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Comparison of the Clinical Features of Hepatitis A between HBsAg-Positive and HBsAg-Negative Patients

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Background/Aims: The notion that acute hepatitis A superimposed on chronic hepatitis B infection leads to a worse outcome than acute hepatitis A alone remains controversial. The aim of this study was to determine the influence of the presence of hepatitis B surface antigen (HBsAg) on the severity of acute hepatitis A. **Methods:** We retrospectively analyzed 449 patients hospitalized for acute hepatitis A from January 2000 to February 2010 and compared clinical outcomes based on the presence of HBsAg. **Results:** Of the 449 patients, 30 patients were in the HBsAg-positive group and 419 in the HBsAg-negative group. The HBsAg-positive group was older than the HBsAg-negative group (36.1±8.3 vs 31.8±8.5 years, p=0.004); however, other baseline characteristics were similar between the 2 groups. Mean peak values of prothrombin time, serum total bilirubin, and serum creatinine at admission were significantly higher in the HBsAg-positive group. When comparing clinical outcomes between the 2 groups, gastrointestinal bleeding, acute renal failure, and acute liver failure were more frequently observed in the HBsAg-positive group. In particular, the incidence of acute liver failure was approximately 9-fold higher in the HBsAg-positive group than in the HBsAg-negative group (23.3% vs 3.3%; odds ratio [OR], 8.80; p<0.001). Multivariate analysis showed that HBsAg (OR, 7.43; 95% confidence interval [CI], 2.56 to 21.57) and age (OR, 1.07; 95% CI, 1.02 to 1.13) were independent risk factors for the occurrence of acute liver failure. **Conclusions:** In patients with chronic hepatitis B infection, acute hepatitis A is associated with more severe clinical outcomes, including acute liver failure, compared with patients with acute hepatitis A alone. **(Gut Liver 2011;5:500-505)**

Key Words: Acute liver failure; Hepatitis A; Hepatitis B surface antigen

INTRODUCTION

The incidence of acute hepatitis A in Korea has been increasing significantly because the rate of seropositivity of anti-HAV(IgG) has been decreasing with socioeconomic development and improvements in public health and environment.[1] In a recent survey, approximately half of Korean individuals infected with the hepatitis A virus (HAV) had to be hospitalized with acute hepatitis.[2] Most patients with HAV infection have a favorable clinical course and spontaneous recovery, and only a few suffer from serious complications of acute hepatitis A such as acute fulminant hepatitis, acute renal failure, or cholestatic hepatitis. In some previous reports, the clinical course and outcome of hepatitis A in patients with underlying chronic hepatitis B virus (HBV) infection was associated with higher peak laboratory abnormalities and more severe outcomes, including acute liver failure and a higher fatality rate.[3] However, there is controversy over the influence of HBV infection on the outcome of acute hepatitis. Vaccines have been available against hepatitis B and hepatitis A since 1981 and 1995, respectively.[4] Formalin-inactivated hepatitis A vaccination is considered safe and effective in patients with chronic liver disease, including chronic hepatitis B. Nevertheless, in Korea, an area with endemic HAV and HBV infection, hepatitis A has not been designated a mandatory vaccination. In addition, there are very few comparative studies of clinical outcome in acute hepatitis A according to the presence of hepatitis B surface antigen (HBsAg). In this study, we retrospectively compared the clinical outcome of acute hepatitis A between HBsAg-positive and HBsAg-negative patients, and analyzed the incidence of acute liver failure as a measure of the

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severity of acute hepatitis A.

MATERIALS AND METHODS

1. Patients

Between January 2000 and February 2010, 452 consecutive patients who were admitted to Samsung Medical Center, Seoul, Korea for acute hepatitis A were retrospectively reviewed. Three patients who were positive for hepatitis C virus (HCV) RNA with anti-HCV were excluded from this study. A total of 449 patients were included and classified into 2 groups: HBsAg-positive group (n=30) and HBsAg-negative group (n=419).

