PREVALENCE AND CLINICAL OUTCOME OF HEPATITIS C INFECTION IN CHILDREN WHO UNDERWENT CARDIAC SURGERY BEFORE THE IMPLEMENTATION OF BLOOD-DONOR SCREENING

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ABSTRACT

Background and Methods There are few data on the prevalence and clinical outcome of hepatitis C infection in children. We studied 458 children who underwent cardiac surgery in Munich, Germany, before 1991, when blood-donor screening for hepatitis C was introduced in Germany. Their mean age at first operation was 2.8 years; none of the children had received blood transfusions before or after cardiac surgery, and none of their mothers had antibodies to hepatitis C virus (anti-HCV). We compared these patients with 458 control subjects matched for age and sex.

Results Sixty-seven (14.6 percent) of the 458 patients who had undergone cardiac surgery had anti-HCV, as compared with 3 (0.7 percent) of the control subjects ($P<0.001$). At a mean interval of 19.8 years after the first operation, 37 (55 percent) of the 67 patients who were positive for anti-HCV had detectable HCV RNA in their blood. The infection had cleared in the other 30 patients, as evidenced by negative results on three polymerase-chain-reaction analyses performed at six-month intervals. Only 1 of the 37 patients who were positive for HCV RNA had elevated levels of liver enzymes; that patient had severe right-sided congestive heart failure. Of the 17 patients who underwent liver biopsies, only 3 had histologic signs of progressive liver damage. These three patients had additional risk factors: two had congestive heart failure, and the third had also been infected with hepatitis B virus.

Conclusions Children who had undergone cardiac surgery in Germany before the implementation of blood-donor screening for hepatitis C had a substantial risk of acquiring the infection. However, after about 20 years, the virus had spontaneously cleared in many patients. The clinical course in those still infected seems more benign than would be expected in people infected as adults. (N Engl J Med 1999;341:866-70.)

THE hepatitis C virus (HCV) is the most common cause of hepatitis after blood transfusion. Severe liver damage from hepatitis C has become one of the leading indications for liver transplantation.[1-4] Children who have had multiple transfusions as a result of chronic anemia, cancer, or hemophilia, as well as patients who have received extracorporeal membrane oxygenation or long-term parenteral nutrition, are at high risk for HCV infection; the reported prevalence ranges from 10 to 85 percent.[5-12] Intrafamilial and mother-to-baby transmission have been reported.[13-17]

There are few data on the epidemiology, histologic features, and clinical outcome of hepatitis C or risk factors for it in persons who acquired the infection as infants.[8,11] A multicenter study found a benign clinical course in children who were infected as infants.[18] In contrast, a U.S. study of liver histology in children with post-transfusion hepatitis C showed a high risk of cirrhosis, similar to that in adults.[19] In a Japanese study of hepatitis C infection in 161 children after cardiac surgery, the prevalence of infection was 13.6 percent.[20] The prevalence of positive tests for antibodies to HCV (anti-HCV) among blood donors is probably higher in Japan and other Asian countries than in Europe and the United States. Thus, such data may not be generalizable.[4] We studied the prevalence of and risk factors for HCV infection in children who had undergone cardiac surgery before the introduction of anti-HCV blood-donor screening in Germany. We compared the clinical outcome of infection in these children with that of infection in adults, as reported in other studies.

METHODS

Study Subjects and Design

We studied 458 patients (213 female patients and 245 male patients; mean age, 19 years) who had undergone cardiac surgery as infants in Munich, Germany, before 1991. They were followed up in the outpatient clinic of the German Heart Center between October 1996 and December 1997. None of the patients had received blood products before or after surgery, and none had a history of intravenous drug abuse. We ruled out mother-to-baby transmission through an analysis of anti-HCV in the patients' mothers. Thus, it is likely that the HCV infections in the children were due to perioperative blood transfusions. The screening of blood donors for hepatitis C was introduced in Germany in 1991.

We also tested blood samples from 458 control subjects who were matched for age and sex and were representative of the regional population. We screened patients and control subjects for anti-HCV by enzyme immunoassay (EIA II, Abbott, Wiesbaden, Germany) and Western blot assay (recomBlot, Microgen, Munich, Germany). In all subjects, we measured serum levels of alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, bilirubin, lactate dehydrogenase, glutamate dehydrogenase, alkaline phosphatase, and albumin, as well as the coagulation time. We used a method that conformed to the recommendations of

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the Deutsche Gesellschaft für klinische Chemie.[21] To establish risk factors for HCV infection, we compared the date and number of operations, sex, age at first operation, and amount and type of blood supply in anti-HCV–positive and anti-HCV–negative patients.

