The Rate of Spontaneous Hepatitis B Surface Antigen Seroclearance in Inactive Hepatitis B Carriers: A Study from Medium Endemic Area

İnaktif Hepatit B Taşıyıcılarında Spontan Hepatit B Yüzey Antijeni Seroklirens Oranı: Orta Endemik Bir Bölgeden Veriler

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ABSTRACT Objective: In this study, we aimed to determine the rate of spontaneous hepatitis B surface antigen (HBsAg) seroclearance in inactive chronic hepatitis B virus (HBV) carriers. We compared demographic and laboratory characteristics between the patients with and without seroclearance. **Material and Methods:** This study included retrospective evaluation of 2428 patients with chronic hepatitis B (CHB). The patients with HBsAg positivity for at least 6 months with HBV-DNA levels lower than 104 copies/ml, with normal serum alanine transaminase (ALT) levels, negative for HBeAg, and with detectable anti-HBe antibodies were enrolled in the study. HBsAg seroclearence rates were determined, and the groups with and without seroclearance were compared in demographic and laboratory aspects. **Results:** The annual rate of spontaneous HBsAg seroclearance in the study group was 0.17%. Among patients with seroclearance, the annual rate of seroconversion was 1%. There was no statistically significant difference between groups for demographic characteristics. HBV DNA levels were significantly lower in patients with seroclearance ($p<0.001$). **Conclusion:** This study revealed that annual HBsAg seroclearance rate in inactive chronic HBV infection was 0.17% after 11 years of follow-up. The rate may increase with longer duration of follow-up. The association with viral/host genotypes and seroclearence rate demands further analysis.

Key Words: Hepatitis B, chronic; hepatitis B surface antigens

ÖZET Amaç: Bu çalışmada inaktif kronik hepatit B taşıyıcılarının spontan hepatit B yüzey antijen seroklirens oranının belirlenmesi ve seroklirens olmayan kontrol grubu ile kıyaslanması amaçlanmıştır. **Gereç ve Yöntemler:** Retrospektif olarak 2428 kronik hepatit B hastası incelendi. En az 6 ay süreyle HBsAg pozitif, HBV-DNA düzeyleri 104 kopya/ml'den az, HBeAg negatif/anti HBe pozitif ve serum alanin aminotransferaz (ALT) düzeyleri normal olan hastalar çalışmaya alındı. Çalışma grubunda spontan HBsAg seroklirens oranı belirlendi ve seroklirens olmayan kontrol grubu ile demografik/laboratuvar özellikleri kıyaslandı. **Bulgular:** Çalışma grubumuzda yıllık HBsAg seroklirens oranı %0,17 idi. Seroklirens olan hastalarda yıllık serokonversiyon oranı ise %1 olarak saptandı. Gruplar karşılaştırıldığında demografik özellikler farklılık göstermezken, HBV DNA düzeyleri seroklirens gelişen grupta anlamlı olarak düşük bulundu ($p<0,001$). **Sonuç:** Bu çalışma inaktif kronik HBV enfeksiyonunda yıllık spontan HBsAg seroklirens oranının 11 yıllık izlem sonunda %0,17 olduğunu göstermektedir. Uzun süreli izlemlerde bu oran artabilir. Viral/konakçı genotipleri ile seroklirens oranları arasındaki ilişkinin belirlenmesi için daha kapsamlı çalışmalara gereksinim vardır.

