Research Article

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Clinical and Laboratory Characteristics of Patients with Hepatitis B Patients with Atypical Serologic Profiles

Atipik Serolojik Profilli Hepatit B Hastalarının Klinik ve Laboratuvar Özellikleri

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ABSTRACT

Objectives: To investigate atypical serological profiles in patients diagnosed and followed up with hepatitis B virus (HBV) infection and to clinically evaluate patients with those have atypical profiles.

Materials and Methods: This study was a single-centre, retrospective cross-sectional cohort study. Six thousand five hundred and sixty-four hospital applications were evaluated. We reviewed 3,372 patient records, of which 145 met the inclusion criteria.

Results: Of the 3,372 patients followed up for HBV infection, 2,072 (61.4%) were male, and the mean age was 50.3±13.6 years. Data from 145 patients with atypical HBV serology were analyzed. Eighty-six (59.3%) of the patients were male. The mean age was 49.2±13.6 years. The prevalence of simultaneous positivity for hepatitis B surface antigen (HBsAg) and anti-HBs (group 1), dual positivity for hepatitis B e antigen (HBeAg) and anti-HBe (group 2), isolated positivity for anti-HBc-IgG (group 3) and isolated HBsAg positivity were found 2.13% (71/3,327), 1.47% (49/3,327), 0.75% (25/3,327) and 0.03% (1/3,327), respectively. Concomitant hypertension was more common in group 1; younger age, elevated alanine aminotransferase (ALT) and HBV-DNA levels and treatment with antiviral drugs were more common in group 2; comorbidities (p=0.07), and hematologic diseases were more common, HBV-DNA levels were negative and treatment with antiviral drugs were less in group 3.

Conclusion: Groups 1 and 2 cases had higher ALT and HBV-DNA levels and are at risk for developing cirrhosis, progressive liver disease and hepatocellular carcinoma. Patients with isolated anti-HBc-IgG should be treated when the risk of HBV reactivation exists.

Keywords: Hepatitis B virus, prevalence, serology, Turkey

ÖZ

Amaç: Hepatit B virüsü (HBV) enfeksiyonu tanısı konan ve takip edilen hastalarda atipik serolojik profilleri araştırmak ve bu hastaları klinik olarak değerlendirmektir.

Gereç ve Yöntemler: Bu çalışma, tek merkezli, retrospektif kesitsel bir kohort çalışmasıdır. Altı bin beş yüz altmış dört hastane başvurusu değerlendirildi. Yüz kırk beşi dahil edilme kriterlerini karşılayan 3.372 hastanın kayıtları incelendi.

Bulgular: HBV enfeksiyonu nedeniyle takip edilen 3.372 hastanın 2.072'si (%61,4) erkekti ve yaş ortalaması 50,3±13,6 yıldı. Atipik HBV serolojisi olan 145 hastanın verileri analiz edildi. Hastaların 86'sı (%59,3) erkekti. Ortalama yaş 49,2±13,6 yıldı. Hepatit B yüzey antijeni (HBsAg) ve anti-HBs için eş zamanlı pozitiflik (grup 1), hepatit B e antijeni (HBeAg) ve anti-HBe için ikili pozitiflik (grup 2), izole anti-HBc-IgG için pozitiflik (grup 3) ve izole HBsAg pozitiflik prevalansı hastalarda sırasıyla %2,13 (71/3.327), %1,47 (49/3.327), %0,75 (25/3.327) ve %0,03 (1/3.327) bulundu. Eşlik eden hipertansiyon grup 1'de daha sık görülürken; daha genç yaş, yüksek alanin aminotranferaz (ALT) ve HBV-DNA seviyeleri ve antiviral ilaçlarla tedavi grup 2'de daha yaygındı; grup 3'te komorbiditeler (p=0,07), hematolojik hastalıklar daha sık, HBV-DNA düzeyleri negatif ve antiviral ilaç tedavisi daha azdı.

