HEPATITIS C VIRUS IN SICKLE CELL DISEASE

Mohamed Hassan, MD; Syed Hasan, MD, FABHP; Samuel Giday, MD; Laila Alamgir, MD; Alpha Banks, MD; Winston Frederick, MD; Duane Smoot, MD; and Oswaldo Castro, MD
Washington, DC

Purpose: To determine the prevalence of hepatitis C virus antibodies (anti-HCV) in patients with sickle cell disease.

Patients and Methods: Between 1983 and 2001, 150 patients from the Howard University Hospital Center for Sickle Cell Disease were screened for HCV antibody (52% women, 48% men, mean age 34 years). Frozen serum samples from 56 adult sickle cell patients who had participated in previous surveys (1983–92) of HIV and HTLV-1 serology and who were tested in 1992 for anti-HCV antibody—when commercial ELISA test (Ortho) became available—were included in this paper. Of the 150 patients in the study, 132 had sickle cell anemia genotype (SS), 15 had sickle cell hemoglobin-C disease (SC) and three had sickle β thalassemia. Clinical charts were reviewed for history of blood transfusion, IV drug abuse, homosexuality, tattooing, iron overload, and alcohol abuse.

Results: Antibodies to HCV were detected in 53 patients (35.3%). Of the 55 patients who had frozen serum samples tested in 1992, 32 (58%) were reactive for anti-HCV, while only 21 of the 95 patients (22%) tested after 1992 were positive for HCV antibodies ($P<0.001$). Thirty-nine of 77 patients (51%) who received more than 10 units of packed red blood cells were positive for HCV antibody, and only 14 of 61 patients (23%) who received less than 10 units of packed red blood cells transfusion were positive for HCV antibodies ($P<0.001$). None of the 12 patients who never received transfusion were positive for HCV antibody. In the 53 anti-HCV positive patients, the mean alanine amino-transferase (ALT) value was 98- and 81 U/L, respectively, for males and females. These values were normal for the HCV-antibody negative patients. The aspartate amino-transferase (AST) and the total bilirubin were also higher in the anti-HCV positive patients compared to patients in the anti-HCV negative group. Forty-four patients (57.1%) who were transfused more than 10 units developed iron overload defined by a serum ferritin level higher than 1,000 ng/ml. A total of 20 of the patients with iron overload underwent liver biopsies. Seven of these 20 patients (35%) were HCV positive. These patients often had more severe liver disease and higher degree of iron deposition.

Conclusion: The prevalence of HCV antibody and iron overload is directly related to the number of blood transfusions in patients with sickle cell disease. The prevalence of HCV infection has decreased significantly, since blood donor screening for HCV became available. Chronic HCV infection and iron overload place sickle cell patients at risk for significant liver disease. (*J Natl Med Assoc.* 2003;95:939–942.)

Key words: hepatitis C virus infection ♦ sickle cell disease ♦ blood transfusion

 From the Division of Gastroenterology (Hassan, Giday, Banks, Smoot), Division of Hematology (Hasan, Castro), and the Division of Infectious Diseases (Alamgir, Frederick), Howard University Hospital, Washington, DC. Send correspondence and reprint requests for *J Natl Med Assoc.* 2003;95:939–942 to: Duane T. Smoot, MD, Gastroenterology Section, Department of Medicine, 2041 Georgia Avenue NW, Washington, DC 20060; phone: (202) 865-6100; fax: (202) 865-7268; e-mail: dsmoot@howard.edu

INTRODUCTION

Before 1992, hepatitis C infection was a major problem in patients with hereditary hemoglobinopathies. Screening for anti-HCV was introduced in 1992[1-4]. Patients with sickle cell anemia are at a high risk of been infected with hepatitis C infection and are also prone to iron overload because of the large number of blood transfusions required to control the debilitating complications associated with the disease[3,4]. The combination of

Table 1. HCV Serology in Patients with Sickle Cell Disease Tested Before 1992 and During or After 1992

	Anti-HCV+	Anti-HCV-	Number of Patients
Before 1992	32 (58%)	23 (42%)	55
1992 and after	21 (22%)	74 (78%)	95
Total	53	97	150

Anti-HCV: antibody to hepatitis C virus.

iron overload and chronic HCV infection lead to a more devastating liver disease[5-9]. The risk of hepatitis C, secondary to blood transfusions, dramatically decreased after 1992 when mandatory HCV screening of donated blood was introduced in the United States. A large number of patients with sickle cell anemia receive treatment at the Howard University Hospital, and most of these patients have had multiple transfusions in the past. Therefore, the aim of this study is to determine the prevalence and risk factors for HCV infection in sickle cell disease patients at the Howard University Hospital Center for Sickle Cell Disease.

