Large-Scale Survey of Hepatitis B Virus Infection in Families

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Abstract To investigate HBV transmission in families on three islands in Okinawa, Japan, prevalence of HBV markers in two groups of inhabitants was determined. One group consisted of members of families in which there was at least one HBsAg carrier (carrier families); the other group consisted of members of families in which there were no HBsAg carriers (non-carrier families). A total of 3,261 serum samples were collected from subjects on Iriomote Island, Hateruma Island, and Yonaguni Island. These samples were tested for HBsAg by reversed passive hemagglutination (RPHA) and for antibody to hepatitis B core antigen (anti-HBc) by radioimmunoassay. Overall prevalences of HBsAg and anti-HBc were 8.2 and 65.8 per cent respectively. The prevalence of anti-HBC among members of carrier families (80.8%) was significantly higher than that among members of non-carrier families (61.6%) (P<0.001). The prevalence of anti-HBc among members of carrier families was higher in all age groups, and was particularly so in children. Within carrier families, the prevalence of anti-HBc was significantly higher in families in which there was at least one HBsAg carrier with HBeAg (94.5%) than in families with no HBeAg-positive carriers (76.1%). This difference was especially marked in young children. These data suggest that in families with HBsAg carrier(s), the risk of transmitting HBV to members, particularly to young children, is higher than in families without carriers, and that the risk is further increased in families with HBeAg-positive carrier(s).

It is well known that, since hepatitis B virus (HBV) infection can result from close contact with individuals who are viremic with HBV, they provide a source of HBV for the spread of infection in the community (6). The family would be a setting where this type of HBV transmission frequently occurs. Many investigators have documented that HBV markers are much more prevalent in people living in families with hepatitis B surface antigen (HBsAg)-positive individuals than in the general population (3, 4, 8, 10, 20, 25, 27, 31).

This survey was carried out to investigate HBV transmission in families on three islands in the Yaeyama district of Okinawa, Japan. Prevalences of HBV markers in two groups of inhabitants were determined. One group consisted of members of families in which there was at least one HBsAg carrier; the other group consisted of
members of families in which there were no HBsAg carriers.

MATERIALS AND METHODS

A total of 3,261 serum samples were available: 783 collected on Iriomote Island, 823 on Hateruma Island and 1,655 on Yonaguni Island. All samples were taken in 1980. The collecting of samples on Iriomote and Hateruma Islands has already been described elsewhere (11). The same method was employed on Yonaguni Island. Serum samples were collected from more than 95 per cent of the residents of Iriomote and Hateruma Islands, and from about 79.0 per cent (1,655 out of 2,100) on Yonaguni Island. Families that were not completely sampled were included in the study.

Serum samples were assayed for HBsAg and antibody to hepatitis B core antigen (anti-HBc). All HBsAg-positive sera were assayed for hepatitis Be antigen (HBeAg) and antibody to HBeAg (anti-HBe).

The residents of the three islands were divided into two groups: (1) carrier family members (C) (171 families representing the members of families in which there was at least one HBsAg carrier, and (2) non-carrier family members (CN) (1,074 families) representing the members of families in which there were no HBsAg carriers. The C group was further divided into two sub-groups: (1) HBeAg family members (E) (33 families) representing the members of families in which there was at least one HBsAg carrier with HBeAg, and (2) Non-HBeAg family members (NE) (138 families) representing the members of families in which there were no HBsAg carriers with HBeAg.

HBsAg was tested by reversed passive hemagglutination (RPHA) (Reverscell, Meguroken, Osaka, Japan) and anti-HBc, HBeAg, and anti-HBe by radioimmunoassay (RIA) (Corab and ABBOTT-HBe, Abbott Laboratories, North Chicago, IL). Chi-square analysis of the results was performed. Because there were some cases in which the odds ratio was infinity, modified odds ratios were calculated (7).