Sonuç: Grup 1 ve 2 olguları daha yüksek ALT ve HBV-DNA seviyelerine sahiptir ve siroz, ilerleyici karaciğer hastalığı ve hepatoselüler karsinom geliştirme riski altındadır. İzole anti-HBc-IgG pozitif hastalarda HBV reaktivasyonu riski olduğunda tedavi edilmelidir.

Anahtar Kelimeler: Hepatit B virüs, prevalans, seroloji, Türkiye

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Introduction

Infection with hepatitis B virus (HBV) attacks the liver and can cause both acute and chronic disease and it is a major global public health problem with significant morbidity and mortality (1). The World Health Organization estimates that 296 million people will live with chronic hepatitis B (CHB) infection in 2019, with 1.5 million new infections each year. In 2019, hepatitis B resulted in an estimated 820,000 deaths, mostly from cirrhosis and hepatocellular carcinoma (HCC) (2). Therefore, the diagnosis and treatment of patients is of great importance in the fight against HBV.

Serological tests are widely used for the diagnosing of HBV infection. During the natural course of HBV infection, four serological biological markers are observed: hepatitis B surface antigen (HBsAg) and its antibody (anti-HBs); surface antigens associated with HBsAg particles and their antibodies; HBV core antigen (HBc) and its antibody (anti-HBc); and an antigen structurally related to HBcAg, namely, hepatitis B e antigen (HBeAg) and its antibody (anti-HBe) (3).

The diversity of HBV antigens and of the antibodies production may vary during the infection natural course, impact of methodology, mutations of virus itself, the immune status and genetic factors of the hosts (3). This situation complicates the evaluation of serological results and affects the treatment orientation (4). Table 1 shows the antigen and counter-antibody serologic profiles and the interpretation of the profile, that can be encountered in the natural course of infection (3,4).

The purpose of this study was to investigate atypical serological profiles in patients diagnosed and followed up with HBV infection and to clinically evaluate patients with those have atypical profiles.

Materials and Methods

Study Design and Population

This study was a single-centre, retrospective cross-sectional cohort study. We included all aged 18 years and older patients who followed up in outpatient clinics of Ankara City Hospital with HBV infection between January 1, 2020 and December 31, 2020. The results of all included patients in all their applications until the end of December 31, 2021 were evaluated. Patients with atypical serological profile were selected for this study. We excluded patients with serologic profiles might have been in the natural course of infection. Patients who underwent plasmapheresis and received intense chemotherapy, had a history of liver and hematopoetic stem cell transplantation were also excluded due to higher rates of atypical serologic profiles. Six thousand five hundred and sixty-four hospital applications were evaluated. We reviewed 3,372 patient records, of which 145 met the inclusion criteria (Figure 1).

Study Variables

Serological markers of patients were analyzed and included according to HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc-immunoglobulin M (IgM), anti-HBc-IgG and HBV-DNA appearances from hospital automation systems. Patients with atypical serological profile were examined in terms of age, gender, underlying comorbidities (including diabetes mellitus, hypertension, malignancy, hematologic, rheumatic and renal diseases), treatment status of HBV infections, the presence of immunosuppression, cirrhosis, HCC and laboratory parameters.

Microbiological Evaluation

For this study, we obtained results of HBsAg, anti-HBs, HBeAg, anti-HBe, anti-HBc IgM, anti-HBc-IgG, hepatitis delta antigen (HD-Ag) and antibodies against hepatitis delta virus (anti-HDV), human

Table 1. Serological profiles that can be encountered in the natural course of HBV infection and its interpretation

