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REVIEW

Is liver biopsy still needed in children with chronic viral hepatitis?

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Abstract

Liver biopsy is a standard method used for obtaining liver tissue for histopathological evaluation. Since reliable serological and virological tests are currently available, liver biopsy is no longer needed for the etiological diagnosis of chronic hepatitis B and C. However, liver histology remains the gold standard as a prognostic tool, providing information about the liver disease progression (grading of necroinflammatory activity and staging of fibrosis) and serving clinicians in the management and therapeutic decisions. In general, histopathological evaluation is indicated before starting the antiviral treatment. Main limitations of the liver biopsy include its invasive and painful procedure, sampling errors and the inter- and intra-observer variability. In addition, indications for the liver biopsy in pediatric patients with chronic viral hepatitis were questioned recently, and efforts have been made toward the development of non-invasive methods as an alternative to the liver biopsy. The most commonly used methods are novel imaging studies (elastography) and combinations of biomarkers. However, to date, none of these tests was validated in children with chronic viral hepatitis. In this review, we present the current status of the liver biopsy in the management of chronic viral hepatitis B and C in pediatric population, including specific indications, complications, contraindications, problems, limitations, and alternative non-invasive methods.

Key words: Liver biopsy; Hepatitis B; Hepatitis C; Pathology; Elastography; Fibrosis; Children

Core tip: The role of liver biopsy in pediatric patients with chronic viral hepatitis was questioned recently due

to the development of non-invasive alternative methods (novel imaging studies and combinations of biomarkers) used for the assessment of the severity of liver fibrosis. However, none of these methods has been validated in children so far, and therefore liver biopsy remains the gold standard for the evaluation of liver disease progression in children with chronic viral hepatitis. In addition, it is a crucial tool for the management and for therapeutic decisions.

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INTRODUCTION

Liver biopsy is a standard procedure used to obtain the liver tissue for histopathological evaluation[1,2]. Most commonly, it is performed percutaneously, without contemporaneous ultrasonographic guidance in determining the puncture site ("blind" liver biopsy, with a percussion-guided transthoracic approach, which is considered as the classic percutaneous method) or as ultrasound/computerized tomography-guided liver biopsy[1-3]. However, the role of ultrasonography in biopsy site determination is controversial. Among adult patients, ultrasonographic guidance was shown to be associated with decreased rates of hospitalization, but it did not influence rates of bleeding and hypotension[4,5]. Other less frequently used techniques include transjugular, plugged, and intraoperative or laparoscopic liver biopsy. Two main types of devices, available in different diameters, are used to obtain the liver tissue: suction and cutting needles. Liver biopsy is an invasive procedure. Thus, it is performed under general anesthesia or sedation in order to reduce pain and anxiety in patients[2]. Because of pediatric patients' lack of cooperation, general anesthesia is usually required[3]. Before performing the procedure, a written informed consent for the biopsy should be obtained from the patient and/or parents/guardians.

Three main indications for the liver biopsy include diagnostic and prognostic purposes, evaluating disease severity and monitoring response to treatment[2]. Liver diseases of different etiologies (*e.g.,* viral, autoimmune, nonalcoholic, and drug-induced hepatitis), as well as inherited metabolic diseases, cholestasis, liver tumors, acute liver failure, abnormal liver tests of unknown etiology, and others are considered as indications for liver biopsy in children. In recent years, due to the development of alternative methods of diagnosis of the liver diseases and advancement of imaging techniques (elastography), the role of the liver biopsy in chronic viral hepatitis has significantly evolved and is being questioned[2,3]. Thus, the aim of this review was to analyze the current status of the liver biopsy in the management of chronic viral hepatitis B and C in pediatric population, including specific indications, complications, contraindications, problems, limitations, and alternative non-invasive methods.

HISTOPATHOLOGICAL EVALUATION

In general, histopathological expression of the chronic viral hepatitis comprises the following three components: inflammation, fibrosis/cirrhosis, and hepatocellular changes[6]. Lesions typical for viral hepatitis, which enable the differential diagnosis with other chronic liver disorders, include portal tract inflammation consisting of mononuclear cells, common presence of interface hepatitis, usually focal lobular necrosis of variable degree, and mild bile duct damage (common in hepatitis C)[7,8]. Histopathological evaluation of the liver tissue in case of chronic viral hepatitis B or C should provide the following information: the extent of necroinflammation and fibrosis, the presence of any adjunctive lesions (steatosis, hemosiderosis, liver cell dysplasia), and detection of any comorbid conditions. In about 20% of patients with chronic hepatitis B or C, liver biopsy reveals other liver diseases which may affect disease progression and management (*e.g.,* non-alcoholic fatty liver disease)[7,9].

