

Occult Hepatitis B in Patients Co-Infected With Hepatitis C and Human Immunodeficiency Viruses

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Abstract

Objectives: Diagnosis of the occult hepatitis B virus (HBV) infection in patients co-infected with human immunodeficiency virus (HIV) and hepatitis C virus (HCV) is important due to the fact that the HBV infection may have a clinical impact on liver disease in coinfecting HIV/HCV patients. Isolated hepatitis B core antibody (HBcAb) positive HBV infection has been reported in HIV patients. The aim of this study was to determine the occult hepatitis B in patients co-infected with HCV-HIV.

Methods: In a cross-sectional study, hepatitis B surface antigen (HBsAg) and HBcAb tests were performed for all HIV-HCV co-infected patients, referred to the HIV Clinic of Hamadan. HBsAg was requested for HBsAg negative-HBcAb positive individuals and in the case of negative HBsAg, HBV-DNA PCR was performed. Finally the collected data was analyzed with SPSS.

Results: Of 103 HIV-HCV coinfecting patients, both HBsAg and HBcAb were positive in 7 patients (6.8%), negative in 44 (42.7%) patients and 52 (50.5%) of all patients were HBsAg negative and HBcAb positive, which positivity of HBsAg had statistical correlation with positivity of HBcAb. In the last group HBsAg and HBV-DNA PCR were done, which resulted in the titer of antibody to be positive in 4 patients (7.7%) and the PCR to be negative in all (100%) patients.

Conclusions: The significant number of coinfecting HIV-HCV patients only had HBcAb positive test without detectable HBV-DNA. Further studies for detection of HBV-DNA in both serum and liver biopsy specimens may help clarify the impact of HBV infection in coinfecting HIV/HCV patients.

Keywords: HIV, Hepatitis B, Hepatitis C, Diagnosis

1. Background

Co-infection of the hepatitis B virus (HBV) and hepatitis C virus (HCV) is common in high-risk populations (1, 2). In the presence of co-infection, replication of two viruses is unusual. In this situation, the replication of HBV may be inhibited; however, the risk of the severity of liver disease and progression to hepatocellular carcinoma may increase. On the other hand, in patients co-infected with human immunodeficiency virus (HIV) and HBV, increased serum level of HBV DNA and histological changes are observed, while the levels of transaminases are not elevated. Antiretroviral therapy reactivates the course of inactive hepatitis B (3). Thus, it is recommended that all HIV patients should be screened for hepatitis B and C (4). If the hepatitis B surface antigen (HBsAg) is negative but the anti-hepatitis B core immunoglobulin G (IgG anti-HBc) is posi-

tive then hepatitis B has been reported in HIV patients (5, 6). Considering the above-mentioned points, it seems that HBsAg testing alone is not enough for the diagnosis of HBV infection in HCV/ HIV coinfecting patients. Other markers including HBcAb and HBV-DNA polymerase chain reaction (PCR) may need to be assessed for the diagnosis of hepatitis B in HCV-HIV coinfecting patients.

2. Objectives

The aim of this study was to evaluate the occult hepatitis B in patients coinfecting with HCV-HIV.

3. Methods

In a cross-sectional study, during November 2013 to September 2014, all patients with co-infection of HCV and

HIV, who referred to the HIV Clinic in Hamadan, Iran, were included. Co-infection was defined as simultaneous positive titres of anti-HCV and anti-HIV antibodies in a patient.

After taking informed consent, a questionnaire including demographic characteristics and risk-factors for HCV and HIV infections was fulfilled for each patient and a serum sample was obtained and stored at -20°C until use.

Patients with negative HBsAg but positive HbCAb were tested for HBsAb to determine those with cured hepatitis B. The remaining HBsAb negative patients were tested for HBeAg, HBeAb and HBV-DNA.

Serologic markers of hepatitis B including, HBsAg and HbCAb were measured by ELISA using specific kits (Biokit. S. A, Barcelona, Spain). Serum HBV DNA was detected by a conventional polymerase chain reaction assay (Sinaclon, Karaj, Iran).

DNA was extracted from serum by Cinnagen DNA kits and amplified by thermocycler. The PCR product of 353 bp was separated in 2% agarose gel electrophoresis.

The study and signed informed consent were approved by the ethical committee of Hamedan University of Medical Sciences, Hamadan, Iran.

Data was analysed using the SPSS statistical package version 18 and a $P < 0.05$ was considered statistically significant.

4. Results

103 patients with HCV/HIV coinfection, including 101 (98.1%) male and 2 (1.9%) female were diagnosed. The mean age was 38.6 ± 7.8 (range: 27 - 67) years. HBsAg and HbCAb were positive in 6.8% and 57.3% of patients, respectively.

