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EPIDEMIC PATTERNS OF HEPATITIS TYPE B VIRUS (HBV) AND HUMAN T LYMPHOTROPIC VIRUS TYPE I (HTLV-I) IN TWO ATL-ENDEMIC ISLANDS IN KYUSHU, JAPAN

KAZUNORI TACHIBANA[1], SHIN-ICHIRO ITO[1], SATOSHI SHIRAHAMA[2], MASAZUMI NAGATOMO[3], KEN-ICHIRO KINOSHITA[3], and KAZUO TAJIMA[4,*]

[1]Izuhara Hospital, Izuhara-cho, Shimoagata-gun, Nagasaki 857—23, [2]Kamigoto Hospital, Aogata 1549—11, Kamigoto-cho, Minami-matsuura-gun, Nagasaki 857—44, [3]Nagasaki National Central Hospital, Kubahara-goh, Omura, Nagasaki 856, [4]Division of Epidemiology, Aichi Cancer Center Research Institute, Kanokoden 1-1, Chikusa-ku, Nagoya 464, Japan.

ABSTRACT

To evaluate the relationships between human T lymphotropic virus type I (HTLV-I) and hepatitis virus type B (HBV) infections, we compared both individual and geographical distributions of carriers of HTLV-I and HBV, and antibody positives to HBV in two ATL-endemic islands in Kyushu, Japan. The positive rates of antibodies to HTLV-I (anti-HTLV-I-Ab) in sera among healthy inhabitants older than 30 years of age were 27.5% (617/2,232) in Nakadohri, Goto Island and 24.0% (500/2,048) in Shimo-agata, Tsushima Island. The postive rates for surface antigen of hepatitis B virus (HBs-Ag) in sera among the same subjects were 6.4% and 2.5%, respectively. In Nakadohri, the age-adjusted positive rates of HBs-Ag and antibody to HBs-Ag (anti-HBs-Ab) in anti-HTLV-I-Ab positives (so-called HTLV-I carriers) differed little from those in negatives. In Shimo-agata, the geographical distribution of HBs-Ag positives (so-called HBV carriers) showed no positive association with that of HTLV-I carriers. These results did not support the postive correlations between HTLV-I and HBV infections among the general population in ATL-endemic areas in Japan.

Key Words: HTLV-I, HBV, Epidemiology

INTRODUCTION

From a descriptive epidemiological analysis on the geographical patterns of cancer by site in Japan, the mortality rate from malignant lymphomas in the Kyushu district was found to be remarkably high compared with that of Japan as a whole[1, 2]. The higher incidence of malignant lymphomas in Kyushu was due to the excessive incidence of adult T-cell leukemia/lymphoma (ATL), which is known to be highly prevalent in the rural areas of southwestern Japan, especially in Kyushu and southern Shikoku, and including Okinawa Prefecture[3, 4], the southernmost prefecture in Japan. Human T-lymphotropic virus type I (HTLV-I) was strongly suggested to be a main causal agent of ATL[5, 6, 7], and carriers of HTLV-I were clustered in the ATL-endemic areas in the Kyushu district of Japan[8–10]. On the other hand, the mortality rate for liver cancer was relatively high in the southwestern parts of Japan, especially in the Kyushu district[1]. Carriers of hepatitis type B virus (HBV), which is strongly suspected of being one of the important etiological agents of primary hepatocellular carcinoma (HCC)[11, 12], were found mainly in the rural

著者名：

立花一憲・伊藤新一郎・白浜　敏・長友正澄・木下研一郎・田島和雄

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* To whom all correspondence should be addressed.

areas of the Kyushu distict, including Okinawa Prefecture[13].

It is of interest for cancer epidemiologists that both virus-associated malignancies, ATL and HCC, were mainly clustered in the southwestern parts of Japan. The actual transmission routes of HTLV-I are different from those of HBV. However, it is known that both viruses are mainly transmitted by vertical infection from mother to child, and by horizontal infection between men and women through sexual contact under natural conditions[14–17]. It was suggested that some portion of HTLV-I carriers showed diminution of the T-cell-mediated immune function[18], and a positive association between HTLV-I and HBV infections in Okinawa, Japan was reported[19]. However, no association between HTLV-I and HBV infections was shown in the other study in Japan[20], where the sample size was too small to conclude that there was no relation between HTLV-I infection and HBV infection. There are many carriers of HTLV-I in Kyushu, Japan; however, most of them are healthy and do not contract HTLV-I associated diseases even once in their lifetime. It is important for HTLV-I carriers to clarify whether or not they are at excess risk for infection with other viruses. To elucidate this issue, a large scale community-based study on the postivie relationships between HTLV-I and HBV infections was conducted in two ATL-endemic islands in Japan.

