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Can Viral Load Predict Liver Histology in Patients With Chronic Hepatitis B?

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Abstract

Introduction: Hepatitis B virus (HBV) infection is a global public health problem. Serum HBV DNA measurement is a non-invasive test that predicts the liver disease progression. The aim of this study was to determine the HBV DNA level and look for a relation between the HBV DNA level and liver histology.

Methods: This was a cross sectional study on chronic hepatitis B infected patients in Tehran Hepatitis Center from 2006 to 2010. Percutaneus liver biopsy was performed in all patients. Patients with a history of any treatment and co-infection of HCV, HDV and HIV were excluded.

Results: 301 patients were included in this study. The mean age was 34.63±13.25 years. Mean serum HBV DNA level was 1.35* 108 ± 10.5*109 copies/ml. Mean inflammatory score (grade) was 5.54±3.26 and fibrosis (stage) was 1.93±1.56. There wasn't any significant relation between age and sex with liver histology. No significant relation was seen between liver histology and the HBV DNA level. HBe Ag positive patients had a higher serum HBV DNA level.

Conclusion: There wasn't any significant relation between liver histology and the HBV DNA level. We suggest using liver biopsy as a golden standard. In addition we need more studies in this field.

Keywords: Chronic Hepatitis B, Liver Histology, Serum HBV DNA

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1. Introduction

Chronic infection with hepatitis B virus (HBV) represents a worldwide health problem with continuing new infections being an important cause of liver disease, morbidity and mortality [1]. Around 400 million people worldwide, comprising 6% of the world population are chronically infected with the HBV, and 2 billion people have serological evidence of past or present HBV infection [2]. 75 % of patients with CHB are Asian [3] and the prevalence of the HBV infection in Iran is estimated to be 2.14 % in the entire population [4]. The relationship between hepatitis B viremia and progression to cirrhosis in chronic hepatitis B (CHB) has been well established, HBV-DNA level is very strongly predictive of the risk of disease progression [5]. The viral load is probably a significant factor in the natural history of CHB infection, with active replication being at greater risk of disease progression than those without detectable HBV-DNA in serum [6, 7]. CHB is characterized by the inflammatory liver disease of variable severity, 15%-40% of patients who have CHB infection progress to cirrhosis and end stage liver disease, and 25% of these later develop HCC [8, 9]. In order to decrease the cost, the side effects and the probability of resistance, the timing of the initiation of the treatment is crucial. The most important indicator for the decision related to the treatment is the histology of the liver which is the best predictor for the prognosis of the disease [10]. Nevertheless, the relationship between serum HBV DNA level and liver histology remains controversial.

2. Methods

Total 301 chronic hepatitis B naive patients (HBs Ag positive more than six months) were studied. The patients were selected from those referred to Tehran Hepatitis Centre (THC) which is a referral centre for hepatitis in Tehran from January 2006 to September 2010. Patients with co-infection of HIV, HCV and HDV infection were excluded. Informed consent was obtained from each patient. The HBV-DNA level, blood chemistry and complete blood count were tested by using standards commercially available assays. The Serum HBV-DNA level quantification was performed by PCR (Roche Diagnostics Kit, GmbH; UK) according to the manufacturer's instructions. The detection of HBV DNA ranged 10^3-10^{10} copies/mL. Percutaneus liver biopsy was performed in all patients. All histological preparations were examined by the single pathologist who was an expert in liver histopathology and was unaware of the clinical and viral HBV-DNA status. Liver histology was graded according to the Ishak et al [11] scoring system, which includes a fibrosis score (0-6) and necroinflammatory score (0-18). The latter is the sum of four scores, piecemeal necrosis (0-4); confluent necrosis (0-6); focal lytic necrosis, apoptosis and focal inflammation (0-4); portal inflammation (0-4). We used the

Statistical Package for the Social Sciences (SPSS) version 16 for analysis. Statistical methods included the chi and Fisher exact test, the T-test and ANOVA. A two-sided p value of less than 0.05 was considered to be statistically significant.

