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Risk Factors for Long-Term Persistence of Serum Hepatitis B Surface Antigen Following Acute Hepatitis B Virus Infection in Japanese Adults

Kiyoaki Ito,[1,13*] Hiroshi Yotsuyanagi,[2*] Hiroshi Yatsuhashi,[3] Yoshiyasu Karino,[4] Yasuhiro Takikawa,[5] Takafumi Saito,[6] Yasuji Arase,[7] Fumio Imazeki,[8] Masayuki Kurosaki,[9] Takeji Umemura,[10] Takafumi Ichida,[11] Hidenori Toyoda,[12] Masashi Yoneda,[13] Eiji Mita,[14] Kazuhide Yamamoto,[15] Kojiro Michitaka,[16] Tatsuji Maeshiro,[17] Junko Tanuma,[18] Yasuhito Tanaka,[19] Masaya Sugiyama,[1] Kazumoto Murata,[1] Naohiko Masaki,[1] and Masashi Mizokami,[1] and the Japanese AHB Study Group

The proportion of patients who progress to chronicity following acute hepatitis B (AHB) varies widely worldwide. Moreover, the association between viral persistence after AHB and hepatitis B virus (HBV) genotypes in adults remains unclear. A nationwide multicenter study was conducted throughout Japan to evaluate the influence of clinical and virological factors on chronic outcomes in patients with AHB. For comparing factors between AHB patients with viral persistence and those with self-limited infection, 212 AHB patients without human immunodeficiency virus (HIV) coinfection were observed in 38 liver centers until serum hepatitis B surface antigen (HBsAg) disappeared or a minimum of 6 months in cases where HBsAg persisted. The time to disappearance of HBsAg was significantly longer for genotype A patients than that of patients infected with non-A genotypes. When chronicity was defined as the persistence of HBsAg positivity for more than 6 or 12 months, the rate of progression to chronicity was higher in patients with genotype A, although many cases caused by genotype A were prolonged cases of AHB, rather than chronic infection. Multivariate logistic regression analysis revealed only genotype A was independently associated with viral persistence following AHB. A higher peak level of HBV DNA and a lower peak of alanine aminotransferase (ALT) levels were characteristics of AHB caused by genotype A. Treatment with nucleotide analogs (NAs) did not prevent progression to chronic infection following AHB overall. Subanalysis suggested early NA initiation may enhance the viral clearance. *Conclusion*: Genotype A was an independent risk factor for progression to chronic infection following AHB. Our data will be useful in elucidating the association between viral persistence after AHB, host genetic factors, and treatment with NAs in future studies. (HEPATOLOGY 2014;59:89-97)

Abbreviations: AHB, acute hepatitis B; ALT, alanine aminotransferase; anti-HBc, antibody to hepatitis B core antigen; anti-HBs, antibody to HBsAg; HBeAg, hepatitis B e-antigen; CLIA, chemiluminescent enzyme immunoassay; EIA, enzyme immunoassay; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IgM, immunoglobulin M; anti-HBe, antibody to HBeAg; NAs, nucleotide analogs; RPHA, reverse passive hemagglutination.

From the [1]The Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, Ichikawa, Japan; [2]Department of Internal Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, Japan; [3]Clinical Research Center, NHO Nagasaki Medical Center, Nagasaki, Japan; [4]Department of Gastroenterology, Sapporo Kosei General Hospital, Sapporo; [5]First Department of Internal Medicine, Iwate Medical University, Morioka, Japan; [6]Department of Gastroenterology, Yamagata University School, Yamagata, Japan; [7]Department of Hepatology, Toranomon Hospital, Tokyo, Japan; [8]Department of Medicine and Clinical Oncology, Chiba University, Graduate School of Medicine, Chiba, Japan; [9]Division of Gastroenterology and Hepatology, Musashino Red Cross Hospital, Tokyo, Japan; [10]Department of Medicine, Shinshu University School of Medicine, Matsumoto, Japan; [11]Department of Gastroenterology and Hepatology, Juntendo University Shizuoka Hospital, Shizuoka, Japan; [12]Department of Gastroenterology, Ogaki Municipal Hospital, Ogaki, Japan; [13]Department of Gastroenterology, Aichi Medical University School of Medicine, Nagakute, Japan; [14]National Hospital Organization Osaka National Hospital, Osaka, Japan; [15]Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Okayama, Japan; [16]Department of Gastroenterology, Ehime University Graduate School of Medicine, Toon, Japan; [17]First Department of Internal Medicine, University Hospital, Faculty of Medicine, University of the Ryukyu, Okinawa, Japan; [18]AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan; [19]Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.

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Hepatitis B virus (HBV) infection is one of the most common persistent viral infections in humans. Approximately 2 billion people worldwide have been exposed to HBV and 350 million of them remain persistently infected.[1] The incidence of HBV infection and the patterns of transmission vary greatly worldwide among different population subgroups.[2] In Western countries, chronic HBV infection is relatively rare and acquired primarily in adulthood by way of sexual transmission or the use of injectable drugs. Meanwhile, in Asia and most of Africa, the majority of infections are the result of transmission from an infected mother to her newborn. However, very few studies of acute hepatitis B (AHB) in adults have been reported.

HBV genomic sequences vary worldwide and have been classified into at least eight genotypes (A through H) based on an intergroup divergence of 8% or more over the complete nucleotide sequence.[3,4] These genotypes have distinct geographic distributions.[5-7] In particular, genotype A is predominant in Northwestern Europe, the United States, Central Africa, and India.[8,9] The Japanese have been infected with genotypes B and C since prehistoric times.[10] Recently, many lines of evidence have revealed among the Japanese an increase in acute infection with HBV genotype A following sexual transmission.[11,12] As a result of this increasing transmission of genotype A, the distribution of HBV genotypes in Japan clearly differs among patients with acute and chronic infections.[13] Moreover, recent studies suggest that acute infection with HBV genotype A may be associated with an increased risk of progression to persistent infection.[15] Indeed, the prevalence of HBV genotype A in chronic hepatitis B patients doubled in Japan between 2000-2001 and 2005-2006 (1.7% versus 3.5%).[11]

Human immunodeficiency virus (HIV)-1 infection results in an immunodeficient state, with the virus sharing routes of transmission with HBV. HIV-related immunodepletion influences the natural history of HBV infection, and epidemiological studies have revealed that HIV-positive patients are more likely to have a prolonged acute illness following HBV infection and lower rates of hepatitis B e-antigen (HBeAg) clearance.[16] Therefore, in this study patients with coinfection of HIV were excluded to examine the influence of HBV genotype directly without the confounding influence of HIV.

From 2005 to 2010, a multicenter cohort study was conducted throughout Japan on 212 patients with AHB. The aim of this cohort study was to assess the influence of clinical and virological factors, including HBV genotypes and treatment with nucleotide analogs (NAs), on AHB patients who became persistently infected.

Patients and Methods

Patients With AHB. The multiple-source cohort included 212 randomly selected AHB patients without coinfection of HIV. From 2005 through 2010, the study participants were recruited from 38 liver centers throughout Japan. The cohort included patients who were admitted to the hospital because of AHB and who visited the hospital every month after being discharged. The diagnosis of AHB was contingent on the rapid onset of clinical symptoms accompanied by elevated serum alanine aminotransferase (ALT) levels, the detection of serum hepatitis B surface antigen (HBsAg), and a high-titer antibody to hepatitis B core antigen (anti-HBc) of the immunoglobulin M (IgM) class. Patients with initial high-titer anti-HBc (>10.0 S/CO) were diagnosed as having an exacerbation of chronic hepatitis B and were excluded. If the patient had been tested previously, the absence of serum HBsAg and anti-HBc before admission was verified from the medical record to discriminate a new infection from an acute exacerbation of a persistent infection. Patients with acute hepatitis A, hepatitis C, and drug- or alcohol-induced acute hepatitis were also excluded; hepatitis D virus infection was not determined because of its extreme rarity in Japan. The study protocol conformed to the 1975 Declaration of

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**These authors contributed equally to this work.*

Address reprint requests to: Masashi Mizokami, M.D., Ph.D., Research Center for Hepatitis and Immunology, National Center for Global Health and Medicine, 1-7-1, Konodai, Ichikawa 272-8516, Japan. E-mail:mmizokami@hospk.ncgm.go.jp; fax: +81-(0)47-375-4766.

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Table 1. Characteristics of Patients With Genotype A or a Non-A Genotype Acutely Infected With Hepatitis B Virus

Features	Genotype A (n = 107)	Non-A Genotypes (n = 105)*	*P* Value
Age (years)	36.3 ± 12.0	40.7 ± 14.3	0.032
Male sex	102 (95.3)	75 (71.4)	<0.001
HBeAg positive	104 (97.2)	79 (75.2)	<0.001
ALT (IU/L)	1210 ± 646	2225 ± 2851	0.045
Total bilirubin (mg/dL)	9.9 ± 9.4	7.5 ± 6.7	0.115
HBV DNA (log copies/mL)	7.0 ± 1.5	5.8 ± 1.5	<0.0001
Duration until disappearance of HBsAg (month)	6.7 ± 8.5	3.4 ± 6.5	<0.0001
Persistence of HBsAg positivity more than 6 months	25 (23.4)	9 (8.6)	0.003
Persistence of HBsAg positivity more than 12 months	8 (7.5)	1† (0.9)	0.018
Sexual transmission	81/84 (96.4)‡	71/79 (89.9)§	0.095
Treatment with NAs	61 (57.0)	42 (40.0)	0.013

Data are presented as n (%), mean ± standard deviation. HBV, hepatitis B virus; HBeAg, hepatitis B e-antigen; ALT, alanine aminotransferase; NAs, nucleotide analogs.

*Non-A genotypes include genotypes B, C, D, F and H (n = 25, 77, 1, 1, and 1, respectively).

†One patient had genotype C.

‡Transmission routes were unknown for 23 patients.

§Transmission routes were unknown for 26 patients.

Helsinki and was approved by the Ethics Committees of the institutions involved. Every patient gave informed consent for this study.