2. Methods

Acute hepatitis A was diagnosed when patients were hospitalized with typical symptoms of acute viral hepatitis and presence of serum IgM anti-HAV (Abbott, HAV Ab-M). The presence of IgM anti HAV and HBsAg and the absence of IgM anti-HBc established the diagnosis of acute hepatitis A superimposed on a chronic HBsAg carrier. We adjusted the data for age, sex, the route of virus infection, and comorbidity in both positive-HBsAg and negative-HBsAg groups. The following blood tests were performed at the initial time of admission and regularly during admission: hemoglobin, platelet count, prothrombin time (PT), serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), serum total bilirubin, alkaline phosphatase (ALP), serum albumin, γ-glutamyl transferase (GGT), and serum creatinine. Patients who were HBsAg-positive were compared with patients without HBsAg with respect to complete blood count at the time of admission and the most severe laboratory abnormality of the biochemical profile, including liver function tests, at admission. We also compared the incidences of prolonged jaundice, gastrointestinal bleeding, acute renal failure, acute liver failure, liver transplantation, death, and the mean durations of hospitalization between the 2 groups to determine the differences in clinical outcome. Postoperative hospital stay was included in the estimation of hospitalization time for patients who underwent liver transplantation. Patients were considered to have acute liver failure (ALF) according to the widely accepted definition of ALF, which includes evidence of coagulation abnormality, usually an international normalized ratio (INR) ≥1.5, and any degree of mental alteration (encephalopathy) in a patient without pre-existing cirrhosis and with an illness of <26 weeks duration, with the exception of liver cirrhosis caused by vertically-acquired HBV if the disease has been recognized for <26 weeks.[5] The definition for acute renal failure (ARF) was an increase in serum creatinine concentration ≥0.5 mg/dL or by 50% compared with baseline value.[6] Gastrointestinal bleeding was defined as when patients presented with hematemesis, melena or hematochezia and had a drop in hemoglobin ≥1.5 g/dL. This study's protocol was approved by the Ethics Committee of Samsung Medical Center and the study was conducted in accordance with the principles of the Declaration of Helsinki.

3. Statistical analysis

Statistical analyses were performed using PASW Statistics 17.0 (SPSS Inc., Chicago, IL, USA). Statistical analyses were performed using the χ^2 test or the Fisher's exact test for categorical variables and the Mann-Whitney test for continuous variables. Continuous variables are expressed as mean and standard deviations, and dichotomous variables are expressed as simple proportions with 95% confidence intervals (CI). p-values of less than 0.05 were considered statistically significant.

Table 1. Baseline Characteristics of Patients with Acute Viral Hepatitis A

Characteristic	HBsAg(+) group (n=30)	HBsAg(-) group (n=419)	p-value
Age, yr			
Mean±SD	36.1±8.3	31.8±8.5	0.004
<30	5 (16.7)	175 (41.8)	0.007
30-39	14 (46.7)	180 (43.0)	0.692
40-49	10 (33.3)	54 (12.9)	0.002
≥50	1 (3.3)	10 (2.4)	0.746
Sex			
Male	22 (73.3)	245 (58.5)	0.109
Female	8 (26.7)	174 (41.5)	
Excessive alcohol consumption*	2 (6.7)	29 (6.9)	0.786
Infection source			
Unknown origin	28 (93.3)	398 (95.0)	0.691
Contact with hepatitis A patient	1 (3.3)	15 (3.6)	0.944
Intake of contaminated foods	1 (3.3)	6 (1.4)	0.417
Clinical findings and symptoms on admission			
Jaundice	25 (83.3)	347 (82.8)	0.942
Nausea/vomiting	24 (80.0)	359 (85.7)	0.396
Anorexia	22 (73.3)	315 (75.2)	0.821
Fever	16 (53.3)	248 (59.2)	0.529
General weakness	23 (90.0)	324 (77.3)	0.934
Abdominal pain	17 (40.6)	181 (43.2)	0.151
Underlying diseases			
Diabetes mellitus	1 (3.3)	9 (2.1)	0.671
Hypertension	2 (6.7)	12 (2.8)	0.247
Chronic kidney disease	0 (0.0)	2 (0.2)	
Malignancy	0 (0.0)	4 (1.0)	
Others†	1 (3.3)	12 (2.7)	0.882
Total	4 (13.0)	39 (9.3)	0.469

Data are presented as mean±SD or number (%).
*Alcoholic intake >40 g/day; †Thyroid disease, asthma, epilepsy, pulmonary tuberculosis.