Anahtar Kelimeler: Hepatit B, kronik; hepatit B yüzey antijenleri

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The epidemiologic and clinical features of hepatitis B virus (HBV) infection considerably varies between endemic areas, with HBsAg seroclearance rates predominantly occurring much rarer in high

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endemic areas.[1] The course of chronic HBV infection is considered to consist of 4 phases: Immune tolerance, immune clearance (HBeAg-positive chronic hepatitis), inactive carrier, and reactivation (HBeAg-negative chronic hepatitis), although not all patients go through every phase. First two phases are characterized by HBeAg positivity accompanied by normal ALT levels in the former and abnormal ALT levels in the latter. Patients in the third phase, termed "inactive carriers", are HBeAg-negative, hepatitis B e antibody (anti-HBe)-positive, with normal ALT levels, and serum HBV-DNA levels lower than 10^4 copies/mL with a normal structure or minimal changes in liver biopsy.[2,3] Epidemiological studies have shown that the prevalence of inactive carriers in the general population of Turkey is approximately 5%. The rate varies according to geographical regions, and the genetic susceptibility of the host.[4]

The reported annual incidence of HBsAg seroclearance in chronic hepatitis B (CHB) patients is estimated to be approximately 0.1-0.8% in patients infected early in life and 0.4-2% in patients infected during adolescence.[5-7] Serum hepatitis B surface antigen (HBsAg) may become negative with time in inactive carriers and this has been associated with a good prognosis in the absence of preexisting cirrhosis or viral superinfection.[8-10] However, whether the patients with seroclearance of HBsAg could be really cleared of serum HBV DNA or not is under debate.[11]

In this study, we determined the spontaneous HBsAg seroclearance rate in inactive hepatitis B carriers, and compared demographic and laboratory characteristics of the patients with and without seroclearance.

MATERIAL AND METHODS

PATIENTS

A total of 2428 CHB patients who had been followed up every 3 to 6 months in the Hepatitis Clinic of Izmir Tepecik Reserach and Training Hospital between May 2000 and May 2011 were evaluated retrospectively. The clinical and laboratory data at baseline and during follow-up were recorded. Patients were enrolled in this study if they had the following criteria: (1) HBsAg positive for at least 6 months; (2) HBeAg negative, anti-HBe–positive, normal ALT, no evidence of cirrhosis based on the clinical ground and liver ultrasonography findings**,** and no concomitant hepatitis C or D virus infection at baseline; (3) no antiviral or immunomodulatory therapy before entry and during follow-up; (4) regular follow-up at least every year. Patients with other possible etiologies of hepatitis (i.e. alcohol or drugs) were excluded. Out of 2428 patients, 221 patients who did not attend regular follow-up visits were excluded from the study. Overal, 2207 patients met the criteria for this study.

HBsAg seroclearance was defined as persistent loss of serum HBsAg for at least one year and until last visit.

METHODS

All enrolled patients were followed at 3-month intervals for 3 times, if ALT levels were lower than 1 times the upper limit of normal (ULN), and then every 6 to 12 months intervals if still < 1 x ULN. Liver biochemistry, HBV serologic tests (HBsAg), antibody to hepatitis B core antigen (Anti HBcIgG), HBeAg, Anti-HBe, and serum HBV DNA levels were checked in each follow-up visit. Antibodies against hepatitis C virus (Anti HCV) hepatitis D virus (Anti HDV) were tested in the case of elevated ALT levels to more than twice the ULN. HBsAg, anti-HBs, and anti-HCV were tested by commercially available enzyme immunoassay (EIA) kits (Abbott Diagnostics, USA). Anti-HBcIgG , HBeAg, and anti-HBe were tested by chemiluminescence EIA (Liaison Diasorin, Italy), and anti HDV by EIA (Diasorin, Italy). Initially, HBV DNA levels were measured qualitatively as negative or positive. For the last six years, HBV-DNA has been studied quantitatively by COBAS Ampli Prep/COBAS, TaqMan, HBV Test, version 2.0 (Roche Diagnostics, Sweeden).

Alphafetoprotein (AFP) levels and liver ultrasonography were checked every 6 months.

Liver cirrhosis was defined clinically as a platelet count of 100,000/mm^3 and splenomegaly or documented varices (5).

Fifty-six patients without seroclearance matched for sex, age, and the duration of follow-up were recruited as controls.

