Importance of markers of hepatitis B virus in alcoholic liver disease

J B SAUNDERS, A D WODAK, P MORGAN-CAPNER, Y S WHITE, B PORTMANN, M DAVIS, ROGER WILLIAMS

Abstract

To determine the importance of the presence of serological markers of hepatitis B virus infection in patients with alcohol related liver disease we compared cumulative alcohol intake and clinical and histological features in patients with markers of hepatitis B virus infection and in those without. Hepatitis B surface antigen (HBsAg) was detected in five (2%) out of 285 patients studied and antibody to HBsAg (anti-HBs) in 41 (14%); one patient had antibody to hepatitis B core antigen alone. The combined prevalence of markers of hepatitis B virus infection was similar in patients with alcoholic cirrhosis (18%) and precirrhotic liver disease (13%). Two patients positive for HBsAg had histological features of both alcoholic liver disease and chronic active hepatitis, with stable HBsAg. Patients with anti-HBs were, however, histologically indistinguishable from patients without markers, and the mean cumulative alcohol intake of patients with anti-HBs was similar to or even higher than that of patients with liver disease of comparable severity who had no evidence of previous infection. The presence of markers of hepatitis B virus infection was related to former residence in countries with a high prevalence of the infection and to previous parenteral treatment and blood transfusions. Infection with hepatitis B virus does not enhance the development of chronic liver disease in heavy drinkers, except in the small number who remain positive for HBsAg.

Introduction

It is well recognised that some patients develop alcohol related cirrhosis after drinking relatively modest amounts of alcohol over five to 10 years whereas others escape liver damage after a lifetime of heavy drinking. The basis for this variation in susceptibility is only partly understood. Genetic factors play a part: women develop liver disease more rapidly and at a lower alcohol intake than men, and the histocompatibility antigens HLA-B8 and B40 have been associated with a higher incidence and more rapid development of cirrhosis. Even so, much of the variation in susceptibility remains unexplained.

One hypothesis that has gained popularity recently is that chronic exposure to alcohol renders the liver more liable to injury from hepatotropic viruses or environmental toxins. The possibility that infection with hepatitis B virus might favour the development of chronic liver disease in heavy drinkers was suggested by reports that serological markers of past or current infection with hepatitis B virus were found more often in patients with alcoholic cirrhosis than in alcoholics who had no liver disease or in healthy non-alcoholic subjects.

If infection with hepatitis B favoured the development of cirrhosis in heavy drinkers patients who had evidence of past or continuing infection with hepatitis B virus would be expected to present with cirrhosis, hepatitis and alcoholic liver disease than patients who had no evidence of infection. As part of a research programme into genetic and environmental factors predisposing to alcohol related liver disease we analysed serum samples from 285 patients with various types of alcoholic liver disease for hepatitis B surface antigen (HBsAg), antibody to HBsAg (anti-HBs), and antibody to hepatitis B core antigen (anti-HBc). We compared cumulative alcohol intake, established by a standardised interview schedule, and clinical and histological features in patients with and without hepatitis B virus infection. We also examined the importance of known risk factors for infection with the virus in determining the presence, or absence of serological markers and by discriminant analysis assessed their relative contribution. Levels of antibodies to other viruses were determined to assess susceptibility to infection and antibody response in relation to the severity of liver damage and the presence or absence of markers of hepatitis B virus infection.

Patients and methods

Over a three year period we studied 189 men aged 23-74 and 96 women aged 22-71. All had been drinking at least 40 g alcohol a day for four years or more, and in 263 (92%) habitual daily consumption had exceeded 80 g. They represented a consecutive series of British white subjects who had been admitted to the liver unit for the first time and in whom biopsy appearances were compatible with alcohol related liver disease. During the period of study we also interviewed 36 patients who drank similar quantities of alcohol but had no features of alcoholic liver disease on biopsy. These included four patients with chronic active hepatitis positive for HBsAg.

Liver biopsy appearances were classified by a specialist histopathologist (BP) into one of the following categories*: fatty liver with or without fibrosis (41 patients), alcoholic hepatitis (46), cirrhosis (90), cirrhosis with alcoholic hepatitis (97), and cirrhosis with superimposed hepatocellular carcinoma (11). Individual histological features including fatty change, fibrosis, steatosis, binuclear cholangitis, and parenchymal inflammatory cell infiltration were scored on a five point scale (0, 1+, 2, 3+, 4+) in ascending order of severity.

