Original paper

Determinants of liver disease progression in children with chronic hepatitis C virus infection

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Histopathological features and determinants of liver disease progression were analyzed in 42 treatment-naïve children (mean age: 10.7 ±3.7) with chronic hepatitis C (14/42 infected vertically and 26/42 horizontally). Histopathological evaluation was performed according to Knodell's modified system. Predictors of necroinflammation and fibrosis were identified using linear regression analyses. Most children presented with mild necroinflammation and fibrosis (mean grade 4.3 ±2.7, mean staging 1.2 ±0.8), irrespective of the mode of transmission. Vertically infected children were younger than those infected horizontally (8.6 ±2.5 vs. 11.5 ±3.7 years, $p = 0.02$). Alanine and aspartate aminotransferase (ALT and AST) levels were associated with necroinflammation ($p = 0.003$ and $p = 0.01$ for ALT and AST, respectively) and fibrosis ($p = 0.01$ and $p = 0.04$, respectively). Other positive independent predictors of fibrosis included duration of infection ($p = 0.03$) and body mass index (BMI) z-score ($p = 0.03$).
Children with chronic hepatitis C presented with mild liver changes over a decade after the infection, irrespective of the mode of transmission. Since fibrosis is a time-dependent process, progression of the liver disease in vertically infected children may occur at a younger age compared to patients infected horizontally. Aminotransferase levels were associated with necroinflammation and fibrosis. Longer duration of infection and a higher BMI z-score were associated with more severe fibrosis.

Key words: chronic hepatitis, grading and staging, hepatitis C virus, liver biopsy, mother-to-child transmission.

Introduction

Hepatitis C virus (HCV) infection is recognized as a major public health problem worldwide with an estimated global prevalence of 2.8% [1, 2]. In Europe, hepatitis C prevalence is estimated at 1.5-3.0% and in European children at 1.0-1.5% [2]. Hepatitis C is a progressive disease, with 10-20% of infected patients developing cirrhosis and about 7% of adult patients with cirrhosis progressing to hepatocellular carcinoma [3, 4]. However, little is known about the disease progression in patients infected in childhood and, to date, only sparse and inconsistent data are available regarding liver histopathology in HCV-infected children [5, 6, 7]. In addition, the relevance of different markers as predictors of chronic disease progression is not well studied [4, 6]. Therefore, the aim of this study was to analyze histopathological features in children with chronic hepatitis C and compare them with clinical data and laboratory values in order to assess the determinants of liver disease progression.

Material and methods

Patients

Liver biopsy results from consecutive treatment-naïve children with chronic hepatitis C were analyzed retrospectively. The biopsies were performed between 2002 and 2013 as part of the qualification procedure for the antiviral treatment protocol. Patients were qualified for the liver biopsy on the basis of the current practical guidelines of the European Association for the Study of the Liver (EASL) [8]. We included children over 3 years of age with detectable HCV RNA regardless of the aminotransferase pattern. The diagnosis of chronic hepatitis C was made in patients with over 6-month duration of the disease, based on positive serological testing (positive anti-HCV antibodies), and confirmed with nucleic acid testing. Anti-HCV antibodies were determined using a third-generation ELISA test (Ortho Vitros ECi, Ortho-Clinical Diagnostics, Johnson & Johnson). HCV RNA was detected using real – time polymerase chain reaction (RT-PCR; Amplico, Roche and Cobas TaqMan, Roche). Alanine and aspartate aminotransferase (ALT and AST) serum levels were measured at the time of the liver biopsy using commercially available laboratory tests (Vitros, Ortho-Clinical Diagnostics, Johnson & Johnson). For both ALT and AST, 40 IU was considered the upper limit of normal (ULN). Probable modes and dates of transmission were determined based on the available medical records. The putative age at infection and the duration of disease were calculated from the beginning of risk exposure. Mother-to-child (vertical) transmission was diagnosed in children of HCV-infected mothers, according to the guidelines of the European Paediatric HCV Network: children were diagnosed for infection if they had two or more positive qualitative PCR results and/or were anti-HCV positive beyond 18 months of age [1, 6]. HBV, HDV or HIV-infected children were not included in the study. Additionally, other well established causes of liver disease such as autoimmune hepatitis, Wilson's disease, α1-antitrypsin deficiency or non-alcoholic fatty liver disease (NAFLD) were considered as exclusion criteria for this study.

