history from the patient and family members, as well as clinical and biochemical evidence of chronic alcohol consumption. Viral and autoimmune hepatitis can be diagnosed serologically, while metabolic diseases can often be identified using genetic testing (Table 2). On the other hand, nonalcoholic steatohepatitis, a common cause of chronically abnormal liver enzymes, cannot be accurately diagnosed either clinically or radiologically (6). Therefore, many clinicians are now reconsidering the need for liver biopsy in patients with chronic liver enzyme abnormalities, and there is considerable disagreement among hepatologists on this issue.

INDICATIONS FOR LIVER BIOPSY

Liver biopsies are performed for diagnostic and prognostic reasons. Histopathological examination is the best method for making the diagnosis when noninvasive tests are inconclusive. In cases in which the diagnosis has already been established by other means, it may reveal additional diagnoses as well as information on disease severity. For example, although laboratory and imaging tests may suggest the presence of cirrhosis,

Le rôle de la biopsie du foie dans le traitement des hépatopathies

Le rôle de la biopsie du foie dans le diagnostic et le traitement des hépatopathies ne fait pas l'unanimité même parmi les hépatologues. Même si en général une anamnèse minutieuse et les examens de laboratoire permettent de trouver la cause de l'augmentation des enzymes hépatiques ou, tout au moins, d'en soupçonner l'origine, l'étude histologique constitue l'examen de référence pour la plupart des maladies du foie. Elle peut confirmer ou infirmer le diagnostic clinique et donner une indication du degré de gravité et d'évolution de la maladie. La biopsie du foie peut même parfois déboucher sur un diagnostic supplémentaire. Les stéatoses hépatiques non alcooliques sont à l'origine d'un nombre important de cas d'augmentation chronique des enzymes hépatiques, et seule la biopsie du foie permet de poser un diagnostic fiable. De plus, l'examen peut fournir des renseignements sur le pronostic de la maladie chez les patients atteints et chez ceux qui présentent une hépatopathie alcoolique ou une hépatite virale, et il peut même aider à orienter le traitement.

liver biopsy remains the definitive procedure for this purpose. Moreover, it can help stage the disease and estimate its prognosis. Serial biopsies can document the progression of chronic conditions such as hepatitis C (HCV).

CONTROVERSIES REGARDING LIVER BIOPSY

If liver biopsies provide useful information for the management of patients with liver disease, why is there so much debate in the medical community about performing them? The explanation is that the procedure is associated with inconvenience, pain, and a risk of significant bleeding, albeit small (7). Therefore, experts disagree as to whether histologic assessment should be part of the standard management in patients with liver disease.

Sherwood and colleagues (5) retrospectively assessed the outcome of nearly 1000 patients with abnormal liver enzymes in the primary care setting. They found that only 57% of patients (531 of 933) were referred for specialized care. Of the remaining 342 patients who had follow-up visits, 157 had persistently abnormal liver enzymes, and were invited to return for further assessment. Liver biopsies were eventually performed in 101 (64%) patients from this cohort, and yielded a definitive diagnosis in 81 patients despite normal serological tests. The authors concluded that a substantial proportion of patients with treatable and sometimes communicable chronic liver dis-

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TABLE 1
Causes of abnormal liver enzymes

Alcohol
Nonalcoholic steatohepatitis: Diabetes, hyperlipidemia, obesity
Viral: Hepatitis B, hepatitis C, other viruses
Autoimmune: Autoimmune hepatitis
Cholestasis: Primary biliary cirrhosis, primary sclerosing cholangitis, drugs
Hereditary: Wilson's disease, hemochromatosis, α -1-antitrypsin deficiency

TABLE 2
Diagnosis of abnormal liver enzymes

Alcohol: History
Nonalcoholic steatohepatitis: Physical exam, biochemistry
Viral: Serology, hepatitis B viral DNA, hepatitis C viral RNA
Autoimmune: Serology, immunoglobulins
Cholestasis: Serology, history
Hereditary: Biochemistry, genetic testing

ease would not have been diagnosed had they not undergone liver biopsy, and that the procedure remains a useful diagnostic tool.

In another retrospective study of 365 patients at university hepatology clinics, Spycher and colleagues (2) found that liver biopsy yielded an additional diagnosis in at least 10% of patients, and led to a change in diagnosis in 6.8%. Overall, liver biopsy led to a change in the management of 12.1% of subjects. The authors therefore advised that, notwithstanding the presence of advanced virological, immunological and molecular genetic testing, there is an important role for liver biopsy.

In a prospective study involving 36 patients, Sorbi and colleagues (1) confirmed that liver biopsy changed the diagnosis in 14% of cases, and affected the frequency of liver test monitoring in 36%. Treatment recommendations were altered in 12 of 36 cases, 10 of whom were offered investigational therapies. The authors, however, cautioned that the risks and benefits of a liver biopsy should be carefully weighed, especially in settings in which neither proven treatments nor investigational therapies are available.

