Past and Present Hepatitis G Virus Infections in Areas Where Hepatitis C Is Highly Endemic and Those Where It Is Not Endemic

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Received 14 July 1997/Returned for modification 22 September 1997/Accepted 8 October 1997

We reported previously on an area in Japan where over 30% of the inhabitants were positive for hepatitis C virus (HCV) antibody. In the present study, clinical features of hepatitis G virus (HGV) infection in this area of high endemicity were compared to those in an area where HCV is not endemic. A total of 400 individuals were selected randomly from those who were medically screened for liver disease in 1993; 200 were from the high-endemicity area, and the other 200 were from the no-endemicity area. HGV RNA was measured by reverse transcription and PCR with primers in the 5′ noncoding region. Antibody to HGV envelope protein E2 was measured by an enzyme-linked immunosorbent assay. Prevalence of any HGV marker in the high-endemicity area (32%) was significantly (P < 0.0001) higher than that in the no-endemicity area (6%); similar differences, 32% versus 3% (P < 0.0001), had been observed for HCV markers (HCV RNA and HCV antibody). In areas of both high and no endemicity, HCV markers were significantly more prevalent in individuals with any HGV marker than in those without HGV markers, and age-specific prevalence of HGV markers was distributed similarly to that of any HCV marker. Among possible routes of HGV transmission that were analyzed, folk medicine was significant in the high-endemicity area, but blood transfusion was the major route in the no-endemicity area. The rate of accompanying viremia in HGV infection (15%) was significantly lower than that in HCV infection (78%) (P < 0.0001). In conclusion, HGV infection was highly prevalent in the area of high HCV endemicity and was closely associated with HCV infection. HGV seemed to be transmitted via the practice of folk medicine as well as blood transfusion. HGV resulted in a chronic carrier state less frequently than did HCV.

The GB virus C and the hepatitis G virus (HGV) were identified recently as possible causative agents of human viral hepatitis (12, 17). Molecular characterization of these two agents has shown them to be closely related strains of the same virus, and they are supposed to represent a new genus in the family Flaviviridae (3). As the nomenclature of the new virus has not been settled, the term HGV is used in this paper. HGV, like hepatitis C virus (HCV), is transmissible through blood transfusion and is associated with acute and chronic infections (4, 5, 15, 22, 24). Studies on HGV have depended on the measurement of HGV RNA in serum, which reflects active infections. Noncoding region. Antibody to HGV envelope protein E2 (HGV-E2 antibody), which indicates recovery from HGV infection, has been developed (6, 16, 18, 19). The combined use of these assays has allowed for more comprehensive epidemiological studies of both past and present HGV infection.

We previously reported on an area in which HCV is highly endemic, where over 30% of the inhabitants were infected with HCV (10). In that study, analyses of risk factors for HCV infection elucidated apparent modes of parenteral transmission, particularly folk medicine procedures. In the present study, we determined the prevalence and patterns of HGV infection in areas of high and low HCV endemicity to compare the transmission patterns of these two common Flaviviridae infections.

MATERIALS AND METHODS

Patients. A total of 420 individuals over 18 years old (62% of total inhabitants with corresponding ages) in an area in which HCV infection was endemic were medically screened for liver diseases in July 1993. Of those, the first 200 individuals who prepared for screening were selected randomly for evaluation in this study. Those subjects included 79 males and 121 females aged 18 to 84 years (mean ± standard deviation [SD], 56.3 ± 17.7 years). Medical screening was also conducted in an area in which HCV was not endemic and which is located near the high-endemicity area. Of 482 individuals (65% of total inhabitants with corresponding ages) who underwent medical screening in the no-endemicity area, 200 individuals were selected randomly for evaluation in the same manner as in the high-endemicity area. These control subjects included 48 males and 152 females aged 20 to 89 years (mean ± SD, 56.8 ± 13.4 years). Data from the HCV high-endemicity area (Arahiro) were reported previously (10), but the no-endemicity area (Sakase) was not involved in the previous study. In both areas the main source of income is forestry, most people are middle class, Buddhism is the predominant religion, and the lifestyle does not seem to differ from that in other parts of Japan. Folk remedies in the areas of high and no endemicity include acupuncture with needles and so-called “Suiz宋代” therapy, in which the skin is cut with knives (10). Nonsterilized knives and needles had been used in the high-endemicity area, but the use of sterilized instruments began after 1986 under direction of the public health center. Use of nonsterilized tools had not been noted in the no-endemicity area. Health screening and blood sample collections were done in the same manner as reported previously (10). Informed consent was obtained from each subject. Serum samples were stored at −70°C until assayed.