Body mass index standard deviation (SD) scores (BMI z-scores) were calculated according to the WHO Child Growth Standards and Growth reference data using the WHO Anthropometric calculator AnthroPlus v.1.0.4. Obesity was diagnosed in children with the BMI z-score > 2 SD.

Liver biopsy

Percutaneous liver biopsy was performed using the Menghini needle (Hepafix kit 1.4 or 1.6 mm, Braun) after obtaining a written informed consent for the biopsy from the patient and/or parents/guardians. All biopsy specimens were evaluated by one pathologist experienced in hepatopathology (BWZ), who was blinded to the clinical data. This assessment was made according to Knodell's numerical scoring system modified by international experts [9, 10, 11]. The grading of necroinflammatory activity was expressed as the final sum of points in three categories: periportal and bridging necrosis, intralobular necrosis and portal inflammation, which gave a histologic activity index (HAI) ranging from 0 to 18 points. The necroinflammation grade was considered minimal when HAI was 0-3 points, mild if 4-8 points, moderate if 9-12 points, and severe if 13-18 points. The stage of the fibrosis was assessed using a 5-point scale: 0 – no fibrosis; 1 – portal fibrosis, fibrous portal expansion; 2 – periportal fibrosis, periportal or scarce portal-portal septa; 3 – septal fibrosis, fibrous septa with architectural distortion; and 4 – cirrhosis. In addition, the presence of the three histopathological lesions typical for chronic hepatitis C in adults was analyzed: portal lymphoid aggregates/follicles, steatosis and bile duct damage [12, 13, 14].

Statistical analysis

All continuous variables were expressed as either mean ± SD or medians with interquartile ranges (IQR) and were tested for normal distribution using the Kolmogorov-Smirnov test. Data were compared with the use of either the Student t test or the Mann-Whitney test for continuous variables and with either the χ^2 test or Fisher's exact test for categorical variables.

Mean grading and staging scores were calculated as in other papers, in order to make the comparison with the results of other authors possible [15, 16, 17].

A linear regression analysis was conducted to identify the predictors of necroinflammation and fibrosis, and Pearson correlation coefficients were obtained. Multiple regression was performed with the following variables (candidate predictors) entered into the model irrespective of the results of the univariate analysis: sex, duration of infection, age at liver biopsy, age at infection, alanine aminotransferase (ALT) level, aspartate aminotransferase (AST) level, viral load, BMI z-score, mode of infection (the genotype was not included due to the small number of patients with genotype other than 1). Considering a strong correlation between ALT and AST levels ($r = 0.87$, $p < 0.0001$), two separate multivariate models were constructed to avoid multicolinearity: Model I (including ALT), and Model II (including AST). After entering all the variables into the model, those variables that showed the least significant associations were subsequently excluded until all variables remained significant ($p < 0.05$).

The model fit for the multiple regression was assessed with the coefficient of determination R^2 – and the adjusted R^2 – the coefficient of determination adjusted for the number of independent variables in the model.

A two-sided p-value of < 0.05 was considered to indicate significance. All statistical analyses were performed using MedCalc Statistical Software ver. 12.1.4.0 trial software (MedCalc, Mariakerke, Belgium).

Ethical standards

The local ethics committee approved this study. Each patient and/or parents/guardians provided written informed consent for the percutaneous liver biopsy. The investigation was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Results

Study population

The analysis concerned 42 treatment-naïve patients chronically infected with HCV (29 boys and 13 girls, aged 5-17 years, mean 10.7 ±3.7 years). The baseline characteristics of the study group are presented in Table I. Amongst the analyzed patients, 14/42 (33%) were infected vertically (mother-to-child transmission) and 26/42 (62%) horizontally (16 – through blood transfusion, 10 – nosocomially during hospitalization or surgery). In two (5%) children the putative mode of transmission remained unknown. Most of the children infected horizontally (18/26) became infected during the neonatal period. The group of children infected vertically differed significantly compared to children infected horizontally with respect to the age at liver biopsy ($p = 0.02$) and the age at infection acquisition ($p < 0.0001$; Table I). The predominant genotype was 1 (mainly 1b, determined in 36/42, 86% cases).