All patients who were positive for anti-HCV were further tested for HCV RNA by reverse-transcription polymerase chain reaction (PCR) (in-house method), HCV genotype (in-house method), and viral load (Amplicor, Roche, Grenzach-Wyhlen, Germany). Seventeen patients with detectable HCV RNA in peripheral blood provided consent for a liver biopsy for the evaluation of possible cell damage. All liver specimens were examined by the same pathologist, who did not have any information about the patients. Biopsy specimens were categorized according to the Ishak scoring system.[22]

The study protocol was reviewed and approved by the institutional review committee of the Technical University of Munich, Munich, Germany.

Statistical Analysis

We compared age distribution, number of operations, number of blood products used, and biochemical indicators with a combination of the Mann–Whitney U test and the Wilcoxon rank-sum test. We performed a Kruskal–Wallis one-way analysis of variance for Western blot and PCR results.[23]

RESULTS

Prevalence of HCV and Characteristics of the Patients

Characteristics of the 458 patients are shown in Table 1. Anti-HCV was found in 67 (14.6 percent) of the patients (34 female and 33 male), as compared with 3 (0.7 percent) of the control subjects ($P<0.001$). We confirmed positivity for anti-HCV by second-generation enzyme immunoassay and Western blot analysis. Thirty-seven patients were positive for HCV RNA at the follow-up evaluation. The median age at first cardiac surgery was similar among anti-HCV–positive patients and anti-HCV–negative patients (2.8 years in both groups).

Blood Products and HCV Infection

Patients who were positive for anti-HCV had significantly more operations than patients who were negative for anti-HCV (2.1 vs. 1.6, $P<0.001$) and required a higher number of all blood products (20.3 units per patient vs. 7.1 units per patient, $P<0.001$). For all patients, the average number of blood products required during each cardiac surgery was 9.2 units. Fresh blood was transfused significantly more often in patients who were positive for anti-HCV (3.3 units per patient vs. 2.1 units per patient, $P<0.001$). Human plasma and whole blood were used more frequently in the patients who were positive for anti-HCV, but the frequency of use did not differ significantly from that in anti-HCV–negative patients. Data on blood products used in the patients are summarized in Table 2.

Clinical Outcome

At the follow-up evaluation, the mean age of the anti-HCV–positive patients was 19.8 years (mean follow-up period, 17 years; range, 12 to 27), as compared with 17.2 years ($P=0.004$) for the anti-HCV–negative patients (mean follow-up period, 14.4 years; range, 10 to 25). Serum levels of alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, bilirubin, lactate dehydrogenase, glutamate dehydrogenase, alkaline phosphatase, and albumin, as well as coagulation time, were within the normal range in all but one patient in each group (Table 3). One eight-year-old patient with a positive test for HCV RNA and with Down's syndrome and persistent pulmonary hypertension after correction of an atrioventricular septal defect had clinical and biochemical evidence of liver disease. He presented with severe hepatosplenomegaly and peripheral edema. His serum levels of alanine aminotransferase and aspartate aminotransferase were 306 U per liter and 259 U per liter, respectively. Consent was not given for a liver biopsy. One patient who was negative for HCV RNA had congestive heart failure after he underwent the Fontan procedure; he had substantially elevated serum levels of γ-glutamyltransferase (97 U per liter).

Natural History of the Infection

At a mean interval of 19.8 years (range, 12 to 27) after cardiac surgery, 37 (55 percent) of 67 patients were still positive for HCV RNA (21 patients had

TABLE 1. CHARACTERISTICS OF THE 458 PATIENTS.*

CHARACTERISTIC	PATIENTS POSITIVE FOR ANTI-HCV (N=67)	PATIENTS NEGATIVE FOR ANTI-HCV (N=391)	P VALUE
Age — yr			
At first operation	2.8±4.4 (0.1–12.1)	2.8±4.5 (0.1–11.3)	0.42
At follow-up evaluation	19.8±5.7 (10.7–31.4)	17.2±6.4 (6.1–28.6)	0.004
No. of operations per patient	2.1±1.0 (1–5)	1.6±0.8 (1–6)	<0.001
Total no. of blood products per patient	20.3±36.2 (1–175)	7.1±11.6 (1–117)	<0.001

*Plus–minus values are means ±SD; ranges are shown in parentheses. HCV denotes hepatitis C virus, and anti-HCV antibodies to HCV.