Laboratory tests. Second-generation HCV antibody, hepatitis B surface (HBs) antigen, HBs antibody, and hepatitis B core (HBC) antibody were detected with...
TABLE 1. Comparison of clinical and virological characteristics between individuals in high- and no-endemicity areas

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>High endemicity (n = 200)</th>
<th>No endemicity (n = 200)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical operation</td>
<td>50 (25.0)</td>
<td>45 (22.5)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>14 (7.0)</td>
<td>20 (10.0)</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>Folk remedy</td>
<td>91 (45)</td>
<td>54 (27.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hbs antigen</td>
<td>4 (2.0)</td>
<td>2 (1.0)</td>
<td>&gt;0.2*</td>
</tr>
<tr>
<td>Hbs antibody</td>
<td>50 (25.0)</td>
<td>36 (18.0)</td>
<td>0.0884</td>
</tr>
<tr>
<td>Hbc antibody</td>
<td>54 (27.0)</td>
<td>38 (19.0)</td>
<td>0.0573</td>
</tr>
<tr>
<td>Any HBV marker</td>
<td>64 (32.0)</td>
<td>42 (21.0)</td>
<td>0.0127</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>50 (25.0)</td>
<td>3 (1.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HCV antibody</td>
<td>64 (32.0)</td>
<td>5 (2.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any HCV marker</td>
<td>64 (32.0)</td>
<td>5 (2.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HGV RNA</td>
<td>9 (4.5)</td>
<td>2 (1.0)</td>
<td>0.0323</td>
</tr>
<tr>
<td>HGV-E2 antibody</td>
<td>58 (29.0)</td>
<td>10 (5.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Any HGV marker</td>
<td>63 (31.5)</td>
<td>12 (6.0)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Obtained by Fisher’s exact test; all other P values were obtained by the chi-square test.

RESULTS

Backgrounds and viral markers in areas of endemicity versus areas of no endemicity. Clinical and virological features of the 200 individuals in the high-endemicity area were compared to those of the 200 individuals in the no-endemicity area (Table 1). A history of folk remedies was significantly more prevalent in the high-endemicity area than in the no-endemicity area, while histories of surgery and blood transfusion were similar in the two areas. Prevalence of HGV-related markers was significantly higher in the area of endemicity than in the no-endemicity area, as was observed for HCV-related markers. Prevalence of HBs antigen did not differ between the two areas, but that of any hepatitis B virus (HBV) marker was significantly higher in the area of endemicity. Of the 400 subjects, 75 (19%) were positive for HGV RNA and/or HGV-E2 antibody, 7 (9%) were positive for HGV RNA only, 4 (5%) were positive for both HGV RNA and HGV-E2 antibody, and 64 (86%) were positive for HGV-E2 antibody only.

Age-specific prevalence. Age-specific prevalences of hepatitis viruses in the high-endemicity and no-endemicity areas are shown in Fig. 1. Individuals who had a marker indicating the presence of viremia were defined as having ongoing infection, the presence of HBs antigen was defined as indicating HBV infection, the presence of HCV RNA was defined as indicating HCV infection, and the presence of HGV RNA was defined as indicating HGV infection. On the other hand, individuals who had antibody in the absence of viremia were considered to have resolved or past infection. Age-specific prevalences of total infection (viremia plus antibody) were similar for HBV, HCV, and HGV in the high-endemicity area. The prevalence was around 10% in groups under 50 years old and around 40% in groups over 50 years old. This difference in distribution between groups under and over 50 was statistically significant (chi-square test) for each hepatitis virus: 10% versus 42% for HBV (P < 0.0001), 8% versus 42% for HCV (P < 0.0001), and 10% versus 41% for HGV (P < 0.0001). In the no-endemicity area, the prevalence did not differ between the two age groups for either HBV, HCV, or HGV.

Current versus past infection. To analyze the proportion of present HGV infections to total HGV infections, cases in the high- and no-endemicity areas were combined, because the proportions were similar in each area for each hepatitis virus (6% versus 5% for HBV, 79% versus 60% for HCV, and 14% versus 17% for HGV). The overall percentage of current (to total) infections (15%, 11/75) was significantly higher for HGV than for HBV (6%, 6/106 [P = 0.04 by the chi-square test]) but significantly lower than for HCV (78%, 53/68 [P < 0.0001]).

HGV-infected versus noninfected groups. Clinical and virological features were compared between groups with and without HGV infection (including past and present infections) in the high- and low-endemicity areas (Table 2). A history of exposure to folk remedies was more frequent in HGV-positive subjects than in HGV-negative subjects in the high-endemicity area but not in the no-endemicity area. In contrast, a history of blood transfusion was significantly more common among HGV-positive subjects than among HGV-negative subjects in the no-endemicity area. The prevalence of HVB-related markers did not differ between the two groups, while that of HCV-related markers was significantly higher in the HGV-positive group.