Liver histopathology

In the studied liver biopsy specimens, the necroinflammatory activity correlated significantly with the extent of fibrosis ($r = 0.64$, $p < 0.0001$). Most children presented with minimal to mild necroinflammation (the mean grade was 4.3 ±2.7 points) and staging of fibrosis of 0-2 points (mean 1.2 ±0.8; Table II). No case of liver cirrhosis was diagnosed. Neither necroinflammation nor fibrosis differed according to the mode of transmission of infection (vertical vs. horizontal – Table II). Among the histopathological features typical for chronic HCV infection in adult patients, the presence of lymphoid aggregates was

Table I. Baseline characteristics of the study group

Characteristics		Total[a]	Vertical transmission (Group I)	Horizontal transmission (Group II)	p (Group I vs. Group II)
Number of patients (%)		42	14	26	
Sex	Male (%)/Female (%)	29 (69)/13 (31)	6 (43)/8 (57)	6 (23)/20 (77)	0.35
Age at liver biopsy (years)	Mean ± SD	10.7 ±3.7	8.6 ±2.5	11.5 ±3.7	0.02
Duration of infection (years)	Mean ± SD	9.6 ±3.6	8.6 ±2.5	10.1 ±4.1	0.22
Age at infection[b]	Median (IQR)	0.1 (0.0-0.1)	0 (0.0-0.0)	0.1 (0.1-2.0)	< 0.0001
ALT	Median (IQR)	67 (40-109)	65.5 (46-79)	80 (50-122)	0.24
AST	Median (IQR)	50.5 (36-80)	56 (43-65)	53 (36-80)	0.89
Viral load (IU/ml)	Median (IQR)	8.12×10^5 (3.43×10^5 - 1.6×10^6)	1.11×10^6 (4.2×10^5 - 1.6×10^6)	5.15×10^5 (3.18×10^5 - 1.57×10^6)	0.18
Genotype (%)	1 (a or b)	38 (90)	13 (93)	23 (88)	0.52
	3	2 (5)	0	2 (8)	
	4	2 (5)	1 (7)	1 (4)	
BMI z-score (SD)	Mean ± SD	0.6 ±1.3	0.4 ±0.9	0.76 ±1.5	0.36
	> 2 SD (obesity)	7 (17%)	0	7 (27)	0.07

[a] *Including two patients with unknown mode of transmission, not included in either Group I or Group II*
[b] *Age 0.0 years indicates vertical transmission, age 0.1 years indicates horizontal infection during the neonatal period; data available for 40 patients with known source of the infection.*

the most common (in 33% of patients), steatosis was assessed in 21% of cases, whereas bile duct damage was not observed (Table II).

Determinants of necroinflammatory activity and fibrosis

Univariate linear regression analysis revealed that both ALT and AST serum levels were associated with necroinflammation ($p = 0.002$ and $p = 0.006$, respectively). This observation was confirmed by the multivariate analysis, which revealed that ALT and AST were independently associated with necroinflammatory activity ($p = 0.003$ and $p = 0.01$, respectively, Table III).

Aminotransferase levels proved to be associated with fibrosis, which was confirmed by both univariate analysis ($p = 0.02$ for ALT and $p = 0.04$ for AST) and multivariate analysis ($p = 0.01$ for ALT and $p = 0.04$ for AST). Additionally, multivariate analysis revealed that the duration of infection and BMI z-score were independent positive predictors of fibrosis ($p = 0.03$ and $p = 0.03$, respectively, Table IV).

Other analyzed parameters (sex, age at liver biopsy, age at infection, viral load, BMI, mode of infection) were not associated with necroinflammation or fibrosis. Additionally, none of the studied predictors were associated with the presence of lymphoid aggregates or steatosis.

Discussion

Data reporting the liver disease progression in pediatric population infected with the hepatitis C virus are conflicting. This is usually described as a mild disease in children and adolescents; however, severe cases have also been described occasionally [5, 6, 15, 18, 19]. This study presents a cohort of children with an average of a decade-long history of chronic hepatitis C. In most of these children, the described histopathological changes were mild. The mean grade of necroinflammation, expressed as HAI, in our group of patients was 4.3 ±2.7 points, which is comparable with the observations of Goodman *et al*. (mean HAI: 5.1 points) [16]. Studies of other authors, mainly from Europe and Japan, also suggest a rather benign course of liver disease in HCV-infected children [7, 17, 20, 21]. This is in contrast with other findings, mainly from the United States, pointing out that chronic hepatitis C may lead to severe fibrosis, cirrhosis and even hepatocellular carcinoma in childhood [5, 15, 22]. In our study, however, a number of children (5% in the whole group and 8% in children with horizontal mode of transmission) presented with more advanced fibrosis (3 points) indicating septal

