Original Article

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The Relationship of Hepatits B Core Antibody Positivity with Demographic and Laboratory Parameters in Hemodialysis Patients

Ilter Bozaci, Selma Tosun*

University of Health Sciences Turkey, Bozyaka Training and Research Hospital, Clinic of Nephrology, Izmir, Turkey

**University of Health Sciences Turkey, Bozyaka Training and Research Hospital, Clinic of Clinical Microbiology and Infectious Diseases, Izmir, Turkey*

Abstract

Aim: The presence of hepatitis B core antibody (HBcAb) is an indication of exposure to hepatitis B virus infection. We aimed to investigate the rates of positive HBcAb and its' association with demographical and laboratory parameters among patients undergoing hemodialysis.

Methods: Patients were divided into two groups as HBcAb positive and HBcAb negative. This study was conducted at a training and research hospital over 3 months period between October and December 2020. Demographical data and laboratory results were recruited from most recent medical records.

Results: A sum of 237 patients on hemodialysis were enrolled in the study. Fifty nine patients (25%) were HBcAb positive and 178 patients (75%) were HBcAb negative. Statistically significant difference was found between groups in terms of anti-HBs positivity (96.6% vs 79.2%; p=0.002), diabetes mellitus (DM) prevalence (32% vs 19%; p=0.036) and white blood cell count (WBC) levels (7.7±2.5 x10^3/µL vs 7.1±2.1 x10^3/µL; p=0.044). In linear regression analysis (variables: age, HBsAb, WBC and DM) HBcAb was found independently associated with age (t: 3.139; p=0.002), HBsAb (t: 3.998; p<0.001), WBC (t: 2.166; p=0.031) and DM (t: 2.749; p=0.006).

Conclusion: We found high rates of positive HBcAb. Positive HBcAb should be taken into account in immune-compromised patients such as dialysis patients.

Keywords: Hepatitis B virus, hepatitis B antibodies, hepatitis B core antigens, hemodialysis

Introduction

Patients on hemodialysis are under increased risk for hepatitis B virus (HBV) infection (1,2). The incidence of hepatitis B infection was about 0.12% in patients undergoing dialysis in the United States in 2002 (3). The incidence of HBV infection in dialysis differ worldwide according to the endemicity at in that region (4). The presence of hepatitis B core antibody (HBcAb) is an indication of exposure to HBV infection. In patients with HBcAb positive, when HBsAg is negative, HBV-DNA testing is not performed because these patients are not considered to be infectious. In case of receiving immune suppressive treatment, immune-suppressed patients such as hemodialysis patients with positive HBcAb, must receive prophylactic antiviral therapy against hepatitis B reactivation. Despite high antibody titers, reactivation of HBV infection has been shown in the literature after immunosuppressive therapy in HBcAb positive patients (5). Another important issue related to positive HBcAb is occult hepatitis B infection (OBI) which occurs as the result of mutations at the genes those encode surface antigen of HBV (6). Two subgroups of OBI according to the presence of serological markers had been described. If only HBV-DNA is positive whereas both HBsAg and HBcAb are negative, this situation is called seronegative OBI. On the other hand, if HBV-DNA is positive with the seropositivity of either HBcAb and HBsAg together or with the seropositivity of HBcAb alone, this situation is

Yazışma Adresi/Address for Correspondence: Ilter Bozaci, University of Health Sciences Turkey, Bozyaka Training and Research Hospital, Clinic of Nephrology, Izmir, Turkey
Phone: +90 232 240 50 50 E-mail: ilterbozaci@gmail.com ORCID: orcid.org/0000-0001-7535-9403
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called seropositive OBI. In both types, common laboratory finding is the positivity of HBV-DNA (7). In the literature, it was shown that the incidence of seronegative OBI is about 20% of all OBI cases (8). After the routine clinical use of the HBsAg test, there has been a serious decrease in HBV infection rates. However, testing for HBsAg solely is not sufficient to detect OBI cases. The clinical significance of OBI is based on its possible clinical consequences. The undetected and untreated OBI may result with hepatocellular complications including carcinoma and cirrhosis (9). In addition, if OBI cases are not properly isolated, HBV infection can be transmitted in dialysis units.

In the present study, we investigated the rates of positive HBcAb and its' association with demographical data and laboratory parameters among patients undergoing hemodialysis in our cohort.

Methods

Study Design

The study was approved by institutional ethics committee of Izmir Bozyaka Training and Research Hospital at the (number; 4, date: 28.10.2020). This study was conducted at a training and research hospital and its satellite dialysis units over 3 months period between October and December 2020. The study included hemodialysis patients who were older than 18 years old. All patients were enrolled in the study after providing written informed consent. Patients with overt HBV infection with positive HBsAg and HBV-DNA were excluded. The patients included in the study were divided into two groups according to the presence of IgG type HBcAb positivity.

