Available online at www.sciencedirect.com
ScienceDirect
Diagnostic Microbiology and Infectious Disease 69 (2011) 400–404
DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE
www.elsevier.com/locate/diagmicrobio

Virology

Initial laboratory predictors of severe hepatitis and acute kidney injury in patients with acute hepatitis A

Sun Young Cho, Seong-Ho Choi, Ji-Hoon Park, Jin-Won Chung*

Department of Internal Medicine, Chung-Ang University College of Medicine, Seoul, South Korea

Received 16 July 2010; accepted 21 October 2010

Abstract

The number of adult patients with acute hepatitis A (AH-A) has markedly increased during the last 10 years in Korea. Of special note, an increase in severe complications of AH-A, such as severe liver dysfunction and acute kidney injury (AKI), has emerged as a significant problem. The objective of this study was to identify the initial predictors for development of severe AH-A and AKI in AH-A. We retrospectively reviewed the medical records of 194 patients with AH-A from January 2007 to March 2009. Severe AH-A and AKI developed in 16 (9.3%) and 11 (6.4%) patients, respectively. Independent predictors for severe AH-A were low albumin [odds ratio (OR), 10.91; 95% confidence interval (CI), 2.324−51.215; $P = 0.002$], low total cholesterol (OR, 5.54; 95% CI, 1.389−22.113; $P = 0.015$), and elevated alanine aminotransferase (OR, 20.87; 95% CI, 4.581–95.067; $P < 0.001$). Also, high level of C-reactive protein was independently associated with AKI occurrence in AH-A (OR, 10.91; 95% CI, 2.324−51.215; $P = 0.002$).

Keywords: Hepatitis A; Severe hepatitis A; Acute kidney injury

1. Introduction

The number of adult patients with acute hepatitis A (AH-A) has markedly increased during the last 10 years in Korea with the changing seroprevalence of anti-hepatitis A virus (HAV) IgG according to rapid improvement of socioeconomic status (Kim and Lee, 2010; Jung et al., 1995). Of special consideration, an increase in severe complications of AH-A, such as severe liver dysfunction and acute kidney injury (AKI), has emerged as a significant problem. Although most severe AH-A patients recover with conservative treatment, some cases progress to fulminant hepatic failure, requiring liver transplantation. Also, AKI complicating nonfulminant hepatitis A was found in 1.5–4.7% of AH-A patients and occasionally required dialysis (Jeong and Lee, 2010). Although these complications would have a significant clinical influence, there have been few reports about the reliable predictors for severe complications of AH-A. Therefore, we investigated the early predictors of severe AH-A and AKI in adults patients with AH-A.

* Corresponding author. Tel.: +82-2-6299-1420; fax: +82-2-825-7571.
E-mail address: drjwchung@cau.ac.kr (J.-W. Chung).

0732-8893/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.diagmicrobio.2010.10.015

2. Materials and methods

2.1. Patient selection and data collection

We reviewed the medical records of 194 adult AH-A patients consecutively, from January 2007 to March 2009, admitted to the Chung-Ang University Medical Center in Seoul, Korea. Diagnosis of AH-A was made by the detection of anti-HAV IgM using electrochemiluminescence immunoassay along with compatible symptoms and laboratory findings. Patient demographic characteristics, other underlying diseases, and laboratory data were reviewed. The following laboratory tests were performed upon admission: a complete blood count including the white blood cell count, hemoglobin, hematocrit, and platelet counts; prothrombin time (PT); total bilirubin; albumin; cholesterol; creatinine; aspartate aminotransferase (AST); alanine aminotransferase (ALT); lactate dehydrogenase (LDH); γ-glutamyl transferase; alkaline phosphatase (ALP); and C-reactive protein (CRP). Subsequent follow-up laboratory data were collected during hospitalization. We also checked serologic markers for Hepatitis B virus (HBV), Hepatitis C virus (HCV), Hepatitis E virus (HEV), Epstein-Barr virus (EBV), Cytomegalovirus (CMV), and Herpes simplex virus (HSV) to

exclude other causes of acute hepatitis. Among 194 patients, 7 were positive for HBs Ag and 1 was positive for anti-HCV Ab. None of patient was positive for CMV or HSV.

