World Journal of Gastroenterology

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DOI: 10.3748/wjg.v22.i39.8720

World J Gastroenterol 2016 October 21; 22(39): 8720-8734
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Update on occult hepatitis B virus infection

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Author contributions: Makvandi M solely wrote this paper.

Conflict-of-interest statement: The author declares that there are no conflicts of interest in the content of this review.

Manuscript source: Invited manuscript

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Received: March 28, 2016
Peer-review started: March 29, 2016
First decision: May 30, 2016
Revised: June 13, 2016
Accepted: July 20, 2016
Article in press: July 21, 2016
Published online: October 21, 2016

Abstract

The event of mutations in the surface antigen gene of hepatitis B virus (HBV) results in undetectable hepatitis B surface antigen with positive/negative anti-hepatitis B core (anti-HBc) antibody status in serum and this phenomenon is named occult hepatitis B infection (OBI). The presence of anti-HBc antibody in serum is an important key for OBI tracking, although about 20% of OBI cases are negative for anti-HBc antibody. The diagnosis of OBI is mainly based on polymerase chain reaction (PCR) and real-time PCR assays. However, real-time PCR is a more reliable method than PCR. OBI is a great issue for the public health problem and a challenge for the clinical entity worldwide. The persistence of OBI may lead to the development of cirrhosis and hepatocellular carcinoma. With regard to OBI complications, the screening of HBV DNA by the highly sensitive molecular means should be implemented for: (1) patients with a previous history of chronic or acute HBV infection; (2) patients co-infected with hepatitis C virus/human immunodeficiency virus; (3) patients undergoing chemotherapy or anti-CD20 therapy; (4) recipients of organ transplant; (5) blood donors; (6) organ transplant donors; (7) thalassemia and hemophilia patients; (8) health care workers; (9) patients with liver related disease (cryptogenic); (10) hemodialysis patients; (11) patients undergoing lamivudine or interferon therapy; and (12) children in time of HBV vaccination especially in highly endemic areas of HBV. Active HBV vaccination should be implemented for the close relatives of patients who are negative for OBI markers. Thus, the goal of this review is to evaluate the rate of OBI with a focus on status of high risk groups in different regions of the world.

Key words: Nested polymerase chain reaction; Occult hepatitis B infection; Cryptogenic; Real-time polymerase chain reaction

Core tip: Occult hepatitis B infection (OBI) is defined as negative hepatitis B surface antigen and positive/negative anti-hepatitis B core immunoglobulin G status but hepatitis B virus (HBV) DNA is detectable in serum and liver tissue. Genotypes A, C, G, E and D have been

found among patients with OBI in different regions of the world. Genotype D is the only dominant genotype among Iranian OBI patients. OBI has been reported among many high risk groups, including blood donors, liver transplant recipients, patients co-infected with hepatitis C virus/human immunodeficiency virus, patients undergoing immunosuppressive therapy or hemodialysis, patients with liver cirrhosis, cryptogenic liver disease, or abnormal alanine transaminase, healthcare workers, patients with lymphoma or rheumatoid arthritis. It is recommended that to manage and reduce OBI and HBV carriage, the screening of HBV DNA be implemented among high risk groups by means of highly sensitive molecular assays periodically. In addition, comprehensive investigations are needed to understand the epidemiology of OBI worldwide.

Makvandi M. Update on occult hepatitis B virus infection. *World J Gastroenterol* 2016; 22(39): 8720-8734 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i39/8720.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i39.8720

