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Occult hepatitis B infection in Turkish HIV-infected patients: a multicentre, retrospective, cross-sectional study, Schindler Study

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ABSTRACT

Objective: Occult hepatitis B infection (OHBI) appears to have a higher prevalence in populations at high risk for hepatitis B virus (HBV) infection with concomitant liver disease. The aim was to assess the prevalence of OHBI in a sample of human immunodeficiency virus -1 positive and HBV surface antigen negative (HIV-1+/HBsAg-) Turkish patients.

Methods: Ten centers in Turkey were included in the study. Patients were selected on the basis of a power calculation with a known population size of HIV positive patients and a reported prevalence of OHBI. Gender, age, occupation, place of residence, treatment and clinical status, and laboratory results, including immunodeficiency panel, antibody tests, hemogram, biochemistry and coagulation studies, were evaluated retrospectively.

Results: The number of HIV-infected patients followed in these centers was 3172 and the sample population numbered 278. All 278 were HBsAg negative. The mean age of the sample was 37.2±13.1 years and 235 (84.5%) were male. All but one patient (99.6%) had been treated with antiretroviral therapy. Of the 278 patients, 169 (60.6%) were positive for Anti-HBs and 125 (44.8%) were positive for Anti-HBc IgG. HIV RNA was detected in 203/278 (73%) of the patients. Four HBV DNA (1.4%) were diagnosed with OHBI. There was no significant difference in hemogram, hemoglobin or bilirubin concentrations in those with OHBI compared to the other patients.

Conclusion: In a representative sample of HIV+ patients from ten Turkish centers, the prevalence of OHBI was found to be 1.4%. In HIV positive patients it is important to identify those with OHBI for optimal clinical management and prognosis

Key Words: Coinfection, HBV DNA, HIV, HIV RNA, Occult Hepatitis B Infection

INTRODUCTION

Globally, 245 million people are infected with Hepatitis B virus (HBV), 40 million are infected with human immunodeficiency virus (HIV), and 7.4% of HIV-infected patients are co-infected with HBV. Acute and chronic HBV infection causes approximately 887 thousand deaths annually. However, when compared with HBV mono-infection, the mortality and morbidity of HIV and HBV coexistence is higher (1).

HIV transmission routes, such as sexual intercourse, use of infected blood and blood products, infected stab injuries, and unsafe injection, also increase the risk of developing HBV infection. Individuals with HIV infection should also be screened for HBV. However, in HIV-infected individuals, a situation, which is known as Occult Hepatitis B infection (OHBI) can occur. In OHBI patients the Hepatitis B surface antigen (HBsAg) antibody test is negative while anti HBc IgG +/-, anti HBs +/-, and HBV DNA level in serum or plasma is generally lower than 200 IU/mL. There are two possible scenarios in HBsAg-negative cases with suspected HIV/OHB coinfection. The first is that HBV infection is in the acute period after virus ingestion, when the surface antigen is not yet positive. The second is that although blood tests are negative for HBsAg, anti-HBc, and anti-HBs antibodies, the patient is in the chronic period when there is covalent, closed, circular viral DNA (cccDNA) in the liver cell nucleus. In HIV infected patients, OHB infection can therefore be detected by identifying HBV DNA in serum or liver tissue in cases where cccDNA persists in the liver cell nucleus, even if HBsAg is negative (2,3).

Immunosuppressive conditions such as HIV positivity, hematological malignancies, and solid organ transplantations may cause hepatitis B reactivation. Mechanisms suggested for the development of OHBI include mutations in the PreS/S regions of HBV, the presence of HBV DNA molecules integrated into the HBV genome, HBV infection in mononuclear cells in peripheral blood, presence of HBV particles complexing with immunoglobulin (Ig) in the blood despite the formation of anti HBs antibodies, decrease in cellular humoral immune response and co-infection. HBsAg antibody negativity can be associated with analytical sensitivity of laboratory methods and also viral genotypes (4). Differentiating between resolution of HBV infection and occult HBV infection may be challenging. In cases where HBV is eradicated and HBsAg loss occurs, in the presence of mechanisms that cause occult disease, the disease may flare up

again. In a study in which 16 patients with occult HBV infection developing secondary to acute HBV infection were examined, anti HBc IgG positivity was found in all cases 30 years after the infection, and anti HBs positivity was found in 11 of them. In the same study, while HBV DNA was below the detectable level in the serum of the patients, it was positive in liver tissues from two patients (5).

