

**Chronic Hepatitis B Remains an Important Health Problem; A Single-Center Study
Kronik Hepatit B Önemli Bir Sağlık Sorunu Olmaya Devam Etmektedir; Tek
Merkezli Çalışma**

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Özet

Giriş: Bu çalışmanın amacı, kronik hepatit B hastalarının genel özelliklerini tanımlamak, hastalığın ilerleyişi hakkında laboratuvar histopatolojik ve klinik bulgular ile birlikte veri toplamak ve sonraki tedavi planlarına yardımcı olmaktır.

Gereç ve Yöntem: Çalışmaya 167 hasta dahil edildi. Hastaların serum HBsAg, HBeAg, Anti HBe, HBV DNA düzeyleri analiz edildi. Modifiye edilmiş İshak Skorlama Sistemi'ne (HAİ) göre bildirilen biyopsi sonuçlarına göre histolojik aktivite indeksi ve fibrozis değerleri kaydedildi. Alanin aminotransferaz, aspartat aminotransferaz, albümin seviyeleri de kaydedildi.

Bulgular: Çalışmamıza yaş ortalamaları 42.84±13.28 yıl olan 109 (%65.3) erkek ve 58 (%34,7) kadın olmak üzere 167 kronik hepatit B hastası dahil edildi. Ortalama HAİ değeri 29 yaş ve üstü hastalar için 8.78±2.81 iken 30-40 yaş arası hastalar için 8.47±2.70 ve > 40 yaş hastalar için 9.63±2.74 olarak bulundu.

Sonuç: Hastaların çoğunluğunun genç veya orta yaşlı olması, HBV enfeksiyonunun bölgemiz için önemli bir sağlık sorunu oluşturduğunu düşündürmektedir.

Anahtar Kelimeler: Kronik hepatit B, sağlık sorunu, bölgemiz

Abstract

Introduction: The purpose of this study is to define the general attributes of patients with chronic hepatitis B, to collect data about the progress of the disease along with laboratory histopathological and clinical findings, and to help the subsequent treatment plans.

Materials and Methods: 167 patients were included in the study. Serum HBsAg, HBeAg, Anti HBe, HBV DNA levels of the patients were analysed. According to the biopsy results reported based on the modified Ishak Scoring System (HAÍ), histological activity index and fibrosis values were recorded. Alanine aminotransferase, aspartate aminotransferase, albumin levels were also recorded.

Findings: A total of 167 patients with chronic hepatitis b, 109 (65.3%) males and 58 (34.7%) females whose mean age was 42.84 ± 13.28 , were included in our study. The mean HAÍ value for patients ≤ 29 years was found to be 8.78 ± 2.81 while for patients between 30-40 years it was 8.47 ± 2.70 and for patients > 40 , it was 9.63 ± 2.74 .

Conclusion: The fact that the majority of the patients are young or middle-aged suggests that HBV infection poses an important health problem for our region.

Keywords: Chronic hepatitis B, health problem, our region

Introduction

For approximately one-third of the world's population, hepatitis b virus (HBV) related infection has serological evidence and 350-400 million people carry chronic HBV surface antigen (HBsAg). Hepatitis B virus (HBV) infection remains

a global public health problem with changing epidemiology due to several factors including vaccination policies and migration. This Clinical Practice Guideline presents updated recommendations for the optimal management of HBV infection. Average HBsAg positivity of the studies carried out in the last decade with individuals from different segments of the society was reported as 5.01%. The spectrum of the disease and the natural course of the HBV infection are various and can range from inactive carriers to cirrhosis and hepatocellular carcinoma (HCC). HBV related-end stage liver failure or HCC is responsible for more than 0.5-1 million deaths per year and represents 5-10% of liver transplant cases (1-3).

Patients with chronic hepatitis b are at risk of developing various complications in the long term. Simultaneous portal hypertension with ascites and variceal hemorrhage, hepatorenal syndrome and hepatocellular carcinoma are the most important ones of these complications. These complications usually cause death. Prognosis in chronic hepatitis b virus infection depends on the viral replication situation and the level of histopathological damage in the liver (2,3).

