HEPATITIS B SURFACE ANTIGEN DISAPPEARANCE AND HEPATITIS B SURFACE ANTIGEN SUBTYPE: A PROSPECTIVE, LONG-TERM, FOLLOW-UP STUDY OF JAPANESE RESIDENTS OF OKINAWA, JAPAN WITH CHRONIC HEPATITIS B VIRUS INFECTION

NORIHIRO FURUSYO, JUN HAYASHI, YASUNORI SAWAYAMA, YASUHIRO KISHIHARA, AND SEIZABURO KASHIWAGI

Department of General Medicine, Kyushu University Hospital, Fukuoka, Japan

Abstract. To determine the natural course of hepatitis B surface antigen (HBsAg) disappearance in chronic hepatitis B virus (HBV) infection and the factors related to its disappearance, 946 HBsAg carriers in Okinawa, Japan, were prospectively followed for up to 19 years (mean = 9.2 years). The disappearance of HBsAg, as determined by radioimmunoassay (RIA), was observed in 62 (6.6%) and the overall annual disappearance rate was 0.79%/year. Its disappearance was more frequent in 60 (7.4%) of 815 serum samples negative for hepatitis B e antigen (HBeAg) by RIA at entry compared with only two (1.5%) of 131 serum samples that were HBeAg positive by RIA at entry (P < 0.05). Stepwise logistic regression analysis showed that age and HBsAg subtype were significantly associated with HBsAg disappearance (both P < 0.05), and that carriers with subtype adr (odds ratio = 2.87) had an increased probability of clearing HBsAg compared with carriers with subtype adw. Conversely, HBeAg disappearance was earlier in those with the adw subtype than in those with adr. Hepatitis B virus DNA was not detected by the polymerase chain reaction after HBsAg disappearance in any of the 62 from whom it had disappeared. The HBsAg titer, as measured by reverse passive hemagglutination, was related to the time to its disappearance; the higher the titer, the longer the time to disappearance. These findings suggest that HBeAg negativity, a more advanced age, and lower titers of HBsAg are favorable factors for HBsAg disappearance in the natural course of chronic HBV infection. Moreover, HBsAg subtype adr was a predictive factor for HBsAg disappearance, whereas subtype adw was predictive of early HBeAg disappearance.

It has been conservatively estimated that there are 350 million chronic hepatitis B virus (HBV) carriers throughout the world. This virus is a serious problem in many countries since it causes chronic liver disease and hepatocellular carcinoma. Diagnosis is made by the detection of hepatitis B surface antigen (HBsAg) in serum. The disappearance of HBsAg and the appearance of antibody to HBsAg (anti-HBs) have been reported to indicate the clearance of HBV particles and the cessation of hepatocyte injury.

Our laboratory previously reported that the Yaeyama District of Okinawa, Japan was highly endemic for HBV infection, and that the number of newly infected residents has decreased there, as estimated in our long-term study. In another Okinawa study, we found that the rate and age of seroconversion from hepatitis B e antigen (HBeAg) to antibody to HBeAg (anti-HBe) were higher and younger in cases with the HBsAg subtype adw than in those with subtype adr, suggesting that the HBsAg subtype may be closely associated with the HBeAg/anti-HBe status.

Although various investigators have reported the disappearance of HBsAg, there has been no documentation on the relationship between the natural course of chronic HBV infection and the HBsAg subtype. We recently reported the relationship between HBsAg disappearance and its subtype in residents of a small area of Iriomote Island, part of the district studied in this paper. However, an accurate, reliable statistical analysis was impossible because of the small population of chronic HBsAg carriers. To rectify this, we performed a large, long-term, prospective survey that included an analysis of possible predictive factors, in residents with chronic HBV infection in the Yaeyama District of Okinawa, Japan.

Study population. We have surveyed residents of the Yaeyama District of Okinawa, Japan for HBV markers since 1968. Okinawa is in the subtropical zone about 1,000 kilometers south of the main islands of Japan. The Yaeyama District is in the southwestern part of Okinawa near Taiwan and consists of Ishigaki, Hateruma, Iriomote, Kohama, Taketomi, Kuroshima, and Yonaguni Islands. All residents studied were Japanese, and born and raised in this area. We provided free health examinations to all residents. These were announced by distributing written notices to all households. Informed written consent to participate in the study was obtained from each resident or their legal guardian. The protocol of the study was reviewed and approved by the Ethic Committee of Kyushu University Hospital.