3. Results

Among 301 patients, 212 (70.4%) were male and 89 (29.6%) were female. The mean age was 34.63 ±13.25 years (min. 8 and max. 70 years). No significant differences were seen between the age of the male and female. HBe Ag was tested among 256 patients. Among them, 104 (40.6%) were positive and 152 (59.4%) were negative. Mean laboratory values were as follows: ALT 102.31±214.21 IU/L, AST 69±144.63 IU/L and HBV DNA level $1.35\times10^{8}\pm1.05\times10^{9}$ copies/mL and histological findings were: mean grade score was 5.54±3.26 and mean fibrosis score 1.93±1.56 (Table 1). 54% (17.9%) patients had stage 0 and 7% (2.3%) had stage IV (Figure 1), also 91% (30.2%) had mild grade and 4 (1.3%) had severe grade (Figure 2).

Mean serum HBV-DNA level in HBe Ag positive was $3.68\times10^{8}\pm1.77\times10^{9}$ copies/mL and in HBe Ag negative patients was $7.77\times10^{6}\pm4.54\times10^{7}$ copies/mL (p=0.041). No significant differences were seen between ALT and AST of HBe Ag positive and negative patients, mean ALT level of HBe Ag positive patients was 124.12±257.27 IU/L and in HBe Ag negative patients was 95.94±210.61 IU/L (p>0.05). The mean AST level of HBe Ag positive patients was 82.8±279.72 IU/L and in HBe Ag negative patients was 64.12±136.52 IU/L (p>0.05).

Table 1. Patients' basic data, laboratory and histology findings

	Minimum	Maximum	Mean
Age (years)	8	70	34.63±13.25
Body mass index(BMI)	13.3	43.85	24.47±4.27
AST (U/L)	9	1600	69±144.63
ALT (U/L)	6	2440	102.31±214.21
PLT	19000	402000	195000±55274
PT	11	17.6	13.9±1.07
INR	1	1.8	1.07±0.13
Grade	0	15	5.54±3.26
Stage	0	6	1.93±1.56
HBV-DNA	21	1.58×10^{10}	1.35×108±1.05109

Figure 1. Frequency of staging

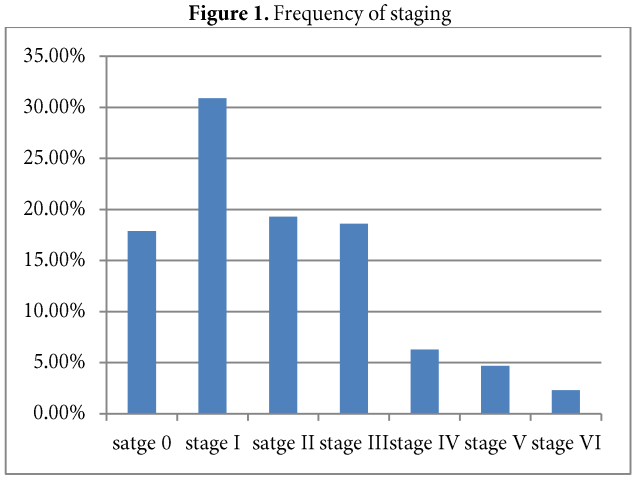
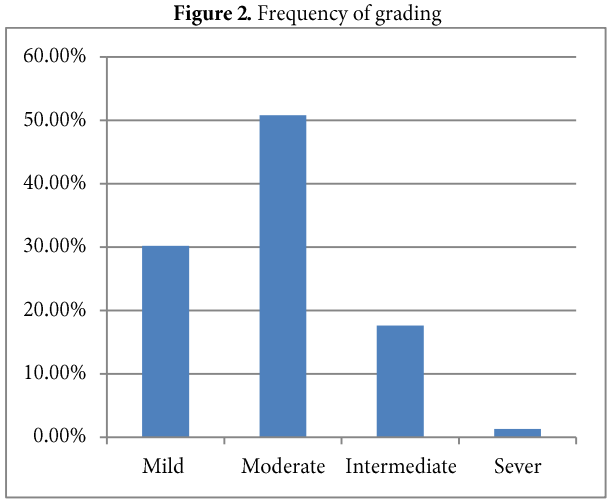