2.2. Definitions

Severe AH-A was defined as AH-A having a prolonged PT of <40% activity at any time during the hospital course (Takikawa et al., 2006; Fujiwara K et al., 2008), and the definition for AKI was an increase in serum creatinine concentration ≥0.5 mg/dL or 50% compared with the baseline value at any time during the illness (Kim et al., 2008a, 2008b; Thadhani et al., 1996). Fulminant hepatitis A was defined as hepatic encephalopathy occurring within 8 weeks of illness onset (Kim et al., 2008a, 2008b; Rezende et al., 2003).

2.3. Statistical analysis

To investigate the predictors for severe AH-A and AKI, we compared the characteristics between the patients with and those without severe AH-A or AKI. Categorical variables were compared with χ^2 test or Fisher exact test, and continuous variables were compared with Student *t* test or Mann–Whitney *U* test. The receiver operating characteristic curve was used to determine the cutoff values for the prediction of severe AH-A and AKI. Some continuous variables were dichotomized according to the cutoff values and changed to categorical variables for the comparison. To indentify the independent predictors, logistic regression analysis was used. A *P* value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS software, version 11.5 (SPSS, Chicago, IL).

3. Results

3.1. Study population and patient characteristics

During the study period, a total of 194 patients with AH-A were admitted to the Chung-Ang University Medical Center. Among these patients, one male patient was referred to our hospital because of the development of fulminant hepatitis at another hospital. He was excluded from this study because his initial laboratory recording was not available. An anti-HEV antibody test was performed on 76 patients, and 11 patients had both anti-HEV IgM and anti-HAV IgM. Preexisting underlying disease was present in 10 patients (5.5%), including 7 with hepatitis B carrier state, 1 with chronic hepatitis C, 1 with chronic kidney disease, and 1 with dilated cardiomyopathy. After excluding these patients, a total of 172 patients were qualified and subsequently analyzed in our study. Their mean age (±SD) at diagnosis was 30.7 (±5.9) years, and the proportion of males was 64.0% (110 out of 172). Sixteen patients (9.3%) showed severe AH-A and none among these 16 patients developed fulminant hepatitis. Eleven patients (6.4%) showed AKI and 3 patients received dialysis. The median days from the admission to the onset of severe AH-A and AKI was 3 and 2 days, respectively. The mean laboratory test values of patients at admission included hemoglobin of 14.8 ± 1.6 g/dL, white blood cells of 5.1 ± 2.5 × 10^9/L, platelet of 172 ± 81 × 10^9/L, creatinine of 1.1 ± 1.2 mg/dL, AST of 1966 ± 2260 IU/L, ALT of 2405 ± 1906 IU/L, LDH of 1315 ± 1806 IU/L, ALP of 177 ± 79 IU/L, total bilirubin of 4.4 ± 3.9 mg/dL, total cholesterol of 112 ± 34 mg/dL, albumin of 3.6 ± 0.4 mg/dL, and CRP of 16.9 ± 17.7 mg/dL.

3.2. Initial predictors for severe AH-A

The patients with severe AH-A were more likely male (87.5% versus 61.5%, $P = 0.039$) and diagnosed with azotemia (25.0% versus 4.5%, $P = 0.012$) than those without. The following initial laboratory findings were more commonly observed in patients with severe AH-A: Hb ≥15 g/dL, platelet count <130 × 10^9/L, LDH ≥840 IU/L, AST ≥3000 IU/L, ALT ≥3400 IU/L, albumin <3.5 g/dL, and total cholesterol <90 mg/dL. Among these variables, low albumin, total cholesterol, and elevated ALT were significant independent factors related to the development of severe AH-A [odds ratio (OR), 10.91; 95% confidence interval (CI), 2.324−51.215; $P = 0.002$; OR, 5.54; 95% CI, 1.389−22.113; $P = 0.015$; and OR, 20.87; 95% CI, 4.581–95.067; $P < 0.001$, respectively] (Table 1). The predictive value of these factors for severe AH-A is shown in Table 2.

3.3. Initial predictors for AKI

Patients with AKI had the following initial laboratory findings more commonly than those without AKI: CRP ≥16 mg/L (87.5% versus 33.3%, $P = 0.004$), AST ≥2500 IU/L (81.8% versus 25.2%, $P < 0.001$), and a platelet count of ≤140 × 10^9/L (72.7% versus 38.4%, $P = 0.025$). In a multivariate analysis, high level of CRP was independently associated with AKI occurrence in AH-A (OR, 10.91; 95% CI, 2.324−51.215; $P = 0.002$) (Table 3).

