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Etiology and Outcome of Acute Viral Hepatitis in Korean Adults

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One hundred and sixteen Korean adults with biopsy-proven acute viral hepatitis were studied to determine the etiology and the outcome of the disease using paired sera obtained during acute and convalescent phases. The prevalence of acute viral hepatitis A, B, D and non-A non-B were 3.4%, 60.3%, 0.9% and 35.3%, respectively: hepatitis B virus infection was the most common cause and the hepatitis D virus superinfection was almost negligible. Only eleven (26.8%) of 41 patients with AVH NANB were negative for all serological markers of HBV. The rest (73.2%) were positive for at least one HBV marker: HBsAg was positive in 31.7%. Therefore, the presence of HBV serologic markers in the sera does not exclude the diagnosis of AVH NANB in Korea. In patients with acute viral hapatitis B, 27% remained positive for HBsAg. Chronic hepatitis developed in 12.8% and 17% patients with acute hepatitis B and non-A non-B, respectively. Progression to chronic hepatitis in patients with acute viral hepatitis B and non-A non-B occurred more commonly, although statistically not significant, in male sex and in patients who did not have clinical jaundice during the acute phase and who showed bridging necrosis in their liver biopsies. Age did not influence the progression to chronic hepatitis.

Key Words: *Korea, Acute viral hepatitis, Hepatitis B virus, non-A Non-B hepatitis, Hepatitis D virus, Progression to chronic hepatitis.*

INTRODUCTION

Acute viral hepatitis (AVH) is a serious and still a common infectious disease in Southeast Asia. Viral hepatitis actually encompasses diseases caused by at least five distinct viral agents (Lee and Vyas, 1987): A, B, D (delta), non-A non-B (NANB) and other viruses such as Epstein-Barr virus (EBV) and cytomegalovirus. Recent advances in hepatitis virology led to the development of very sensitive and specific serologic assays for distinguishing various forms of viral hepatitis except NANB hepatitis. Choo et al. (1989) cloned and sequenced what was called NANB hepatitis agent and Kuo et al. (1989) subsequently developed a serological assay to detect antibody to an epitope of this virus, now designated as hepatitis C virus (HCV). However, with the currently available assay, at least a six-month follow-up will be required in patients with sus pected acute hepatitis C to make the final diagnosis (Alter MJ, 1989): the more timely diagnosis of acute hepatitis C during symptomatic stage must await the development of new and more sensitive serological assay. Therefore, the diagnosis of AVH NANB is still based on exclusion of known viral agents. The diagnosis of AVH NANB is very difficult particularly in Korea where the prevalence of hepatitis B virus (HBV) infection is very high: HBsAg is positive in about 10% and anti-HBc is positive in about 60% of general population (Hong and Kim, 1982). Furthermore, spontaneous reactivation of chronic hepatitis B is characterized by clinical and biochemical signs of AVH (Law et al.,

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1987), and progressive liver disease in chronic HBsAg carriers which is attributed to superinfection by HDV or NANB agents mimics AVH B (Farci et al., 1983). Ac curate etiologic diagnosis of such reactivated or su perinfected cases can not be made by the initial or single serologic profile but by the serial serologic studies, especially taken during acute and convales- cent phases.

This study was designed to investigate the etiology and outcome of AVH in Korean adult patients with biopsy-proven AVH, using paired sera obtained dur- ing acute and convalescent phases.

MATERIALS AND METHODS

1. Patients

One hundred ana sixteen patients who were diag- nosed as AVH by peritoneoscopic liver biopsy at Seoul National University Hospital from 1973 to 1984 and who were followed up more than a year were studied retrospectively. The pathologic diagnosis of AVH was based on microscopic appearance described by Ishak (1976) and by Bianchi et al (1979). No patients had a history of potentially hepatotoxic drug adminis- tration, transfusion and hepatic dysfunction in the previ- ous 6 months. None were intravenous drug abusers or homosexuals. The HBsAg positive patients who had a previous history of abnormal liver function test (LFT) and piecemeal necrosis on liver biopsy were consi- dered undergoing a reactivation of chronic active hepatitis (CAH) B and excluded from the study.

There were 89 men and 27 women (male: female=3:1). The mean age was 34.2 years (range: 18 to 67 years). The morphological patterns of 102 (88%) patients were classical acute hepatitis with spot- ty necrosis (Ishak, 1976) and those of remaining 14 (12%) patients were acute hepatitis with bridging necrosis. Eight of the 102 with classical AVH showed markedly elevated level of serum alkaline phospha- tase (>×3 of normal) and they were clinically classi- fied as cholestatic hepatitis.