Out of 103 coinfecting patients 7 (6.8%) were HBsAg/HbCAb positive and 44 (42.7%) were both HbCAb/HBsAg negative.

HbCAb was positive in 52 (50.5%) HBsAg negative patients, of whom, 4 (7.7%) were HBsAb positive with a history of hepatitis B immunization. HBeAg and PCR for HBV-DNA were negative in all of the isolated HbCAb positive/HBsAg negative patients.

5. Discussion

HBsAg is considered as a marker of HBV infection. However, HbCAb positivity may indicate a recent or past HBV infection.

Isolated HbCAb seropositivity may be due to occult hepatitis B, false positive result and recovery from an old infection with very low titer of HBsAb. Accordingly, in individuals with isolated HbCAb, detection of HBV-DNA in blood or liver biopsy is needed for confirmation of occult HBV infection.

The prevalence of HBV infection in HIV- infected individuals varies in different populations. Previous studies have reported the prevalence of 12.6% in China, 7.7% in Nigeria, 6% in Kenya and 3.3% in Iran (5-8). A higher prevalence of occult HBV infection (35%) was reported by Piroth et al. (9).

The role of HBV infection in the progression of the liver disease in HIV/HCV coinfecting patients has been evaluated in several studies with conflicting results (10,11). The frequency of HBV infection in those with coinfection of HIV/HCV has been reported from 1 to 35% in different studies (12,13). A limited study from Iran reported that three out of the 18 patients (16.7%) had HBV infection (14)

In the present study, 50.5% of 103 HIV/HCV coinfecting individuals were isolated and HbCAb positive. None of them had any detectable HBV-DNA in their serum.

In a study of 837 HIV-positive patients by Gupta S et al. (15), HBV-DNA was assessed using a highly sensitive qualitative PCR. Occult HBV infection was seen in 20.7% anti-HBs positive patients. However, in the seronegative patients, none of them detected HBV-DNA.

Morsica G et al. reported a study of occult HBV infection in 175 HIV-positive patients using a highly sensitive PCR assay. Quantification was performed by real-time PCR. HBV-DNA was detected in plasma of 15% of patients (10).

In a study conducted by Fabris et al. (16), 52 HIV/HCV coinfecting patients were evaluated by PCR for HBV infection. HBV-DNA was detected in 7 (13.4%) of the liver specimens and 3 of serum samples. Raffa et al. (17) reported a higher prevalence (41%) of HBV-DNA by PCR testing of liver biopsy specimens of the 101 HBsAg negative individuals with HIV/HCV coinfection. The discrepancies between our results and above-mentioned studies may be explained in part by the type of PCR technique and the specimen investigated (liver or serum). PCR testing for detection of HBV-DNA in liver tissue is considered as the 'gold standard' approach for occult HBV detection.

Considering the negative results of all PCR tests, in this study and most of similar studies, it seems that the most probable cause of isolated HbCAb is not occult hepatitis. In like manner, seropositivity of HbCAb, per se, does not affect the course of HIV/HCV coinfection.

5.1. Conclusion

A significant number of coinfecting HIV/HCV patients had only isolated HbCAb positive test. However, according to the previous studies, occult HBV infection may be more prevalent in HIV/HCV coinfecting patients and underestimated by serological tests. HbCAb status, per se, is not useful for HBV infection screening. Further studies with proper techniques for detection of HBV-DNA in both serum

and liver biopsy specimens are needed to clarify the clinical impact of HBV infection in coinfecting HIV/HCV patients.

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Footnote

Conflict of Interest: None declared.

