Hepatitis C in children after transfusion : assessment by look-back studies

E. A. Roberts, M.D., FRCPC ; S. M. King, M.D. C.M., FRCPC ;
Margaret Fearon, M.D., FRCPC ; Nancy McGee, M.Sc.N.

Abstract

Look-back studies to identify paediatric patients with post-transfusion hepatitis C have been conducted at several tertiary-care hospitals in Canada. A general look-back study was conducted at the Hospital for Sick Children in Toronto for the time period December 1985 to May 1990. All patients transfused at the Hospital for Sick Children during this time period were identified from hospital Blood Bank records. Letters of notification were sent by registered mail to all recipients excluding those known to have died. In the letter anti-HCV testing was recommended. Letters were mailed to 6332 transfusion recipients ; 4496 letters were delivered. Of these 146 anti-HCV-positive transfusion recipients (92 pts < 18 yrs old ; 54 pts > 18 yrs old) were identified. Sixty-four of these patients were definitely transfused only during this time period. Assuming that all notified patients were tested, the minimum prevalence of new infection in this time period was 1.4%. When possible, identified patients were tested for presence of HCV RNA in the serum by RT-PCR. The proportion of patients anti-HCV positive but HCV RNA negative on one or more occasions was similar in both whole cohort and subset : approximately one-third. These data suggest that chronic hepatitis C may be less likely to develop after transfusion in children than in adults. (Acta gastroenterol. belg., **1998**, 61, **195-197**).

Key words : hepatitis, hepatitis C virus, children, epidemiology, transfusion.

Introduction

The prevalence and natural history of transfusion-related hepatitis C in children is uncertain. In adult patients chronic hepatitis C develops after acute infection in approximately 85% and appears to pursue a slowly-progressive course (1) ; however, cirrhosis and hepatocellular carcinoma may complicate chronic hepatitis C (2). In some adult patients the underlying, non-hepatic disease is the greater source of morbidity (3). While considerable evidence suggests that chronic alcohol use may enhance hepatic damage in chronic hepatitis C, the importance of other environmental factors on the natural history of the disease is less clear. It is difficult to generalize from these studies in adults to the natural history of chronic hepatitis C in children. Many children are in good health following an intensive though circumscribed medical or surgical treatment including transfusion. Alcohol use is uncommon among children. Developmental factors may influence response to infection differently in children compared to adults. Post-transfusion chronic hepatitis C may be less severe in children (4).

Since chronic hepatitis C is frequently asymptomatic, without a screening programme the prevalence may be greatly underestimated. In 1995 at the Hospital for Sick Children in Toronto, we endeavoured to address this issue by setting up a look-back study of children transfused between December 1985 and May 1990. One of the major factors that led to this study was our belief that patients and/or their families needed to be informed of blood transfusions administered during a time period when blood products were not routinely screened for hepatitis C. This conclusion arose from the results of a similar look-back study to inform transfused patients of the risk of both human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection for the years 1980-November 1985, which had recently been completed (5). The aim of the hepatitis C look-back study was to identify as many patients as possible who had been transfused in the late-1985 to mid-1990 time-frame and were positive for serum anti-HCV antibodies. It would then be possible to estimate the prevalence of HCV infection in this cohort and assess severity of liver disease.

Materials and methods used

All patients transfused at the Hospital for Sick Children between December 1985 and May 1990 were identified from hospital Blood Bank records. The list was reviewed extensively by various clinicians in order to exclude patients known to have died. Letters of notification were sent by registered mail to all recipients excluding those known to have died. In the letter anti-HCV testing was recommended. Recipients of the letter were asked to mail back a tear-sheet indicating whether the anti-HCV results were positive or negative. A special brochure with information about hepatitis C was included with the letter. A news conference was held prior to mailing in order to inform the public of the project in advance. A telephone "hotline" was provided for recipients to call for further information or counseling and for assessment if they were anti-HCV positive. This phone centre was staffed by nurses, mainly from the Gastroenterology ward, who received extra training regarding hepatitis C. A consultation clinic was established so that patients could be referred

