

Original Article

Prevalence and Outcomes of Acute Hepatitis B in Okayama, Japan, 2006-2010

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Hepatitis B virus (HBV) is one of the major viruses causing acute hepatitis. Recently, the incidence of acute hepatitis with genotype A has been increasing in Japan. The aim of this study was to investigate acute hepatitis B (AHB) in Okayama prefecture, with special attention to HBV genotype A. AHB patients who visited one of 12 general hospitals in Okayama prefecture between 2006 and 2010 were retrospectively analyzed. Over the course of the study period, 128 patients were diagnosed with AHB. Sexual transmission was supposed in the majority of patients (78 patients, 61%), including 59 (76%) having sex with heterosexual partners. The genotypes of HBV were assessed in 90 patients (70%), of whom 27 patients were infected with genotype A, 5 with genotype B, and 58 with genotype C. The prevalence of genotype A was significantly higher among male patients (28.7%), aged 20-29 (35.6%, $p < 0.01$), among men who had sex with men (100%, $p < 0.005$), and among patients having sex with unspecified partners (44.8%, $p < 0.005$). Genotype A was not a significant factor associated with delayed HBsAg disappearance. Caution should be exercised with regard to sexually transmissible diseases in order to slow the pandemic spread of AHB due to genotype A.

Key words: acute hepatitis, hepatitis B virus

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Hepatitis B virus (HBV) is one of the major viruses causing acute hepatitis. In Japan, the causative viruses during the 1990s were the HBV

genotypes B and C [1]. Recently, however, acute hepatitis due to HBV genotype A has been increasing in large metropolitan areas such as Tokyo or Osaka in Japan, where it is assumed to have been imported from outside Japan [2]. When adults are infected with HBV, acute hepatitis due to HBV genotypes B and C can generally be cured, while 10% of acute hepatitis cases due to HBV genotype A become chronic [3]. The incidence of chronicity is especially high in patients co-infected with HBV and human immunodeficiency virus (HIV).

Among hepatitis cases in Japan, that portion with acute viral hepatitis due to HBV genotype A was 6.0% between 1991 and 1996 but has expanded since 2000, to reach 52% in 2008 [4]. The Ministry of Health, Labor and Welfare has started an epidemiological investigation of the prevalence of acute or chronic hepatitis due to HBV genotype A, undertaken by a study group on the natural history of HBV genotype A. The aim of the present study was to investigate acute hepatitis due to HBV in Okayama prefecture, with special attention to HBV genotype A.

Materials and Methods

Patients. There are 12 general hospitals in Okayama prefecture that possess 300 or more beds for in-patient care. All patients who visited one of these hospitals and had a diagnosis of acute hepatitis B (AHB) between 2006 and 2010 were retrospectively analyzed. AHB was diagnosed by the results of elevated titer of anti-IgM HBc antibody and the exclusion of patients who may have had chronic HBV infection. Patients with drug-induced liver injury, alcoholic liver injury and autoimmune hepatitis were excluded from the study. Information regarding the cause and place of infection, HBV genotype, the positivity of the anti-HIV antibody, and the use of nucleotide analogues in the treatment of acute hepatitis, was collected from all patients. The study was performed in accordance with the Helsinki Declaration and was approved by the ethical committees of all participating institutions.

Statistical analysis. Data are expressed as means \pm standard deviations. Patient characteristics were compared among groups using the Mann-Whitney U test or Kruskal-Wallis test. Factors associated with the presence of Hepatitis B surface antigen (HBsAg) 12 months after the diagnosis (*i.e.*, persis-

tence) were analyzed by stepwise logistic regression analysis. Negativity of HBsAg was presumed by using the Kaplan-Meier method, and the results among groups were compared with the log rank test. *P* values < 0.05 were considered to indicate significance.

Results

Patient characteristics of the patients with acute hepatitis B.