Hepatitis B and other viral serology

Serum samples taken at admission were tested initially for HBsAg and anti-HBs by standard radioimmunoassay methods (HBsAg test kit, Travensol Laboratories Ltd, and Ausab, Abbott Laboratories Ltd). Sera positive for HBsAg were also tested for the presence of hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe) (HBe and anti-HBe test kit, Abbott Laboratories Ltd). If sera were negative for both HBsAg and anti-HBs they were tested additionally for anti-HBe (Corab, Abbott Laboratories Ltd). Twenty-six of the 41 samples positive for anti-HBs were also tested for anti-HBe. Results were accepted as positive if counts per minute exceeded 2·1 times the negative control mean.

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Liver, Hepatitis B, and the Liver-Fan Cover Page.png
Cumulative alcohol consumption was also found to be a significant factor in the development of alcoholic liver disease. The results of this study indicate that patients with high alcohol intake are at greater risk of developing alcoholic liver disease. The prevalence of markers of hepatitis B virus was significantly higher in patients who consumed alcohol compared to those who did not. These findings support the hypothesis that alcohol consumption is a risk factor for the development of alcoholic liver disease.

**Results**

Serum from five patients (18%) were positive for HBsAg (Table I), and two of these were positive for HBeAg. Anti-HBs was found in samples from 41 patients (14%), and one patient had anti-HBc alone. Anti-HBc was also found in 16 (62%) of 26 sera positive for anti-HBs.

**Risk Factors for Infection with Hepatitis B Virus**

The two factors that were significantly associated with the presence of markers of hepatitis B virus were residence in a country with a high prevalence of infection and previous blood transfusions or courses of antiviral therapy. The prevalence of markers of hepatitis B virus was significantly higher in patients who had received blood transfusions or had courses of antiviral therapy compared to those who had not. These findings highlight the importance of blood transfusion policies and antiviral therapy in the prevention of hepatitis B virus infection.

### Table 1: Prevalence of markers of hepatitis B virus in alcoholic liver disease

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
<td>HBsAg</td>
</tr>
<tr>
<td>Fat fibrosis</td>
<td>30</td>
<td>1</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Cirrhosis + alcoholic hepatitis</td>
<td>43</td>
<td>3</td>
</tr>
<tr>
<td>Hepatoma</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>189</td>
<td>31</td>
</tr>
</tbody>
</table>

### Table 2: Comparison of age and alcohol intake in patients with cirrhosis with anti-HBs and without markers of hepatitis B virus. (Results expressed as means (SE))

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-HBs present (n = 10)</td>
<td>No markers (n = 70)</td>
</tr>
<tr>
<td>Age at diagnosis (years)</td>
<td>56.1 (2.8)</td>
<td>49.1 (1.3)</td>
</tr>
<tr>
<td>Duration of drinking &gt; 40 g/day (years)</td>
<td>25.6 (3.7)</td>
<td>22.2 (1.2)</td>
</tr>
<tr>
<td>Mean cumulative alcohol intake when &gt;40 g/day (g)</td>
<td>117 (16)</td>
<td>134 (9)</td>
</tr>
<tr>
<td>Cumulative alcohol intake when &gt;40 g/day (kg)</td>
<td>1208 (209)</td>
<td>1063 (80)</td>
</tr>
<tr>
<td>Cumulative lifetime alcohol intake (kg)</td>
<td>1257 (208)</td>
<td>1103 (79)</td>
</tr>
</tbody>
</table>
TABLE III—Potential risk factors for infection with hepatitis B virus and prevalence of history of jaundice in patients with cirrhosis with and without markers of hepatitis B virus (figures are numbers (n), of patients)

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Patients with markers (n = 24)</th>
<th>Patients without markers (n = 112)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admission for major illness or surgery</td>
<td>15 (63)</td>
<td>53 (47)</td>
<td>0.10</td>
</tr>
<tr>
<td>Blood transfusions or injections</td>
<td>8 (33)</td>
<td>12 (11)</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Residence for over 1 year in country with high prevalence of hepatitis B virus</td>
<td>14 (58)</td>
<td>21 (19)</td>
<td>0.001</td>
</tr>
<tr>
<td>Service in armed forces</td>
<td>7 (29)</td>
<td>26 (23)</td>
<td>&lt;0.20</td>
</tr>
<tr>
<td>Jaundice in childhood</td>
<td>2 (8)</td>
<td>4 (4)</td>
<td>0.50</td>
</tr>
<tr>
<td>Jaundice in adult life</td>
<td>7 (29)</td>
<td>11 (10)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