Detecting OHBI in HIV-infected patients is important for determining optimal treatment and predicting the survival of patients. It has been reported that the use of highly active antiretroviral therapy (HAART) reduces morbidity and mortality and delays the occurrence of complications in HIV-infected and HIV/HBV co-infected patients (6). The aim of this study was to investigate the prevalence, demographic and clinical characteristics of occult HBV co-infection in a multicenter study in patients infected with HIV who received antiretroviral therapy and did not receive treatment.

MATERIALS AND METHODS

Ten centers in Turkey were included in the study. The number of HIV-infected patients followed in these centers was 3172. In a study with similar methodology to the present study, the prevalence of OHBI was found to be 7.5% (7). Therefore, given the population of 3172, the sample size was calculated as 255 people assuming a 7.5% prevalence, with 5% error, 80% power, and a 95% confidence level. The patients included in the study were determined as HIV-positive patients who presented to the centers during the study period. Among 3172 HIV-infected patients who were followed up until February 1, 2020 in the centers participating in the study, 278 patients who met the inclusion criteria were HIV positive treatment naïve and undergoing treatment included in the study. Gender, age, occupation, place of residence, treatment status, clinical status, immunodeficiency panel, eliza tests, HB sAg, antiHB c IgG, anti HIV, antiHBs, hemogram, biochemistry and coagulation laboratory results of the patients were evaluated retrospectively. Serum HbsAg level was measured mostly by Abbot Architect Plus i2000 analyzer (Abbott Park, IL, USA). Serum HBV DNA was measured mostly by Roche COBAS AmpliPrep/COBAS TaqMan HBV Quantitative Test, Version 2.0 (Roche Diagnostics, Indianapolis, IN, USA).

Statistical analysis

Our study is a cross-sectional study, and descriptive data are given together with number, percentage, mean and standard deviation values. In statistical analysis, analysis of categorical variables was done with the Fisher's exact test. A $p<0.05$ was considered statistically significant at a 95% confidence interval. All analysis was performed with SPSS, version 21.0 (IBM Inc., Armonk, NY, USA).

RESULTS

A total of 278 HIV-infected patients followed in ten centers were included in the study, representing 8.8% of the total HIV infected population from these centers. The centers and distribution of patients included in the study are shown in Table 1. The range age of the patients was 37.2 ± 13.1 years, median 34 (19-75) and 235 were male (84.5%) and 43 (15.5%) female. Nearly all (278, 99.6%) of the patients received antiretroviral treatment.

Table 1. Centers included in the study and distribution of patients

CENTERS	**Total number of HIV-infected patients followed-up**	**Number of HIV-infected patients included in the study**	
		Number (n)	**%**
Cukurova University	815	18	2.2
Akdeniz University	650	9	1.4
Antalya EAH	591	15	2.5
Gaziantep University	316	26	8.2
Dicle University	295	81	27.5
University of Kocaeli	200	7	3.5
Mustafa Kemal University	115	94	81.7
İnönü University	110	9	8.2
University of Health Science, Kocaeli Derince EAH	56	14	25.0
Mardin State Hospital	24	6	25.0
TOTAL	3172	278	8.8

HBsAg was negative in all 278 patients while 169 were positive for anti-HBs and 125 were positive for anti-HBc IgG. HIV RNA was detected in 203/278 (73%) of the patients. Four (1.4%) of the patients were diagnosed with OHBI. Anti-hepatitis C virus (HCV) positivity was detected in two patients (0.72%). Delta antibody positivity was not found in any of the 121 patients whose delta antibody was tested (Table 2).

Table 2.Viral serological and molecular test results of the patients

OHBI: Occult Hepatitis B Infection

	Negative	Positive
	Number (%)	**Number (%)**
HBsAg	278 (100%)	0
Anti-HBs	110 (39.4%)	169 (60,6%)
Anti-HBc IgG	93 (42.7%)	125 (57.3%)
HBV DNA (IU/mL)	275 (98.6%)	4 (1.4%)
OHBI	275 (98.6%)	4 (1.4%)
HIV RNA (copies/mL)	75 (27%)	203 (73%)
Delta Antibody	121 (100%)	0
Anti HCV	275 (99.3%)	2 (0.7%)

Analysis of risk factors associated with OHBI was performed. Of the four diagnosed with OHBI, all were male, three were homosexual and the other was heterosexual. Amongst these four patients, all were Anti HBc IgG positive and all were HIV RNA positive, while two (50%) had a CD4 count of 200/mm^3 (Table 3).

