Occult Hepatitis B Infection and its Possible Impact on Chronic Hepatitis C Virus Infection

Peiman Habibollahi¹, Saeid Safari², Nasser E. Daryani³, Seyed M. Alavian⁴

ABSTRACT

As a well-recognized clinical phenomenon, persistent detectable viral genome in liver or sera in the absence of other serological markers for active hepatitis B virus (HBV) replication is called occult HBV infection. The main mechanism through which occult infection occurs is not completely understood and several possible explanations, such as integration into human genome and maintenance in peripheral mononuclear cells, exist. Occult HBV infection has been reported in different populations, especially among patients with Hepatitis C (HCV) related liver disease. The probable impact of occult HBV in patients with chronic HCV infection has been previously investigated and the evidence suggests a possible correlation with lower response to anti-viral treatment, higher grades of liver histological changes, and also developing hepatocellular carcinoma. However, in the absence of conclusive results, further studies should be conducted to absolutely assess the impact of occult HBV contamination on the HCV related liver disease.

Key Words: Hepatitis B, hepatitis C, occult

Received 14.08.2009, Accepted 22.08.2009

The Saudi Journal of Gastroenterology 2009 15(4): 220-4
of disease as a transmissible infection. Based on these preliminary results, several other studies were planned. The presence of seronegative HBV infection in patients with chronic hepatitis due to HCV was frequently reported.[11,16] In 1999, Cacciola et al. studied the existence of HBV genome in patients with HCV related chronic hepatitis and reported a prevalence rate of about 33% among these patients.[23] These findings suggested a coincidence for HBV and HCV infection and mentioned a possible role for occult HBV infection in the clinical and pathologic features of chronic HCV-related liver disease.

**PROBABLE MECHANISMS OF OCCULT INFECTION**

There are several explanations for silent or undetectable HBV infection. The development of more sensitive and improved techniques for HBV DNA detection has led to introduction of occult HBV which was not traceable earlier.[17] This is similar to the increase in the prevalence of disease with improvement of diagnostic tools and seems to be correct at least in some cases, although other possible mechanisms have also been suggested.

HBV reactivation in immunosuppressed patients reveals a role for the host immune system in occult form of HBV infection. The immune system might keep the viral replication at very low levels which are not detectable by normal screening.[18-20] Likewise, hepatic cytokines such as TNF-α and IFN-β may inhibit viral replication and activation.[21,22] Integration of viral genome in human DNA and mutations modifying the viral antigens are also among the other possible theories[4,5] but these mutations have not been shown in other studies.[2,10] Tamori et al. demonstrated HBV DNA integration in human genome and suggested a role for occult HBV in accelerating the hepatocarcinogenesis in chronic hepatitis due to HCV.[25] HBV variants according to the surface genes, and different response of the host to these variants are other possible presumptions for the presence of HBV DNA in HBsAg negative patients.[3]

Early viral genome integration in liver and peripheral mononuclear cells,[21] existence of immune complexes which contain HBV DNA[24] and modified immunological response in the patient[25] are among the other probable explanations. Some other studies also suggest that the presence of other viral infections such as HCV may interfere with HBV course and detection.[26,27] This hypothesis has been empowered by in vitro analysis which showed inhibition of HBV replication by NS2 and core HCV proteins.[28,29] The exact mechanism of occult infection with HBV is not fully understood, and it is feasible that the hypotheses mentioned above could all in part contribute in the course of the disease.

### OCCULT HBV IN HCV PATIENTS

Several studies have reported occult HBV infection in patients with HCV related disease. However, due to a heterogeneous study population, a net conclusion linking these results is not very straightforward. Table 1 briefly describes the results of the most important studies regarding occult HBV prevalence in HCV related liver disease. The prevalence of occult HBV in different studies has been reported between zero and 52.3% among patients with diverse liver disease due to HCV infection.[30,31,32]

Several factors could be responsible for this dissimilarity among studies. The most important of all might be heterogeneity of study populations. Higher probability of acquisition for “at risk populations” such as patients undergoing dialysis for both HBV and HCV infection might lead to higher prevalence rates[33] compared to those who do not have such risk factors. A common source of transmission such as intravenous drug use is also another factor which can affect these rates.

In contrast, different techniques used to detect the HBV DNA have different sensitivities so it might lead to different and incomparable results.[36-39] Regional differences in original HBV and HCV prevalence are other important factors.