RESULTS

1. Clinical characteristics

Basic characteristics of the 449 patients are shown in Table 1. Among the 30 patients in the HBsAg-positive group, the males outnumbered the females 22 (73.3%) to 8 (26.7%). Mean age at the time of admission was 36.1 years and 31.8 years in the HBsAg-positive group and HBsAg-negative group, respectively, and the HBsAg-positive group was significantly older than the HBsAg-negative group (p=0.004). In both HBsAg-positive and HBsAg-negative groups, the majority of patients were in the age group of 30 to 39 years. The infection source of acute hepatitis A was almost exclusively unknown origin in both groups (93.3% in the positive group vs 95.0% in the negative group). Two patients in the HBsAg-positive group had liver cirrhosis at the time of admission for acute hepatitis A: one patient had been diagnosed with Child-Pugh class B liver cirrhosis 1 year previously, and the other patient was newly diagnosed with Child-Pugh class A liver cirrhosis. Seven patients of the HBsAg-positive group were HBeAg-positive and 5 of these had received antiviral drugs such as lamivudine for chronic hepatitis B. Of 30 patients with acute hepatitis A and chronic HBV infection, HBV DNA was detectable in 20 patients at the time of admission. From 2000 to 2005, the detection rate for HBV DNA was lower than in the 5 years since 2006 (42.9% vs 73.9%), primarily because HBV DNA has been measured in International Units (IU) using highly sensitive reverse transcription-polymerase chain reaction since 2006, whereas between 2000 and 2005, HBV DNA was measured in picograms by a hybrid capture method with a lower limit of detection of 0.5 pg/mL.

Table 2. Laboratory Parameters of Patients with Acute Viral Hepatitis A during Admission

Parameter	HBsAg(+) group (n=30)	HBsAg(-) group (n=419)	p-value
Hb, g/dL*	14.7±1.9	14.6±1.9	0.895
Platelet count, $\times10^3$/mm^3*	137±69	177±84	0.006
PT (INR)†	2.8±2.3	1.7±1.9	0.016
Serum albumin, g/dL†	3.0±1.0	3.3±0.5	0.119
AST, IU/L†	3,747±5,108	2,874±2,997	0.494
ALT, IU/L†	2,603±2,230	3,120±2,075	0.107
Serum total billirubin, mg/dL†	19.9±17.6	11.1±9.3	<0.001
ALP, IU/L†	244±366	217±85	0.080
GGT, IU/L†	281±224	312±215	0.233
Serum creatinine, mg/dL†	2.1±2.1	1.5±2.2	<0.001

Data are presented as mean±SD.
HBsAg, hepatitis B surface antigen; Hb, hemoglobin; PT (INR), prothrombin time (international normalized ratio); AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase.
*Initial value at the time of admission; †Most severe value at admission.

2. Laboratory findings

We compared the initial values for hemoglobin level and platelet count at the time of admission, and the most severe value of PT, serum albumin, AST, ALT, and serum total bilirubin, which are directly correlated to liver function, during admission between the 2 groups of patients with acute hepatitis A (Table 2). Mean platelet count at the time of admission was significantly lower in patients of the HBsAg-positive group compared with the HBsAg-negative group (137±69 vs 177±84×10^3/mm^3, p=0.006). Mean peak values of PT (2.8±2.3 vs 1.7±1.9 INR, p=0.016), serum total bilirubin (19.9±17.6 vs 11.1±9.3 mg/dL, p<0.001) and serum creatinine (2.1±2.1 vs 1.5±2.2 mg/dL, p<0.001) during admission were also significantly higher in patients of the HBsAg-positive group. In contrast, the mean values of hemoglobin, serum albumin, AST, ALT, GGT, and serum creatinine did not differ significantly between the HBsAg-positive and HBsAg negative groups.