INTRODUCTION

Hepatitis B virus (HBV) infection is a considerable global health problem and approximately two billion of the world population have been infected, of which 250 million live with HBV infection[1]. HBV infection is linked with a wide range of clinical manifestations, including acute or fulminant hepatitis to various forms of chronic infection, including asymptomatic carriers, chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). Although the implementation of screening tests for hepatitis B surface antigen (HBsAg) has significantly reduced the spread of HBV infection among blood donors, it fails to detect occult HBV infection (OBI) cases. In the 1970s, a new form of clinical HBV infection was reported in a patient with acute hepatitis, who was positive for anti-hepatitis B core (anti-HBc) immunoglobulin G (IgG), but negative for HBsAg[2]. Subsequently, by developing highly sensitive molecular means, the clinical entity of OBI was characterized, which resulted in the concept of "occult" or "silent" HBV infection[3,4]. The presence of mutations was demonstrated in the preS1, preS2 and S regions of the *HBsAg* gene, which results in undetectable HBsAg by enzyme-linked immunosorbant assay[5-8]. In the absence of serum HBsAg, low quantity of HBV DNA even < 200 IU/mL was detected in the serum and liver tissue biopsy by real-time polymerase chain reaction (PCR), and this new form of clinical entity of HBV infection was called OBI[9,10]. OBI is a clinical class of HBV infection and can appear in two forms: seropositive OBI and seronegative OBI. In seropositive OBI, serum HBV DNA is detectable and both anti-HBc/anti-hepatitis B surface (HBs) IgGs are positive or only anti-HBc IgG is positive, while in seronegative OBI, only HBV DNA is detectable in serum/or liver tissue, but anti-HBc IgG/anti-HBs IgGs are negative in serum[4]. The clinical feature of OBI remains unknown and more studies are required to understand the characteristics of OBI among the high risk group worldwide. With the present data on the OBI, several groups are believed to be at risk of OBI. The reactivation of OBI may take place in individuals with a previous history of HBV infection along with immunosuppression or chemotherapy status. Lastly, to prevent the spread of OBI, the screening of HBV DNA should be implemented in blood donors, immunosuppressive patients, organ transplant donors, organ transplant recipients, and individuals with acute rheumatoid arthritis before and after treatment with anti-tumor necrosis factor (TNF)-α[11]. In this paper, a search of MEDLINE database was performed to retrieve suitable articles to explain the epidemiology, diagnosis and prevention of OBI.

DEFINITION OF OBI

Most of OBI cases are asymptomatic and clinically not well defined. OBI has been investigated only in high risk groups with different serological and molecular descriptions. Several definitions of OBI have been described. In the international workshop (2008) in Italy, OBI was defined as the detection of HBV DNA in the liver (with or without HBV DNA in serum) without HBsAg[12]. OBI can be defined by the presence of HBV DNA in serum or liver tissue with either seropositive or seronegative status. Seropositive OBI is characterized by the detection of anti-HBc antibody with or without anti-HBs antibody, while seronegative OBI is described by undetectable both anti-HBc and anti-HBs antibodies. Seropositive OBI accounts for the enormous majority of OBI cases which can be attributed to the larger proportion of resolved HBV infections. It has been reported that more than 20% of OBI cases are seronegative for all the HBV markers[13]. In chronic occult infections, viral covalently closed circular DNA (cccDNA) persists as an episome in the nucleus of infected cells. Although the clinical features between OBI-seropositive and OBI-seronegative cases remain entirely cryptic, OBI may be exhibited in one of three clinical forms: (1) in a window period of acute HBV infection; (2) detectable HBV DNA and undetectable HBsAg in patient serum without a previous history of overt HBV infection; and (3) in patients with a history of chronic HBV infection. At present there is no standard assay for diagnosis of OBI in liver tissue or in serum, and the only reliable method is the detection of HBV DNA by nested PCR or real-time PCR. It has been illustrated that the application of real-time PCR possesses better outcomes provided that the specific primers are capable to cover all HBV genotypes[14]. The viral load lower than 200 IU/mL has been defined for OBI diagnosis, interestingly, in more than 90%

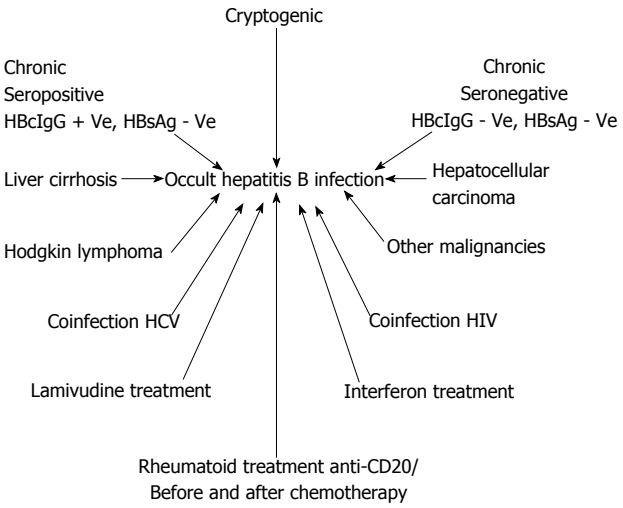

Figure 1 Schematic representation of clinical entity of occult hepatitis B infection. HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HBsAg: Hepatitis B surface antigen.

of OBI patients, the viral load in serum was reported to be around 20 IU/mL[15]. Several mechanisms and factors may affect or suppress the HBV replication, which result in mutations in the *HBsAg* gene, although host immune response and epigenetic factors also play crucial roles in OBI (Figure 1).

