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Non-B hepatocellular carcinoma: influence of age, sex, alcohol, family clustering, blood transfusion and chronic liver disease.

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Abstract

In 144 cases of hepatocellular carcinoma (HCC), 166 cases of cirrhosis without HCC and 142 cases of chronic hepatitis, we examined HBsAg, anti-HBs and anti-HBc in sera and compared the following factors between hepatitis B virus marker-negative and -positive patients: age, sex, alcohol consumption, family clustering of liver diseases, and histories of blood transfusion and post-transfusion hepatitis. Results of this study demonstrated several distinct differences in clinical backgrounds between non-B (negative for HBsAg, anti-HBs and anti-HBc) and B (positive for HBsAg) patients with HCC. Non-B patients were significantly older, had a lower frequency of familial tendencies for liver diseases, and more frequently had cancers other than HCC in their families. Some of these differences were also observed between non-B and B patients with cirrhosis and chronic hepatitis. Among patients with chronic hepatitis, the non-B patients had received blood transfusion or had post-transfusion hepatitis more frequently than the B patients. However, this difference was not apparent in patients with liver cirrhosis or HCC, suggesting that progression of non-A, non-B post-transfusion hepatitis to cirrhosis and HCC may not be as frequent as progression to chronic hepatitis.

KEYWORDS: non-B hepatocellular carcinoma, type non-A, non-B hepatitis, type B hepatitis, post-transfusion hepatitis

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NON-B HEPATOCELLULAR CARCINOMA : INFLUENCE OF AGE, SEX, ALCOHOL, FAMILY CLUSTERING, BLOOD TRANSFUSION AND CHRONIC LIVER DISEASE

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Abstract. In 144 cases of hepatocellular carcinoma (HCC), 166 cases of cirrhosis without HCC and 142 cases of chronic hepatitis, we examined HBsAg, anti-HBs and anti-HBc in sera and compared the following factors between hepatitis B virus marker-negative and -positive patients : age, sex, alcohol consumption, family clustering of liver diseases, and histories of blood transfusion and post-transfusion hepatitis. Results of this study demonstrated several distinct differences in clinical backgrounds between non-B (negative for HBsAg, anti-HBs and anti-HBc) and B (positive for HBsAg) patients with HCC. Non-B patients were significantly older, had a lower frequency of familial tendencies for liver diseases, and more frequently had cancers other than HCC in their families. Some of these differences were also observed between non-B and B patients with cirrhosis and chronic hepatitis. Among patients with chronic hepatitis, the non-B patients had received blood transfusion or had post-transfusion hepatitis more frequently than the B patients. However, this difference was not apparent in patients with liver cirrhosis or HCC, suggesting that progression of non-A, non-B post-transfusion hepatitis to cirrhosis and HCC may not be as frequent as progression to chronic hepatitis.

Key words : non-B hepatocellular carcinoma, type non-A, non-B hepatitis, type B hepatitis, post-transfusion hepatitis.

Patients with hepatocellular carcinoma (HCC) show high frequencies of hepatitis B surface antigen (HBsAg), particularly in areas of the world in which hepatitis B virus (HBV) infection is endemic (1, 2), and there may be a direct or indirect role of HBV in the pathogenesis of HCC (3). The distribution of non-A, non-B hepatitis appears to be worldwide. Non-A, non-B hepatitis is transmitted by blood transfusion, and more than 90 % of post-transfusion hepatitis now is attributed to infection by non-A, non-B hepatitis virus (es) (4). It has been speculated, at least in Japan, that infection with non-A, non-B hepatitis virus (es) also is responsible for chronic liver diseases leading to HCC, including HBsAg-negative cases of HCC (5).

Cases of acute non-A, non-B hepatitis, especially of non A, non-B post-transfusion hepatitis, have progressed to chronic active hepatitis (CAH) with or without cirrhosis (6-8). However, little is known about the evolution to HCC as a consequence of chronic non-A, non-B hepatitis. We have compared the following factors between HBV marker-negative and -positive patients out of 144 cases of HCC, 166 cases of cirrhosis without HCC and 142 cases of chronic hepatitis : age, sex, alcohol consumption, family clustering of liver diseases, and history of blood transfusion and post-transfusion hepatitis. In patients with HCC, past history of chronic liver disease was also analyzed for progression of the disease to HCC.