Table II. Necroinflammatory activity and fibrosis in the studied group

Histopathological feature		Total[a] (n = 42)	Vertical transmission (Group I, n = 14)	Horizontal transmission (Group II, n = 26)	p (Group I vs. Group II)
Grading of necroinflammation n (%)	Mean ± SD	4.3 ±2.7	4.6 ±3.1	4.2 ±2.6	0.68
	Minimal (0-3)	14 (33)	5 (36)	7 (27)	0.35
	Mild (4-8)	25 (60)	7 (50)	18 (69)	
	Moderate (9-12)	3 (7)	2 (14)	1 (4)	
	Severe (13-18)	0	0	0	
Staging of fibrosis n (%)	Mean ± SD	1.2 ±0.8	1.2 ±0.7	1.2 ±0.9	0.83
	0	9 (21)	2 (14)	7 (27)	1.0
	1	18 (43)	7 (50)	10 (38)	
	2	13 (31)	5 (36)	7 (27)	
	3	2 (5)	0	2 (8)	
	4 (cirrhosis)	0	0	0	
Grading (0-3) + Staging (0)		7 (17)	2 (14)	5 (19)	1.0
Grading (9-18) + Staging (3-4)		1 (2)	0	1 (4)	1.0
Lymphoid aggregates		14 (33)	7 (50)	6 (23)	0.27
Steatosis		9 (21)	3 (21)	5 (19)	1.0
Bile duct damage		0	0	0	–

[a] *Including two patients with unknown mode of transmission, not included in either Group I or Group II*

Table III. Determinants of necroinflammatory activity

Predictors	Univariate analysis		Model I Multivariate analysis (ALT)		Model II Multivariate analysis (AST)	
	β (SE)	p value	β (SE)	p value	β (SE)	p value
Sex (for male sex)	–1.22 (0.89)	0.18	–	–	–	–
Duration of infection	0.08 (0.12)	0.50	–	–	–	–
Age at liver biopsy	0.03 (0.12)	0.77	–	–	–	–
Age at infection	–0.14 (0.25)	0.57	–	–	–	–
ALT	0.016 (0.005)	0.002	0.016 (0.005)	0.003	–	–
AST	0.014 (0.005)	0.006	–	–	0.014 (0.005)	0.01
Viral load / 10^5	–0.014 (0.016)	0.38	–	–	–	–
BMI z-score	0.59 (0.31)	0.06	–	–	–	–
Mode of infection (for vertical vs. horizontal)	0.38 (0.92)	0.68	–	–	–	–
Model performance						
R2	–		0.21		0.22	
Adjusted R2	–		0.19		0.19	

Considering a strong correlation between ALT and AST ($r = 0.87$, $p < 0.0001$), two separate multivariate models were constructed to avoid multicolinearity: Model I (including ALT), and Model II (including AST). Candidate predictors were entered into the model irrespective of the results of the univariate analysis. After entering all variables to the model, the variables that showed least significant associations were subsequently excluded until all variables remained significant ($p < 0.05$)
β – coefficient; SE – standard error

Table IV. Determinants of fibrosis

Predictors	Univariate analysis		Model I Multivariate analysis (ALT)		Model II Multivariate analysis (AST)	
	β (SE)	p value	β (SE)	p value	β (SE)	p value
Sex (for male sex)	0.49 (0.27)	0.07	–	–	–	–
Duration of infection	0.06 (0.036)	0.10	–	–	0.07 (0.03)	0.03
Age at liver biopsy	0.05 (0.03)	0.14	–	–	–	–
Age at infection	–0.05 (0.07)	0.48	–	–	–	–
ALT	0.004 (0.0016)	0.02	0.005 (0.0018)	0.01	–	–
AST	0.003 (0.0016)	0.04	–	–	0.003 (0.0015)	0.04
Viral load / 10^5	0.001 (0.004)	0.81	–	–	–	–
BMI z-score	0.21 (0.09)	0.03	–	–	0.20 (0.089)	0.03
Mode of infection (for vertical vs. horizontal)	0.06 (0.28)	0.83	–	–	–	–
Model performance						
R^2	–		0.19		0.30	
Adjusted R^2	–		0.17		0.24	

