

Occult Hepatitis B

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Occult hepatitis B (OHB) is a mysterious but clinically important entity and has gained increasing attention recently.^{1,2} Occult hepatitis B is the presence of hepatitis B virus (HBV) DNA in the liver and sometimes in the serum of individuals who are hepatitis B surface antigen (HBsAg) negative.³ The early phase of hepatitis B before the appearance of HBsAg in the serum is not labeled as OHB.⁴ Allain defined occult hepatitis B as “the presence of HBV DNA in patients who are HBsAg negative, with or without HBV antibodies except for the early window period of HBV infection”.⁵ A study reported that 2 blood donors screened negative for HBsAg and HBV DNA transmitted hepatitis B and developed acute hepatitis afterward. These cases represent the acute early phase of hepatitis B infection. Hepatitis B surface antigen remains negative during the entire course of OHB.⁶ An international workshop was held in which occult hepatitis B was defined as the “presence of HBV DNA in the liver of individuals negative for HBsAg with the currently available enzyme-linked immunosorbent (ELISA) assays”. A cut-off value for serum HBV DNA was defined as <200 IU/ml. The term occult hepatitis B infection (OBI) shows that infectious viral particles are present. But HBV DNA does not always reflect infectivity. It was suggested that occult hepatitis B (OHB) is the preferred term instead of occult hepatitis B infection (OBI).^{7,8} Occult hepatitis B has 2 important features: absent HBsAg and decreased viral replication.⁹ Occult hepatitis B can occur after past hepatitis B, chronic hepatitis B caused by escape mutants of HBsAg gene, chronic carrier state with the presence of anti-HBc but very low HBsAg and chronic hepatitis B with no serological markers other than HBV DNA.⁵ Occult hepatitis B was first documented by Brechot in 1985 by the detection of viral DNA in chronic liver disease patients without any other serological marker.¹⁰ Hoofnagle et al. reported that hepatitis B was transmitted by the transfusion of anti-HBc positive donor blood.¹¹ In the early 1990s, Sanchez-Quijano et

al. and Joller-Jemelka et al. detected HBV DNA in 42% and 40% individuals respectively with isolated anti-HBc.^{12,13} Occult hepatitis B is common in the patients with chronic hepatitis C, acquired immunodeficiency syndrome (AIDS), cryptogenic liver disease and hepatocellular carcinoma.¹⁴

Prevalence of Occult Hepatitis B

There is limited literature on the prevalence of occult hepatitis B in the general population. Minuk et al. reported occult hepatitis B in 18% of individuals who had serological evidence of previous HBV infection and in 8% of HBV seronegative individuals.¹⁵ Kim et al. detected HBV DNA in 16% of Korean healthy population. These individuals had normal transaminase levels and were HBV/HCV negative.¹⁶ Another study reported that occult hepatitis B was present in 66(33%) of hepatitis C patients. He also stated that there was a positive correlation between cirrhosis among hepatitis C patients and occult hepatitis B as 22(33%) patients with occult hepatitis B had cirrhosis. The prevalence of occult hepatitis B ranges from 19% to 31% in patients with cryptogenic liver disease. According to the published data, the prevalence of occult hepatitis B in AIDS patients ranges between 0% to 89%. The reason for this variation is the difference in the prevalence of disease worldwide, different assays used for its diagnosis and the different CD4 cell counts in these patients.¹⁷ In the Middle East and Asia, HBV DNA was detected in 1.09-3% of blood donors who were HBsAg negative.¹⁸ The prevalence of occult hepatitis B among blood donors who were HBsAg negative in Europe was 0-1.59%.¹⁹ The frequency of occult hepatitis B is highly variable ranging from 0 to 58% among hemodialysis patients. The prevalence rate of occult hepatitis B in hemodialysis patients was 4.9% in India, 3.7% in North America, 0 to 26.6% in Italy and 2.7% to 12.4% in Turkey.^{20,21}

Pathogenesis of Occult Hepatitis B

The etiology of occult hepatitis B is uncertain. Both the host and viral factors have an important role in its pathogenesis. The viral factors include infection with S gene mutants of HBV which does not express S protein or produce a modified S antigen not detectable by the HBsAg kits.^{22,23} Mutations in the polymerase domain or transcription control region also inhibit HBV replication and HBsAg expression.⁷ The escape mutations can also lead to occult hepatitis B. It was