It would seem obvious that, for patients with persistently abnormal liver enzymes of unknown etiology, liver biopsy would be regarded as a necessary diagnostic tool (8,9). Indeed, Daniel and colleagues (3) reported that 73 of 81 patients with chronic liver disease of unknown etiology had abnormal liver biopsies, the most prevalent diagnosis being either steatosis or steatohepatitis. Because there is a poor correlation between the histological findings and the presence of obesity, hyperlipidemia or diabetes mellitus, liver biopsy remains the gold standard. Despite these findings, Kirsch (4) argued that the risks of liver biopsy far outweigh its benefits, especially since there is no definitive treatment for steatosis/steatohepatitis, and because histological diagnosis does not have a significant clinical impact for these patients.

Thus, it appears that the role of liver biopsy in the management of patients with liver disease remains controversial. The following is a summary of the published literature.

Alcoholic liver disease

There is a prevailing belief that alcoholic liver disease can be diagnosed with an acceptable degree of accuracy based on clinical findings together with biochemical tests (10). However,

solid evidence to support this statement is lacking. In one study, only 39% of physicians caring for patients with heavy alcohol intake used liver biopsy to make the diagnosis of alcoholic liver disease (10). In another prospective study, 347 men who chronically consumed more than 50 g of alcohol underwent liver biopsies irrespective of clinical or biochemical findings (11). Using specific clinical signs, including facial telangiectasia, vascular spiders, white nails, dilated abdominal wall veins, fatness and peripheral edema, the authors were able to accurately diagnose alcoholic cirrhosis in 90% of cases. They concluded that liver biopsy was probably unnecessary in the diagnosis of alcoholic cirrhosis.

All patients with alcoholic liver disease should undergo tests to exclude chronic HCV, because the two conditions frequently coexist. If abnormalities in liver biochemistry persist despite abstinence, or if the diagnosis of alcoholic liver disease is in doubt, a liver biopsy should be performed (12). Some studies suggest that, without histological confirmation, the diagnosis of alcoholic hepatitis is inaccurate in 10% to 20% of patients (10).

Serum biochemistry and the currently available imaging modalities have severe limitations in determining the relative contributions of fatty liver, alcoholic hepatitis and cirrhosis to the patient's disease. Histological examination is, therefore, of value in determining the prognosis for these patients. The characteristic features of alcoholic hepatitis include polymorphonuclear infiltrates, centrilobular hepatocyte swelling and degeneration, macrovesicular and microvesicular steatosis, Mallory bodies, and pericentral-perisinusoidal fibrosis (Figure 1). In 50% to 93% of cases, alcoholic hepatitis is superimposed on fully developed cirrhosis (13) and is associated with a significantly worse prognosis.

Hepatitis C

HCV infection is usually identified by the presence of HCV antibody or HCV RNA. The role of liver biopsy is to establish disease activity and the extent of fibrosis (14), which can significantly affect the outcome. Furthermore, data from studies involving serial biopsies have provided convincing evidence that the grade of fibrosis and the extent of inflammatory changes in the initial biopsy can predict the likelihood of eventual progression to cirrhosis (15). Therefore, a pre-treatment liver biopsy has been recommended to guide management (16,17), especially since antiviral treatment is not necessarily benign and a successful outcome is not guaranteed.

With improvements in the outcome of treatment of HCV, however, many experts now question the need for liver biopsy. In the Consensus Conference of the National Institutes of Health held in 2002, it was concluded that liver biopsy, although not mandatory, should still be performed in patients with HCV infection (18). The rationale of this decision is that patients with moderate to severe hepatitis on liver biopsy are likely to develop cirrhosis and therefore warrant immediate treatment, while treatment can be postponed for milder cases until more effective and tolerable options become available.

Pretreatment biopsy can help determine the prognosis after treatment. Although noninvasive laboratory markers can provide a crude estimate of the severity of inflammation and the extent of fibrosis, they are far less accurate than liver biopsy. In a systematic review of the literature, Gebo et al (19) reported that advanced fibrosis or cirrhosis on initial biopsy is associated with a modestly decreased likelihood of a sustained virolog-

ical response to treatment. Biochemical and serological tests were best at identifying patients with no or minimal fibrosis, or those with advanced fibrosis/cirrhosis, but who were poor at grading intermediate levels of fibrosis. On the other hand, liver biopsy is useful at predicting the efficacy of treatment. This is particularly true for patients with coexisting steatosis or alcohol abuse, as both conditions have been shown to hasten the development of fibrosis (20,21).