SUBJECTS and METHODS

Two islands of the Goto and Tsushima group in Kyushu were selected for this study (Fig. 1). The Goto Islands are located 100 km west of Nagasaki City in Kyushu, where malignant lymphoma is endemic[21]. Nakadohri Island, belonging to the Goto Islands and a typical ATL-endemic area, was selected as the island from which to study the individual distribution of carriers of both HTLV-I and HBV. The total population of Nakadohri Island, from 70 villages, was

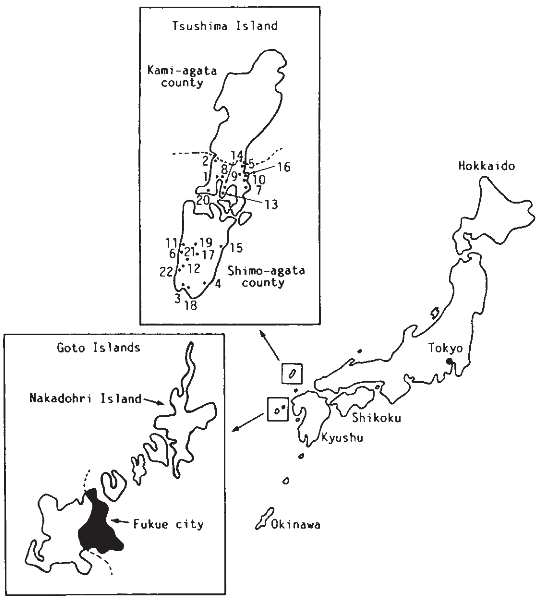

Fig. 1. Location of Nakadohri Island in the Goto Islands and Shimo-agata county in Tsushima Island in Kyushu, Japan. Serial numbers in Shimo-agata county correspond to the name of villages in Table IV.

29,628 in 1985. Shimo-agata county of Tsushima Island was selected for studying the geographical distribution of carriers of both HTLV-I and HBV by village. The total population of shimo-agata county was 33,550, from 79 villages. On Nakadohri Island blood samples for sero-epidemiological studies of HTLV-I and HBV were collected from 5,677 arbitrarily selected outpatients who visited Kamigoto Hospital during 1985–1986. Most outpatients had no serious diseases. On Tsushima Island, samples from 2,084 inhabitants older than 30 years of age from 22 arbitrarily selected villages throughout Shimo-agata county were used (Fig. 1). They were collected from those who participated in an annual mass health examination conducted by the local government in 1984 and 1985 and were a part of the samples collected for the former study on HTLV-I epidemics in Tsushima Island[22].

To evaluate the epidemiological conditions of both HTLV-I and HBV among the inhabitants of Nakadohri in the Goto Islands, sero-positivity in sera for anti-HTLV-I antibody (anti-HTLV-I-Ab), that for HBV surface antigen (HBs-Ag) and that for antibody to HBs-Ag (anti-HBs-Ab) in the same subejcts were examined. To study the relation of HBV infection to HTLV-I infection and vice versa, proportional frequencies of sero-positives of anti-HTLV-I-Ab were calculated for subejcts according to anti-HBs-Ab positivity and vice versa. Furthermore, to compare the geographical distribution between HTLV-I and HBV carriers on Shimo-agata county in Tsushima Island, the percentage frequencies of positives for HBs-Ag in sera (so-called HBV carriers) among inhabitants older than 30 years were compared with those of anti-HTLV-I-Ab positives (so-called HTLV-I carriers) among the same subjects in each village.

