LIVER, PANCREAS, AND BILIARY TRACT

Transmission of Hepatitis C in an Isolated Area in Japan: Community-Acquired Infection

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Background/Aims: The spread of hepatitis C virus (HCV) infection not due to drug needle sharing or transfusion is largely unknown in communities. A search for risk factors for HCV infection in an endemic area might elucidate inapparent modes of transmission. Methods: We conducted screening for hepatitis virus markers and parenteral exposures to blood among 435 inhabitants in an isolated area known for its endemicity for non-A, non-B hepatitis and in a nonendemic area with 1542 inhabitants. Results: The prevalence of hepatitis B surface antigen was the same in both areas. The prevalence of antibody to HCV verified by the recombinant immunoblot assay was 32.4% in the highly endemic area and 2.3% in the nonendemic area (P < 0.001). Risk factors for HCV infection in the highly endemic area were complex but included folk remedies such as acupuncture and "vacuuming" for congested blood in muscle by the use of a warm glass bottle. Conclusions: Folk remedies such as acupuncture and cutting of the skin using nonsterilized knives should be considered as possible routes of HCV transmission not associated with blood transfusion or sharing of drug paraphernalia.

Hepatitis C virus (HCV) is believed to be the major cause of not only blood-borne non-A, non-B hepatitis but also sporadic cases of non-A, non-B hepatitis. HCV infection leads to chronic liver disease such as cirrhosis of the liver and eventually hepatocellular carcinoma. It has been suggested that the mode of spread of HCV infection in the community is similar to that of hepatitis B virus (HBV) infection.

In Japan, the prevalence of antibodies to HCV (anti-HCV) increases with age. This indicates that HCV infection is occurring at all ages. There have been several reports on outbreaks of nonwater-borne non-A, non-B hepatitis in isolated areas of Japan. Many outbreaks are now linked to HCV. The Arahiro area in South Kiso Town, located in the central region of Japan, represents one such endemic area. We began studying the cause of hepatitis in this area in 1985.

The diagnosis of type C hepatitis was first made by detecting antibody to hepatitis C virus using the first generation test, anti-C100-3 (anti-HCV 1). Subsequently, a second-generation assay (designated anti-HCV 2) and a supplemental assay (recombinant immunoblot assay, RIBA II) were used to diagnose cases of non-A, non-B hepatitis. The anti-HCV 2 assay has increased sensitivity for detecting HCV infection. To determine HCV infection in our epidemiological study, we used an anti-HCV 2 assay to initially screen samples; those that were reactive on the supplemental RIBA II were considered true positives.

Our primary objective was to determine whether HCV was the cause of the frequent hepatitis found in the Arahiro area. Our second objective was to identify risk factors that might correlate with HCV infection using multivariate analysis.

Materials and Methods

Background

The Arahiro area is part of South Kiso Town in the southwestern region of Nagano Prefecture, which is in the middle of Hoshu Island. This area is surrounded by mountains and is relatively isolated from other communities. The main source of income is forestry; most people are middle class.

Abbreviations used in this paper: anti-HCV 1, first generation antibody to hepatitis C virus; anti-HCV 2, second generation antibody to hepatitis C virus; ELISA, enzyme-linked immunosorbent assay; GITT, γ-glutamyl transpeptidase; RIBA II, second generation recombinant immunoblot assay; ZTT, zinc turbidity test.

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class. Buddhism is the predominant religion. The life style does not seem to differ from that in other parts of Japan. However, there was a small outbreak of community acquired, non-A, non-B acute hepatitis among adults in 1981 and 1982. Thereafter, patients acquiring this infection were observed sporadically. Thus, in 1984, Kiso Public Health Center conducted a preliminary survey, performing liver function tests on 147 inhabitants over 41 years of age. An elevated serum alanine aminotransferase (ALT) value was found in 59 persons (40%). To determine the cause of the endemic hepatitis and to prevent its spread, a committee was established in 1985 that consisted of representatives from the Kiso Public Health Center, South Kiso Town office, the district medical association, Sakashita Hospital and members of the Department of Internal Medicine, Shinshu University.