### SEVERITY AND HISTOLOGY OF HCV RELATED LIVER DISEASE

Several investigators have studied the relationship between severity of HCV-linked liver disease and concomitant occult HBV infection. Cacciola et al., reported a high percentage of cirrhotic patients with occult HBV and no association with chronic hepatitis.[2] In the same year, occult HBV was reported to be seen in patients with higher hepatitis activity index although this association could not reach a statistically significant level.[33]

Several other studies have shown that there is no correlation between clinical outcomes and severity of liver disease and silent HBV infection.[28,38,40-41] Although recent studies have contradicted earlier reports, and emphasized on the clinical impact of silent HBV in patients suffering from chronic liver disease as a result of HCV and reported that higher levels of histological changes and hepatocellular carcinoma are seen among these patients.[7,8,44] It should be taken into consideration that most of these studies are cross sectional and therefore more precise cohort studies have to be performed to measure the real impact of occult HBV in patients with HCV linked chronic liver disease.[18]
Some studies have shown higher prevalence of occult HBV infection in HCV genotype 1b infected patients\[^{33}\] compared to HCV genotype 2a. Following these findings most other studies failed to demonstrate such relationship between the HCV genotypes and occurrence of occult HBV infection.\[^{7,28,40,41,43,45}\]

A relationship between the associated silent HBV and chronic HCV disease and high aminotransferases levels has been suggested by preliminary studies. Fukuda \textit{et al}, found higher serum alanine aminotransferase levels in occult HBV-infected patients although, the study failed to demonstrate a significant correlation.\[^{33}\]

To the best of our knowledge, almost none of the studies report a relationship between silent HBV infection and high aminotransferases levels in patients suffering from chronic liver disease due to HCV infection\[^{7,29,40,41,47}\] and it can be concluded that aminotransferase level in patients with chronic HCV infection cannot predict the presence of silent HBV replication or activation.

---

**Table 1: Characteristics of various studies on occult HBV in HCV-infected patients**

| Authors            | Year  | Target population                                                                 | Occult HBV prevalence (%) | Comments                                                                                                                                 |
|--------------------|-------|----------------------------------------------------------------------------------|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Cacciola\(^{2}\)   | 1999  | 200 with chronic HCV-related liver disease 50 with unrelated to HCV              | 33                        | 33 patients with occult HBV had cirrhosis compared to 19 percent without \(P=0.04\)                                                       |
| Fukuda\(^{22}\)    | 1999  | 66 with chronic HCV-related liver disease                                        | 52.3                      | Higher prevalence for genotype 1b than in 2a \((63.4\% \text{ vs } 28.6\%, \ P < 0.01)                                               |
| Kao\(^{21}\)       | 2002  | 210 with HCV-related liver disease 100 healthy controls                           | 14.8                      | Study concluded that occult HBV has no significance in HCV-related liver disease                                                         |
| Besisik\(^{22}\)   | 2003  | 33 HBsAg negative hemodialytic patients with HCV-related liver disease           | 33.4                      | -                                                                                                                                       |
| Giannini\(^{24}\)  | 2003  | 119 with HCV-related liver disease                                               | 6.7                       | No difference in the presence of occult HBV infection was seen between various degrees of liver disease                                      |
| Georgiadou\(^{25}\)| 2004  | 187 with HCV-related liver disease                                               | 26.2                      | HBV-DNA was neither associated with HBV markers, nor with the clinical status of HCV patients.                                       |
| Khattab\(^{26}\)   | 2005  | 53 HBsAg-negative patients with chronic hepatitis C                               | 7.5                       | Study could not show any impact of occult HBV in these patients.                                                                        |
| Goral\(^{27}\)     | 2006  | 50 HBsAg negative hemodialytic patients with HCV-related liver disease           | 0                         | -                                                                                                                                       |
| Branco\(^{28}\)    | 2007  | 46 with HCV related liver disease                                                | 19.5                      | Occult HBV infection was much more in cases with hepatocellular carcinoma                                                              |
| Toyoda\(^{29}\)    | 2007  | 95 patients with HCV related hepatocellular carcinoma                             | 2.1                       | HBV infection does not appear to play an important role in hepatocarcinogenesis                                                         |
| Altindis\(^{30}\)  | 2007  | 40 HCV infected hemodialytic patients 41 HCV infected non hemodialytic patients   | 27.5                      | Higher rates of HBV infection in hemodialysis patients                                                                                   |
| Alencar\(^{31}\)   | 2008  | 33 patients with HCV related cirrhosis 17 patients with HCV related hepatocellular carcinoma | 0                         | Study showed higher prevalence of HCV genotype 3 among Brazilian patients with cirrhosis and hepatocellular carcinoma                  |
| Miura\(^{7}\)      | 2008  | 141 patients with chronic HCV-related liver disease                              | 5.6                       | Study showed HBV as a risk factor for hepatocellular carcinoma development in patients with HCV                                          |
| Ramia S\(^{32}\)   | 2008  | 98 HCV infected patients from different institutions 85 controls with anti-HBC antibody 85 healthy controls | 16.3                      | As the severity of liver disease increases the rate of positivity for HBV DNA increases                                                |
| Shetty\(^{33}\)    | 2008  | 56 patients with HCV cirrhosis                                                   | 50                        | Occult HBV is associated with hepatocellular carcinoma                                                                               |
| Sagnelli\(^{34}\)  | 2008  | 89 patients with biopsy proven chronic HCV                                       | 41.6                      | No association was found between occult HBV infection and the degree of liver necroinflammation and fibrosis                             |
RESPONSE TO ANTIVIRAL TREATMENT

