Occult Hepatitis B in Hemodialysis Patients

Pelin Adar, Şükran Köse, Bengü Tatar

ABSTRACT

Objectives: We aimed to detect occult hepatitis B (OHB) in hemodialysis patients at a higher-risk for OHB.

Materials and Methods: The study included 567 patients with chronic renal failure aged 18 years and older who underwent hemodialysis in 10 dialysis centers in İzmir province between May 2013 and July 2013. Hepatitis B surface-antigen (HBsAg), anti-hepatitis B core (HBc) immunoglobulin G (IgG) and anti-HBs were detected by ELISA and HBV-DNA levels with polymerase chain reaction (PCR). Detection of HBsAg negativity with HBV-DNA positivity was considered as OHB.

Results: Of 567 patients, 49% were male and the mean age was 62.2 years. All the patients were HBsAg-negative. Isolated anti-HBc IgG positivity was detected in 8 patients while HBV-DNA was negative. Serum HBV-DNA level was 270 IU/mL in only one patient (0.2%) who was anti-HBc IgG-negative.

Conclusion: HBsAg alone is not an adequate serological test to detect HBV infection. HBV-DNA should be tested using molecular diagnostic methods in patients with suspected OHB. Further studies investigating cost-effectiveness and the role of PCR in diagnosis are warranted.

Keywords: Chronic viral hepatitis, hemodialysis, occult hepatitis B

Introduction

Being one of the most important causes of chronic liver disease, hepatitis B virus (HBV) is a significant cause of morbidity and mortality all over the world. HBV infection is a major health problem with 400-500 million people chronically infected worldwide. It is a known fact that 5% of people with acute hepatitis B develop chronic infection and a substantial number of these cases develop cirrhosis associated with higher risk of, hepatocellular carcinoma (HCC) (1).

HBV infection is diagnosed by detection of various antigens belonging to this virus or the antibodies developed by the host against these antigens with specific serological tests. Hepatitis B surface antigen (HBsAg) is one of the most important markers of HBV infection. HBsAg positivity in serum for more than six months indicates chronic HBV infection (2,3). Antibody to anti-HBs appears
following the disappearance of HBsAg. Anti-HBs shows recovery and immunity. Anti-hepatitis B core (HBC) immunoglobulin G (IgG) positivity, which is detected together with anti-HBs, is defined as natural immunity (2,4,5). Presence of HBV-DNA is the most sensitive indicator of viral replication.

Detection of serological markers is important in the identification of infection but has little clinical importance. Polymerase chain reaction (PCR) detects low levels of viral DNA in serum or liver in some patients whose HBsAg levels are undetectable or in patients who have HBsAg disappearance with HBV treatment. Occult hepatitis B (OHB) infection (OBI) is defined as the presence of HBV-DNA in serum or liver in the absence of HBsAg. OBI has also been defined as a serological condition characterized by the presence of isolated hepatitis B core antigen anti-HBc in the absence of HBsAg and anti-HBs. OBI can be classified into 2 groups on the basis of the HBV antibody profile: seropositive OBI (anti-HBc and/or anti-HBs-positive) and seronegative OBI (anti-HBc and anti-HBs-negative) (6). HBV-DNA level in OBI is generally measured lower than 200 IU/mL (7).

OBI has been reported to be more prevalent in patients with HCC, chronic hepatitis C virus (HCV) infection, cryptogenic cirrhosis, hemodialysis patients, substance users, intravenous drug abusers, patients with human immunodeficiency virus infection, and patients who receive frequent blood transfusions (8). If patients with OBI diagnosis undergo dialysis in the same dialysis machines with HBsAg-negative patients, HBV transmission may occur.

There are not sufficient studies performed on the frequency of OBI in our country and our province. In this study, we aimed to detect OHB in hemodialysis patients who are at a higher risk for OBI.

Materials and Methods

This randomized prospective study included 567 patients with chronic renal failure (CRF) aged 18 and older who underwent hemodialysis in 10 dialysis centers in İzmir province between May 2013 and July 2013. Patients younger than 18 years of age, having a previous diagnosis of HBV infection and undergoing peritoneal dialysis were excluded. Ethic committee approval was taken from the Ethics Committee Board of University of Health Sciences, İzmir Tepecik Training and Research Hospital (approval number: 47/1, date: 24.04.2013).