PATIENTS AND METHODS

Over a 19-year period (1983–2001), 150 adult sickle cell disease patients (48% male, 52% female; mean age 34 +/-10 years) were screened for HCV at the Howard University Center for Sickle Cell Disease. The medical records were reviewed for demographics information, risk factors for acquisition of HCV, laboratory data (including serum transaminases, bilirubin, alkaline phosphatase, albumin, and hepatitis viral markers) and, when available, the liver histology findings in liver biopsies and/or autopsies. Included among our study sample were 55 frozen serum specimens of adult sickle cell patients who had participated in previous serology surveys (1983–92) for HIV and HTLV-1. These samples were tested for HCV antibody in 1992, when commercial ELISA test (Ortho) became available.

The hemoglobin genotype distribution of the 150 SCD patients was as follows: 132 patients, or 88%, had sickle cell anemia (SS), 15 (10%) had sickle cell hemoglobin-C disease (SC), and three (2%) had sickle β thalassemia. The HCV antibody testing was performed at American Medical Laboratories, Chantilly, Virginia by Enzyme Immuno Assay (EIA) method (PPC-Abbott). The Chi-square test was used to test the significance of differences in HCV antibody prevalence according to number of blood units transfused and the year of transfusion. Values of $p<0.05$ were considered to be significant.

RESULTS

Antibodies to HCV were detected in 53 (35.3%) of 150 patients tested. Of the 55 patients who had frozen serum samples tested in 1992, 32 (58%) were reactive for anti-HCV antibodies. Only 21 of the 95 patients (22%) who were tested after 1992 were positive for HCV antibodies (P value<0.0001). The overall anti-HCV positivity rate for men was 40%, compared to 31% for females. The patients were stratified according to the number of transfusions received. An arbitrary number of 10 units was selected to divide the patients into two subgroups. Thirty-nine of 77 patients (51%) who received 10 or more units of packed red blood cells were positive for HCV antibody, while only 14 out of the 61 (23%) patients receiving less than 10 red cell units were positive for HCV antibodies. None of the 12 patients (0%) who were never transfused were positive for HCV antibody. Of the 53 anti-HCV patients positive by ELISA, the mean ALT value was 98- and 81U/L, respectively, for males and females. There was no statistically significant difference between men and women in both groups. These values were in the normal range for HCV-antibody negative patients. The AST and the total bilirubin were also higher in the anti-HCV positive patients compared to those in the anti-HCV negative group. The average albumin level was low for both HCV-positive and -negative patients but it was lower in the anti-HCV positive group. The difference in transaminases, bilirubin, and albumin were statistically significant between the two groups (Table 2).

Forty-four patients (57.1%) who were trans-

Table 2. Liver Function Test Results in HCV Positive and HCV Negative Sickle Cell Disease Patients.

Test	HCV+ve (mean)	HCV–ve (mean)	P – Value
AST	142.770	114.350	<0.0046
ALT	87.060	46.350	<0.0001
Albumin	2.930	3.200	<0.0172
T. Bilirubin	3.196	2.425	<0.0002
Alkaline Phosphatase	159.620	150.000	<0.6745

Anti-HCV: antibody to hepatitis C virus; ALT: alanine amino-transferase; AST: aspartate amino-transferase; T. bilirubin: total bilirubin.

fused 10 or more units developed iron overload as defined by a high ferritin level of more than 1000 ng/ml. Twenty of these patients with iron overload underwent liver biopsies. Five of these patients had liver cirrhosis and all but one of them was anti-HCV positive. Patients with transfusion history of 10 or more units and those with transfusions given earlier than 1992 were significantly more likely to be infected with hepatitis C (P<0.001).