PREVALENCE OF OBI

The prevalence of OBI varies from region to region worldwide. This variability relies upon the sensitivity of HBV DNA detection assays, the sample size, and the detection of HBV DNA in liver tissue and serum by nested PCR or real-time PCR. The prevalence of OBI varies from 1% to 87% in different regions of the world[16,17]. OBI has been reported even in some geographical regions with low HBV endemicity[16]. The prevalence of OBI among the general population has been reported to be 45.5% with genotypes B and C[18] in China, and 1.7%-6.6% with genotype C2[19,20] in South Korea. In Taiwan, the prevalence was 10.9% in HBV vaccinated children[21] and 0.11% in blood donors[22]. In Egypt, it varied from a low 4.1% to high 26.8% in hemodialysis patients[23,24]. In Iran the prevalence of OBI has been reported to be 2 in 50000 in blood donors[25] and 14% in cryptogenic patients[26], while the prevalence of seropositive OBI was 2.27%[27] and 0% among blood donors[28].

MOLECULAR MECHANISMS OF OBI

Mutations in the "a" determinant of HBsAg

A mutation in the "a" determinant of the surface antigen is one of the known mechanisms which may result in OBI. Mutations in the HBsAg gene bring about the structural arrangement of the protein, which may lead to undetectable HBsAg by commercially HBsAg test kits[29]. The occurrence of sG145R mutation in the "a" determinant of the HBsAg gene also results in OBI[29]. It has been shown that the sG145R mutation in the HBsAg gene leads to a low binding affinity to monoclonal antibody against HBsAg[30]. In addition, within the "a" determinant several other mutations have been shown to cause a low affinity to monoclonal antibody against HBsAg[30-32].

Mutations in the pre S1 and preS2 regions

Mutations in the S region have been associated with reduced expression of HBV surface proteins. Subsequently, mutations in preS1/preS2 promoters are frequently observed in OBI patients, which make HBsAg become undetectable[33,34].

RNA splicing

Splicing steps have a critical effect on gene expression in HBV. In patients with OBI, it has been found that the substitution of nt G-to-A at position 458 of the surface gene interferes with the splicing of S gene mRNA and was associated with a lack of HBsAg expression and low replication of HBV DNA[35].

POSSIBLE OBI OUTCOMES OF LAMIVUDINE OR INTERFERON THERAPY

Treatment of chronic patients with lamivudine may result in amino acid changes in YMDD motif, in HBV polymerase Q563S and in sS207R surface genes, and thus contributes to OBI[36]. The nucleotide deletions in the pre-S1 and pre-S2 regions following the interferon therapy have resulted in the low replication of HBV DNA with low detection of HBsAg in cell culture systems[37].

OBI and chronic hepatitis C virus infection

The mutations in the *HBsAg* gene have been observed among patients coinfected with hepatitis C virus (HCV)[38-40]. Several studies have reported that low HBV DNA replication occurs in patients coinfected with HCV infection. It has been described that about one-third of patients with chronic HCV infection had detectable serum HBV DNA but undetectable HBsAg[41,42]. The presence of OBI in chronic HCV infected patients increases the risk of HCC[43,44]. When the coexistence of both HBV and HCV genomes occurs in the same hepatocyte, the replication of HBV is inhibited due to the interference of HCV molecules, which therefore results in the creation of OBI with low replication of HBV DNA[45]. Moreover, the HBX protein is a transactivator and activates HBV promoters and enhances HBV gene transcription[46,47]. The HCV core protein can interact with HBV X gene and prevent HBV gene transcription[48]. In addition, HCV "core", NS2 and NS5A proteins could strongly inhibit HBV replication[34,43,49-51]. Table 1 shows the distribution of OBI among patients with HCV infection[52-66].

