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Prevalence of occult hepatitis B virus infection

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Abstract

Occult hepatitis B virus (HBV) infection (OBI) is characterized by the persistence of HBV DNA in the liver tissue in individuals negative for the HBV surface antigen. The prevalence of OBI is quite variable depending on the level of endemic disease in different parts of the world, the different assays utilized in the studies, and the different populations studied. Many studies have been carried out on OBI prevalence in different areas of the world and categories of individuals. The studies show that OBI prevalence seems to be higher among subjects at high risk for HBV infection and with liver disease than among individuals at low risk of infection and without liver disease.

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INTRODUCTION

Chronic hepatitis B virus (HBV) infection is characterised by persistence of HBV surface antigen (HBsAg) and presence of HBV DNA in serum.

Occult HBV infection (OBI) is the persistence of viral genome in the liver tissue in individuals negative for HBsAg. OBI is defined by the presence of HBV DNA in the liver (with detectable or undetectable HBV DNA in the serum) in patients with serological markers of previous infection (anti-HBc and/or anti-HBs positive) or in patients without serological markers (anti-HBc and/or anti-HBs negative). The prevalence of OBI is quite variable depending on the level of endemic disease in different parts of the world, the different assays utilized in the studies, and the different populations studied^[1]. The populations in which prevalence of OBI has been investigated are: patients with liver disease (HCV infected patients and patients with cryptogenetic liver diseases), patients at high risk of parenteral-transmitted infection (intravenous drug addicts, hemophiliacs), patients on hemodialysis, human immunodeficiency virus (HIV) infected patients and apparently healthy individuals (blood donors, general population)^[1]. The purpose of this review is to provide comprehensive information on overall OBI prevalence as well as in patients with different chronic liver diseases.

HCV INFECTED PATIENTS

As HBV and HCV share many of the same transmission

routes, and infection with both viruses is common, the high prevalence of OBI in patients with hepatitis C is not unexpected. HCV infected patients have the highest prevalence of OBI^[2,3]. Cacciola *et al*^[2] published the first study of prevalence of OBI in patients with chronic hepatitis C; in this study HBV sequences were found in liver tissue from 66 of the 200 (33%) HCV infected patients and in 7 of the 50 (14%) HCV negative patients, 46 of the 66 patients were anti-HBc positive and 20 of the 66 were anti-HBc negative. They also found very low levels of viremia and the prevalence of OBI was particularly high among patients with anti-HBV antibodies although OBI was also detected in patients who were negative for all HBV serum markers^[2]. The study of Cacciola *et al*^[2] also demonstrated that OBI was significantly correlated with cirrhosis among HCV infected patients; 22 of the 66 patients (33%) with HCV infection and OBI had cirrhosis as compared with 26 of the 134 (19%) with HCV infection and no OBI, suggesting that OBI can accelerate the evolution to cirrhosis in HCV infected patients. Bréchet *et al*^[4] reviewed all the studies published in anti-VHC patients using PCR on serum and liver and the conclusion was that about 20%-30% and 40%-50% of serum and livers respectively showed HBV DNA positivity.

CRYPTOGENETIC LIVER DISEASE

In patients with cryptogenetic liver disease there is less available information than in HCV patients but the prevalence is thought to range from 19% to 31%^[5,6]. Chemin *et al*^[6] studied 50 patients with chronic hepatitis non-A non-E and reported a high prevalence of low-grade HBV infection. HBV DNA was detected by PCR in serum in a high proportion of cases (15/50; 30%); in all cases HBV DNA detection in serum was further confirmed on liver biopsies. 11 of the 15 (73%) patients who were HBV DNA positive were found to be anti-HBc positive, and all the patients had 10⁴ or less HBV DNA copies per mL. Among the positive HBV DNA patients 8/15 (53%) had severe fibrosis and cirrhosis and none of the patients had steatosis, so low-grade HBV infection was associated with more severe liver disease. The histopathological follow-up showed that some patients progressed to cirrhosis^[5]. Berasain *et al*^[5] investigated 1075 patients with chronic liver disease and in 109 (10%) the aetiology could not be defined by clinical, biochemical and serological data. In these cases liver biopsy was reviewed, then the histopathological findings and implication of hepatitis viruses B and C was investigated in cryptogenetic liver disease. HBV DNA and HCV RNA were determined in serum by PCR. HBV DNA and HCV RNA were detected in the serum of 18% and 8% patients with cryptogenetic and noncryptogenetic liver diseases respectively. Liver biopsies showed non specific changes or non-alcoholic steatohepatitis (NASH) in 48% and chronic hepatitis or cirrhosis in 52%. The proportion of cases with detectable HBV DNA or HCV RNA was 14% in the first group, 30% in the group with

chronic hepatitis and 61% in the group with cirrhosis, so occult viral infection was found in a high proportion of patients with chronic hepatitis or cirrhosis and in a low percentage of patients with NASH or non-specific changes. Two patients with cryptogenetic cirrhosis underwent liver transplantation, and in these 2 cases HBV DNA was detected in the explanted liver^[6].

DIALYSIS

Hemodialysis patients are at high risk of acquiring parenterally transmitted infections, not only because of the large number of received blood transfusions, and the invasive procedures that they undergo, but also because of their immunosuppressed state. Several reports have been published about prevalence in haemodialysis patients ranging from 0% to 36%. Most of these studies show that OBI is usually associated with low levels of HBV and have investigated the presence of of OBI in the context of chronic HCV infection^[7-13]. These studies demonstrated HBV DNA by PCR in serum samples; there were no studies demonstrating HBV DNA in liver extracts because of the lack of available liver tissue in the setting of haemodialysis. The studies of Fabrizi *et al*^[9] and Minuk *et al*^[10] show that conventional serological features of HBV DNA positive subjects do not distinguish these individuals from the remainder of the dialysis patient population; therefore, routine serological testing is not able to identify the occult infection in this population. Several studies have demonstrated that the prevalence of OBI is not associated with the presence of anti-VHC antibodies in hemodialysis patients^[14-16]. Recently, one study has shown an OBI prevalence of 9.8% in continuous ambulatory peritoneal dialysis (CAPD)^[17].