RESULTS

The overall prevalences of HBsAg and anti-HBc on the three islands were determined to be 8.2 and 65.8 per cent, respectively (267 and 2,145 out of 3,261). They were 8.7 and 59.9 per cent, respectively (68 and 469 out of 783) for Iriomote Island, 7.3 and 72.8 per cent (60 and 599 out of 823) for Hateruma Island, and 8.4 and 65.1 per cent (139 and 1,077 of 1,655) for Yonaguni Island. The prevalence of HBsAg increased with age up to the 15–19-year-old group and then decreased with age. All persons positive for HBsAg were positive for anti-HBc; the prevalence of anti-HBc included the percentage of people positive for both HBsAg and anti-HBc, plus the percentage of people positive for only anti-HBc. Although there is a slight possibility that some subjects had only anti-HBs, we considered anti-HBc as the marker of HBV infection.

Age-specific prevalence of HBsAg and anti-HBc among members of the C
HEPATITIS B INFECTION IN FAMILY SETTING

The prevalence of anti-HBc in the C group (80.8 per cent) was significantly higher than the prevalence in the NC group (61.6 per cent). For both groups, the overall prevalence of anti-HBc increased with age up to the 30–39-year-old group and then remained higher than 85 per cent in persons of ages 40 years or older. In all age groups, particularly in the younger ones, anti-HBc was significantly more prevalent in the C group. Odds ratios of infection for members of the C group compared to members of the NC group were calculated. As shown in Table 1, the ratio was highest in the 15–19-year-old group and followed by the 20–29-year old group. These data show that members of families in which there was at least one HBsAg carrier were infected with HBV earlier than the members of families in which there were no HBsAg carriers. The data also suggest that the presence of one or more HBsAg carriers in a family increased the risk of HBV infection remarkably.

To determine the role of HBeAg, the C group was divided into the E group and the NE group. Overall, 171 families (from all three islands) had at least one HBsAg carrier. Among them, 33 had at least one HBsAg carrier with HBeAg. The E group included 13 HBsAg carriers with HBeAg in eight families on Iriomote Island, 13 in nine families on Hateruma Island, and 21 in 16 families on Yonaguni Island. These 47 HBsAg carriers with HBeAg were distributed by age group as follows: 16 in the 0–9 group (88.9 per cent of the 18 HBsAg carriers in this age group), 22 in the 10–19 group (40.0 per cent out of 55), 8 in the 20–29 group (12.5 per cent out of 64), and one in the 30–39 group (3.4 per cent out of 29).

Age-specific prevalences of HBsAg and anti-HBc among members of families with or without HBsAg carriers on three islands in Okinawa, Japan, in 1980

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Carrier families (C)</th>
<th>Non-carrier families (NC)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. tested</td>
<td>HBsAg</td>
<td>Anti-HBc</td>
</tr>
<tr>
<td>0–4</td>
<td>43</td>
<td>8 (18.6)</td>
<td>10 (23.3)</td>
</tr>
<tr>
<td>5–9</td>
<td>69</td>
<td>10 (14.5)</td>
<td>26 (37.7)</td>
</tr>
<tr>
<td>10–14</td>
<td>91</td>
<td>21 (23.1)</td>
<td>55 (60.4)</td>
</tr>
<tr>
<td>15–19</td>
<td>63</td>
<td>34 (54.0)</td>
<td>62 (98.4)</td>
</tr>
<tr>
<td>20–29</td>
<td>107</td>
<td>64 (59.8)</td>
<td>102 (95.3)</td>
</tr>
<tr>
<td>30–39</td>
<td>70</td>
<td>29 (41.4)</td>
<td>67 (95.7)</td>
</tr>
<tr>
<td>40–49</td>
<td>96</td>
<td>42 (43.8)</td>
<td>89 (92.7)</td>
</tr>
<tr>
<td>50–59</td>
<td>82</td>
<td>34 (41.5)</td>
<td>78 (95.1)</td>
</tr>
<tr>
<td>60+</td>
<td>83</td>
<td>25 (30.1)</td>
<td>80 (96.4)</td>
</tr>
<tr>
<td>Total</td>
<td>704</td>
<td>267 (37.9)</td>
<td>569 (80.8)</td>
</tr>
</tbody>
</table>

* a) Because there were some cases in which the odds ratio was infinity modified odds ratios were calculated (11).