Laboratory Assessment

The plasma samples were obtained during monthly periodic visits of hemodialysis patients enrolled in the study. The serological markers of HBV, hepatitis C virus (HCV) and human immunodeficiency virus (HIV) were determined via ELISA (Access and Bio Rad, Beckman-Coulter, California, USA) kits. HBV-DNA and HCV-RNA were measured by polymerase chain reaction (PCR) technique with the manufacturers Artus GmbH HBV RG PCR kit, Hamburg, Germany and Cobas Amplicor HCV Monitor test, version 2.0 kit, Roche Diagnostic Systems, California, USA, respectively. The information about the vaccination and the history of blood transfusion of each patients was obtained from medical records. Arrangement of the normal limits of alanine and aspartate aminotransferases were done according to the data in the literature (10). Demographical data such as age and gender, laboratory data such as complete blood count results, albumin levels, haemoglobin A1c levels [in patients with diabetes mellitus (DM)], kt/V and urea reduction ratio (URR) results were obtained from most recent medical records.

Statistical Analysis

Categorical variables those were compared using the chi-square test and Fischer's Exact test, were reported as number and percentages. Besides, continuous parametric variables those were compared using Student's t-test, were reported as means ± standard deviation. Mann-Whitney U test was used to compare parameters not showing normal distribution such as aspartate transaminase (AST), alanine aminotransferase (ALT), time of last vaccination and antibody titers. Linear regression analysis was made for HBcAb. In linear regression analysis of HBcAb variables were age, HBsAb, WBC and DM. The comparison was made using the Enter method. SPSS18.0 (Chicago, IL USA) was used in performing statistical analysis. The threshold value in terms of statistical significance was $p<0.05$.

Results

A sum of 237 hemodialysis patients were enrolled in the study. Fifty-nine patients (25%) were HBcAb positive and 178 patients (75%) were HBcAb negative. Twenty patients (34%) in HBcAb positive patients and 76 patients (43%) in HBcAb negative patients were female. There was no statistically significant difference between HBcAb positive and HBcAb negative patients in terms of gender [34/66 female (F)/male (M) (%) vs 43/57 F/M (%); p=0.23]. There was statistically significant difference between HBcAb positive and HBcAb negative patients in terms of age (64±11 vs 60±15; p=0.018), respectively. There were 2 patients (0.8%) with isolated positive HBcAb. HBV-DNA results were negative in HBcAb positive patients including either isolated HBcAb or in patients with positive HBcAb and/or HBsAb. Demographical and laboratory results of HBcAb positive and HBcAb negative patients are presented in Table 1. The distribution of patients in HBcAb positive and HBcAb negative patients in terms of gender is presented in Figure 1.

HBsAb was positive in 57 of 59 patients in HBcAb positive patients; 141 of 178 patients in HBcAb negative patients and there was statistically significant difference between HBcAb positive and HBcAb negative patients in terms of HBsAb positivity (96.6% vs 79.2%; p=0.002), respectively. In terms of HBsAb titers, there was no significant difference between HBcAb positive and HBcAb negative patients [196.6 (469.1) mIU/mL vs 136.2 (425.6) mIU/mL; p=0.111]. There was statistically significant difference between HBcAb positive and HBcAb negative patients in terms of the mean time of last vaccination [12 (30) months vs 5 (17) months; p=0.012], respectively.

Type-2 DM was in 19 of 59 patients in HBcAb positive patients and 34 of 178 patients in HBcAb negative patients

and there was statistically significant difference between groups (32% vs 19%; p=0.036), respectively. The history of blood transfusion was in 11 of 59 patients in HBcAb positive patients and 27 of 178 patients in HBcAb negative patients and there was no statistically significant difference between groups (19% vs 15%; p=0.528). In terms of dialysis sufficiency, there was no statistically significant difference between HBcAb positive and HBcAb negative patients in terms of kt/V (1.5±0.3 vs 1.6±0.4; p=0.104) and URR (71±7% vs 72±8%; p=0.490), respectively.

In terms of laboratory parameters that we evaluated between HBcAb positive and HBcAb negative patients, although the results were close, there was statistically significant difference in terms of WBC levels (7.7±2.5 x103/μL vs 7.1±2.1 x103/μL; p=0.044). There were 3 patients with positive anti-HCV. None of them were with positive HBcAb and HBsAb. Also, HCV-RNA was found negative for each individual as well. Variables those found significantly associated with HBcAb were assessed in linear regression analysis (variables: age, HBsAb, WBC and DM). HBcAb was found independently associated with age (t: 3.139; p=0.002), HBsAb (t: 3.998; p<0.001), WBC (t: 2.166; p=0.031) and DM existence (t: 2.749; p=0.006).