HCC

While the prevalence of OBI among patients with

Table 1 Profile of various studies on occult hepatitis B infection in patients with hepatitis C virus infection

Ref.	Years	Study population	OBI
Fukuda *et al*[52]	1999	65 patients with HCV-related liver disease	34/65 (52.3%)
Kao *et al*[53]	2002	210 patients with HCV-related liver disease	31/210 (14.8%)
Besisik *et al*[54]	2003	33 HCV positive patients on hemodialysis	12/33 (36.4%)
Georgiadou *et al*[55]	2004	187 patients with HCV-related liver disease	49/187
Khattab *et al*[56]	2005	53 patients with chronic HCV infection	4/53 (7.5%)
Goral *et al*[57]	2006	50 HCV positive patients on hemodialysis	0/50
Branco *et al*[43]	2007	46 patients with HCV-related liver disease	9/46 (19.5%)
Toyoda *et al*[58]	2007	95 HCV positive patients with HCC	2/95 (2.1%)
Shetty *et al*[59]	2008	44 HCV positive patients with liver cirrhosis	22/44 (50%)
Tamori *et al*[60]	2009	50 HCV positive patients with HCC	21/50 (42%)
Chen *et al*[61]	2010	126 patients with chronic HCV infection	6/126 (5%)
Jang *et al*[62]	2011	32 patients with chronic HCV infection	9/32 (28.1%)
Joukar *et al*[63]	2012	59 HCV positive patients on hemodialysis	0/59
Vakili Ghartavol *et al*[64]	2013	50 patients with chronic HCV infection	18/50(36%)
Kishk *et al*[65]	2014	162 patients with chronic HCV infection	3/162 (1.85%)
Mandour *et al*[66]	2015	210 patients with chronic HCV infection	53/210 (25.2%)

HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus.

Table 2 Rates of occult hepatitis B infection among HIV positive patients in some countries

Ref.	Country	Prevalence %	Year
Vargas *et al*[73]	Chile	0/192 (0)	2016
Alvarez-Muñoz *et al*[74]	Mexico	24/49 (49.0)	2014
Chadwick *et al*[75]	England	15/335 (4.5)	2014
Coffin *et al*[76]	Canada	19/45 (42.0)	2014
Dapena *et al*[77]	Spain	6/254 (2.4)	2013
Khamduang *et al*[78]	Thailand	47/200 (23.5)	2013
Bell *et al*[79]	Africa	45/298 (15.1)	2012
Panigrahi *et al*[80]	India	12/112 (10.7)	2012
Bagaglio *et al*[81]	Italy	9/29 (31.0)	2011
Gupta *et al*[82]	India	24/53 (45.3)	2010
Hakeem *et al*[83]	Scotland	2/70 (2.8)	2010
Morsica *et al*[84]	Italy	27/175 (15)	2009
Azadmanesh *et al*[85]	Iran	3/22 (13.6)	2008
Tsui *et al*[86]	United States	8/400 (2.0)	2007

HCV related liver disease is controversial, some data have approved this issue. For improving treatment and consequence of OBI, it is recommended that the screening of anti-HBc and HBV DNA be implemented for pretreatment of HCV-infected patients.

Coinfection of OBI with human immunodeficiency virus infection

Both HBV and human immunodeficiency virus (HIV) share the same rout of transmission. Mostly the coinfection of OBI and HIV occurs among intravenous drug users. It was found that coinfection of HIV and HBV may lead to faster progression of liver fibrosis, development of cirrhosis and HCC, even without coinfection with HIV[67]. The persistence of coinfection of OBI and HIV may result in severe and sometimes fulminant hepatitis[68]. The low HBV replication and undetectable surface antigen may be due to host cell epigenetic genome and polymorphisms in host cytokine and chemokine receptors[68-70]. Mutations in the X, precore/core, and Pol regions of HBV genome may result in mutations within the preS/S open reading frame and bring about OBI[29-51]. However, the effect of HIV components in HBV genome to lead to OBI remains unknown. While the occurrence of OBI may be related to host immune response and co-infections with HCV[50,51] or HIV[67,68], it has been postulated that HIV components are not major factors for the occurrence of OBI[71,72]. Table 2 shows the distribution of co-existence of OBI with HIV infection in different countries[73-86].

Thus, with regard to the aforementioned data for improving treatment and outcomes of OBI, it is recommended that the screening of anti-HBc and HBV DNA be carried out for pretreatment of HIV patients.