Treatment failure in chronically infected patients with HCV has been investigated widely due to its high priority among contemporary health problems. Several factors as well as concomitant occult HBV infection were tested; the diverse results obtained throughout the studies, make it impossible to come to a convincing conclusion about the role of silent HBV. Preliminary studies showed a trend towards weaker response to interferon mono-therapy in the presence of occult HBV. However, these were followed by several studies which differed in their views and emphasized a minimal role for occult HBV in occult contamination in response to interferon mono-therapy or its combination with ribavirin.[23,46-48,49]

Due to the differing results obtained in various studies, and the absence of prospective controlled trials, it becomes imperative to perform such trials to clarify the role of occult HBV infection and its impact on anti-HCV treatment. There is dissimilarity in results obtained and no prospective controlled investigations. Hence it is of utmost importance to perform such investigations to clarify the role of occult HBV infection in response to anti-HCV treatment.

CONCLUSION

In conclusion, available data, concerning the impact and prevalence of occult HBV infection in chronically infected patients with HCV, points to a considerable concomitance which may accompany higher grades of liver involvement and poorer response to anti-viral treatment. However, due to a scarcity of well-designed cohort studies, adequate conclusions can only be arrived at following further research on the subject.

REFERENCES

1. Brechot C, Degos F, Lugassy C, Thiers V, Zafrani S, Franco D, et al. Hepatitis B virus DNA in patients with chronic liver disease and negative tests for hepatitis B surface antigen. N Engl J Med 1985;312:270-6.
2. Cacciola I, Pollicino T, Squadrato G, Cenenzia G, Orlando ME, Raimondo G. Occult hepatitis B virus infection in patients with chronic hepatitis C liver disease. N Engl J Med 1999;341:22-6.
3. Zignego AL, Foschi M, Laffi G, Monti M, Careccia G, Romanelli RG, et al. "Inapparent" hepatitis B virus infection and hepatitis C virus replication in alcoholic subjects with and without liver disease. Hepatology 1994;19:577-82.
4. Hou J, Wang Z, Cheng J, Lin Y, Lau GK, Sun J, et al. Prevalence of naturally occurring surface gene variants of hepatitis B virus in nonimmunized surface antigen-negative Chinese carriers. Hepatology 2001;34:1027-34.
5. Tamori A, Nishiguchi S, Kubo S, Enomoto M, Koh N, Takeda T, et al. Sequencing of human-viral DNA junctions in hepatocellular carcinoma from patients with HCV and occult HBV infection. J Med Virol 2003;69:475-81.
6. Honarkar Z, Alavian SM, Samiee S, Saeedfar K, Baladast M, Ehsani MJ, et al. Occult Hepatitis B as a cause of cryptogenic cirrhosis. Hepat Mon 2004;4:155-60.
7. Mrani S, Chemin I, Menouar K, Guillaud O, Pradat P, Borghi G, et al. Occult HBV infection may represent a major risk factor of non-response to antiviral therapy of chronic hepatitis C. J Med Virol 2007;79:1075-81.
8. Miura Y, Shibuya A, Adachi S, Takeuchi A, Tsuchihashi T, Nakazawa T, et al. Occult hepatitis B virus infection as a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C in whom viral eradication fails. Hepatol Res 2008;38:546-56.
9. Honarkar Z, Alavian SM, Samiee S, Saeedfar K, Zali MR. Occult hepatitis B among chronic liver disease patients. Saudi Med J 2005;26:601-6.
10. Gonzalez S, Navas S, Madejon A, Bartolome J, Castillo I, Moraleda G, et al. Hepatitis B and D genomes in hepatitis B surface antigen negative patients with chronic hepatitis C. J Med Virol 1995;45:168-73.