A total of 128 patients were diagnosed with AHB at the 12 participating hospitals between 2006 and 2010; the incidence of AHB was between 20 and 30 cases annually (Fig. 1). Eighty-seven patients (68%) were male, and the peak age was between 20 and 29 (45 patients, 35%). Ten patients were 60 or older. Sexual transmission had caused the viral infection in the majority of patients (78 patients, 61%), including 59 patients (76%) having sex with heterosexual partners and 4 male patients getting infected from homosexual partners. Forty-two patients got infected from a specified partner (54%), and 9 patients from non-Japanese partners (12%). Tattooing and needle stick accidents were suspected as the causes of viral infection for one and 4 patients, respectively. The places of viral infection were somewhere in Okayama prefecture for 31 patients (40%), other places than Okayama in Japan for 10 patients (13%), and Southeast Asian countries during travels for 8 patients (10%). Anti-hepatitis C virus antibody was tested for in 124 patients (97%), and 3 patients had positive results, while anti-HIV antibody was

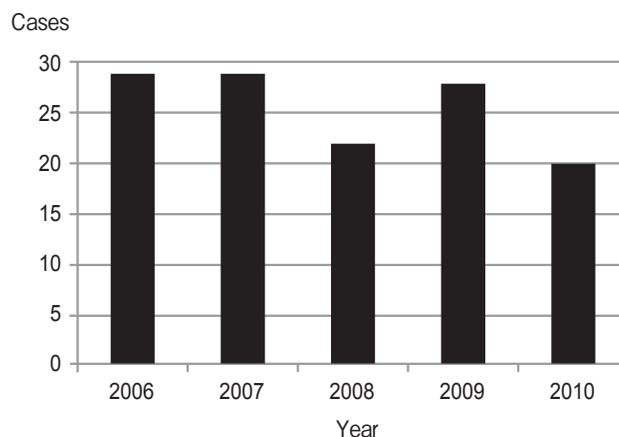


Fig. 1 Annual incidence of AHB between 2006 and 2010. The incidence of AHB was between 20 and 30 annually between 2006 and 2010.

examined in only 68 patients (53%), with positive results for 2 patients. One male patient in his 20s may have been infected by sex with an unspecified female partner. His HBV genotype was not assessed. The other was a male in his 20s who had sex with unspecified men in Fukuoka prefecture, and got infected with HBV genotype A.

Prevalence of HBV genotype A in patients with AHB. As shown in Fig. 2, the genotypes of HBV were assessed in 90 patients (70%); 27 patients

were infected with HBV genotype A (21%), 5 with HBV genotype B (4%), and 58 with HBV genotype C (45%). The percentages of HBV genotype A did not change much over the 5-year study period. The prevalence of HBV genotype A was significantly higher among male patients (25 patients, 28.7%) than females (2 patients, 4.9%, $p < 0.005$), among those aged 20–29 (16 patients, 35.6%, $p < 0.01$), among men who had sex with men (4 patients, 100%, $p < 0.005$), and among patients having sex with unspecified