Serological Markers of HBV Infection. HBsAg, HBeAg, antibodies to HBsAg (anti-HBs), HBeAg (anti-HBe), and HBcAg, and anti-HBc of the IgM class were tested by a chemiluminescent enzyme immunoassay (CLIA) by ARCHITECT (Abbott Japan, Tokyo, Japan). HBV DNA measurements were performed using a real-time polymerase chain reaction (PCR) assay (Cobas TaqMan HBV Auto; Roche Diagnostics, Tokyo, Japan).

Genotyping of HBV. The six major HBV genotypes (A through F) were determined serologically by enzyme immunoassay (EIA) using commercial kits (HBV GENOTYPE EIA; Institute of Immunology, Tokyo, Japan). This method is based on the pattern of detection by monoclonal antibodies of a combination of epitopes on preS2-region products, which is specific for each genotype.[17,18] Samples for which EIA could not determine the genotype were examined by direct sequencing of the pre-S2/S gene, followed by phylogenetic analysis.

Treatment With NAs. Treatments with NAs were performed using lamivudine or entecavir for more than 3 months. The individual clinicians determined if NAs were administered to patients, and when the treatment was to be started. The time to onset of treatment with NAs was measured in days from onset of AHB.

Statistical Analysis. Categorical variables were compared between groups by the chi-squared test and noncategorical variables by the Mann-Whitney *U* test. A *P* value less than 0.05 was considered significant. Multivariate analysis was performed using a backward stepwise logistic regression model to determine independent factors for viral persistence following AHB. Variables in the multivariate analysis were selected based on variables that were marginally significant with $P < 0.1$ in univariate analysis. Maintenance of HBsAg positivity was analyzed using the Kaplan-Meier method and significance was tested with the log-rank test. STATA Software (StataCorp, College Station, TX) v. 11.0 was used for analyses.

Results

Comparison of Characteristics Between Genotype A and Non-A Genotype AHB Patients. A total of 107 AHB patients (50.5%) were infected with genotype A while 105 AHB patients (49.5%) were infected with non-A genotypes, including genotypes B (25 [11.8%]), C (76 [35.8%]), D (1 [0.5%]), F (1 [0.5%]), and H (1 [0.5%]). Compared to those infected with non-A genotypes, genotype A patients were significantly younger (36.3 ± 12.0 versus 40.7 ± 14.3 years, $P = 0.032$), predominantly men (95.3% versus 71.4%, $P < 0.001$), and more frequently positive for HBeAg (97.2% versus 75.2%, $P < 0.001$). Moreover, genotype A patients had a lower peak ALT levels (1,210 ± 646 versus 2,225 ± 2,851 IU/L, $P = 0.045$) and a higher peak level of HBV DNA (6.7 ± 8.5 versus 3.4 ± 6.5 log copies/mL, $P < 0.0001$). A significantly higher percentage of genotype A patients were treated with NAs (57% versus 40%, $P = 0.013$). These data are summarized in Table 1.

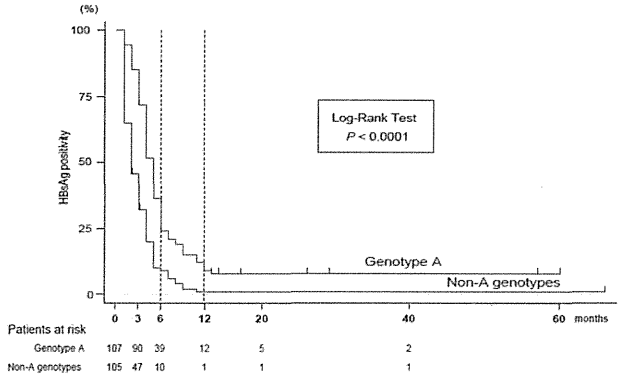

Fig. 1. Comparison of the cumulative proportion of AHB patients maintaining HBsAg positivity between genotype A and non-A genotypes, analyzed using the Kaplan-Meier test. $P < 0.0001$, genotype A: red line, non-A genotypes: blue line.

Cumulative Maintenance of HBsAg Positivity During Follow-up in Patients With Genotype A and Non-A Genotypes. In the patients infected with genotype A and non-A genotypes, the mean durations of HBsAg positivity maintenance were 6.7 ± 8.5 and 3.4 ± 6.5 months, respectively ($P < 0.0001$; Table 1, Fig. 1). For 6 months after AHB onset, the number of patients with genotype A and non-A genotypes maintaining HBsAg positivity were 39/107 (36.4%) and 10/105 (9.5%), respectively ($P < 0.001$). However, in many patients HBsAg disappeared between 7 and 12 months after AHB onset; that is, HBsAg disappeared in 31/107 (29.0%) of patients with genotype A and in 9/105 (8.6%) of patients with non-A genotypes during this time period. However, in some patients HBsAg never disappeared after persisting for more than 12 months following AHB onset. When chronicity after AHB was defined as the persistence of HBsAg for more than 12 months, chronicity developed in 7.5% (8/107) of patients with genotype A and in 0.9% (1/105) of patients with non-A genotypes ($P = 0.018$).

Comparison of Characteristics Between Patients in Whom HBsAg Persisted More Than 6 or 12 Months and Those With Self-Limited AHB Infection. Table 2 compares the demographic and clinical characteristics between patients in whom HBsAg disappeared within 6 months and those in whom HBsAg persisted for more than 6 months from AHB. The peak ALT levels ($1,882 \pm 2,331$ versus $1,018 \pm 696$ IU/L, $P = 0.0024$) and peak HBV DNA levels (6.3 ± 1.6 versus 7.4 ± 1.6 mg/dL, $P = 0.0004$) were significantly higher and lower in the former group than in the latter group, respectively. Moreover, marked differences were present in the distribution of genotypes between the two groups. The percentage of the HBV genotype A (46.1% versus 73.5%, $P = 0.003$) was significantly higher among patients in whom HBsAg was persistent for more than 6 months. In addition, we compared the demographic and clinical characteristics between patients in whom HBsAg disappeared within 12 months and those in whom HBsAg persisted for more than 12 months from AHB. Peak ALT ($1,787 \pm 2,118$ versus 775 ± 513 IU/L, $P = 0.0089$) and peak total bilirubin (8.7 ± 8.2 versus 3.8 ± 6.6 mg/dL, $P = 0.0039$) levels were significantly higher in the former group than in the latter group. In contrast, the peak HBV DNA levels (6.4 ± 1.6 versus 7.9 ± 1.4 mg/dL, $P = 0.0046$) were significantly lower

Table 2. Comparison Between Patients With Chronicity Following Acute Hepatitis B and Those With Self-Limited Acute Infections Determined by the Persistence of HBsAg for More Than 6 or 12 Months

Features	Disappearance of HBsAg Within 6 Months (n = 178)	Persistence of HBsAg for More Than 6 Months From AHB (n = 34)	*P* Value	Disappearance of HBsAg Within 12 Months (n = 203)	persistence of HBsAg for More Than 12 Months From AHB (n = 9)	*P* Value
Age (years)	38.2 ± 13.1	40.0 ± 14.5	0.454	38.1 ± 13.2	46.7 ± 14.0	0.061
Male sex	147 (82.6)	30 (88.2)	0.416	169 (83.3)	8 (88.9)	0.677
HBeAg positive	150 (84.3)	32 (94.1)	0.131	175 (86.2)	8 (88.9)	0.815
ALT (IU/L)	1882 ± 2331	1018 ± 696	0.0024	1787 ± 2118	775 ± 513	0.0089
Total bilirubin (mg/dL)	8.6 ± 7.5	8.7 ± 11.3	0.137	8.7 ± 8.2	3.8 ± 6.6	0.0039
HBV DNA (log copies/mL)	6.3 ± 1.6	7.4 ± 1.6	0.0004	6.4 ± 1.6	7.9 ± 1.4	0.0046
HBV genotype						
Non-A	96 (53.9)	9 (26.5)		104 (51.2)	1 (11.1)	
A	82 (46.1)	25 (73.5)	0.003	99 (48.8)	8 (88.9)	0.018
Sexual transmission	128/137 (93.4)*	24/26 (92.3)†	0.711	146/157 (93.0)‡	6/6 (100.0)§	0.356
NAs treatment (+)	82 (46.1)	21 (61.8)	0.093	98 (48.3)	8 (88.9)	0.017

Data are presented as n (%) and mean ± SD. HBsAg, hepatitis B surface antigen; AHB, acute hepatitis B, HBeAg, hepatitis B e-antigen; ALT, alanine aminotransferase; HBV, hepatitis B virus; NAs, nucleotide analogs.

*Transmission routes of 41 patients were unknown.

†Transmission routes of 8 patients were unknown.

‡Transmission routes of 46 patients were unknown.

§Transmission routes of 3 patients were unknown.

Table 3. Multivariate Analysis of Factors Independently Associated With Persistence of HBsAg Positivity Following Acute Hepatitis B

	Persistence of HBsAg More Than 6 Months From AHB		
Factors	Odds Ratio	95% CI	*P* Value
ALT (per 1 IU/L increase)	1.000	0.999-1.000	0.035
HBV DNA (per 1 log copy/mL increase)	1.176	0.931-1.484	0.173
Genotypes			
Non-A	1.00		
A	4.224	1.853-9.631	0.001

95% CI, 95% confidence interval; ALT, alanine aminotransferase; HBV, hepatitis B virus.

in the former group than in the latter group. The percentages of HBV genotype A (48.8% versus 88.9%, $P = 0.018$) and NAs treatment (+) (48.3% versus 88.9%, $P = 0.017$) were significantly higher among patients in whom the HBsAg persisted for more than 12 months.

Factors Independently Associated With Viral Persistence Following AHB. A stepwise logistic regression model was used to perform multivariate analysis which explains relationships between some factors and persistence of HBsAg positivity more than 6 months following AHB. Peak ALT level, peak HBV DNA level, genotype A, and treatment with NAs were retained in the final multivariate logistic model in a backward stepwise manner ($P < 0.1$). For predicting the persistence of HBsAg for more than 6 months, only genotype A was independently associated with progression of AHB to the persistence of HBsAg (odds ratio [OR]: 4.224, $P = 0.001$, Table 3).

