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The Serum Ammonia Level and Serum Factor V Activity in Chronic Hepatitis B İnfection

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Abstract

Research Article

This study aimed to measure and compare serum factor V activity and the serum ammonia level in chronic hepatitis B patients with and without acute exacerbation of chronic hepatitis B infection. Patients were divided into the following 2 groups: group 1 consisted of 67 patients with chronic hepatitis B infection without exacerbation; group 2 consisted of 67 patients with acute exacerbation of chronic hepatitis B infection. The serum level of ALT, AST, ammonia, and serum factor V activity were measured and compared between groups. Mean age in group 1 was 38 years and the mean laboratory findings were as follows: serum ALT: 32.3 ± 17.3 U L^{-1}; factor V activity: 112.42% ± 22.67%; ammonia: 13.85 ± 8.32 µg mL^{-1}. Mean age in group 2 was 34 years and the mean laboratory findings were as follows: serum ALT: 1087.2 ± 911.9 U L^{-1}; factor V activity: 101.13% ± 32.65%; ammonia: 34.20 ± 42.35 µg mL^{-1}. Factor V activity was significantly lower in group 2 ($P \leq 0.022$) and the serum ammonia level was significantly higher in group 2 ($P = 0.0001$). In the patients with hepatic exacerbation the serum ammonia level was higher, independent of the presence of hepatic encephalopathy in the absence of hepatic cirrhosis or hepatic failure, and was indicative of hepatic damage. Low serum factor V activity in the patients with hepatic exacerbation indicate insufficient liver regeneration capacity.

INTRODUCTION

Spontaneous reactivation of chronic hepatitis B is a clinical condition characterized by alanine transaminase (ALT) and aminotransferase (AST) levels >5-fold higher than normal or >2-fold higher than baseline values in patients with inactive disease or in those that have recovered with treatment[1]. Reactivation can be spontaneous, or can be induced via chemotherapy and immunosuppression. Reactivation can result in clinically severe acute hepatic failure and mortality; however, the majority of cases of reactivation are subclinical or occur spontaneously[2]. The level of factor V activity is an indicator of liver regeneration capacity.

In cases of acute hepatic failure low factor V activity is used as a marker of poor prognosis and as an indication for hepatic transplantation. An elevated serum ammonia level occurs due to advanced hepatic damage or direct entrance into systemic circulation via portovenous shunts. Ammonia neurotoxicity is a significant component of cerebral dysfunction in patients with acute hepatic failure[1,3]. The present study aimed to measure and compare serum factor V activity and the serum ammonia level in chronic hepatitis B patients with and without acute exacerbation of chronic hepatitis B infection.

MATERIALS and METHODS

Ethics statements

The research was approved by decision dated 02 November 2011 and numbered 306 decision of Local Ethics Committee for Dicle university school of medicine ethics committee.

Patients and study design

All of the patients had chronic hepatitis B infection with known HBsAg positivity for at least 6 months. Diagnosis of acute hepatic exacerbation was made based on aminotransferase activity, which is intermittently elevated over fivefold the upper limit of normal or increased over twofold the baseline value.

The study included 2 patient groups: group 1 consisted of 67 patients with chronic hepatitis B infection without exacerbation and group 2 consisted of 67 patients with acute exacerbation of chronic hepatitis B infection. Patients that were diagnosed with cirrhosis based on laboratory, radiological, and

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endoscopic findings were excluded from the study.

Demographic data, laboratory values (serum levels of ALT, AST, factor V, and ammonia), and virological markers (HBV DNA, HbsAg, and antiHBs) were recorded in all patients. Hepatitis A, C, and D, use of drugs, alcohol, and herbal drugs, ischemia, pregnancy, chemotherapy, and other hepatotropic viruses (HSV, CMV, and EBV) that might lead to similar biochemical profiles were exclusionary criteria. Serum factor V activity and the serum ammonia level in patients with acute exacerbation of chronic hepatitis B infection were compared to those in patients with chronic hepatitis B infection. Dicle university school of medicine ethics committee approved this study(No.306).