### Subjects

Mass screening for liver disease was conducted in the Arahiro area and in the neighboring areas of Yomisho, Tatachi, and Sumago, identified as nonendemic areas, for liver disease. These areas all belong to South Kiso Town, which is located at the midpoint between Matsumoto City and Nagoya City (Figure 1). The four areas of South Kiso Town are separated by a river and small mountains; the height above sea level of the Arahiro area is 200 m higher than that of the other areas. There were three physicians in South Kiso Town: Dr. A was in the Arahiro area and Dr. B and Dr. C were in the Yomisho area. The 728 inhabitants in the Arahiro area and the 2129 inhabitants in the nonendemic areas who were older than 5 years were invited to participate in mass screening. Of those, 435 (59.7%) in the former and 1542 (72.4%) in the latter were screened. Informed consent to participate in this survey was obtained from each inhabitant. For children under the age of 15 years, informed consent was obtained from their parents and teachers.

### Health Screening and Blood Sample Collection

Health screening for liver disease was conducted in July 1985 by a team of investigators including physicians and public health nurses. After informed consent was obtained, each subject was interviewed for demographic data that included age, sex; occupation; past medical history, especially of blood transfusion, hemodialysis, or hemophilia; surgery; tattooing; intravenous drug use; daily intake of ethanol exceeding 80 g; and folk remedies such as acupuncture; and information on family members known to have liver disease. Body height and weight were recorded. Thereafter, 20 mL of blood were withdrawn, and the serum was separated. Each serum sample was divided into three parts. One part was used for standard liver tests including ALT (normal, <35 IU/L), total bilirubin (normal, <1.2 mg/dL), γ-glutamyl transpeptidase (GGT) (normal, <40 IU), and zinc turbidity test (ZTT) (normal < 12 Kunkel Units). The ZTT test reflects the γ-globulin level, and its value is usually elevated in patients with chronic liver disease. A second part was tested for hepatitis B surface antigen (HBsAg), antibody to HBs (anti-HBs), antibody to hepatitis B core antigen (anti-HBc) and antibody to hepatitis A virus (anti-HAV) at the time; the third part was stored at −80°C until needed. Individuals with abnormal laboratory findings were referred to an area hospital for medical evaluation.

### Laboratory Tests

Anti-HCV 1 (the antibody to C100-3 antigen) was detected by the HCV enzyme-linked immunosorbent assay (ELISA) test (Ortho Diagnostic Systems, Inc., Raritan, NJ). Anti-HCV 2 was tested by Immuchek-HCV Ab ELISA test (International Reagents Co., Kobe, Japan), which can detect antibodies against core protein (C11 antigen) and a nonstructural protein (C7). Samples positive by either ELISA test were evaluated by the second generation RIBA II (Ortho Diagnostic Systems, Inc.). Anti-HCV detected by either ELISA was considered "confirmed" if the RIBA II was reactive.

HBsAg, anti-HBs, anti-HBc and anti-HAV were tested by ELISA using commercially available test kits (Abbott Laboratories, North Chicago, IL). Standard liver tests were performed on a multichannel autoanalyzer (Technicon Instrument Co., New York, NY).

### Statistical Analysis

Univariate analysis, the χ² test, or the analysis of variance (ANOVA) were performed for HCV infection with the variable of interest, including sex, age, past history of surgical operation, blood transfusion, intravenous drug use, tattooing, daily intake of ethanol exceeding 80 g, and use of folk remedies such as acupuncture. The existence of liver disease in other family members was defined as those households with two or more persons with liver disease. Between-group differences were tested by ANOVA with Bonferroni's method. Discreetly distributed variables are presented as percent of each subject group. Differences in proportions were assessed by the χ² test with Yates' correction, supplemented by Fisher's Exact Test when required by sample size. A two-tailed critical P value of < 0.05 was used throughout.