Characteristics of Patients Who Progressed to Chronicity That Was Defined as the Persistence of HBsAg for More Than 12 Months Following Acute Hepatitis B. Table 4 shows the clinical and virological characteristics of nine patients who progressed to chronicity defined as the persistence of HBsAg for more than 12 months following AHB. Among the nine patients who progressed to chronicity from AHB, eight (88.9%) were men and eight (88.9%) were HBeAg-positive. In general, among the patients who progressed to chronicity following AHB, the peak HBV DNA levels were high, and the peak total bilirubin and ALT levels were low. In eight (88.9%) patients, entecavir was administered; however, the duration until the onset of NA treatment from AHB onset was long (75-570 days).

Early Onset of Treatment With NAs Was Able to Prevent Viral Persistence After AHB Caused by Genotype A. The cumulative proportion maintaining HBsAg positivity during follow-up, expressed in terms of time after AHB onset, were significantly longer in patients with NAs treatment than in those without NAs treatment ($P = 0.046$, Fig. 2A). Table 5 shows the percentages of patients in whom HBsAg persisted for more than 6 or 12 months among patients categorized based on the period of time (i.e., duration) until the onset of NAs treatment. For patients in whom the onset of NAs treatment was less than 4 weeks from the onset of AHB, 12.7% of the patients showed persistent HBsAg for more than 6 months, while none showed HBsAg positivity for more than 12 months. For patients in whom the onset of NAs treatment was at 5-8 weeks, 37.5% of the patients showed persistent HBsAg for more than 6 months, whereas none showed persistent HBsAg for more than 12 months. For all groups, the period of HBsAg positivity in patients starting NAs treatment within 8 weeks from AHB onset was significantly shorter than that in patients beginning NAs treatment after more than 8 weeks from AHB onset ($P < 0.0001$, Fig. 2B). Patients starting NAs treatment within 8 weeks from AHB onset never progressed to chronicity after AHB caused by genotype A.

Table 4. Characteristics of Patients Who Progressed to Chronicity Following Acute Hepatitis B

Case	Age	Gender	HIV	HBeAg	HBV DNA (log copies/mL)	Total Bilirubin (mg/dL)	ALT (IU/L)	Observation Period (Months)	NAs Treatment	Duration Until NAs Treatment (Days)	Transmission Routes	Genotype
1	23	Male	(−)	(+)	7.6	1.7	1271	26	ETV	570	Heterosexual	A
2	40	Male	(−)	(−)	8.8	1.4	568	13	ETV	240	Heterosexual	A
3	45	Male	(−)	(+)	7.7	0.9	867	57	ETV	135	Heterosexual	A
4	37	Male	(−)	(+)	7.6	3.4	384	29	ETV	75	Unknown	A
5	54	Male	(−)	(+)	9	2	455	17	ETV	155	Homosexual	A
6	45	Male	(−)	(+)	4.8	21.2	512	60	(−)	(−)	Homosexual	A
7	61	Male	(−)	(+)	9.1	1.5	804	17	ETV	88	Unknown	A
8	56	Male	(−)	(+)	9.0	1.1	1820	14	ETV	118	Unknown	A
9	31	Female	(−)	(+)	7.4	0.8	296	66	ETV	150	Blood transfusion	C

HIV, human immunodeficiency virus; HBeAg, hepatitis B e-antigen; HBV, hepatitis B virus; ALT, alanine aminotransferase; NAs, nucleotide analogs; ETV, entecavir.

Table 5. Proportion of Patients in Whom HBsAg Persisted for More Than 6 or 12 Months Among Patients Categorized Based on the Number of Weeks Until the Onset of NAs Treatment

Duration Until Onset of NAs Treatment (Weeks)	Persistence of HBsAg for More Than 6 Months	Persistence of HBsAg for More Than 12 Months	Total Patients
<4 weeks (n, %)	9 (12.7)	0 (0)	71
5-8 weeks (n, %)	6 (37.5)	0 (0)	16
9-12 weeks (n, %)	1 (33.3)	1 (33.3)	3
13-16 weeks (n, %)	4 (100)	1 (25.0)	4
>17 weeks (n, %)	9 (100)	6 (66.7)	9
Total	29	8	103

HBsAg, hepatitis B surface antigen; NAs, nucleotide analogs.

Discussion

A multicenter nationwide study was conducted throughout Japan to evaluate the influence of clinical and virological factors on chronic outcomes in Japanese patients who contracted AHB in adulthood. The study was feasible in Japan, where a universal vaccination program for HBV has not been implemented because of the extremely high efficacy of the immunoprophylaxis that is given to babies born to carrier mothers. The implementation of this program has resulted in a decrease in the persistent HBV carrier rate from 1.4% to 0.3%.[19] Selective vaccination means that Japanese are more likely to be infected with HBV by way of horizontal transmission since the percentage of the population possessing anti-HBs is much lower than that in countries in which universal vaccination programs have been established.[20] In addition, Japan is faced with the ever-increasing impacts of globalization: as many as 17 million Japanese travel abroad and over 7 million people visit Japan from overseas each year. This "population mixing" may help to explain the increased prevalence in Japan of AHB due to genotype A, which is transmitted through indiscriminate sexual contact. Consequently, Japan may be the only country in the world where the influences of HBV genotypes, including genotype A (as is predominant in Western countries) and genotypes B and C (as are predominant in Asian countries), on chronic outcomes after AHB can be compared.

Currently, the persistence of HBsAg in serum for more than 6 months is considered to represent a progression to chronic infection.[21] However, our data showed that HBsAg frequently disappeared between 7 to 12 months after the onset of AHB in patients with genotype A (31/107 [29.0%]) and non-A genotypes (9/105 [8.6%]) (Fig. 1). These patients were considered to exhibit prolonged cases of AHB, rather than persistent infection. This finding reflects the higher sensitivity of the most up-to-date assays for HBsAg as compared with previous methods. In the present study, HBsAg was measured by CLIA, which has been reported to be about 150 times more sensitive in the detection of HBsAg than reverse passive hemagglutination (RPHA)-HBsAg, which has been used for the last 30 years in Japan.[22] The use of a more sensitive assay for HBsAg results in a longer period during which HBsAg may be detected. In this study, HBsAg did not disappear in nine patients after remaining continuously detectable for more than 12 months. Therefore, the persistence of HBsAg for more than 12 months, as measured with a highly sensitive method for detecting HBsAg, may be suitable for defining the progression of AHB to chronicity; however, further study is necessary to determine whether this definition is appropriate worldwide.

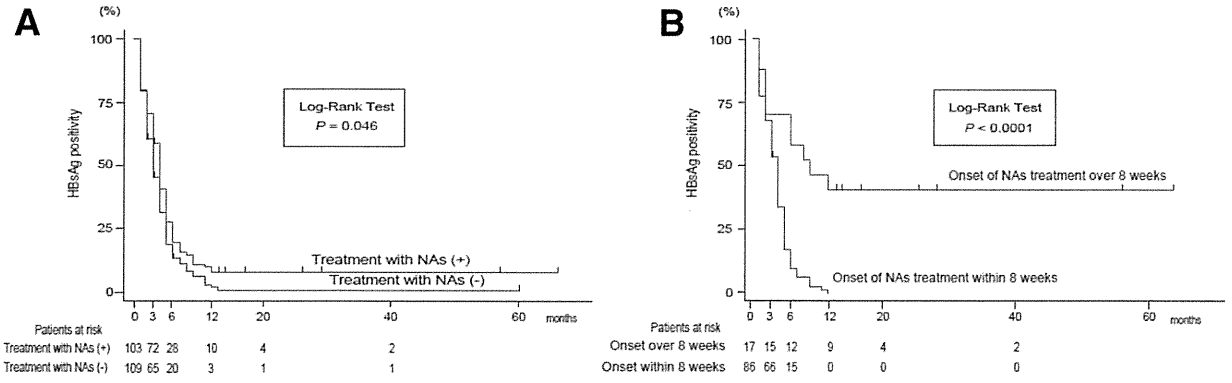

Fig. 2. (A) Comparison of the cumulative proportion of AHB patients maintaining HBsAg positivity between treatment with NAs (+) and treatment with NAs (−), as analyzed using the Kaplan-Meier test. $P = 0.046$, treatment with NAs (+): red line, treatment with NAs (−): blue line. (B) Comparison of the cumulative proportion of AHB patients in genotype A maintaining HBsAg positivity between treatment onset with NAs within 8 weeks and treatment onset with NAs over 8 weeks after onset of AHB, as analyzed using the Kaplan-Meier test. $P < 0.0001$, treatment onset with NAs over 8 weeks: red line, treatment onset with NAs within 8 weeks: blue line.

It has been reported that ~10% of patients who contract HBV as adults do not clear HBsAg from their serum and become carriers.[23] Meanwhile, a wide variation has been seen in the rate of persistence after AHB infection in adults. For example, viral persistence following AHB was seen in 0.2% (1/507) of adults in Greece,[24] 7.7% (5/65) of adult Alaskan Eskimos, and 12.1% (7/58) of adults in Germany.[25] The difference in the proportion of patients progressing from AHB to chronicity in different regions may be attributable to virological and host factors. In this study, 4.2% (9/212) of patients progressed to chronicity after AHB: 7.5% (8/107) of those infected with genotype A and 0.9% (1/105) of those infected with non-A genotypes. The non-A genotypes included genotypes B, C, D, F, and H (n = 25, 77, 1, 1, and 1, respectively). Genotypes B and C are predominant in eastern Asian countries, where the majority of those infected with HBV acquired the virus during the perinatal period by way of vertical transmission.[26] On the other hand, genotype A is predominant in Western countries, where the main route is horizontal transmission later in life.[26,27] Because HBeAg persists long after the infection in the genotype C as compared to other genotypes, this genotype has been shown to be a risk factor for perinatal and horizontal transmission in newborns and children.[28] The predominance of genotype A in Western countries may be attributable to a higher chronicity rate following AHB by way of horizontal transmission in adults.

