Clinical picture of chronic hepatitis C in children — Polish experience

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Abstract

The aim of this study was to investigate long-term clinical, virologic and histologic outcome of hepatitis C virus infection in children. Sixty children (16 girls and 44 boys) have been followed for 1 to 5 years (mean 1.7 ± 0.9 years). HCV RNA and anti-HCV were checked every six months. Biopsy specimens were evaluated for the grade of inflammation and stage of fibrosis (scores 0-4). ALT was measured every 3 months. Presumed duration of HCV infection was from 1 to 16 years (mean 7.4 ± 3 years). Fifteen (25%) children could have been infected by blood transfusion, 5 (8%) during surgical procedures, 29 (50%) were multiply hospitalized. Twenty-five children infected as neonates had lower staging score than 24 infected later in life (p = 0.021). Two girls (aged 13 and 14) were diagnosed with acute hepatitis C, with maximum ALT of 1272 U/l and 1638 U/l respectively. In 11 children (18%) median ALT of more than 3 times the normal value (> 105 U/l) was noted. Six children (10%) had continuously normal ALT. Histopathology revealed mild to moderate inflammatory activity (0-2 points) in 52 children (87%). Seven specimens (11%) were scored for 3 to 4 staging points, 3 of them (5%) were diagnosed with liver cirrhosis. We have found statistically significant correlation between median ALT and grading (r = 0.36 ; p = 0.005) as well as staging scores (r = 0.32 ; p = 0.016), median AST and grading (r = 0.36 ; p = 0.006) as well as staging (r = 0.36 ; p = 0.007) scores but also median GGT and staging score (r = 0.39 ; p = 0.004). (Acta Gastroenterol. Belg., **2000**, 64, **20-24**).

Key words : hepatitis C, children, HCV.

Introduction

Chronic hepatitis C is for many years clinically silent so biochemical and histopathological features are used to estimate its severity (1). The disease is well recognized in adults (mostly because it is possible to gather large population group to perform the analysis), while its the natural course in children is poorly documented in the literature. The aim of this study was to investigate long-term clinical, virologic and histologic outcome of hepatitis C virus infection in children.

Patients and methods

Sixty children : 16 girls (27%) and 44 boys (73%) were enrolled to the study. The age of the children on enrolment was from 3 to 17 years ; the mean age of this study population was 9.2 ± 3.2 years. On enrolment the parents were interviewed for any clinical symptoms or complaints of the disease and detailed history of any hospital stay, blood transfusions surgery or family history of hepatitis was collected. The mothers of HCV infected children were checked for serum anti-HCV antibodies. The children were examined every three months throughout the follow-up period. Every time blood samples were taken for biochemical liver-function tests including measurements of serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) as well as gamma-glutamyltranspeptidase (GGT).

Data were gathered from March 1992 until November 1998. The time of follow-up was from 1 to 5 years (mean 1.7 ± 0.9 years). Duration of HCV infection, calculated according to the data and laboratory tests done outside our Department, was from 1 to 16 years (mean 7.4 ± 3 years).

After being included to the study the children have been followed for six months in our Department before liver biopsy was performed. The diagnosis of chronic hepatitis C was based on the detection in serum antibodies to HCV which were updated in 1998 by the 4th generation enzyme immuno-assay (UBI HCV EIA 4.0, United Biomedical Inc., Hauppauge, NY, USA) and/or detection of HCV RNA in serum by reverse transcription-polymerase chain reaction (Cobas Amplicor, Roche). Both parameters were repeated every six months.

All children had levels of α_1-antitripsin within the range of norms, insignificant levels of anti-nuclear and anti-smooth muscle antibodies, no hemochromatosis or Wilson's disease, no infection with HIV, but also no underlying diseases requiring frequent blood transfusions (anemia, hemophilia). HBsAg in serum and HBV DNA checked in biopsy liver specimens by in situ DNA hybridization were in all 60 children negative. Antibodies for HBc (IgG + IgM) in serum were checked by Microelisa (Organon Teknika, Boxtel, NL). Thirty-two anti-HBc positive children were considered to be previously infected with HBV.

Thick needle percutaneous liver biopsy under short-term general anaesthesia with an informed written consent of parents was performed. The histological sections were reviewed "blindly" by two independent pathologists not connected with the study. Histological evaluation were made according to the system described by Desmet *et al.* (2). The degree of necroinflammatory activity (grading) which included piecemeal necrosis, lobular necrosis and portal inflammation and the amount

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of fibrosis (staging) were assessed and scored from 0 to 4 points.

Statistical analysis

Statistical analysis was performed with the use of *Statgraphics Plus* for Windows. Comparisons were drawn using the Wilcoxon signed rank test, Fisher's exact test and the unpaired Student's t-test. A p value of less than 0.05 was considered significant.