11. Koike K, Kobayashi M, Gondo M, Hayashi I, Osuga T, Takada S. Hepatitis B virus DNA is frequently found in liver biopsy samples from hepatitis C virus-infected chronic hepatitis patients. J Med Virol 1998;54:249-55.
12. Uchida T, Kameita Y, Gotok T, Kanagawa H, Koyama H, Kawanishi T, et al. Hepatitis C virus is frequently coincided with serum marker-negative hepatitis B virus: Probable replication promotion of the former by the latter as demonstrated by in vitro cotransfection. J Med Virol 1997;52:399-405.
13. Sanchez-Quijano A, Jauregui JL, Leal M, Pineda JA, Castilla A, Abad MA, et al. Hepatitis B virus occult infection in subjects with persistent isolated anti-HBc reactivity. J Hepatol 1993;17:288-93.
14. Chazouilleres O, Mamish D, Kim M, Carey K, Ferrell L, Roberts JP, et al. "Occult" hepatitis B virus as source of infection in liver transplant recipients. Lancet 1994;343:142-6.
15. Oesterreicher C, Hammer J, Koch U, Pfeffel F, Sunder-Plassmann G, Petermann D, et al. HBV and HCV genome in peripheral blood mononuclear cells in patients undergoing chronic hemodialysis. Kidney Int 1995;48:1967-71.
16. Paterlini P, Driss F, Nalpas B, Pisi E, Franco D, Berthelot P, et al. Persistence of hepatitis B and hepatitis C viral genomes in primary liver cancers from HBsAg-negative patients: A study of a low-endemic area. Hepatology 1993;17:29-39.
17. Brechot C, Thiers V, Kremsdorf D, Nalpas B, Po, S, Paterlini-Brechot P. Persistent hepatitis B virus infection in subjects without hepatitis B surface antigen: clinically significant or purely "occult"? Hepatology 2001;34:194-203.
18. Carreno V, Bartolome J, Castillo I, Quiroga JA. Occult hepatitis B virus and hepatitis C virus infections. Rev Med Virol 2008;18:139-57.
19. Lok AS, Liang RH, Chiu EK, Wong KL, Chan TK, Todd D. Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy: Report of a prospective study. Gastroenterology 1991;100:182-8.
20. Marcellin P, Giot A, Martinet-Peignoux M, Loriot MA, Jaegle ML, Wolf P, et al. Occult hepatitis B virus in hepatitis C virus-infected chronic hepatitis patients. J Med Virol 1998;54:249-55.
21. Guidotti LG, Chisari FV. Noncytolytic control of viral infections by the innate and adaptive immune response. Annu Rev Immunol 2001;19:65-91.
22. Guidotti LG, Rochford R, Chung J, Shapiro M, Purcell R, Chisari FV. Viral clearance without destruction of infected cells during acute HBV infection. Science 1999;284:825-9.
23. Murakami Y, Minami M, Daimon Y, Okano T. Hepatitis B virus DNA in serum, liver, and peripheral blood mononuclear cells after the clearance of serum hepatitis B virus surface antigen. J Med Virol 2004;72:203-14.
24. Yotsuyanagi H, Yasuda K, Moriya K, Shinintai Y, Fujie H, Tatsuomi T, et al. Occult hepatitis B virus in the sera of HBsAg-negative, anti-HBc-positive blood donors. Transfusion 2001;41:1093-9.
25. Rumi MG, Colombo M, Romeo R, Colucci G, Gringeri A, Mannucci PM. Serum hepatitis B virus DNA detects cryptic hepatitis B virus infections in multitransfused hemophilic patients. Blood 1990;75:1654-8.

26. Rodriguez-Inigo E, Mariscal L, Bartolome J, Castillo I, Navacerrada C, Ortiz-Movilla N, et al. Distribution of hepatitis B virus in the liver of chronic hepatitis C patients with occult hepatitis B virus infection. J Med Virol 2003;70:571-80.

27. De Maria N, Colantoni A, Friedlander L, Leandro G, Idilman R, Harig J, et al. The impact of previous HBV infection on the course of chronic hepatitis C. Am J Gastroenterol 2000;95:3529-36.

28. Kao JH, Chen PJ, Lai MY, Chen DS. Occult hepatitis B virus infection and clinical outcomes of patients with chronic hepatitis C. J Clin Microbiol 2002;40:4068-71.