*** P<0.001, ** P<0.01, * P<0.05.
Table 2. Age-specific prevalence of HBsAg and anti-HBc among HBsAg carrier families with or without at least one HBeAg-positive HBsAg carrier

<table>
<thead>
<tr>
<th>Age</th>
<th>Families with HBeAg (E&lt;sup&gt;a&lt;/sup&gt;) (n = 33)</th>
<th>Families without HBeAg (NE&lt;sup&gt;b&lt;/sup&gt;) (n = 138)</th>
<th>Odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. tested</td>
<td>HBsAg</td>
<td>Anti-HBc</td>
</tr>
<tr>
<td>0-4</td>
<td>8</td>
<td>7 (87.5)</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>5-9</td>
<td>27</td>
<td>10 (37.0)</td>
<td>24 (88.9)</td>
</tr>
<tr>
<td>10-14</td>
<td>31</td>
<td>17 (54.8)</td>
<td>29 (93.5)</td>
</tr>
<tr>
<td>15-19</td>
<td>24</td>
<td>16 (66.7)</td>
<td>24 (100)</td>
</tr>
<tr>
<td>20-29</td>
<td>36</td>
<td>17 (47.2)</td>
<td>36 (100)</td>
</tr>
<tr>
<td>30-39</td>
<td>13</td>
<td>4 (30.8)</td>
<td>11 (84.6)</td>
</tr>
<tr>
<td>40-49</td>
<td>18</td>
<td>5 (27.8)</td>
<td>18 (100)</td>
</tr>
<tr>
<td>50-59</td>
<td>19</td>
<td>2 (10.5)</td>
<td>17 (89.5)</td>
</tr>
<tr>
<td>60+</td>
<td>6</td>
<td>1 (16.7)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>182</td>
<td>79 (43.4)</td>
<td>172 (94.5)</td>
</tr>
</tbody>
</table>

<sup>a</sup> E: Families with at least one HBsAg carrier with HBeAg.

<sup>b</sup> NE: Families with no HBeAg-positive HBsAg carriers.

<sup>c</sup> +: Because there were some cases in which the odds ratio was infinity modified odds ratios were calculated (11).

*** P < 0.001.
The overall prevalence of HBsAg, however, was not significantly different between
the two groups. In the 0-4, 5-9, and 10-14-year-old groups, prevalences of both
HBsAg and anti-HBc were significantly higher in the E group than in the NE group.
In the 50-59-year-old group, however, HBsAg was more prevalent in the NE group
than in the E group. The odds ratio was highest for the 5-9-year-old group followed
by the 0-4-year-old group. For all the age groups above 15-19, odds ratios were
insignificant.

The E and NE families were divided into two age groups, i.e., 0-14 years and
above 15 years. Prevalences of HBsAg and anti-HBc in the 0-14 age group were
significantly higher in E families (51.5 and 90.9 per cent, respectively) than in NE
families (3.6 and 22.6 per cent) \( (P<0.001) \). In the 15 and over age group, however,
prevalences were lower in E families (38.8 and 96.6 per cent), but the differences
were not significant.

In the age groups below 19 years, the proportion of HBsAg carriers to anti-
HBc-positive individuals was higher for the E group than for the NE group. In
age groups over 20 years, however, this situation was reversed. Seven of the eight
E group members (87.5 per cent) in the 0-4-year-old group were HBsAg carriers,
and there were no children positive for anti-HBc and negative for HBsAg. On the
other hand, only one of the 35 NE group members in the 0-4-year-old group was an
HBsAg carrier. These data suggest that HBsAg carriers with HBeAg provide a
source of HBV infection and that HBeAg is an indicator of high infectivity in families.