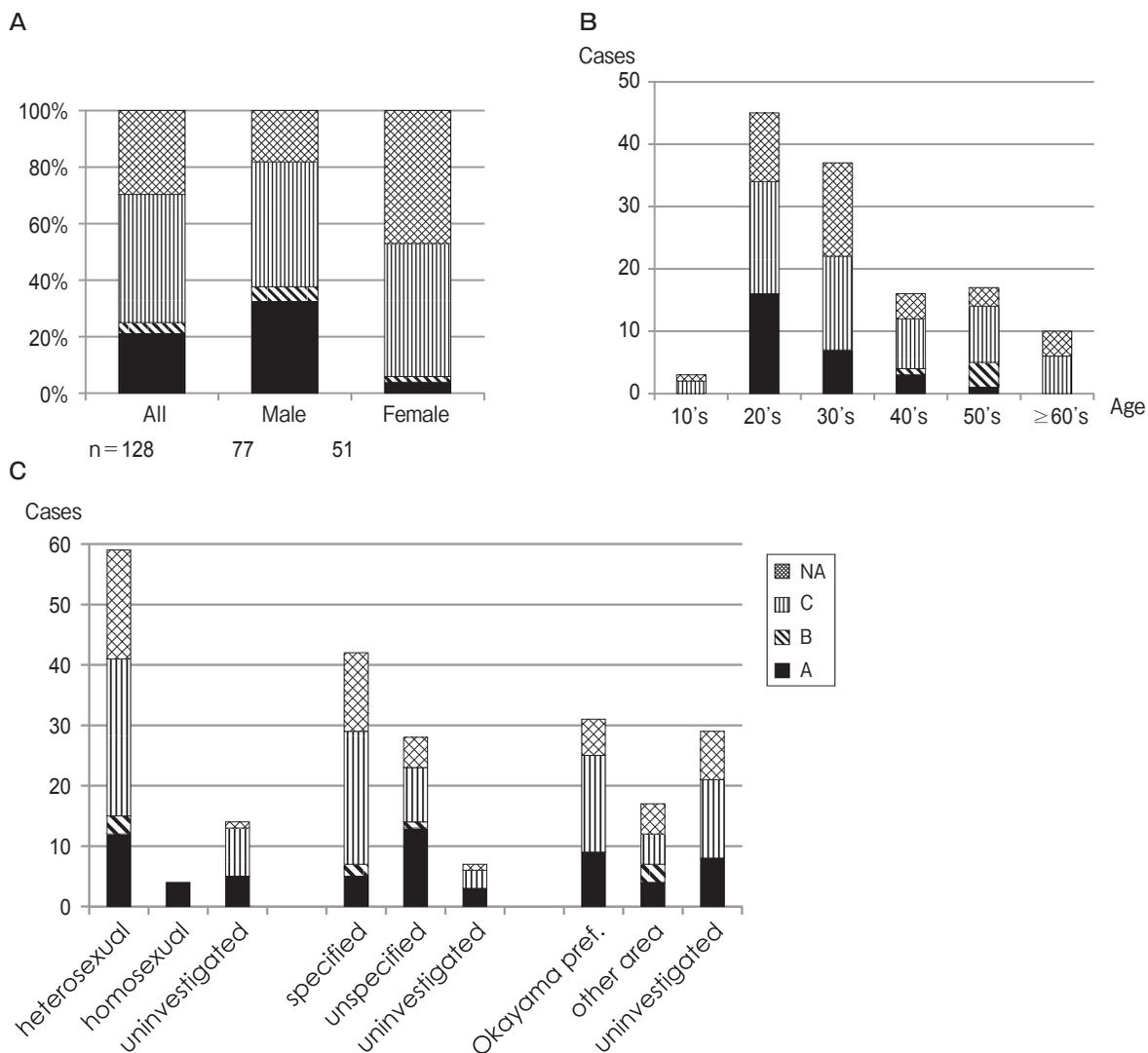


Fig. 2 Comparison of patient characteristics. HBV genotype A, black; B, slashed; C, striped; not analyzed, meshed. The prevalence of HBV genotype A was significantly higher among male patients (28.7%) than females (4.9%, $p < 0.005$, **A**), and in those aged 20–29 (35.6%, $p < 0.01$, **B**). All the patients among the men who had sex with men developed acute hepatitis with HBV genotype A (100%, $p < 0.005$, **C**). Among the patients having sex with unspecified partners and with acute hepatitis, half (44.8%) had HBV genotype A ($p < 0.005$, **C**). HBV genotype A transmission was found to occur both within and outside of Okayama prefecture.

partners (13 patients, 44.8%, $p < 0.005$). About half of the patients (9 patients) with HBV genotype A got infected in Okayama prefecture. These results suggest that HBV genotype A is already prevalent in Okayama prefecture. There were no significant differences in clinical characteristics such as total bilirubin, alanine aminotransferase, or prothrombin time among the patient groups with the different HBV genotypes.

Negativity of HBs antigen. HBsAg became negative in all cases, as shown in Fig. 3A. The median time for negative testing after the initial diagnosis was 4 months; the maximum time was 24 months. Factors associated with negativity of HBsAg within 6 months after diagnosis were investigated but no significant factor was found. Some patients with HBV genotype A achieved negative HBsAg more slowly than those with HBV genotype B or C, but this difference was not significant (Fig. 3B, $p = 0.20$).

A notification at a health center. According to the infectious diseases control law of Japan in 1999, acute hepatitis due to HBV has been classified as a category V infectious disease, with the diagnosis requiring reports to the local public health center for all cases within 1 week. Despite this requirement the number of notifications made by institutions in Okayama from 2006 to 2010 was only 36.

