Research Article

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Relationship of HBeAg Status with ALT DNA Level and Liver Histology in Chronic Hepatitis B Patients

Kronik Hepatit B Hastalarında HBeAg Durumunun ALT, DNA Düzeyi ve Karaciğer Histolojisi ile İlişkisi

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ABSTRACT

Objective: Chronic hepatitis B (CHB) infection is a highly prevalent and important health problem. Hepatitis B virus (HBV) infection is a very important public health problem in our country. Our country is in a mid-hepatitis B virus-endemic area. Hepatitis B virus (HBV) is enveloped DNA virus which causes acute and chronic infections. Liver biopsy is the gold standard procedure for documenting liver damage in chronic hepatitis. In this study, our aim was to determine the relationship of positive or negative HBeAg status in chronic hepatitis B patients with ALT (alanine aminotransferase), DNA level and liver histology.

Materials and Methods: We retrospectively evaluated medical records of 230 hepatitis B patients who underwent liver biopsy in our clinic. Demographic properties, biopsy results, liver enzymes, HBV DNA levels and serological indications were evaluated. HBV DNA was investigated by quantitation of DNA using real-time polymerase chain reaction (PCR) and serological markers by enzyme immunoassay (EIA). Patients were separated into 2 groups according to their HBeAg status (group 1= HBeAg-positive; group 2= HBeAg-negative).

Results: Two hundred and thirty patients participated in the study. The average age of patients in group 1 and group 2 was 36.42±11.76 and 47.01±12.15, respectively. There was a statistically significant difference in average age between the groups ($p<0.000$). The average ALT level was higher in HBeAg-positive group ($p<0.000$). There was no significant difference in fibrosis score between the groups, however, histologic activity index (HAI) was higher in group 2 than in group 1. When the correlation between ALT and HAI was evaluated, a significant and positive correlation was found only in HBeAg negative-patients while no significant correlation could be detected between ALT and fibrosis in both groups. There was not any significant correlation between DNA and fibrosis in group 1 while positive correlation was detected in group 2.

Conclusion: We assume that when evaluating HBV infections, serological tests, HBV DNA level, liver enzymes, previous treatments and clinical status of the patient should be considered as a whole.

Key Words: Hepatitis B virus, DNA, biopsy

ÖZET

Amaç: Kronik hepatit B (KHB) enfeksiyonu tüm dünyada ve ülkemizde oldukça yaygın ve önemli bir sağlık sorunudur. Hepatit B virüs (HBV) enfeksiyonu ülkemiz için önemli bir sağlık sorunu oluşturmaktadır. Ülkemiz HBV enfeksiyonları yönünden orta endemik bölgede yer almaktadır. HBV'ler, akut ve kronik enfeksiyonlara neden zarflı DNA virüslerdir. Karaciğer biyopsisi kronik hepatit hastalığında karaciğer hasarı göstermek için altın standarttır. Bu çalışmada amacımız kronik hepatit B hastalarında HBeAg pozitif ve negatiflik durumunun ALT (alanin aminotransferaz) DNA düzeyi ve karaciğer histolojisi ile ilişkisinin belirlenmesidir.

Gereç ve Yöntemler: Kliniğimizde takip ve tedavi edilen, kronik hepatit B olguları arasında karaciğer biyopsisi yapılan 230 hastanın dosyası retrospektif olarak incelendi. Hastaların demografik özellikleri biyopsi sonuçları karaciğer enzimleri, HBV DNA düzeyleri ve serolojik göstergeleri değerlendirmeye alındı. HBV DNA kantitatif olarak real time polimeraz zincir reaksiyonuyla (PCR), serolojik testler ise enzim immuno assay (EIA) yöntemiyle çalışılmıştır. Çalışmaya alınan hastalar HBeAg durumlarına göre 2 gruba ayrıldı (grup 1= HBeAg pozitif; grup 2= HBeAg negatif).

Bulgular: Bu çalışmaya toplam 230 alındı. Olguların %77'si HBeAg negatifti. Çalışmaya alınan hastaların yaş ortalamasına bakıldığında yaş ortalaması grup 1'de 36,42±11,76 ve grup 2'de 47,01±12,15 idi. Bu sonuç istatistiksel olarak anlamlı bulundu ($p<0,000$). ALT ortalaması gruplara göre bakıldığında HBeAg pozitiflerde daha yüksekti ($p<0,000$). Fibrozis skoru açısından gruplar arasında anlamlı bir fark bulunmazken, histolojik aktivite indeksi (HAİ) HBeAg negatif olgularda daha yüksekti. ALT ile HAİ arasındaki korelasyon değerlendirildiğinde sadece HBeAg negatif hastalarda anlamlı, pozitif yönde korelasyon bulunurken ALT ile fibrozis arasında her iki grupta da anlamlı bir korelasyon yoktu. DNA ile HAİ arasındaki korelasyon değerlendirildiğinde sadece HBeAg negatif hastalarda anlamlı, pozitif yönde korelasyon bulundu. DNA ile fibrozis arasında 1. grupta anlamlı bir korelasyon yoktu, 2. grupta ise pozitif korelasyon tespit edildi.