A form questioning risk factors for HBV contamination including socio-demographic characteristics, medical history such as co-morbidities, IV drug administration, surgery, blood transfusion and time of hepatitis B vaccination was completed by the patients. Written consent form was taken from each patient. Blood samples were taken before dialysis session; serum samples were centrifuged at 3000 rpm for 5 minutes and stored at -80 °C. HBsAg, anti-HBC IgG, and anti-HBs were investigated by the ELISA method (Liaison, Diasorin, Italy) in accordance with the instructions of the manufacturing company. HBV-DNA levels were evaluated by PCR (Roche, Taqman, Switzerland). HBV-DNA levels lower than 20 IU/mL were considered as negative. HBV-DNA presence in serum without HBsAg positivity was defined as OBI.

Results

Forty-nine percent of 567 patients were male and the mean age was 62.2 (range: 24-78) years. The patients were receiving hemodialysis treatment three times a week for four hours. The mean duration of hemodialysis treatment was 60.7 months (range: 4-180 months). The indications for dialysis were diabetes mellitus (42.7%), hypertension (31.3%), glomerulonephritis (12.5%), polycystic kidney disease (4.2%), and others (9.3%) (Table 1). Mean AST: aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were 14 (5-42 u/L) and 17 (8-36 u/L), respectively.

Fifty-seven percent of the patients had a history of vaccination with 40 mcg recombinant DNA vaccine in months 0, 1, 2 and 6 according to the standard vaccine schedule. In 1.5% (n=5), insufficient antibody response (anti-HBs <10 IU/mL) was detected despite administration of vaccine twice. Fifteen percent of the patients were considered to have natural immunity due to past infection.

As shown in Table 2, HBsAg was negative in all cases. Isolated anti-HBc IgG positivity was detected in 8 patients while HBV-DNA was negative. Serum HBV-DNA level was 270 IU/mL in only one patient aged 53 years (0.2%) with anti-HBc and anti-HBs negativity. AST and ALT levels of the patient who was considered as seronegative for OBI, were within the normal range (0-35 IU/L). Hemodialysis duration of the patient was lower than the average (12 months). The patient had a history of diabetes mellitus and hypertension. In terms of chronic hepatitis B, no other risk factors (history of past HBV infection or inactive chronic hepatitis, previous surgery, blood transfusion, suspicious coitus, history of dentist appointment, and family history of hepatitis), beyond hemodialysis and catheterization, were detected.

Table 1. The questionnaire including demographics, dialysis reasons and risk factors for hepatitis B virus infection

| Socio-demographic characteristics | 62.2 |
|----------------------------------|------|
| Gender                           | 49%  |
| History of hepatitis B virus vaccination | 57% |

| Dialysis reasons (%) |        |
|----------------------|--------|
| Diabetes mellitus    | 42.7   |
| Hypertension         | 31.3   |
| Glomerulonephritis   | 12.5   |
| Polycystic kidney disease | 4.2 |
| Others               | 9.3    |

| Risk factors (%) |        |
|-----------------|--------|
| IV drug administration | 32.6  |
| Operation        | 13.8   |
| Blood transfusion| 26.7   |
| Family history   | 3.4    |
| Suspicious coitus| 2.9    |
HBsAg: Hepatitis B surface antigen, HBc: anti-hepatitis B core, HBs: Hepatitis B surface, HBV: Hepatitis B virus

### Discussion

HBV infection continues to be a significant issue in hemodialysis units despite vaccine schedules and precautions. Risk of the HBV transmission between hemodialysis patients is explained by the presence of OBI (HBsAg negative but HBV-DNA positive) in addition to the presence of immunosuppression, shared use of dialysis machines, insufficient response to vaccine, blood transfusions and interventions which are performed more frequently for hemodialysis patients than for normal population (9).