Testing for HBV markers has been done on serum samples collected from these residents once a year since 1978. In this prospective study, which excluded patients from renal units and active drug users, 946 HBV carriers (588 males and 358 females) positive for serum HBsAg by radioimmunoassay (RIA) for at least two years were followed for up to 19 years (mean ± SD = 9.2 ± 4.4 years) during the period from 1978 to 1997. At entry, the 946 carriers ranged from less than six months to 83 years of age (mean ± SD = 37.1 ± 16.4 years). No subject had received hepatitis B vaccine or antiviral or immunosuppressive treatments.

We did not test for the serology of human immunodeficiency virus (HIV) in this population. However, the Blood Center of Okinawa prefecture reported no HIV infection in the district studied through 1997.

Hepatitis B surface antigen, HBeAg, and anti-HBe were serially measured in all carriers during follow-up. The HBsAg subtypes were determined from the serum samples.
of HBsAg carriers at the time of entry into this study. The disappearance of HBsAg in chronic HBsAg carriers is defined as persistent absence of HBsAg determined by RIA in three consecutive serum specimens in a period of more than one year.

To determine the state of serological markers and liver dysfunction after disappearance of HBsAg, alanine aminotransferase (ALT) levels were measured, and tests for anti-HBs, antibody to hepatitis B core antigen (anti-HBc), and HBV DNA were performed using only the serum samples from carriers after HBsAg had disappeared. The HBsAg titer was determined using reverse passive hemagglutination (RPHA) in serum samples taken at entry into the study from carriers from whom HBsAg had disappeared. We analyzed the relationship between the titer and the time to HBsAg disappearance.

**Serologic assays.** All serum samples were separated and stored at −20°C until testing for HBsAg, HBeAg, anti-HBs, anti-HBc, HBsAg subtype, and HBV DNA. All samples were tested for HBsAg, HBeAg, anti-HBc, and antibody to hepatitis C virus (anti-HCV).

To confirm its disappearance, HBsAg was detected by RIA (Austria II; Abbott Laboratories, North Chicago, IL). The HBsAg titer was determined using RPHA (MyCell; Institute of Immunology, Tokyo, Japan). The HBsAg subtypes were determined by enzyme immunoassay (EIA) using monoclonal antibodies (HBsAg subtype EIA; Institute of Immunology). The HBeAg and anti-HBe markers were detected by RIA (HBeAg RIA; Abbott Laboratories). The anti-HBs and anti-HBc markers were detected by RIA (AUSAB and Corab, respectively; Abbot Laboratories). Anti-HCV was detected using a second generation EIA (HCV EIA II; Abbott Laboratories).

**Polymerase chain reaction (PCR) for HBV DNA.** The PCR was used for detection of HBV DNA in serum samples after disappearance of HBsAg. Serum samples (100 μl) were digested with protease K. The HBV DNA was extracted with phenol/chloroform, followed by precipitation with ethanol in the presence of ammonium acetate. Two independent sets of oligonucleotide sequences specific to the HBV surface and core regions were synthesized and used as follows. The primer pair within the core gene, \(^{17}\) 5'-CTGGAGGAACGGTGGGAAGGGA-3' (sense primer) and 5'-CTAACATTGAGATTCCCGAGA-3' (anti-sense primer), amplified a 729-basepair segment. The primer pair within the TTAGGGTTAATGTATACC-3' (antisense primer), amplified a 416-basepair segment. The primer pair within the