TABLE 2. BLOOD PRODUCTS USED DURING CARDIAC SURGERY.*

BLOOD PRODUCT	PATIENTS POSITIVE FOR ANTI-HCV (N=67)	PATIENTS NEGATIVE FOR ANTI-HCV (N=391)	P VALUE
	no. of units/patient		
Fresh blood	3.3±1.9 (1–8)	2.1±1.2 (1–7)	<0.001
Heparinized blood	1.4±0.5 (1–2)	1.2±0.4 (1–3)	0.22
Whole blood	2.6±2.5 (1–12)	2.2±1.8 (1–12)	0.72
Plasma	18.3±39.1 (1–175)	7.9±15.5 (1–111)	0.90
Packed cells	1.3±0.5 (1–2)	1.4±0.8 (1–4)	0.66

*Plus–minus values are means ±SD; ranges are shown in parentheses. HCV denotes hepatitis C virus, and anti-HCV antibodies to HCV.

genotype 1a, with a mean viral load of 420,000 genome equivalents per milliliter; 15 had genotype 1b, with 552,000 genome equivalents per milliliter; and 1 had genotype 3a, with 5000 genome equivalents per milliliter).

Liver biopsies were performed in 17 patients with detectable HCV RNA a mean of 21.2±4.6 years after the first operation (Table 4). In 14 patients, the histologic changes were characterized as minimal lymphocytic infiltrates restricted to the portal tracts, with no evidence of liver-cell damage and no lymphocytes within the lobuli. No evidence of fibrosis could be found. In two other patients, both with congestive heart failure, we found periportal fibrosis, stage 2, and sinus ectasia. Increased central venous and right atrial pressure had developed after correction of truncus arteriosus in one of these patients and after the Mustard operation in the other. They both presented with clinically apparent hepatomegaly. Micronodular cirrhosis (stage 6 fibrosis) was detected in another patient, who was infected with HCV, as evidenced by positivity for HCV RNA, and had been infected with hepatitis B, as evidenced by positivity for antibodies to hepatitis B surface antigen, hepatitis B core antigen, and hepatitis B e antigen.

In 30 of the 67 patients (45 percent), the virus had cleared, as proved by negative results of three PCR analyses performed at six-month intervals. None of the patients who were initially negative for HCV RNA had positive results on the subsequent assays. Patients who were positive for HCV RNA did not differ significantly from patients who were negative for HCV RNA in regard to serum levels of alanine aminotransferase, aspartate aminotransferase, γ-glutamyltransferase, bilirubin, lactate dehydrogenase, glutamate dehydrogenase, alkaline phosphatase, and albumin, as well as coagulation time (Table 3).

DISCUSSION

We found that children who had undergone cardiac surgery in Germany before the implementation of blood-donor screening for hepatitis C were at substantial risk for HCV infection. Anti-HCV was detected in 14.6 percent of our study group, as compared with 0.7 percent of the control group. The presence of anti-HCV reflects ongoing or past infection with HCV, whereas positivity for HCV RNA is evidence of persistent infection. Our data are similar to those on children who underwent cardiac surgery in Japan.[20] The risk of HCV infection in our study group was associated with the total number of operations and correlated strongly with the total number

TABLE 3. MEAN SERUM LEVELS OF ASPARTATE AMINOTRANSFERASE, ALANINE AMINOTRANSFERASE, γ-GLUTAMYLTRANSFERASE, AND GLUTAMATE DEHYDROGENASE IN PATIENTS POSITIVE FOR ANTI-HCV, ACCORDING TO THE PRESENCE OF DETECTABLE HCV RNA IN THE PERIPHERAL BLOOD.*

VARIABLE	PATIENTS POSITIVE FOR HCV RNA (N=37)†	PATIENTS NEGATIVE FOR HCV RNA (N=30)	P VALUE
Aspartate aminotransferase (U/liter)	26.3±47.0 (10–259)	12.9±6.4 (7–32)	0.13
Alanine aminotransferase (U/liter)	41.3±54.7 (12–306)	14.3±4.8 (6–23)	0.09
γ-Glutamyltransferase (U/liter)	34.6±41.7 (7–222)	21.3±21.0 (3–97)‡	0.24
Glutamate dehydrogenase (U/liter)	3.8±2.6 (1.1–14.7)	2.2±1.3 (0.5–3.9)	0.14

*Plus–minus values are means ±SD; ranges are shown in parentheses. HCV denotes hepatitis C virus, and anti-HCV antibodies to HCV.

†One patient had severe congestive heart failure due to Down's syndrome and persistent pulmonary hypertension. He presented with severe hepatosplenomegaly and peripheral edema. His serum levels of aspartate aminotransferase, alanine aminotransferase, and γ-glutamyltransferase reached 259 U per liter, 306 U per liter, and 222 U per liter, respectively.