Multivariate assessment by logistic regression was per-
formed for determining which variables were independently associated with HCV infection using the odds ratios. A multiple logistic regression model was built using the following variables: age, blood transfusion history, gender, surgical operation, folk remedies, tattoo, family clustering of liver disease, home physician, and HBV markers. The purpose of the model was to determine which characteristics of the subjects were independently associated with HCV infection in the endemic area. In this logistic regression analysis procedure, we used Wald statistics for estimation of coefficient, R statistic for assessing the partial contribution of each independent variable, the log of the odds for expressing the equation of the model, and then the classification table and goodness-of-fit statistic with all of the independent variables for assessing the goodness of fit of the model. The results were expressed by description of estimated values of regression coefficient with \( P \)-value, odds ratio, and \( R \) statistic. The same procedure using the above variables was used to determine which characteristics were independently associated with HCV infection in the nonendemic area. The SPSS version 5.0 (SPSS Inc., Chicago, IL) was used for all statistical computations.

Results

Abnormal Liver Function Tests and Prevalence of Hepatitis Virus Markers in the Endemic Versus Nonendemic Areas

The overall frequencies of elevated ALT, GGT, total bilirubin, and ZTT were 10.8%, 8.5%, 0.7% and 26%, respectively, in the Arahiro area, and 1.9%, 3%, 0.3% and 4.3%, respectively, in the nonendemic area. No person between the age of 5 and 15 had abnormal liver tests in either area. The frequency of abnormal values for ALT, GGT, and ZTT increased with age over 15 in both areas, particularly in the Arahiro area. The difference between these areas was significant for ALT and ZTT (\( P < 0.001 \)).

Rates of positivity for anti-HAV, HBV markers (any combination of HBsAg, anti-HBs, and anti-HBc) and anti-HCV appear in Table 1. There was no significant difference in the rates of positivity for anti-HAV (63% vs. 57.6%) between the two areas. However, though there was similar HBsAg prevalence in the two areas (2.4% in the Arahiro area and 0.9% in the nonendemic area), a significant difference was noted for anti-HBs (25.9% vs. 9.3%; \( P < 0.001 \)) and anti-HBc (33.6% vs. 14.3%; \( P < 0.001 \)). Overall, the prevalence of any HBV marker—positive person was 34.9% in the Arahiro area and 15.8% in the nonendemic area, which was significantly different (\( P < 0.001 \)). The prevalence of anti-HCV was 32.4% (141 of 435) in the Arahiro area and 2.3% (35 of 1542) in the nonendemic area, which was significantly different (\( P < 0.001 \)). The rates of positivity of anti-HBs, anti-HBc, and anti-HCV increased with age remarkably in the Arahiro area.

Liver Diseases in Those With Positive Laboratory Findings

A total of 149 persons with one or more abnormal laboratory findings from the Arahiro area, including 121 positive for anti-HCV, were referred to the Sakashita Hospital, Shinshu University Hospital, or Kiso Hospital for further examination by ultrasonography, computerized tomography, and liver biopsy. In these subjects, the diagnoses included hepatocellular carcinoma in 1, cirrhosis of the liver in 11, chronic hepatitis in 124 (chronic active hepatitis in 65, chronic persistent hepatitis in 59), fatty liver in 11, and gallstones in 2. For the 39 persons similarly evaluated from the nonendemic area, 27 had chronic hepatitis (chronic active hepatitis in 13 and chronic persistent hepatitis in 14), 11 a fatty liver, and 1 gallstones.