MATERIALS AND METHODS

The case notes of 144 patients with HCC hospitalized at Okayama University Hospital between 1970 and 1981 were analyzed. The diagnosis was made by autopsy in 93 patients, by liver biopsy in 20, and through various combinations of peritoneoscopy, celiac arteriography, computed tomography (CT), ultrasonography (US) and α-fetoprotein determination in 31. The underlying cirrhosis was confirmed by biopsy at the time of peritoneoscopy or at autopsy in 90 % of the patients. During the past 3 years, 116 cirrhotic patients without HCC and 142 patients with chronic hepatitis also were seen at our hospital. Diagnosis of all the patients was made by peritoneoscopic biopsy together with scintigram, CT and US. Patients with the following diagnoses, by liver biopsy findings and history of the disease, were excluded from this study : autoimmune hepatitis (lupoid hepatitis), primary biliary cirrhosis, hemochromatosis, chronic alcoholic liver injury or alcoholic cirrhosis (in alcoholic liver disease, the alcoholic intake was more than 86.0 g of alcohol per day for more than 10 years).

Hepatitis B surface antigen (HBsAg) in sera was detected by an immune adherence hemagglutination assay (IAHA), a reversed passive hemagglutination assay (RPHA), or a radioimmunoassay (Austria II-125, Abbott Laboratories, North Chicago, Ill.). Serum antibodies to HBsAg (anti-HBs) were detected by an IAHA, a passive hemoagglutination assay, or a radioimmunoassay (Ausab, Abbott). Serum antibodies to hepatitis B core antigen (anti-HBc) were detected by a radioimmunoassay (Anti-HBc RIA kit, Abbott) (9). The patients were divided into three groups as to HBV markers (I : negative for both HBsAg and anti-HBs, II : positive for anti-HBs, and III : positive for HBsAg). The first group was further divided into three subgroups according to anti-HBc (Ia : negative for anti-HBc, Ib : positive for anti-HBc, and Ic : anti-HBc not tested). Patients whose sera were negative for all HBV markers (Ia) were regarded as non-B. Patients with apparently ongoing infection (III : positive for HBsAg) were classified as B. Age, sex, titer of anti-HBc antibodies, history of blood transfusion, alcohol consumption, familial clustering of liver disease, and underlying cirrhosis were evaluated in the non-B patients with HCC. Alcohol consumption was estimated and family histories were obtained by interviews of patients and their families. In patients with HCC, past history of chronic liver disease was followed in detail for the evaluation of progression from viral hepatitis to HCC. The age, sex, alcohol consumption, familial clustering of liver diseases, and history of blood transfusion and post-transfusion hepatitis were compared among the various groups of patients.

RESULTS

Of the 144 patients with HCC, 20 (13.9 %) were negative for all HBV markers (Table 1). The positive rate for HBsAg was 27.6 % in cirrhotic patients, 42.4 % in those with HCC and 50.0 % in those with chronic hepatitis. Conversely, anti-HBs was more frequently positive in patients with cirrhosis (23.3 %) than in those with HCC (13.9 %) or chronic hepatitis (8.5 %). The mean age of HCC patients was 54.0 years, approximately 5 years more than that of cirrhotic patients without evidence of HCC and about 15 years more than that of patients with chronic hepatitis.

Twenty patients with HCC were diagnosed as non-B (Ia group) (Table 2). Their ages ranged from 48 to 76 years. The male/female ratio was 4.0. Two of the patients had received blood transfusions, one 21 years ago and the other 30 years ago, but they had no signs of post-transfusion hepatitis or chronic liver disease. Two patients had drank more than 86.0 g of alcohol daily for more than 10 years. Six patients had drank from 51.6 g to 86.0 g of alcohol daily for more than 10 years. Family clustering of liver disease was found in two HCC patients. Parents or siblings of 8 patients had died of cancers other than HCC. Liver cirrhosis was confirmed histologically in 13 patients and clinically diagnosed in 3 cases. In 7 patients, cirrhosis had been found 1 to 9 years before the development of HCC. Viral hepatitis was implicated as the cause of cirrhosis in one of the 7 patients, but in the other six patients, there was no history of acute or chronic hepatitis. The patient with a history of acute hepatitis (patient No. 9 in Table 2) had complained of general weakness and had abnormal liver function test results 7 years after the onset of acute hepatitis when a liver biopsy specimen showed posthepatitic scarring. Twelve years after the onset of acute hepatitis, splenomegaly was detected, and 4 years later, cirrhosis was suspected because of