Antibody of sera to HTLV-I antigens was evaluated by a gelatine particle agglutination test (PA test: Serodia ATLA Fujirebio, Tokyo, Japan)[23]. All subjects with anti-HTLV-I-Ab titers equal to or more than 16 dilutions of sera were regarded as having positive anti-HTLV-I-Ab and, therefore, were regarded as so-called HTLV-I carriers, based on the observation that HTLV-I antigen could be regularly found in cultures of leukocytes from HTLV-I-Ab positive individuals[24]. HBs-Ag and its antibody in sera were assessed by using phytohemagglutinin tests (Reverse Cell Yamanouchi and PHA Eizai, Tokyo, Japan).

RESULTS

I. Nakadohri-Goto Island

The positive rates for anti-HTLV-I-Ab were 17.6% in males, 22.1% in females and 20.0% for both sexes combined (Table I). Age- and sex-specific positive rates for anti-HTLV-I-Ab on Nakadohri Island are shown in Fig. 2. The positive rates for anti-HTLV-I-Ab increased with age in both sexes, and were higher in females than in males (Fig. 2 and Table I). This difference between male and female was statistically significant ($p < 0.01$). On the other hand, the positive rates for HBs-Ag were 7.1% in males, 4.3% in females and 5.6% for both sexes. The incidence of HBs-Ag carriers did not increase with age and was relatively high in groups aged from 30 to 59 years in both sexes (Fig. 2). The overall incidence of HBs-Ag positives was higher in maels than in females ($p < 0.01$). The positive rates for anti-HBs-Ab were 32.0% in males, 33.2% in females and 32.7% for both sexes, and increased with age until 40 years and then reached a plateau (Fig. 2). As shown in Table II, the distribution of age- and sex-specific positive rates for anti-HTLV-I-Ab in anti-HBs-Ab positives were not very different from those in negatives of anti-HBs-Ab. The age-adjusted positive rates for anit-HTLV-I-Ab were 16.2% and 16.6% in positives and negatives of anit-HBs-Ab, respectively, in males, and were 22.4% and 22.2%, respectively, in females.

Table I. Sex-specific Positive Rates for Anti-HTLV-I Antibody (anti-HTLV-I-Ab), Surface Antigen of HBV (HBs-Ag) and Its Antibody (anti-HBs-Ab) in Sera Among Studied Subjects in Nakadohri-Goto Island (1985–86)

	Male		Female		Total	
	Rate	(Positives/Tested)	Rate	(Positives/Tested)	Rate	(Positives/Tested)
All age groups						
Anti-HTLV-I-Ab	17.6*	(456/2595)	22.1*	(681/3082)	20.0	(1137/5677)
HBs-Ag[1)]	7.1#	(177/2495)	4.3#	(129/3010)	5.6	(306/5505)
Anti-HBs-Ab[2)]	32.0	(802/2503)	33.2	(977/2944)	32.7	(1779/5447)
Older than 30						
Anti-HTLV-I-Ab	22.0*	(405/1837)	27.5*	(617/2242)	25.1	(1022/4079)
HBs-Ag	8.2#	(149/1808)	4.9#	(109/2218)	6.4	(258/4026)
Anti-HBs-Ab	38.5	(671/1745)	39.5	(832/2104)	39.0	(1503/3849)

*# Difference in the positive rate of anti-HTLV-I-Ab and HBs-Ag between males and females was statistically significant ($p < 0.01$).

1) 100 males and 72 females were excluded because of lack of information.

2) 92 males and 138 females were excluded because of lack of information.

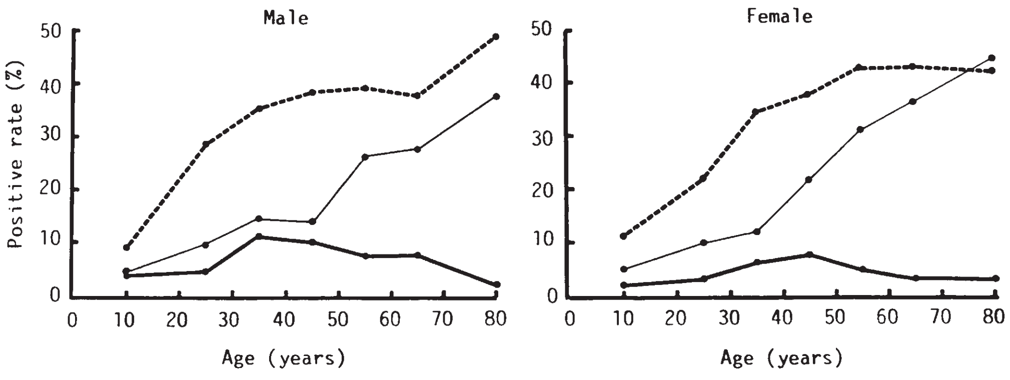

Fig. 2. Age- and Sex-specific sero-positive rates for surface antigens of HBV (HBs-Ag), antibody to HBs-Ag (anti-HBs-Ab) and antibody to HTLV-I (anti-HTLV-I-Ab) in sera among 5,677 study subjects in Nakadohri-Goto Island in 1985-86.