The extent of necroinflammatory activity and fibrosis has important implications for prognosis and therapy[7]. Fibrosis is considered as a better predictor of disease progression than necroinflammation[10,11]. The assessment of necroinflammatory activity and fibrosis is performed using several scoring systems, which take into account *grading* of the necroinflammatory activity and *staging* of fibrosis[7,12,13]. In 1981, Knodell *et al*[14] proposed the first semiquantitative scoring system - The Histological Activity Index (HAI). As HAI combined the necroinflammation and fibrosis, it is now rarely used in its original form and has been replaced by its modifications and other systems: Ishak, Scheuer, METAVIR, and Batts-Ludwig classifications[12,15-19]. All these systems are widely used in routine practice and for clinical trials, and there is no consensus as to which one is the best[7,20]. Clinicians should be familiar with the system used by the pathologist they cooperate with[7,20].

HEPATITIS B

Despite the implementation of universal immunization programs and blood-donor screening, infection with hepatitis B virus (HBV) is still one of the most important causes of liver disease. There are more than 360 million patients (6% of the population) suffering from chronic hepatitis B (CHB) worldwide with a significant number of children still being infected each year[21-24]. The clinical spectrum of CHB

Table 1 Indications for the liver biopsy in children with chronic hepatitis B according to the phase of the infection[21,22,29]

Phase of HBV infection	Immune-tolerant	Immune-active (-clearance)	Immune-inactive	Reactivation/HBeAg-negative chronic hepatitis
HBsAg	Detectable	Detectable	Detectable	Detectable
HBeAg	Detectable	Detectable	Undetectable (anti-HBe positive)	Undetectable (anti-HBe positive)
HBV DNA (IU/mL)/(copies/mL)	> 20000/> 10^5	> 20000/> 10^5	< 2000/< 10^4 or undetectable	> 2000/> 10^4
ALT	Normal	Persistently elevated	Normal	Normal or elevated
Histopathology: necroinflammation and fibrosis	Minimal or absent	Can develop	Liver inflammation absent or minimal, fibrosis regresses over time	Active liver inflammation +/- fibrosis
Liver biopsy	Generally not indicated	Indicated	Generally not indicated	Indicated, especially if ALT elevated
Antiviral therapy	Generally ineffective, risk of drug resistance; continued monitoring recommended	Should be considered	Continued monitoring recommended	Should be considered if moderate or severe inflammation or fibrosis detected

ALT: Alanine aminotransferase; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen.

in children ranges from asymptomatic carriage with minimal liver disease, to progression to cirrhosis and decompensated liver disease[25]. Despite a rather benign course of CHB during childhood, the lifetime risk of developing hepatocellular carcinoma (HCC) is 9%-24%, and the annual incidence of cirrhosis is estimated at 2%-3%[21,26,27]. Chronic HBV infection in childhood usually manifests as a mild liver disease; however, it can lead to cirrhosis in few, but not yet well identified cases[21,25,26,28,29]. The natural history of the disease is complex and, in general, consist of four phases: immune-tolerant, immune-active (-clearance), immune-inactive, and HBeAg-negative chronic hepatitis or reactivation[13,22,29] (Table 1). In children with CHB, liver histopathology evaluation remains crucial for the management of the liver disease, and hence the liver biopsy is essential before making treatment decisions and for predicting possible progression of the liver disease[30]. However, this procedure is performed only in a selected group of patients, based on the clinical evaluation[21,22,29]. Decision to start treatment in patients with CHB is based on alanine aminotransferase (ALT) level, HBeAg positivity, HBV DNA level, liver histology, family history of HCC, and other coexisting liver diseases[22]. In general, according to the current practical guidelines of the European Association for the Study of the Liver (EASL), and the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), liver biopsy is recommended in children with either persistently increased ALT levels and/or HBV DNA levels > 2000 IU/mL[22,23] (Table 1). In particular, before the initiation of the treatment, a histologic assessment of the necroinflammatory activity and the stage of fibrosis is recommended[22,29]. The response to the currently used antiviral drugs is more likely in patients with at least moderate necroinflammation or fibrosis[31,32]. But for children with mild histopathological features, such a benefit has not been established. However, if the child has a family history of HCC, the treatment should always be considered because of the increased risk for HCC development[22,33]. Liver biopsy is a useful tool in establishing prognosis and in predicting response to treatment, as more advanced necroinflammatory activity and fibrosis correlate with response to treatment using both interferon and nucleoside analogues[31,32]. Histological evaluation is also helpful in the diagnosis of cirrhosis, which is essential when interferon therapy is considered, as this may lead to decompensation of the liver disease in cirrhotic patients[3,34]. Liver biopsy findings in children with CHB are presented in Table 2.

