Prevalence and presentation of hepatitis C related chronic liver disease in southern India

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SUMMARY

To determine the importance of hepatitis C virus (HCV) infection in the aetiology of chronic liver disease in southern India, the prevalence of HCV antibodies and HBV markers was estimated in 100 patients with chronic liver disease and in 56 patients with a variety of other gastrointestinal and liver diseases who served as controls. HCV antibody was measured by a second-generation ELISA. HBsAg, anti-HBc, anti-HBs and anti-D were also estimated. HCV antibodies were detected in 26/100 patients with chronic liver disease compared to 0/56 controls. HBV markers were present in 72 of 100 patients with chronic liver disease compared to 21/56 (37.5%) controls. Anti-D was noted in 4/100 patients with chronic liver disease and in none of the controls. Many patients had serological evidence of both B and C infection; 73% of those with anti-HCV also tested positive for HBV markers. HCV related disease presented at a median age of 60 years compared to HBV related disease which presented at a median age of 40. There was no significant difference between HCV and HBV positive patients in symptomatology, but encephalopathy was uncommon and cirrhosis the usual finding at histology in HCV positive individuals, while chronic active hepatitis was found in 30% of biopsied HBV related disease. HCV is a significant cause of chronic liver disease in this geographic region, although HBV infection continues to account for the largest proportion of cases.

Keywords: cirrhosis, hepatitis B virus, hepatitis C virus, liver disease

INTRODUCTION

There are wide geographic differences in the prevalence of infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) and their importance as causes of chronic liver disease. In many developed countries HCV is a more common cause of chronic liver disease than HBV, accounting for 40-45% of non-alcoholic chronic liver disease including cirrhosis (Choo et al. 1990; Schiff 1991; Yano et al. 1991). In Japan, where HBV and HCV infections are endemic, HCV accounts for twice as much chronic liver disease as HBV (Yano et al. 1991). The reverse seems to be the case in some developing countries (Al Karawi et al. 1992; Lee et al. 1992). India is a region of moderate endemicity for HBV, with a carrier rate of 2-4% in the general population (Nayak et al. 1987; Singhvi et al. 1990). There are no population based studies of the prevalence of HCV infection in India, and relatively little information is available on the frequency and presentation...
of hepatitis C related chronic liver disease in this geographic region.

The study was conducted to assess the prevalence of HCV infection in patients with chronic liver disease, including cirrhosis, in southern India and to determine whether the clinical course and biochemical and histological features of HCV associated chronic liver disease were different from those associated with HBV infection.

MATERIALS AND METHODS

Subjects

The study population was selected among all patients diagnosed with chronic liver disease in the Department of Gastrointestinal Sciences from 1990 to 1992. A detailed clinical evaluation was made in every case. Investigations included routine haematological and biochemical tests, coagulation work-up, liver function studies, alpha-fetoprotein estimation, ultrasonography, upper gastrointestinal endoscopy and liver biopsy. Where biopsy was not feasible due to coagulopathy, tense ascites or unwillingness of the patient, the diagnosis of chronic liver disease was confirmed by either isotope scan (Drane 1991) or ultrasonography (Marn et al. 1991). Subjects with chronic liver disease of alcoholic or metabolic aetiology and with primary biliary cirrhosis were excluded from this study population. The remaining 100 consecutive patients with chronic liver disease formed the study population.

Fifty-six patients presenting with a variety of other diagnoses were included as ‘disease’ controls. They had alcoholic liver disease (6 subjects), extrahepatic portal vein obstruction (6), tuberculosis of the liver (4), fatty liver, non-cirrhotic portal fibrosis, granulomatous hepatitis and irritable bowel syndrome (3 each), Budd-Chiari syndrome, primary biliary cirrhosis, Wilson’s disease, periampullary carcinoma, chronic pancreatitis, metastatic carcinoma of the liver (2 each) and miscellaneous diagnoses (16).

Serum samples were obtained from all subjects and the following enzyme-linked immunosorbent assays (EIAs) were done: antibody to hepatitis C virus (HCV EIA-second generation, Abbott, IL, USA), hepatitis B surface antigen (Auszyme, Abbott), anti-HBc (Corzyme, Abbott), anti-HBs (Ausab EIA, Abbott) and anti-D (Anti-delta EIA, Abbott). In the case of HBV markers, the following sequence of testing was used:

Anti-HBc testing was done if the serum was negative for HBsAg. If the serum was negative for anti-HBc, it was tested for anti-HBs. Only sera positive for HBsAg were tested for anti-D.

Statistical significance was tested using the Chi-squared test or two-tailed Student’s t-test as appropriate.

RESULTS

Subjects

Among the 56 disease control subjects, the age ranged from 12 to 66 years with a median of 41 years; 40 were male. Among the 100 study subjects, the age ranged from 12 to 78 with a median of 42 years; 86 were male.