Discussion

We retrospectively investigated AHB cases in Okayama prefecture from 2006 to 2010, and have summarized the characteristics of the patients with HBV genotype A. Though the analysis of HBV genotype was not covered by Japanese national health insurance until 2011, 70% of HBV patients were analyzed for genotype. The most common genotype remains genotype C, but the second most common in Okayama prefecture has become genotype A, replacing genotype B.

The transmission route of genotype A HBV in recent years has included sexual transmission from a committed, non-foreign heterosexual partner as well as that from homosexual, foreign and unspecified heterosexual partners [5]. It is noteworthy that a similar pattern has appeared in Okayama prefecture, reflecting the pandemic spread of HBV genotype A to the general population from the specific groups of men who have sex with men.

As far as our investigations of AHB diagnosed within Okayama prefecture, all patients eventually achieved HBsAg negativity, with HBsAg positivity at 6 months after diagnosis found in only 21% of patients. Delayed HBsAg disappearance was observed in some patients with AHB due to HBV genotype A,

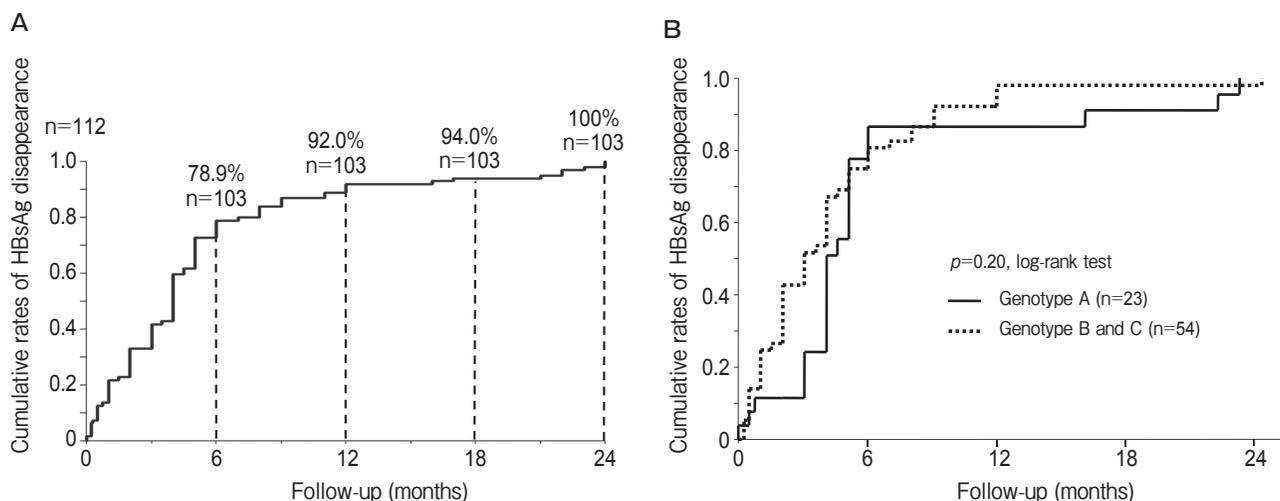


Fig. 3 Cumulative rates of serum HBsAg disappearance. **A**, shows cumulative rates of serum HBsAg disappearance. The median persistence of HBsAg was 4 months after diagnosis. Eight percent of patients retained HBsAg positivity for more than 12 months. **B**, shows the cumulative rates of HBsAg disappearance by HBV genotypes. There was no significant difference in the rates of HBsAg disappearance between the patients with HBV genotype A and others. HBV genotype A, solid line; HBV genotype B and C, dotted line.

as compared with those due to HBV genotype B or C. Though Ito *et al.* reported that AHB due to HBV genotype A was associated with viral persistence [6], our data for that trend were not statistically significant. This might be due to the small number of patients in our study and slightly insufficient follow-up.

In the circumstance of chronic persistence, reporting to a health center is especially important for national surveillance. Clinicians should take care of this responsibility.

In conclusion, a retrospective study of AHB diagnosed in Okayama between 2006 and 2010 was undertaken. The majority of patients with AHB were infected with the HBV genotype C, although it was observed that AHB due to HBV genotype A in Okayama prefecture was now being contracted through sex with heterosexual partners. Caution regarding sexually transmissible diseases is needed to prevent the pandemic spread of AHB due to HBV genotype A.

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