LETTER TO THE EDITOR

INCIDENCE OF HEPATITIS C VIRUS INFECTION IN CHILDREN WITH HEMOPHILIA IN POLAND

D. JANUSZKIEWICZ[1,2,3*], J. WYSOCKI[2], J. NOWAK[2,3]

[1]Institute of Human Genetics, Polish Academy of Sciences, Strzeszyńska 32, 60-479 Poznań, Poland;[2] Karol Marcinkowski University of Medical Sciences, Poznań, Poland; [3] Department of Medical Diagnostics, Poznań, Poland

Received March 2, 2000; accepted April 18, 2000

Key words: HCV; genotypes; hemophiliacs

Hepatitis C virus (HCV) is recognized as the most common causative agent of non-A and non-B hepatitis (*1–4*). The transmission of HCV infection is not fully understood but parental route is most likely to be the case (*5–9*). Children with hemophilia receiving multiple transfusion of blood coagulation factor VIII (BCF VIII) are at risk for HCV infection. Most hemophiliacs who received BCF VIII concentrates before the introduction of effective viral inactivation technique were very likely to be infected with HCV. There is a number of reports showing high incidence of HCV-infected hemophiliacs ranging from 30% up to 100% (*6,10,11*). Some studies have presented direct evidence that prevalence of hepatitis C in hemophiliacs is closely related to type of BCF VIII concentrates (*12,16*). Patients treated exclusively with HCV-safe concentrates were completely free of HCV infection. On the other hand, the group of patients ever treated with large pool of non-HCV-safe BCF VIII concentrates was HCV RNA-positive in 90%. Rationale for this study was that approximately 1% of blood donors in Poland appeared to have antibodies to HCV (HCV antibodies) (*10,17*). In the present study, the incidence of HCV infection and the HCV genotypes have been analyzed in children with hemophilia in Poland before HCV-prevention in blood concentrates had been introduced.

The study involved 58 children with hemophilia who received more then 10 transfusions of BCF VIII concentrates. The blood level of BCF VIII varied from 0% to 5% in studied patients. The hemophiliacs coinfected with hepatitis B virus (HBV) have been excluded from the study. All 58 children have been infected with cytomegalovirus (CMV) as evidenced by the presence of specific serum antibodies. The liver function has been assessed by serum alanine and asparagine aminotransferase (ALT and AST) activities as well as by serum albumin content. The HCV antibodies in the blood were measured by the 2nd generation enzyme immunoassay (Organon Teknika) as described elsewhere (*13,14*). HCV particles and their genotypes were detected in the blood by a nested reverse transcription–polymerase chain reaction (RT-PCR) technique using specific primers for conservative fragments of HCV genome (*13,16*) and by a line-probe assay (Inno-Lipa HCV II, Innogenetics).This assay makes use of biotinylated oligonucleotide primers to generate biotinylated RT-PCR product hybridized with probes specific for all 6 HCV genotypes (*8,14,16*).

All children involved in the study have received multiple transfusions (5 to 10 per year) of BCF VIII concentrates.

*E-mail: nowakjs@vose.man.poznan.pl; fax: +4861-8233235.

Abbreviations: ALT = alanine aminotransferase; AST = asparagine aminotransferase; BCF VIII = blood coagulation factor VIII; CMV = cytomegalovirus; HBV = hepatitis B virus; HCV = hepatitis C virus; HCV antibodies = antibodies to HCV; RT-PCR = reverse transcription–polymerase chain reaction

Some parameters of liver function of studied children with hemophilia

Parameter	Characteristic		
	HCV-RNA$^+$ anti-HCV$^-$ (8/58)	HCV-RNA$^-$ anti-HCV$^+$ (30/58)	HCV-RNA$^-$ anti-HCV$^-$ (28/58)
ALT (IU/l)	59.7±21.3	29.4±16	17.5±11.3
AST (IU/l)	56.4±22.7	22.3±12.6	13.4±11.6
Albumin (mg/l)	30.2±3.1	34.8±2.7	34.8±3.2
Ultrasonography*	2/8	0/30	0/28
Duration of disease (years)	11.3±4.5	7.3±2.9	4.3±3.1
No. of BCF VIII transfusions (mean value ± SD)	5–38 (18.6±4.8)	4–15 (7.8±3.4)	4–17 (6.7±4.3)

*Reinforcement of echogenecity.