2. Laboratory methods

The sera which had been collected on admission and stored at −20°C were tested for HBsAg, anti-HBc, IgM anti-HBc, anti-HBs, IgM anti-HAV and anti-HD. The multiple sera serially collected during convalescent phase (6 months to a year after the onset of symptoms) were assayed for HBsAg, anti-HBc and anit-HBs and biochemical LFT. HBsAg, anti-HBc, IgM anti-HBc, anti- HBs, IgM anti-HAV and anti-HD were analyzed using commercially available radioimmunoassay kits (AUSRIA-II, CORAB, CORAB-M, AUSAB, HAVAB-M and anti-delta; Abbott-Laboratories, Chicago IL, respectively). IgM anti-HBc was assayed by manufac- turer's instruction at a serum dilution of 1:5000. The results were expressed in net cpm divided by the mean cpm of negative controls (S/N ratio). S/N ration higher than 2.1 was interpreted as positive.

3. Diagnostic criteria of AVH with various etiologic agents

Table 1 lists the sequential changes of serologic pro- file in each group and its interpretation of etiology. AVH A (group 1, 2, 3) was diagnosed by positive IgM anti- HAV regardless of the status of HBV serology. AVH B was diagnosed when IgM anti-HBc was positive in the acute phase (group 4, 6, 7, 8, 9) or when HBsAg was lost in the convalescent phase (group 5). AVH NANB (group 10, 11, 12) was diagnosed when the serologic tests were negative for both IgM anti-HBc and IgM anti-HAV, and NANB superinfection (group 13) on preexisting chronic HBsAg carrier state was di- agnosed if sera remained positive for HBsAg but nega- tive for IgM anti-HBc during acute and convalescent phases. HDV superinfection (group 14) was diagnosed by the presence of both HBsAg and anti-HD either on admission or in the convalescent phase.

4. Outcome of AVH B and NANB

The outcome of AVH B and NANB was defined serologically and/or biochemically. The risk of progres sion to chronic hepatitis was analyzed according to age, sex, presence of jaundice and bridging necro- sis on liver biopsy.

5. Statistical analysis

Statistical analyses were conducted using student *t*- test and the standard error of the difference between the two proportions (Hill, 1977).

RESULTS

1. Etiology of AVH

The patients with AVH A, B, D and NANB were 4 (3.4%), 70 (60.3%), 1(0.9%), and 41 (35.3%), respec- tively. The most frequent (82.9%) serologic profile dur- ing acute phase of AVH B was positive for both HBsAg and IgM anti-HBC. Ten (14.2%) of 70 patients with AVH B were negative for HBsAg. Only eleven (26.8%) of 41 patients with AVH NANB were negative for all sero- logical markers for HBV. The rest (73.2%) were posi- tive for at least one HBV marker: HBsAg was positive

in 31.7%.

2. Outcome of AVH B and NANB

Age distribution of each etiological categories is shown in Table 2. Most (78.6%) of the patients with AVH B were between 20 and 39 years of age and 78% of AVH NANB were between 20 and 49 years of age, while all of the patients with AVH A were below 19 years. The serological and/or biochemical outcome of AVH B and NANB are depicted in Figures 1 and 2, respectively. Nineteen patients (27%) with AVH B persistently had HBsAg in their sera: ten (14.2%) became asymptomatic chronic HBsAg carriers and nine (12.8%) had LFT abnormalities for more than one year, suggesting progression to chronic (active) hepatitis. Among 51 patients who cleared HBsAg in their sera, 6 patients (11.8%) did not show seroconversion to anti-HBs. However, none of these patients had persistent LFT abnormalities. The persistent LFT abnormalities in AVH NANB were observed in 7 (17%) of 41 patients. Factors affecting the development of chronic hepatitis in AVH B and NANB are shown in Table 3. There was a tendency, although it was statistically insignificant, that the rate of the development of chronic hepatitis was higher in male (15.7%) than in female (7.4%), in patients without jaundice (25%) than with jaundice (10.2%) and in patients with bridging necrosis (28.6%) on liver biopsies than without. Age did not influence the progression to chronic hepatitis.

