Is liver biopsy mandatory in children with chronic hepatitis C?

Raffaele Iorio, Antonio Verrico, Antonietta Giannattasio

Raffaele Iorio, Antonio Verrico, Antonietta Giannattasio,
Department of Pediatrics, University "Federico II", Naples, Italy
Correspondence to: Dr. Raffaele Iorio, MD, Department of
Pediatrics, University "Federico II", Via Sergio Pansini n. 5,
Naples 80131, Italy. riorio@unina.it
Telephone: +39-8-17464337
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Abstract

Liver biopsy is considered the most accurate means to estimate the necroinflammatory activity and the extent of fibrosis. However, histology evaluation is an invasive procedure associated with risk to the patient, risk of sampling error and diagnostic inconsistencies due to inter- and intra-observer error. On the basis of histological studies performed so far, chronic hepatitis C in children appears morphologically benign in the majority of cases. At the Pediatric Liver Unit of our university, a total of 67 children with chronic hepatitis C underwent liver biopsy. Liver biopsy was repeated 5.5 years after the initial histological evaluation in 21 children. On a total number of 88 liver biopsies, micronodular cirrhosis was detected only in one genotype 1b-infected obese child. Since liver histology investigation of a child with chronic hepatitis C has few chances to highlight severe lesions, we question how liver biopsy helps in the management of children with chronic hepatitis C.

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TO THE EDITOR

Liver biopsy is considered the most accurate means to estimate the necroinflammatory activity of a process and the stage of a disease involving the liver by assessing type and extent of fibrosis together with recognition of architectural disturbances^[1]. The level of aminotransferase elevation does not adequately reflect the severity of the disease and methods measuring fibrosis-related molecules circulating in blood are not yet put into widespread use^[1].

Liver biopsy represents, however, an invasive procedure associated with discomfort and risk to the patient^[1]. In pediatric age, it has been reported that liver biopsy is burden with a 6.8% incidence of overall complications, a 2.4% incidence of major complications and a mortality rate of 0.4%^[2]. Furthermore, histology evaluation carries risk of sampling error because of specimen fragmentation or inadequate length, and interpretation of the biopsy is subject to diagnostic inconsistencies due to inter- and intra-observer error^[3-6].

In initial treatment trials of hepatitis C, liver biopsy was considered an important parameter to guide management and therapy, particularly at a time when response to treatment was low. As a consequence, it was desirable for patients with a more severe liver damage to receive a therapy with potentially serious side effects. In the vast majority of pediatric treatment trials of hepatitis C, patients were candidate for treatment only if liver histology was available^[7-9]. With the improvement in response rate to antiviral therapy, although reduction of fibrosis is still considered a common endpoint of clinical trials, the value of liver biopsy in management of patients with chronic hepatitis C has been questioned, advocating that this procedure may not be necessary for the initiation of therapy^[10]. Indeed, in the recent years, following the encouraging rates of response to combined therapy with pegylated-interferon and ribavirin, also patients with normal aminotransferases and minimal histological liver damage have been considered for therapy^[11,12].

On the basis of the studies available so far, chronic hepatitis C in children seems to be a milder disease with a more favourable natural course when compared to hepatitis C virus (HCV) infection in adults^[13-16]. Recently, pediatric cases of severe chronic hepatitis C requiring liver transplantation have been reported, but in these reports no information was provided about either the total number of transplanted children for diseases other than HCV infection in the same period or the pediatric prevalence of hepatitis C in the area from which transplanted children derived^[17,18]. Furthermore, these data about the severe course of pediatric HCV infection obtained from studies performed in tertiary or quaternary referral centres, do not provide an adequate perception of the real prevalence of worsening prognosis^[17,18]. As a matter of fact, several histological studies have confirmed that in children chronic HCV infection is morphologically benign in the majority of cases, progression of fibrosis is relatively slow and cirrhosis is extremely rare. In an Italian-Spanish multicenter study, Guido *et al*^[13] enrolled 80 children with chronic hepatitis C without underlying systemic diseases to study their liver histology. Liver biopsies were

performed at a mean of 41.5 ± 51.9 mo after the first observation of increased transaminases. The authors reported a rate of 0.8% of cirrhosis. Vogt *et al*^[14], in a study including German patients with a median duration of HCV infection of 20 years at histological evaluation, described only one child with micronodular cirrhosis (this patient was co-infected with hepatitis B virus) out of 17 who underwent liver biopsy. Jara *et al*^[15], in an European multicenter retrospective study, analyzed 92 liver biopsy specimens from children with chronic HCV infection but no underlying systemic diseases. Histological analysis was performed 4 wk to 17 years after the clinical diagnosis. Progressive liver disease was reported only in two HCV infected children (severe hepatitis in one case and cirrhosis in another).

At the Pediatric Liver Unit of the University “Federico II” (Naples, Italy), a total of 67 children with chronic hepatitis C without other underlying systemic diseases (31 males, median age at liver biopsy 8.6 years, range 2-15 years, median duration of HCV infection 7.2 years, range 2-15 years), underwent liver biopsy from 1986 to 2007. Percutaneous liver biopsies were performed after informed consent was obtained from parents or guardians in order to assess the extent of liver damage. Histological examination was performed by the same liver pathologist, who was blinded to biochemical and clinical data. Specimens were scored with regard to hepatitis activity (graded 0-18) and fibrotic changes (staged 0-6), in accordance with the methodology of Ishak *et al*^[19]. Thirty-two children acquired infection through blood transfusion, 22 through vertical transmission, and 8 through minor surgery. The route of infection was unknown in the remaining 5. Forty patients were infected with genotype 1, 16 with genotype 2, 3 with genotype 3 and 8 with other genotypes.

At the time of histological evaluation, all patients had viremia (median serum HCV RNA 218 000 IU/mL, range 40 000-146 7000 IU/mL) and all but two had hypertransaminasemia (median alanine amino-transferase value 85 IU/L, range 40-350 IU/L). Liver biopsy was performed in 47 children before commencement of antiviral treatment and in 20 children who remained untreated. Liver biopsy was repeated 5.5 years (range 2-11.2 years) after the initial histological evaluation in 21 children. On a total number of 88 liver biopsies, micronodular cirrhosis was detected only in one genotype 1b-infected obese child at the second liver biopsy^[16].

In conclusion, liver histology investigation of a child with chronic hepatitis C has few chances to highlight severe lesions. We question how the knowledge of histological assessment could affect the management of chronic HCV infection in children. Is it necessary to systematically perform liver biopsy in children with chronic HCV infection before starting therapy? Which information regarding the treatment will it add?

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