Laboratory parameters

ALT, AST, alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), total bilirubin (T.BIL), and albumin (ALB) levels were measured using the enzymatic method and Architect C 1600 in gel biochemistry tubes. Complete blood count was assessed in EDTA tubes via automated optic laser impedance using a CELL-a DYN 3700 device. Prothrombin time was determined using a Thromborel S kit and a Siemens Sysmex CA-7000 device. Anti-nuclear antibody (ANA) and anti-smooth muscle antibody (ASMA) were determined in gel biochemistry tubes via the immunofluorescence method using an ASTRA kit. HSV, CMV, and EBV positivity were assessed in gel biochemistry tubes via the ELFA method. HBV viral markers were studied via enzyme immunoassay (EIA), and HBV-DNA was studied via COBAS® using the AmpliPrep/COBAS® TaqMan® HBV Test v.2.0 (Roche Diagnostics). Anti-HCV was analyzed using a second-generation EIA test, and total anti-delta was analyzed via EIA. Factor V activity was measured using plasma samples (venous blood sampling) in citrated plasma tubes via the coagulometric method in a cold environment (reference range: 50%-150% of normal activity). The serum ammonia level was measured in plasma (venous blood sampling) collected in the presence of EDTA via the spectrophotometric enzymatic method in a cold environment.

Statistical analysis

All statistical analyses were performed using SPSS v.18.0 for Windows (SPSS, Inc., Chicago, IL, USA). Comparison of normally distributed parameters was done by Student t-test; whereas, comparison of non-normally distributed parameters was done by Mann Whitney U test. Chi-square test and Fisher's exact test were used for the comparison of categorical variables. Correlation between numerical variables was determined using Pearson test for normally distributed parameters and using Spearman's test for non-normally distributed parameters. $P < 0.05$ was considered statistically significant.

RESULTS

Group 1 consisted of 67 patients (41 males [61.2%] and 26 females [38.8%]). Mean age of the patients in group 1 was 38 years. The laboratory findings in group 1 were as follows: ALT: 32.3 ± 17.3 U/L^{-1}; AST: 26.7 ± 10.2 U/L^{-1}; serum factor V activity: 112.42% ± 22.67%; serum ammonia: 13.85 ± 8.32 µg mL^{-1}. Group 2 included 67 patients (44 males [65.7%] and 23 females [34%]). Mean age of the patients in group 2 was 34 years. The laboratory findings in group 2 were as follows: ALT: 1087.2 ± 911.9 U/L^{-1}; AST: 785.4 ± 884.8 U/L^{-1}; serum factor V activity: 101.13% ± 32.65%; serum ammonia: 34.20 ± 42.35 µg mL^{-1}. There wasn't a difference in age or gender between the 2 groups. Demographic and laboratory data for both groups are given in Table 1.

Table 1. Demographic and laboratory findings in groups 1 and 2.

Variable	Group 1 (n = 67)	Group 2 (n = 67)
Male, n (%)	41 (61.2%)	44 (65.7%)
Female, n (%)	26 (38.8%)	23 (34%)
WBC (K/UL)	5915.2 ± 1997.3	6729 ± 2326
PLT (K/UL)	222649 ± 73035	223000 ± 69881
ALT (U/L^{-1})	32.3 ± 17.3	1087.2 ± 911.9
AST (U/L^{-1})	26.7 ± 10.2	785.4± 884.8
T.BIL (mg/dL)	0.8 ± 0.4	5.5 ± 3.5
ALP (U/L)	84.2 ± 27.2	158 ± 98.1
GGT(U/L)	30.7 ± 22.7	181 ± 175
ALB (g/dL)	4.2 ± 0.4	3.6 ± 0.7

Serum factor V activity was significantly lower in group 2 than in group 1 ($P = 0.022$) and the serum ammonia level in group 2 was significantly higher than in group 1 ($P = 0.001$). Serum ALT and AST levels were significantly higher in group 2 than in group 1 ($P = 0.001$). The difference in the serum ammonia level and serum factor V activity between the 2 groups is shown in Table 2.

Table 2. The serum ammonia level and serum factor V activity in groups 1 and 2.

