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Original Article

Clinical and laboratory profiles of hepatitis C in hemophiliac children

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Abstract

Background Hepatitis C virus (HCV) infection is common in hemophiliac receiving multiple coagulation factor transfusions before the introduction of donor screening and viral inactivation techniques. Information on the clinical profiles of HCV infection in children is still limited.

Objective To describe clinical and laboratory profiles of HCV infection in hemophiliac children.

Methods Patients registered at the Hemophilia Society of Department of Child Health, Cipto Mangunkusumo Hospital, who had positive anti-HCV were enrolled. None of them received antiviral treatment. All subjects infected by HCV before the age of 18 years and at least had positive anti-HCV test result for 6 months underwent clinical examination, alanine aminotransferase (ALT), platelets, and HCV RNA tests.

Results Thirty nine subjects were available for review, with the median age of 15 years, and the mean age of the first time getting transfusion was 15 months. Twenty two (56%) of 39 subjects showed clinical manifestations. Liver and spleen enlargement were not found in any of the subjects. Ten (26%) subjects showed elevated ALT. Platelet count was within normal limit in all subjects. Twenty four (61%) patients had chronic hepatitis, whereas the remaining 15 (39%) subjects spontaneously cleared from HCV.

Conclusions Pediatric HCV infection showed mild clinical manifestations. Sixty one percent subjects developed chronic hepatitis. The abnormality of laboratory finding may be associated with the future chronic liver disease. **[Paediatr Indones 2007;47:229-233]**.

Keywords: *HCV, hemophiliacs children,ALT, HCV RNA test*

Hepatitis C virus (HCV) was discovered in 1989 and has been identified as the major cause of transfusion-associated non-A and non-B hepatitis.[1,2] Multiple coagulation factor transfusions are needed in hemophiliacs to prevent bleeding due to coagulation factor deficiency. This condition increases the risk of contracting transfusion-transmitted disease, especially hepatitis C. The risk increases with increasing the severity of coagulation factor deficiency and the duration of transfusions.[3-5] Nearly all hemophiliacs who were infused with clotting factor concentrate before the introduction of donor screening and viral inactivation techniques were infected with HCV.[3-11] The prevalence of hepatitis C in hemophiliacs worldwide is 59–95%.[3-8] Partiwi *et al*[9] reported 56.9% of hemophiliacs in Department of Child Health, Cipto Mangunkusumo Hospital were infected with hepatitis C.

Little is known about the natural history of hepatitis C in children. Most studies on the natural course of HCV infection in childhood report a mild

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clinical course and higher spontaneous viral clearance, compared with those infection in adults.[12,13] Fourteen to 39% pediatric patients have spontaneous viral clearance without antiviral intervention.[14-16] Most (60–89%) HCV-infected children develop chronic hepatitis with, although rare, cirrhosis. End-stage liver disease can occur during childhood or become major problem in adulthood.[15-21] Therefore, it is important to understand the natural history of HCV infection in children to anticipate problem in the adulthood. We aimed to determine spontaneous viral clearance, clinical profiles, and ALT level in HVC-infected hemophiliac children.

Methods

A cross sectional study was carried out to all hemophiliac children who were infected with hepatitis C. Data were obtained from all patients treated at Hematology and Oncology outpatient clinic of Department of Child Health, Cipto Mangunkusumo Hospital, from March to June 2005. Inclusion criteria were all A or B hemophiliac children in whom factor VIII or factor IX examination confirmed the diagnosis. Hepatitis C infection was determined by serological examination at least 6 months before the study. Their age must be below 18 years when the diagnosis of hepatitis C was confirmed. Informed consent was obtained from parents, and assent was obtained from older children (above 7 years of age). Patients with any symptoms of Duchene muscular dystrophy, myositis, infected with HIV or hepatitis B, obesity, alcohol consumption, and history of hepatotoxic drugs administration, were excluded from this study.