Sonuç: Sonuç olarak, HBV enfeksiyonlarını değerlendirirken hastanın serolojik testleri, HBV DNA düzeyi, karaciğer ezimleri, hastanın tedavi alıp almadığı ve hastanın klinik durumu bir bütün olarak değerlendirilmesi gerektiğini düşünmekteyiz.

Anahtar Kelimeler: Hepatitis B virüs, DNA, biyopsi

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Introduction

Chronic hepatitis B virus (HBV) infection is an important, widespread health problem. Approximately, 600.000 people die of liver failure, cirrhosis, and hepatocellular carcinoma (HCC) every year (1). Currently, it is possible to diagnose and follow patients with confidence by monitoring various parameters of hepatitis (2).

Four stages of chronic HBV infection include immune tolerance, immune clearance (response), inactive carrier state, and reactivation. The immune response stage shows active inflammation in the liver biopsy and increasing enzyme levels with liver damage. During this period, the patient has hepatitis B e antigen (HBeAg)-positive chronic B hepatitis (3).

Chronic HBV infection can be HBeAg positive or negative. Patients are HBeAg-positive in the early stages of chronic hepatitis B and become HBeAg-negative in the advanced stages. The number of HBeAg-negative cases has increased over the last 10 years as a result of aging HBV-infected population (4). Most HBeAg-negative chronic HBV screening has been conducted in the Mediterranean region, although it has increased worldwide (5).

During patient monitoring, it is necessary to discuss the biochemical, virological, and clinical features separately according to the e antigen status (6).

The serum transaminase levels can increase at different rates because of the damage to the liver parenchyma. Measurement of aspartate transaminase (AST) and alanine aminotransferase (ALT), indicators of inflammation, is an inexpensive test and frequently used in the clinical practice (7).

Liver biopsy is the gold standard for following and treating chronic HBV. The modified histologic activity index (HAI), necroinflammatory activity, and prevalence of fibrosis are evaluated separately. The modified HAI is scored as follows: 0) no fibrosis, 1) fibrous expansion in some portal areas, with or without short fibrous septa, 2) fibrous expansion in most portal areas, with or without short fibrous septa, 3) fibrous expansion in most portal areas and rare portal-portal (P-P) bridge formation, 4) fibrous expansion in portal areas and obvious bridge formation, 5) obvious bridge formation and rare nodules, and 6) potential or definite cirrhosis (8).

This study determined the relationships of positive and negative HBeAg status in chronic hepatitis B patients with ALT and DNA levels and liver histology.

Materials and Methods

This retrospective study enrolled 230 chronic hepatitis B patients who were treated and followed at İstanbul Education and Research Hospital, Department of Infectious Disease and Clinical Microbiology and underwent liver biopsy. The included patients were known to be HBsAg-positive for more than 6 months, had not been treated before the biopsy, and were not co-infected with hepatitis C virus (HCV) or human immunodeficiency virus (HIV).

Patient age, gender, biopsy results, liver enzyme levels before the biopsy, HBV DNA levels, and serological indicators were evaluated. Liver histology was evaluated by pathologists using the Ishak scoring system. The patients were divided into HBeAg-positive (group 1) and HBeAg-negative (group 2) groups.

Student's t-test was used to compare the means between the groups. The relationships between the histopathological findings and the ALT and DNA levels were evaluated using Spearman's correlation coefficient. Statistical significance was taken as $p<0.05$.

Results

The study enrolled 230 patients: 177 (77%) were HBeAg-negative and 53 (23%) were HBeAg-positive. The mean age of the HBeAg-negative patients was significantly higher than the HBeAg-positive patients (36.42±11.76 vs. 47.01±12.15 years; $p<0.000$). The mean ALT level was higher in the HBeAg-positive group (129.03±89.62 vs. 76.35±75.06; $p<0.000$). The HAI was higher in the HBeAg-negative subjects (6.25±2.3 vs. 7.39±2.88; $p=0.004$) (Table 1). There was no significant difference in the fibrosis score between the groups (1.81±1.06 vs. 2.11±1.19; $p=0.098$).

A significant positive correlation was found between ALT and HAI only in the HBeAg-negative patients ($p=0.005$, $r=0.209$). No significant correlation was found between ALT and fibrosis. A significant positive correlation between DNA and HAI was found only in the HBeAg-negative patients ($p=0.007$, $r=0.201$). No significant correlation was found between DNA and fibrosis in group 1, while a positive correlation was found in group 2 ($p=0.011$, $r=0.191$; Table 2).