In this study the characteristics of AHB associated with genotype A were a higher peak level of HBV DNA and a lower peak level of ALT. These findings were similar to those for patients with HBV-HIV coinfection.[29] Such characteristics of genotype A or coinfection with HIV are assumed to be attributable to milder hepatitis associated with weaker cellular immune responses. More slowly replicating viruses have been reported to evoke weaker cellular responses, enhancing the likelihood of persistence.[30] Indeed, our prior study showed that the replication of genotype A was significantly slower than that of genotype C in immunodeficient, human hepatocyte chimeric mice.[31] Moreover, variation among genotypes in the expression pattern of HBeAg may affect the progression of AHB to chronicity. Another previous study of ours revealed that a single form of HBeAg was detected by western blot analysis in serum samples from patients infected with genotypes B through D, but that two additional larger forms of HBeAg were detected in patients with genotype A.[32] Milich and Liang[33] reported that HBeAg may modulate the host immune response as a tolerogen to promote chronicity. Therefore, the different expression pattern of HBeAg by genotype A HBV may contribute to chronicity following AHB.

Early NAs initiation appeared to enhance the viral clearance across genotypes, although treatment with NAs did not show any overall benefit in duration of HBsAg. Previous studies examining the efficacies of NAs for preventing progression to chronic infection after AHB have reported conflicting results. Some small-scale studies have suggested the efficacy of lamivudine and entecavir in preventing the progression of AHB to chronic hepatitis.[34,35] Another study showed a lower seroconversion rate of HBsAg in lamivudine users.[36] Further, a randomized placebo-controlled trial showed no significant difference in clinical outcomes.[37] However, these previous studies did not mention the prevalence of HBV genotypes in the respective study populations. Although this was a retrospective study, our study included data on the prevalence of HBV genotypes. Additionally, our findings suggested that larger prospective randomized studies for every HBV genotype should be performed to determine whether early treatment with NAs prevented the progression of AHB to a chronic state.

In conclusion, in Japan genotype A was an independent risk factor for progression to chronic infection following AHB in adults. Confirmation of this association in patients with AHB in other countries is desirable and may provide insight into the pathogenetic mechanisms underlying this association. Early NA treatment appeared to reduce the likelihood of chronicity but this potentially important intervention needs to be prospectively studied before recommendations can be made.

Appendix

Members of the Japanese AHB Study Group include Yasuharu Imai (Ikeda Municipal Hospital), Norie Yamada, Hideaki Takahashi (St. Marianna University School of Medicine), Koji Ishii (Toho University School of Medicine), Hideyuki Nomura (Shin-Kokura Hospital), Jiro Nishida (Tokyo Dental Collage Ichikawa General Hospital), Shigeru Mikami (Kikkoman Hospital), Tsuneo Kitamura (Juntendo University Urayasu Hospital), Akihito Tsubota (Kashiwa Hospital Jikei University School of Medicine), Noritomo Shimada (Shinmatsudo Central General Hospital), Tetsuya Ishikawa (Nagoya University Graduate School of Medicine), Yoshiyuki Ueno (Tohoku University Graduate School of Medicine), Tomoyoshi Ohno (Social Insurance Chukyo Hospital), Etsuro Orito (Nagoya

Daini Red Cross Hospital), Michihiro Suzuki (Kawasaki Municipal Tama Hospital), Hitoshi Takagi (Gunma University Graduate School of Medicine), Eiichi Tomita (Gifu Municipal Hospital), Kumada Takashi (Ogaki Municipal Hospital), Toshihiko Mizuta (Saga University Faculty of Medicine), Tetsuya Mine (Tokai University School of Medicine), Jong-Hon Kang (Teine-Keijinkai Hospital), Katsuji Hirano (Juntendo University Shizuoka Hospital), Hirohito Tsubouchi (Kagoshima University Graduate School of Medical and Dental Sciences), Akito Nozaki (Yokohama City University Medical Center), Akito Sakai (Kanazawa University Graduate School of Medical Science), Shuhei Nishiguchi (Hyogo College of Medicine), Akihiro Tamori (Osaka City University Graduate School of Medicine), Satoru Hagiwara (Kinki University School of Medicine), Takahide Nakazawa (University of Kitasato East Hospital), Michio Sata (Kurume University School of Medicine), Toshiro Kamoshida (Hitachi General Hospital) Atsushi Takahashi (Fukushima Medical University School of Medicine), Satoshi Kakizaki (Gunma University Graduate School of Medicine), Yoshimasa Kobayashi (Hamamatsu University School of Medicine), Shigeru Sasaki (Sapporo Medical University), Tadashi Ikegami (Tokyo Medical University Ibaraki Medical Center), Yoichi Hiasa (Ehime University Graduate School of Medicine), Kenji Nagata (University of Miyazaki), Tomoyuki Kubota (Saiseikai Niigata Daini Hospital), Hiroshi Mitsui (Tokyo Teishin Hospital), Norihiko Yamamoto (Mie University School of Medicine), Masataka Tsuge (Hiroshima University), Shuichi Sato (Shimane University Hospital), Yoshito Ito (Kyoto Prefectural University of Medicine), Wataru Sato (Akita University School of Medicine), Shigeharu Uchida (Japanese Red Cross Society), Yuki Tada (National Institute of Infectious Diseases), Toshiaki Mizuochi (National Institute of Infectious Diseases), Norihiro Furusho (Kyushu University), and Shuhei Hige (Hokkaido University Graduate School of Medicine).

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ウイルス肝炎と肝癌の撲滅を目指した実地診療のすすめかた

B型肝炎の自然経過と治療の進歩

—実地医家はどのように対処すればよいのか—

八橋 弘

国立病院機構長崎医療センター臨床研究センター／やつはし・ひろし

HBVキャリアとは

HBs抗原が6ヵ月間以上持続陽性を示す者をHBVキャリアと呼ぶ．HBVキャリアの感染経路は垂直感染と水平感染に大別される．垂直感染はいわゆる母子感染であり，HBe抗原陽性の母親からの出産時に感染が成立し，その約90％がキャリア化するといわれている．一方，乳幼児期のHBVキャリア成立年齢に関する調査では，3歳以下では約80％，4歳から10歳までの感染では約30％がキャリア化したと報告されている．

成人B型急性肝炎例がキャリア化の場合にはHBVgenotype Aタイプの感染の可能性を考慮する必要があるも，現在のわが国に存在する約130万人のHBVキャリアの主な感染経路は，HBワクチンによる母子感染防止事業が開始される20年以上前の垂直感染と3歳以下の乳幼児水平感染である．

HBVキャリアの自然経過

HBVそのものは細胞障害性を有していないことから，HBV持続感染はウイルス，肝細胞，宿主免疫機構の三つの因子のバランスの中で成立する．HBV持続感染者は，従来は，①immune tolerance期，②immune clearance期，③low replicative期またはintegrated期という三つの時相に分類されていた．しかし，1989年以後，HBe抗原産生に関与するPreCore領域やCore Promoter領域のHBV遺伝子変異，遺伝子構造と機能に関する知見が集積され，HBe抗原陰性でもウイルスが増殖し肝病変が進展することが確認されたことから，ALT値，組織所見，HBVウイルスマーカー（HBV-DNA，HBeAg，HBsAg）などを評価した上で，①immune tolerance期，②immune clearance期（HBeAg＋chronic hepatitis B），③low replicative期（inactive carrier state期）④reactivation期（HBeAg-chronic hepatitis B），⑤recovery期という五つの時相に分類し，**図1**のように表記するようになった[1]．

HBe抗原-HBe抗体のセロコンバージョン

immune clearance期にHBe抗原-HBe抗体のセロコンバージョンが認められる．B型慢性肝炎を対象とした場合の年間のセロコンバージョン率は，2.7～21.1％/年，平均10％/年と考えられている．HBe抗原-HBe抗体のセロコンバージョンにかかわる因子として，①高齢であること，②ALT値が高いこと，③肝炎の急性増悪，④HBV genotype（B＞C），⑤人種（アジア人以外）などが報告されている．ALT値に関しては，18ヵ月の観察期間内にセロコンバージョンが生じる確率は，ALT値が正常値の5倍以上を示した場合は60％，5倍未満の場合は15％と報告されている．ALT値の上昇は，宿主免疫によって感染肝細胞が排除されている状態を表し，その後セロコンバージョンが生じ肝炎が沈静化する．ALT値の上昇は予後

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- HBs 抗原が 6 ヵ月間以上持続陽性を示す者を HBV キャリアと呼ぶ．HBV キャリアの感染経路は垂直感染と水平感染に大別される．
- B 型慢性肝炎を対象とした場合の年間のセロコンバージョン率は，2.7～21.1%/年，平均 10%/年と考えられている．HBe 抗原-HBe 抗体のセロコンバージョンにかかわる因子として，① 高齢であること，② ALT 値が高いこと，③ 肝炎の急性増悪，④ HBVgenotype (B > C)，⑤ 人種(アジア人以外)などが報告されている．
- 肝硬変進展の危険因子としては，① 高齢であること，② 男性であること，③ HBV 増殖が活発であること，④ HBV genotype が C タイプであること，⑤ core promoter の変異があること，⑥ ほかのウイルスとの重複感染(HCV，HIV，HDV)，⑦ アルコール飲酒，などが報告されている．