In the high-endemicity area, HGV infection (past and present) was significantly more common (P = 0.0233 by Fisher’s exact test) in individuals exposed to folk remedies before 1986 (44%, 37/82) than in those exposed after 1986 (11%, 1/9). Similarly, HCV infection was significantly more common (P = 0.0160 by Fisher’s exact test) in individuals exposed before 1986 (48%, 39/82) than in those exposed after 1986 (11%, 1/9). Thus, HGV or HCV infection was less common in individuals who were exposed to folk remedies after the use of sterilized tools was adopted in 1986.

Mean levels of ALT in serum were compared according to the status of HCV and HGV RNAs (Table 3). The mean level was significantly higher in those with HCV and HGV RNAs and those with HCV RNA alone than in those without HCV or HGV RNA. Other comparisons among the four groups were not statistically significant, including the comparison between those with HGV RNA alone and those without HCV or HGV RNA.
DISCUSSION

We previously reported that there was a small outbreak of community-acquired, non-A, non-B acute hepatitis among adults in the Arahiro area between 1981 and 1982. Subsequent study (10) showed that the outbreak was due to HCV infection spread mainly via folk remedies in which nonsterilized needles and knives were used. Age-specific prevalence of HCV antibody showed that inhabitants who were infected were predominantly over 40 years old when screened in 1986. By 1993 (present study), a high prevalence was found only in those over 50 years old, suggesting a cohort effect and indicating that the outbreak of HCV infection had already ceased in the Arahiro area following the adoption of sterilized tools in the practice of folk remedies.

HGV-E2 antibody has been reported as a marker of recovery from HGV infection, based on observations that HGV RNA and HGV-E2 antibody are generally mutually exclusive and that clearance of HGV RNA generally coincides with the appearance of HGV-E2 antibody (6, 16, 18). Our results showing that only 5% of individuals with any HGV marker were positive for both HGV RNA and HGV-E2 antibody further support the previous observations.

Tacke et al. (18) reported that 2.5% of healthy blood donors were positive for HGV RNA and that 9% were positive for HGV-E2 antibody. Our data in the no-endemicity area were similar, showing a 1% prevalence of HGV RNA and a 5% prevalence of HGV-E2 antibody. Thus, in an area of low HCV endemicity in Japan, the rates of HGV infection are similar to those in Western nations.

When we previously compared HCV and HGV infections in the high-endemicity area by testing HCV and HGV RNAs (23), the prevalence of HGV infection (5%) appeared much lower than that of HCV infection (34%). However, with the advent of the HGV-E2 antibody assay, it became obvious that prevalence of both past and present HGV infection (32%) was as high as that of HCV (32%) or HBV (32%) infection in the high-endemicity area. The prevalence of total infection (past and present infections) for each virus was significantly higher in the high-endemicity area than in the no-endemicity area. However, the proportions of the infections that were active (viremic) were similar in the low- and high-endemicity areas for each virus. The overall proportions of subjects who were antigenic or viremic were 6% for HBV, 15% for HGV, and 78% for HCV. Seventy to 85% of patients with acute HCV infection become chronic HCV carriers (1, 2, 20) and usually maintain the carrier state for long periods afterwards (7, 9, 20).

Although several reports have shown that HGV can cause a chronic carrier state (4, 5, 13, 15), the frequency with which it occurs and the rate by which it is maintained has not been clarified sufficiently. Our data suggest that the rate of persis-

FIG. 1. Age-specific prevalences of HBV, HCV, and HGV infections in high-endemicity and no-endemicity areas. Prevalence of exposure is indicated by both filled and open bars and reflects a positive test for at least one viral marker (HBs antigen, HBs antibody, and/or HBc antibody for HBV; HCV RNA and/or HCV antibody for HCV; and HGV RNA and/or HGV-E2 antibody for HGV). Filled bars indicate a positive test for a marker of viremia (HBs antigen for HBV, HCV RNA for HCV, and HGV RNA for HGV).
These results are consistent with the findings of previous studies (4, 5, 8, 13, 21) that suggested a minimum-pathogenic-effect HGV.

ACKNOWLEDGMENTS

This research was supported in part by a grant-in-aid from the Ministry of Health and Welfare in Japan and in part by a grant-in-aid from the Ministry of Education, Science, Sports and Culture (no. 09670529).

We thank members of the South Kiso hepatitis study group for assistance at the medical screenings performed in the Arahiko and Sakaue areas. We also thank Kafumi Todori for technical assistance.

REFERENCES