Discussion

The purpose of the study was to draw attention to the overlooked high rates of HBcAb positivity in hemodialysis patients consisting of immune-compromised individuals. In our cohort, we found no HBV-DNA and therefore OBI cases in patients with positive HBcAb. On the other hand, although it was not clearly known if patients were exposed to HBV before or after the initiation of dialysis, we found high rates of positive HBcAb. Despite the low number of patients, 59 of 241 (24%) patients were with positive HBcAb, 2 of them (0.8%) were with isolated positive HBcAb.

In our study, patients with positive HBcAb were older compared to patients with negative HBcAb. This may be due to the higher chance of being exposed to HBV. There is a strong association of DM with age (11). This may be the reason of the statistically significant difference between groups in terms of DM in our cohort.

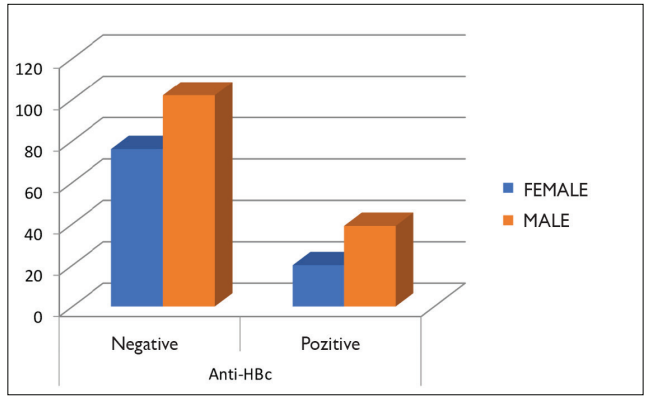

Figure 1. Distribution of patients in group 1 and group 2 in terms of gender
Anti-HBc: Anti-hepatitis B core

Table 1. Demographical and laboratory results of HBcAb positive and HBcAb negative patients

	HBcAb positive (n=59)	HBcAb negative (n=178)	p
Age (years), mean ± SD	64±11	60±15	**0.018***
Gender F/M	34/66	43/57	0.230
AST (U/L) [Median (IQR)]	10 (8)	13 (8)	**0.020****
ALT (U/L) [Median (IQR)]	8 (7)	10 (7)	**0.046****
HbA1c (%), mean ± SD	8.5±1.3	8±1.2	0.151
Kt/V (min: 1.2), mean ± SD	1.5±0.3	1.6±0.4	0.104
URR (%) (min 65%), mean ± SD	71±7	72±8	0.490
HBsAb Titer (m IU/mL) [Median (IQR)]	196.6 (469.1)	136.2 (425.6)	0.111
Transfusion history n, (%)	81%	85%	0.528
DM n, (%)	32%	19%	**0.036*****
Albumin (g/dL), mean ± SD	3.8±0.5	4.1±2.9	0.395
Hemoglobin (g/dL), mean ± SD	11±2	11±1.8	0.690
Hematocrit (%), mean ± SD	33±6	33±5	0.984
Platelet (x103/μL), mean ± SD	227±71	222±72	0.644
WBC (x103/μL), mean ± SD	7.7±2.5	7.1±2.1	**0.044***

F: Female, M: Male, AST: Aspartate transaminase, ALT: Alanine aminotransferase, URR: Urea reduction ratio, DM: Diabetes mellitus, WBC: White blood cell count, IQR: interquartile range, HBcAb: Hepatitis B core antibody, SD: Standard deviation, *: Student's t-test was used and significantly higher result was found in HBcAb positive group, **: Mann-Whitney U test was used and significantly higher result was found in HBcAb negative group, ***: The chi-square test was used and significantly higher result was found in HBcAb positive group

The immunosuppressive nature of chronic kidney disease (CKD) is due to the combined effects of many factors including chronic inflammation, uremia and dysfunction of both adaptive and innate immune system (12).

CKD results in a state of immunosuppression that is likely multifactorial due to a combination innate and adaptive immune system dysfunction, chronic inflammation, endothelial cell dysfunction and uremia (12). Since hemodialysis patients are immune suppressed patients, they are in the high-risk group for OBI reactivation. Although we detected no positive HBV-DNA, these high rates of positive HBcAb carry a high risk of HBV reactivation and possible adverse clinical outcomes.