TABLE 1. COMPARISON OF POSITIVE RATE FOR HBV MARKERS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA, CIRRHOSIS OR CHRONIC HEPATITIS

	HBsAg −, Anti-HBs − (I)			Anti-HBs + (II)	HBsAg + (III)
	Anti-HBc − (I a)	Anti-HBc + (I b)	N.T.[a] (I c)		
Hepatocellular carcinoma (144 cases)	20 (13.9 %)	22 (15.3 %)	21 (14.6 %)	20 (13.9 %)	61 (42.4 %)
Cirrhosis (116 cases)	29 (25.0 %)	21 (18.1 %)	7 (6.0 %)	27 (23.3 %)	32 (27.6 %)
Chronic hepatitis (142 cases)	39 (24.5 %)	16 (11.3 %)	4 (2.8 %)	12 (8.5 %)	71 (50.0 %)

[a] N.T.: not tested

TABLE 2. AGE, SEX, TITER OF ANTI-HBC, BLOOD TRANSFUSION, ALCOHOL CONSUMPTION, FAMILIAL CLUSTERING OF LIVER DISEASES AND UNDERLYING CIRRHOSIS IN NON-B PATIENTS WITH HEPATOCELLULAR CARCINOMA

	Age	Sex	HBsAg	Anti-HBs	Anti-HBc[a]	Blood transfusion	Heavy alcohol Consumption	Family clustering of Liver Diseases	with underlying cirrhosis
1.	62	F	–	–	2 %	–	–	–	LC[b]
2.	49	M	–	–	20	–	–	–	LC
3.	59	M	–	–	17	–	–	–	Liver fibrosis
4.	64	M	–	–	19	–	+ 1	–	LC[b]
5.	67	M	–	–	17	–	–	–	LC
6.	51	M	–	–	8	–	–	–	LC
7.	73	F	–	–	10	–	–	–	LC
8.	70	M	–	–	44	–	+ 1	–	?
9.	54	M	–	–	12	–	–	+	LC
10.	76	M	–	–	15	21 y. ago	–	+	CAH 2B
11.	57	M	–	–	15	–	+ 2	–	LC
12.	52	M	–	–	0	–	–	–	LC
13.	58	M	–	–	0	–	+ 1	–	LC
14.	53	F	–	–	22	–	–	–	Non-specific Liver disease
15.	53	M	–	–	43	–	+ 1	–	LC
16.	48	M	–	–	28	–	+ 1	–	LC
17.	71	F	–	–	2	30 y. ago	–	–	LC
18.	65	M	–	–	24	–	–	–	LC[b]
19.	53	M	–	–	19	–	+ 2	–	LC
20.	52	M	–	–	18	–	+ 1	–	LC

a anti-HBc is shown by inhibition % in radioimmunoassay (8). *b* clinical diagnosis. Alcohol consumption : + 1 = more than 51.6 g/day for over 10 years, + 2 = more than 86.0 g/day for over 10 years.

abnormal liver function tests, jaundice and ascites. In September, 1980, he had and elevated serum level of α-fetoprotein and a space occupying lesion in the liver observed by CT ; HCC was confirmed by liver biopsy.

Follow-up observations of non-B and B HCC patients who had an initial diagnosis of acute hepatitis, chronic hepatitis or cirrhosis are summarized in Figs. 1 and 2. Among the 20 patients with non-B HCC, only one patient (5 %) had been initially diagnosed as having a liver disease at the stage of hepatitis. Six patients already had cirrhosis when liver disease was recognized, and in the other 13 patients, liver disease was not found until the diagnosis of HCC was made (Fig. 1). In contrast, 9 of 61 patients with B HCC (27.8 %) had had liver disease diagnosed at the stage of acute hepatitis and 8 at the stage of chronic hepatitis. The intervals from the first signs of acute hepatitis and chronic hepatitis to the