Profiles	HBsAg	Anti-HBs	HBeAg	Anti-HBe	Anti-HBc IgM/IgG		HBV-DNA	Interpretation of infection
Profile 1	Negative	Negative	Negative	Negative	Negative	Negative	Negative	Susceptible individual Never had contact with HBV
Profile 2	Negative	Positive	Negative	Negative	Negative	Negative	Negative	Immune, vaccine responses
Profile 3	Negative	Positive	Negative	Negative	Negative	Positive	Negative	Immune, old infections
Profile 4	Negative	Positive	Negative	Positive	Negative	Positive	Negative	Immune, recent infection
Profile 5	Negative	Negative	Negative	Negative	Negative	Negative	Positive	Incubation period, early phase
Profile 6	Positive	Negative	Positive/ negative	Negative	Negative	Negative	Positive	Incubation period, late phase
Profile 7	Positive	Negative	Positive	Negative	Positive	Positive	Positive	Acute infection
Profile 8	Negative	Negative	Negative	Negative	Positive	Positive	Negative	Immunologic window period
Profile 9	Positive	Negative	Negative	Positive/ negative	Negative	Positive	Positive	Chronic HBV infection/end of recent infection
Profile 10	Positive	Negative	Positive	Negative	Negative	Positive	Positive	Chronic HBV infection
Profile 11	Positive	Negative	Negative	Positive	Negative	Positive	Negative	Inactive HbsAg carrier
Profile 12	Negative	Positive/ negative	Negative	Negative	Positive/negative		Positive	Occult HBV infection

HBsAg: Hepatitis B surface antigen, Anti-HBs: Hepatitis B surface antibody, HBeAg: Hepatitis B e antigen, Anti-HBe: Hepatitis B e antibody, Anti-HBc IgM and IgG: Immunoglobulin M and G antibody to hepatitis B core antigen, HBV: Hepatitis B virus

immunodeficiency virus (anti-HIV) and hepatitis C virus (anti-HCV), HBV-DNA and HDV-DNA levels available in the hospital database. All the serum samples from patients were quantitatively tested for HBsAg and anti-HBs with the enzyme immunoassay method. HBeAg, anti-HBe, anti-HBc, anti-HIV and anti-HCV was detected by commercially available enzyme-linked immunoassay kits. The HBsAg ≥0.05 IU/mL, anti-HBs ≥10 mIU/mL, HBe antigen ≥10 IU/mL, anti-HBe ≥1.2 IU/mL, anti-HBc-IgM ≥1 s/c, anti-HBc-IgG ≥1 s/c, HD-Ag ≥1.1 s/c, anti-HDV ≥1.1 s/c, anti-HIV ≥1.0 s/c, and anti-HCV ≥1.1 s/c was defined to be positive, respectively. Alanine aminotransferase (ALT) was considered high when the lower level was above 50 U/L.

The concentrations of HBV-DNA and HDV-RNA levels were determined the Rotorgene® Q real-time polymerase chain reaction system (Qiagen, Germany) using Artus® HBV-Rotorgene Q kit (Qiagen, Germany, linear range: 31,6-2x10^7 IU/mL) and HDV Real-TM Quant® kit (Sacace, Italy, linear range: 30-10^8 copy/mL), respectively.

The methods and kits are routinely controlled according to the quality standards prepared by the Republic of Turkey Ministry of Health. This study was approved by the Medical and Health Research Ethics Committee of Ankara City Hospital (approval number: E-21-1893).

Statistical Analysis

Atypical serological profiles were presented in the groups. Nominal variables were given as numbers and percentage, whereas continuous variables were given as mean ± standard deviation or median and interquartile range. The distribution of the continuous variables was performed using the Kolmogorov-Smirnov test. Categorical variables were evaluated with Pearson's chi-square test or the Fisher's exact test; continuous variables were compared Student's t-test or Mann-Whitney U test, or Kruskal-Wallis test, where appropriate. The IBM SPSS version 24 (Chicago, USA) was used to perform all statistics.