Table 3. Analysis of risk factors associated with occult hepatitis B infection

* Fisher's exact test result. OHBI: Occult Hepatitis B Infection

	OHBI absent **Number (percent)**	**OHBI present** **Number (percent)**	**p***
Gender			
Male	231 (84.3%)	4 (100%)	1
Female	43 (15.7%)	0	
Drug addiction			
Negative	258 (97.4%)	4 (100%)	1

Positive	7 (2.6%)	0	
Alcohol addiction			
Negative	248 (93.2%)	4 (100%)	1
Positive	18 (6.8%)	0	
IV drug addiction			
Negative	263 (98.6%)	4 (100%)	1
Positive	3 (1.1)	0	
Sexual preference			
Homosexual	88 (35.3%)	3 (75%)	0.268
Heterosexual	156 (62.7%)	1 (25%)	
Other	5 (2.0%)	0	
Hepatitis C co-infection			
Negative	275 (100%)	4 (100%)	N/A
Positive	0	0	
Anti HBs			
Negative	108 (39.3%)	2 (50%)	0.648
Positive	167 (60.7%)	2 (50%)	
Anti HBcIgG			
Negative	93 (43.5%)	0	0.138
Positive	121 (56.5%)	4 (100%)	
HIV RNA (copies/ml)			
Negative	75 (27.4%)	0	0.577
Positive	199 (72.6%)	4 (100%)	
CD4 count (cells/mm^3)			
200 and below	79 (30.4%)	2 (50%)	0.231

201-499	102 (39.2%)	2(50%)	
500 and above	79 (30.4%)	0	

Of the patients in whom OHBI was not identified 231 were male (84%), seven (2.6%) had drug addiction and the homosexuality rate was 35.3%. In addition, 167 (60.7%) were anti-HBs positive, 121 (56.5%) were anti-HBc IgG positive, and 199 (72.6%) were HIV RNA positive. In 30.4% of the patients, the CD4 count was $\leq 200/mm^3$ (Table 3).

When the laboratory findings of patients with and without OHBI were evaluated, no significant difference was found in terms of hemoglobin concentration, leucocyte and thrombocyte count, and liver function tests including ALT, AST, GGT, ALP and total bilirubin levels. Of the patients 172 were OHBI negative and albumin levels were 3.5-5 g/dl, 91were OHBI negative and albumin levels were <3.5 g/dl, 12 were OHBI negative and albumin levels could not be determined in 12 of the patients. However, albumin values were found to be <3.5 mg/dL in three patients with OHBI (p=0.043) (Table 4).

Table 4. Analysis of the laboratory results of the patients.

***** Fisher's exact test result. OHBI, Occult Hepatitis B Infection; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, Gamma glutamyl transferase; ALP, Alkaline phosphatase. NS; not statistically significant

	OHBI absent **Number (percent)**	**OHBI present** **Number (percent)**	**p***
Hemoglobin (g/dL)			
<12	34 (12.4)	0	0.536
12-16.8	235 (85.5)	4 (100)	
>16.8	6 (2.2)	0	
Leucocyte count **(10^3/µL)**			
<4000	13 (4.7)	0	0.707

4000-10600	252 (91.6)	4 (100)	
>10600	10 (3.6)	0	
Platelet count (10^3/µL)			
<139	29 (10.5)	2 (50)	0.129
139-346	229 (83.3)	2 (50)	
>346	17 (6.2)	0	
ALT (U/L)			
≤45	254 (92.4)	4 (100)	NS
>45	21 (7.6)	0	
AST (U/L)			
≤35	202 (73.5)	1 (25)	0.063
>35	73 (26.5)	3 (75)	
GGT (U/L)			
≤65	153 (90.0)	3 (100)	NS
>65	17 (10.0)	0	
ALP (U/L)			
<40	6 (2.2)	0	0.164
40-150	233 (86.3)	2 (50)	
>150	31 (11.5)	2 (50)	
Total bilirubin (mg/dL)			
≤1.2	162 (90.0)	4 (100)	NS
>1,2	18 (10.0)	0	
Albumin (g/dL)			
<3.5	91 (34.6)	3 (100%)	0.043

3.5-5	172 (65.4)	0	

Demographic, clinical data, laboratory results and radiological findings of the four patients identified with OHBI are shown in Table 5. Anti-retroviral (ART) regimen in two patients was tenofovir/disoproxil/emtristabine/dolutegravir (TDF/FTC+DTG) while the remaining two received tenofovir/alafenamide/emtristabine/cobicistat/elvitegravir (TAF/FTC+COBISTAT+EVG). HBV DNA levels between 60-1128 IU / mL, ALT levels 18-34 U/L, AST levels 22-54 U/L, total bilirubin level was found to be 0.4 -1.2 mg/dl, and albumin levels to be 2.9-3.2 g/dl. USG (ultrasonography) findings of HIV / OHBI co-infected patients were found to be normal (Table 5).