The prevalence of OBI in healthy subjects has been reported to vary between 0% and 90% based on the endemicity (10,11,12). In hemodialysis patients, the prevalence of OBI reported in the literature varies greatly, ranging from 0% to 50% (9,13). In a study investigating the prevalence of anti-HBc in hemodialysis patients, HBV-DNA was detected in 1 of 3 anti-HBc positive patients. HBV-DNA was undetectable in 123 anti-HBc negative patients (14). In a study by Ramezani et al. (15), HBV-DNA was detected in 1% of HBsAg negative patients. Similar to that study, Muche et al. (16) found nil prevalence of OHB in chronic hemodialysis patients and a very low prevalence (<1%) in renal transplant patients suggesting that routine screening for HBV-DNA was not required in chronic hemodialysis population in their region.

The frequency of rate of OBI in hemodialysis patients reported in studies performed in our country varies between 0% and 12.4% (17,18,19). The variability in the reported prevalence is related with the regions where the studies were performed, PCR method used, and patient population included. In our study, it was found to be 0.2%. Possible reasons for low frequency of OBI in our study may be regular vaccination and anti-HBs negativity (28). Further studies investigating cost-effectiveness and the role of PCR in diagnosis are warranted.

Presence of fulminant liver disease, chronic hepatitis, cirrhosis, and HCC has been reported in patients with OBI (26). This suggests a role of OBI in development of cirrhosis and HCC. Carcinogenesis may start with integration of the viral genome into liver cells together with the cytotoxic liver injury due to long-term HBV positivity. Therefore, OHB-seropositive patients without HBV-DNA in serum may also require liver biopsy for further OBI detection. We also detected isolated anti-Hbc IgG positivity in 8 patients and suggested liver biopsy.

Initiation of antiviral treatment should be considered in patients with OBI diagnosis. The patients should be screened for HCC in regular intervals. A favorable response to treatment may be expected in patients with a low viral load (27).

### Conclusion

HBsAg alone is not an adequate serological test to detect HBV infection. HBV-DNA should be tested with molecular diagnostic methods in patients with OHB suspicion. For diagnosis of OHB, DNA nucleic acid tests should be performed especially in high-risk patients, those living in endemic regions, individuals with cryptogenic chronic hepatitis, with potential prior exposure before blood or organ donation, transplantation and chemotherapy, and those receiving hemodialysis, even if these patients have anti-HBc and anti-HBs negativity (28). Further studies investigating cost-effectiveness and the role of PCR in diagnosis are warranted.

### Ethics

**Ethics Committee Approval:** Ethic committee approval was taken from the Ethics Committee Board of University of Health
13. received no financial support.

12. The authors declared that this study received no financial support.

11. Financial Disclosure: The authors declared that this study received no financial support.

10. References

1. Hollinger FB. Hepatitis B virus. In: Fields BN, Knipe DM (eds.), Virology. 2nd ed. New York: Raven Press; 1990.

2. Yağcı S. The history of acute viral hepatitis. Klimik Dergisi. 1988;1:4-5.

3. Klötzting K, Miskt R. Viral hepatitis in Turkey. In: Klötzting K (ed.), Viral Hepatitis’ 94. Istanbul: Turkish Viral Hepatitis Society Press; 1994.

4. Yenen OS, Topcu AW, Söyletir G, Doganay M. Hepatitis B. 1st ed. Istanbul: Nobel Tıp Press; 1996.

5. Robinson WS. Hepadnaviridae and their replication. In: Fields BN, Knipe DM (eds.), Fundamental Virology. 2nd ed. Lippincott: Raven Press; 1991.

6. Kwak MS, Kim YJ. Occult hepatitis B virus infection. World J Hepatol. 2014;6:860-869.

7. Hu KO. Occult hepatitis B virus infection and its clinical implications. J Viral Hepat. 2002;9:243-257.

8. Türkoglu S. Epidemiology and serology of HCV infection. In: Fields BN, Knipe DM, Howley PM (eds.), Viral Immunology. 3rd ed. Philadelphia: Lippincott-Raven Press; 1996.

9. Minuk GY, Sun DF, Greenberg R, Zhang M, Hawkins K, Uhanova J, Gutkin A, Bernstein K, Giulivi A, Osiowy C. Occult hepatitis B virus infection in a North American adult hemodialysis patient population. Hepatology. 2004;40:1072-1077.