Results

Of the 3,372 patients followed up for HBV infection, 2,072 (61.4%) were male, and the mean age was 50.3±13.6 years. Data from 145 patients with atypical HBV serology were analyzed. Eighty-six (59.3%) of the patients were male. The mean age was 49.2±13.6 years. Seventy (91.7%) patients presented with comorbidities. The demographics and clinical characteristics of the patients are shown in Table 2.

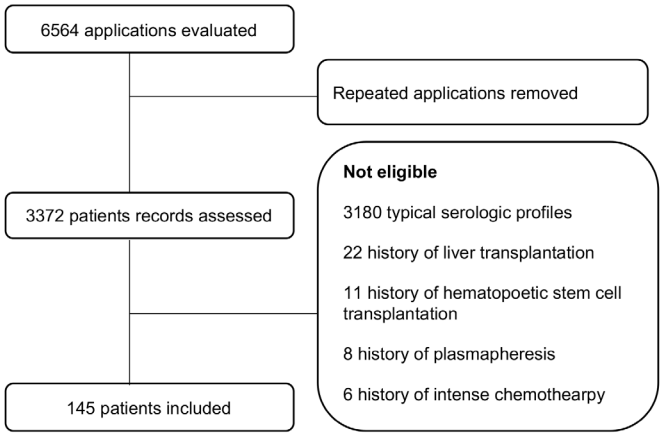

Figure 1. Patient flow chart of the study

The patients were stratified into three groups according to their serologic status as follows: group 1: simultaneous positivity for HBsAg and anti-HBs; group 2: simultaneous positivity for HBeAg and anti-HBe and group 3: positivity for anti-HBc-IgG without detection of HBV-DNA. Only one patient (0.7%) had isolated positivity for HBsAg with undetectable HBV-DNA. One patient was included in both group 1 and group 2 because of serological characteristics. The characteristics of patients with atypical profiles are shown in Table 2.

Patients in groups 1, 2, and 3 were compared with common hepatitis B patients in terms of age and gender. The patients in group 2 were younger than those with common HBV infection (p=0.001), and no difference was found in the groups.

The prevalence of simultaneous positivity for HBsAg and anti-HBs, simultaneous positivity for HBeAg and anti-HBe, positivity for anti-HBc-IgG with or without detection of anti-HBe and isolated HBsAg positivity was found 2.13% (71/3,327), 1.47% (49/3,327), 0.75% (25/3,327) and 0.03% (1/3,327) in all assessed patients, respectively (Table 3).

Concomitant hypertension was more common in group 1; elevated ALT and HBV-DNA levels and treatment with antiviral drugs were more common in group 2. In group 3, comorbidities (p=0.07), and hematologic diseases were more common, HBV-DNA levels were negative and treatment with antiviral drugs were found less (Table 2). Of the 15 (60.0%) patients in group 3, 7 (46.6%) had HBsAg positivity and 1 (6.6%) had anti-HBs positivity in the past years.

Anti-HDV positivity was found in 4 (2.7%) patients (in 2 patients from group 1 and 2) and HDV-RNA positivity was found in 3 (75.0%) out of 4 patients. Elevated ALT (in 2 patients) and positive HBV-DNA (in 1 patient) levels were found in patients with positive HDV-RNA. Anti-HIV and anti-HCV positivity was seen in groups 1 and 3, one patient (0.7%) each.

Discussion

HBsAg/anti-HBs coexistence is an unusual serologic profile seen in the course of HBV infection. Various antiviral treatments, mutations of the virus itself, vaccination and immune responses might be the reason for this coexistence (5). The prevalence of simultaneous anti-HBs and HBsAg positivity was 2.4-5.8% in China (6,7); 2.9-7.0% in South Korea (8,9); 5.0-8.9% in France (10,11) and 0.2-3.6% in Turkey (12,13). In the present study, we found that, of 3,371 HBV-infected patients, 2.13% had HBsAg/anti-HBs coexistence. We observed that, compared with other patients with atypical profiles, the patients with HBsAg/anti-HBs coexistence had higher hypertension rates.