Discussion

The natural course of chronic HBV infection and disease is complicated and quite variable (9). Over all age groups, 2-10% of acute HBV infection progresses to chronic infection. Chronic HBV infection is an important risk factor for hepatocellular cancer (HCC),

Table 1. Biochemical, virological and histopathological findings in our cases

Parameter	HBeAg-positive (n=53)	HBeAg-negative (n=177)	p
Age	36.42±11.76	47.01±12.15	0.000
ALT	129.03±89.62	76.35±75.06	0.000
DNA	44.140.485	12.327.270	0.001
HAI (mean)	6.25±2.35	7.39±2.88	0.004
Fibrosis (mean)	1.81±1.06	2.11±1.19	0.098

Table 2. Correlation of the DNA and ALT levels with liver histology

	HBeAg-positive (n=53)		HBeAg-negative (n=177)	
	r	p	r	p
ALT-HAI	0.054	0.700	0.209	0.005
ALT-fibrosis	0.019	0.891	0.053	0.482
DNA-HAI	0.053	0.707	0.201	0.007
DNA-fibrosis	0.055	0.691	0.191	0.011

Table 3. Results of studies of the relationship between HBeAg status and ALT and DNA levels and liver histology

Study	Year	Result of the study
Peng et al. (5)	2003	There was a correlation between ALT and HAI in HBeAg-negative patients and between fibrosis and ALT in HBeAg-positive patients
Acar et al. (6)	2009	There was a significant positive correlation between ALT and fibrosis in HBeAg-negative patients, positive correlations between HAI and ALT in HBeAg-negative and -positive cases
Ortatalı et al. (20)	2014	No correlation was observed between the ALT level and HAI in HBeAg-negative or -positive patients (p=0.18). There was no significant correlation between HBV-DNA and HAI (p=0.06 and p=0.46 respectively)
Özkara et al. (21)	2011	Although there was no correlation between the ALT and fibrosis degree, there was a weak correlation between ALT and HAI
Seto et al. (22)	2012	No correlation between ALT and fibrosis
Ahmad et al. (23)	2008	There was positive correlation between the ALT level and HAI in HBeAg-negative patients, but no fibrosis There was no correlation between the DNA levels and HAI in HBeAg-negative patients, but there was a positive correlation with fibrosis.
Sarı et al. (24)	2011	There was a relationship between the HBV DNA levels and HAI and fibrosis in HBeAg-negative patients, but not in HBeAg-positive patients.
Yuen et al. (26)		There was no relationship between the DNA levels and histological findings in HBeAg-positive patients.
Present study		There was a significant positive correlation between ALT and HAI in HBeAg-negative patients, but no correlation between ALT and fibrosis. There was a positive correlation between DNA and HAI only in HBeAg-negative patients, but no significant correlation between DNA and fibrosis in HBeAg-positive patients, but a positive correlation in HBeAg-negative patients.

especially in patients with cirrhosis. Their HCC risk is increased 390-fold when compared with the normal population (10).

To treat chronic HBV infection appropriately, the stage of the disease must be known and HBV DNA and ALT levels are important parameters in the treatment approach (11).

In our series, 77% of the subjects were HBeAg-negative. In other studies, the proportion of HBeAg-negative cases ranged from 16.4 to 76.7% (5,6,12,13,14,15,16,17,18,23,25).

Comparing HBeAg-positive and -negative patients, the latter tended to be older, had a higher HAI, and lower average ALT and DNA levels. There was no significant difference in the mean fibrosis score between the groups.

Peng et al. (5) observed that HAI was significantly higher in HBeAg-negative subjects, while the ALT levels were lower, albeit not significantly. Our results are compatible with these results.

Acar et al. reported that the average age of HBeAg-negative patients was 25.87±5.99 years and this was significantly higher than that of HBeAg-positive patients. They also reported lower ALT levels in HBeAg-negative patients, as in our study, and they found no significant difference in the mean fibrosis scores (6). However, the HAI scores in HBeAg-negative patients and in HBeAg-positive patients in their study was significantly different than those in our subjects (4.06±2.02 and 4.78±2.40 vs. 6.25±2.3 and 7.39±2.88) (p=0.001).

Yalçın et al. (17) found no significant difference in the HBeAg status and fibrosis scores in HBeAg-negative and -positive subjects, as in our study, but found higher HAI scores in HBeAg-negative patients.

In our study, the DNA level was significantly higher in the HBeAg-positive patients compared with the HBeAg-negative group, as in other studies (17,19,20).

We observed that the ALT and DNA levels were not correlated with the histopathological findings in the HBeAg-positive patients, although the DNA level was higher than in HBeAg-negative cases; the HAI and fibrosis scores also increased and the ALT level was correlated with the HAI, but not with the fibrosis scores (Table 3).

The changes in the ALT and DNA levels are an important indicator of histopathological activity for diagnosing cirrhosis and HCC stage. We believe that serological tests, HBV DNA level, liver enzymes, and the clinical status of the patient must be evaluated regardless of whether the patient receives therapy or not.

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