Background of Inhabitants Older Than 41 Years

Because the prevalence of abnormal liver tests and presence of anti-HCV were the highest in inhabitants older than 41 years of age, the backgrounds of these subjects in each area were compared (Table 2). A history of surgical treatment, blood transfusion, intravenous

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Table 1. Positivity Rates for Hepatitis A, B, and C Virus Markers by Age and Sex in Highly Endemic Versus Nonendemic Areas

<table>
<thead>
<tr>
<th>Age (range in years)</th>
<th>No. of individuals</th>
<th>Anti-HAV positive no. (%)</th>
<th>HBV markers* positive no. (%)</th>
<th>Anti-HCV* positive no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arahiro</td>
<td>Nonendemic</td>
<td>Arahiro</td>
<td>Nonendemic</td>
</tr>
<tr>
<td>5–15</td>
<td>69</td>
<td>225</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>16–40</td>
<td>72</td>
<td>378</td>
<td>7 (9.7)</td>
<td>46 (12.2)*</td>
</tr>
<tr>
<td>41–</td>
<td>294</td>
<td>939</td>
<td>265 (90.1)</td>
<td>842 (89.7)*</td>
</tr>
<tr>
<td>Total</td>
<td>453</td>
<td>1542</td>
<td>272 (62.5)</td>
<td>888 (57.8)*</td>
</tr>
</tbody>
</table>

*HBV markers, hepatitis B surface antigen, antibody to hepatitis B surface antigen, antibody to hepatitis B core antigen.

NS, ns

Family

A

B

C

Other

Non

Obes

Surg

Bloo

Intra

Tattoo

Folk

Liver cirrhosis

NS, ns

aFolk is a non-

bSee 1

cIn ex

dDrink

drug How by pr

rem bloo

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Table 2. Background of Individuals Older Than 40 Years in the Arariho Area Versus Nonendemic Areas

<table>
<thead>
<tr>
<th>Item</th>
<th>Arariho (n = 294)</th>
<th>Nonendemic (n = 939)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical operation (%)</td>
<td>24.1</td>
<td>18.8</td>
<td>NS</td>
</tr>
<tr>
<td>Blood transfusion (%)</td>
<td>9.5</td>
<td>7.9</td>
<td>NS</td>
</tr>
<tr>
<td>Intravenous drug use (%)</td>
<td>0.3</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Tattoo (%)</td>
<td>0.3</td>
<td>0</td>
<td>NS</td>
</tr>
<tr>
<td>Folk remedy (%)</td>
<td>50.3</td>
<td>27.1</td>
<td>0.001</td>
</tr>
<tr>
<td>Family physician (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>50.0</td>
<td>0.6</td>
<td>0.001</td>
</tr>
<tr>
<td>B</td>
<td>8.2</td>
<td>22.7</td>
<td>0.001</td>
</tr>
<tr>
<td>C</td>
<td>8.8</td>
<td>24.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Others</td>
<td>11.9</td>
<td>32.6</td>
<td>0.001</td>
</tr>
<tr>
<td>None</td>
<td>21.1</td>
<td>19.7</td>
<td>NS</td>
</tr>
<tr>
<td>Obesity (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>7.5</td>
<td>6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Heavy drinker</td>
<td>11.6</td>
<td>10.9</td>
<td>NS</td>
</tr>
<tr>
<td>Liver disease in other family members</td>
<td>29.9</td>
<td>5.4</td>
<td>0.001</td>
</tr>
</tbody>
</table>

NS, not significant. 
*Folk remedy refers to acupuncture or Suidama therapy performed by a nonprofessional. 
*See text and Figure 1. 
*In excess of 20% of ideal body weight. 
*Drinking more than 80 g ethanol daily for more than 10 years.

drug use, and tattoo showed about the same prevalence. However, folk remedies such as acupuncture, performed by an amateur therapist who was not licensed for medical practice, and/or “Suidama” therapy, a traditional folk remedy believed to improve muscle stiffness by drawing blood from a bleeding wound (Figure 2), were performed significantly more frequently in Arariho (P < 0.001). The prevalence of obesity (over 20% in excess of ideal body weight) and that of heavy drinking (ethanol > 80 g/day) were similar in each area. The rate of familial clustering of liver disease, defined as those households with two or more persons with liver disease, was significantly higher in Arariho. Treatment by family physician A was more frequent for those in the Arariho area (P < 0.001).