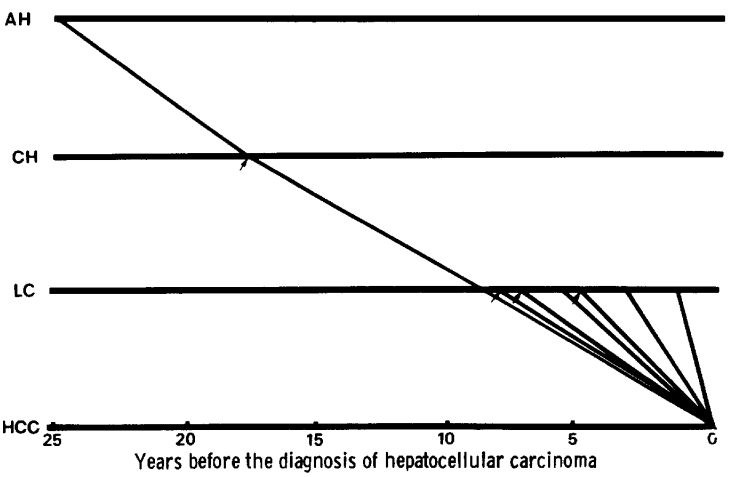

Fig. 1. Non-B patients with hepatocellular carcinoma during a clinical follow-up of chronic liver disease. AH = acute hepatitis (first clinical signs of acute hepatitis). CH = chronic hepatitis. LC = liver cirrhosis. HCC = hepatocellular carcinoma. → = histological diagnosis.

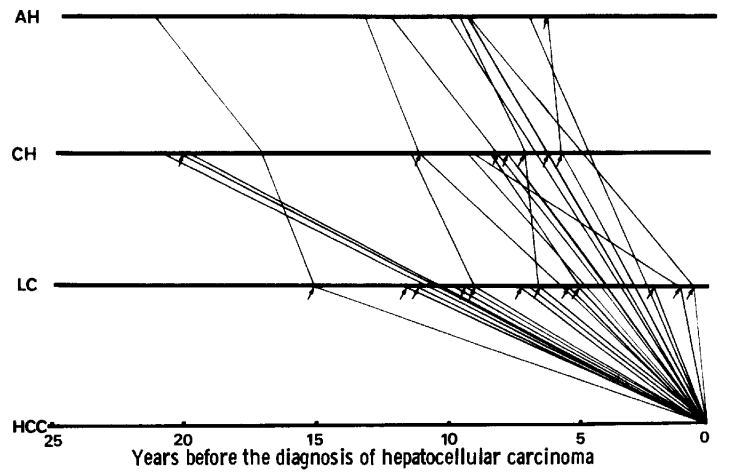

Fig. 2. HBsAg-positive patients with hepatocellular carcinoma during a clinical follow-up of chronic liver disease. AH = acute hepatitis (first clinical signs of acute hepatitis). CH = chronic hepatitis. LC = liver cirrhosis. HCC = hepatocellular carcinoma. → = histological diagnosis.

diagnosis of HCC were from 6 to 21 years (mean, 9.7 years) and from 5 to 20 years (mean, 9.9 years), respectively (Fig. 2).

As shown in Table 3, the mean age of non-B (Ia) patients was about 9 years more than that of B patients (III) with HCC, cirrhosis or chronic hepatitis ($p < 0.01$). No significant difference in sex distribution (Table 4) between group III and

TABLE 3. MEAN AGE OF PATIENTS WITH HEPATOCELLULAR CARCINOMA, CIRRHOSIS OR CHRONIC HEPATITIS AMONG DIFFERENT GROUPS OF HBV MARKERS

	HBsAg −, Anti-HBs − (I)			Anti-HBs + (II)	HBsAg + (III)	Statistical analysis between Ia & III
	Anti-HBc − (Ia)	Anti-HBc + (Ib)	N.T.[a] (Ic)			
Hepatocellular carcinoma (144 cases)	59.4± 8.6 (Mean±S.D.)	58.0±8.5	51.4±9.0	53.7±8.2	51.3±10.6	$p<0.01$
Cirrhosis (116 cases)	54.0±11.3	56.6±9.8	53.1±4.5	57.7±8.3	44.8±12.4	$p<0.01$
Chronic hepatitis (142 cases)	42.9±11.9	51.3±6.3	48.0±7.6	44.4±7.7	34.0±10.9	$p<0.01$

a N.T.: not tested

TABLE 4. SEX DISTRIBUTION (MALE/FEMALE) OF PATIENTS WITH HEPATOCELLULAR CARCINOMA, CIRRHOSIS, OR CHRONIC HEPATITIS AMONG DIFFERENT GROUPS OF HBV MARKERS