HEPATITIS C

Hepatitis C virus (HCV) infection is considered as an important public health problem worldwide with an estimated global prevalence of 2.8% and 160 million people infected chronically[35,36]. Chronic hepatitis C (CHC) is a progressive disease, with 10%-20% of infected patients developing cirrhosis and about 7% of cirrhotic adult patients progressing to HCC[37,38]. In children and adolescents, CHC is usually described as a mild disease; however, severe cases with advanced fibrosis, cirrhosis, and even HCC in childhood have also been reported[39-43] (Table 2). It is estimated that about 5% of infected pediatric patients develop significant liver disease and 1.8% develop cirrhosis in childhood[39,44].

Since reliable serological and virological tests are currently available, liver biopsy is no longer needed for the diagnosis of CHC. The role of this procedure in the management of patients with CHC has also evolved with the development of non-invasive alternative methods and with the availability of the new, more effective treatment regimens, based on the direct-acting antivirals (DAAs). However, DAAs have not been implemented for routine practice in pediatric patients so far. Although histological inflammatory activity and fibrosis are likely to be mild in children with CHC, liver

Table 2 Liver biopsy findings in children with chronic hepatitis B and C *n* (%)

Type of infection	Patients (*n*)	Age,yr (mean ± SD or range)	Grading of necroinflammatory activity			Staging of fibrosis				Ref.
			mean HAI ± SD	Minimal/mild	Moderate/ severe	mean ± SD	No/low grade	Severe/ cirrhosis	Cirrhosis	
HBV	30	12.9 ± 2.5	5.4 ± 3.4	25 (84)	5 (16)	1.7 ± 0.9	24 (80)	6 (20)	1 (3)	Pokorska-Śpiewak *et al*[52]
HBV	35	10.2 (2.0-20.2)	-	33 (94)	2 (6)	-	28 (80)	7 (20)	2 (7)	Boxall *et al*[77]
HBV	190	7.5 ± 4.1	6.07 ± 3.22	135 (71)	55 (29)	1.71 ± 0.78	183 (96)	7 (4)	1 (0.5)	Mozer-Lisewska *et al*[30]
HBV	47	9 (1-17)	-	34 (72)	13 (28)	-	41 (87)	6 (13)	0	Dzierzanowska-Fangrat *et al*[78]
HCV	30	11.5 ± 3.6	4.2 ± 2.5	29 (97)	1 (3)	1.2 ± 0.9	28 (93)	2 (7)	0	Pokorska-Śpiewak *et al*[52]
HCV	44	8.6 ± 4.1	-	32 (73)	12 (27)	-	39 (89)	5 (11)	-	Mohan *et al*[43]
HCV	44	14.5 ± 4.0	-	33 (75)	11 (25)	-	35 (80)	9 (20)	-	Mohan *et al*[43]
HCV	112	8.6 (1-19)	-	-	-	-	107 (96)	5 (4)	1 (1)	Guido *et al*[79]
HCV	80	9.1 ± 4.8	-	62 (78)	17 (21)	-	66 (83)	13 (16)	1 (1)	Guido *et al*[80]
HCV	121	9.8 ± 3.7	5.1	72 (60)	49 (40)	-	114 (94)	7 (6)	2 (2)	Goodman *et al*[46]
HCV	42	13.4 ± 4.1	-	30 (71)	12 (29)	-	37 (88)	5 (12)	-	Mohan *et al*[42]
HCV	109	8.8 ± 4.2	3.3 ± 1.5	-	-	1.36 ± 0.5	105 (97)	4 (3)	-	Kage *et al*[81]
HBV/ HCV	10	12.6 ± 2.7	6.2 ± 3.0	7 (70)	3 (30)	1.7 ± 0.8	9 (90)	1 (10)	0	Pokorska-Śpiewak *et al*[52]