Comparison of Clinical Findings Between Anti-HCV-Positive and -Negative Individuals

Table 3 compares the characteristics of anti-HCV-positive and -negative inhabitants of the Arariho area and the nonendemic area. In the Arariho area, the mean age was higher in the anti-HCV-positive group (56.7 vs. 48.0 years; P < 0.01). There was no significant difference in male gender and frequency of heavy drinking. The relative numbers of people exposed to blood transfusion, surgical operations, and folk remedies were significantly higher in the anti-HCV-positive group than in the negative group (P < 0.02, P < 0.001, and P < 0.001, respectively). Family clustering of persons with liver disease was more frequent in the anti-HCV-positive group (P < 0.001). Evidence of HBV infection was significantly more frequent in the same group (P < 0.001).

We performed multivariate logistic regression model-

Figure 2. The so-called “Suidama” therapy, which is popular as a folk remedy in the Arariho area. It is claimed to relieve muscle stiffness by the removal of blood. (A) The skin is cut over the muscle with a nonsterile knife. (B) The wound is then covered by a warming bottle containing cotton wetted with ethanol so that blood is drawn from the wound into the bottle. This is usually performed by a member of the family.
Table 3. Comparison of Personal History and Clinical Data Between Anti-HCV–Positive and -Negative Individuals in the Arahiko Area and Nonendemic Areas

<table>
<thead>
<tr>
<th>Item</th>
<th>Arahiko area</th>
<th>Nonendemic areas</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-HCV (+)</td>
<td>Anti-HCV (-)</td>
</tr>
<tr>
<td>Mean age (yr)</td>
<td>56.7</td>
<td>48.0</td>
</tr>
<tr>
<td>Male (%)</td>
<td>41.8</td>
<td>42.5</td>
</tr>
<tr>
<td>History of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical operation (%)</td>
<td>31.9</td>
<td>9.5</td>
</tr>
<tr>
<td>Blood transfusion (%)</td>
<td>11.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Family physician (Dr. A) (%)</td>
<td>53.1</td>
<td>50.0</td>
</tr>
<tr>
<td>Intravenous drug use (%)</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td>Tattoo (%)</td>
<td>0.7</td>
<td>0</td>
</tr>
<tr>
<td>Folk remedies (%)</td>
<td>61.7</td>
<td>25.9</td>
</tr>
<tr>
<td>Liver disease in other family members (%)</td>
<td>38.3</td>
<td>12.0</td>
</tr>
<tr>
<td>Heavy drinking (%)</td>
<td>9.2</td>
<td>10.9</td>
</tr>
<tr>
<td>Any HBV marker (%)</td>
<td>61.0</td>
<td>27.1</td>
</tr>
</tbody>
</table>

NS, not significant.

n, number of individuals.

The findings of an elevated ALT level (10.8% vs. 1.0%), ZTT level (25.9% vs. 4.3%), prevalence of HBV markers (34.9% vs. 15.8%), and anti-HCV (32.4% vs. 2.3%) were significantly greater in subjects from the Arahiko area than in those from the nonendemic area. The prevalence of HBsAg carriers, the rates of obesity, and heavy drinking were similar in both areas. These data indicate that ongoing liver disease in the Arahiko area is attributed primarily to hepatitis C although there is evidence of more hepatitis B infection in the past.