Blood specimen was taken from all subjects; sera were stored at -60ºC within 1 hour after collection to achieve optimal condition for RNA determination. Qualitative HCV-RNA polymerase chain reaction was performed by Cobas Amplicor HCV test (Roche Diagnostic Systems, Branchburg, NY). Serum alanine aminotransferase (ALT) and aspartate amino-transferase (AST) levels were measured using enzymatic colorimetric method. ALT or AST levels of greater than 40 mU/mL was considered as increased. Platelet was determined by manual counting where a value below 200,000/mL considered as decreased level. Factor VIII, factor IX, and anti-HCV were obtained as secondary data from the previous study. Chronic hepatitis C was defined as hepatitis C viraemia for at least 6 months, diagnosed by the presence of HCV-RNA in plasma.

Statistical analysis was based on prevalence ratio. All statistical procedures were done on SPSS 10.0 for Windows program. This study was approved by The Committee for Medical Research Ethics of the Faculty of Medicine, University of Indonesia.

Results

There were 39 HVC-infected hemophiliac children enrolled in this study; 36 were hemophilia A and 3 were hemophilia B. Twenty-four out of 39 subjects had chronic hepatitis C and 15 subjects cleared HCV spontaneously. The median age at the time of enrollment was 15 years. Twenty-three of 39 subjects had severe hemophilia. The median age at first exposure was 15 months. Ten of the 39 subjects had increased ALT values. The overall median ALT, AST level and platelet count were within normal limits. The characteristics of study subjects are shown in **Table 1**.

Table 2 shows that subjects with coagulation factor concentration less than 1% had the highest proportion for chronic hepatitis C (15/23) compared

Table 1. Characteristic of study subjects (n = 39)

Characteristic of subjects	
Factor VIII/IX concentration (n)	
< 1%	23
1 – 5%	12
> 5%	4
Age (years)	
Range	7-23
Median	15
Age at the first time transfusion (months)	
Range	1-60
Median	15
AST (mU/mL)	
Range	13-126
Median	26
ALT (mU/mL)	
Range	8–294
Median	22
HCV-RNA (n)	
Positive	24
Negative	15
Platelet (/mm^3)	
Range	304000-475000
Median	347000

Table 2. Distribution of HCV-RNA in subjects based on coagulation factor concentration, duration of transfusions, and history of clinical manifestations

	HCV-RNA status			
	Positive (n)	Negative (n)	Total (n)	PR (CI 95%)
Coagulation factor concentration				
< 1%	15	8	23	
1 – 5 %**	7	5	12	1.46
> 5 %**	2	2	4	(0.33;6.61)
Duration of transfusions				
< 10 years	2	2	4	1.69
≥ 10 years	22	13	35	(0.15;19.89)
History of clinical manifestations				
Present	17	8	25	2.3
Not present	7	7	14	(0.46;10.10)

PR: prevalence ratio; CI: confidence interval; **combined

to the others. Subjects with duration of transfusions of more than 10 years (22/35) have chronic hepatitis compared to those who were transfused less than 10 years. Although factor concentration of less than 1% and the duration of transfusions of more than 10 years had higher proportion of chronic hepatitis C compared to the others, it gained no statistical significance.

Subjects with history of clinical manifestations tended to have higher proportion for chronic hepatitis C (17/25) compared to non-symptomatic subjects (7/14). However, there was no statistically significant.

When the study started, there were no subjects with clinical manifestations of hepatitis. **Table 3** shows distribution of the history of clinical manifestations. It shows that nausea was the most frequent symptom reported. Hepatomegaly or splenomegaly was not found in any of the subjects.

In our study, 8 subjects had both ALT and AST increased. Thirty-one subjects had only increased either in AST or ALT. We could examine AST to ALT ratio in subjects who had increased ALT and AST level.

Table 3. Distribution of subjects based on the history of clinical manifestations

Clinical manifestations	n
Nausea	12
Malaise	10
Dark urine	9
Headache	8
Anorexia	7
Jaundice	4
Dyspepsia	3
Fever	2
Diarrhea	1
Vomit	1

Table 4 shows the distribution of subjects based on duration of transfusions, coagulation factor concentration, and HCV-RNA status. Subjects who received coagulation factor transfusions for less than 10 years had median ALT of 14.5 mU/mL (range 8–31 mU/mL). Subjects underwent coagulation factor transfusions more than 10 years had median ALT 22 mU/mL (range 8–294 mU/mL). Subjects with coagulation factor concentration less than 1% had higher proportion of increased ALT compared to other groups (8/23) although it was not statistically significant. Ten of 24 subjects with chronic hepatitis C had increased ALT with median ALT of 69.5 mU/mL (range 41–294 mU/mL).