HAI: Histological activity index; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

Table 3 Indications for the antiviral treatment in patients with chronic hepatitis C according to the stage of fibrosis[45]

Stage of fibrosis (METAVIR)	Treatment
Significant fibrosis (F3) or cirrhosis (F4), including decompensated cirrhosis	Should be prioritized
Moderate fibrosis (F2)	Is justified
No or mild liver disease (F0, F1)	Can be deferred

biopsy is recommended by EPGHAN as a baseline investigation before the HCV infection treatment in clinical trials[44]. According to the recent EASL Recommendations on Treatment of Hepatitis C (2015), before the initiation of the therapy, the assessment of liver disease severity should be performed[45]. As the post-treatment prognosis depends on the stage of fibrosis, identifying patients with advanced fibrosis or cirrhosis is particularly important. If significant fibrosis is absent, the timing of therapy is possible (Table 3). The evaluation of liver disease severity is important regardless of ALT levels, as significant fibrosis may also be present in patients with repeatedly normal ALT[45,46]. For many years, for the assessment of liver disease severity in patients with CHC, liver biopsy was the only method of choice. On the contrary, at present time, according to the recent EASL guidelines[45], in patients with CHC, the stage of fibrosis can be assessed prior to the treatment by non-invasive methods: liver stiffness measurement or well-established panels of biomarkers. However, these methods perform well in identifying cirrhosis or no fibrosis but are less reliable in resolving intermediate degrees of fibrosis. The combination of both methods (liver stiffness measurement and a blood test) may improve their accuracy and reduce the need for liver biopsy to resolve uncertainty[47,48]. Castera[49] proposed an algorithm for treatment-naïve patients with CHC, that combines two unrelated non-invasive methods: transient elastography (TE) and serum biomarker as first-line assay of fibrosis stage. According to this algorithm, liver biopsy might be necessary in patients infected with HCV genotype 1 or 4, before the treatment, if the results of TE and biomarker test are discordant[49]. Histopathological evaluation is also needed in cases of potential additional etiologies (HBV infection, metabolic syndrome, alcoholism or autoimmunity)[45]. It is essential to identify the adjunctive liver lesions like autoimmune hepatitis (especially in patients with positive LKM1 autoantibodies) or steatosis, which is a prognostic factor for the treatment response[44,50]. In pediatric patients, although several non-invasive tests alternative to liver biopsy have been investigated, none of them was validated so far and therefore this recommendation of EASL to replace liver biopsy by non-invasive tests should be approached with caution in children with CHC.

Antiviral treatment is indicated in all treatment-naive and treatment-experienced patients with compensated and decompensated liver disease due to HCV infection[45]. However, some prioritization of patients is necessary. One of the main factors considered is liver fibrosis (Table 3).

COINFECTIONS

Coinfection with HBV/HCV is usually associated with more severe liver disease, and with a frequent progression to cirrhosis and HCC compared to the monoinfection with either virus[13]. However,

there is some evidence on a reciprocal replicative suppression between both viruses[13,51]. A recent study on pediatric patients showed that HBV/HCV coinfection is an independent predictor of moderate-to-severe necroinflammatory activity[52] (Table 2). In patients with CHB, the HDV coinfection may lead to more severe liver disease with accelerated fibrosis progression, an earlier hepatic decompensation, and an increased risk for HCC[13,53]. A potential or confirmed mixed etiology of the liver disease is considered as an indication for a liver biopsy and histopathological evaluation[45,50].

COMPLICATIONS AND CONTRAINDICATIONS

In general, complications after liver biopsy are rare[3]. It is estimated that 0.9% patients suffer from complications requiring hospitalization associated with percutaneous liver biopsy[13]. The most commonly reported complication is transient and localized abdominal pain and/or right shoulder discomfort, which occur in 20%-84% of patients[3,54]. Pain after liver biopsy is usually mild, well tolerated, and easily controlled by minor analgesia[2]. Major complications occur with the prevalence of 0%-4.6% and include: hemorrhage, pneumothorax, hemothorax, visceral perforation, cholangitis, bile leak, bile peritonitis, hemobilia, infection, arteriovenous fistula, neuralgia, sedation-related injury[1,3]. The risk of death following liver biopsy in adults is estimated at 1:10000 cases[2]. In one study performed in children, 3 deaths have been reported among 469 patients (0.6%), all these patients had a history of malignancy or hematological disease[55]. In other two recent studies, no death was reported among pediatric patients[56,57].