Table 5. Detailed analysis of demographic, clinical data, laboratory results and radiological findings of HIV / OHBI co-infected patients

* Fisher's exact test result. OHBI, Occult Hepatitis B Infection; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; GGT, Gamma glutamyl transferase; ALP, Alkaline phosphatase. ART; Anti-retroviral treatment.

	OHBI 1	**OHBI 2**	**OHBI 3**	**OHBI 4**
Gender / Age (years)	Male/56	Male /33	Male /23	Male /37
ART regimen	TDF/FTC+DTG	TAF/FTC+ COBISISTAT+E VG	TDF/FTC+DTG	TAF/FTC+ COBISISTAT+E VG
ART usage period (years)	8	2	4	3
HBsAg	NEG	NEG	NEG	NEG
Anti HBs	NEG	POS (12 IU/ mL)	NEG	POS (23 IU/mL)
Anti HBc IgG	POS	POS		POS
HBV DNA (IU/mL)	60	924	1128	932
HIV RNA (copies/mL)	285000	14000	2090	1287
Delta Antibody	Normal	Normal	Normal	Normal
CD4 count (cells/mm^3)	433	199	200	235

Hemoglobin (g/dL)	14,8	13	13	15
Leukocyte (10^3/µL)	7500	7200	5100	5300
Platelet (10^3/µL)	287000	119	121	231
ALT (U/L)	18	34	34	34
AST (U/L)	22	44	54	44
ALP (U/L)	69	56	181	220
Total bilirubin (mg/dL)	0.4	1.2	1.2	1.2
Albumin (g/dL)	N/A	3.2	2.9	2.9
ULTRASOUND OFLIVER	Normal	Normal	Normal	Normal

DISCUSSION

In HIV-infected patients, especially those who have not received treatment, OHBI, defined as HBsAg negativity, and anti-HBc IgG +/-, anti HBs +/- and/or the presence of HBV DNA in serum or plasma is frequently reported. The mechanisms responsible for HBsAg negativity in occult infection are controversial. Among the causes of HBsAg negativity, decrease or absence of HBsAg expression, decrease of HBsAg secretion from hepatocytes, and change of HBs antigenicity can be counted. The presence of mutations in the HBV genome, particularly the envelope gene, is an important cause of HBsAg negativity (1,8).

OHBI has been investigated in many patient groups, such as blood donors, pregnant women, those receiving immunosuppressive therapy, and hemodialysis patients, and OHBI is encountered in HIV-infected patients. It has been reported that the prevalence of OHBI in HIV-infected individuals varies widely from 0% to 89.5% (9). One of the reasons for the difference in the prevalence of OHB infection is the use of diagnostic methods with different sensitivity and specificity (1). In our cohort, the frequency of OHB in 279 patients was found to be 1.4%.

In HIV/OHBI co-infected individuals, although antibody positivity against HBV core antigen (anti-HBc) is a marker of HBV exposure, OHBI and HIV/OHBI co-infected cases have been reported in regions with high rate of endemic HBV infection where anti-HBc is negative (2). Recent studies show that approximately 20% of OHBI are serologically negative, and anti-HBc positivity, which was used as a

marker for the detection of OHBI, is not sufficient for the diagnosis of OHBI. In one study, serological evidence of HBV infection could not be shown in 2.2% of OHBI patients (2). In studies conducted in South Africa and the USA, HBV DNA positivity was reported in 2.2% and 0.55% of seronegative individuals, respectively (8). In our population of HBsAg negative HIV patients, 60.6% were positive for anti-HBs and 57.3% for anti-HBc IgG. In addition, 2/4 OHBI patients were anti-HBs positive, 4/4 were anti-HBc IgG positive, and the HBV DNA levels of these patients were between 60-1128 IU/ mL. Our results support the hypothesis that routine HBV antibody tests are not sufficient for OHBI screening. It has been highlighted that the gold standard diagnostic test for OHBI is the demonstration of the presence of HBV DNA in the liver. Since routine liver biopsy is not performed in HIV-infected patients, blood samples are generally used in the diagnosis of OHBI infection. No evidence has been shown that HIV infection changes the sensitivity or specificity of these tests (10).

Some studies have reported a trend towards elevated liver transaminases (ALT and AST) in HIV/OHBI co-infected individuals. In a study investigating the prevalence of OHBI and the long-term effects of OHBI in HIV-infected women, OHBI was detected in 2% of HIV-infected women who were anti-HBc positive, and it was reported that increased aminotransferase levels were not associated with detectable HBV DNA (17). In our study, no significant relationship was found between OHBI and liver enzyme elevation.