Table 4. Distribution of ALT level subjects based on duration of transfusions, coagulation factor concentration and HCV-RNA status

	ALT (mU/mL)			
	<40 (n)	≥40 (n)	Total (n)	PR (CI 95%)
Duration of transfusions				
< 10 years	4	0	4	*
≥ 10 years	25	10	35	
Coagulation factor concentration				
< 1 %	15	8	23	
1 – 5 %**	10	2	12	3.73
> 5 %**	4	0	4	(0.56 ; 30.87)
HCV-RNA status				
Positive	14	10	24	*
Negative	15	0	15	

PR: prevalence ratio; CI: confidence interval; * undefined; ** combined

AST to ALT ratio was examined in 8 subjects with increased AST and ALT level. The range of AST to ALT ratio was 0.43 to 0.96. They were 12–18 years of age, who underwent coagulation factor transfusions more than 10 years and had chronic hepatitis C.

Discussion

There are several risk factors in hemophiliacs associated with hepatitis infection, particularly hepatitis C, for example, age, disease severity, and the use of factor concentrate. In this study subjects were 39 hemophiliacs infected with HCV. Prior to the era of blood donor screening, HCV infection probably occurred in hemophiliacs on the very first time of transfusion.[16]

In this study chronic hepatitis C were present in 24 of 39 subjects, while 15 of 39 patients had cleared HCV spontaneously. Previous reports showed HCV clearance in children varied from 11 to 45%;[15,22-24] it appears that children have a better chance to clear HCV.[16,17] This might be caused by difference in immune system; children may have a better control on virus replication. Besides, the number of transfusions with clotting factor products is lower in children compared to that n adults.[15]

The age of the first time transfusion may play a role in morbidity and mortality of the liver disease.[17,25] In our study, the median age for the first time transfusions was 15 months so the liver disease course might be less severe. The most common history of clinical manifestations in our study were nausea and malaise. Liver or spleen enlargement was commonly reported in adult patients, but we did not find this in our series.[26] This might be caused by the maturity of the immune response in children is different from that in adults so that liver destruction is less severe in children. Gerlach *et al*[27] reported patients with history of clinical manifestations in which 50% of them became chronic hepatitis C. They also reported that all patients without clinical manifestations became chronic hepatitis. In our series 17 of 25 subjects with history of clinical manifestations became chronic hepatitis C and in patients without clinical manifestations 7 of 14 became chronic hepatitis, as shown in **Table 2**. The difference of the proportion of chronic hepatitis in subjects with or without history of clinical manifestations might only be caused by chance.

Increased ALT value was seen in 10 out of 39 subjects in our series; this was less than other studies on HVC in hemophiliacs (28.7% to 78%).[3,5,7] Park *et al*[28] reported AST to ALT ratio in adult patients with chronic hepatitis; ratio of more than 1 was useful to predict liver cirrhosis. In available 8 subjects in our series, none of them had AST to ALT ratio more than 1. It seems that our patients were in early stage of liver involvement and this may partly explain the low occurrence of increased ALT level. Since HCV has very slow growth rate and in the next 2–3 decades may cause liver failure, subjects should be screened for HCV to have proper early management. We did not perform liver biopsy so we could not asses the correlation between severity of liver histology and the ALT level.

Blood donor screening was reported to be able to reduce the incidence of transfusions-transmitted disease, especially HCV infection.[11] Blood donor screening in Indonesia began in 1996. Indonesian Red-Cross in Jakarta reported that the prevalence of HCV in blood donors was reduced from 0.55% in 2000 to 0.35% in 2002.[29] Partiwi *et al*[9] also reported none of the hemophiliacs who received transfusions after 1997 had HVC infection. We found 4 patients below 10 years of age got infected with HCV. This might be the result of intra-familial infections or serological silent period of HCV in blood donors.[19] We did not examine the anti-HCV in the rest of the family.

In conclusion, our study confirms that the proportion of spontaneous viral clearance in HVC infected pediatric population is higher than that in adults. Accordingly most patients are asymptomatic or show mild manifestations. However patients should be informed about long term complication of hepatitis C.

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