Results

Clinical characteristics of 60 children infected with HCV was gathered in Table I. Except for two acute cases, the disease was recognized by chance (laboratory tests done due to other reasons). Presumed source of HCV infection was established in 20 children (Table I), others had no overt parenteral exposure, however 29 of them had been multiply hospitalized. Twenty five children could have been infected in the first year of their lives. Comparison of the group of 25 children presumably infected with HCV in the first year of their lives with 24 children who were probably infected later revealed no difference in the respect of mean ALT ($p = 0.274$), but statistically significant lower S-score in the former group ($p = 0.021$). Children infected as neonates were older at the time of biopsy than the others (mean age 6.3 years versus 4.1 year, $p = 0.008$).

A comparison between the group of 32 children previously infected with HBV and 28 children with no history of such exposure revealed no statistically significant difference in the mean ALT values, grading and staging scores. Patients in both groups were similar with the respect to age, sex, history of blood transfusion and presumable duration of hepatitis. Out of four children with liver cirrhosis, two were previously infected with HBV.

Two children developed severe sequelae of hepatitis. These were : an episode of ascites in a 10 year old boy with liver cirrhosis, and an episode of bloody stools in a 13 year old girl whose histopathology was described as severe fibrosis with architectural distortion (S_3) but who developed esophageal varices grade II/III and eventually was classified on the basis of clinical symptoms as cirrhosis of the liver.

Table I. — **Clinical characteristics of 60 children infected with HCV**

Age (years)	9.2 ± 3.2 (3-17)
Sex (M/F)	44/16
Source of infection:	
Transfusion	15 (25%)
Surgery	5 (8%)
Multiple hospitalisation	29 (50%)
Anti-HCV positive mother	0
Infection in the first year of life	25
Previous infection with HBV	32
Anti-HCV negative	3
Hepatomegaly	56 (93%)
Splenomegaly	17 (28%)

Biochemical parameters of hepatitis

Six children (10%) had no biochemical symptoms of hepatitis in most evaluations : median ALT did not exceed 35 U/l (upper range of the laboratory norm), 43 children (72%) presented with mild hepatitis with ALT up to 105 U/l (3 times the norm). However 11 children (18%) had constantly elevated serum ALT, with median above 105 U/l.

Acute form of hepatitis C

Very high maximum ALT values (above 1000 U/l) were found in two cases — all other measurements did not exceed 450 U/l. These two girls, aged 14 and 13 were admitted to the clinic with the diagnose of acute viral hepatitis C. One of them was most probably infected during the surgical operation, the other at the time of acute hepatitis type A, six months earlier. Patterns of ALT, serum antibodies and HCV viraemia in the latter girl is shown in Fig. 1. None of the girls had had previous exposure to HBV. Antibodies to CMV (IgM), Paul-Bunell-Davidhson test and anti HAV IgM (in the former girl) were negative. The acute phase of hepatitis with maximum ALT of 1272 U/l and 1638 respectively, lasted two months in the former and three in the latter case. Then biochemical parameters stabilized with medians of about 30-40 U/l, but HCV RNA was continuously positive. Biopsies that were performed six months afterwards revealed acute chronic hepatitis C with moderate piecemeal necrosis and fibrosis with architectural distortion (G_3S_3) in the first patient and mild piecemeal necrosis with periportal septa (G_2S_2) in the other.

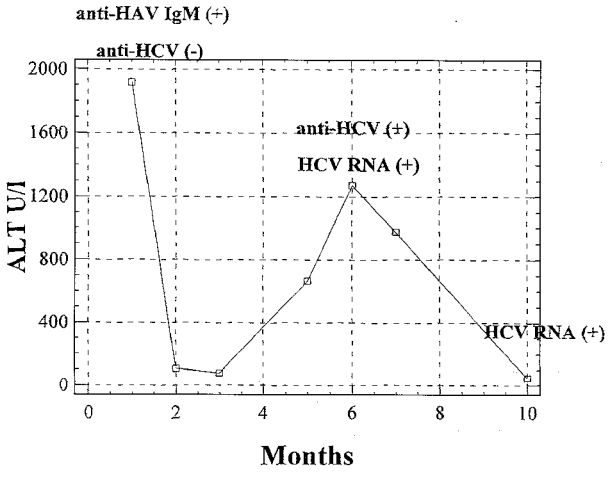

Fig. 1. — Pattern of ALT in a girl infected with HAV and HCV

Table II. — **Clinical and laboratory features of children diagnosed with liver cirrhosis**

Sex	M	F	M	F
Age (years) [1]	10	8	10	13
Presumed source of infection	Unknown	Unknown	Multiple prolonged hospitalisations (respiratory tract infections)	Blood product transfusion at the age of 2
Previous infection with HBV	Yes	No	Yes	No
Clinical symptoms of hepatitis or portal hypertension	Hepatomegaly, splenomegaly	Hepatomegaly, splenomegaly	Hepatomegaly, splenomegaly, jaundince, ascites	Hepatomegaly, splenomegaly. An episode of bloody stool (13 years old)
The highest ALT (U/1)	720	30	190	121
Median ALT (U/1)	147	24	210	89
Additional features connected with hepatitis	Treatment with azathioprine for 12 months prior the diagnosis	Antibodies to HCV negative, continually normal ALT	High levels of IgG- 2530 mg%[2]	Reye Syndrome when she was 2 years old
Histopathological definition	Cirrhosis of the liver	Moderate piecemeal necrosis with architectural distortion, probable cirrhosis	Cirrhosis of the liver	The specimen defragmentated. Diagnose of liver cirrhosis stated on the basis of clinical symptoms
Grading (points)	4	3	4	2
Staging (points)	4	4	4	3

(1) calculated referring to the time when the biopsy was performed.
(2) laboratory norms of IgG : 850-1300 mg%.