SPSS 15.0 for Windows program (IL, Chicago) was used for statistical analyses. Mann-Whitney U test was used to compare the variables between two groups. P values less than 0.05 were considered significant.

RESULTS

The median age in years (range, min.-max) was 37 (15-76) years and 1291 (58.5%) participants were males. The baseline characteristics of two groups were summarized in Table 1.

There were no significant differences regarding age (p=0.553), sex (p=0.895) or inactive carriage periods (p=0.173) between the two groups.

Spontaneous HBsAg seroclearance occurred in 43 (0.17%) patients during 24,277 person-years of follow-up. There was no statistically significant difference regarding seroclearance rates between genders. The median time to HBsAg seroclearence from the initial visit was 67 months (range, 14 to 90 months).

HBV DNA levels were significantly lower in the patient group compared to the control group (p<0.001).

Among patients with seroclearance, anti-HBs developed (seroconversion) in 15 patients (34.8%) of whom eight were females and median age was 38 (15-76) years. These patients had 1410 person-years follow-up, and annual rate of seroconversion was 1%.

DISCUSSION

The prevalence of HBV carrier state in Turkey is reported to be around 4%. This is in line with other Mediterranean and Middle Eastern countries and meets the criteria for intermediate endemicity level. However, the rate actually varies from 1 to 14.3% depending on geographic regions, and the genetic susceptibility of the host.[12,13]

Spontaneous HBsAg seroclearance rates for inactive HBV carriers at high and low endemic regions have been reported as 0.1-0.8% and 1-2.1%, respectively.[14] This study from Izmir, which is located in Western part of Turkey, showed that the annual rate of spontaneous HBsAg seroclearance in inactive HBsAg carriers was 0.17%. The study conducted by Liu et al. showed that HBV-DNA levels at baseline and follow-up evaluation were the most significant predictor of seroclearance.[15] Higher HBV viral loads conferred significantly lower HBsAg seroclearance rates. A spontaneous decrease in follow-up HBV-DNA level was associated significantly with seroclearance, showing an adjusted odds ratio of 4.17 (95% confidence interval, 2.55-6.82). Among those with seroclearance, 95.8% had undetectable HBV-DNA levels before

TABLE 1: Overal characteristics of the patients.

	Patients with spontaneous HBsAg seroclearance	Patients without spontaneous HBsAg seroclearance	p value
Gender			
Male (n,%)	24 (55,8)	32 (57,1)	0,895
Female (n,%)	19 (44,2)	24 (42,9)	
Age (years)	37 (15-76)	38 (17-60)	0,553
Median (min.-max.)			
Inactive hepatitis B carrier period (months)	36 (6-184)	60 (12-120)	0,173
Median (min.-max.)			
DNA (copy/mL)	120 (0-266)	2430 (10-74000000)	<0,001
Median (min.-max.)			

seroclearance. This study revealed that a low viral load was an important factor affecting the natural seroclearance of HBsAg, indicating significant clinical implications for the treatment of chronic HBV.[15]

In accordance with previous observations reported from high-endemic countries, the rate seemed to be higher in males compared to females, but this difference was not statistically significant. The rate was significantly higher in patients who were older than 45 years age. This finding may be attributed to long-term follow-up of these patients. As shown in the study by Chu and Liaw, the cumulative probability of spontaneous HBsAg seroclearence increased from 8.1% to 24.9% after 10 years, and to 44.7% after 20 years.[1]

In this study, the annual rate of seroconversion among those with seroclearance was 1%. The rate was compatible with previously reported rates from our country. In inactive HBV carriers, the annual rate of seroconversion was reported to range from 0.5% to 2.5% depending on age and follow-up years.[14]

In conclusion, this study showed that the seroclearance rate in inactive HBV carriers at medium endemicity area was low. The follow-up strategies for inactive carriers can be determined with their HBV DNA levels. In terms of seroclearance, the patients with low viral load may require close follow-up. The causative relationship between rate and host/virologic characteristics requires further population based studies.

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