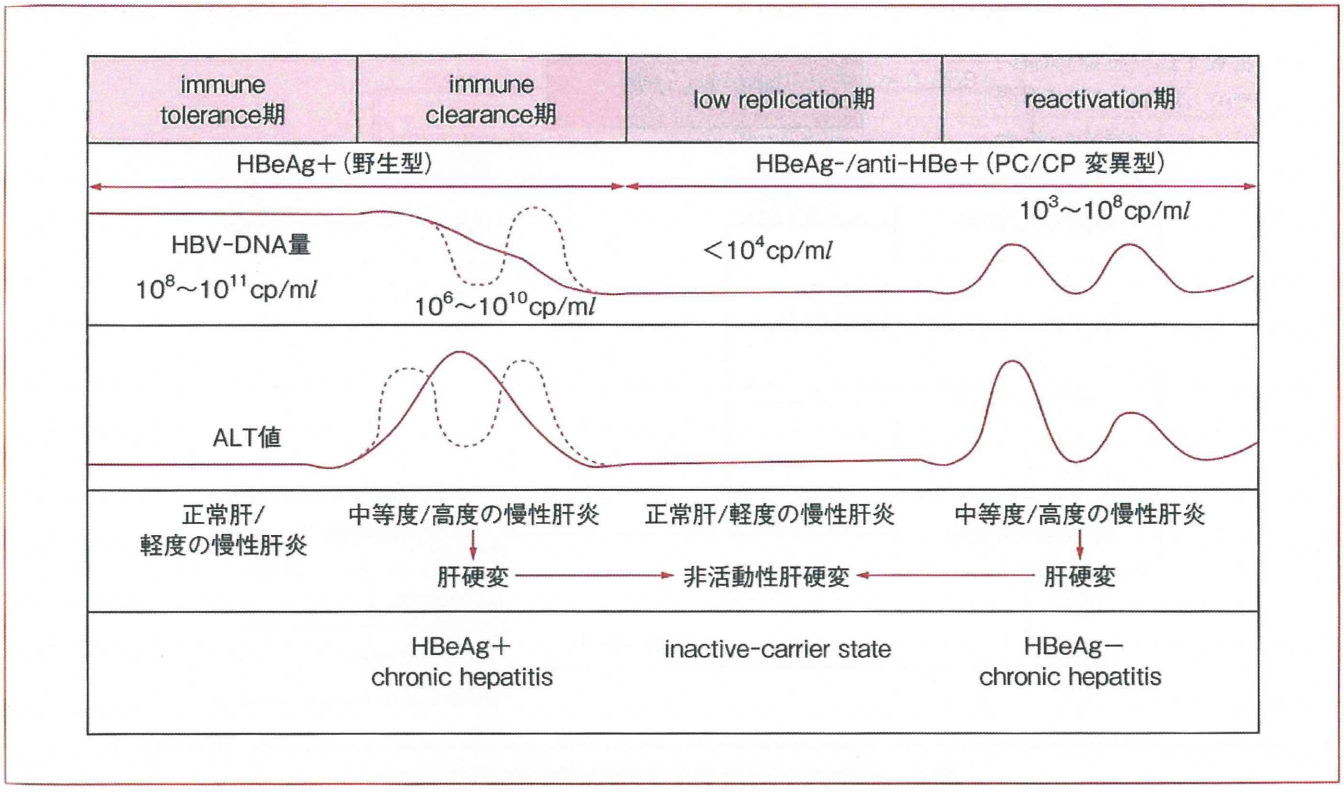

図 1　HBV キャリアの自然経過

不良のサインだけでなく，予後良好のサインでもあることを理解すべきである．

肝硬変への進展

immune clearance 期の長さと炎症の重症度によって肝硬変進展が規定される．B 型慢性肝炎からの年間の肝硬変進展率は，HBeAg 陽性 B 型慢性肝炎で 2～6%，HBeAg 陰性 B 型慢性肝炎で 8～10% と報告されており，HBeAg 陰性 B 型慢性肝炎において肝硬変進展リスクが高い．これは，この対象群が高齢であり，また慢性肝炎の中でも肝線維化進展例が多いことに起因している．

肝硬変進展の危険因子としては，① 高齢であること，② 男性であること，③ HBV 増殖が活発であること，④ HBV genotype が C タイプであること，⑤ core promoter の変異があること，⑥ ほかのウイルスとの重複感染(HCV，HIV，HDV)，⑦ アルコール飲酒，などが報告されている．

肝癌への進展

HBV 感染者は，非感染者に比して肝癌発生のハイリスク群である．東アジアなどの HBV

■ 年間肝癌発生率は，inactive carrier では 0.2% 以下，肝硬変を伴わない慢性肝炎では 1% 以下，代償性肝硬変では 2～3%，非代償性肝硬変では 7～8% である．
■ 肝癌進展の危険因子として，①高齢であること，②男性であること，③肝硬変があること，④肝癌の家族歴がある，⑤人種差(アジア人，アフリカ人)，⑥ HBV 増殖が活発であること，⑦ HBV genotype が C タイプであること，⑧ core promoter の変異があること，⑨ほかのウイルスとの重複感染(HCV，HIV，HDV)，⑩アルコール飲酒，⑪アフラトキシンなどが報告されている．

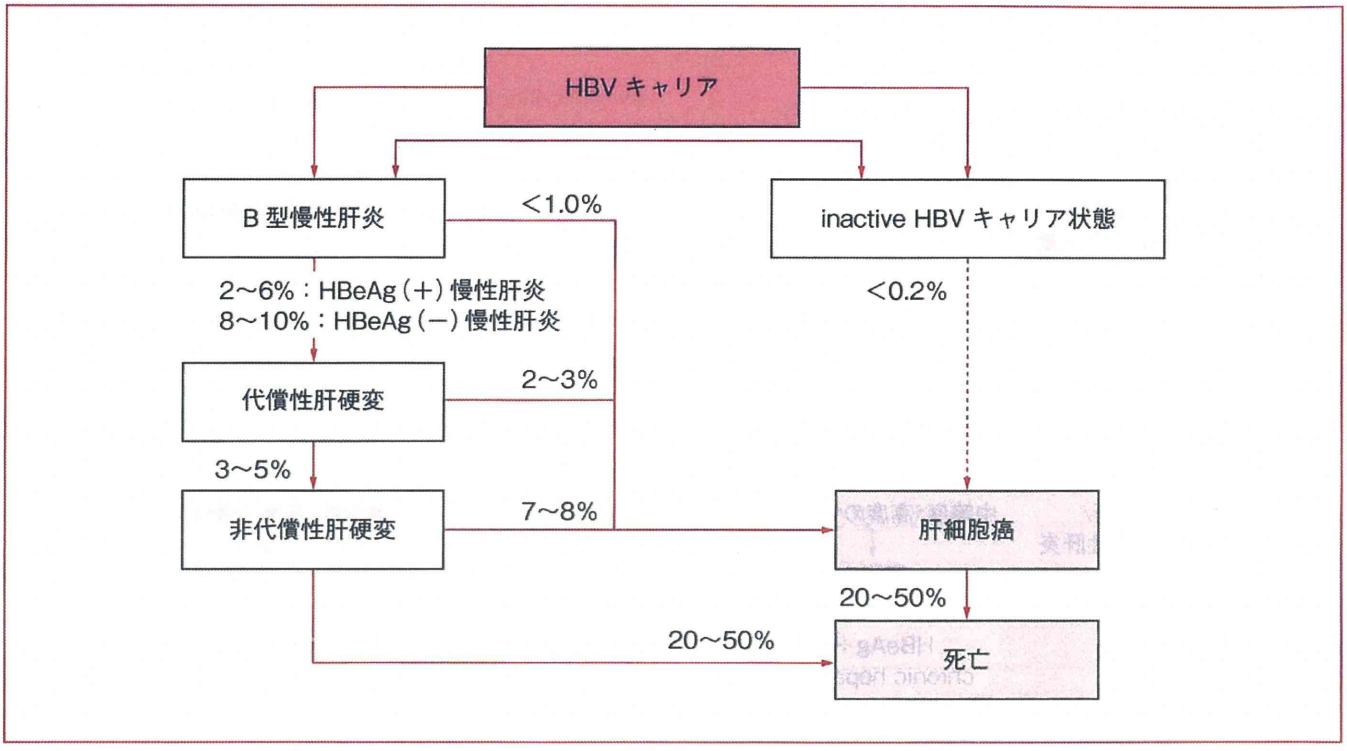

図 2　HBV キャリアでの年間肝病変進展率の推定

高罹患国での HBV キャリアの年間肝癌発生率は，inactive carrier で 0.2%，肝硬変を伴わない慢性肝炎で 1.0%，代償性肝硬変で 3.2～4.3% と報告されている．一方，欧州などの HBV 低罹患国での年間肝癌発生率は，inactive carrier で 0.02%，肝硬変を伴わない慢性肝炎で 0.1%，代償性肝硬変で 2.2% と報告されており，同じ病態でも HBV 高罹患国と低罹患国では肝癌発生リスクが異なる．

HBV 感染者での肝癌発生リスクをまとめたものが**図 2** である．年間肝癌発生率は，inactive carrier では 0.2% 以下，肝硬変を伴わない慢性肝炎では 1% 以下，代償性肝硬変では 2～3%，非代償性肝硬変では 7～8% である．

肝癌進展の危険因子として，① 高齢であること，② 男性であること，③ 肝硬変があること，④ 肝癌の家族歴がある，⑤ 人種差(アジア人，アフリカ人)，⑥ HBV 増殖が活発であること，⑦ HBV genotype が C タイプであること，⑧ core promoter の変異があること，⑨ ほかのウイルスとの重複感染(HCV，HIV，HDV)，⑩ アルコール飲酒，⑪ アフラトキシンなどが報告されている．

2006 年，台湾から報告された HBV キャリアを対象とした肝癌発生リスクに関する論文，REVEAL Study は，肝発癌に HBV-DNA 量が

- 注目すべき点は，ALT 値正常でかつ肝硬変を伴わない集団においても，HBV-DNA 量高値例では，低値に比して 10 倍以上肝発癌リスクが高いと報告している点である．
- 年間の HBs 抗原消失率は 0.5% から 2.5% で平均 1.0% で，長期的には 25 年間で 40% 消失すると報告されている．
- B 型肝炎の抗ウイルス治療法は，大きく① インターフェロン（IFN）治療と② 核酸アナログ抗ウイルス薬 nucleoside analogue（NA）に大別される．

表 1　HBV キャリアを対象とした肝発癌に関連する危険因子に関する台湾での検討結果

リスク	全対象患者 n = 3,653		HBeAg 陰性者 n = 3,088		HBeAg 陰性，ALT 値正常，肝硬変を伴わない者，n = 2,925	
	multivariable-adjusted HR	p 値	multivariable-adjusted HR	p 値	multivariable-adjusted HR	p 値
性差：男性	2.1	0.001	2.0	0.03	1.5	0.24
HBeAg 陽性	2.6	< 0.001				
肝硬変，あり	9.1	< 0.001	7.9	< 0.001		
HBV-DNA 量，< 300 copies/ml（検出感度以下）	1.0	< 0.001	1.0	< 0.001	1.0	< 0.001
HBV-DNA 量，10,000～99,999 copies/ml	2.3	0.02	2.6	0.01	4.5	0.001
HBV-DNA 量，100,000～999,999 copies/ml	6.6	< 0.001	6.1	< 0.001	11.3	< 0.001
HBV-DNA 量，1 milion copies/ml 以上	6.1	< 0.001	10.6	< 0.001	17.7	< 0.001