Address for reprints : E. A. Roberts, Room 8415, University Wing, Division of Gastroenterology and Nutrition, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada.
From the Divisions of Gastroenterology/Nutrition and Infectious Diseases, The Hospital for Sick Children and the University of Toronto, Toronto, Ontario, Canada.
"Viral Hepatitis throughout Infancy to Adulthood", Brussels, Session of 25 May 1998.

to see a paediatric hepatologist ; patients living at a great distance from Toronto were encouraged to consult specialists closer to home.

Anti-HCV testing consisted of an initial EIA test, followed by an immunoblot assay. Some testing was performed in private laboratories, but the majority was at the Provincial Laboratory. Follow-up testing included detection of HCV RNA by RT-PCR (Amplicor P.C.R., Roche) performed at the Provincial Laboratory.

Results

Patients identified

Letters were mailed to 6332 transfusion recipients ; 4496 letters were delivered. Of these 146 anti-HCV-positive transfusion recipients (92 pts < 18 yrs old ; 54 pts > 18 yrs old) have been identified. These patients were in the following broad disease categories : haemophilia 52 ; thalassemia 26 ; haematology/oncology 15 ; prematurity/NICU 10 ; cardiac surgery 26 ; urology/nephrology 4 ; gastroenterology/liver disease 6 ; plastic surgery 4 ; orthopedics/neurosurgery 3. The apparent prevalence of HCV infection in this cohort is 3.2% (146/4496). Out of the 6332 transfusion recipients identified for notification, the apparent prevalence was 2.3%. Of 67 children with positive anti-HCV who were tested for presence of HCV RNA in serum, 45 (67%) were positive and 21 (31%) were negative on one or more occasions ; one patient was positive for HCV RNA on one occasion and negative on two others. Most children were clinically well and asymptomatic ; no child was found to have any evidence of hepatitis C-associated vasculitis. Serum ALT at the time of review was highly variable.

Although all these 146 anti-HCV positive patients had received transfusions between December 1985 and May 1990, some of these patients had in all likelihood been transfused before then. Therefore it was impossible to confirm that infection had occurred in this specific time period. A subset of the patients was identified through review of the medical history and/or transfusion records in whom the first transfusion had taken place during this time period. This group comprised 64 patients with the following diagnoses : haemophilia 3 ; haematology/oncology 14 ; prematurity/NICU 10 ; cardiac surgery 21 ; urology/nephrology 3 ; gastroenterology/liver disease 6 ; plastic surgery 4 ; orthopedics/neurosurgery 3. The estimated minimum prevalence in this group is 1.4%. Of this cohort, HCV RNA testing by RT-PCR has been performed in 28 patients on one or more occasion : 9 of 28 patients (32%) have been found negative. On repeated testing, no patient in this cohort has shown any variation in test results. Patients initially positive for serum HCV RNA have remained positive, and patients initially negative have remained negative. Seven of these patients have been tested for HCV RNA on 3-5 occasions spaced several months apart, and 5 of these seven are repeatedly negative, although anti-HCV has remained positive in all of them. Most children in this cohort of 64 are well, without symptoms of chronic liver disease. One of two patients with persistently elevated serum ALT underwent percutaneous liver biopsy which showed minimal chronic hepatitis.

Mechanics of the look-back study

There were over 600 calls to the information hotline in the first week after the notification letters were sent out ; there were approximately 150 calls per week over the next four weeks. Many callers were upset or angry, and most required some clarification of the information in the letter. In particular, many sought reassurance that HCV was different from HIV, even though this was stated clearly in the brochure. Other calls to the information hotline were from adult patients with chronic hepatitis C who simply wanted to discuss their disease. Some calls were not related to hepatitis C but to other diseases occasionally associated with transfusions, such as hepatitis B or Jacob-Creutzfeld disease. This special information line was later converted to a permanent phone information service relating to all aspects of transfusions.