	HBsAg −, Anti-HBs − (I)			Anti-HBs + (II)	HBsAg + (III)	Statistical analysis between Ia & III
	Anti-HBc − (Ia)	Anti-HBc + (Ib)	N.T.[a] (Ic)			
Hepatocellular carcinoma (144 cases)	16/4 (4.0)	22/0 (∞)	19/2 (9.5)	16/4 (4.0)	54/7 (7.7)	N.S.[b]
Cirrhosis (116 cases)	19/10 (1.9)	20/1 (20.0)	4/3 (1.3)	22/5 (4.4)	25/7 (3.6)	N.S.
Chronic hepatitis (142 cases)	24/15 (1.6)	14/2 (7.0)	3/1 (3.0)	12/0 (∞)	55/16 (3.4)	N.S.

a N.T.: not tested, *b* N.S.: not significant

TABLE 5. ALCOHOL CONSUMPTION (> 86.0 G/DAY, > 10 YEARS) OF PATIENTS WITH HEPATOCELLULAR CARCINOMA, CIRRHOSIS OR CHRONIC HEPATITIS AMONG DIFFERENT GROUPS OF HBV MARKERS

	HBsAg −, Anti-HBs − (I)			Anti-HBs + (II)	HBsAg + (III)	Statistical analysis between Ia & III
	Anti-HBc − (Ia)	Anti-HBc + (Ib)	N.T.[a] (Ic)			
Hepatocellular carcinoma (144 cases)	2/20 (10.0 %)	6/22 (27.3 %)	3/21 (14.3 %)	4/20 (20.0 %)	3/61 (4.9 %)	N.S.[b]
Cirrhosis (116 cases)	8/29 (27.6 %)	8/21 (38.1 %)	0/7 (0 %)	7/27 (25.9 %)	3/32 (9.4 %)	N.S.
Chronic hepatitis (142 cases)	1/39 (2.6 %)	4/16 (25.0 %)	0/4 (0 %)	3/12 (25.0 %)	2/71 (2.8 %)	N.S.

a N.T.: not tested, *b* N.S.: not significant

group Ia patients was observed. However, the male/female ratio of 7.5 : 1 in patients with HCC was significantly higher than the 3.5 : 1 in those with cirrhosis ($p < 0.05$) and 3.2 : 1 in those with chronic hepatitis ($p < 0.01$). Concerning alcohol consumption, 19 patients (13.2 %) with HCC, 26 patients (22.4 %) with cirrhosis, and 10 patients (7.0 %) with chronic hepatitis had drunk more than 86.0 g of alcohol daily for more than 10 years (Table 5). In these patients with cirrhosis or chronic hepatitis, etiological participation of hepatitis virus infection was suggested histologically despite heavy alcohol intake. Therefore, the alcohol intake was regarded as only a contributing factor in the disease. Among patients with HCC, there was no significant difference in the numbers of heavy drinkers between the non B group (Ia) and the B group (III) (Table 5).

TABLE 6 FAMILY CLUSTERING OF LIVER DISEASES IN PATIENTS WITH HEPATOCELLULAR CARCINOMA, CIRRHOSIS OR CHRONIC HEPATITIS AMONG DIFFERENT GROUPS OF HBV MARKERS

	HBsAg −, Anti-HBs − (I)			Anti-HBs + (II)	HBsAg + (III)	Statistical analysis between I & III
	Anti-HBc − (Ia)	Anti-HBc + (Ib)	N.T.[a] (Ic)			
Hepatocellular carcinoma (144 cases)	2/20 (10.0 %)	7/22 (31.8 %)	2/21 (9.5 %)	4/20 (20.0 %)	25/61 (41.0 %)	$p < 0.05$
Cirrhosis (116 cases)	5/29 (17.2 %)	1/21 (4.8 %)	0/7 (0 %)	4/27 (14.8 %)	16/32 (50.0 %)	$p < 0.01$
Chronic hepatitis (142 cases)	7/39 (17.9 %)	6/16 (37.5 %)	0/4 (0 %)	2/12 (16.7 %)	23/71 (32.4 %)	N.S.[b]