HBs-Ag; Anti-HBs-Ab; Anti-HTLV-I-Ab

Table II. Age- and Sex-specific Positive Rate (%) for Anti-HTLV-I Antibody by Positivity of Anti-HBs-Ab Among Studied Subjects in Nakadohri-Goto Island (1985–86)

Age (years)	Males		Females	
	Anti-HBs-Ab (+)	Anti-HBs-Ab (−)	Anti-HBs-Ab (+)	Anti-HBs-Ab (−)
−19	10.5 (38)[2]	4.1 (393)	5.0 (40)	4.7 (317)
20–29	8.6 (93)	9.8 (234)	9.5 (105)	9.8 (378)
30–39	18.4 (158)	12.3 (292)	14.2 (176)	11.0 (337)
40–49	11.7 (137)	13.0 (223)	24.2 (153)	19.9 (256)
50–59	25.4 (181)	26.2 (286)	31.0 (203)	31.2 (279)
60–69	30.9 (110)	27.9 (183)	36.4 (184)	35.6 (247)
70–	38.8 (85)	30.0 (90)	42.9 (112)	49.7 (153)
Total	21.2 (802)	15.1 (1701)	25.8 (977)	19.9 (1967)
APR[1]	16.2	16.6	22.4	22.2

1) Age-adjusted positive rate (APR) standardized by the age distribution of total subjects
2) Figures in parentheses indicate the number of subjects.

Table III. Crude and Age-adjusted[1] Positive Rate (%) of HBV Surface Antigen (HBs-Ag) and Its Antibody (Anti-HBs-Ab) in Sera by Antibody Positivity against HTLV-I Among Studied Subjects in Nakadohri-Goto Island (1985–86)

	Males		Females	
	Anti-HTLV-I (+)	Anti-HTLV-I (−)	Anti-HTLV-I (+)	Anti-HTLV-I (−)
HBs-Ag[2]				
Crude	6.8 (444)[4]	7.2 (2051)	5.1 (665)	4.1 (2345)
Adjusted	6.3	7.0*	4.6	4.0*
Anti-HBs-Ab[3]				
Crude	39.8 (427)	30.4 (2076)	39.2 (645)	31.5 (2301)
Adjusted	36.5	32.5	34.4	33.0

1) Standardized by the age distribution of total subjects
2) 100 males and 72 females were excluded because of lack of information.
3) 92 males and 138 females were excluded because of lack of information
4) Figures in parentheses indicate the number of subjects.
* Difference between male and female was statistically significant ($P<0.01$).

The proportional frequencies of HBs-Ag positives among HTLV-I-Ab positives and negatives were calculated at 6.8% and 7.2% in males and 5.1%, 4.1% in females, respectively (Table III). The age-adjusted positive rate of HBs-Ag in anti-HTLV-I-Ab positives did not differ from that in anti-HTLV-I-Ab negatives in either sex. However, the difference between male (7.0%) and female (4.0%) was statistically significant ($p<0.01$) in the group of anti-HTLV-I-Ab negatives alone. On the other hand, the proportional frequency of anit-HBs-Ab positives among males and females was calculated at 39.8% and 39.2%, respectively, in anti-HTLV-I-Ab positives, and at 30.4% and 31.5%, respectively, in anti-HTLV-I-Ab negatives (Table III). The positive rate of anti-HBs-Ab in anti-HTLV-I-Ab positives was obviously higher than that in negatives, but more subjects of advanced age were included in HTLV-I-Ab positives than in negatives. After adjusting for age distribution of total subejcts, these differences decreased and showed no statistical significance (Table III).