3. Clinical outcomes

To evaluate the influence of chronic HBV infection on the severity of acute hepatitis A, the incidences of prolonged jaundice, gastrointestinal bleeding, ARF, ALF, liver transplantation, death, and the mean durations of hospitalization were compared in terms of clinical outcomes between the 2 groups (Table 3). Of the 30 patients who were carriers of HBsAg, 7 developed ALF. Two of these patients had been taking lamivudine, and the other 5, including 1 patient newly diagnosed with Child-Pugh class A liver cirrhosis, had not received prior treatment. All 7 patients had detectable HBV DNA at the time of admission. HBV DNA level of 7 patients at the time of admission were varied from 65 to 45,919 IU/mL. Two patients who had been taking lamivudine had maintained viral suppression (HBV DNA levels <2,000 IU/mL). However, 1 of 2 patients showed viral reactivation of HBV replication, which was characterized by HBV DNA levels >2,000 IU/mL, at the time of admission. One of the 2 patients with liver cirrhosis, who had been diagnosed with Child-Pugh class B liver cirrhosis 1 year previously, had a favorable clinical course and spontaneous recovery. The incidence of ALF was significantly higher among patients with acute hepatitis A and chronic HBV infection than among patients with acute hepatitis A alone (23.3% vs 3.3%; odds ratio [OR], 8.80; p<0.001). Among the total 449 patients with acute hepatitis A, 21 patients had ALF, 11 patients underwent liver transplantation, and 4 died secondary to ALF. Among the 10 ALF patients who did not undergo liver transplantation, 2 patients in deep coma died before a donor liver could be found, whereas the other 8 patients recovered spontaneously. Two patients with ALF died in the postoperative period after undergoing liver transplantation. One patient died due to vascular compression caused by huge hematoma around the transplanted liver, and the other died due to primary graft

Table 3. Clinical Outcomes of Patients with Acute Viral Hepatitis A

Clinical outcome	HBsAg(+) group (n=30)	HBsAg(-) group (n=419)	OR (95% CI)	p-value
Prolonged jaundice*	4 (13.3)	27 (6.4)	2.23 (0.73-6.86)	0.143
Gastrointestinal bleeding	2 (6.7)	3 (0.7)	9.91 (1.59-61.72)	0.038
Acute renal failure	8 (26.7)	38 (9.1)	3.64 (1.52-8.75)	0.007
Acute liver failure	7 (23.3)	14 (3.3)	8.80 (3.24-23.93)	<0.001
Liver transplantation	5 (16.7)	6 (1.4)	13.77 (3.93-48.22)	<0.001
Death	2 (6.7)	2 (0.5)	14.89 (2.02-109.7)	0.024
Hospitalization time, mean days±SD	21.6±4.1	10.0±0.4		0.007

Data are presented as mean±SD or number (%).
HBsAg, hepatitis B surface antigen; OR, odds ratio; CI, confidence interval.
*Serum total bilirubin level did not normalize within 3 months.

Table 4. Multiple Logistic Regression Analysis of Prognostic Factors for Acute Liver Failure

Covariate	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
Age, yr	1.08 (1.03-1.13)	0.001	1.07 (1.02-1.13)	0.006
Sex, M/F	0.91 (0.37-2.19)	0.824	0.61 (0.23-1.66)	0.334
HBsAg-positive	8.80 (3.24-23.93)	0.000	7.43 (2.56-21.57)	<0.001
Underlying disease	3.21 (1.11-9.30)	0.031	2.54 (0.80-8.03)	0.113
Excessive alcohol consumption	2.38 (0.66-8.57)	0.184	2.73 (0.67-11.07)	0.161

OR, odds ratio; CI, confidence interval; HBsAg, hepatitis B surface antigen.