Among 58 examined children with hemophilia 30 (52%) were positive for HCV antibodies, 8 (15.5%) contained HCV particles as detected by the nested RT-PCR, and 28 contained neither HCV antibodies nor HCV particles. Some parameters of liver function in the studied hemophiliacs are presented in the table. The group of children positive for HCV-RNA and HCV antibodies had the longest duration of the disease in contrary to group of the children negative for HCV-RNA and HCV antibodies, in which the duration of the disease was relatively short. All HCV RNA-positive children were infected with a single genotype of HCV. The most common genotype, 1b, was found in 7 of 8 children. The HCV genotype 3a, exceptionally rare in Poland, was found in one child who had received transfusions of an imported BCF VIII. It is worth mentioning that only in the group of children positive for HCV RNA and HCV antibodies the ALT and AST activities have been markedly elevated, and that in 2 children of this group a reinforcement of liver echogenecity has been observed.

In the present work a relatively high incidence of HCV infection in children with hemophilia was found. The data concerned the period when no HCV inactivation procedure for BCF VIII concentrates was used. More then 50% of hemophiliacs showed signs of HCV infection. The degree of liver damage measured by ALT and AST activities was higher in patients with HCV particles present in the blood. On the other hand, children with HCV antibodies but without HCV particles, did not have elevated levels of ALT and AST.

It is worthwhile stressing a strict correlation between the duration of the disease and the presence of the HCV antibodies with or without HCV particles. The duration of the disease corresponded to the degree of liver damage. Moreover, it may be postulated that the risk for HCV infection in hemophiliacs increased with their age. This can be easily explained by the higher possibility of exposure to HCV during multiple transfusions of BCF VIII concentrates.

Analysis of HCV genotypes confirmed the hypothesis that the main source of HCV infection in hemophiliacs is the BCF VIII concentrate. In the majority of the patients the infection with HCV of genotype 1b, which is dominant among Polish blood donors, was found.

It can be concluded that children with hemophilia are at high risk for HCV infection, as over 50% of the tested patients appeared to be HCV-infected. As an optimistic finding may be regarded the presence of HCV particles in only 27% of hemophiliacs positive for HCV antibodies, what strongly argues for spontaneous elimination of HCV from the blood of these patients.

Acknowledgement. This work has been sponsored by KBN grant No. 4 PO5E 05617.

References

1. Alberti A, Chemello L, Benvegnu L, *J. Hepatol.* **31** (suppl.), 17–24, 1999.
2. Allander T, Gruber A, Naghavi M, *Lancet* **345**, 603–605, 1995.
3. Marcellin P, *J. Hepatol.* **31** (suppl.), 9–16, 1999.
4. Nakagiri I, Ichiharra K, Ohmoto K, Hirokawa M, Matsuda N, *J. Clin. Microbiol.* **31**, 2974–2980.
5. Allain JP, Coghlan PJ, Kenrick KG, *Blood* **78**, 2462–2468, 1991.
6. Alter MJ, *N. Engl. J. Med.* **330**, 784–786, 1994.
7. Brillanti S, Foli M, Gaiani S, Masci C, Miglioli M, Barbara L, *Lancet* **341**, 464–465, 1993.
8. Mondelli MU, Silini E, *J. Hepatol.* **31** (suppl.), 65–70, 1999.
9. Skidmori S, *J. Med. Microbiol.* **7**, 321–322, 1993.
10. Januszkiewicz D, Wysocki J, Nowak J, *Eur. J. Paediatr.* **156**, 454–456, 1997.
11. Jarvis LM, Ludlam CA, Ellender JA, *Blood* **87**, 3007–3011, 1996.
12. Hanley JP, Jarvis LM, Andrews J, *Blood* **87**, 1704–1709, 1996.
13. Naoumov NV, *J. Hepatol.* **31** (suppl.), 84–87, 1999.
14. Pawlotsky JM, *J. Hepatol.* **31** (suppl.), 71–79, 1999.
15. Tagariello G, Pontisso P, Davoli PG, Ruvoletto MG, Traldi A, Alberti A, *Br. J. Heamatol.* **91**, 708–713, 1995.
16. Zaaijer HL, Cuypers HTM, Reesink HW, Winkel IN, Grken G, Lelie PN, *Lancet* **341**, 722–724, 1993.
17. Telfer PT, Devereux H, Savage K, Scott F, Dhillon AP, Dusheiko G, Lee CA, *Thromb. Haemostasis* **74**, 1259–1264, 1995.