### RESULTS

The distribution of HBsAg subtypes among carriers was 561 adw (59.3%), 206 adr (21.8%), 12 adwr (1.3%), three ayr (0.3%), one ayr (0.1%), one ayw (0.1%), and 162 (17.1%) subtype not determined. No significant differences by sex were found in the distribution of HBsAg subtypes. Carrier characteristics at entry by subtype are shown in Table 1. The subtype not determined group carriers were significantly different from the detectable subtype group carriers in mean age, age ≥ 50 years, and HBeAg positivity at entry. The overall HBeAg positive rate at entry was 96 (59.3)§. The distribution of HBsAg subtypes among carriers was 561 adw (59.3%), 206 adr (21.8%), 12 adwr (1.3%), three ayr (0.3%), one ayr (0.1%), one ayw (0.1%), and 162 (17.1%) subtype not determined. No significant differences by sex were found in the distribution of HBsAg subtypes. Carrier characteristics at entry by subtype are shown in Table 1. The subtype not determined group carriers were significantly different from the detectable subtype group carriers in mean age, age ≥ 50 years, and HBeAg positivity at entry. The overall HBeAg positive rate at entry was 96 (59.3)§.

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(\(P = 0.0025\), by chi-square test). Positivity for HBeAg at entry was lower in the subtype adw group than in the adr group, but the difference was not statistically significant.

Table 2 shows the age-specific annual HBsAg disappearance rate in HBsAg carriers (person-year method). During a mean ± SD follow-up of 9.2 ± 4.4 years (range = 3–19 years) of 946 HBsAg carriers, HBsAg disappearance was observed in 62 (6.6%) carriers (34 males and 28 females, mean age ± SD at its disappearance = 54.2 ± 14.9 years, range = 24–89 years). The overall annual HBsAg disappearance rate in 946 HBsAg carriers was 0.79%/year. The HBsAg disappearance rate gradually increased with age. The frequency of HBsAg disappearance in carriers 50 years of age and older was 10.7% (39 of 365) and was significantly higher than the 3.9% (23 of 581) observed in the 0–49 years of age group, but the difference was not statistically significant.

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Table 3 shows the distribution of HBsAg disappearance by subtype and HBeAg status. Only two (1.5%) of 131 HBeAg-positive individuals at entry cleared HBsAg, while 60 (7.4%) of 815 HBeAg-negative individuals at entry cleared HBsAg. During follow-up, HBsAg disappearance was always subsequent to HBeAg disappearance. A significant difference between the presence and absence of HBeAg at entry was found (\(P = 0.0206\), by chi-square test). The disappearance of HBsAg was observed in 3.6% of the subtype adw group, 9.7% of the subtype adr group, and 13.0% of the subtype not determined group. Carriers with subtype adr and subtype not determined had a significantly higher frequency of HBsAg disappearance than did subtype adw (adr versus adw; \(P = 0.0015\); subtype not determined versus adw; \(P < 0.0001\), by chi-square test). In HBsAg carriers who were HBeAg negative at entry, similar results were obtained (adr versus adw; \(P = 0.0009\); subtype not determined versus adw; \(P = 0.0001\), by chi-square test).

Figure 1 shows cumulative probabilities of HBeAg and HBsAg disappearance. The time to HBeAg disappearance in individuals with HBsAg subtype adw was shorter than in those with subtype adr, but there was no statistically significant difference (\(P = 0.0801\), by log-rank test). The time to HBsAg disappearance in individuals with subtype adr and those with subtype not determined was significantly different from those with subtype adw (adr versus adw; \(P = 0.0006\); subtype not determined versus adw; \(P < 0.0001\), by log-rank test).

Table 4 shows a stepwise logistic regression analysis done to determine the relationship between the clinical features at entry and disappearance of HBsAg. Age (\(P = 0.0003\)) and HBsAg subtype (\(P = 0.0021\)) were significantly associated with HBsAg disappearance in HBsAg carriers. As age increased, there was a tendency for the probability of HBsAg disappearance to increase. For carriers with subtype adr and subtype not determined, there was an increased probability to clear HBsAg (estimated odds ratio = 2.87 [adr], 2.97 [not determined]) compared to carriers with adw. Negativity for

### Table 2

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of carriers</td>
<td>No. of disappearance cases</td>
<td>ADR</td>
</tr>
<tr>
<td>0–9</td>
<td>6</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>10–19</td>
<td>50</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>20–29</td>
<td>37</td>
<td>1</td>
<td>0.46</td>
</tr>
<tr>
<td>30–39</td>
<td>143</td>
<td>7</td>
<td>0.69</td>
</tr>
<tr>
<td>40–49</td>
<td>138</td>
<td>4</td>
<td>0.29</td>
</tr>
<tr>
<td>50–59</td>
<td>77</td>
<td>10</td>
<td>1.02</td>
</tr>
<tr>
<td>≥60</td>
<td>137</td>
<td>12</td>
<td>0.92</td>
</tr>
<tr>
<td>Total</td>
<td>588</td>
<td>34</td>
<td>0.71</td>
</tr>
</tbody>
</table>

* ADR = annual disappearance rate (person-year method).
† Indicates the age at last follow-up year or the year of HBsAg disappearance of carriers.