DISCUSSION

Sickle cell patients have a high incidence of hepatitis C positivity. Before the availability of HCV testing of blood donors, the liver abnormalities in these patients were attributed to the sickle cell disease itself or to transfusional hemosiderosis. Autopsy series reported liver cirrhosis in 16–29% of sickle cell disease patients[10,11]. The etiology of cirrhosis in the majority of these autopsy cases was unknown, but in 27% of the cases it was attributed to iron overload. A condition designated as sickle-liver was also described in these patients[12]. De Vault et al., in their 1994 study[3], showed HCV to be the most important cause of liver disease in sickle cell patients. They reported anti-HCV in 20.7% of patients transfused with more than 10 units of blood products, while the rates for those who received less than 10 units were 8.6%. Hasan et al.[4] also reported similar findings: a 23% of anti-HCV positivity in SCD patients who received 10 or more units of blood products, and only 7.9% in those who received less than 10 units of blood products.

Iron, per se, is hepatotoxic and acts synergistically with HCV in causing liver injury[8]. Liver iron content has been shown to influence response to interferon therapy in non-SCD patients with chronic hepatitis C infection[6,7]. In a study of 79 patients with chronic hepatitis, 54 of whom had hepatitis C, the hepatic iron concentration was twice as high in the patients who did not respond to interferon therapy compared to that of patients who had biochemical end-of-treatment response (43% vs. 57%)[6,7].

In our study, more than one-third of the patients had markers for hepatitis C, and since approximately 80% of HCV-positive subjects in the general population have ongoing viral replication[13,14], it is safe to assume that the liver disease in our SCD patients is in part due to HCV infection. These patients often had elevated amino-transferases and total bilirubin. In this study, the albumin level was significantly lower in the anti-HCV positive group, compared to the anti-HCV negative patients. The same was true for transaminases and bilirubin between the two groups. The fact that the AST and total bilirubin were elevated in both the anti-HCV positive and negative groups could be explained by the chronic hemolysis, which all sickle cell patients have regardless of HCV status. The only laboratory result that was not found to be statistically significant was the alkaline phosphatase. One possible explanation for this is the fact that HCV and iron overload causes a parenchymal damage that is mainly manifested as an elevation of transaminases. The mean age of the anti-HCV negative patients was three years lower than that of the anti-HCV positive group.

The number of transfusions was directly correlated with the anti-HCV positivity. Patients who received 10 or more units had significantly higher incidence of anti-HCV markers than those receiving less than 10 units of blood products. In the present study, 12 patients who had no documented history of prior transfusions tested negative for anti-HCV antibody. The presence of other risk fac-

tors for HCV infection in our patients was low. Only five patients had history of intravenous drug abuse, and all of them were negative for hepatitis B and C markers.

When we compared the rates of anti-HCV positivity, we found that patients who had serum samples drawn before 1992 had higher prevalence of anti-HCV positivity than those tested after 1992. This can be explained by the introduction of mandatory testing of all blood donors in the U.S. Patients who were anti-HCV antibody positive often had a more severe liver disease and a higher degree of iron overload. Regarding serological markers for hepatitis B, only one patient, a recent immigrant from Africa, had positive hepatitis B surface antigen. This finding is in tune with our theory that the most important risk factor for the acquisition of viral hepatitis in the United States was blood transfusion.

CONCLUSION

Patients with sickle cell disease have a high incidence of chronic liver disease[3,15]. Possible etiologies mentioned in the literature include HCV infection and iron overload, due to multiple transfusions and increased iron absorption from chronic hemolysis, and direct liver injury due to tissue hypoxia during sickle cell-related vascular occlusion.

The prevalence of HCV antibody and iron overload are directly related to the number of blood transfusions in SCD patients. The presence of HCV and iron deposition in the liver can lead to a more rapid liver disease. In order to estimate the relative contributions of HCV and iron overload to the etiology of chronic liver disease in SCD patients, it will be necessary to undertake studies concentrating on the differences in the liver histology between HCV positive and negative groups. Although the incidence of HCV infection has decreased significantly since the screening for HCV of donor blood became available, chronic HCV infection and iron overload are still common in SCD patients and can cause significant liver disease. Further studies are required to clarify the etiology, clinical history, and proper management of chronic liver disease in these patients.

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