An unanticipated result of this look-back study was that some patients previously found to be positive for anti-HCV antibodies were referred for assessment. These patients had not received this mailing but only heard about the project indirectly.

Of the 1836 letters which were returned undelivered, the majority were sent out subsequently with updated addresses ; this second mailing has produced few newly-identified patients. Some additional patients transfused during the time period of this look-back study were later identified through a targeted look-back study initiated by the Red Cross.

Discussion

Two types of look-back study have been used to examine post-transfusion hepatitis C. In a general look-back study the objective is to detect post-transfusion infection in all recipients of potentially contaminated blood products : infection by one or more blood-borne agents may be sought. In a targeted look-back study recipients of blood units from donors later found to be positive for a specific infection are identified. Targeted look-back studies for hepatitis C have been performed more frequently than general look-back studies. Although they are more focused, with smaller numbers, they are still fraught with logistical problems (6).

A general look-back study in the paediatric age group is easier to organize than an adult study because patient numbers are relatively smaller than in the total population of hospitalized adults, underlying diseases tend to progress less rapidly and therefore fewer have died, and the population as a whole may be less mobile.

Thus far three such studies have been performed in Canada : this one in Toronto, Ontario, in Hamilton, Ontario, and in Vancouver, British Columbia. In this latter study the proportion of patients tested who were found positive for anti-HCV antibodies was 3.2%. Although this is similar to findings in the larger Toronto study, our study is limited by its design relying on voluntary compliance with testing and communication of results by patients or their families. Therefore, while this study provides important data on patterns of disease and its natural history, prevalence of hepatitis C infection in this paediatric population cannot be determined precisely.

In conclusion, in a large, diverse group of Canadian pediatric patients prevalence of hepatitis C infection after transfusion (between December 1995 and May 1990) was estimated at 2-3%, with a minimum estimate of 1.4% in this time period. There were two broad categories of affected patients : (1) those with haematological conditions requiring regular or repeated transfusion with blood or blood products over years, and (2) those with severe illness (congenital heart disease, neoplasia, prematurity) requiring a brief, but often intensive, period of transfusion. In this study the rate of chronic infection was approximately 67%, lower than reported for adults. Most patients were asymptomatic with respect to hepatitis C infection.

Acknowledgements

We are indebted to Julie Avolio, R.N. and Phyllis McGee, M.S.N. in the Liver Clinic at the Hospital for Sick Children, and to Mindy Goldman, M.D., Transfusion Centre of Quebec, Canadian Red Cross Society, for helpful discussions and kind provision of her review article.

References

1. HOOFNAGLE J.H. Hepatitis C : the clinical spectrum of disease. *Hepatology*, 1997, **26** (suppl. 1) : 15S-20S.
2. TONG M.J., EL-FARRA N.S., REIKES A.R., CO R.L. Clinical outcomes after transfusion-associated hepatitis C. *N. Engl. J. Med.*, 1995, **332** : 1463-1466.
3. SEEFF L.B., BUSKELL-BALES Z., WRIGHT E.C. *et al.* Long-term mortality after transfusion-associated non-A, non-B hepatitis. The National Heart, Lung, and Blood Institute Study Group. *N. Engl. J. Med.*, 1992, **327** : 1906-1911.
4. BORTOLOTTI F., JARA P., DIAZ C. *et al.* Posttransfusion and community-acquired hepatitis C in childhood. *J. Pediatr. Gastroenterol. Nutrit.*, 1994, **18** : 279-283.
5. KING S.M., MURPHY T., COREY M. *et al.* The HIV information project for transfusion recipients a decade after transfusion. *Arch. Pediatr. Adolesc. Med.*, 1995, **149** : 680-685.
6. GOLDMAN M., JUODVALKIS S., GILL P., SPURIL G. Hepatitis C lookback. *Transfusion Med. Rev.*, 1998, in press.