HIV INFECTED PATIENTS

OBI in HIV infected patients may be viewed as the result of opportunistic reactivation of HBV due to cellular immune deficiency, as reflected by the decreased CD4 counts in HIV infection. The prevalence of OBI in HIV infected patients remains controversial and the available data are widely divergent. Published studies report a prevalence between 0% to 89%^[18-26]. The cause of these variations is the same as in HIV-negative patients: level of endemic disease in differences parts of the world, the different assays utilized in the studies, and the different populations studied. HIV patients with OBI have significantly lower CD4 counts and high plasma HIV RNA loads^[20,27]. The risk factors, the clinical significance and the effect of highly active antiretroviral therapy (HAART) are unknown. Recently, Cohen Stuart *et al*^[28] analyzed the prevalence of OBI in 191 HIV and anti-HBc positive before HAART and also during the immune reconstitution phase that follows initiation of HAART. Anti-HBs was positive in 128/191 (67%), and negative in 45/191 (24%). Plasma HBV DNA was detected in 9/191 corresponding to a prevalence of 4.7%. In the isolated anti-HBc group

the prevalence was 11.1%, whereas in those anti-HBs positive the prevalence was 3.1%; this difference was not significant. The study demonstrated the absence of hepatic flares after start of HAART and showed that HBV DNA remained undetectable in all patients after starting HAART. Therefore OBI has no clinical impact when immune reconstitution is achieved with HAART containing at least one HBV inhibiting compound.

BLOOD DONORS

Despite continuous technical improvement in blood donation screening, hepatitis B infection remains a major risk of transfusion-transmitted viral infection. Reduction of HBV residual risk is achieved by developing more sensitive HBsAg tests, by adopting anti-HBc screening if appropriate and implementing HBV nucleic acid test (NAT).

The prevalence of OBI among HBsAg negative blood donors is quite variable depending on the level of endemic disease and on the assays employed in routine serological or NAT screening. Screening of anti-HBc is feasible in non-endemic areas, but would cost an unnecessary loss of blood donations in endemic areas (where nearly 90% of adults are positive for both anti-HBc and anti-HBs due to past exposure to HBV).

Hollinger^[29] provide an excellent summary of the prevalence of serological markers in HBsAg negative blood donors in different regions of the world. The studies of prevalence in North America reveal that HBV DNA was detected in 0.1%-1.05% of those who were HBsAg negative and anti-HBc-positive (with or without anti-HBs) and that HBV DNA was detected in 2.03%-2.8% in the anti-HBc only category (no anti-HBs)^[30-34]. The studies of prevalence in Europe reveals that HBV DNA was detected in 0%-1.59% of those who were HBsAg negative and anti-HBc-positive (with or without anti-HBs) and HBV DNA was not detected in patients who were anti-HBc only^[35-38]. In the study of Allain *et al.*^[35] no occult hepatitis B was detected in any of the samples because the level of sensitivity was only approximately 1300 copies/mL. The studies of prevalence in the Middle East and Asia revealed that HBV DNA was detected in 1.09%-3% of those who were HBsAg negative and anti-HBc-positive (with or without anti-HBs) and that HBV DNA was detected in 8.1% in the anti-HBc only category (no anti-HBs)^[39-41].

GENERAL POPULATION

There are few studies about OBI prevalence in the general population. Minuk *et al.*^[42] detected a prevalence of OBI in 18% of those with serological evidence of previous HBV infection and in 8% of HBV seronegative individuals. Kim *et al.*^[43] found HBV DNA in 16% of Korean healthy subjects with normal transaminase values and who were HBV/HCV negative. Hui *et al.*^[44] detected occult HBV genomes in 15% of healthy hematopoietic stem cell donors from Hong-Kong. Raimondo *et al.*^[45] investigated the prevalence of OBI in subjects free from liver disease

through the analysis of liver DNA extracts by performing four different in-house nested-PCR amplification assays. HBV DNA sequences were detected in liver tissues from 16 of the 98 cases examined (16.3%). DNA was detected in 10 of the 16 (62.5%) anti-HBc positive cases vs 6 of the 82 (7.3%) HBV marker negative cases, so OBI status was strongly related with the anti-HBV antibody positive status.

CONCLUSION

Although studies on OBI prevalence have been extensive, the precise prevalence of this clinical entity remains very difficult to define for several reasons. These studies show that OBI prevalence seems to be higher among subjects at high risk of HBV infection and with liver disease than among individuals at low risk of infection and without liver disease. In general about 20% of OBI individuals are negative for all serological markers, and 80% are positive for serological markers of previous infection. Most studies show that OBI is usually associated with low levels of HBV DNA. The importance of this entity is that OBI may have significant impact in several clinical contexts. It might favour the progression of liver fibrosis and the development of hepatocellular carcinoma in patients with additional causes of liver damage; OBI may become reactivated when an immunosuppressive status occurs; and it may be transmitted through blood transfusion and organ transplantation. While awaiting for more sensitive methods for blood HBV DNA measurement, anti-HBc should be recommended in patients undergoing chemotherapy or immunosuppressive treatments as well as all organ donors.

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