Variable	Group 1 (n = 67) (Mean ± SD)	Group 2 (n = 67) (Mean ± SD)	P
Ammonia (μg /mL^{-1})	13.85 ± 8.32	34.20 ± 42.35	0.0001
Factor V activity (%)	112.42 ± 22.67	101.13 ± 32.65	0.022

DISCUSSION

Hepatitis B virus (HBV) is a major cause of acute and chronic liver disease. It is estimated that 350-400 million people worldwide have chronic HBV infection[4]. Hepatic exacerbation typically presents with jaundice, which occurs a short time before the onset of clinical symptoms, and very high levels of ALT and AST. Most instances of hepatic exacerbation in patients with chronic HBV infection are associated with the interaction between immune responses that develop against HBV and viral replication[5]. Many studies have reported HBV reactivation due to alcohol, human immunodeficiency virus (HIV) infection, sepsis, superinfection with hepatitis A, C, D, and E viruses, and immunosuppressive chemotherapy[6-10]. As a general rule, the greatest risk of HBV reactivation occurs during the period following discontinuation of chemotherapy [11-13].

The level of factor V activity is indicative of the regenerative capacity of liver. As low-level factor V activity indicates poor prognosis—especially in patients with acute hepatic failure—it may be considered an indication for liver transplantation[12,14]. The level of factor V activity was noted to be low due to a decrease in synthesis in patients with acute hepatic failure and an increase in consumption in patients with disseminated intravascular coagulation (DIC) [11,14]. The level of factor V activity may also be used for the differential diagnosis of liver disease and vitamin K deficiency. Whereas factor V activity and coagulation factors synthesized in association with vitamin K (factor II, VII, IX, and X) are low in patients with parenchymal liver diseases, normal factor V activity and low levels of other factors are observed in those with vitamin K deficiency, increasing the significance of the levels of factor V and VII activity[14]. Gupta[15] reported that 65% of 40 patients that developed acute hepatic failure due to viral hepatitis died. The level of factor V activity measured in the patients that died was low (0%-10%). The survival rate was higher in the patients with factor V activity between 7%-25%.

In the present study the mean level of factor V activity was 112.42% ± 22.67% in chronic hepatitis B infection without exacerbation group, versus 101.13% ± 32.65% in acute exacerbation of chronic hepatitis B infection group (patients that developed hepatic exacerbation); the difference was significant (P = 0.022) . The low level of factor V activity in the patients with acute hepatic exacerbation is indicative of acute hepatocellular injury and a reduction in liver regeneration capacity, supporting the use of the factor V activity level for detecting these conditions.

Ammonia is the best-known neurotoxin involved in the pathogenesis of hepatic encephalopathy. Ammonia is formed via destruction of amino acids by erythrocytes and catabolism of nitrogen sources by colonic bacteria in the intestine. Ammonia enters the blood stream through the portal vein. The liver converts ammonia to urea and glutamine. An increase in the serum ammonia level occurs due to an advanced stage of impaired hepatic function and arteriovenous shunts. Ammonia neurotoxicity is a significant component of cerebral dysfunction in patients with acute hepatic failure[16,17].

The ammonia level was reported to be higher in patients with acute hepatic failure than in those with compensated and decompensated cirrhosis. The blood ammonia level is elevated in 90% of patients with hepatic encephalopathy; however, the plasma ammonia level does not correlate with the stages of hepatic encephalopathy[18]. Hsiu-Lung Fan et al. retrospectively reviewed 113 patients with acute-on-chronic HBV infection and reported that the ammonia level after the first week of treatment differed significantly between the patients that died and survived[14] . In the present study the mean serum ammonia level was 13.85 ±8.32 μg mL^{-1} in chronic hepatitis B infection without exacerbation group and 34.20 ± 42.35 μg mL^{-1} in acute exacerbation of chronic hepatitis B infection group ; the difference was significant (P = 0.0001). This finding indicates that the serum ammonia level in the patients with acute hepatic exacerbation increased secondary to the failure of hepatic detoxification due to hepatic damage in the absence of hepatic failure and hepatic cirrhosis.

In conclusion, few studies have investigated the serum ammonia level and serum factor V activity in patients with acute exacerbation of chronic hepatitis B infection, as compared to patients with chronic hepatitis B infection without

exacerbation. According to the present findings, the serum ammonia level increases in patients with acute hepatic exacerbations independent of the presence of hepatic encephalopathy in the absence of hepatic cirrhosis and hepatic failure, and is indicative of detoxification deficiency due to hepatocellular damage. In the current hepatological practice, factor V determination can be used to evaluate patients with acute liver failure, and can be taken into account when deciding on liver transplantation, especially in cases of acute viral hepatitis Furthermore, low-level factor V activity is indicative of insufficient liver regeneration capacity in patients with hepatic exacerbation.

Conflict of interest

The authors declare that there is no conflict of interest.

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