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EDITORIAL

Occult hepatitis B virus infection: A complex entity with relevant clinical implications

Juan Ramon Larrubia

Juan-Ramon Larrubia, Translational Hepatology Unit, Guadalajara University Hospital, University of Alcalá, 19002 Guadalajara, Spain
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Correspondence to: Juan-Ramon Larrubia, MD, MSc, PhD, Translational Hepatology Unit, Guadalajara University Hospital, University of Alcalá, Donante de Sangre st, 19002 Guadalajara, Spain. jlarrubiam@meditex.es
Telephone: +34-949-209200 Fax: +34-949-209259
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Abstract

Occult hepatitis B virus (HBV) infection is a world-wide entity, following the geographical distribution of detectable hepatitis B. This entity is defined as the persistence of viral genomes in the liver tissue and in some instances also in the serum, associated to negative HBV surface antigen serology. The molecular basis of the occult infection is related to the life cycle of HBV, which produces a covalently closed circular DNA that persists in the cell nuclei as an episome, and serves as a template for gene transcription. The mechanism responsible for the HBsAg negative status in occult HBV carriers is a strong suppression of viral replication, probably due to the host's immune response, co-infection with other infectious agents and epigenetic factors. There is emerging evidence of the potential clinical relevance of occult HBV infection, since this could be involved in occult HBV transmission through orthotopic liver transplant and blood transfusion, reactivation of HBV infection during immunosuppression, impairing chronic liver disease outcome and acting as a risk factor for hepatocellular carcinoma. Therefore it is important to bear in mind this entity in cryptogenetic liver diseases, hepatitis C virus/HIV infected patients and immunosupressed individuals. It is also necessary to increase our knowledge in this fascinating field to define better strategies to diagnose and treat this infection.

Key words: Hepatitis B virus; Occult infection; Persistent infection

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EDITORIAL

The persistence of hepatitis B virus (HBV) in hepatitis B surface antigen (HBsAg) negative individuals is termed occult HBV infection (OBI)[1]. Since the early 80's it was suspected that hepatitis B virus could persist in the host despite not being detectable. In the last decade after the appearance of highly sensitive molecular biology techniques the presence of HBV in the liver and serum of HBsAg negative individuals has been shown[2]. OBI-infected subjects maintained HBV infection due to the peculiar HBV life cycle which is characterised by the production of covalently closed circular DNA that serves as a template for gene transcription[3]. In occult HBV carriers the viral replication from this episome is strongly suppressed and several factors could contribute to this situation[4]. A high HBV-specific immunological pressure could contribute to the development of occult HBV infection and this could

explain why in immunosuppressive condition an HBV infection reactivation is observed. Another hypothetical factor associated with OBI is the co-infection with other pathogens. HCV infection is strongly associated with HBV occult infection and moreover it has been shown that HCV core protein is able to inhibit *in vitro* HBV replication. Finally, there is some evidence that epigenetic factors could contribute to reduce HBV replication efficiency through the regulation of the HBV transcriptional program. The prevalence of this entity is difficult to assess due to the difference in the technical procedures and the tissues studied. The distribution is similar to the HBVAg positive HBV infection being more prevalent in certain groups such as HCV and HIV populations[5,6]. Anyway epidemiological data are still scarce and more studies in the general population and cryptogenetic hepatitis are necessary[7]. From the clinical point of view this entity is extremely relevant because it could be the cause of liver disease in different scenarios not well described currently. Carriers of occult HBV infection may be a source of HBV transmission in the case of blood transfusion[8]. Moreover, HBV occult infection can be also transmitted during orthotopic liver transplantation from anti hepatitis B core positive individuals as well as from HBV seronegative cases[9]. Another important clinical manifestation of HBV occult infection is its reactivation of the infection during immunosuppression. After the restoration of the immune system after finishing immunosuppressive treatment it is possible that acute hepatitis may occur. This is important in haematological malignancies, hematopoietic stem cell transplantation and organ transplantation[10]. Clinicians should be aware of these clinical events to prevent this situation with the appropriate prophylaxis. Moreover, hepatologists should not think that this infection in immunocompetent individuals is an inoffensive condition. The long-lasting persistence of the virus in the liver may provoke a mild but continuous inflammation which could have clinical implications in cases of previous liver damage. Different reports suggest that HBV occult infection could be responsible for the acceleration of chronic HCV progression and interfere with treatment response[5]. More studies are needed to clarify this important issue. Finally HBV occult infection could be related to the development of hepatocellular carcinoma among HBsAg negative chronic hepatitis patients[11]. This could be through the induction of chronic inflammation and by means of HBV DNA integration into the host's genome. In summary, it is clear that a large amount of information has been produced in recent years about this topic but the data are still too incomplete to describe properly the clinical impact of this infection and more bio-medical research is still needed in this fascinating field. In this issue of *World Journal of Gastroenterology* the current knowledge on the HBV occult infection field is updated, addressing all the topics[12-18] with a practical point of view to make this "Topic Highlight" interesting and useful to most clinicians.