密接に関係していることを示したものとして注目されている[2]．3,653 名の HBV キャリアを平均 11.4 年間，観察を行い経過発癌例を検討している．**表 1** に示すように，全体では，男性，HBeAg 陽性例，肝硬変例，HBV-DNA 量高値例で肝癌リスクが高いことを確認されているが，注目すべき点は，ALT 値正常でかつ肝硬変を伴わない集団においても，HBV-DNA 量高値例では，低値に比して 10 倍以上肝発癌リスクが高いと報告している点である．本論文は，HBV キャリアでの肝癌発生ハイリスク群の囲いこみの方法として HBV-DNA 量の測定が有用性であること，また抗ウイルス薬を用いての治療介入により持続的に HBV-DNA 量を低下させることで肝癌抑止が可能であることを示唆している．

HBs 抗原-抗体のセロコンバージョン

HBV 持続感染者においても一部の者では HBs 抗原が消失，HBs 抗体陽性の recovery 期に移行する．年間の HBs 抗原消失率は 0.5% から 2.5% で平均 1.0% で，長期的には 25 年間で 40% 消失すると報告されている．HBs 抗原の消失は，一般的には予後良好と考えられているが，HBs 抗原消失にもかかわらず，肝硬変，肝癌進展例が少なくないという報告もある．

B 型慢性肝炎に対する治療の進歩

B 型肝炎の抗ウイルス治療法は，大きく① インターフェロン（IFN）治療と② 核酸アナログ抗ウイルス薬 nucleoside analogue（NA）に大別される．B 型慢性肝炎治療薬の承認年の

■ 一般的に35歳以上のB型慢性肝炎患者は，自然治癒しがたいことが明らかとなっており，NAは，これらの対象者においても確実な抗ウイルス効果を発揮し，肝炎の沈静化効果が明らかな薬剤である．NAの中でも，特にETVは，初回投与例での薬剤耐性出現の頻度は5年間投与でも1%前後と低いことから，35歳以上でかつ自然治癒しがたいと判断したB型慢性肝炎症例での治療薬の第一選択薬剤となっている．

■ Peg-IFNを用いた治療では，NAに比較すると，その治療効果は20～30%と確実ではないものの，通常は1年投与で治療を終了しdrug freeになれること，NAよりもHBs抗原量を低下させる作用があること，HBs抗原消失率がコントロール群に比較して高いことなどが報告されている．

表2　B型慢性肝炎治療薬の承認年，日米の比較

	米国	日本
1. 従来型インターフェロン(IFN)	1991	1986
2. ラミブジン(LMV)	1998	2000
3. アデホビル(ADV)	2002	2004
4. エンテカビル(ETV)	2005	2006
5. ペグインターフェロン(Peg-IFN)	2005	2011
6. テノホビル	2008	治験中

日米での比較を**表2**に示す．

NAは，2000年以後，わが国では，ラミブジン(LMV)，アデホビル(ADV)，エンテカビル(ETV)の順にその使用が許可され，現在7万人以上のB型慢性肝炎患者に対して，これらのNAが投与されている．一般的に35歳以上のB型慢性肝炎患者は，自然治癒しがたいことが明らかとなっており，NAは，これらの対象者においても確実な抗ウイルス効果を発揮し，肝炎の沈静化効果が明らかな薬剤である．NAの中でも，特にETVは，初回投与例での薬剤耐性出現の頻度は5年間投与でも1%前後と低いことから，35歳以上でかつ自然治癒しがたいと判断したB型慢性肝炎症例での治療薬の第一選択薬剤となっている．NAの問題点は，治療中止時期が明確でなく安易に中止すると肝炎の再燃が高率にみられること，また通常は数年間に及ぶ長期投与が必要なことである[2)]．

一方，わが国では米国に先がけて，従来型IFNは1986年から使用可能となっていたが，その当時の従来型IFNの治療期間は4週間に限定されていたことから，その効果も限定的であり普及しなかった．しかし2011年にペグインターフェロン(Peg-IFN)が，わが国でも使用可能となり，48週間の投与が可能となった．Peg-IFNを用いた治療では，NAに比較すると，その治療効果は20～30%と確実ではないものの，通常は1年投与で治療を終了しdrug freeになれること，NAよりもHBs抗原量を低下させる作用があること，HBs抗原消失率がコントロール群に比較して高いことなどが報告されている．

なお，現在，わが国では，NAとPeg-IFN治療に伴う薬剤費，検査費などの患者負担分に対する公的助成制度が適応されている．

ラミブジン(LMV)

LMVは，本来HIVに対する抗ウイルス薬の開発の過程で作られたNAである．HBVに対してもウイルス増殖抑制効果を示すことが明らかとなり，2000年11月からB型慢性肝炎に対して保険適応となった．B型慢性肝炎に対するLMVの用法用量は，成人には100 mg 1日1回経口内服投与である．投与期間の明確な規定はなく，通常は数年にわたって投与する．保険診療上の適応は，(B型肝炎ウイルスの増殖を伴う肝機能の異常が確認されたB型慢性肝炎患者)であり，治療前にはHBV-DNA量を確認する．HBe抗原陰性でもALT値異常を伴いHBV-DNA量が4.0 log/copy以上の例，慢性肝炎だけでなく肝硬変例にも保険適応がある．

LMVのウイルス増殖抑制効果は強力だが，

- LMV のウイルス増殖抑制効果は強力だが，LMV 治療例の多くは，投与の中止でウイルスの再増殖とともに肝炎がしばしば再燃する．
- LMV 単剤投与中の YMDD 変異出現の頻度は，投与 1 年目 24%，2 年目 38%，3 年目 49%，4 年目 71% と高率である．

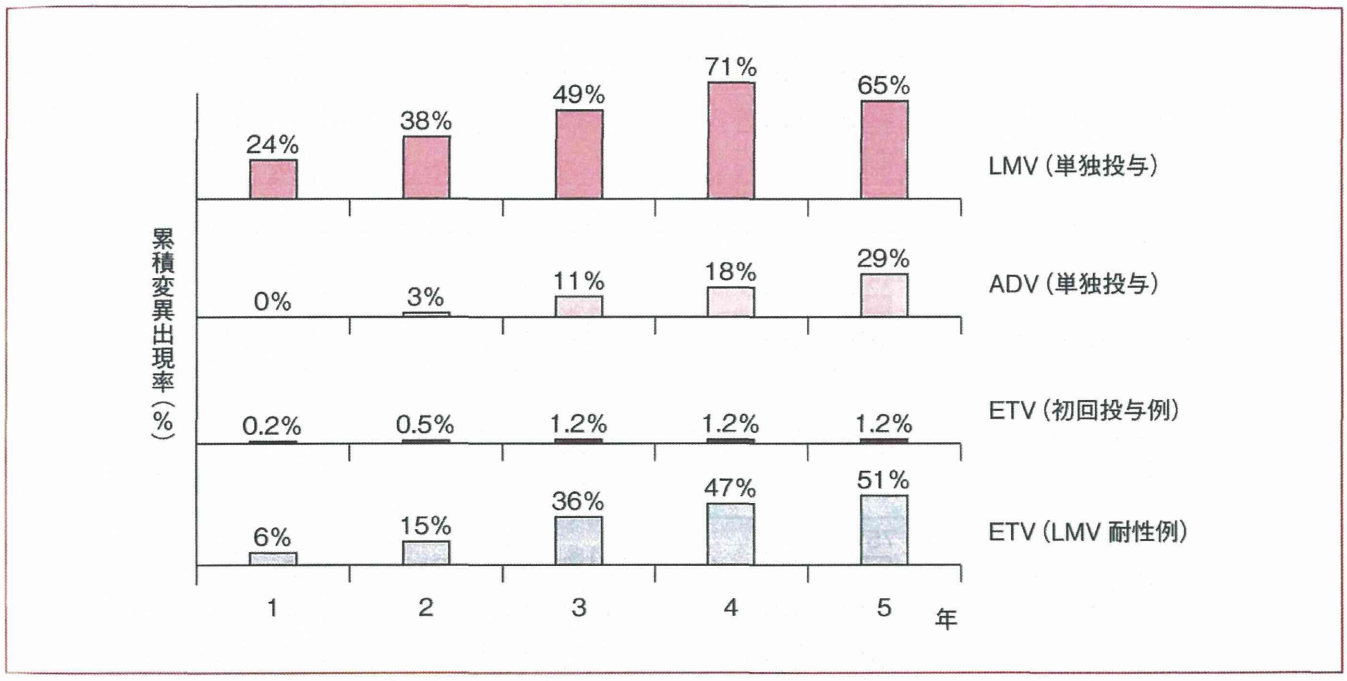

図 3　各種抗ウイルス薬長期使用時の HBV ポリメラーゼ領域の遺伝子変異の出現頻度

LAM による YMDD 変異出現の頻度は，投与 1 年目 24%，2 年目 38%，3 年目 49%，4 年目 71% と報告されている．ADV 単独投与例では 2 年目 3%，3 年目 11%，4 年目 18%，5 年目 29% の ADV 薬剤耐性ウイルスの出現が報告されている．ETV では，初回投与では 5 年目でも 1.2% の ETV 変異出現率であるが，LMV 耐性例に対する ETV 投与では 2 年目 15%，3 年目 36%，4 年目 47%，5 年目 51% の頻度で ETV 薬剤耐性ウイルスが出現する．