II. Shimo-agata County in Tsushima Island

The percentage frequencies of anit-HTLV-I-Ab positives (so-called HTLV-I carriers) and HBs-Ag positives (so-called HBV carriers) in sera were 24.0% (500/2084) and 2.5% (52/2084), respectively (Table IV). The villages with high percentage frequencies of HTLV-I carriers did not necessarily correspond to the villages with high percentage frequencies of HBV carriers in Shimo-Agata county. The scatter diagrams of percentage frequencies of positives of anti-HTLV-I-Ab and HBs-Ag (or anti-HBs-Ab) in each village showed no positive correlation ($R < 0.05$). There was no difference in the crude postivie rate of HBs-Ag and anti-HBs-Ab between postivies and negatives of anti-HTLV-I-Ab (Table V).

Table IV. Crude Positive Rate of Anti-HTLV-I Antibody (HTLV-I-Ab), HBV Surface Antigen (HBs-Ag) and Its Antibody (HBs-Ab) Among Healthy Inhabitants (Older than 30 Years) of 22 Villages in Shimo-agata County (1985–86)

Serial number and initial of village[a)]		Number of subjects	Rate of positives (%)		
			HTLV-I-Ab	HBs-Ag	HBs-Ab
1	SAB	54	42.6	3.7	18.5
2	TAH	101	35.6	3.0	10.9
3	TSU	365	35.6	0.5	18.6
4	KUW	100	32.0	2.0	10.0
5	CHI	103	31.0	8.7	17.5
6	KUN	88	29.5	5.7	21.6
7	KAM	129	27.9	0.8	5.4
8	UMU	42	26.2	0	19.0
9	YAR	20	25.0	0	20.0
10	GAY	132	22.7	5.3	0
11	KOM	124	22.6	5.6	17.7
12	SHI	99	22.2	0	23.2
13	SAG	56	19.6	1.8	0
14	SAS	55	18.2	0	10.9
15	KOU	74	17.6	0	24.3
16	YOK	29	17.2	3.4	12.1
17	KAM	33	15.2	0	0
18	AZA	101	14.9	0	0
19	SHM	75	14.7	2.7	21.3
20	MIZ	132	10.6	3.0	12.1
21	KAS	76	5.3	1.3	11.8
22	KUN	96	2.1	6.3	20.8
	Total	2084	24.0	2.5	14.2

a) Serial numbers of villages correspond to those in Figure 1.

Table V. Crude Positive Rate of HBV Surface Antigen (HBs-Ag) and Its Antibody (anti-HBs-Ab) by Positivity of Anti-HTLV-I Antibody (anti-HTLV-I-Ab) Among Inhabitants (older than 30 Years) in Shimo-agata County (1985–86)

	Anti-HTLV-I-Ab (+) (n = 500) Positives (%)	Anti-HTLV-I-Ab (−) (n = 1,584) Positives (%)
HBs-Ag	13 (2.6)	39 (2.5)
Anti-HBs-Ab	72 (14.4)	224 (14.1)

DISCUSSION

It is well known that there are several tumor viruses that act as causative agents for human malignancies, i.e., HTLV-I for ATL[5–7], EBV for Burkitt's lymphoma in Africa and nasopharyngeal cancer in China[25, 26] and papilloma virus types 16, 18, etc. for uterine cervical cancer [27–29]. From descriptive epidemiological studies on cancer deaths in Japan[1], virus-associated cancers such as malignant lymphomas, especially ATL, liver cancer and uterine cancer had higher incidence in the southwestern parts of Japan. It is well known that HTLV-I for ATL and HBV for HCC were highly prevalent in these areas[1, 2, 4, 12].

In HTLV-I, it is thought the two main routes of transmission under natural conditions are from mother to children through breast milk[15] and from husband to wife through semen[16]. The epidemiological evidence that the transmission of HTLV-I is one-way from husband to wife helps explain the discrepancy in the HTLV-I carriers' (anti-HTLV-I-Ab positives) rate between males and females (Fig. 2 and Table I) previously reported[14]. However, most of the seroconverted persons against HBV surface antigens (anti-HBs-Ab positives), who rarely transmit HBV to other persons, seem to be non-carriers of HBV. Only HBs-Ag positives, especially carriers with HBe-Ag, are more likely to transmit HBV to susceptible persons. Generally, persistent carriers of HBs-Ag are generated on the occasion of HBV transmission from carrier mothers, especially from mother with HBe-Ag, to newborn children mainly by perinatal infection and/or through the placenta under natural conditions[30, 31]. On the other hand, even seroconverted persons against HTLV-I transmit HTLV-I to other susceptible persons. Under natural conditions, however, HTLV-I is less contagious than HBV and mainly spreads through intimate and repeated contact to susceptible persons. The reason for the different infectivity between the two viruses is that HBV is transmitted through virus particles in body fluids but HTLV-I is transmissible only through infected lymphocytes.

