Is liver biopsy needed in children with chronic hepatitis ?

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Introduction

The management of liver disease, or of any other pathology for that matter, involves making a correct diagnosis, identifying the cause, providing the patient with prognostic information, implementing treatment, and verifying its effects.

How may the pathologist contribute to the diagnosis, prognosis and treatment of chronic viral hepatitis ?

It is generally thought that a liver biopsy can significantly contribute to the characterization of any liver damage, providing information on etiology, on the severity of necro-inflammatory changes (hepatitis grading), and on the progression of the disease towards the end-stage of cirrhosis (hepatitis staging).

This review discusses the usefulness of the liver biopsy in the clinical management of chronic viral hepatitis in children.

Chronic hepatitis B

A wide spectrum of pathological changes has been reported in children with chronic hepatitis B virus infection (HBV), ranging from minimal (mainly non-specific) lesions to chronic hepatitis, to cirrhosis and, eventually, to hepatocellular carcinoma. The natural history and clinical-pathological patterns relating to hepatitis B infection have been found significantly correlated with the route and the age of infection (1). In children born to HBeAg-positive mothers, the disease is usually asymptomatic, with normal ALT levels and a high level of viral replication. Mild histological changes have been described in such patients. Children infected in the postnatal period more often show abnormal liver function test findings, with lower levels of viral replication and morphological changes consistent with chronic hepatitis of variable severity.

Histology and etiology

The etiological diagnosis of hepatitis B is easily made by the detection of serological viral markers, including HBeAg, and HBV-DNA to assess the viral replication status. Serology may be unclear in immunodepressed patients (with malignancies or AIDS, or transplanted patients), however, in which case a liver biopsy may significantly contribute to the etiological diagnosis by excluding other causes of liver damage and providing evidence of a specific etiology (2,3). Ground-glass cells, indicative of HBsAg excess in the liver cell cytoplasm, are easily detected on routine sections stained with Hematoxylin and Eosin. However, immunohistochemical stains for HBs and HBc antigens should be performed in these cases to confirm the nature of the ground-glass cells and to assess viral replication status.

Children with chronic hepatitis B may have a concomitant hepatitis delta virus (HDV) infection. Detection of serum antibody to HDV does not always enable the distinction between past and ongoing infection, and the value of IgM antibody to HDV has also been questioned (4). The method of choice for the diagnosis of ongoing HDV infection is currently the demonstration of HDVAg in hepatocytes by immunohistochemistry and HDV-RNA detection in the liver by in situ hybridization (5). More sensitive techniques have been developed, such as reverse transcription-PCR, but PCR methods are expensive and extremely complex and must be performed under carefully-controlled conditions, so they are not available at all laboratories.

Histology and prognosis

Studies on the natural history of chronic hepatitis B in children have shown that the outcome of disease is favorable in most cases, being characterized by the disappearance of viral replication before adulthood, with HBeAg to anti-HBe seroconversion, followed by an improvement in the morphological picture (6). The prognosis for chronic HBV infection may depend on the extent of liver damage at presentation. Severe necro-inflammatory changes, including the presence of piecemeal necrosis, and a focal distribution of HBcAg in the liver tissue have been found associated with high chance of clearing viral replication (7,8). Serological tests are inaccurate for assessing the severity of liver damage. In fact, although subjects with persistently high ALT levels are more likely to have more severe liver lesions, there are many differences in individual cases. Alternative methods for assessing liver fibrosis have recently been proposed in adults (9), but the correlation between biochemical test results and the degree of fibrosis is usually poor and well-compensated cirrhosis may be underdiagnosed on the basis of the clinical-serological background alone. It is generally agreed that liver histology is the gold standard for assessing the severity of liver disease, in terms of both

the severity of the necro-inflammatory changes and the extent of fibrosis.

Histology and therapy

In a subgroup of patients, therapy with interferon has proved to efficiently accelerate viral clearance and anti-HBe seroconversion (10,11). Elevated ALT and marked histological activity before treatment are factors that predict a favorable response (12). In this context, a baseline liver biopsy represents an useful tool for evaluating the severity of hepatitis in order to select candidates for treatment and discuss treatment options with parents. In the presence of minimal lesions, the treatment may be postponed. The need for and timing of a follow-up biopsy after the treatment of chronic hepatitis B are under discussion. As few information is available on the long-term evolution of liver damage in patients who respond to therapy, a follow-up biopsy comparing post-therapy with baseline findings and performed not less than two years after completing the treatment, would seem reasonable.