### Table 3

Hepatitis B surface antigen (HBsAg) disappearance by subtype and hepatitis B e antigen (HBeAg) in 946 HBsAg carriers living in the Yaeyama District, Okinawa, Japan

<table>
<thead>
<tr>
<th>HBsAg subtype</th>
<th>HBsAg-positive at entry</th>
<th>HBsAg-negative at entry</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of carriers</td>
<td>No. (%) of disappearance cases</td>
<td>No. of carriers</td>
</tr>
<tr>
<td>adw</td>
<td>88</td>
<td>1 (1.1)</td>
<td>473</td>
</tr>
<tr>
<td>adr</td>
<td>41</td>
<td>1 (2.4)</td>
<td>165</td>
</tr>
<tr>
<td>Others†</td>
<td>2</td>
<td>0 (0.0)</td>
<td>15</td>
</tr>
<tr>
<td>Not determined</td>
<td>0</td>
<td>–</td>
<td>162</td>
</tr>
<tr>
<td>Total</td>
<td>131</td>
<td>2 (1.5)</td>
<td>815</td>
</tr>
</tbody>
</table>

* Represents \(P < 0.01\) by chi-square test compared with subtype adw group.
† Consists of 12 adwr, 3 adyr, 1 ayr, and 1 ayw carriers.
‡ Represents \(P < 0.05\) by chi-square test compared with HBeAg-positive group.
HBsAg DISAPPEARANCE IN HBsAg CARRIERS

Figure 1. Cumulative probability of disappearance of hepatitis B e antigen (HBeAg) and hepatitis B surface antigen (HBsAg) by HBsAg subtype in carriers with chronic hepatitis B virus infection in the Yaeyama District of Okinawa, Japan. A, for disappearance of HBeAg, the difference between subtypes adw and adr was $P = 0.0636$ (adw = 88 cases, adr = 41 cases). B, for the disappearance of HBsAg, the differences among subtypes were adr versus adw, $P = 0.0006$; subtype not determined (N.D.) versus adw, $P < 0.0001$; adr versus subtype N.D.; $P = 0.3855$ (adw = 561 cases; adr = 206 cases; others = 17 cases; N.D. = 162 cases).

HBeAg at entry was not statistically significant in this analysis ($P = 0.0765$ compared with positivity for HBeAg at entry).

The RPHA assay was used to determine the HBsAg titer in serum samples that were obtained at entry into the study from 29 of 62 carriers who cleared HBsAg (Figure 2). There was a significant, inverse, weak correlation between HBsAg titer by RPHA before HBsAg disappearance and time to HBsAg disappearance by RIA ($r = -0.509$, $P = 0.0042$). The higher the HBsAg titer, the longer the time to HBsAg disappearance. The HBsAg titer of carriers with subtype not determined was lower than that of the detectable subtypes, and only the subtype not determined was found at titers less than $2^2$.

Table 5 shows the serologic profiles after HBsAg disappearance in 62 carriers who cleared HBsAg. Of the 62, 55 (88.7%) had anti-HBe, but none had HBeAg and 52 (83.9%) of the 62 were anti-HBs positive. Hepatitis B virus DNA was not detected by the PCR in any of the 62, including the 10 who did not develop detectable anti-HBs. The mean ALT level of the 62 carriers with HBsAg disappearance was 20.3 IU/L. All but three had normal ALT levels (< 36 IU/L). Three with abnormal elevations of ALT levels had a history of alcohol consumption of 108.0–162.0 grams/day.

Only 10 (1.1%) of 946 were positive for anti-HCV, none of whom cleared HBsAg during follow-up.