In Nakadohri-Goto Island, there was no difference in the positive rate of anti-HBs-Ab between males and females, probably because HBV is more contagious compared with HTLV-I and the horizontal transmission from HBs-Ag carriers to non-carriers is both-way between male and female, the mode of which is quite diffrerent from that of HTLV-I. Though the crude positive rates of anti-HTLV-I-Ab in positives of anti-HBs-Ab were slightly highter than those in negatives of anti-HBs-Ab in both sexes, this difference disappeared after being standardized by the age distribution of total subjects (Table II). Furthermore, the small difference in the crude positive rate of HBs-Ag and anti-HBs-Ab between positives and negatives of anti-HTLV-I-Ab diminished when standardized by the age distribution of total subjects (Table III). These results did not support the positive correlation between HTLV-I and HBV infections.

It is well known that both viruses can be transmitted by blood transfusion. However, no concordant distribution of age-adjusted seroconverters between HBV and HTLV-I was shown in the present study because blood transfusion made less of a contribution to the spread of both these viruses than the natural transmission in these rural ageas in the past (unpublished information).

As shown in the previous report[19], the positive rate of HBs-Ag in females (4.3%) was significantly lower than that in males (7.1%), especially in non-carriers of HTLV-I (Table I and III). There is no evidence to clearly explain this discrepancy, however, the possibility that females are more resistant than males against HBs-Ag infection or less susceptible to HBs-Ag under natural conditions could not denied. It may also be that more than a few women moved to Nakadohri-Goto Island because of marriage from other districts where neither HTLV-I nor HBV was so prevalent. Though these effects may not be very serious, the lower positive rate of HBs-Ag in non-HTLV-I-carrier females compared with that in males was statistically significant (Table III). On the other hand, the positive rate of anti-HTLV-I-Ab increased with age, and positive rate of HBs-Ag among the middle-aged (30–49 years) group was remarkably higher than those of both the younger (under 30 years) and older (over 49 years) aged groups (Fig. 2). The manner of seroconversion of HBs-Ag may be different from that of HTLV-I. Nevertheless, some unknown factors increased the chance of HBs-Ag transmission in the middle-aged generation in these districts.

The distribution of HTLV-I carriers by village on Nakadohri-Goto Island was not characteristic of HTLV-I distribution in that region, in that most of the villages on Nakadohri were highly endemic for HTLV-I, and in that there was little difference in the average rates of HTLV-I carriers among villages. In the present study, therefore, we analysed the individual distribution of HTLV-I carriers, HBV carriers and its antibody positives in Nakadohri Island. No positive correlation of HBV infection with HTLV-I infection (Table II) and vice versa (Table III) in these populations was shown.

The prefecture-based geographical distribution of HTLV-I carriers in Japan remarkably resembled that of HBV carriers in Japan as a whole[8–10, 13, 32]. However, the community-based detailed analysis of the geographical distribution of carriers of HBV and HTLV-I in Shimo-agata county in Tsushima Island showed no positive correlation between the two distributions (Table IV), which suggested that in the past the carriers of HTLV-I were originally clustered in families and communities different from those of the carriers of HBV, on Tsushima Island.

It has been suggested that some HTLV-I carriers have possible disorders of the T-cell mediated immune system, and that some are more susceptible to other viruses than non-carriers[18]. It has also been suggested that HBV-infected persons have a higher chance of HTLV-I infection compared with those without HBV infection in Okinawa, Japan[19]. In the present large-scale community-based study, in addition to the previous report[20], however, no positive evidence to support the positive correlations between HTLV-I and HBV epidemics could be found. Thus, it seems unlikely that, among most healthy people in the ATL-endemic areas of Japan, HTLV-I infection under natural conditions suppresses the immune function of its hosts and makes them susceptible to HBV infection.

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