BLOOD TRANSFUSION AND OBI PROBLEM

Blood transfusion is a main risk factor for transmission of OBI provided that the screening of blood donors is done with less security[87,88]. In the most developed countries, to boost blood safety, the nucleic acid amplification testing (NAT) has been established for screening of blood donors for detection of HCV, HIV and HBV or OBI. It is well documented that the application of NAT for HBV DNA, HCV RNA and HIV RNA detection is more sensitive than serological HBsAg, HCVAb, and HIV Ab tests[89,90]. Thus, the implementation of HBV-DNA detection by NAT is more sensitive than HBsAg assay as a preventive measure for HBV or OBI transmission *via* blood transfusion[89,90]. The prevalence of OBI among blood donors varies from country to country and has been reported in South Korea (HBV DNA, 0.016%)[91], India (anti-HBc, 10.22%; HBV DNA, 0.15%)[92], Turkey (anti-HBc, 20%; HBV DNA, 0)[93], Egypt (anti-HBc, 22.7%; HBV DNA, 22.7%)[94] and Iran (0% OBI)[95], (HBVDNA, 2/5000)[25], (anti-HBc, 20%; HBV DNA, 0)[93], (HBV DNA, 12.2%)[96]. In

the most developing countries the screening of HBV among blood donors relies only on serological detection of HBsAg. While the screening of HBV by the NAT is expensive, it is effective in reducing the transmission of OBI *via* blood transfusion and blood products[89,90]. The detection of anti-HBc is a good test for OBI tracking, but it accounts for about 80% of OBI cases[97,98]. Thus, with regard to what was stated previously the implementation of anti-HBc test for blood donors can be considered a second safeguard policy for reducing the transmission of HBV *via* blood transfusion[99,100], although NAT is more sensitive and effective than serological HBsAg test as a preventive measure for HBV or OBI transmission *via* blood transfusion.

OBI AND HEAMODIALYSIS

Heamodialysis (HD) patients are at high risk of viral bloodborne infections (HBV, HIV, and HCV)[101-103] and tracking of the diagnosed liver disease based on aminotransferase levels in HD patients is difficult. Mostly aminotransferase is suppressed by reduced immune competence which results in weak inflammatory reactions and consequently reduces hepatocyte destruction[104]. It has been hypothesized that status of chronic uremia in HD patients may suppress the inflammatory reactions in the liver and consequently, no hepatocyte destruction will occur[105,106]. Therefore, the evaluation of quantitative HBV DNA was found to be the most efficient method to evaluate OBI in HD patients[101]. The prevalence of OBI has been studied in many countries, but varies from region to region worldwide. In Tehran, OBI was studied among HD patients by Ramezani *et al*[107], and they isolated HBV DNA in 1% of 100 HBsAg negative HD patients. In Tehran, Aghakhani *et al*[108] detected HBV DNA in 9/289 (3.1%) HD patients, who were negative for HBsAg but positive for HBcIgG. In Ahvaz, Neisi *et al*[109] detected HBV DNA in 10/250 (4%) of HD patients, who were negative for HBsAg but positive for anti-HBc. Also in Ahvaz, Rastegarvand *et a*[110] isolated HBV DNA in 6/216 (2.9%) HD patients, who were negative for HBsAg but positive for anti-HBc. The prevalence of OBI in HD patients was also reported in Spain (58%)[111], Egypt (26.9%)[24], United Kingdom (2.2%)[101], Greece (20.4%)[112] and Italy (0%)[113].

It is recommended that all the patients on HD be routinely screened for viral bloodborne infections (HBV, HIV and HCV), including OBI, using highly sensitive molecular techniques to prevent nosocomial transmission.

OBI AND CRYPTOGENIC LIVER DISEASE

The rate of cryptogenic liver diseases varies greatly in different regions of the world. Patients with long-term persistent ALT abnormality or with the lack of overt viral detection and autoimmune markers, have been shown to be positive for HBV DNA (OBI)[114]. While the etiology of cryptogenic liver disease remains unknown, the association of occult hepatitis C has been reported in patients with abnormal alanin aminotransaminase[115]. OBI has been regarded as an additional risk factor for progression of liver cirrhosis and HCC[26,116]. The prevalence of OBI in cryptogenic chronic liver disease varies from 3.88% to 55.6%[117,118]: in Brazil, 4.4%[119]; in China, 28.3%[120]; and in Iran, 1.9%[121], 10%[114], and India 9.5%[122]. With regard to the mentioned data, it is recommended that for improving treatment and management, the sera and PBMCs or liver biopsy of patients with cryptogenic hepatitis be screened for HBV DNA by highly sensitive molecular means before developing signs of cirrhosis or HCC.