### Table 4
Factors contributing to hepatitis B surface antigen (HBsAg) disappearance in HBsAg carriers living in the Yaeyama District, Okinawa, Japan: results of a stepwise logistic regression analysis*

<table>
<thead>
<tr>
<th>Factors</th>
<th>Category</th>
<th>Coefficient</th>
<th>Coefficient/standard error</th>
<th>Odds ratio†</th>
<th>95% Confidence interval of odds ratio</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age‡</td>
<td></td>
<td>0.030</td>
<td>3.57</td>
<td>1.03</td>
<td>1.01–1.05</td>
<td>0.0003</td>
</tr>
<tr>
<td>HBsAg subtype§</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.0021</td>
</tr>
<tr>
<td>adr</td>
<td></td>
<td>1.054</td>
<td>3.19</td>
<td>2.87</td>
<td>1.50–5.49</td>
<td></td>
</tr>
<tr>
<td>Not determined</td>
<td></td>
<td>1.075</td>
<td>3.18</td>
<td>2.93</td>
<td>1.51–5.68</td>
<td></td>
</tr>
<tr>
<td>Others¶</td>
<td></td>
<td>0.495</td>
<td>0.46</td>
<td>1.64</td>
<td>0.20–13.30</td>
<td></td>
</tr>
</tbody>
</table>

* Constant = $-4.475$.
† Odds ratio was defined as the ratio of the odds for carriers with HBsAg disappearance to carriers with HBsAg persistently positive.
‡ Continuous data (years).
§ Compared with carriers with subtype adw.
¶ Consists of 12 adwr, 3 adyr, 1 ayr, and 1 ayw carriers.
The disappearance of HBsAg has been reported in several studies from non-Asian countries, where HBV infection usually occurs in adults and from Asian countries, where HBV infection is hyperendemic and usually occurs during early childhood through either perinatal or child-to-child transmission. Annual rates of HBsAg disappearance have been estimated to be from 0.5%/year to 1.7%/year. We found the rate of HBsAg disappearance to be within the reported range at 0.79%/year in HBsAg carriers in Okinawa, Japan, an area highly endemic for HBV infection. Although there was a higher frequency (10.7%) of HBsAg disappearance in a report of 65 cases of chronic hepatitis B, our data, including these previous reports, showed that natural disappearance of HBsAg was an unusual event in subjects with chronic HBV infection.

The disappearance of HBsAg was frequently found in carriers 50 years of age and older who were HBeAg negative at entry into the study. This was consistent with the results of a study in Taiwan, an area geographically close to the district we studied. Because low HBeAg positivity was found in carriers 50 years of age and older at entry into the study, the age factor might be overshadowed by the HBeAg factor in determining disappearance of HBsAg. In fact, our stepwise logistic regression analysis showed age to be the most important factor in HBsAg disappearance, and that HBeAg negativity was not a significant factor. The chronic HBV carrier state is generally thought to develop when exposure to HBV occurs mainly at an early age. We previously reported that the carrier state occurred in children less than four years of age in the district studied. Most individuals in this study must have been exposed at such an early age and became carriers of HBsAg. Therefore, the age of the HBsAg carrier and the interval from acquisition of infection could be viewed in the same light. However, from the outcome of present study, we cannot determine that HBsAg disappearance is a time-related phenomenon because we cannot document when carriers were infected.

Low levels of HBsAg expression are also a favorable factor in the disappearance of HBsAg because the HBsAg titer decreased gradually until the disappearance of HBsAg. Our study showed that the not determined HBsAg subtype carriers most frequently lost HBsAg, and that these carriers had lower HBsAg titers before its disappearance than did other detectable subtype carriers. These observations indicate that a low HBsAg titer is likely to be a favorable factor for disappearance of HBsAg in chronic HBV infection. The results of the RPHA may imply that the HBsAg titer gradually decreases until it is no longer detectable. Therefore, we defined HBsAg disappearance by the results of the RIA in this study.