Histopathology

In 52 children (87%) histopathological changes were graded and staged for 0-2 points indicating either none or mild to moderate inflammatory activity without major sequelae for the architecture of the liver. However in 7 children (11.6%) staging was estimated for 3 or 4 points (fibrosis with architectural distortion or cirrhosis) and in three of them the diagnose of liver cirrhosis was stated. The detailed history, clinical picture, laboratory and histologic parameters of these three children and the girl with clinical diagnosis of liver cirrhosis are summed up in table II.

Statistically significant but mild correlation was found between grading and staging score and median serum levels of ALT, AST and GGT- detailed data and p values are presented in Table III. Neither biochemical nor histopathologic features were correlated with the age or sex of the patients.

Discussion

It has been estimated that 1.4% of Polish population are infected with hepatitis C virus, which means that about 490 000 people are chronic carriers of the virus (3,4). Vertical transmission of HCV is rare (0-15%) (5,6) and it was not documented in even one of our children. The most typical source of infection with HCV in adults and children were blood products donated before surrogate markers of the virus were widely introduced (7). Adults infected by transfusion developed more aggressive hepatitis and are at greater risk of cirrhosis than adults infected via other routes (8).

On the contrary half of the children exposed to HCV by blood transfusion had after about 20 years no detectable serum HCV RNA (9,10). Both chronicity rate as well as clinical course of HCV infection seem to be more benign in children than in adults (11). Chang *et al.* (12) and Ni *et al.* (13) suggest that younger children develop milder hepatitis and we have also found that children infected with HCV in the first year of life develop less fibrosis (lower S-score) than others. Serum ALT activities are described to fluctuate but they do not exceed 10 times the maximum normal values (14,15,16), which would be 450 U/l in our study, and which is confirmed by most of our results. Acute hepatitis C in children has rarely been reported (12). One of our girls was infected during the course of hepatitis A and this might have contributed to the acute onset of hepatitis C. Co-infection with these two viruses in adults may result in fulminant hepatitis (17)). We cannot give any reasonable explanation for the other case of acute hepatitis C. High amount of fibrosis in both biopsy specimens are hard to explain in such a short course of hepatitis unless one considers a possibility of reactivation of silent hepatitis C, rather than newly acquired infection.

Table III. — **Correlation between medians of ALT, AST and GGT and grading/staging scores**

	G	S
Median ALT	r = 0.36 p = 0.005	r = 0.32 p = 0.016
ALT at the time of biopsy	r = 0.43 p = 0.0006	r = 0.29 p = 0.024
Median AST	r = 0.36 p = 0.006	r = 0.36 p = 0.007
Median GGT	NS	r = 0.39 p = 0.004

In spite of a similar pattern of liver enzymes, histological activity of HCV hepatitis is more pronounced in our children than in other papers. A study by Bortolotti *et al.* (14) of 21 children with hepatitis C, revealed cases of mild to moderate hepatitis in 18 of them and cirrhosis only in 3. In another paper by the same author (15) one case of cirrhosis out of nine HCV infected children was found. Three out of five (children with ALL) were reported by Inui *et al.* (18). In the papers by Inui *et al.* (18), Locasciulli *et al.* (19) more severe histologic activity was explained by the coexistence of malignant diseases or aplastic anemia. Three of our children were in long remission of ALL, none of them developed cirrhosis or even high grade fibrosis, which was confirmed by findings of Locasciulli *et al.* (20). Statistical analysis made by Guido *et al.* (21) supports our conclusion of significant correlation between ALT and fibrosis score in children. She has found liver cirrhosis in 1/80 children, while Badizadegan *et al.* (22) obtained from children with hepatitis C found cirrhosis in 8% and fibrosis with architectural distortion in 22% of 40 biopsy specimens, which is an odd ratio similar to that found in adult patients (23). We have searched for conditions that could have aggravated the liver damage in children diagnosed with liver cirrhosis. High levels of IgG expressed autoimmune process which sometimes accompanies chronic hepatitis C in children (24). Reye syndrome found in the other girl was another such condition. Although biopsy performed in this case did not give a definite diagnosis, esophageal varices grade II/III, USG of the liver and laboratory results (cholestasis, hypoalbuminaemia) supported the clinical diagnosis of liver cirrhosis. Coexistence of HCV and HBV does not seem to have an effect on the severity of hepatitis, although it may play some role in fulminant hepatitis or development of hepatocellular carcinoma in adults with liver cirrhosis (25).

Conclusion

Chronic hepatitis C in children usually runs a mild course. The disease is not aggravated by contracting the virus early in life or previous exposure to HBV. However every infected child should be thoroughly investigated as liver cirrhosis may develop even in a very young age.

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