Despite intensive vaccine programs, HBV infection, which causes approximately one million deaths in the world each year, is still one of the contemporary and important infectious diseases both in the world and in Turkey. Liver biopsy is essential to determine the severity of and the treatment for chronic hepatitis b. Chronic hepatitis histology presents a wide range of morphological symptoms from minor damage to severe fibrosis (1-4). The purpose of this study is to define the general attributes of patients

with chronic hepatitis b, to collect data about the progress of the disease along with laboratory histopathological and clinical findings and to help the subsequent treatment plans and outcome of HBV infection in a single center from Turkey.

Material and Methods

The study was based on retrospective screening of patients, who are aged between 18 to 75, who had a liver biopsy did not receive antiviral treatment before, diagnosed with chronic hepatitis B and are followed up in Internal Diseases gastroenterology polyclinic of Erzurum Ataturk University Medical School. Ethical consent was taken, and 167 patients were included in the study. Patients with metabolic liver disease, autoimmune hepatitis, liver cirrhosis, alcoholic liver disease, inactive HBV carrier, hepatitis C, delta hepatitis, or HIV co-infection were excluded from the study. Tenofovir disoproxil was given to 102 patients (61%) and entecavir was given to 65 patients (39%).

Serum HBsAg, HBeAg, Anti HBe levels of the patients were analyzed with Alirad (Radim Laboratories) device by using Dia.pro Diagnostik bioprobes (Italy) commercial kits with ELISA method, while HBV-DNA levels were analyzed with quantitative PCR method (QIAGEN Diagnostic Systems). According to the biopsy results reported based on the modified Ishak scoring system, histological activity index (HAI) and fibrosis values were recorded. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total bilirubin levels were also recorded.

Patients were divided into two groups, HBeAg positive and HBeAg negative (anti-HBe positive), based on their HBeAg

condition. Patients aged ≤ 29 were classified as age group 1; while 30-40 years old patients as age group 2, and >40 years old patients as age group 3. Patients with a fibrosis score of 1-3 were classified as group 1, and those with a fibrosis score of 4-6 as group 2. Above mentioned groups were compared with each other.

Statistical Analysis

Statistical analyses were conducted with SPSS 20.0 for windows software. Data were provided as a count, percentage, average and standard deviation. T-test was used for between-group comparison of continuous variables when the parametric conditions were met, while categorical variables were analyzed with the chi-square test. Pearson correlation analyses were conducted for certain continuous variables. One-way ANOVA was used for analyzing continuous variables age, ALT, fibrosis, HAI group comparison. Bonferroni correction was applied by carrying out Post hoc analysis in order to determine which group caused the discrepancy. Statistical significance level was defined as $p < 0.05$.

Results

A total of 167 patients with chronic hepatitis b 109 (65.3%) males and 58 (34.7%) females whose median age was 42.84 (17-74), were included in our study. The average demographic, histological, and laboratory features of the patients who participated in the study are shown in Table 1.

We examined patients with chronic hepatitis b infection by dividing them into two groups based on their HBeAg states. Demographic, histological and laboratory features of HBeAg positive CHB and HBeAg negative CHB cases are shown in

Table 1. No significant difference was detected between the two groups in terms of the AST, ALT, total bilirubin, albumin, HBV DNA, fibrosis and histological

activity index. The mean age of serum HBeAg positive patients was less than that of HBeAg negative patients (p=0.000).

Table 1. Baseline characteristics of the study population

Patient Information	Overall (n=167) (%)	HBeAg (+) (n=51) (%)	HBeAg (-) (n=116) (%)	P- value
Age (Mean±SD)	42.84±13.28	34.49±13.48	46.51±11.45	0.000
HBV DNAx10⁶ (IU/ml)	928.59±6737.48	859.76±3620.74	958.85±7734.46	0.931
AST (U/L)	68.60±76.52	86.18±93.23	60.87±66.91	0.084
ALT (U/L)	111.87±140.13	137.18±148.71	100.75±135.36	0.122
T. bilirubin (mg/dl)	0.66±0.35	0.67±0.43	0.66±0.31	0.812
Albumin (gr/dl)	4.3±0.35	4.24±0.37	4.34±0.33	0.114
HAI	9.16±2.77	8.92±2.72	9.26±2.80	0.472
FIBROSIS	2.43±1.08	2.45±1.04	2.41±1.11	0.840