Serology

Among the 56 control subjects, six (10.7%) were positive for HBsAg and 15 (26.8%) for anti-HBc, giving an overall prevalence of HBV markers of 37.5%, as shown in Table 1. None was positive for anti-HCV or anti-D.

Among the 100 study subjects, 26 tested positive for anti-HCV (see Table 1). The difference in prevalence of anti-HCV between study and control subjects is highly significant (P<0.005). Of the 26 patients with antibody to HCV, 6 were also positive for HBsAg, while another 12 had anti-HBc (Table 1), and 2 also had anti-D. HBV markers in the absence of anti-HCV were found in 53 patients, with HBsAg in 36, and anti-HBc or anti-HBs in 17 (Table 1). The overall prevalence of HBV markers in study subjects was 72%. Neither HCV nor HBV markers were present in 21 study subjects.

Clinical presentation

A history of blood transfusion was obtained in 15 of the 100 study subjects; 5 of them were positive for anti-HCV, while 7 had HBV markers (HBsAg 3, anti-HBc 3, anti-HBs 1). Eleven (19.6%) of the 56 control subjects had received blood transfusions in the past. None was positive for anti-HCV, while HBV markers were detected in 9 (HBsAg 5, anti-HBc 4).
Table 1. Prevalence of virus markers in disease controls and patients with chronic liver disease

<table>
<thead>
<tr>
<th>Subjects</th>
<th>n</th>
<th>HBsAg</th>
<th>Anti-HBc</th>
<th>Anti-HBs</th>
<th>Any marker</th>
<th>Anti-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>56</td>
<td>6 (10.7)</td>
<td>15 (26.8)</td>
<td>0</td>
<td>21 (37.5)</td>
<td>0</td>
</tr>
<tr>
<td>Study</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-HCV positive</td>
<td>26</td>
<td>6 (23.1)</td>
<td>12 (46.2)</td>
<td>1 (3.8)</td>
<td>19 (73.1)</td>
<td>2 (7.7)</td>
</tr>
<tr>
<td>Anti-HCV negative</td>
<td>74</td>
<td>36 (48.6)</td>
<td>14 (18.9)</td>
<td>3 (4.1)</td>
<td>53 (71.6)</td>
<td>2 (2.7)</td>
</tr>
<tr>
<td>Study total</td>
<td>100</td>
<td>42</td>
<td>26</td>
<td>4</td>
<td>72</td>
<td>4</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages

Table 2. Histological changes in the liver in relation to aetiology of chronic liver disease

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Chronic active hepatitis</th>
<th>Cirrhosis</th>
<th>Lymphoid aggregates</th>
<th>Fatty change (focal)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>inactive</td>
<td>active</td>
<td></td>
</tr>
<tr>
<td>Anti-HCV alone</td>
<td>7</td>
<td>0</td>
<td>1 (14)</td>
<td>6 (86)</td>
<td>5 (71)</td>
</tr>
<tr>
<td>Anti-HCV with HBV marker</td>
<td>4</td>
<td>0</td>
<td>3 (75)</td>
<td>1 (25)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>HBV marker alone</td>
<td>9</td>
<td>3 (33)</td>
<td>2 (22)</td>
<td>4 (44)</td>
<td>3 (33)</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>16</td>
<td>2 (12.5)</td>
<td>10 (62.5)</td>
<td>4 (25)</td>
<td>5 (31)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages

Based on the viral serology, patients with chronic liver disease were categorized into four groups: anti-HCV alone, HBV markers alone, anti-HCV together with HBV markers, and cryptogenic (no viral markers). The median age at presentation with chronic liver disease differed among the groups, being 60 years (range 47–60) for the 7 patients with anti-HCV alone, 40 years (range 12–60) for those with HBV markers alone (53 subjects), 40 years (range 27–70) for those with both HBV and HCV markers (19 subjects), and 53 years (range 26–78) for the cryptogenic group (21 subjects). The male preponderance was consistent in all groups.

Analysis of the various symptoms indicated that jaundice was more common in HCV-related disease (47, 57.1%) than in HBV-related disease (11/53, 20.8%). There was no other significant difference in symptomatology, in clinical estimates of liver size, or in the presence of ascites and oedema between the groups. Similarly, there was no statistically significant difference between the groups in biochemical parameters although there was a tendency towards a lower serum albumin (2.90±0.08 g dl⁻¹, mean ± s.e.) in HBV-related liver disease compared to HCV-related disease (3.19 ± 0.19 g dl⁻¹).