[a] N.T.: not tested, [b] N.S.: not significant

TABLE 7. FAMILIAL CLUSTERING OF HEPATOCELLULAR CARCINOMA AND OTHER CANCER IN PATIENTS WITH HEPATOCELLULAR CARCINOMA OR CIRRHOSIS AMONG DIFFERENT GROUPS OF HBV MARKERS

		HBsAg −, Anti-HBs − (I)			Anti-HBs + (II)	HBsAg + (III)	Statistical analysis between I & III
		Anti-HBc − (Ia)	Anti-HBc + (Ib)	N.T.[a] (Ic)			
Hepatocellular carcinoma (144 cases)	Familial occurrence of HCC	0/20 (0 %)	1/22 (4.5 %)	0/21 (0 %)	0/20 (0 %)	5/61 (8.2 %)	N.S.[b]
	Familial occurrence of cancer besides HCC	8/20 (40.0 %)	5/22 (22.7 %)	2/21 (9.5 %)	3/20 (15.0 %)	3/61 (4.9 %)	$p < 0.01$
Cirrhosis (111 cases)	Familial occurrence of HCC	2/29 (6.9 %)	0/22 (0 %)	0/10 (0 %)	1/27 (3.7 %)	4/32 (12.5 %)	N.S.
	Familial occurrence of cancer besides HCC	4/29 (13.8 %)	6/22 (27.3 %)	1/10 (10.0 %)	6/27 (22.2 %)	4/32 (12.5 %)	N.S.

[a] N.T.: not tested, [b] N.S.: not significant

B patients had a higher frequency of liver diseases among first-degree relatives than did non-B patients (Table 6). As for the familial clustering of cancer, there was no significant difference between non-B (Ia) patients with HCC and B (III) patients, but there was an increased frequency of non-HCC cancers in relatives of the non-B patients ($p<0.01$) (Table 7).

TABLE 8. PAST HISTORY OF BLOOD TRANSFUSION AND POST-TRANSFUSION HEPATITIS IN PATIENTS WITH HEPATOCELLULAR CARCINOMA, CIRRHOSIS OR CHRONIC HEPATITIS AMONG DIFFERENT GROUPS OF HBV MARKERS

		HBsAg −, Anti-HBs − (I)			Anti-HBs + (II)	HBsAg + (III)	Statistical analysis between Ia & III
		Anti-HBc − (Ia)	Anti-HBc + (Ib)	N.T.[a] (Ic)			
Hepatocellular carcinoma (144 cases)	Blood transfusion	2/20 (10.0 %)	2/22 (9.1 %)	1/21 (4.8 %)	4/20 (20.0 %)	7/61 (11.5 %)	N.S.[b]
	Post-transfusion hepatitis	0/20 (0 %)	0/22 (0 %)	0/21 (0 %)	1/20 (5.0 %)	2/61 (3.3 %)	N.S.
Cirrhosis (111 cases)	Blood transfusion	4/29 (13.8 %)	3/21 (14.3 %)	1/7 (14.3 %)	7/27 (25.9 %)	3/32 (9.4 %)	N.S.
	Post-transfusion hepatitis	0/29 (0 %)	1/21 (4.8 %)	0/7 (0 %)	2/27 (7.4 %)	0/32 (0 %)	N.S.
Chronic hepatitis (142 cases)	Blood transfusion	15/39 (38.5 %)	2/16 (12.5 %)	1/4 (25.0 %)	0/12 (0 %)	2/71 (2.8 %)	$p<0.01$
	Post-transfusion hepatitis	9/39 (23.1 %)	2/16 (12.5 %)	0/4 (0 %)	0/12 (0 %)	0/71 (0 %)	$p<0.01$

[a]N.T.: not tested, [b]N.S.: not significant

Among patients with chronic hepatitis, a history of blood transfusion or post-transfusion hepatitis was more frequent in the non-B group than in the B group ($p<0.01$) (Table 8), but among patients with cirrhosis or HCC, no apparent difference in the frequency of these factors was observed. In total, 6 non-B patients with cirrhosis or HCC had received blood transfusions 16 to 22 years before the diagnosis was made, but no symptoms or signs indicating post-transfusion hepatitis were manifest in any of them.