The coexistence of HBsAg and anti-HBs might be associated with important clinical conditions and this profile could be linked to progressive liver disease, HCC, active replication, or reactivation of virus in previous reports (9,14). In our study, HBV-DNA and ALT

Table 2. The demographics and clinical characteristics of the patients

Characteristics	Group 1 71 (49.0)	Group 2 49 (33.8)	Group 3 25 (17.2)	Total, n (%) 145 (100)	p-value
Mean age (±SD), years Median age (IQR), years	- 55 (22)	44.3±11.8	54.1±12.2	49.2±13.6	**0.002**[a]
Male gender	38 (53.5)	32 (65.3)	15 (60.0)	86 (59.3)	0.50[b]
Comorbidities	36 (50.7)	18 (36.7)	16 (64.0)	70 (48.3)	0.07[b]
Hypertension	18 (25.4)	4 (8.2)	1 (4.0)	23 (15.9)	**0.008**[c]
Diabetes mellitus	11 (15.5)	2 (4.1)	2 (8.0)	15 (10.3)	0.12[c]
Malignancy	2 (2.8)	3 (6.1)	-	5 (3.4)	NA
Hematologic disease	6 (8.5)	1 (2.0)	5 (20.0)	12 (8.3)	**0.03**[c]
Rheumatic disease	1 (1.4)	1 (2.0)	2 (8.0)	4 (2.8)	NA
Renal disease	2 (2.8)	-	2 (8.0)	4 (2.8)	NA
Others[*]	4 (5.6)	3 (6.6)	-	7 (4.8)	NA
Immunosuppression	3 (4.2)	2 (4.1)	3 (12.0)	8 (5.5)	0.26[c]
Cirrhosis	6 (8.5)	5 (10.2)	-	11 (7.6)	0.31
Hepatocellular carcinoma	1 (1.4)	1 (2.0)	-	2 (1.4)	NA
Detectable HBV-DNA	32 (45.1)	24 (49.0)	-	56 (38.6)	**<0.001**[c]
Elevated ALT	26 (36.6)	24 (49.0)	3 (12.0)	52 (35.9)	**0.01**[c]
Treatment with antivirals	29 (40.8)	33 (67.3)	2 (8.0)	64 (44.1)	**<0.001**[c]
TDF	17 (58.6)	19 (57.6)	-	36 (56.3)	NA
TAF	2 (6.9)	2 (6.1)	-	4 (6.3)	NA
Entecavir	9 (31.0)	10 (30.3)	2 (100.0)	21 (32.8)	NA
Lamivudine	1 (3.4)	1 (3.0)	-	2 (3.1)	NA
Telbivudine	-	1 (3.0)	-	1 (1.6)	NA

Data were presented as mean ± standard deviation, median and interquartile range (IQR) or n (%). Percentages belong to columns. [*]Others: Thyroid, cardiovascular, cerebrovascular, chronic pulmonary diseases. NA: Not applicable, HBV: Hepatitis B virus, ALT: Alanine aminotransferase, TDF: Tenofovir disoproxil fumarate, TAF: Tenofovir alafenamide fumarate, [a]Kruskal-Wallis test, [b]Pearson's chi-square test, [c]Fisher's exact test

Table 3. The distribution of atypical serology in patients

Serology	Number of patients (n)	Percentages (%)
HBsAg (+) and anti-HBs (+)	71/3,372	2.10
HBeAg (+) and anti-HBe (+)	49/3,372	1.45
Isolated anti-HBc-IgG (+)	25/3,372	0.74
Isolated HBsAg (+)	1/3,372	0.03

Data are presented as n (%). HBsAg: Hepatitis B surface antigen, anti-HBs: Antibody against HBsAg, HBeAg: Hepatitis B e antigen, anti-HBe: Antibody against HBeAg, anti-HBc: Antibody against HBV core antigen immunoglobulin G

levels in group 1 were higher than that in group 3. Therefore, these patients should be closely followed up for the development of advanced liver disease in out-patient settings.