TABLE IV—Results of discriminant analysis to distinguish patients with markers of hepatitis B virus from those without

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Whole group (n = 198)</th>
<th>Change in $\text{Rao^3 V}$</th>
<th>p</th>
<th>Patients with cirrhosis (n = 136)</th>
<th>Change in $\text{Rao^3 V}$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resident in country</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>with high prevalence of hepatitis B virus</td>
<td>32 4</td>
<td>-0.001</td>
<td></td>
<td>14 2</td>
<td>-0.001</td>
<td></td>
</tr>
<tr>
<td>Previous infections or blood transfusions</td>
<td>7 4</td>
<td>0.01</td>
<td></td>
<td>4 7</td>
<td>-0.05</td>
<td></td>
</tr>
<tr>
<td>Social class IV or V</td>
<td>3 0</td>
<td>-0.05 p&lt;0.01</td>
<td></td>
<td>1 5</td>
<td>-0.20</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>2 2</td>
<td>-0.10</td>
<td></td>
<td>2 0</td>
<td>-0.10</td>
<td></td>
</tr>
</tbody>
</table>

These risk factors were entered in a discriminant analysis together with age, sex, social class, marital status, duration of drinking, mean daily intake, histological features, and the presence or absence of ascites, encephalopathy, and variceal haemorrhage. Former residence in an area with a high prevalence of infection was confirmed as the variable that most clearly distinguished patients with markers of the virus from those without (table IV). Neither of the measures of alcohol intake discriminated these two groups from each other.

LEVELS OF ANTIBODIES TO OTHER VIRUSES

There were no significant differences in the proportions of patients in each histological category who had detectable levels to antibodies to measles, rubella, or any of the influenza strains, or in the levels of antibody to these viruses. Similarly, there were no differences between patients with anti-HBs and those without markers of the virus in the proportions showing seropositivity or in antibody levels (table V).
of chronic active hepatitis but none of alcoholic liver disease, and they were not included in the analysis. In a Danish study, no patients with typical alcoholic cirrhosis were serologically positive for HBsAg, although among a small group of alcoholic cirrhosis who had no features of alcoholic liver damage 26% had HBsAg present in serum.

The presence of anti-HBs indicates recovery from infection with cessation of viral replication. Usually it represents recovery from acute hepatitis, but some patients may have undergone seroconversion after being positive for HBsAg for many years, during which chronic liver damage may have occurred. Hepatitis B viral DNA is found integrated into the host genome in some patients with anti-HBs, indicating that permanent changes at the molecular level take place that might influence sensitivity to alcohol. The results of the present study suggest, however, that heavy drinkers who have had infection with hepatitis B virus in the past do not develop cirrhosis more rapidly, as judged by how long our patients had been drinking hepatotoxic quantities of alcohol, and do not develop it at a lower daily alcohol intake. Indeed, they tend to be older and to have higher alcohol intakes. Anti-HBs was not associated with any particular historical features of chronic liver disease, although it was more common in the small group of patients with hepatoma.

The most important determinant of the presence of markers of virus in the present series was whether the patient had lived in a ward with high prevalence of markers with HBsAg, whereas previous blood transfusion or injections was the only other factor definitely identified. The way in which infection with hepatitis B virus had been contracted by patients who had lived abroad was not established, although transmission via insect vectors and sexual contacts are possibilities. The development of hepatitis B in patients with alcoholic liver disease receiving blood transfusions or blood products is well recognised and occurs despite screening of donors for HBsAg. Variation in the risk of exposure to hepatitis B virus probably explains the difference in prevalence of markers reported in previous studies among groups of alcoholic patients. In a study in France those with alcoholic cirrhosis were on average 14 years older than alcoholics without liver damage and would potentially have been at risk of infection for a correspondingly longer time. The higher prevalence of markers in alcoholic compared with non-alcoholic subjects is probably explained simply by a higher prevalence of exposure to the virus, although chronic alcohol consumption may possibly favour the development of hepatitis in subjects exposed to the virus by depressing immune response.

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References

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