References

1. Schuttler CG, Fiedler N, Schmidt K, Repp R, Gerlich WH, Schaefer S. Suppression of hepatitis B virus enhancer 1 and 2 by hepatitis C virus core protein. *J Hepatol.* 2002;**37**(6):855-62. [PubMed: [12445429](#)].
2. Drosten C, Nippraschk T, Manegold C, Meisel H, Brixner V, Roth WK, et al. Prevalence of hepatitis B virus DNA in anti-HBc-positive/HBsAg-negative sera correlates with HCV but not HIV serostatus. *J Clin Virol.* 2004;**29**(1):59-68. [PubMed: [14675872](#)].
3. Thio CL, Hawkins C. In: Principles and practice of infectious diseases. 8 ed. Mandell GL, Bennett JE, Dolin R, editors. Elsevier Churchill Livingstone; 2015.
4. Sulkowski MS. Viral hepatitis and HIV coinfection. *J Hepatol.* 2008;**48**(2):353-67. doi: [10.1016/j.jhep.2007.11.009](#). [PubMed: [18155314](#)].
5. Muriuki BM, Gicheru MM, Wachira D, Nyamache AK, Khamadi SA. Prevalence of hepatitis B and C viral co-infections among HIV-1 infected individuals in Nairobi, Kenya. *BMC Res Notes.* 2013;**6**:363. doi: [10.1186/1756-0500-6-363](#). [PubMed: [24016453](#)].
6. Zhao YS, Su SI, Lv CX, Zhang XF, Lin L, Sun XG, et al. Seroprevalence of hepatitis C, hepatitis B virus and syphilis in HIV-1 infected patients in Shandong, China. *Int J STD AIDS.* 2012;**23**(9):639-43. doi: [10.1258/ijisa.2012.011411](#). [PubMed: [23033517](#)].
7. Sadoh AE, Sadoh WE, Iduoriyekemwen NJ. HIV co-infection with hepatitis B and C viruses among Nigerian children in an antiretroviral treatment programme. *SAJCH.* 2011;**5**(1):7-10.
8. Nokhodian Z, Yaran M, Adibi P. Seroprevalence of hepatitis B markers among incarcerated intravenous drug users. *J Res Med Sci.* 2014;**19**:13-6.
9. Piroth L, Lafon ME, Binquet C, Bertillon P, Gervais A, Lootvoet E, et al. Occult hepatitis B in HIV-HCV coinfecting patients. *Scand J Infect Dis.* 2008;**40**(10):835-9. doi: [10.1080/00365540801918511](#). [PubMed: [18609222](#)].
10. Morsica G, Ancarani F, Bagaglio S, Maracci M, Cicconi P, Cozzi Lepri A, et al. Occult hepatitis B virus infection in a cohort of HIV-positive patients: correlation with hepatitis C virus coinfection, virological and immunological features. *Infection.* 2009;**37**(5):445-9. doi: [10.1007/s15010-008-8194-9](#). [PubMed: [19669092](#)].
11. Levast M, Larrat S, Thelu MA, Nicod S, Plages A, Cheveau A, et al. Prevalence and impact of occult hepatitis B infection in chronic hepatitis C patients treated with pegylated interferon and ribavirin. *J Med Virol.* 2010;**82**(5):747-54. doi: [10.1002/jmv.21695](#). [PubMed: [20336715](#)].
12. Rodriguez-Torres M, Gonzalez-Garcia J, Brau N, Sola R, Moreno S, Rockstroh J, et al. Occult hepatitis B virus infection in the setting of hepatitis C virus (HCV) and human immunodeficiency virus (HIV) coinfection: clinically relevant or a diagnostic problem?. *J Med Virol.* 2007;**79**(6):694-700. doi: [10.1002/jmv.20836](#). [PubMed: [17457912](#)].
13. Mphahlele MJ, Lukhwareni A, Burnett RJ, Moropeng LM, Ngobeni JM. High risk of occult hepatitis B virus infection in HIV-positive patients from South Africa. *J Clin Virol.* 2006;**35**(1):14-20. doi: [10.1016/j.jcv.2005.04.003](#). [PubMed: [15916918](#)].
14. Ramezani A, Mohraz M, Aghakhani A, Banifazl M, Eslamifar A, Khadem-Sadegh A, et al. Frequency of isolated hepatitis B core antibody in HIV-hepatitis C virus co-infected individuals. *Int J STD AIDS.* 2009;**20**(5):336-8. doi: [10.1258/ijisa.2008.008377](#). [PubMed: [19386971](#)].
15. Gupta S, Singh S. Occult hepatitis B virus infection in ART-naive HIV-infected patients seen at a tertiary care centre in north India. *BMC Infect Dis.* 2010;**10**:53. doi: [10.1186/1471-2334-10-53](#). [PubMed: [20205948](#)].
16. Fabris P, Biasin MR, Giordani MT, Berardo L, Menini V, Carlotto A, et al. Impact of occult HBV infection in HIV/HCV co-infected patients: HBV-DNA detection in liver specimens and in serum samples. *Curr HIV Res.* 2008;**6**(2):173-9. [PubMed: [18336266](#)].
17. Raffa G, Maimone S, Cargnel A, Santantonio T, Antonucci G, Massari M, et al. Analysis of occult hepatitis B virus infection in liver tissue of HIV patients with chronic hepatitis C. *AIDS.* 2007;**21**(16):2171-5. doi: [10.1097/QAD.0b013e3282ee504](#). [PubMed: [18090043](#)].