nonfunction. ARF was noted in 46 of 449 patients with acute hepatitis A. With 2 of the deaths from hepatitis A occurring in patients with chronic HBV infection, the case fatality rate in this subset of patients was 6.7%. One of these patients had died after receiving a liver transplant. Among the 46 patients with ARF, 8 were in the HBsAg-positive group and 38 were in the HBsAg-negative group. The incidence of ARF in patients with acute hepatitis A and chronic HBV infection was also significantly higher than in patients with acute hepatitis A alone (OR, 3.64; p=0.007). In comparison of hospitalization time according to the presence of HBsAg, the average duration of hospitalization for the HBsAg-positive and -negative groups was 21.6±4.1 days and 10.0±0.4 days, respectively. Thus, the hospitalization time reflecting the morbidity caused by acute hepatitis A was significantly longer in the HBsAg-positive group than in the HBsAg-negative group (p=0.007).

To evaluate the potential risk characteristics of acute hepatitis A-associated ALF, we performed multivariate analysis. Table 4 shows odds ratios for the incidence of ALF associated with acute hepatitis A based on covariates that include age, sex, HBsAg, comorbidity, and excessive alcohol consumption. Logistic regression analysis showed that HBsAg positivity (OR, 7.43; 95% confidence interval [CI], 2.56 to 21.57) and age (OR, 1.07; 95% CI, 1.02 to 1.13) were independent predictors for the occurrence of ALF. Other factors such as sex, comorbidity, and excessive alcohol consumption were not significant.

DISCUSSION

ALF is a rare complication of HAV infection. Fulminant hepatitis in HAV infection occurs in approximately 0.1% to 0.5% of cases.[7] HAV infections in the Korean adult population have been increasing considerably due to the decreased opportunity for HAV infection in younger individuals.[8] As a result, a higher frequency of clinically severe hepatitis, including ALF, has been observed. In addition, the increase in HAV infection in adults has resulted in a relative increase in the number of cases of acute hepatitis A among HBsAg carriers. HAV-related liver disease is known to be caused by immunologic mechanisms rather than direct toxicity of the virus.[9] INF-γ produced by HAV-specific T cells may play an important role in the pathogenesis of infection.[10] During infection with HAV and HBV, it is possible that INF-γ produced in response to HAV stimulus has an antiviral effect on HBV infection. It has also been reported that HAV superinfection in patients with chronic hepatitis B suppresses hepatitis B viral replication.[11-13] However, because a reduction in HBV viral load is associated with an increase in the immune response of the host, in some cases an excessive host response may induce severe damage of hepatocytes. Although their study was not on hepatitis B, Cacopardo *et al*.[14] suggested

that HAV and HCV-related liver cell damage and viral clearance might be mediated by HAV-specific T cell responses with enhanced production of INF-γ. Several studies have reported that HAV superinfection in patients with pre-existing liver disease is associated with a high rate of morbidity and mortality.[15-19] However, not all reported studies are consistent with this view. Some reports have indicated that new HAV infections in patients with chronic viral hepatitis showed no hepatic decompensation and were similar to those of patients with hepatitis A alone.[20-22] Regarding superinfection with HAV in patients with hepatitis B virus, the clinical implications are more controversial. The largest case series reported an outbreak of hepatitis A in Shanghai in 1988,[18] in which 310,746 cases were reported with a fatality rate of 0.015%. When the number of HBsAg-positive cases was calculated from an assumed 8.8% HBsAg carrier rate in this region of China, the case fatality rate was 6.2-fold greater in chronic HBsAg carriers (15 deaths among 27,346 patients, 0.05%) than in patients without HBV infection (25 deaths among 283,400 patients, 0.009%). An analysis of cases of acute hepatitis A in the United States from 1983 through 1998 reported an overall case fatality rate of 0.33% (381 deaths/115,551 patients), with a much higher percentage of mortality (27 deaths/231 patients, 11.7%) in chronic HBsAg carriers; thus the case fatality rate of acute hepatitis A in HBsAg carriers was 58.5-fold higher than in patients who were not HBsAg carriers.[16] In recent years, two studies have investigated the influence of acute HAV superinfection in Taiwan and Thailand, areas with endemic HAV and HBV infection. Chu and Liaw[15] reported that HBsAg carriers were at a nine-fold increased risk of fulminant hepatitis compared with non-carriers, and Pramoolsinsap[17] reported that fulminant or submassive hepatitis occurred in 10 of 20 (55%) HBsAg carriers and in 4 of 12 (33%) patients with HBV- or HCV-related chronic liver disease.

