Review Article

Occult Hepatitis B infection (OBI) a hidden threat for blood/organ donation & immunosuppression: An update

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ABSTRACT

Hepatitis B infection is still a significant public health problem. After the incorporation of the hepatitis B vaccine into the universal immunization program, the prevalence of hepatitis B infection declined dramatically in the post-vaccination era. In the developing countries due to lack of expensive screening before blood/organ donation & immunosuppressive therapy occult hepatitis-B infection(OBI) remains as an occult threat for transmission or reactivation of hepatitis-B infection ultimately leading to progressive liver disease Nucleic acid testing (NAT) should be implemented for detection of OBI-HBV DNA, when highly sensitive NAT testing not able to performed, anti-HBc could be used as a possible surrogate marker for identifying potential OBI.

Keywords: HBV infection, OBI, HBsAg, (TNF)-x

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Introduction

Hepatitis B virus (HBV) infection is a considerable global health problem, and approximately two billion people in the world have been infected, of which 250 million live with HBV infection.[1] The regional prevalence of HBV is highest in sub-Saharan Africa and Southeast Asia, and Bangladesh belongs to at 5-10%to an intermediate prevalent region, which is about 4.2%.[2] Data on hepatitis-B disease burden in Bangladesh is limited; some previous small-scale studies suggest that hepatitis B surface antigen (HBsAg) prevalence ranges from 3-7% among the general population,[3] 1.5 – 12% in children under five,[4] and <0.1% in the post-vaccine era.[5] 5HBV infection is linked with a wide range of clinical manifestations, including acute or fulminant hepatitis to different forms of chronic infection, like asymptomatic carriers, chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). A new form of clinical HBV infection was reported in the 1970s, which was a patient with acute hepatitis, who was positive for anti-hepatitis B core (anti-HBc) immunoglobulin G (IgG), but negative for HBsAg. 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.[6] In the absence of serum HBsAg, a low level of HBV DNA (< 200 IU/mL) was detected in serum and liver tissue by real-time polymerase chain reaction (PCR). This new clinical entity of HBV infection was called OBI.[7] The clinical features of OBI remain unknown, and further studies are needed to characterize it in high-risk populations worldwide. In the majority of cases, OBI does not appear to lead to any clinical sequelae. However, OBI may result in transmission of HBV infection to blood or organ transplant recipients, and reactivation of HBV replication occurs in patients receiving

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cancer chemotherapy or other immunosuppressive therapies, or those with a previous history of HBV infection.[8] Although the implementation of screening tests for hepatitis B surface antigen (HBsAg) has significantly reduced the spread of HBV infection among blood donors, these tests fail to detect occult HBV infection (OBI). To control the spread of OBI, HBV DNA screening should be required among blood donors, immunosuppressed patients, organ transplant donors, organ transplant recipients, and individuals with acute rheumatoid arthritis before and after treatment with anti-tumor necrosis factor (TNF)-α.[9] In this paper, I reviewed related publications to explain the epidemiology, diagnosis, treatment, and prevention of OBI.

Definition of OBI

Most of the OBI cases are asymptomatic and clinically not well defined. OBI has been investigated only in high-risk groups with different serological and molecular descriptions. There are different types of definitions of OBI that have been described. In Italy(2008), in the first international workshop (2008), OBI was defined as the detection of HBV DNA in the liver (with or without HBV DNA in serum) in the absence of HBsAg.[10] After 10 years of the first meeting, a new workshop dedicated to OBI was again held in Italy on 2018, updated the definition as, the presence of replication-competent HBV DNA (i.e.episomal HBV covalently closed circular DNA[cccDNA)] in the liver and/or HBV DNA in the blood of people who test negative for hepatitis B surface antigen (HBsAg) by currently available assays.[8] There are two types of OBI: seropositive or seronegative. The characteristics of Seropositive OBI are the detection of anti-HBc antibody, with or without anti-HBs antibody. At the same time, seronegative OBI is characterized by the undetectability of 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. According to the report, more than 20% of OBI cases are seronegative for all the HBV markers.[11]

Prevalence of OBI

The prevalence of OBI varies worldwide. This variability depends on the sensitivity of HBV DNA detection assays, the sample size, and the detection of HBV DNA in liver tissue and serum by nested or real-time PCR. The prevalence of OBI varies from 1% to 87% in different regions of the world. [12,13] HBV DNA was found in 0% to 4.6% of those who were HBsAg-negative and anti-HBc positive with or without anti-HBs, with a median prevalence of 1%. [12]

Molecular mechanisms of OBI

The molecular basis of OBI is relevant to the stability and long-term persistence of cccDNA in the nucleus of infected hepatocytes. A lower level of transcriptionally active cccDNA in OBI cases results in low or undetectable HBV RNA transcription and, consequently, reduced protein translation and expression.[14,15] However, cccDNA in OBI cases is fully replication competent. HBV DNA may be integrated into the host's genome and remain in the hepatocytes of HBV-infected individuals after spontaneous or treatment-induced HBsAg clearance. However, integrated HBV DNA is not replication-competent, and its detection is not required for diagnosing OBI, since OBI is defined as the persistence of replication-competent HBV DNA.[16]