4. Discussion

Recently, HAV infection has propagated among adults in Korea due to an epidemiologic shift in the age-specific HAV seroprevalence. Also, there has been an apparent increase in symptomatic patients with severe course. Among various clinical courses, we especially focused on 2 severe complications with AH-A: (1) severe AH-A and (2) AKI. Because severe AH-A occasionally shows rapid progress during the course of the illness and some patients with AKI need hemodialysis, the prediction for disease severity at an early stage may help in treatment for patients, such as preparation for liver transplantation or dialysis. Therefore, we evaluated the value of laboratory data at admission for predicting these complications. As most patients with AH-A showed similar clinical symptoms regardless of the disease

Table 1
Comparisons between patients with and without severe AH-A

Characteristics	Nonsevere AH-A (n = 156)	Severe AH-A (n = 16)	Univariate P	Multivariate OR (95% CI)
Age (years)	30.5 ± 5.8	32.5 ± 7.1	0.190	
Male	96 (61.5)	14 (87.5)	0.039	
WBC ($\times 10^9$/L)	5.1 ± 2.4	5.1 ± 3.0	0.988	
Hb (g/dL)	14.7 ± 1.6	15.9 ± 1.3	0.006	
Hb (>15 g/dL)	67 (42.9)	12 (75.0)	0.008	
PLT ($\times 10^9$/L)	177 ± 83	123 ± 40	<0.001	
PLT (<130 × 10^9/L)	49 (31.6)	10 (62.5)	0.013	
Creatinine (mg/dL)	1.1 ± 1.0	1.8 ± 2.5	0.268	
CRP (mg/dL)	15.5 ± 16.0	28.3 ± 26.8	0.116	
AST (IU/L)	1620 ± 1711	5336 ± 3825	0.001	
AST (≥3000 IU/L)	29 (18.6)	13 (81.3)	<0.001	
ALT (IU/L)	2200 ± 1705	4411 ± 2576	<0.001	
ALT (≥3400 IU/L)	33 (21.2)	13 (81.3)	<0.001	20.87 (4.38–95.07)
Total bilirubin (mg/dL)	4.6 ± 4.0	3.7 ± 2.6	0.237	
Cholesterol (mg/dL)	115.2 ± 34.1	81.4 ± 19.1	<0.001	
Cholesterol (<90 mg/dL)	31 (20.1)	12 (75.0)	<0.001	5.54 (1.39–22.11)
Albumin (g/dL)	3.6 ± 0.4	3.2 ± 0.3	<0.001	
Albumin (<3.5 g/dL)	58 (37.2)	13 (81.3)	0.001	10.91 (2.32–51.22)
LDH (IU/L)	1095 ± 1362	3413 ± 3529	0.019	
LDH (>840 IU/L)	57 (37.5)	14 (87.5)	<0.001	

WBC = white blood cell; Hb = hemoglobin; PLT = platelet.
Continuous data are expressed as mean values ± SD and categorical values are expressed as number (percentage).

severity, we investigated only laboratory data to search for reliable predictive factors.

We evaluated the severe AH-A based on PT and defined severe AH-A as a PT below 40% of control activity. Although several definitions about the severity of AH-A were suggested in other reports, the most important point in definition about severe AH-A is how well these can reflect the possibility of progress to fulminant hepatitis, the most serious complication in AH-A. Regarding this point, our definition of severe AH-A had several advantages. First, PT values of 40% or less and hepatic coma grade II or more are accepted as the 2 major diagnostic criteria for fulminant hepatic failure in Japan (Fujiwara and Mochida, 2008). Second, it was suggested that the frequency of developing encephalopathy in severe acute hepatitis was approximately 30% among patients with a prolonged PT of 40% or less of normal activity in a recent reports (Takikawa et al., 2006). Therefore, severe AH-A with a PT below 40% of control activity may be valuable for evaluation of severity in AH-A. Also, we expressed PT values as percentages because the prothrombin activity percentage is more valuable than seconds or the international normalized ratio for international comparisons of liver failure (Robert and Chazouilleres, 1996; Wei and Zheng, 2010).

Table 2
Predictive values for severe AH-A

	Sensitivity	Specificity	PPV	NPV
ALT, ≥3400 IU/L	81.3	78.8	28.3	97.6
Albumin (<3.5 g/dL)	81.3	62.8	18.3	97.0
Cholesterol (<90 mg/dL)	75.0	80.1	27.9	96.9

PPV = positive predictive value; NPV = negative predictive value.