Histology

Liver biopsies were available in 36 patients, 7 of whom had anti-HCV alone, 4 had HCV with HBV markers, 9 had HBV markers alone, and 16 had no viral markers. The histological findings in these groups are shown in Table 2. All patients with anti-HCV had established cirrhosis, often with mild activity, while in those with HBV markers the activity was of mild or moderate degree. Lymphoid aggregates or follicles were more common in biopsies from subjects with anti-HCV (71%) compared to the HBV (33%) or the cryptogenic (31%) groups. Mild fatty change was noted in biopsies from patients with anti-HCV (43%) and with cryptogenic cirrhosis (31%), but not in the HBV group.

DISCUSSION

This study reports the prevalence of anti-HCV in patients with chronic liver disease in southern India using a second-generation enzyme immunoassay. This test is more sensitive and specific than the first-generation assay, which detected antibody to the non-structural antigen C100-3 of the hepatitis C virus. The present most sensitive indicator of active HCV replication is the reverse polymerase chain reaction (PCR) for viral RNA. However, as is the case in most developing countries, the technology for the latter is not available to us. The second-generation assays for HCV antibody are nearly as sensitive as the assays for viral RNA by PCR (Yano et al. 1991). Particularly in chronic liver disease, the sensitivity of the second-generation test approaches 100% (Hagiwara et al. 1993; Lau et al. 1993). It is therefore likely that patients in the study population who were negative for anti-HCV in this study were in fact not infected with the virus.

In this study, none of 56 disease controls had serological evidence of HCV infection. There is unpublished data from our hospital to show that the prevalence rate of anti-HCV (by the second-generation ELISA used in this study) in voluntary blood donors is low, occurring in 0.48% (S. Christopher, R.B. Pulimood and T.J. John, unpublished observations). Reports from other countries indicate that the prevalence of HCV infection in the general population may vary from 0.2 to 1.5% (Kuhni et al. 1989; Nishimura et al. 1990; Chan et al. 1992). Studies in some tropical communities have indicated a high rate of infection in the general population, up to 6.4% in Zaire (Tibe et al. 1991).

The hepatitis B virus (HBV) carrier rate in the disease controls in this study was higher (10.7%) than the prevalence figures for the general population of 2–4% (Nayak et al. 1987; Singhvi et al. 1990). These control subjects had primary diagnoses requiring medical interventions which may have resulted in a higher carrier rate, and 11 of the 56 controls (19.6%), including five of the six HBsAg positive controls, had had blood transfusions in the past.

In addition to chronic post-transfusion hepatitis, HCV is now recognized as a major cause of non-transfusion-related (sporadic) chronic liver disease in developed countries (Weiland & Schwarze 1992). Cumulative data indicate that HCV markers are found in more than 70% of these patients in Europe, in approximately 60% in the USA, and approximately 45% in Japan (Alter et al. 1990; Choo et al. 1990; Schiff 1991; Yano et al. 1991; Weiland & Schwarze 1992). In these countries, HBV infection is significantly less common as a cause of chronic liver disease. The present study demonstrates that HBV-associated chronic liver disease continues to be more common than HCV-associated disease in India.

Coincident infection with both HBV and HCV was not uncommon in this study. Amongst HBs positive patients, 4/42 (9.5%) were also anti-HCV positive, compared to 22/58 (37.9%) HBs negative patients. In Saudi Arabian patients, 13.9% of HBs positive patients were positive for anti-HCV, compared to 37.5% of HBs negative patients (Al Karawi et al. 1992). Prevalences of anti-HCV in HBs positive and negative patients are reported to be 0 and 69.5% respectively in Hong Kong (Chan et al. 1992), 6.94 and 27.7% in China (Lee et al. 1992), and 18.5 and 14.1% in Delhi (Ramesh et al. 1992). The high prevalence of anti-HBc in patients with anti-HCV noted in this study (12/26 subjects, 46.1%) has also been reported by other authors (Fattovich et al. 1991; Sansonetti & Damasceno 1992).

HBV infection continues to be a more common cause than HCV of chronic liver disease in India. The latter presents at a later age, with oedema or ascites being more common than encephalopathy. Sporadically occurring HCV infection in this population seldom appears to present with chronic active hepatitis, the histology invariably showing cirrhosis with or without activity. These differences may relate to the fact that HCV infection is usually slowly progressive when compared to HBV infection. There continues to be a large group of patients with chronic liver disease who are negative for B markers and for anti-HCV. Since the second-generation ELISA for anti-HCV reliably detects almost all C positive patients with chronic liver disease (Hagiwara et al. 1993; Lau et al. 1993), it is likely that this group has cryptocogenic chronic liver disease. This group has features intermediate between those of B and C virus infections. The cause of this may be other hepatitis viruses which are not identified, or a variant of the hepatitis C virus (Houghton et al. 1991), such as has been described in Japan.

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REFERENCES