In contrast to the above reports, other reports have shown an uncomplicated course of acute hepatitis A in patients with chronic hepatitis B. For example, Tassopoulos and Papaevangelou[21] found no case of fulminant hepatitis among 10 HBsAg carriers with acute hepatitis A and suggested that HAV superinfection of HBsAg carriers did not adversely influence the course of chronic hepatitis B. Similarly, Vento *et al*.[23] revealed that, unlike patients with chronic hepatitis C, most patients with chronic hepatitis B who acquired HAV infections had uncomplicated courses. In addition, no cases of fulminant hepatitis or death were observed in a retrospective study of 177 Korean patients with acute hepatitis A, including 10 HBsAg-positive patients.[24]

In our study, there were higher prevalences of ALF, emergency liver transplantation for ALF, and ARF among the patients with acute HAV superimposed on chronic HBV infection, and our data also showed that these patients were associated with higher peak laboratory abnormalities and longer hospital stays. The present study confirmed previous findings that acute HAV infection could cause severe liver injury in patients with chronic HBV infection. Whether the presence of HBsAg itself has a negative effect on clinical outcomes of acute hepatitis A is open to dispute. Several studies suggest that the severity of acute hepatitis A is correlated to the severity of the underlying chronic HBV infection since the risk from hepatitis A is increased in the presence of chronic hepatitis or liver cirrhosis, compared with healthy HBsAg carriers.[9,25] This explanation of the conflicting influence of chronic hepatitis B infection on clinical features of acute hepatitis A has become the commonly accepted view. However, in the majority of cases it is hard to determine the state of the HBsAg carrier (for example healthy carrier, chronic hepatitis, or liver cirrhosis) at the time of treatment for acute hepatitis A, because in most cases the state of their liver has not been regularly checked. In our study, only seven HBsAg-positive patients, including five patients who had been treated for chronic hepatitis B, had been followed up with their doctors. Therefore, we are not convinced that there is no substantial risk of fulminant hepatitis in healthy HBsAg carriers. In Korea, an area with a high prevalence of HBV infection, a progressive decrease in natural immunity against HAV has been observed. Moreover, the seroprevalance of HAV infection in patients with chronic liver disease is similar to that in the general population classified by age.[26,27] Therefore we suggest that individuals with chronic HBV infection should be considered as candidates for anti-HAV vaccination, especially as the HAV vaccine is known to be equally safe in patients with chronic liver diseases and the general population.[28]

In conclusion, our study indicates that acute hepatitis A superimposed on chronic HBV infection is associated with serious morbidity and mortality. Especially in terms of ALF, HBsAg-positive patients with acute hepatitis A are at an approximately nine-fold increased risk. Increasing age is known to be related to increased HAV morbidity and mortality, as well as underlying liver disease. Indeed, in our study the incidence of ALF was significantly associated with advanced age; however, when we performed multiple regression analysis the statistical significance of age was reduced compared with the significance of the presence of HBsAg. The main shortcomings of the present study are its retrospective nature and the fact that the study was conducted in a tertiary referral hospital, therefore there may be selection bias for patients who were referred for intensive care or liver transplantation. In other words, there may be a possibility that when patients with acute HAV infection were expected to have a poor prognosis, these patients were likely to be referred to specialty hospital for liver transplantation. Despite these, our study is significant in the sense that it is one of few analyses on the difference in clinical features between HBsAg-positive and HBsAg-negative patients in this HBV endemic area. Furthermore, the results of this study also indicate that acute hepatitis A is no longer a mild disease, at least in HBsAg carriers.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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