10. Conjeevaram HS, Lok AS. Occult hepatitis B virus infection: a hidden menace? Hepatology. 2001;34:204-206.

11. Hollinger FB. Hepatitis B virus infection and transfusion medicine: science and the occult. Transfusion. 2008;48:1001-1026.

12. Gutiérrez-García ML, Fernandez-Rodríguez CM, Lledo-Navarro JL, Buhigas-García I. Prevalence of occult hepatitis B virus infection. World J Gastroenterol 2011;17:1538-1542.

13. Yoo JH, Hwang SG, Yang DH, Son MS, Kwon CI, Ko KH, Hong SP, Park PW, Rim KS. Prevalence of occult hepatitis B virus infection in hemodialysis patients. Korean J Gastroenterol. 2013;61:209-214.

14. Ayatollahi J, Jahanabadi S, Sharif Yazdi M, Hemayati R, Vakhili M, Shahcheraghi SH. The Prevalence of Occult Hepatitis B Virus in the Hemodialysis Patients in Yazd, Iran. Acta Med Iran. 2016;54:784-787.

15. Ramezani A, Aghasadeghi MR, Ahmadi F, Razeghi E, Eslamifar A, Banifazl M, Sofian M, Bahramali G, Hekmat S, Aghakhani A. Isolated anti-Hbc and occult HBV infection in dialysis patients. Nephrourol Mon. 2014;7:e22674.

16. Mucu M, Berg T, Rimpler S, Stadlter A, Böhm S, Nickel P. Baid-Agrawal S. Low prevalence of occult hepatitis B virus infection in chronic haemodialysis and kidney transplant patients. Liver Int. 2019;39:263-270.

17. Besisik F, Karaca C, Akyüz F, Horosanli S, Onel D, Badur S, Sever MS, Danaloglu A, Demir K, Kaymakoglu S, Cakaloglu Y, Okten A. Occult HBV infection and YMDD variants in hemodialysis patients with chronic HCV infection. J Hepatol. 2003;38:506-510.

18. Yakaryılmaz F, Gurbuz OA, Gültürk S, Mert A, Songur Y, Karakan T, Keles H. Prevalence of occult hepatitis B virus and hepatitis C virus infections in Turkish hemodialysis patients. Ren Fail. 2006;28:729-735.

19. Goral V, Ozkul H, Tekes S, Süt D, Kadiroğlu AK. Prevalence of occult HBV infection in haemodialysis patients with chronic HCV. World J Gastroenterol. 2006;12:3420-3424.

20. Xu L, Wei Y, Chen T, Lu J, Zhu CL, Ni Z, Huang F, Du J, Sun Z, Qu C. Occult HBV infection in anti-HBs positive young adults after neonatal HB vaccination. Vaccine. 2010;28:5986-5992.

21. Serdergenci K, Süleymanlar G, Altiparmak MR, Seyahi N. Registry of the Nephrology, Dialysis and Transplantation in Turkey, Istanbul: Turkish Society of Nephrology Press; 2009.

22. London WT, Drew JS, Lustbader ED, Werner BG, Blumberg BS. Host responses to hepatitis B infection in patients in a chronic hemodialysis unit. Kidney Int. 1977;12:51-58.

23. Alhababi F, Sallam TA, Tong CY. The significance of “anti-HBc only” in the clinical virology laboratory. J Clin Virol. 2003;27:162-169.

24. Noborg U, Gusdal A, Horal P. Levels of viremia in subjects with serological markers of past or chronic hepatitis B virus infection. Scand J Infect Dis. 2000;32:249-252.

25. Kasapoglu B, Türkay C. Occult hepatitis B infection. Güncel Gastroenterol. 2007;11:51-56.

26. Brecht C, Thiers V, Kremsdorf D, Nalpas B, Pol S, Paterlini-Bréchet P. Persistent hepatitis B virus infection in subjects without hepatitis B surface antigen. clinically significant or purely “occult”? Hepatology. 2001;34:194-203.

27. Torres J, Locarnini S. Antiviral chemotherapy for the treatment of hepatitis B virus infections. Gastroenterology. 2000;118(2 Suppl 1):83-103.

28. Zobeiri M. Occult hepatitis B: clinical viewpoint and management. Hepat Res Treat. 2013;2013:259148.