Figure 2. Frequency of grading



We divided patients in two groups: normal (ALT less than 40 IU/L) and abnormal (ALT more than 40 IU/L) ALT groups. No differences were seen in serum HBV-DNA level between higher ALT and in less than 40 IU/L group. The mean serum HBV-DNA level of patients with normal ALT was $5.19\times10^{7}\pm1.85\times10^{8}$ copies/mL and in abnormal ALT patients it was $1.66\times10^{8}\pm1.22\times10^{9}$ copies/mL. No significant differences were seen between different stages and grades of liver histology in HBV-DNA level. Mean serum HBV-DNA of patients with stage 0 was $1.96\times10^{8}\pm1.15\times10^{9}$ copies/mL and stage VI was $6.9\times10^{7}\pm5.1\times10^{7}$ copies/mL (P>0.072) (Table 2). Mean HBV-DNA level of patients with mild grade was $1.72\times10^{8}\pm9\times10^{8}$ copies/mL and in severe grade patients was $3.2\times10^{7}\pm5.35\times10^{7}$ copies/mL (p>0.05) (Table 3).

Table 2. Comparison of serum HBV-DNA levels in different stages

Stage	St. Deviation	Mean	P.value
Stage 0	1.15×10^{9}	1.96×10^{8}	p>0.072
Stage I	1.44×10^{8}	4.48×10^{7}	
Stage II	2.02×10^{8}	4.92×10^{7}	
Stage III	4.4×10^{8}	9.49×10^{7}	
Stage IV	3.61×10^{9}	8.98×10^{8}	
Stage V	3.27×10^{7}	1.51×10^{7}	
Stage VI	5.1×10^{7}	6.9×10^{7}	

Table 3. Comparison of serum HBV-DNA levels in different grades

Grade	St. Deviation	Mean	P.value
Mild	9×10^{8}	1.72×10^{8}	p>0.05
Moderate	1.3×10^{9}	5.08×10^{9}	
Intermediate	1.13×10^{8}	3.5×10^{7}	
Severe	5.35×10^{7}	3.2×10^{7}	

4. Discussion

Liver biopsy has several well-documented drawbacks, including sampling error, variability in pathologist interpretation, cost, and morbidity. We aimed to investigate the relationship between the serum HBV-DNA level and the histology of the liver, which is considered to be the most important prognostic indicator. Serum HBV-DNA level was higher in HBe Ag positive patients in comparison with HBe Ag negative patients. In our study, the HBV DNA level did not correlate with the stage between HBeAg positive and negative patients with CHB, as previously reported in Shao et al.'s [12]

study that had no correlation between liver histology and HBV DNA level in HBe Ag positive and negative patients. Additionally Ghanaei et al [13] reported no significant relationship between the serum HBV DNA level and the liver histological stage, gender, age, BMI, or HBeAg.. Additionally, in our study there was a correlation between the HBV DNA level and the liver histology in grading HBe Ag negative patients; however, there wasn't any difference in the HBV-DNA level and staging in either HBe Ag positive or negative patients. Higher stage and grade had a higher AST and ALT level however; there was no statistically significant difference in the AST and ALT level in different stages and grades of liver histology. We found that different stages and grades didn't differ in normal ALT groups. In contrast, Vardar et al [14] reported that normal ALT always indicated a lower grade of histology, but was not associated with lower fibrosis scores. Also the HBV DNA level didn't differ in normal ALT patients in comparison with the abnormal ALT level. When we divided patients into two groups, grade ≤ 4 and > 4, there was a significant difference in the AST and ALT levels and patients with grades more than 4 had a higher ALT and AST level without any differences in the serum HBV DNA level. In our study there was no relation between the HBV DNA levels, AST and ALT with liver histology. One of the limitations of this study was the difference in stages of the disease which the patients were possibly facing. Thus, it is possible that some were in immune tolerance phases (with high DNA and low ALT) and others were in immune clearance phases (high but relatively lower DNA and high ALT). If a study includes patients in different phases of the disease, it would be difficult to identify an association between the HBV DNA levels and ALT, even if a relation exists within a particular type of patient. Another limitation was related to the method of DNA count. We used simple means for HBV DNA analysis. HBV DNA levels are on log scale and hence either a geometric mean or mean log DNA levels should be used for comparisons. However, a previous study [15] reported that the best model for predicting significant inflammation included the variables age, HBV DNA levels, AST and albumin, and said that in HBeAg positive patients no factor could accurately predict the stages of liver fibrosisand the best factor for predicting significant inflammation was AST.

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Authors' Contribution

All authors contributed in all the steps of this study.

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