Mechanism of liver damage

The mechanism of liver damage due to OBI is still not well elucidated. However, there is some data indicating the persistence and transcription of HBV cccDNA in hepatocytes, and that, subsequently, the production of cytokines, such as TNF-α and interferon-γ, may result in hepatocyte damage.[17] Liver cancer is considered a major global health problem. Viral hepatitis B and C are the main risk factors for the development of liver cancer.[18] The prolonged persistence of cccDNA in the hepatocyte nucleus has been detected in patients with HCC. In addition, HBV DNA is integrated into host chromosomes in individuals with HCC.[19] Most findings described that OBI is an important risk factor for hastening the progression of liver disease and the development of cirrhosis and HCC.[20] 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.[21]

Diagnosis

Diagnosis of OBI is based on the detection of HBV DNA in the blood or the liver of HBsAg-negative individuals. In liver detection of HBV DNA is the gold standard; it is commonly used in the blood. Detection of anti-HBc in the blood is often used as a surrogate.[8]

Clinical impact of OBI

In the vast majority of cases, OBI does not appear to lead to any clinical sequelae. However, OBI may result in transmission of HBV infection to blood or organ transplant recipients. Reactivation of HBV replication in patients receiving cancer chemotherapy or other immunosuppressive therapies may accelerate the progression toward cirrhosis and the development of HCC in patients with chronic liver disease caused by other factors (e.g., HCV, alcohol, non-alcoholic steatohepatitis).[8]

Blood transfusion and OBI **-** Blood transfusion is a significant risk factor for OBI transmission, provided that blood donor screening is less secure.[22] In the most developed countries, to boost blood safety, nucleic acid amplification testing (NAT) with a limit of detection of 2–4 IU/ml and 99.9% specificity has been established for screening blood donors for HBV or OBI. It is well documented that NAT for HBV DNA detection is more sensitive than serological tests. In most developing countries, the screening of HBV among blood donors relies only on serological detection of HBsAg, as the screening of HBV by NAT is expensive.[23] The detection of anti-HBc is a good test for OBI tracking, but it accounts for about 80% of OBI cases.[24] Thus, implementation of anti-HBc testing for blood donors can be considered a second safeguard policy to reduce the transmission of HBV via blood transfusion.[25] although NAT is more sensitive and effective than the serological HBsAg test as a preventive measure for HBV or OBI transmission via blood transfusion.

Cirrhosis and hepatocellular carcinoma -Liver cirrhosis has been regarded as an end-stage liver disease, histologically characterized by diffuse nodular regeneration surrounded by dense fibrotic septa caused by different chronic liver diseases, including CHB, chronic hepatitis C, alcoholic liver disease, and non-alcoholic fatty liver disease. OBI patients typically have suppressed HBV replication activity and low viral load. Thus, most of the OBI patients have normal histology or minimal fibrosis. However, they are still at risk of developing liver cirrhosis. The prevalence of OBI in cirrhotic patients ranges widely from 4 to 38% among different regions. Worldwide. [26]

OBI and hemodialysis **-** Hemodialysis (HD) patients are at high risk of viral blood-borne infections (HBV, HIV, and HCV)[27] and diagnosing liver disease based on aminotransferase levels in HD patients is difficult. Mostly, aminotransferase is suppressed by reduced immune competence, leading to weak inflammatory responses and, consequently, reduced hepatocyte destruction.[28] Therefore, the most efficient method for evaluating OBI in HD patients was found to be the quantitative HBV DNA Test. [27]

OBI in immunosuppression - during immunosuppression therapy, occult hepatitis B infection reactivation may take place with increasing HBV DNA replication. OBI reactivation may result in fulminant hepatitis in cancer patients who have received chemotherapy. The risk of HBV reactivation ranges from 21 to 67% when immunosuppression is potent, particularly in onco-hematological patients,[29] those receiving hematopoietic stem cell transplantation and treated with the antiCD20 monoclonal antibody (e.g., rituximab) or with the monoclonal anti-CD52 antibody (e.g., alemtuzumab),[27] as these agents often lead to long-lasting potent immunosuppression even more than two years after stopping these agents.

OBI and organ transplant- Liver transplantation is the only option for patients with end-stage chronic liver disease. However, 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.[30] 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.

OBI and health care workers- In comparison to the general population, health care workers are more often at high risk of HBV infection/ OBI.[31] They may contract HBV transmission via exposure to potentially infected material, as well as mucocutaneous and percutaneous exposure to HBV from HBV carriers.[32] The majority of the population with OBI are clinically asymptomatic and remain undiagnosed unless a sudden development of cirrhosis or HCC occurs. The prevalence of OBI among health care workers varies worldwide. OBI was mainly reported in regions with high HBV endemicity.

Treatment

Currently, antiviral therapy is not recommended for individuals with OBI. [8]

Preventive measure

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 factor for developing cirrhosis and HCC. OBI can be controlled in high-risk groups, provided that highly sensitive molecular methods for detecting HBV DNA are implemented as a preventive measure. About 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 anti-CD20 therapychemtherapy ; (4) organ transplant recipient ; (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) In highly endemic areas of HBV children, HBV vaccination should be in time. Also, proper disinfection should be performed for dialysis, endoscopy, colonoscopy, and endoscopes, and an effective HBV vaccination program should be implemented 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.[33, 34]

Conclusion

OBI has recently gained increasing attention. Although the exact mechanism of OBI is unknown, OBI can be transmitted through blood and organ donation, without appropriate screening, may cause reactivation of HBV, and contribute to the development of progressive liver disease and liver cancer. Nucleic acid testing (NAT) should be implemented to detect OBI-HBV DNA. It is recommended that, when highly sensitive NAT testing cannot be performed, anti-HBc can be used as a surrogate marker to identify potential seropositive OBI in cases of blood donation or organ donation, or in those receiving immunosuppressive therapy.

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