DISCUSSION

Acute hepatitis A, B, D, and NANB are worldwide in distribution. Geographic differences in the incidence of AVH and in the distribution of various etiologies have been described (Chu et al., 1989). The differences in

Table 1. Etiological diagnostic criteria of serologic profiles during acute and convalescent phases and then relative frequency

Group	Acute					Convalescent*			No.	Etiology (n=116)	Frequency (100%)
	HBsAg	anti-HBc	IgManti-HBc	anti-HBs	IgM anti-HAV	HBsAg	anti-HBc	anti-HBs			
1	-	-	-	-	+	-	-	-	1	HAV	
2	-	+	-	-	+	-	+	-	2	HAV	4 (3.4%)
3	-	+	-	+	+	-	+	+	1	HAV	
4	+	+	+	-	-	-	+	+	39	HBV	
5	+	+	-	-	-	-	+	-	2	HBV	
6	+	+	+	-	-	+	+	-	19	HBV	70 (60.3%)
7	-	+	+	-	-	-	+	+	4	HBV	
8	-	+	+	-	-	-	+	-	4	HBV	
9	-	+	+	+	-	-	+	+	2	HBV	
10	-	-	-	-	-	-	-	-	11	NANB	41 (35.3%)
11	-	+	-	-	-	-	+	-	10	NANB	
12	-	+	-	+	-	-	+	+	7	NANB	
13	+	+	-	-	-	+	+	-	13	NANB	
14	+	+	-	-	-	+	+	-	1+	HDV	1 (0.9%)

* Convalescent phase: between 6 months and one year after the onset of symptoms
\+ Anti-HD was positive during the acute and convalescent phases.

Table 2. Age distribution of acute viral hepatitis A, B, D, and non-A non-B (NANB)

Age (years)	Eitology			
	A	B	D	NANB
15-19	4 (100%)			3 (7.3%)
20-29		23 (32.9%)		9 (21.9%)
30-39		32 (45.7%)		11 (26.8%)
40-49		14 (20.0%)	1 (100%)	12 (29.3%)
50-59		1 (1.4%)		5 (12.2%)
60-69				1 (2.4%)
Total	4 (100%)	70 (100%)	1 (100%)	41 (100%)

Table 3. Factors affecting the development of chronic hepatitis

Age		Sex		Jaundice		Bridging necrosis	
Chronic hepatitis/recovered		Male	Female	Icteric	Anicteric	Absent	Present
33.4±8.2/34.3±9.8*		14/89 (15.7%)	2/27 (7.4%)	9/88 (10.2%)	7/28 (25.0%)	12/102+ (11.7%)	4/14 (28.6%)
p value	>0.5	>0.05		>0.05		>0.05	

* mean age ± SD

\+ None of the 8 patients with cholestatic hepatitis progressed to chronic hepatitis.

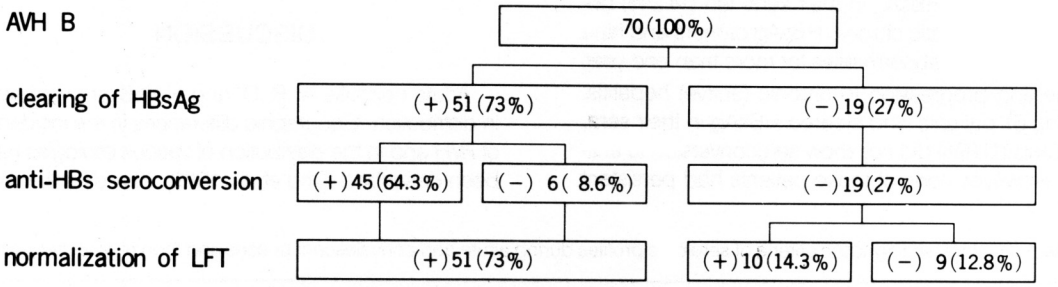

Fig. 1. The outcome of acute viral hepatitis B (AVH B). Clearing of HBsAg, anti-HBs seroconversion and normalization of liver function test (LFT) were studied during convalescent phase between 6 months and one year after the onset of symptoms.

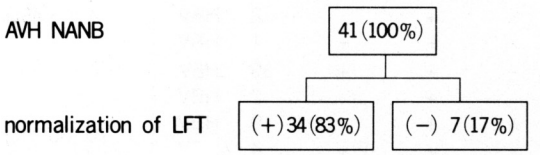

Fig. 2. The outcome of acute viral hepatitis non-A non-B (AVH NANB). Normalization of liver function test (LFT? was studied during convalescent phase between 6 months and one year after the onet of symptoms.

environments and biological predisposition of the population to AVH appear to be mainly responsible for this geographic variation but other factors such as a failure to distinguish the etiologic agents due to the use of insensitive tests and misdiagnoses arising from the misinterpretation of limited number of serum tests over a short period of time may be responsible for part of reported difference (Koff and Galambos, 1987). To overcome these problems, we included only the patients with biopsy-proven AVH, and studied the paired sera of both acute and convalescent phases, using the most sensitive radioimmunoassays.

