Prevalence of Hepatitis C Virus Antibody in a Cohort of Hemophilia Patients

By D.B. Brettler, H.J. Alter, J.L. Dienstag, A.D. Forsberg, and P.H. Levine

One hundred thirty-one patients followed at the New England Hemophilia Center (Worcester, MA) were tested for antibody to hepatitis C virus (HCV). All but two had used factor concentrate that had not undergone viral inactivation; two patients had used only cryoprecipitate. The overall prevalence of HCV antibody positivity was 76.3%. There was no significant difference in age or the amount of non-heat-treated factor concentrate used between the group that was HCV antibody positive and negative. There was also no significant difference between aminotransferase levels in the two groups. There was a positive association between HCV antibody and the presence of antibody to hepatitis B core antigen and antibody to human immunodeficiency virus. A group of 31 patients were tested twice for HCV antibody at intervals of 35 to 71 months. In this subset, 25 were repeatedly seropositive, 4 were repeatedly seronegative, and 2 went from seropositive to seronegative. These data confirm the previous impression that non-A, non-B hepatitis is a major sequela to the use of pooled coagulation factor concentrates. HCV infection may account for most of the chronic liver disease observed in this population. Anti-HCV testing of plasma donors and improved methods of viral inactivation should prevent new cases from developing.

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ANTI-HLV IN HEMOPHILIA

An elevated ALT at the time the HCV antibody test was obtained or intermittently within the 2 years before the sample was drawn. Conversely, in the seropositive group, 27 (27%) patients had normal ALT levels at the time of testing and on yearly testing in the preceding 2 years.

As can be seen in Table 2, there was a positive association between the presence of anti-HBc and anti-HCV. The correlation occurred only when the patients were seropositive for both anti-HBs and anti-HBc, and not when they were anti-HBc positive alone. There was also a positive correlation between the presence of anti-HIV and anti-HCV (*P < .025). There was no correlation between antibody to HCV and the presence of either HBsAg or anti-HBs.

**Repeat testing.** A group of 31 patients had HCV serology performed on two different occasions separated by 35 to 71 months. This subgroup did not differ from the group as a whole. The age ranged from 3.6 to 60.2 years (median 26.9). The majority had hemophilia A (30) and one had hemophilia B. All had used clotting factor concentrate that was not viral-inactivated. In this group, 25 were repeatedly seropositive, 4 were repeatedly seronegative and 2 appeared to lose antibody (being positive when first tested and negative on repeat testing). Of the 25 that were repeatedly seropositive, 24 had persistent or intermittently elevated ALT; one seropositive patient had consistently normal ALT although he had infused regularly with noninactivated clotting factor concentrate. Of the four patients that were seronegative on repeat testing, two had abnormal ALT and two had persistently normal ALT. One patient remained seronegative and had persistent normal ALT despite multiple infusions of factor concentrate, including products prepared before 1984. In the second seronegative patient with normal ALT on repeat testing, a high titer factor VIII inhibitor was present and the patient infused infrequently with prothrombin complex concentrates.

Both patients that appeared to lose anti-HCV maintained seropositivity for HIV over the same time period. One patient remains asymptomatic from HIV infection and the second patient has undergone a splenectomy secondary to HIV-induced thrombocytopenia.

**Table 1. A Comparison Between HCV Antibody Positive and Negative Hemophilic Patients**

<table>
<thead>
<tr>
<th></th>
<th>HCV Antibody Positive (n = 100)</th>
<th>HCV Antibody Negative (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (y)</td>
<td>27.3 (3.6-71.5)</td>
<td>23.2 (5.3-62.0)</td>
</tr>
<tr>
<td>Median factor usage (U/kg/y)</td>
<td>1,119 (125-4,271)</td>
<td>1,433 (92-6,906)</td>
</tr>
<tr>
<td>Median ALT levels (IU/mL)</td>
<td>69 (26-329)</td>
<td>85 (14-621)</td>
</tr>
<tr>
<td>No. (%) of patients with ALT elevation</td>
<td>73 (73%)</td>
<td>19 (61%)</td>
</tr>
</tbody>
</table>

**Table 2. Comparison of Viral Serology Between HCV Positive and Negative Hemophilic Patients**

<table>
<thead>
<tr>
<th></th>
<th>HCV Antibody Positive (n = 100) (%)</th>
<th>HCV Antibody Negative (n = 31) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV Serology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBs Ag positive</td>
<td>12/98 (12.2)</td>
<td>2/31 (6.5)</td>
</tr>
<tr>
<td>Anti-HBsAb positive</td>
<td>81/93 (82.7)</td>
<td>26/31 (83.9)</td>
</tr>
<tr>
<td>Anti-HBc positive, total</td>
<td>64/73 (87.7)</td>
<td>14/23 (60.9)</td>
</tr>
<tr>
<td>Anti-HBC positive, anti-HBs positive</td>
<td>55/73 (75.3)</td>
<td>12/23 (52.2)</td>
</tr>
<tr>
<td>Anti-HBc positive alone</td>
<td>9/73 (12.9)</td>
<td>2/23 (8.7)</td>
</tr>
<tr>
<td>HIV serology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HIV positive</td>
<td>69/80 (88.3)</td>
<td>19/26 (73.1)</td>
</tr>
</tbody>
</table>

**Discussion**

In this study, we used the anti-HCV assay to analyze a hemophilia cohort in which 81.6% of patients had chronic or intermittently elevated ALT. The anti-HCV test has been shown to be a reliable indicator of NANB hepatitis infection. Anti-HCV was detected in 76% of patients, confirming the high prevalence of HCV infection in this population and supporting the etiologic role of this virus in the development of chronic liver disease in the hemophilic. Similar high anti-HCV prevalences had been reported. In this study, we found that the prevalence of antibodies to HBV and HCV was approximately equal.

Not all patients with transaminase elevation and presumed NANB hepatitis were seropositive for anti-HCV. There are several possible explanations for this: (1) ALT elevations may have been medication-related or due to other nonviral causes; (2) anti-HCV antibody may have been previously present, but become undetectable with time; (3) the anti-HCV response may have been diminished by coexistent HIV infection as has been demonstrated in HBV infection; (4) the NANB hepatitis could be related to an additional NANB hepatitis agent. A second agent has been suggested by both clinical and chimpanzee transmission studies and such a possibility can now be explored using the same approaches that elucidated HCV; and (5) the sensitivity of the first generation assay may be too low to detect all cases of HCV infection. It is probable that some anti-HCV negative cases will be shown to be HCV-related when newer serologic techniques and in situ hybridization studies are applied.

We found no correlation between elevation of ALT and HCV seropositivity. Of the 31 HCV seronegative patients, 19 (61%) had elevated ALT, and of the 100 seropositive patients, 27 (27%) had consistently normal ALT over a period of 6 to 7 years. However, there was a definite correlation between anti-HCV and the presence of HIV antibody and anti-HBc. Before procedures to inactivate viruses in the production of factor concentrates, these concentrates, made from donor pools as large as 20,000, were uniformly contaminated with HCV, HIV, and HBV. Thus, the evidence for exposure to each of these agents in this cohort is not unexpected. The concurrence of hepatitis markers in populations at high risk for blood-borne and sexually transmitted virus infections was reflected in studies that showed a correlation between donor anti-HBc and recipient NANB hepatitis, and in blood bank policy deci-
tions to use the anti-HBc assay as a surrogate index for NANB hepatitis virus carriers.

It appears that as with HIV antibody, the presence of anti-HCV antibodies in persons with hemophilia. JAMA 253:2219, 1985


Prevalence of hepatitis C virus antibody in a cohort of hemophilia patients [see comments]

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