The clinical effect of OHBI in HIV-infected patients is still controversial. There is evidence that OHBI is associated with hepatic exacerbations, advanced liver fibrosis, decreased response to interferon therapy, and hepatocellular carcinoma (HCC) (12). In patients with HIV/OHBI co-infection, HIV-induced immunodeficiency may accelerate the progression to cirrhosis and HCC. In patients with OHBI the fibrosis score has been reported to be increased (13). However, since fibrosis scoring was not routinely performed in HIV/OHBI co-infected patients in the centers participating in our study, it is not possible to make comparison with this finding. There is a need for large-scale studies investigating the clinical course, liver enzyme levels, and fibrosis scoring in patients with HIV/OHBI.

In a study conducted with HIV-1 infected pregnant women, it was reported that low CD4 count, cases over 35 years of age and HCV co-infection were independent risk factors for isolated anti-HBc positivity (11). Suppression of the immune system has been associated with a CD4 T cell count of <100 cells/μL, loss of anti-HBs and isolated anti-HBc in HIV-infected patients. The authors suggested that anti-HBs antibody production decreased as patients' age increases (11). In the study conducted by Walz et al., it was reported that 7/105 babies born from isolated anti-HBc positive women were infected with HBV. In the study of Khamduang et al. 47 women with occult HBV infection had HBV DNA levels (>15 IU/mL) but none of their babies were infected with HBV (11). In our study, a significant correlation was found between OHBI and CD4 count. Our data suggest that the possibility of OHBI should be kept in mind in cases with low

CD4 cell count. Viremia is suppressed in OHBI patients due to the strong host defense that occurs during acute or chronic infection (12). Similarly, in our study, HBV DNA levels in patients with OHBI were between 60-1128 IU/mL.

In our study, no significant difference was found in hemoglobin and bilirubin levels and complete blood count results in patients with HIV-OHBI co-infection. However, albumin concentrations were low in 3/4 OHBI patients (p=0.043)

The pooled HBV nucleic acid test (NAT) can be used to detect HIV/OHBI co-infection. In a study conducted in India, OHB infection was detected in 10% of HIV-infected participants. It has been argued that the pooled HBV NAT test is a cost-effective and highly specific test. It has been reported that the sensitivity of this method is low in patients with low HBV DNA levels (14). In a study conducted in Cameroon, anti-HBc positivity was detected in more than 50% of blood donors. OHBI has been shown in 1% of patients negative for HBsAg but positive for anti-HBc. Gachara et al suggested that performing HBsAg test alone is not sufficient to eliminate the risk of HBV transmission through transfusion and for screening of potential donors. These authors recommended the use of the HBV NAT test in addition to anti-HBc screening (16).

In our study, all patients diagnosed with OHBI had been receiving ART for between 2 and 8 years. Most of them 242 (87%) patients using tenofovir regimens. The HIV / OHBI co-infected patients patients had received two different regimens of ART - TDF/FTC+DTG and TAF/FTC+COBISTAT+EVG. Thus it appears that OHBI may be present, even in HIV infected patients receiving anti-retroviral therapies (19).

Routine serological markers and especially isolated anti-HBc positivity may be insufficient in the diagnosis of OHBI in HBsAg negative patients. This study has some limitations. It is likely that performance of molecular tests differed and there for this is limiting factor for study. And the number of patient applications during the working period of the centers created heterogeneity. Therefore, differences in epidemiological distribution of the number of patients in the centers by regions created heterogenity. The most reliable method in the diagnosis of OHBI in these patients is HBV DNA detection. HBV DNA levels in these patients are usually low (<1000 IU/mL). A low CD4 count and age >35 years are among the independent risk factors for OHBI. In our study, no significant difference was found in patients with HIV-OHBI co-infection in terms of liver enzyme levels, hemoglobin and bilirubin levels, and complete blood count, but a significant correlation was found between OHBI and CD4 count. In addition, we found that albumin values in patients with OHB tended to be significantly reduced. There was no significant relationship between transmission routes, sexual preferences and OHBI. All patients with OHBI were under ART treatment. Our results show that HIV-infected patients should be evaluated in terms of OHBI co-

infection. For the diagnosis of OHBI, investigation for HBV DNA should be performed and that the test should be performed before starting HAART. Following this a decision can be made to use drugs effective against HBV in the treatment of affected HIV-infected patients. There is a need for large-scale studies investigating the clinical course, liver enzyme levels, liver histopathology, and treatment options in HIV-OHBI co-infected patients.

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