OBI IN CRYPTOGENIC CIRRHOSIS AND HCC

Liver cirrhosis is an endangering public health problem worldwide. Most of liver cirrhosis patients may progress to upper gastrointestinal bleeding, hepatic encephalopathy, and HCC. HBV infection or OBI, HCV infection or occult HCV, and alcohol consumption are major etiologies for development of liver cirrhosis[123-125].

During the last phase of the natural course of chronic HBV infection, the inactive carrier phase is represented by HBeAg negativity, anti-HBe positivity, low HBV DNA levels (< 200 IU/mL) with minimal or no fibrosis[14,15]. The rates of spontaneous seroclearance of HBsAg (OBI) among inactive carriers range from 0.5% to 40% per year[126,127]. There have been reports on progression of inactive carriers to cirrhosis[128,129].

The prevalence of OBI among cirrhotic patients varies from region to region worldwide. The prevalence rates of OBI in cirrhotic patients have been reported: in Iran, 14% and 38%[26,130]; India, 38%[131], Italy, 23.4% and 27%[132,133]; Egypt, 2.7%[134]; Japan, 18.1%[135]; France, 60%[136]; United States, 19.4%[137]; Brazil, 20%[138]; China, 32%[139]; and China, 3.88%[117].

The mechanism of liver damage due to OBI is still not well elucidated, but there are some data that described the persistence and transcription of HBV cccDNA in hepatocytes and subsequently, production of cytokines, such as TNF-α and interferon-γ may result in damage to heptocytes[140,141]. The occurrence of mutations in the X region of HBV may bring about a reduction in the ability of the transactivation of X protein, which is essential for viral replication, and also result in low HBV DNA replication and undetectable HBsAg in serum[142].

Liver cancer is considered a major global health problem. Viral hepatitis B and C are main risk factors for the development of liver cancer[135,143]. The prolonged persistence of cccDNA in the hepatocyte nucleus has been detected in patients with HCC[144]. In addition, HBV DNA has been found to be integrated within the host chromosomes of individuals with HCC[145]. Most

findings described that OBI is an important risk factor for hastening the progression of liver disease and the development of cirrhosis and HCC[146]. Several studies have documented that in patients with HCC who were negative for all HBV serum markers, including HBsAg, HBV DNA was detected in hepatocytes[147-160].

Several mechanisms may be involved in OBI-induced hepatocarcinogenesis. When HBV DNA is integrated into the host genome, the integrated HBX and truncated pre-S2/S genomic sequences may alter the cellular gene expression and result in the development of HCC[161-163]. OBI DNA, either in the form of free episomes or in integrated forms, is able to replicate, transcribe, and synthesize proteins, at very low levels[144-165].

The advances in molecular approaches have made it possible to disclose several virological features of OBI, and describe different clinical settings. Thus the persistence of OBI is an important risk factor for development of cirrhosis and HCC. But more investigations are needed to understand the relationship between OBI and cryptogenic liver disease. It is recommended that for improving and management of patients in the initial stage of cryptogenic liver diseases, the sera and PBMCs of the patients be screened for HBV DNA by highly sensitive molecular means as a preventive measure before the development of cirrhosis and HCC.

OBI AND TRANSPLANT

Liver transplantation is the only option for patients with end-stage chronic liver disease. But in liver transplant recipients with OBI, the reactivation of HBV is enhanced by the induced immunosuppression factors and rapidly leads to graft failure and death[166-168].

The occult HBV transmission from HBsAg-negative and anti-HBc-positive liver organ donors is possible, especially when the organ liver recipient is negative for all HBV serum markers[169]. Dickson *et al*[170] reported the *de novo* HBV infection was developed in 18/23 (78%) liver organ transplant recipients from donors who were positive for anti-HBc compared with 3/651 (0.5%) recipients of organ transplant liver from donors who were negative for anti-HBc ($P < 0.0001$). Although the prevalence of OBI among kidney or bone marrow transplant recipients is controversial, limited data are available on this subject. Franz *et al*[171] detected HBV DNA in 1% of 207 kidney transplant recipients negative for HBsAg. Cinzia Lo Giudice *et al*[5] detected HBV DNA in a bone marrow transplant recipient who was negative for HBsAg and required constant blood transfusion.