Considering a strong correlation between ALT and AST ($r = 0.87$, $p < 0.0001$), two separate multivariate models were constructed to avoid multicolinearity: Model I (including ALT), and Model II (including AST). Candidate predictors were entered into the model irrespective of the results of the univariate analysis. After entering all variables to the model, the variables that showed least significant associations were subsequently excluded until all variables remained significant ($p < 0.05$).
β – coefficient; SE – standard error

fibrosis with architectural distortion. No case of cirrhosis in our study group was observed. In contrast, Bortolotti *et al.* observed 6 cases of decompensated cirrhosis in children with a mean age of 9.6 years among a group of 332 patients with chronic hepatitis C. Moreover, 4 of the children with cirrhosis had had only moderate hepatitis in a previous liver biopsy performed 2-9 years earlier. The authors concluded that over a decade following exposure 2% of children who acquired the infection vertically and as many as 6.5% of those infected with HCV genotype 1a would develop symptomatic cirrhosis [18].

On the other hand, in our study the proportion of children in whom no significant morphological changes in the liver were found was relatively low (17%). This is in contrast with the findings by Goodman *et al*., who reported nearly normal biopsy results or only minimal inflammation in 52 (43%) of 110 studied liver biopsies in children with chronic hepatitis C [16].

The histopathological triad of features typical for hepatitis C in adult patients, lymphoid aggregates, steatosis and bile duct damage (according to Fiel occurring in 17-85%, 50-74% and 15-91% of HCV-infected adults, respectively), was not as common in our study group (33%, 21% and 0%, respectively) [13]. The observation that these histopathological lesions are rare in children has also been confirmed by other authors: Mahon *et al*. detected lymphoid aggregates in 44% of 41 liver biopsy specimens, steatosis in 10% and bile duct damage in 7%, whereas Goodman *et al*. found those lesions in respectively 23%, 41% and 6% of their 121 studied liver biopsies [5, 16].

The determinants of liver disease progression in HCV-infected patients, especially in the pediatric population, are not well studied. Analyses of the natural history of HCV infection have identified several modifiable and non-modifiable factors potentially associated with disease progression, including: age at acquisition of infection, duration of infection, sex, race, host genetic factors, viral genotype, ALT level, coinfections and comorbidities, metabolic factors, alcohol consumption, and smoking [4].

The predictive value of ALT and AST levels for the severity of the liver disease in adults is conflicting [1, 4]. In a systemic evaluation of published studies elevated serum ALT levels were determinants of progression to cirrhosis [23]. In our study, multivariate analysis revealed that ALT and AST serum levels were independently associated with necroinflammation and fibrosis. This positive correlation between ALT levels and necroinflammation has also been confirmed by other authors [5, 15, 16]. In the study by Guido *et al.* ALT was significantly associated with the severity of intralobular focal necrosis, but not with any other necroinflammatory lesion [20]. However, it should be noted that a normal ALT level does not exclude progressive liver disease [16].

Available data suggest an association between the duration of infection and fibrosis progression [1, 12, 16, 20, 24]. The same observation was made in our study: duration of infection (but not age at liver biopsy or age at acquisition of infection) was an independent positive predictor of fibrosis. A study by Jara *et al*. demonstrated that children who were 15 years or older had a significantly higher fibrosis score than younger patients [25]. In a study by Mohan *et al*. fibrosis correlated with the age at infection [5]. Results of the studies in which repeated liver biopsies in children with chronic hepatitis C were analyzed indicate that in a significant number of children an increase in the fibrosis score occurs (in 54% children 3-17 years after the first biopsy in a study by Guido *et al.* and in 29.5% after 5.8 $\pm$3.5 years in a study by Mohan *et al*.) [19, 26]. Other authors suggest that children who become chronically infected vertically or perinatally have a slow progression of fibrosis [4, 21, 27]. Mohan *et al*. pointed out that the progression of the disease is slower in children than in adults and the rate of cirrhosis development before adulthood does not exceed 10% [19]. However, according to Niederau *et al*., when standardized mortality ratios are calculated, those who are infected with HCV at a young age have more than 5 times higher rates than patients infected after the age of 50 years. Moreover, patients who acquire the infection early in life have a markedly increased mortality even when cirrhosis is absent at diagnosis [28]. Based on the observation that fibrosis increases with age and the duration of infection, it may be suggested that chronic hepatitis C in children is a progressive, time-dependent disease and an end-stage liver disease may develop in young adulthood, in spite of its benign clinicopathologic presentation, especially in children infected vertically or perinatally [20].