29. Chun SY, Kao CF, Chen CM, Shih CM, Hsu MJ, Chao CH, et al. Mechanisms for inhibition of hepatitis B virus gene expression and replication by hepatitis C virus core protein. J Biol Chem 2003;278:591-607.

30. 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 Med Virol 2003;70:571-80.

31. Shih CM, Lo SJ, Miyamura T, Chen SY, Lee YH. Suppression of hepatitis B virus expression and replication by hepatitis C virus core protein. J Med Virol 2002;37:12-20.

32. Shih CM, Lo SJ, Miyamura T, Chen SY, Lee YH. Suppression of hepatitis B virus expression and replication by hepatitis C virus core protein in Huh-7 cells. J Med Virol 1993;37:5823-32.

33. Fukuda R, Ishimura N, Niigaki M, Hamamoto S, Shih CM, Tanaka S, et al. Serologically silent hepatitis B virus coinfection in patients with hepatitis C virus-associated chronic liver disease: Clinical and virological significance. J Med Virol 1999;58:201-7.

34. Goral V, Ozkul H, Tekes S, Sit D, Kadiroglu AK. Prevalence of occult hepatitis B virus infection in haemodialysis patients with chronic HCV. World J Gastroenterol 2006;12:3420-4.

35. Aitindis M, Uslan I, CETINKAYA Z, Yuksel S, Giftci IH, Demirturk N, et al. Investigation of hemodialysis patients in terms of the presence of occult hepatitis B. Mikrobiyol Bul 2007;41:227-33.

36. Toyoda H, Kamada T, Kiriyama S, Sone Y, Tanikawa M, Hisanaga Y, et al. Prevalence of low-level hepatitis B viremia in patients with HBV surface antigen-negative hepatocellular carcinoma with and without hepatitis C virus infection in Japan: Analysis by COBAS TaqMan real-time PCR. Intervirology 2007;50:241-4.

37. Alencar RS, Gomes MM, Sitnik R, Pinho JR, Malta FM, Mello IM, et al. Low occurrence of occult hepatitis B virus infection and high frequency of hepatitis C virus genotype 3 in hepatocellular carcinoma in Brazil. Braz J Med Biol Res 2008;41:235-40.

38. Ramia S, Sharara AI, El-Zaatari M, Ramlawi F, Mahfoud Z. Occult hepatitis B virus infection in Lebanese patients with chronic hepatitis C liver disease. Eur J Clin Microbiol Infect Dis 2008;27:217-21.

39. Shetty K, Hussain M, Nei L, Reddy KR, Lok AS. Prevalence and significance of occult hepatitis B in a liver transplant population with chronic hepatitis C. Liver Transpl 2008;14:534-40.

40. Fabris P, Brown D, Tositti G, Bozzola L, Giordani MT, Bevilacqua P, et al. Occult hepatitis B virus infection does not affect liver histology or response to therapy with interferon alpha and ribavirin in intravenous drug users with chronic hepatitis C. J Clin Virol 2004;29:160-6.

41. Georgiadou SP, Zachou K, Rigopoulou E, Liaskos C, Mona P, Gerouvasilis F, et al. Occult hepatitis B virus infection in Greek patients with chronic hepatitis C and in patients with diverse nonviral hepatic diseases. J Viral Hepat 2004;11:358-65.

42. Hasegawa I, Urito E, Tanaka Y, Hrashima N, Sakakibara K, Sakurai M, et al. Impact of occult hepatitis B virus infection on efficacy and prognosis of interferon-alpha therapy for patients with chronic hepatitis C. J Med Virol 2005;25:247-53.

43. Silva C, Goncalves NS, Pereira JS, Escanhoela CA, Pavan MH, Goncales FL Jr. The influence of occult infection with hepatitis B virus on liver histology and response to interferon treatment in chronic hepatitis C patients. J Clin Virol 2004;8:431-9.

44. Branco F, Mattos AA, Coral GP, Vanderbrught B, Santos DE, Franca P, et al. Occult hepatitis B virus infection in patients with chronic liver disease due to hepatitis C virus and hepatocellular carcinoma in Brazil. Arq Gastroenterol 2007;44:58-63.

45. Khattab E, Chemin I, Vuillermoz I, Vieux C, Mrani S, Guillaud O, et al. Analysis of HCV co-infection with occult hepatitis B virus in patients undergoing IFN therapy. J Clin Virol 2005;33:150-7.

Source of Support: Nil, Conflict of Interest: None declared.