Conventional serologic testing used in most dialysis centers is not able to identify the OBI (13). HBcAb was shown to be a useful marker for the detection of OBI in the literature (14). In a study, 996 healthy blood donors were evaluated and 2.4% revealed isolated positive HBcAb. Two of 23 patients (8.6%) were with positive HBV-DNA (15). Tarif et al. (16) evaluated the prevalence of isolated positive HBcAb status in non-vaccinated CKD patients in terms of previous exposure and found 51% among HBsAg negative CKD patients. In our study, we found 2 (0.8%) patients with isolated positive HBcAb, who were non-vaccinated. The reason why the rates of isolated positive HBcAb in our cohort were found relatively low might be due to the tight vaccination program of hemodialysis patients.

Studies in the literature about the OBI prevalence among hemodialysis patient era revealed low level of OBI. In a study, Aghakhani et al. (17) detected OBI in 50% of patients with positive anti-HBcAb. On the other hand, in agreement with our study, neither Fabrizi et al. (18) nor Jardim et al. (19) found positive HBV-DNA in their hemodialysis patients with positive HBcAb. Ramezani et al. (20) found 1% of patients on hemodialysis had OBI with positive HBV-DNA. The clinical importance of OBI depends on its' possible consequences associated with immune status. In the literature, although HBsAb was positive, both HBV transmission from OBI cases and HBV reactivation under immunosuppressive therapy in patients with OBI were shown in the studies (21). This reflects the importance of HBcAb screening even in patients with positive HBsAb. Also, dialysis patients may receive a kidney transplant at a later time in their course. Having an HBV infection may affect several aspects on their kidney transplant care in which immune suppressive medications are used to avoid rejection. Therefore, positive HBcAb, either isolated or with positive HBsAb, should be taken into account in immune-compromised patients such as dialysis patients and the possibility of OBI should be excluded be checking HBV-DNA.

In fact, patients with positive isolated HBcAb those admitted to the hospital with immediate need of dialysis, should be dialyzed on HBV positive machines in order to avoid exposing HBsAg negative patients to potential infection. Hypo-transaminase is a well-recognized feature in dialysis patients with or without liver disease. The normal range of transaminases should be adjusted downwards; otherwise, the incidence or severity of clinical liver disease might be underestimated. In this regard, levels of 24 and 17 IU/L have been recommended as the upper limits of normal AST and ALT levels, respectively, in dialysis patients (10). In our study, mean AST and ALT levels in HBcAb positive and HBcAb negative patients were 10 (8) U/L vs 13 (8) U/L and 8 (7) U/L vs 10 (7) U/L, respectively.

The OBI prevalence was found to be increased in patients with positive HCV probably due to the inhibition of HBV replication via interference of HCV in the hepatocyte (22,23).

On the contrary, in the literature, there are several studies those found no association between HCV and OBI (24-26). In our study, there were 3 patients with HCV. None of them were with either positive HBcAb or HBV DNA. This might be due to the insufficient number of patients with HCV in our cohort. Elevation of markers associated with liver damage may not be seen in dialysis patients due to suppression of inflammatory reactions due to chronic uremia (27). For this reason, to rule out OBI, HBV-DNA testing is crucial in dialysis patients (28). This can be considered as another justification for the necessity of administering HBV-DNA in the routine evaluation of hemodialysis patients with positive HBcAb.

In the literature, in vast majority of OBI cases serum viral load was reported about 20 IU/mL or undetectable (29). In our study, we found no viral load in patients with positive HBcAb. This might be due to fluctuation of viral load or relatively small number of patients.

Using erythropoiesis-stimulating agents in dialysis patients resulted in diminished need for transfusion. In addition, tight vaccination programs and screening blood products for viral markers contributed to decreasing of HBV infection in dialysis. In our study, we evaluated the transfusion rates and found no a significant difference between groups. Between groups, there was significant difference in terms of HBsAb titers. This may be due to the contribution of natural immunity after exposure to HBV to vaccination-associated immunity in patients with positive HBcAb. Also, we evaluated the mean time after the last vaccination dose and its' correlation with antibody titers and found no statistically significant difference between patients with positive HBsAb. The mean antibody levels were above the protective levels, which is accepted to be above 100 IU/L, at both groups. This may be related to

tight vaccination program and close follow-up procedures in our cohort.

Study Limitations

Number of patients was relatively small in our cohort. Also, we could not rule out seronegative OBI because not of not checking HBV-DNA in patients with HBcAb and HBsAb are both negative.

Conclusion

Due to the risk of viral reactivation, the importance of HBcAb should not be underestimated particularly in patients with immune suppression such as dialysis patients. HBsAg and HBcAb must be checked together. In addition, HBV-DNA testing should be performed in patients with positive HBcAb.

Authorship Contributions

Concept: I.B., S.T., Design: I.B., Data Collection or Processing: I.B., Analysis or Interpretation: I.B., S.T., Literature Search: I.B., S.T., Writing: I.B.

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