The detection of simultaneous HBeAg and anti-HBe positivity is a rare but well-established profile in HBV infected patients. Previous studies have shown that the prevalence of this profile is 0.2-5.9% in CHB patients and 10.4% in the immune-active phase of HBV infections (15-18). In our study, 1.47% of patients had dual positivity for HBeAg and anti-HBe, which was similar to the reported 1.5% in other study from Turkey (4).

The patients with simultaneous HBeAg and anti-HBe positivity were mostly male, slightly younger, had higher levels of ALT, HBV-DNA, a higher risk of developing liver failure and cirrhosis in the literature (15,18). In the present study, we also found that the mean age was 44.3 years and 65.3% of them were male, had less comorbidities (probably associated with young age), had higher biochemical indicators of liver and virus function and had a higher rate of treatment with antiviral drugs. Mutations, antigen-antibody complex and increased immunological response associated with these complexes may be the reasons for the high HBV-DNA and ALT levels and the increased risk of liver failure in patients with dual HBeAg and anti-HBe positivity (18). These patients are at higher risk of hepatic dysfunction, should be closely monitored.

Hepatitis B core antibody is a sensitive biomarker in identifying patients infected or exposed to HBV (19). Isolated anti-HBc-IgG can be seen in the natural course of HBV infection (Table 1) and this serology may also represent other clinical entities, including

the late stage of prior infections after HBsAg or anti-HBs has fallen down, cross-reactivity and false positivity (12,19). The importance of this serology arises in risk groups such as pregnant women, hemodialysis patients, co-infected patients with HCV and HIV, organ transplant recipients, intravenous drug users and immunosuppressive patients due to the possibility of HBV reactivation. Isolated anti-HBc-IgG positivity has been reported between 1.0%-32% in different populations (20). Studies from Turkey, this rate varies between 1.9% and 5.8% (12,21,22). In our study, the prevalence of isolated anti-HBc-IgG positivity was 0.75% and HBsAg or anti-HBs positivity was found in 8 (53.3%) out of 15 patients in previous years. This result was somewhat lower than that reported rates by prior studies.

Patients with isolated anti-HBc-IgG had more comorbidities, had higher rates of hematologic diseases and had lower ALT levels with undetectable HBV-DNA in our study. The above results were present, probably because anti-HBc positivity in these patients was found by chance because of research on underlying disease. Antiviral treatment was given to 2 (8.0%) patients to prevent reactivation due to the treatment of hematologic or rheumatic disease. It is strongly advised that hemato-oncological patients and candidates for transplantation and immunosuppressive treatment should be screened for anti-HBc-IgG markers with HBV-DNA.

Study Limitations

There are some limitations to our study. Firstly, it is single-center, retrospective study, and includes a specific follow-up period. Secondly, while patients with atypical profile are evaluated with clinical and laboratory results, these data are not available for patients with common HBV. Therefore, no larger scale comparison could be made.

Conclusion

Atypical serological profiles are not uncommon in patients with HBV infection. The interpretation of these results, patients follow-up and their treatment require care in clinical practice. Patients who are likely to develop liver failure, cirrhosis, HCC and HBV reactivation should be followed more closely and necessary active treatments are mandatory, where appropriate. In the presence of such atypical serologies, mutation analyzes should be requested if possible.

Ethics

Ethics Committee Approval: This study was approved by the Medical and Health Research Ethics Committee of Ankara City Hospital (approval number: E-21-1893).

Informed Consent: This was a retrospective study for which no formal consent was required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ç.M.A., B.B., R.G., Design: Ç.M.A., B.B., R.G., Data Collection and Processing: Ç.M.A., B.B., R.G., Analysis or Interpretation: Ç.M.A., B.B., R.G., Literature Search: Ç.M.A., Writing: Ç.M.A., B.B., R.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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