The mean age of HBeAg positive patients was found to be 34.49±13.48. On the other hand, the mean age of HBeAg negative patients was found to be 46.51±11.45. A statistically significant difference (p<0.001) was found in terms of mean age between the two groups. HBeAg positive patients were significantly younger than HBeAg negative patients. 19.3% (n:21) of males and 51.7% (n:30) of females were found to be HBeAg positive, while 80.7% (n:88) of males and 48.3% (n:28) of females were found to be HBeAg negative. This was a statistically significant result. (X²:18.801, p:0.000). Mean ALT values of HBeAg positive patients were 137.18±148.71, while the mean ALT values of HBeAg negative patients were 100.75±135.36. No statistical significance was found between two groups (p>0.05). For the HBeAg positive patients, mean HBV-DNA value was found to be 859.76±3620.74. And for the HBeAg

negative patients, the mean HBV-DNA value was found to be 958.85±7734.46. No statistical significance was found between the two groups. When the HBeAg positive group was compared to the HBeAg negative group in terms of HAI averages, HBeAg positive group had a mean HAI value of 8.92±2.72, while the HBeAg negative had a mean HAI value of 9.26±2.80. No significant difference was found between the two groups. The mean HAI value of HBeAg negative group was higher than that of the HBeAg positive group. When the HBeAg positive group patients was compared to the HBeAg negative group patients in terms of fibrosis levels, the HBeAg positive group had an average fibrosis level of 2.45±1.04, while the HBeAg negative had an average fibrosis level of 2.41±1.11. No statistical significance were determined between the two groups.

HBV-DNA, ALT, HAI and fibrosis features of the patients are shown in Table 2 according to age groups.

Table 2. HBV-DNA, ALT, HAI and Fibrosis Features of the Patients According to Age Groups.

Age group (n) (%)	HBV DNA (IU/mL)x10 ⁶	ALT (U/L)	HAI	Fibrosis
1 (32) (%19)	1346.58±4527.70	129.59±110.19	8.78±2.81	2.03±0.96
2 (45) (%27)	40.33±97.63	105.69±128.14	8.47±2.70	2.42±1.15
3 (90) (%54)	1224.10±8773.35	108.67±155.36	9.63±2.74	2.57±1.07
P	0.586	0.726	0.049	0.057

Age Group 1: ≤ 29 years old, Age Group 2: 30-40 years old, Age Group 3: > 40 years old

The mean HAI value for patients ≤ 29 years was found to be 8.78±2.81, while for patients between 30-40 years it was 8.47±2.70, and for patients > 40, it was 9.63±2.74 (Figure 1). A statistical significance (p<0.05) was found between the groups. However, the analysis made to determine which group caused the discrepancies have shown no statistical difference. The mean fibrosis value for patients ≤ 29 years was found to be 2.03±0.96, while for patients between 30-40 years it was 2.42±1.15, and for patients > 40, it was 2.57±1.07. The statistical difference between the groups was at the

border value and insignificant (p=0.057). As the age levels increased, an increase in fibrosis levels was also observed.

We divided our patients into 2 groups: the first group consisting of patients with fibrosis stage 3 and below (Stage 1-3), and the second group consisting of patients with fibrosis stage 4 and above (Stage 4-6). Between these two groups, no statistically significant difference was found in terms of HBV-DNA, ALT, AST, Albumin, AFP, and PT levels (Table 3).