（文献 3），文献 4）より引用）

LMV 治療例の多くは，投与の中止でウイルスの再増殖とともに肝炎がしばしば再燃する．LMV で血中ウイルスの増殖を抑制できても肝細胞内ウイルスの増殖の鋳型が，容易には排除されないことが中止後の再燃と関係するといわれている．また一方で LMV の長期投与によりウイルス遺伝子変異出現，薬剤耐性となることが知られており，変異出現例の約半数の例で肝炎が再燃する．LMV 単剤投与中の YMDD 変異出現の頻度は，投与 1 年目 24%，2 年目 38%，3 年目 49%，4 年目 71% と高率である（**図 3**）．

自然治癒する可能性が低い 35 歳以上の B 型慢性肝炎，35 歳未満でも肝組織病変進展例では LMV や ETV 投与のよい対象である．しかし一度服用を開始すると数年間の長期投与が必要で，中止の判断がむずかしいことから，どの患者にいつから投与するのかなどは，肝臓専門医が最終判断すべきである．

アデホビル（ADV）

LMV に対する薬剤耐性（YMDD 変異ウイル

- **単独投与例では薬剤耐性が少なからず出現することから，ADV は LMV との併用投与が推奨されている．**
- **重大な副作用として腎機能障害，腎不全，乳酸アシドーシスおよび脂肪沈着による重度の肝腫大(脂肪肝)などが報告されている．**

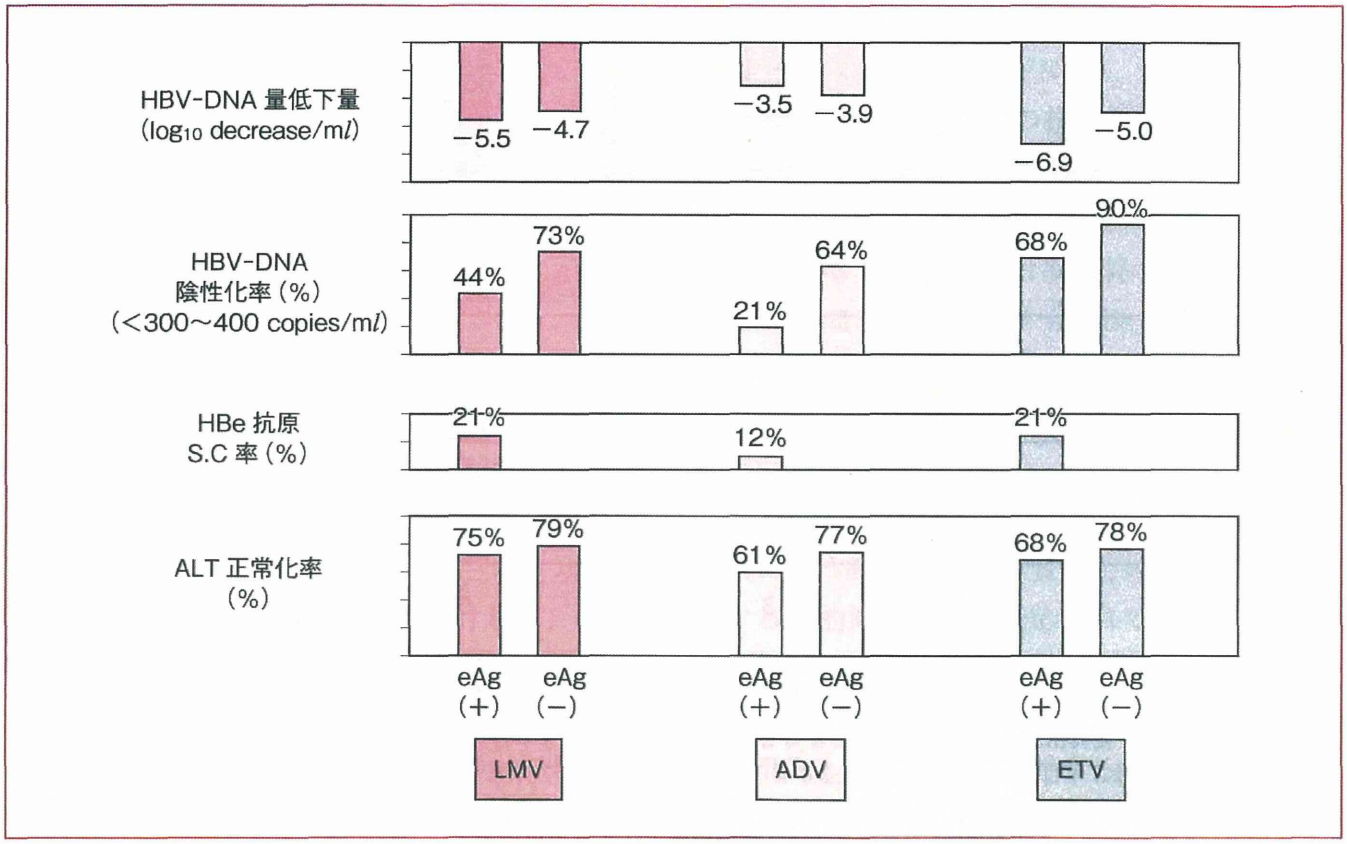

図 4　各種抗ウイルス薬の治療効果の比較，48 週目の治療効果
(文献 5)より引用)

ス出現)に対する治療法として，わが国でも 2004 年 12 月から ADV が使用可能となった．保険診療上，ADV は，LMV との併用投与および ADV 単独投与ともに可能だが，単独投与例では薬剤耐性が少なからず出現することから，ADV は LMV との併用投与が推奨されている(図 3)．ADV の用法用量は，成人には 10 mg 1 日 1 回経口内服投与である．30 mg 以上の過量投与例では，腎機能障害が出現しやすく，10 mg が至適用量となっている．

LMV と ADV の間の交差耐性の報告はきわめて少なく，LMV と ADV の併用投与で YMDD 変異出現例においても持続的な抗ウイルス効果が期待される．重大な副作用として腎機能障害，腎不全，乳酸アシドーシスおよび脂肪沈着による重度の肝腫大(脂肪肝)などが報告されている．

エンテカビル(ETV)

ETV は 2006 年 9 月に保険適応薬剤として認

- ETV の最大の特徴は，LMV 耐性がない初回投与例では，ETV 薬剤耐性頻度がきわめて低いことである．
- 腎排泄型の薬剤であり，腎機能低下患者では，投与間隔を延長するなどして調節を行う．

可された．ETV の最大の特徴は，LMV 耐性がない初回投与例では，ETV 薬剤耐性頻度がきわめて低いことである．ETV の5年目の薬剤耐性出現頻度は1.2% と明らかに低いことから，現在では第一選択薬となっている(図3)．なおLMV 耐性例へのETV 投与では，2年で約15%，5年で51% の頻度でETV 耐性が出現すると報告されている(図3)．ETV の用法用量は，通常，成人には0.5 mg を1日1回である．食事の影響で薬物吸収率が低下するため，空腹時(食後2時間以降かつ次の食事の2時間以上前)に服用する．なお，LMV 不応(LMV 投与中にB 型肝炎ウイルス血症が認められる，またはLMV 耐性変異ウイルスを有するなど)患者には，ETV 1 mg を1日1回経口投与することが保険診療上認められているも，ETV 耐性が出現しやすくなることから特別な事情がない限り安易に投与を行うべきではないと考える．

海外で行われたLMV，ADV とETV の比較試験では，HBV-DNA 低下率，HBV-DNA 陰性化率，ALT 正常化率，組織学的改善率などは，ETV が有意にまさっていることが報告されている(**図4**)．

副作用は他の2剤とほぼ同様で，本剤投与中，自他覚症状を呈する副作用はほとんど認められない．腎排泄型の薬剤であり，腎機能低下患者では，投与間隔を延長するなどして調節を行う．妊婦または妊娠している可能性のある婦人に対するNA の投与は，胎児に対する安全性が確認されていないため，治療上の有益性が危険性を上回ると判断される場合にのみにすべきといわれている．

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Special Report

Etiology and prognosis of fulminant hepatitis and late-onset hepatic failure in Japan: Summary of the annual nationwide survey between 2004 and 2009

Makoto Oketani,[1] Akio Ido,[1] Nobuaki Nakayama,[2] Yasuhiro Takikawa,[3] Takafumi Naiki,[4] Yoshiyuki Yamagishi,[5] Takafumi Ichida,[6] Satoshi Mochida,[2] Saburo Onishi,[7] Hirohito Tsubouchi[1] and the Intractable Hepato-Biliary Diseases Study Group of Japan

[1]Digestive and Lifestyle Diseases, Human and Environmental Sciences, Health Research, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima, [2]Department of Gastroenterology and Hepatology, Saitama Medical University, Moroyama, [3]Department of Gastroenterology and Hepatology, School of Medicine, Iwate Medical University, Morioka, [4]Department of Gastroenterology, Gifu University Graduate School of Medicine, Gifu, [5]Department of Internal Medicine, School of Medicine, Keio University, Tokyo, [6]Department of Gastroenterology and Hepatology, Shizuoka Hospital, Juntendo University, Izunokuni, and [7]Department of Gastroenterology and Hepatology, Kochi Medical School, Nankoku, Japan

Aim: To summarize the annual nationwide survey on fulminant hepatitis (FH) and late-onset hepatic failure (LOHF) between 2004 and 2009 in Japan.

Methods: The annual survey was performed in a two-step questionnaire process to detail the clinical profile and prognosis of patients in special hospitals.

Results: Four hundred and sixty ($n = 227$ acute type; $n = 233$ subacute type) patients had FH and 28 patients had LOHF. The mean age of patients with FH and LOHF were 51.1 ± 17.0 and 58.0 ± 14.4 years, respectively. The causes of FH were hepatitis A virus in 3.0%, hepatitis B virus (HBV) in 40.2%, other viruses in 2.0%, autoimmune hepatitis in 8.3%, drug allergy-induced in 14.6% and indeterminate etiology in 29.6% of patients. HBV reactivation due to immunosuppressive therapy was observed in 6.8% of FH patients. The short-term survival rates of patients without liver transplantation (LT) were 48.7% and 24.2% for the acute and subacute type, respectively, and 13.0% for LOHF. The prognosis was poor in patients with HBV reactivation. The implementation rate for LT in FH patients was equivalent to that in the previous survey. The short-term survival rates of total patients, including LT patients, were 54.2% and 40.8% for the acute and subacute type, respectively, and 28.6% for LOHF.