‡One patient with no detectable HCV RNA had congestive heart failure after he underwent the Fontan procedure and subsequently had severe hepatomegaly. His γ-glutamyltransferase levels reached 97 U per liter.

TABLE 4. HISTOPATHOLOGICAL FINDINGS IN 17 PATIENTS WITH HCV RNA.*

HISTOPATHOLOGICAL FINDING	NO. OF PATIENTS
Periportal lymphocytosis	17
Sinusoidal lymphocytosis	2
Steatosis	2
Bile-duct damage	1
Lymphoid aggregates	1
Portal fibrosis	2†
Cirrhosis	1‡

*All 17 patients had HCV of genotype 1.

†Both patients had stage 2 fibrosis according to the Ishak scoring system. Increased central venous and right atrial pressure developed after correction of truncus arteriosus in one patient and after the Mustard operation in the other patient. Both presented with hepatomegaly.

‡This patient had also been infected with the hepatitis B virus (HBV) as evidenced by positivity for antibodies to hepatitis B e antigen, antibodies to hepatitis B surface antigen, and antibodies to hepatitis B core antigen, as well as HCV RNA (with a viral load greater than 1 million genome equivalents per milliliter). The patient was negative for HBV DNA. A biopsy of the liver revealed micronodular cirrhosis without apparent inflammation within the portal triads (stage 6 fibrosis).

of blood products administered. Among the various blood components, only transfusion of fresh blood was associated with an elevated risk of infection. Retrospective analyses have shown an even higher risk of HCV infection for children with thalassemia (55 to 83 percent) and for those with hemophilia (22 to 46 percent), probably as a result of the higher frequency of transfusions in these children.[12,24]

Since the introduction of programs to screen blood donors, the residual risk of post-transfusion hepatitis C has declined from 1 in 5000 to 1 in 103,000.[3,4] Of 120 children who underwent cardiac surgery after 1992, none have become positive for anti-HCV (unpublished data). Other investigators have reported similar findings, although the number of children studied has been small.[1,7,20]

The natural course of HCV infection in children is not well understood. Children with HCV infection that was acquired from their mothers seem to be at lower risk for progressive liver disease and have a higher spontaneous clearance of HCV than adults.[14,15] Eleven percent of children with cancer who were positive for HCV RNA became negative for HCV RNA after a median follow-up of 14 years,[8] and in 28 percent of patients with cured childhood leukemia, the virus cleared within a period of 17 years.[6] In our study, the virus cleared in 30 (45 percent) of the 67 patients who had been positive for anti-HCV antibodies. Because HCV RNA levels fluctuate and cannot be detected below a concentration of 100 to 1000 genome equivalents per milliliter, we performed two subsequent HCV RNA analyses within two years in each patient who was initially negative for HCV RNA, to rule out persistent infection.[25]

In our study, past or persistent HCV infection was not associated with clinical or biochemical signs of liver disease. This finding suggests that HCV infection in pediatric patients who are at risk can be detected only by specific screening programs. Almost all the patients who were positive for HCV RNA had normal results on liver-enzyme tests.

In adults, HCV infection is associated with a high risk of cirrhosis and hepatocellular carcinoma.[26] Cirrhosis develops within 20 years after infection in about 20 percent of infected adults, and 10 percent of infected adults with cirrhosis have hepatocellular carcinoma. To verify the degree of liver disease, we performed biopsies in 17 of the patients with HCV RNA. At a mean interval of 21.2 years after infection, only three patients had histologic signs of progressive liver disease. All three patients had additional risk factors: two had congestive heart failure, and one had been infected with hepatitis B virus. The remaining 14 patients had only mild periportal inflammation.

All our patients who underwent liver biopsy were infected by HCV of genotype 1, which is thought to be the most aggressive genotype. We did not find severe liver-cell damage, however. These findings suggest that in our study group, chronic hepatitis C was mild and had a low rate of progression even after two decades. In patients infected at a younger age, the interval between blood transfusion and the development of chronic liver disease seems to be longer than in patients infected at an older age.[26,27] Our data suggest that elimination of the virus without antiviral treatment is more frequent in patients infected as infants than in those infected as adults.

Our clinical observations and the low rate of sustained response (15 to 25 percent) to interferon treatment underline the weakness of the rationale for early therapeutic intervention with interferon alfa in children.[28-34] Because most of our patients were infected with genotype 1a or 1b, both of which are associated with response rates to interferon treatment of less than 10 percent,[28] treatment with interferon alfa alone does not seem worthwhile. Combination therapy with interferon alfa and ribavirin might be more effective when treatment is indicated.[28,35,36]

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