To date, it has been suggested that the disease severity of AH-A is mainly dependent on the characteristics of individual patients, such as old age and underlying chronic liver diseases, especially chronic hepatitis C (Keeffe, 1995; Vento et al., 1998; Willner et al., 1998). However, the effect of old age on severity was not significant in our study. There are 2 explanations for this result. First, there was a low number of patients older than 40 years (8.1%) enrolled in our study. In contrast, previous reports with high proportion (21.0%) of older patients suggested an association between age and disease severity (Willner et al., 1998). Second, because we focused on only severe AH-A and AKI among various complications of AH-A compared to other studies, the effect of age could be underestimated.

Some reports suggested that thrombocytopenia was considered the reliable predictive factor of clinical course of AH-A, according to the various mechanisms including direct virus–platelet interaction, secondary splenomegaly, liver regulation factor depressing platelet release, and immunologically mediated platelet destruction (Avci et al., 2002). Similarly, our study showed that low platelet count had a significant association with severe AH-A and AKI in univariate analysis.

The independent predictors for development of severe AH-A were low albumin, low cholesterol, and a high ALT level. Although hypoalbuminemia usually reflects severe liver damage and decreased hepatic synthetic function, albumin is not considered to be a helpful biomarker in the diagnosis of acute liver dysfunction, such as acute viral hepatitis, because of its long half-life of 21 days. We speculated that because most patients with AH-A in our study were admitted to hospital for jaundice after a 2- to 7-week incubation period, albumin may be a reliable marker

Table 3
Comparisons between patients with and without AKI

Characteristics	Without AKI (n = 161)	With AKI (n = 11)	Univariate P	Multivariate OR (95% CI)
Age (years)	30.6 ± 6.0	32.5 ± 5.3	0.304	
Male (%)	101 (63.5)	7 (63.6)	1.000	
WBC ($\times 10^9$/L)	5.0 ± 2.0	9.0 ± 5.7	0.040	
Hb (g/dL)	14.8 ± 1.6	15.4 ± 1.6	0.194	
PLT ($\times 10^9$/L)	176 ± 83	123 ± 25	<0.001	
PLT, ≤140 × 10^9/L (%)	(38.4)	9 (72.7)	0.025	
CRP (mg/L)	15.9 ± 17.8	30.9 ± 13.3	0.022	
CRP, >16 mg/L (%)	38 (33.3)	7 (87.5)	0.004	14.0 (1.66–117.95)
AST (IU/L)	1788 ± 2305	4514 ± 3710	<0.001	
AST (≥2500 IU/L)	40 (25.2)	9 (81.8)	<0.001	
ALT (IU/L)	2355 ± 1897	3421 ± 1830	0.067	
Total bilirubin (mg/dL)	4.5 ± 4.0	4.5 ± 2.3	0.988	
Cholesterol (mg/dL)	113.3 ± 34.4	94.0 ± 32.7	0.073	
Albumin (g/dL)	3.6 ± 0.4	3.5 ± 0.5	0.320	
GGT (IU/L)	290.3 ± 229.0	399.5 ± 309.0	0.138	
ALP (IU/L)	178.2 ± 80.9	178.7 ± 60.6	0.983	
LDH (IU/L)	1147 ± 1457	3633 ± 4057	0.085	

WBC = white blood cell; Hb = hemoglobin; PLT = platelet; GGT = γ-glutamyl transferase.
Continuous data are expressed as mean values ± SD and categorical values are expressed as number (percentage).

for reflecting hepatic synthetic function in our study. Also, a low cholesterol level may reflect the decreased hepatic reserve as albumin does.

In fact, the absolute elevation of aminotrasferase was considered of no prognostic significance in acute liver disorder and even the aminotransferase levels decreased upon development of hepatic encephalopathy as liver size was rapidly shrinking. However, the aim of our study was to identify predictors for severe AH-A, not the prediction of hepatic encephalopathy. If we intend to predict the development of hepatic encephalopathy, additional studies will be necessary to investigate the association between the change of ALT level during illness and hepatic encephalopathy.

Patients with AH-A may be at increased risk of developing prerenal AKI because of volume depletion. And previous reports suggested that acute tubular necrosis (ATN) may be a cause of AKI development in AH-A (Betjes and Bajema, 2006; Coratelli and Passavanti, 1990; Tagle et al., 2004). Our laboratory findings revealed that 60% of the patients with AKI had a urinary sodium concentration ≥40 mEq/L and FeNa >1%. Therefore, although prerenal factors might have contributed to the AKI, ATN was the important cause in AKI development for most patients in this study (Kim et al., 2008c).