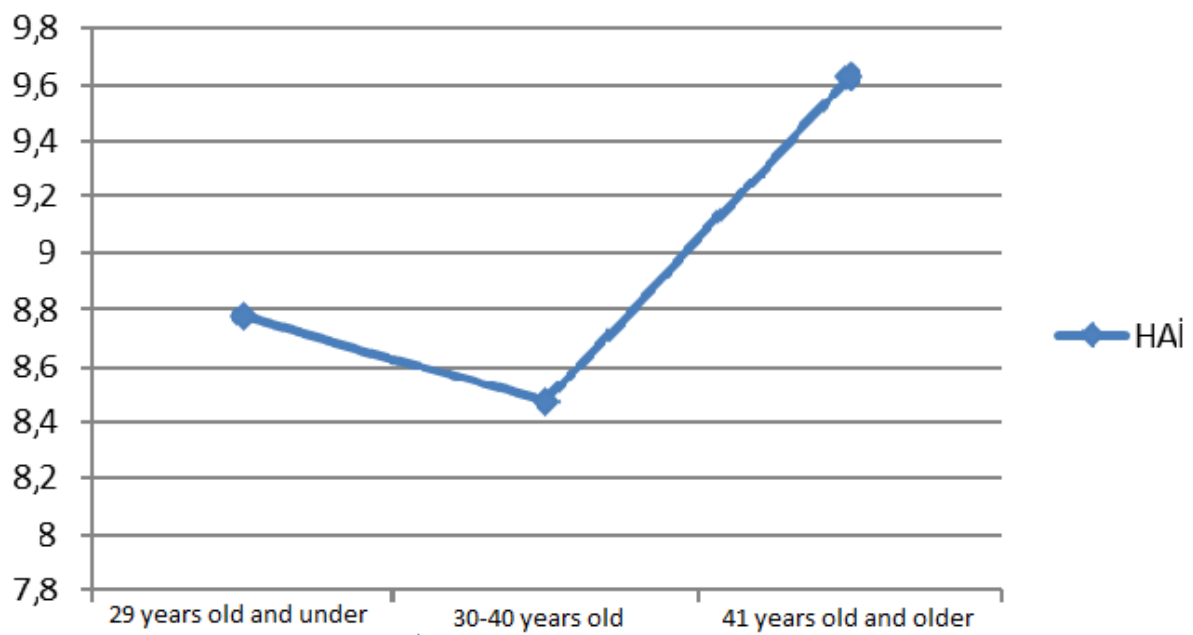


Figure 1. HAI averages among the age groups

Table 3. Averages according to fibrosis

Patient Information	Fibrosis 1-3 (n=143)	Fibrosis 4-6 (n=23)	P value
Age (years old) (mean)	42.25	46.57	0.150
HBV DNAx10⁶ (IU/ml)	1073.51±7273.93	65.18±236.35	0.508
AST (U/L)	68.30±75.03	72.13±88.10	0.825
ALT (U/L)	110.01±123.31	127.00±222.43	0.592
Albumin (gr/dl)	4.31±0.35	4.31±0.31	0.950
HAI	8.80±2.62	11.30±2.80	0.001

However, a difference in the negative direction was found between HAI and fibrosis groups ($t: 4.207, p < 0.001$).

Correlation analyses between the parameters (age, HBV-DNA, AST, ALT, HAI and fibrosis) used in the study were carried out. A significant correlation in the positive direction was determined between AST and ALT and between HAI and fibrosis ($r: 0.919, p: 0.001$). No statistically significant correlation was determined between other parameters ($p > 0.05$).

Discussion

This study was conducted because there was no previous study showing the general characteristics of hepatitis B infection in our region. It is extremely important to consider which situations when making a treatment decision for these patients. HBV infection is an important cause of acute and chronic liver diseases in Turkey. Society's contact with HBV at an early age leads to quite different "chronic HBV infection" states. Accordingly, a significant number of carriers, chronic hepatitis at early ages as well as liver cirrhosis are seen (5,6).

In European-Mediterranean and African countries, the incidence of HBeAg negative/anti-HBe positive CHB is 7-9 times more than the incidence of HBeAg positive CHB. While HBeAg negative cases constitute the majority of the biochemical and histological active diseases (>85%) in European-Mediterranean and African countries, HBeAg positive CHB diseases are more dominant in Asia, Northern Europe and the United States of America. The average age of HBeAg negative CHB patients is higher compared to HBeAg positive patients in the same regions. Although socioeconomic

and hygiene levels, as well as regional conditions and habits of the studied population, play an important role as much as the genetics and environmental conditions, today common viral factors, in particular, becomes evident in the natural course of chronic HBV infection. 69.4% of the patients in the study were HBeAg negative CHB patients, and the average age of patients was higher in the HBeAg negative group (7).