Although we found no significant difference between the sexes regarding HBsAg disappearance, Alward and others reported that there was a significantly higher percentage of women who cleared HBsAg than men. It is well documented that HBsAg is more prevalent in men than in women, and that female HBsAg carriers clear HBeAg more rapidly than male carriers. Our laboratory has also reported that the number of liver function abnormalities was significantly higher in male carriers than in female carriers. These findings are related to genetic differences in the immune response between the sexes.

Geographic distribution of HBsAg subtypes and their relationship to epidemiologic factors have attracted a great deal of attention. In the Japanese population living in Japan, two main subtypes have been found: adr and adw. Negativity for HBeAg usually indicates cessation of HBV replication and represents a later stage of chronic HBV infection. Therefore, HBeAg-positive carriers may go through an HBeAg-negative stage before they clear HBsAg. Our laboratory previously reported that HBsAg carriers with subtype adw tended to seroconvert from HBeAg to anti-HBe at a higher rate and at a younger age than those with subtype adr in the Yaeyama District. This was confirmed by the cumulative probability of HBeAg disappearance in our long-term follow-up study. Conversely, subtype adr was a favorable factor for HBsAg disappearance in chronic HBV infection compared with subtype adw in a stepwise logistic regression analysis. These results raise the question of whether or not the mechanism of HBsAg disappearance differs from that of HBeAg disappearance. The disappearance of HBeAg is caused by a point mutation of the precore region of HBV DNA. In carriers from whom HBsAg disappeared from the sera, HBV DNA sequence analysis of the complete viral genome identified numerous mutations in the envelope region of the viral genes obtained from the liver. These findings of genetic variability may be related to HBsAg secretion into the serum and HBsAg disappearance from serum.

The disappearance of HBsAg and the appearance of anti-HBs in sera have been reported to indicate the clearance of HBV. We found that HBV DNA was not detectable in the serum of any carrier who showed disappearance of HBsAg, even in those who did not develop detectable anti-HBs. The detection of anti-HBs in carriers with HBsAg disappearance is not definitive evidence that they have recovered from HBV infection because concurrence of HBsAg and anti-HBs was observed in 26.1% of the HBsAg carriers in this district. Although the PCR assay is exquisitely sensitive, extremely low copy numbers of HBV DNA (< 50/ml) can go undetected in serum samples. Therefore, we cannot conclusively state that HBV DNA completely disappeared from the serum of the carriers in whom serum HBsAg disappeared. Several investigators reported that HBV DNA was detectable by PCR in hepatocytes of HBsAg carriers as long as five years after disappearance of HBsAg from sera. These findings suggest that the disappearance of HBsAg does not necessarily indicate termination of chronic HBV infection.
Our study did not include either histologic data or HBV DNA detection data from the liver of any carriers with disappearance of HBsAg. Therefore, these individuals should be followed carefully because of the risk of subsequent development of cirrhosis and hepatocellular carcinoma.

There are several reports suggesting that HCV superinfection might have suppressed HBV replication. The laboratory has reported a low prevalence of HCV infection in the district studied. The present study showed that no anti-HCV-positive carriers cleared HBsAg, but there was no evidence of HBsAg disappearance influenced by HCV infection because of the very small population with HCV superinfection.

In conclusion, HBsAg disappearance was an unusual event in HBsAg carriers of Okinawa, Japan. Negativity for HBeAg, an age greater than 50, and low titers of HBsAg were favorable factors for disappearance of HBsAg in the natural course of chronic HBV infection. Moreover, HBsAg subtype adr was a predictive factor for disappearance of HBsAg, whereas subtype adw was predictive of early disappearance of HBsAg. In addition, HBsAg disappearance was an unusual event in HBsAg carriers of Okinawa, Japan. Negativity for HBeAg, an age greater than 50, and low titers of HBsAg were favorable factors for disappearance of HBsAg in the natural course of chronic HBV infection. Moreover, HBsAg subtype adr was a predictive factor for disappearance of HBsAg, whereas subtype adw was predictive of early disappearance of HBsAg.

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Authors’ address: Norihiro Furusyo, Jun Hayashi, Yasunori Sawamuya, Yasuhiro Kishihara, and Seizaburo Kashiwagi, Department of General Medicine, Kyushu University Hospital, Higashi-ku, Fukuoka 812-8582, Japan.

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