For the management and prevention of the consequences of OBI in organ transplant recipients, it is suggested that the screening of HBV DNA be carried out in both donors and organ transplant recipients by highly sensitive molecular means.

EPIGENETIC CHANGES

Methylation

Methylation of cytosines in CpG dinucleotides within CpG islands affects the HBV DNA promoter, which may lead to gene silencing[172]. Methylation was found in both HBV DNA integrated in the host hepatocyte genome as well in the free episomal form of HBV cccDNA[159,168]. Methylation of HBV DNA symbolizes a novel epigenetic mechanism, and it can alter HBV proteins, HBV replication, and HBV virion production, which may lead to OBI[173]. Hypermethylated HBV DNA sequences are frequently detected in HCC patients with OBI[174]. The integrated HBX and carboxy-terminally truncated preS or S polypeptide genes in the host genome may modify the host gene expression and cellular phenotypes and result in the acceleration of growth factor-independent proliferation, metastasis and the development of HCC[175,176].

Acetylation

Both experimental *in vivo* and *in vitro* data have shown that HBV replication is regulated by the acetylation of H3/H4 histones bound to viral cccDNA[177]. Besides, the histone deacetylase onto the cccDNA is associated with low HBV replication *in vitro* and low viremia *in vivo*[178].

OBI AND HODGKIN AND NON-HODGKIN LYMPHOMAS

The etiology of lymphoma remains unknown, although genetic, environment, and some infectious agents have been implicated in the development of Hodgkin and non-Hodgkin lymphomas. The association between viruses and lymphomas has been investigated, although the precise mechanisms behind this association are still unknown. The hepatotropism and lymphotropism of HBV have been well documented[179,180].

The association between HBV and non-Hodgkin lymphoma has been well investigated[181,182]. In a study conducted by Elbedewy *et al*[182] in Egypt, HBV DNA was detected in 5/72 (6.94%) of patients with diffuse large B-cell lymphoma who were positive for anti HBc (191). In a study conducted by Kamyar *et al*[183] in Ahvaz, Iran, HBV DNA was isolated in 3/12 (25%) of patients with Hodgkin lymphoma and in 7/ 29 (24.13%) of patients with non-Hodgkin lymphoma. In this study, the results of sequencing exhibited a substitution of the amino acid proline with leuicin in position 88 of the HBs gene in six patients with Hodgkin or non-Hodgkin lymphoma. Cheung *et al*[184] in Hong Kong detected HBV DNA in 10/47 (21%) patients with lymphoma who were negative for HBsAg but positive for anti-HBc.

With regard to the aforementioned data, it is recommended that for improving the treatment, patients with Hodgkin and non-Hodgkin lymphomas be screened for HBV DNA by highly sensitive molecular means prior to chemotherapy treatment.

Table 3 Prevalence of occult hepatitis B infection among healthcare workers

Ref.	Country	No. of samples	No. of OBI cases	No. of cases positive for anti-HBc	Year
Borzooy *et al*[188]	Iran	120	4 (3.3)	0 (0)	2015
Chiarakul *et al*[189]	Thailand	36	4 (11)	4 (100)	2011
Slusarczyk *et al*[185]	Poland	961	6 (4)	4 (100%)	2012
Shim *et al*[190]	Korea	334	0	0	2011
Sukriti *et al*[191]	India	120	6 (5)	6 (100)	2008
Yen *et al*[192]	Taiwan	250	16 (6.4)	13 (81)	2005

OBI: Occult hepatitis B infection. HBc: Hepatitis B core.

OBI AND HEALTH CARE WORKERS

Health care workers are more often at high risk of HBV infection/OBI than the general population[185,186]. They may contract HBV transmission *via* exposure to potentially infected material as well as mucosal-cutaneous and percutaneous exposure to HBV from HBV carriers[187]. Most of individuals with OBI are clinically asymptomatic and remain undiagnosed unless a sudden development of cirrhosis or HCC occurred[188]. The prevalence of OBI among health care workers varies from region to region worldwide. The occurrence of OBI was mostly reported in regions of high endemicity of HBV[117]. Table 3 shows the prevalence of OBI among healthcare workers[188-192].