In a study carried out by Chan et al. in Hong Kong where 350 patients (mostly males) with chronic hepatitis B were included, 107 (31%) of the patients were HBeAg positive and 243 (69%) of them anti-HBe positive. The mean age was calculated as 36 for HBeAg positive patients while it was 45 for anti-HBe positive patients. Also, anti-HBe positive patients were older than HBeAg positive patients (8). It was noteworthy that our patients closely resembled those of Chan et al. in terms of demographic features of the patients, and correspondingly, data in our region showed similarity to that in the Asian region.

In another study carried out by Feld et al. in the USA, among 106 patients with chronic hepatitis B, 74 (69.8%) of them were Anti-HBe positive and 32 (30.1%) were HBeAg positive (9). In this study where the majority of the patients were male, the mean age of HBeAg positive patients was 36.5 and that of Anti-HBe positive patients was 48.2, which showed similarities to the average age values of our study.

In a study carried out by Yalcin et al. where 53 patients with chronic hepatitis B were included, similar to our study, no significant difference was found between HBeAg positive and HBeAg negative patients in terms of ALT levels and HAI

scores (10). Although Yalcın et al. did not find a statistical difference between HBeAg (+) and anti-HBe (+) patient groups in terms of average age, HBeAg (-) patients had a higher average age like in our study. Since HBeAg negativity develops in the later stages of chronic hepatitis b infection, these values obtained from our study conform to the expected results.

In a study carried out by Shao et al. on 21 CHB patients, among HBeAg positive and negative patients, no difference was found in terms of AST, ALT and histological findings from the liver. Similarly, Yalcın et al. found that the ALT level of HBeAg positive patients was 126 IU/l, while the ALT level of anti-HBe positive patients was 161.5 IU/l. In this study where cirrhotic patients were not included, no difference was found between HBeAg positive patients and anti-HBe positive patients in terms of ALT levels and necroinflammatory activity, as in our study. In contrast to our study, Yalcın et al. determined a statistical difference in terms of HBV-DNA levels. These findings indicate that in the case of CHB, the severity of the disease is not directly associated with the virus replication levels. Necroinflammation in the liver is not always parallel with viral replication and in this case, it appears that the host immune mechanism probably has a dominant role (10,11). This study also found no statistical difference between the groups in terms of the average ages. However, in our study, a statistical difference was found in terms of the average ages. These findings appear to be compatible with the studies demonstrating that during the course of the chronic HBV infection, age and duration of the disease are closely associated with the

hepatic histological changes and HBV replication (12,13).

Our study found that the degree of inflammation and fibrosis was higher in HBeAg positive patient compared to HBeAg negative patients. In HBeAg positive patients no significant difference was found between the DNA groups in terms of average HAI and fibrosis scores. In anti-HBe positive patients, no significant difference was found between the DNA groups in terms of average HAI. However, a low level of HBV-DNA in anti-HBe positive patients does not mean that a progressive liver disease does not exist. It was found that 15% of the patients with developing HCC had an HBV-DNA level of 104 IU/ml. In particular, in HBeAg negative patients with chronic hepatitis b or cirrhosis, low levels of HBV-DNA may be related to a progressive liver disease and may require treatment. Even if the serum HBV-DNA level is always < 20.000 IU/ml, the patient may have progressive liver disease (14).

This study shows the general characteristics and the results of hepatitis B in a single centre from Turkey. Current therapeutic agents for HBV are highly effective in controlling disease activity, prevent or regress disease fibrosis progression and prolong survival in a high majority of the patients. Therefore, when evaluating the chronic hepatitis b patients in order to minimize the complications related to the chronic hepatitis b and not to delay the treatment of it, it is important to closely monitor and interpret together the serologic indicators, transaminase levels and viral burden as well as to be aware that the liver biopsy is still the gold standard. The fact that the majority of the patients are young or middle-aged suggests that the

HBV infection poses an important health problem for our region.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ataturk University Medical School, Date: 26.12.2013 and Number: 17.

Informed Consent: Informed Consent form was signed by all patients who participated in the study.

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