Contraindications for liver biopsy are rather relative than absolute. The most common contraindication is severe coagulopathy. There are no specific cutoffs for laboratory parameters for impaired hemostasis, and every center at which liver biopsy is performed should define ranges for coagulation parameters that either preclude liver biopsy or require blood product administration[1,3]. However, INR > 1.5 and platelet count < 60000/mL usually indicate an increased risk of bleeding[1,3]. In case of high-risk patients (with coagulopathy and severe liver disease, pancytopaenia, or clinically evident ascites ascites) and in patients with contraindications to percutaneous liver biopsy (*e.g.*, haematological conditions), a transjugular instead of percutaneous approach is recommended[1,2]. Morbid obesity, possible vascular lesions, extrahepatic biliary obstruction, and bacterial cholangitis are other potential contraindications to percutaneous liver biopsy[1,3].

PROBLEMS AND LIMITATIONS

Since liver biopsy is an invasive procedure, it is frequently more complicated and more expensive in pediatric patients compared to adults. There are often technical problems with obtaining appropriate tissue specimen because of the size of the patient and/or liver[3]. In chronic hepatitis, sample size can affect the diagnostic accuracy of liver biopsy specimen because it is estimated that the biopsy represents approximately only 1/50000 of the total mass of the liver[10]. Thus, the sampling error can approach 20%-30%[3]. It is estimated that at least 11 complete portal tracts and a biopsy specimen of at least 20 mm length are required for an accurate diagnosis[58,59]. Bedossa *et al*[60] demonstrated that for reliable staging of fibrosis in patients with CHC, a 25 mm biopsy specimen length is adequate to overcome variation due to sampling. In pediatric patients it is frequently not achieved due to the size of the patient or liver.

Another important issue is the interpreter. There is a well-recognized possibility of inter- and intra-observer variability in the assessment of liver biopsy specimen, which may be a major potential limiting factor in liver biopsy interpretations[61,62]. Diagnostic errors made by pathologists without specialty experience in pediatric liver diseases were reported in more than 25% of samples[63]. However, when the pathologist interpreting the specimen has subspecialty expertise in liver histopathology and over 10 years of experience at an academic center, it leads to improved consistency and accuracy, minimizing problems related to the sample size[64].

ALTERNATIVES TO LIVER BIOPSY

Limitations of liver biopsy have paved the way for the development of new alternative non-invasive methods of evaluation of liver disease. In case of chronic viral hepatitis, novel imaging studies (elastography) and combinations of biomarkers are used.

Elastography enables determination of liver fibrosis by measuring liver tissue mechanical properties, in particular its stiffness (elasticity), which is reduced in case of fibrosis[1,3,65]. Elastography techniques include TE, acoustic radiation force impulse imaging (ARFI), shear wave elastography (SWE), and magnetic resonance elastography (elasto-MR). TE is the most commonly used method based on shear wave, which is generated by an external mechanical impulse. Its speed is measured by an ultrasound one-dimensional probe. The elasticity is measured at depth ranging from 25 mm to 65 mm in a 1 cm × 4 cm area, which makes the assessed liver volume two hundred times greater than that examined during the liver biopsy[65]. Since 2008, liver stiffness can be measured also in small children, since a new probe with a smaller diameter (S-probe 5 mm) compared to the regular probe (M-probe 7 mm) is available. ARFI is a new method for quantifying elasticity of tissue by measuring the shear wave velocity induced without manual compression, but using acoustic radiation

Table 4 Diagnostic performance of the main non-invasive methods used to determine significant liver fibrosis (METAVIR F ⩾ 2) and cirrhosis (METAVIR F4) in adult and pediatric patients