The elevated CRP, AST, and low platelet count were associated with the development of AKI in our study. These findings were observed in a previous report (Kim et al., 2008a, 2008b). Of special consideration, the elevated AST and high CRP concentration in association with AKI suggests that the severity of acute hepatic injury is more important than hepatic reserve in determining the severity of renal injury caused by AH-A.

Although a few studies have reported the risk factors of severe complication in patients with AH-A, up to now, no attempt has been made to suggest the cutoff value of predictors for severe AH-A or AKI. Thus, our findings may help to predict the development of severe AH-A or AKI in patients with AH-A. Because none of the patients developed fulminant hepatic failure in our study, we could not investigate the association between these initial predictors and fulminant hepatitis. A large-scale study with a sufficient number of patients developing fulminate hepatic failure should be undertaken to identify the role of initial laboratory predictors for fulminate hepatic failure.

In summary, in this study, we showed that low albumin and cholesterol levels and an elevated ALT level at presentation were independent predictors for the development of severe AH-A. Also, high level of CRP was independently associated with AKI occurrence in AH-A.

Acknowledgments

This study was supported by the Chung-Ang University Research Grants in 2011.

References

Avci Z, Turul T, Catal F (2002) Thrombocytopenia and emperipolesis in a patient with hepatitis A infection. *Pediatr Hematol Oncol* 19:67–70.

Betjes MG, Bajema I (2006) The pathology of jaundice-related renal insufficiency: cholemic nephrosis revisited. *J Nephrol* 19:229–233.

Coratelli P, Passavanti G (1990) Pathophysiology of renal failure in obstructive jaundice. *Miner Electrolyte Metab* 16:61–65.

Fujiwara K, Mochida S (2008) Fulminant hepatitis and late onset hepatic failure in Japan. *Hepatol Res* 38:646–657.

Jeong S-H, Lee H-S (2010) Hepatitis A: clinical manifestations and management. *Intervirology* 53:15–19.

Jung GM, Yun JE, Bak YT (1995) Epidemiologic study of hepatitis A viral infection in Seoul. *Korean J Gastroenterol* 27:110–117.

Keeffe EB (1995) Is hepatitis A more severe in patients with chronic hepatitis B and other chronic liver diseases? *Am J Gastroenterol* 90:201–205.

Kim YJ, Lee HS (2010) Increasing incidence of hepatitis A in Korean adults. *Intervirology* 53:10–14.

Kim HS, Kim HS, Lee JY (2008a) Initial thrombocytopenia as a simple, valuable predictor for clinical manifestation in acute hepatitis A. *Scand J Gastroenterol* 43:81–88.

Kim JM, Lee YS, Lee JH (2008b) Clinical outcomes and predictive factors of spontaneous survival in patients with fulminant hepatitis A. *Korean J Hepatol* 14:474–482.

Kim SH, Yoon HE, Kim YK (2008c) Acute hepatitis A-associated acute renal failure in adults. *Nephron Clin Pract* 109:127–132.

Rezende G, Roque-Alfonso MA, Samuel D (2003) Viral and clinical factors associated with the fulminant course of hepatitis A infection. *Hepatology* 38:613–618.

Robert A, Chazouilleres O (1996) Prothrombin time in liver failure: time, ratio, activity percentage, or international normalized ratio. *Hepatology* 24:1392–1394.

Tagle M, Barriga JA, Gutierrez S (2004) Relapsing viral hepatitis type A complicated with renal failure. *Rev Gastroenterol Peru* 24:92–96.

Takikawa Y, Endo R, Suzuki K (2006) Prediction of hepatic encephalopathy development in patients with severe acute hepatitis. *Dig Dis Sci* 51:359–364.

Thadhani R, Pascual M, Bonventre JV (1996) Acute renal failure. *N Engl J Med* 334:1448–1460.

Vento S, Garofano T, Renzini C (1998) Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med* 338:286–290.

Wei Y, Zheng D (2010) Comparison of modes of prothrombin time reporting in patients with advanced liver disease associated with viral hepatitis. *J Thromb Thrombolysis* 29:81–86.

Willner IR, Howard SC, Williams EQ (1998) Serious hepatitis A: an analysis of patients hospitalized during an urban epidemic in the United States. *Ann Intern Med* 128:111–114.