Conclusion: The demographic features and etiology of FH patients has gradually changed. HBV reactivation due to immunosuppressive therapy is problematic. Despite advances in therapeutic approaches, the prognosis of patients without LT has not improved.

Key words: acute liver failure, fulminant hepatitis, Japan, liver transplantation, viral hepatitis

INTRODUCTION

IN JAPAN, FULMINANT hepatitis (FH) is defined as having hepatitis, when grade II or worse hepatic encephalopathy develops within 8 weeks of the onset of disease symptoms, with a prothrombin time of 40% or less.[1,2] FH is further classified into two subtypes, acute and subacute types, in which encephalopathy occurs within 10 days and later than 11 days, respectively, of the onset of the disease symptoms. Patients showing a prothrombin time of 40% or less, with hepatic encephalopathy developing between 8 and 24 weeks of disease onset are classified as having late-onset hepatic failure (LOHF).[3] Etiologies with hepatitis present in the histology, such as viral infection, autoimmune hepatitis and drug allergy-induced liver injury are defined as causes of

Correspondence: Dr Makoto Oketani, Digestive and Lifestyle Diseases, Human and Environmental Sciences, Health Research, Kagoshima University Graduate School of Medical and Dental Sciences, 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan.
Email: oketani@m2.kufm.kagoshima-u.ac.jp
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FH and LOHF. In contrast, acute liver failure due to other causes with the absence of hepatitis in the histology, such as drug toxicity, circulatory disturbance and metabolic disease, are excluded as causes of FH and LOHF. Recently, a novel diagnostic criteria for acute liver failure in Japan was established by the Intractable Hepato-Biliary Disease Study Group.[4,5] These criteria included other causes with liver damage without the absence of hepatitis in the histology in addition to the present criteria.

Among viral infection, hepatitis B virus (HBV) is a major cause of FH in Japan.[6,7] HBV infection is classified into transient HBV infection type and acute exacerbation in an HBV inactive carrier. With advances in cytotoxic chemotherapy and immunosuppressive therapy, reactivation of hepatitis B is becoming a clinical problem.[8] Moreover, recent introduction of rituximab plus steroid combination therapy for non-Hodgkin's lymphoma has been associated with HBV reactivation in transiently infected patients, namely, de novo hepatitis. However, the prevalence of HBV reactivation in patients with FH and LOHF is unknown.

Advances in therapeutic strategies for FH and LOHF have improved the prognosis. Since 1988, living-donor liver transplantation (LT) has been adopted in patients who are beyond the supportive care of a critical unit.[6] Recently, artificial liver support with high-flow or on-line hemodiafiltration (HDF) has been used. Since 2006, a nucleoside analog, entecavir, has been used as a substitute for lamivudine, as an antiviral agent for HBV. However, it is unknown whether these new treatments improve the prognosis of FH.

The Intractable Hepato-Biliary Diseases Study Group has annually performed a nationwide survey of patients with FH and LOHF since 1983.[6] Since 2000, approximately 600 hospitals have been enrolled in the survey. This report summarizes the results of the survey between 2004 and 2009 to addresses the trends in the etiology and prognosis of patients with FH and LOHF and compares them with the previous survey.[7]

METHODS

THE NATIONWIDE SURVEY was performed annually. The number of hospitals for survey has changed in each year. Maximum (608) was in 2007 and minimum (544) was in 2006, with active members of the Japan Society of Hepatology and the Japanese Society of Gastroenterology between 2005 and 2010. The survey was performed in a two-step questionnaire process to detail the clinical profile and prognosis of patients who were diagnosed as FH or LOHF in the previous year. The recovery rate of the first and second questionnaire was 39–59% and 60–100%, respectively. Patients who met the diagnostic criteria for FH or LOHF were entered into the survey. Patients under 1 year of age, those with alcoholic hepatitis, those with chronic liver diseases and those with acute liver failure with no histological features of hepatitis were excluded from the analysis.

According to criteria described in previous reports,[7,9] the etiology of FH and LOHF was classified into five categories: (i) viral infection; (ii) autoimmune hepatitis; (iii) drug allergy-induced liver injury; (iv) indeterminate etiology despite sufficient examinations; and (v) unclassified due to insufficient examinations. Patients with viral infection consisted of those with hepatitis A virus (HAV), HBV, hepatitis C virus (HCV), hepatitis E virus (HEV) and other viruses. The patients with HBV infection were classified into three subgroups according to serum markers of HBV, hepatitis B core antibody (HBcAb) and immunoglobulin (Ig)M-HBcAb: (i) transient HBV infection; (ii) acute exacerbation in HBV carriers; and (iii) indeterminate infection patterns. In the present study, we classified acute exacerbation in HBV carriers into three subgroups according to the new criteria:[4,5] (i) inactive carriers, without drug exposure; (ii) reactivation in inactive carriers by immunosuppressant and/or anticancer drugs; and (iii) reactivation in transiently infected patients by immunosuppressant and/or anticancer drugs (i.e. de novo hepatitis). Because not every patient was examined for serological markers of transient HBV infection before the onset of FH and LOHF (with HBcAb and/or hepatitis B surface antigen [HBsAg] in serum), we defined HBV reactivation as that occurring in transiently infected patients when they developed HBV-related hepatitis due to immunosuppressive therapy or cytotoxic chemotherapy with reappearance of HBsAg in the serum and did not conform to the criteria of transient HBV infection.

The statistical significance of differences between groups was assessed using Student's *t*-test, Fisher's exact test or Kruskal–Wallis one-way ANOVA. Data are shown as mean ± standard deviation. The study was conducted with the approval of the Ethical Committee of Kagoshima University Graduate School of Medical and Dental Sciences.

RESULTS

Demographic features and survival rates

FROM 2004–2009, 582 PATIENTS were enrolled in the survey. Ninety-four patients were excluded from

the survey according to the exclusion criteria. Consequently, 460 patients ($n = 227$ acute type; $n = 233$ subacute type) were classified as having FH and 28 as having LOHF (Table 1). The incidence of the acute and subacute types of FH was similar and the incidence of LOHF was one-sixteenth of FH. The male : female ratio was higher for the acute type and lower for the subacute type of FH and LOHF. The mean age of patients was significantly higher for the subacute type of FH and LOHF than that for the acute type of FH. Almost half of the patients with FH and LOHF had complications which preceded the onset of acute liver failure. Furthermore, approximately 60% of patients with FH had received daily medication. This tendency for receiving medication was more obvious in patients with the subacute type of FH and LOHF.

The survival rates of patients without LT were 48.7% for the acute type and 24.2% for the subacute type of FH, and 13.0% for LOHF. The survival rates of the subacute type of FH and LOHF was worse than that of the acute type. The prognosis of both the acute type and the subacute type of FH appeared to be equivalent annually. The survival rates of patients with LT were 79.6% for FH and 100% for LOHF, with no difference in these rates among the disease types.

Clinical profile

Symptoms, imaging findings and complications are shown in Table 2. Since 2006, diagnostic criteria of systemic inflammatory response syndrome (SIRS) for fever, tachycardia and tachypnea have been adopted in the survey.[10] Icterus, flapping tremor, ascites, hepatic fetor, tachycardia, tachypnea and pretibial edema were frequently found. The frequency of patients with ascites and pretibial edema was significantly greater in the subacute type of FH and LOHF than in the acute type of FH. In contrast, fever appeared more frequently in patients with the acute type of FH. The frequency of liver atrophy was greater in the subacute type of FH, and even higher in LOHF, than in the acute type of FH.

With regard to complications, disseminated intravascular coagulation, renal failure and bacterial infection were found in more than 30% of patients with FH and LOHF. Brain edema was less frequent in the subacute type than in the acute type of FH.

Causes of FH and LOHF

The cause of FH was identified as viral infection in 46.1% of the patients (Table 3). The frequencies of viral infection were highest for the acute type of FH. HAV infection was found in 3% of patients with FH. HBV infection was found in 40.2% of patients with FH and 32.1% of patients with LOHF. Transient HBV infection was more frequent in the acute type than in the subacute type of FH, whereas the frequency of acute exacerbation in HBV carriers was greater in the subacute type than in the acute type of FH. HBV reactivation in inactive carriers and in transiently infected patients were found in 3.3% and 3.5% of patients with FH, respectively. With regard to underlying diseases in patients with HBV reactivation, non-Hodgkin's lymphoma/mucosa-associated lymphoid tissue lymphoma was most prevalent in 50% of inactive carriers and in 76% of those with transiently infected patients. Among patients with HBV

Table 1 Demographic features and survival rates of patients with fulminant hepatitis (FH) and late-onset hepatic failure (LOHF)

	FH			LOHF ($n = 28$)
	Total ($n = 460$)	Acute type ($n = 227$)	Subacute type ($n = 233$)	
Male/female	227/233	127/100	100/133**	9/19*
Age (years; mean ± SD)	51.1 ± 17.0	48.8 ± 16.9	53.4 ± 16.7**	58.0 ± 14.4**
HBV carrier (%)	13.1 (52/397)	10.5 (19/181)	15.3 (33/216)	22.2 (6/27)
Complications preceding acute liver failure (%)†	46.4 (208/448)	40.0 (88/220)	52.6 (120/228)**	50.0 (14/28)
History of medication (%)	59.9 (260/434)	51.2 (108/211)	68.2 (152/223)**	71.4 (20/28)*
Survival rates				
All patients	47.4 (218/460)	54.2 (123/227)	40.8 (95/233)**	28.6 (8/28)*
No LT	37.5 (132/352)	48.7 (93/191)	24.2 (39/161)**	13.0 (3/23)**
LT	79.6 (86/108)	83.3 (30/36)	77.8 (56/72)	100 (5/5)

*$P < 0.05$, **$P < 0.01$ vs acute type.
†Diseases such as metabolic syndrome, malignancy and psychiatric disorders.
Data in parenthesis indicate patient numbers.
HBV, hepatitis B virus; LT, liver transplantation; SD, standard deviation.