Test	Patients (*n*)	Disease	AUROC		Ref.
			F ⩾ 2	F4	
Fibrotest	3501	HCV	0.85	-	Poynard *et al*[82]
Fibrotest	1457	HBV	0.80	-	Poynard *et al*[82]
Fibrotest	116[1]	Chronic liver disease	-	0.73	de Lédinghen *et al*[69]
APRI	6259	HCV	0.77	0.83	Lin *et al*[83]
APRI	116[1]	Chronic liver disease	-	0.73	de Lédinghen *et al*[69]
TE	251	HCV	0.79	0.97	Ziol *et al*[84]
TE	183	HCV	0.83	0.95	Castéra *et al*[47]
TE	165	HCV	0.88	0.90	Nitta *et al*[85]
TE	400	HCV	0.818	0.932	Sporea *et al*[86]
TE	173	HBV	0.81	0.93	Marcellin *et al*[87]
TE	175	HBV	0.95	0.98	Zhu *et al*[88]
TE	116[1]	Chronic liver disease	-	0.88	de Lédinghen *et al*[69]
TE	30[1]	HCV	0.815	1.00	Awad *et al*[89]
ARFI	911	HCV	0.792	0.842	Sporea *et al*[86]

[1]Children. AUROC: Area under the receiver operator characteristic curve; APRI: Aspartate-to-platelet ratio index; ARFI: Acoustic Radiation Force Impulse Imaging; TE: Transient elastography; HCV: Hepatitis C virus.

propagating in the tissue. ARFI provides a single one-dimensional measurement of tissue elasticity and is performed using a conventional ultrasound diagnostic device. SWE is a novel method introduced in 2005, based on the generation of a radiation force and measuring the shear wave propagation speed in the liver tissue. SWE provides a real time two-dimensional map of tissue elasticity and, as ARFI, it is incorporated into a conventional ultrasound diagnostic device. Elasto-MR is a technique, which can diagnose severe fibrosis or cirrhosis with high accuracy[66]; however, it is an expensive and currently not available method for the clinical use[1,3].

Many combinations of serum biomarkers, measured in routine blood tests, were evaluated for their ability to indicate alterations in hepatic function and to determine stage of liver fibrosis[49]. The simplest one is aspartate-to-platelet ratio index (APRI). In case of chronic viral hepatitis, the most commonly used biomarker test is Fibrotest, which combines alpha-2 macroglobulin, haptoglobin, GGT, apolipoprotein A1, and total bilirubin serum levels[67].

The diagnostic performance of non-invasive methods is evaluated by calculation of the area under the receiver operator characteristic curve (AUROC), with liver biopsy as a reference standard. An analyzed method is defined as being perfect when the AUROC is 100%, excellent if AUROC is over 90%, and good if AUROC is over 80%[49,65]. In clinical studies, detection of significant fibrosis (METAVIR F ⩾ 2) and detection of cirrhosis (METAVIR F4) are considered as relevant end points[49]. The non-invasive methods have been evaluated for their ability to determine stage of liver fibrosis mainly in adult patients with CHC and less frequently with CHB. Data regarding evaluation of this methods in children are only sparse and inconsistent (Table 4). In adults, different elastography methods show sensitivity and specificity of almost 90% in detecting advanced fibrosis[68]. In limited pediatric studies, TE accurately discriminated patients with severe fibrosis or cirrhosis from those without fibrosis[69,70]. However, elastography does not enable differentiation between stages of fibrosis and, to date, only a few studies have correlated liver stiffness as assessed by elastography with histological staging of fibrosis in pediatric patients[71]. In addition, the role of this method is limited in patients with edema, inflammation, extrahepatic cholestasis, and congestion, which can also dampen elasticity[72]. The role of biomarker tests was analyzed in several cohorts of patients, including children[69,73-76]. As for the liver stiffness measurement, biomarkers identify the cirrhosis or no fibrosis, but they fail to resolve intermediate degrees of fibrosis[45]. In addition, there is some evidence on discordance between Fibrotest and METAVIR scores in children with CHC and CHB[75,76]. According to the international experts, the non-invasive methods used to assess the stage of liver fibrosis are still not fully validated; they do not evaluate necroinflammatory activity, and therefore cannot substitute for liver biopsy in children with chronic viral hepatitis[22].

CONCLUSION

For the evaluation of necroinflammation and fibrosis in pediatric patients with chronic viral hepatitis, liver biopsy remains a gold standard despite its invasive procedure. Until the non-invasive methods of grading and staging of the chronic liver disease in children are fully validated, histological evaluation remains crucial for monitoring liver disease severity and for therapeutic management decisions. Further prospective studies on larger cohorts of pediatric patients are required

before liver biopsy could be replaced by non-invasive methods in children suffering from chronic HBV or HCV infection.

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