This is supported by histological examination of persons having liver dysfunction, most had chronic persistent or chronic active hepatitis as shown in this paper, as well as elsewhere.13

The difference in liver disease frequency between the Arahiko and nonendemic areas was most pronounced for persons over 41 years of age. For those in the Arahiko area, there was more use of folk remedies (acupuncture and Suidama therapy), familial clustering of liver disease, and care by one physician. Compared with those in the nonendemic area, Arahiko residents had the same exposure to surgical operations, blood transfusions, injection drug use, and tattoos, all considered common infectious routes of HCV. When the clinical data were compared for the anti-HCV–positive and -negative groups in the AH area, a significant difference was seen in mean age, familial history of liver disease, folk remedies, HBV markers, and surgical operations. In the nonendemic area, a significant difference was also seen for those with anti-HCV for a history of a blood transfusion, male gender predominance, and surgical operations but not in the use of folk remedies, familial clustering of liver disease, or

Table 4. Results of Multivariate Analysis in the Arahiko Area for HCV Infection

<table>
<thead>
<tr>
<th>Variable</th>
<th>Regression coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated value</td>
</tr>
<tr>
<td>Increasing age</td>
<td>0.037</td>
</tr>
<tr>
<td>Family history of liver disease</td>
<td>0.836</td>
</tr>
<tr>
<td>Folk remedies</td>
<td>0.614</td>
</tr>
<tr>
<td>Any HBV marker</td>
<td>0.501</td>
</tr>
<tr>
<td>Surgical operation</td>
<td>0.454</td>
</tr>
</tbody>
</table>
past HBV infection for those with and without anti-HCV. These findings indicate that the increase in prevalence of HCV infection in the endemic area of Arahori was apparently spread through additional blood-related procedures.

There was a correlation between older age and prevalence of anti-HCV in this study. The same tendency was seen in Japanese blood donors. However, the reason for these findings in the Arahori area are quite unique. Reusing syringes for some vaccination and sporadic intravenous drug abuse did not contribute to HCV infection in the Arahori area.

Previous reports have suggested that HCV infection might be due to intrafamilial contact and mother-to-infant transmission. In this study, there were no school children with anti-HCV or evidence of liver dysfunction even when their mothers had type C chronic liver disease (data not shown). Little vertical transmission of HCV has been shown and does not explain the spread of HCV infection in the Arahori area. Sexual transmission of HCV may be important but may be confounded by other common factors. Several Japanese researchers reported a high seropositivity rate for anti-HCV markers in married couples. One report from China suggested possible sexual transmission of HCV. However, these couples lived in the same area where HCV was highly endemic. In contrast, Osmond et al. found no anti-HCV or HCV RNA in heterosexual partners of 50 HCV carriers; this was also noted by others. Thus, though there were 14 anti-HCV concordant couples in the Arahori area (data not shown), sexual transmission may not be an important infectious route among this population.

Folk remedies seem to be the important risk factor for hepatitis B and C in the Arahori area. Acupuncture and Suidama therapy are traditional practices for the Arahori area. Acupunturists usually treat several patients at the same time using the same needle without sterilization. Suidama therapy is performed mainly by a family member using nonsterilized instruments. After warning about the use of unsterilized medical instruments, the number of patients with acute viral hepatitis decreased. The close relationship between anti-HBc presence and non-A, non-B hepatitis (now hepatitis C) has been documented.

In this study, we found an association of anti-HCV with HBV markers, suggesting spread of both viruses by the same practices in the Arahori area. One possibility for the spread of HCV infection is via a family physician (Dr. A), who was observed to use nonsterilized syringes on some occasions. However, most individuals with and without anti-HCV in the Arahori area visited Dr. A. Furthermore, though it would be important to ascertain which persons received an injection, we could not determine this. These factors were interconnected with treatment by Dr. A in multivariate analysis.

According to Setoguchi et al., the number of patients with hepatocellular carcinoma is increasing in highly endemic hepatitis areas in Japan. In the Arahori area, 6 patients with hepatocellular carcinoma and 15 patients with liver cirrhosis died between 1985 and 1991 (data not shown). This means that the ground for hepatocellular carcinoma has already been laid in such endemic areas. Thus, epidemiologic studies are important for preventing not only viral hepatitis, but also subsequent hepatocellular carcinoma due to HCV and HBV.

References


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