Another factor associated with the progression of fibrosis in our study was the BMI z-score. Other authors report that the observed association between high BMI and fibrosis may be confounded by underlying relationships with steatosis and diabetes [4]. However, no association between BMI z-score and steatosis in our study group was confirmed. Moreover, none of our patients were diagnosed for diabetes or impaired glucose tolerance. In another study, the correlation between overweight and higher staging in HCV-infected children was found [16].

The influence of the HCV genotype and HCV viral load on the disease progression is considered, but available studies on adult patients suggest that these viral factors cannot predict the severity of liver damage [1, 4]. In our study, the HCV viral load did not appear to exert any influence on the liver histopathology and the effect of the genotype (due to the strong predominance of genotype 1b in the study group) was not analyzed.

Moreover, in our study no correlation between the mode of transmission of infection and the severity of histopathological changes in the liver was found, which is in agreement with the observations of other authors [18, 29]. However, in our study group, children who acquired the infection vertically differed significantly from the group with horizontal transmission with respect to the age at infection acquisition and the age at liver biopsy (8.6 ±2.5 vs. 11.5 ±3.7 years, $p = 0.02$), but not according to the duration of infection. This indicates that in the case of the mother-to-child HCV transmission progression of liver disease may occur at a younger age than in children infected horizontally in the later years of life. Since fibrosis is a time-dependent process, it is possible that some vertically infected children will develop severe liver disease in their teens or in young adulthood [1]. This may also suggest the need for early treatment intervention in this group of patients.

Some findings suggest that in HCV-infected children severe clinical or morphological liver damage could indicate the possibility of other comorbidities [20]. In particular, coinfections with HBV or HIV may lead to more severe liver disease and frequently progression to cirrhosis and hepatocellular cancer [13, 30, 31]. Our observations suggest that HBV/HCV coinfection leads to significantly higher grading scores compared to HCV monoinfection. Moreover, this coinfection is an independent predictor of moderate to severe necroinflammatory activity [32].

Despite the fact that many efforts have been made toward an understanding of the predictors of liver progression in HCV-infected patients, many factors remain unknown. Various demographic and environmental variables from large published regression models have accounted for only 18-30% of the variation noted in the rates of fibrosis progression [4]. In our study, the R^2 values in the multivariate analysis models ranged between 0.19 and 0.30, which means that 70-81% of the variation remain unexplained. This underscores the fact that other factors play a crucial role in determining the liver disease progression. It is possible that other host and viral factors will account for the variability in the natural disease progression in different ethnic and racial groups [19]. Therefore further studies should be directed toward the design of predictive models for effective risk stratification based on clinical and biochemical variables [4].

Limitations

Because of its retrospective design, our study did not allow us to distinguish between causes and effects. Thus, the causal relationship between the variables demonstrating an association in this study needs to be confirmed in prospective cohort studies. However, it should be pointed out that all the patients were consecutively enrolled, therefore limiting the possible risk of a selection bias. Another methodological issue is the relatively small number of patients in our study group. However, nowadays liver biopsy is rarely performed in children, and there is an absence of similar studies from this part of Europe. Moreover, in contrast to the reported results obtained during clinical trials with larger groups of highly selected children, this paper presents a group of consecutive patients referring to the tertiary health center. In our study, the slides were read by one pathologist. Taking into consideration the possible impact of interobserver variation, an additional pathologist could make the results more reliable.

In conclusion, children with chronic hepatitis C presented with mild liver changes over a decade after the acquisition of the infection, irrespective of the mode of HCV transmission. Since fibrosis is a time-dependent process, progression of the liver disease in vertically HCV-infected children may develop at a younger age compared to patients infected horizontally. Aminotransferase levels were positively associated with necroinflammation and staging. A longer duration of infection and higher BMI z-score were associated with more severe liver fibrosis.

The authors declare no conflict of interest.

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