REFERENCES

1 **Raimondo G**, Allain JP, Brunetto MR, Buendia MA, Chen DS, Colombo M, Craxì A, Donato F, Ferrari C, Gaeta GB, Gerlich WH, Levrero M, Locarnini S, Michalak T, Mondelli MU, Pawlotsky JM, Pollicino T, Prati D, Puoti M, Samuel D, Shouval D, Smedile A, Squadrito G, Trépo C, Villa E, Will H, Zanetti AR, Zoulim F. Statements from the Taormina expert meeting on occult hepatitis B virus infection. *J Hepatol* 2008; **49**: 652-657

2 **Paraskevis D,** Beloukas A, Haida C, Katsoulidou A, Moschidis Z, Hatzitheodorou H, Varaklioti A, Sypsa V, Hatzakis A. Development of a new ultra sensitive real-time PCR assay (ultra sensitive RTQ-PCR) for the quantification of HBV-DNA. *Virol J* 2010; **7**: 57

3 **Levrero M,** Pollicino T, Petersen J, Belloni L, Raimondo G, Dandri M. Control of cccDNA function in hepatitis B virus infection. *J Hepatol* 2009; **51**: 581-592

4 **Raimondo G,** Pollicino T, Cacciola I, Squadrito G. Occult hepatitis B virus infection. *J Hepatol* 2007; **46**: 160-170

5 **Levast M,** Larrat S, Thelu MA, Nicod S, Plages A, Cheveau A, Zarski JP, Seigneurin JM, Morand P, Leroy V. Prevalence and impact of occult hepatitis B infection in chronic hepatitis C patients treated with pegylated interferon and ribavirin. *J Med Virol* 2010; **82**: 747-754

6 **Shire NJ,** Rouster SD, Stanford SD, Blackard JT, Martin CM, Fichtenbaum CJ, Sherman KE. The prevalence and significance of occult hepatitis B virus in a prospective cohort of HIV-infected patients. *J Acquir Immune Defic Syndr* 2007; **44**: 309-314

7 **Fang Y,** Shang QL, Liu JY, Li D, Xu WZ, Teng X, Zhao HW, Fu LJ, Zhang FM, Gu HX. Prevalence of occult hepatitis B virus infection among hepatopathy patients and healthy people in China. *J Infect* 2009; **58**: 383-388

8 **Candotti D,** Allain JP. Transfusion-transmitted hepatitis B virus infection. *J Hepatol* 2009; **51**: 798-809

9 **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**: 534-540

10 **Ceneli O,** Ozkurt ZN, Acar K, Rota S, Aki SZ, Yeğin ZA, Yağci M, Ozenirler S, Sucak GT. Hepatitis B-related events in autologous hematopoietic stem cell transplantation recipients. *World J Gastroenterol* 2010; **16**: 1765-1771

11 **De Mitri MS,** Cassini R, Bernardi M. Hepatitis B virus-related hepatocarcinogenesis: molecular oncogenic potential of clear or occult infections. *Eur J Cancer* 2010; **46**: 2178-2186

12 **Manzano-Alonso ML**, Castellano-Tortajada G. Reactivation of hepatitis B virus infection after cytotoxic chemotherapy or immunosuppressive therapy. *World J Gastroenterol* 2011; **17**: 1531-1537

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

14 **Aller de la Fuente R**, Gutiérrez ML, Garcia-Samaniego J, Fernández-Rodriguez C, Lledó JL, Castellano G. Pathogenesis of occult chronic hepatitis B virus infection. *World J Gastroenterol* 2011; **17**: 1543-1548

15 **Romero M**, Madejón A, Fernández-Rodríguez C, García-Samaniego J. Clinical significance of occult hepatitis B virus infection. *World J Gastroenterol* 2011; **17**: 1549-1552

16 **Ocana S**, Casas ML, Buhigas I, Lledo JL. Diagnostic strategy for occult hepatitis B virus infection. *World J Gastroenterol* 2011; **17**: 1553-1557

17 **Fernandez-Rodriguez CM**, Gutierrez ML, Lledó JL, Casas ML. Influence of occult hepatitis B virus infection in chronic hepatitis C outcomes. *World J Gastroenterol* 2011; **17**: 1558-1562

18 **Lledó JL**, Fernández C, Gutiérrez ML, Ocaña S. Management of occult hepatitis B virus infection: An update for the clinician. *World J Gastroenterol* 2011; **17**: 1563-1568

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