Hepatitis B

The literature about the role of liver biopsy in the management of patients with hepatitis B (HBV) infection is much less extensive. This may be related to several aspects of the disease itself and of the available treatment options. Firstly, HBV is not cytotoxic; rather, it is the host's immune response to the virus that injures the liver. Therefore, the mere presence of an infection does not warrant a liver biopsy, which is most likely to be normal. Secondly, compared with HCV, the treatment for HBV is much more easily tolerated and widely applicable across the spectrum of infection, especially if nucleoside analogues like lamivudine or adefovir are used. Therefore, liver biopsy is not required to predict treatment outcome.

In the 2002 Consensus Conference of the European Association for the Study of Liver Disease (22), it was suggested that histological assessment of the extent of necroinflammation and the stage of fibrosis by an expert pathologist is an integral part of the management of patients with HBV infection. Liver biopsy could also identify other liver diseases. Serial biopsies have demonstrated significant histological improvement in 56% of patients who receive long-term lamivudine (23).

Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of disorders ranging from simple fatty liver to steatonecrosis and nonalcoholic steatohepatitis. It is associated with obesity, type II diabetes mellitus, hyperlipidemia, jejunoileal bypass and certain medications, but NAFLD can occur without identifiable risk factors (24). Patients typically present with unexplained chronic elevation of liver enzymes. Without treatment, a small number of patients with NAFLD develop cirrhosis (6,25). This process is accelerated by the presence of HCV and iron overload (20,26,27).

There are no direct correlations among the histological findings, liver enzyme abnormalities, radiological findings and the presence of obesity, hyperlipidemia or diabetes mellitus (3). Necroinflammatory changes on biopsy, however, may indicate an aggressive course with progression to liver cirrhosis (6). Therefore, many hepatologists advocate liver biopsy for all patients with abnormal liver enzymes who are suspected of having NAFLD.

Day (28) proposed the following indications for liver biopsy in patients with suspected NAFLD:

- alanine aminotransferase levels more than twice the upper limit of normal
- aspartate aminotransferase greater than alanine aminotransferase
- risk factors, including 'moderate' central obesity, non-insulin dependent diabetes mellitus, hypertension and hypertriglyceridemia

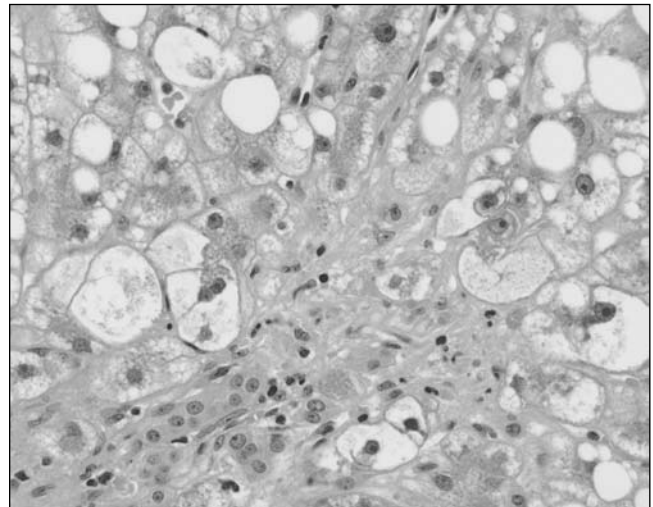


Figure 1 Photomicrograph of alcoholic steatohepatitis with inflammatory cells (including neutrophils), Mallory bodies and necrosis

On the other hand, McNair (29) argued that, since the only proven treatment for NAFLD is weight loss, liver biopsy was pointless. He stated that it is difficult to justify liver biopsy simply to provide better prognostic information. Indeed, it is not clear that patients with simple steatosis and mild fibrosis will not, with time, develop more severe liver disease. Likewise, Kirsch (4) did not feel that liver biopsy in patients with persistently abnormal liver enzymes should undergo a liver biopsy simply to make the diagnosis of NAFLD, since there is no defined therapy and knowing the histology is unlikely to have any clinical impact.

Matteoni and colleagues (6), in their 18-year study of patients with NAFLD, seem to have provided the answer. They found that patients with an isolated finding of steatosis had a benign course, while those with active inflammation, Mallory bodies, necrosis and fibrosis tend to develop cirrhosis. Therefore, liver biopsy not only provides important prognostic information but also remains crucial in the development of therapeutic protocols for NAFLD (30).

CONCLUSION

From the foregoing discussion, it can be seen that the role of liver biopsy in the management of patients with liver disease remains a contentious issue. Therefore, each case should be assessed on its own merits. For many patients, liver biopsy continues to provide important information about the cause and severity of the liver disease, and must be regarded as a crucial part of the patient's management. Emerging diagnostic tools, such as fibrosis markers, might make it possible to obtain this information noninvasively in the future. In the meantime, liver biopsy is required in selected patients with liver disease.

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