Histology and risk of hepatocellular carcinoma

Chronic HBV infection is a risk factor for hepatocellular carcinoma (HCC), especially once cirrhosis has developed. This complication has also been described in children (13), mainly in certain geographical areas, such as in Asian and African countries. Periodical serum alpha-fetoprotein (AFP) evaluation and abdominal ultrasound (US) are usually used as screening tests. HCC is suspect when a hypo- or dys-echoic node larger than 2 cm is detected, though both non-neoplastic lesions larger than 2 cm and neoplastic nodes smaller than 2 cm may also be observed. In patients with small hepatocellular carcinomas, AFP rarely reaches or exceeds the diagnostic value of 400 ng/ml (14), so only liver biopsy (even fine-needle) can ensure a reliable diagnosis.

Chronic hepatitis C

To date, little is known on the natural history or treatment of chronic hepatitis C in pediatric patients. Children with thalassemia, leukemia and hemophilia have represented patients at the highest risk of infection before the introduction of HCV screening for blood donors (15,16). In children without any underlying systemic disease the infection is relatively uncommon (17,18). Available data indicate a relatively stable course of the disease in both the high-risk groups and in children without underlying disease (19).

Histology and etiology

The diagnosis of HCV infection relies on the detection of anti-HCV antibody in the serum. The identification of HCV-RNA using PCR-based methods is indicative of ongoing viral replication and of infectivity.

In some conditions (i.e. immunodepressed patients with delayed appearance of anti-HCV antibodies (20,21)) there may be doubts on the etiology of the hypertransaminitis. In such cases liver biopsy may provide etiological information. In fact, a number of histological features have been cited for their characteristic association with HCV infection, including bile duct damage, lymphoid follicles in the portal tract, and fatty changes. These lesions, which have also been observed in children with chronic hepatitis C (22,23), may be relevant in the correct etiological allocation of controversial cases. To date, no commercial products have been made available for the immunohistochemical identification of HCV antigens in routine liver specimens. HCV-RNA may be detected in liver tissue by PCR-based methods. Fresh or rapidly-frozen liver specimens give the best results in testing HCV-RNA. Of course, this cannot be considered a routine method and its use has to be reserved for special cases.

Histology and prognosis

Only few data have been published on the histopathology and natural history of chronic hepatitis C. In our experience, based on the observation of a consistent number of children with no other disease (23), chronic hepatitis was mild in most cases. However, the severity of fibrosis increased with the duration of disease, suggesting that end-stage disease may be expected to develop in young adulthood in some cases. ALT levels were found to strongly reflect intralobular focal necrosis, but no other lesions, confirming liver biopsy as the only tool for evaluating the severity, and hence the prognosis, of the hepatitis (23). The grade of portal inflammation and interface hepatitis (or piecemeal necrosis) was related to the extent of fibrosis, suggesting a prognostic value of these lesions in the progression of the disease. If these observations are confirmed in larger series of prospectively-followed patients, liver biopsy would have in important role not only in defining the status of liver disease, but also in identifying subjects at the highest risk of developing cirrhosis.

Histology and therapy

As for therapy, experience with chronic hepatitis C in children is very limited (24). At the moment, no "evidence-based" data are available on the importance of histology in the prediction of response.

Histology and hepatocellular carcinoma risk

In adult populations, retrospective and prospective analyses demonstrated that patients with HCV related cirrhosis are at risk of HCC. However, no studies have specifically addressed this topic in children, who very rarely show fully developed cirrhosis at presentation. Theoretically, the same observation as was made for children with HBV-related cirrhosis (see below) can be taken to apply to the rare cases of HCV-related cirrhosis.

Conclusion

In conclusion, in chronic hepatitis in children histology remains the only method for a "sensitive" assessment of the liver disease ("activity" and fibrosis, in particular) ; nevertheless, the need for liver biopsy should be always carefully evaluated in each individual child. Particularly in chronic HCV infection, several questions remain unanswered. Some answers will probably come from a liver biopsy without immediate benefit for the single patient. In this respect, it may be useful to bear in mind that "the research of today will be the clinical practice of tomorrow".

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