DISCUSSION

Results of this study demonstrated several distinct differences in clinical backgrounds between HBV marker-negative and -positive patients with HCC. Non-B patients were significantly older, had a lower frequency of familial clusterings of liver diseases, and more frequently had cancers other than HCC in their families. Some of these differences were also observed between non-B and B

patients with cirrhosis and chronic hepatitis. Among patients with chronic hepatiti, the non-B group more frequently had received blood transfusion or had post-transfusion hepatitis than was the case in the B group. However, this difference was not apparent in patients with liver cirrhosis or HCC, suggesting that progression of non-A, non-B post-transfusion hepatitis to cirrhosis and HCC may not be as frequent as progression to chronic hepatitis.

The reported frequency of positive HBsAg tests in HCC is approximately 40 %. In Japan, 15 to 25 % of HCC patients are negative for all three HBV markers (HBsAg, anti-HBs and anti-HBc) (10, 11). These rates are compatible with our results, in which 20 patients with HCC (13.9 %) were negative for the three markers. Two of the 20 patients with HCC had histories of blood transfusion. In Japan, a large portion of post-transfusion hepatitis has been reported to due to be non-A, non-B hepatitis infection (4). Moreover, recent evidence indicates that non-A, non-B post-transfusion hepatitis commonly progresses to chronic hepatitis (7, 12). Our data also demonstrate a significantly higher frequency of blood transfusion or post-transfusion hepatitis in non-B patients with chronic hepatitis than in B patients.

Sporadic non-A, non-B hepatitis also has been reported to progress to chronic hepatitis (13). In this study, 1 of the 20 patients with non-B HCC had a history of acute hepatitis, but in the other patients, liver disease was not recognized until cirrhosis or HCC had already developed. This observation is in contrast with patients with B HCC, in about 30 % of whom liver diseases had been recognized at a stage of hepatitis. One possible interpretation of this difference is that the well-developed screening system for HBsAg makes it possible to find and follow asymptomatic carries of HBV. However, experimental transmission of non-A, non-B hepatitis virus to human volunteers and chimpanzees has indicated that most recipients were asymptomatic even when biochemical or histologic evidence of liver injury was present (14). The review of cases of acute non-A, non-B hepatitis that progressed to chronic active hepatitis with or without cirrhosis also revealed that chronic active non-A, non-B hepatitis was often associated with long symptom-free periods accompanied by nearly normal values of liver function tests (13). Our observation that liver disease was recognized at a late stage in non-B HCC patients is compatible with the finding that non-A, non-B hepatitis virus infection progresses latently with a long symptom-free period.

Another interesting observation in patients with non-B HCC was their higher frequency of a family history of non-HCC cancers. Since the discovery of HBV, evidence for the oncogenic role of HBV has accumulated. A particularly high frequency of HCC has been reported in cirrhosis following HBsAg-positive chronic active hepatitis (15) and malignant changes of liver cells are closely associated with the presence of HBsAg (16). The recent demonstration of the HBV genome in DNA of HCC has provided more direct evidence for the oncogenecity of HBV. However, the relationship of non-A, non-B virus to oncogenesis in HCC is entirely

unclear, even though there have been some well-documented cases of HCC in non-B chronic active hepatitis (17, 18). Our observations have led us to believe that in cirrhotic patients who have chronic non-A, non-B hepatitis virus infection, an underlying genetic background plays a more important role as an accelerating factor for the development of HCC than in patients with HBV infection.

Other characteristics observed in the non-B HCC patients was that their mean age was 9 years greater and the frequency of familial occurence of liver disease was lower than in the B group. These differences were also observed in patients with cirrhosis or chronic hepatitis. These findings suggest that the mechanism of infection for non-A, non-B hepatitis virus may be different from HBV, *i.e.*, vertical transmission, so common in HBV infection in Japan, may not be the main route of transmission of non-A, non-B hepatitis virus. Non-A, non-B hepatitis virus (es) has come to our attension gradually. With the development of reliable serologic tests to detect non-A, non-B virus infection, it will be possible to assess more precisely the importance of non-A, non-B hepatitis virus infection in the pathogenesis of non-B chronic liver disease and HCC.

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