DISCUSSION

It has been reported that HBsAg clusters in families (3, 15, 25, 29, 31), and
prevalences of HBV markers are high in families with one or more HBsAg carriers
(3, 4, 8, 10, 20, 25, 27, 31). These findings were based on studies on a small scale,
however. These has never been a family study of hepatitis B infection on a scale as
large as in the present study.

It is well established that the HBV has three distinct antigen-antibody systems:
HBsAg and the antibody to HBsAg (anti-HBs), HBcAg and anti-HBc, and HBeAg
and anti-HBe (1, 9, 14). We found that the prevalence of anti-HBs alone was lower
than the prevalence of anti-HBc alone (11). Furthermore, Perrillo et al pointed out
that low-level anti-HBs reactors without anti-HBc were not reproducibly positive
(19). Anti-HBc, even alone, is a sensitive marker of previous infections (19, 25, 26,
30). In this study, therefore, we determined the prevalence of anti-HBc.

Our finding that the risk of HBV infection in families with at least one HBsAg
carrier was higher than the risk of infection in families with no HBsAg carriers is
consistent with previous studies (3, 4, 8, 10, 20, 25, 27, 31). In addition, we found
that members of families with at least one HBsAg carrier were infected with HBV
earlier in their lives than members of families with no HBsAg carriers.

The following routes of HBV transmission within families have been docu-
menced: mother-to-child (17, 24), father-to-child (18, 29), and sibling-to-sibling
(13). In families on Iriomote Island, one of the three islands studied, we found
cases of possible maternal transmission, but cases of possible sibling-to-sibling transmission were even more common. We analyzed 37 families with at least one HBsAg carrier. In five of the 15 families with HBsAg-positive mother and HBsAg-negative father, one or more HBsAg-positive children were found. An HBsAg-positive child was found in only one of the eight families with a HBsAg-negative mother and HBsAg-positive father. In the remaining 14 families both parents were HBsAg-negative and there was at least one HBsAg-positive child; nine of these families had two or more HBsAg-positive children (12). This study was a cross-sectional survey of carrier and non-carrier families; we could not analyze the mode of intrafamilial HBV transmission or factors influencing HBV transmission, such as family size. A further analysis of HBV transmission in families living on Hateruma and Yonaguni Islands, is underway.

The risk of HBV infection was higher for families in which there were one or more HBeAg-positive members. The risk was especially high for younger members of such families. It is likely that HBsAg carriers with HBeAg are highly infectious in family settings. It is well known that HBeAg is closely related to HBV infectivity (2, 5, 13, 16, 18, 22, 23). The results of the present study agree with these previous findings. For the E group, HBsAg and anti-HBc prevalences were significantly higher in the group below 14 years than in the group above 15 years old. For the NE group, however, the prevalence of HBsAg was higher in the group above 15 years than in the group below 14 years old. This finding may be due to the following reasons: there were many individuals with HBeAg in the group below 14 years, and families with no HBeAg perhaps had HBsAg carriers with HBeAg before.

A large proportion of the members of the carrier family (C) group who were 0–4-years-old and anti-HBc-positive was HBsAg-positive. This applied especially for 0–4-year-old, anti-HBc-positive members of families in which there were no HBeAg-positive persons; all such children were HBsAg carriers. We have already reported that the carrier state developed in children under 4 years of age on Iriomote Island (12). The results obtained in the present study are consistent with our previous findings and the findings of other workers who have reported that age at the first exposure to HBV appears to be the major determinant of antigen persistency (21, 28).

We can draw two conclusions from this study on three islands of Okinawa. First, compared to families in which there were no HBsAg carriers, the members of families in which there were one or more HBsAg carriers had a higher risk of hepatitis B virus infection when young. Second, in family settings, HBsAg carriers with HBeAg were more infectious than HBeAg-negative carriers.

REFERENCES


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