The role of HAV as an etiologic agent of AVH in Korean adults is almost negligible because almost all of the general population over 30 years were anti-HAV-positive and thus were immune against HAV infection (Hong and Kim, 1982). The vast majority of AVH in Korean adults was due to HBV infection. In AVH B, HBsAg and IgM anti-HBc were positive in 85.7% and in 97.1%, respectively. Thus, testing for HBsAg alone would have failed to detect 14.3% of AVH B because they already cleared HBsAg before clinical screening on admission. The absence of IgM anti-HBc in 1:5000 dilution of serum virtually excluded a diagnosis of AVH B (Friedman and Dienstag, 1986). However, there were two IgM anti-HBc-negative patients (2.8%) who were considered to have AVH B. Although there is the possibility of reactivation of CAH B and of NANB superinfection in previously anti-HBc positive carriers, AVH B is more likely in that these two patients revealed AVH on liver biopsy and cleared HBsAg in their sera during convalescent phase. The negative reaction of IgM anti-HBc in these two patients might be due to the lower sensitivity of CORAB-M than CORAB.

HDV infection superimposed on HBsAg carrier in this study was very infrequent (0.9%), and comprised 7.1% of AVH superimposed on previously unrecognized asymptomatic HBsAg carriers: the rest were NANB infection. The proportion of AVH NANB was 35.3% which was far less than 60.3% of AVH B. For the diagnosis of AVH NANB, EBV infection should be excluded as well as HAV, HBV and HDV infection. The frequency of EBV infection is inversely related to so-

cioeconomical status of the population: antibodies to EBV are positive in about 50% of children in North America and in Western Europe (Lee and Vyas, 1987), in over 60% of infants between 6 and 12 months of age in Japan (Numazaki et al., 1969) and in 100% of the children over 5 years in Korea (Hong et al., 1977). Thus, the frequency of EBV-associated hepatitis in Korean adults is considered negligible. Thirty patients (73.2%) with AVH NANB had at least one of HBsAg, anti-HBc and anti-HBs markers. Therefore, the presence of HBV serologic markers in the sera does not exclude the diagnosis of AVH NANB in Korea. Even HBsAg was positive in 31.7% among AVH NANB. This HBsAg-positive rate was much higher than 10% of general population (Hong and Kim, 1982). The possible explanation is that NANB viruses share common features with HBV especially with respect to the mode of transmission (Dienstag, 1983, tong et al., 1981).

The rate (27%) of the development of chronic HBsAg carrier state in our patients was remarkably higher in comparison to 10% and 0.2% by Redecker (1975) and Tassopoulos et al (1987), respectively. Our rate (12.8%) of progression to chronic hepatitis was accordingly higher than that (3%) previously reported by Redecker. The reason for the discrepancy among above studies was not clear. Tassopoulose et al (1987) tried to explain it by the inadvertent inclusion of reactivated cases or acute flare-up of CAH B. However, the possible inclusion of reactivated cases does not adequately explain the higher rates of progression in this study because all AVH B were diagnosed by liver biopsy. Another explanation for our high rate or progression to chronic HBsAg carrier was that this was a retrospective study and therefore, the patients who were persistently HBsAg-positive were more apt to be followed up over a year than those who cleared HBsAg, recovered from LFT abnormalities and were symptomless. Finally, it could be attributed to the failure of obtaining liver biopsies from the patients who recovered earlier after admission and the tendency to have obtained liver biopsies mostly from the patients with protracted course.

Acute NANB hepatitis also resembles hepatitis B clinically and has striking propensity to chronic hepatitis (Lee and Vyas, 1987). Whereas chronic hepatitis develops in fewer than 10% of patients with acute sporadic NANB hepatitis, as many as 40 to 60% of transfusion associated NANB hepatitis become chronic (Friedman and Dienstag, 1986). In our study, chronic hepatitis developed in 17% of AVH NANB. These differences might be due to the possible diversity in NANB agents.

The development of HBsAg carrier state after AVH B can be affected by age, sex, clinical hepatitis and genetic factors (Tong et al., 1981). The risk was inversely related to the age of the patients: 28.8% became HBsAg carriers in children under 4 years of age, as compared with 7.7% in adults over 30 years of age (McMahon et al., 1985). However, there was no age difference between the patients who recovered completely and those who became carrier in this study. The reason seemed that the patients were all adults. In the present study, the absence of jaundice and the presence of bridging necrosis appeared to play a role in the development of chronic hepatitis in AVH B and NANB. These findings were in accordance with McMahon et al (1985) and Bianchi et al (1979). None of our six patients with cholestatic hepatitis progressed to chronic hepatitis. Of note, male patients with AVH B and NANB had a higher tendency to develop chronic hepatitis, the reason of which was not known. However, this finding might be explained by Childs (1965) who has theorized that a gene involved in the synthesis of immunoglobulin is present on X-chromosome. Females, therefore, are more effectively resistant to chronic hepatitis.

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