Based on the mentioned data, it is recommended that the screening of HBV DNA be implemented for health care workers. Besides, regardless to OBI, effective HBV vaccination should be carried out for health care workers. Also a booster dose of HBV vaccine should be put into practice for individuals with a low titer of anti-HBs (< 100 IU/mL).

OBI REACTIVATION

In OBI patients, HBV DNA may persist in two forms: episomal free cccDNA or integration into the DNA of hepatocytes. OBI may be generated by subsequently resolved acute HBV infection, occurrence of mutation in "a" determinant of the HBsAg gene, coinfection with HCV or HIV, and cellular epigenetic changes. In OBI, HBsAg is undetectable in serum with positive/negative anti-HBc status[172,175,193]. OBI reactivation may take place with increasing HBV DNA replication in patients during immunosuppression therapy[185,186,189-199]. OBI reactivation was described with enhancing HBV DNA replication in HIV patients during anti-retroviral therapy[200]. OBI reactivation resulted in the development of fulminant hepatitis in patients with cancer who underwent chemotherapy[200,201]. The risk of HBV reactivation is considered as high as 21% to 67% when immunosuppression is distinct, particularly in onco-hematological patients, in those receiving hematopoietic stem cell transplantation and in those treated with the anti-CD20 monoclonal antibody rituximab or with the monoclonal anti-CD52 antibody alemtuzumab, which account for long-lasting immunosuppression[193,194,202-208]. Under these situations, HBV reactivation causes a mortality rate about 20%, due to hepatic failure[209,210]. Seto *et al*[211] reported reactivation of hepatitis B in lymphoma patients with a past history of HBV infection, who were treatd with rituximab-containing chemotherapy. Hsu *et al*[212] studied the chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection. Dominguez *et al*[213] (2015) observed reactivation of OBI in a patient with chronic lymphocytic leukemia after treatment with a rituximab and fludarabine-based regimen. A recent study conducted by Liu *et al*[214] revealed that reactivation of HBV was observed in patients with breast cancer receiving chemotherapy.

The risk of HBV reactivation in cancer patients receiving chemotherapy is impressed by inducing factors related to the virus, the host and specific immunosuppressive treatment, although the complete dimension of risk remains unknown.

With regard to the aforementioned data, the screening of HBV DNA by highly sensitive molecular means be implemented in all patients before and after immunosuppression status.

CONCLUSION

OBI is a life-threatening public health problem worldwide. The detection of OBI is costly, especially for developing countries, therefore many patients with OBI may remain undiagnosed. OBI is an important risk fact for developing cirrhosis and HCC.

OBI can be controlled in high risk groups, provided that the implementation of highly sensitive molecular means used for detection HBV DNA as a preventive measure.

With regard to the consequence of OBI, for improving the treatment and management, the screening of HBV DNA by real-time PCR should be implemented in the following groups: (1) patients with a previous history of HBV infection; (2) HBV patients coinfected with HCV/HIV; (3) patients undergoing chemtherapy anti-CD20 therapy; (4) recipients of organ transplant; (5) blood donors; (6) organ transplant donors; (7) thalassemia or hemophilia patients; h) health care workers; (8) patients with cryptogenic hepatitis or cryptogenic liver related disease (cirrhosis and HCC); (9) HD patients; (10) patients treated with lamivudine or interferon; and (11) children in time of HBV vaccination, especially in highly endemic areas of HBV. Besides, recent data revealed that reactivation of HBV was observed in patients with breast cancer receiving chemotherapy. Therefore, the screening of OBI should be implemented in patients with breast cancer.

In addition, proper disinfection should be performed for dialysis, endoscopy, colonoscopy and endoscopy

units.

The effective HBV vaccination program should be carried out for the close relatives of patients who are negative for OBI. The third generation HBV vaccines containing preS1 and preS2 antigens have been developed with excellent immunogenicity in humans, and rapid antibody responses may be able to control the further incidence of OBI[215,216].

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P- Reviewer: Franz C, Hoshina T, Yeung CY **S- Editor**: Yu J
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ISSN 1007-9327