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reported that RNA splicing occurs that do not affect the polymerase, core and X protein functions but inhibit surface gene expression and produce viruses that lack surface protein.⁶ Formation of HBsAg-anti-HBs complexes also causes decreased expression of HBsAg.²⁴ The HBV DNA incorporates into the host genome reducing the viral replication and in turn the expression of HBsAg.²⁵ The viral replication at an extrahepatic site such as peripheral blood mononuclear cells can also result in the absence of HBV DNA and other hepatitis B serological markers in the serum.²⁶

There is a strong suppression of viral replication in occult hepatitis B. Hypotheses have explained various mechanisms responsible for it including host immune response, epigenetic factors and coinfection with other infectious agents. The immune response of the host is the most important factor.²⁷ After recovery from acute hepatitis B, the virus is still present in the body but it replicates at a very low rate.²⁸ The epigenetic factors also regulate HBV replication.³⁰ The viral transcription is suppressed by methylase and deacetylase enzymes that cause post-translational modifications of HBV DNA molecule. These modifications are induced by chemical agents, cytokines and coinfection with other infectious agents.²⁷ The coinfection with other infectious agents is another factor that decreases viral replication and gene expression. Hepatitis C virus inhibits the replication of the hepatitis B virus.²⁹ *Schistosoma mansoni* also suppresses HBV replication.²⁷

Clinical Presentation of Occult Hepatitis B

In most of the cases, occult hepatitis B is asymptomatic and is diagnosed on screening. So far guidelines are not available for the screening of occult hepatitis B in specific population groups. However, the screening should be considered in hepatitis C patients, donated blood products for immunocompromised recipients, patients taking immunosuppressive drugs and unexplained liver disease.⁹

Clinical Implications of Occult Hepatitis B

There are various clinical implications of occult hepatitis B. The patients of occult hepatitis B can develop acute hepatitis B and fulminant hepatitis B. The viral reactivation occurs in patients who are immunodeficient or taking immunosuppressive drugs depending on the severity and duration of the immunosuppression.³²

The virus induces a mild, continuous inflammatory response in the liver that can lead to the progression of chronic liver disease and cirrhosis.³¹ In a study conducted by Hollinger et al., it was reported that occult hepatitis B causes an increase in ALT levels in hepatitis C patients.⁷

As HBV has the pro-oncogenic potential, occult hepatitis B can cause hepatocellular carcinoma.^{31,32} A study was done in Japan in which 82 patients with chronic liver disease negative for HBsAg and anti-HCV antibodies were included. After a period of 5 years, 27% of patients who had HBV DNA developed HCC as compared to 11.8% of patients with negative HBV DNA after 5 years.^{33,34}

Occult hepatitis B is transmitted by blood transfusion and organ transplantation. The transmission by organ transplantation has been documented in liver transplants. However, the transmission occurs at a very low rate in heart and kidney transplants.^{7,35} Nosocomial transmission of occult hepatitis B occurs in hemodialysis patients and staff.³⁶ A study in Italy reported that occult hepatitis B is present in hemodialysis patients especially in anti-HBc positive patients. Most of the research work done to detect occult hepatitis B in HD patients included patients who also had chronic hepatitis C.³⁷

Diagnosis of Occult Hepatitis B

The patients of occult hepatitis B have normal liver function tests and liver histology.¹ The detection of HBV DNA in the liver biopsy sample is the best way to diagnose occult hepatitis B. As liver biopsy is an invasive procedure, it is not done routinely.⁷ A study conducted in Italy enrolled 98 individuals with negative HBsAg. Hepatitis B virus PCR was done on their liver specimens and DNA was detected in 16 individuals. Ten of these individuals were also anti-HBc positive.⁵

The PCR assay, its sensitivity and specificity affect the detection of hepatitis B virus. The detection of HBV DNA also depends on the sample and its volume tested. The detection rate is higher with a large volume of serum. The chances of HBV DNA detection are also higher in the liver or peripheral blood mononuclear cells as compared to serum. The negative controls should be run and the contamination of samples should be avoided.²⁸ Three different PCR primers should be run to prevent false positive PCR results. The results should be verified by detecting HBV DNA from at least two regions of the genome.³⁸ The lower detection limit for HBV DNA is 5 IU/ml.⁵ According to Poisson distribution, the detection rate of HBV DNA can be enhanced by repeated DNA extraction and testing.³²

Association of Occult Hepatitis B with Serological Markers

Occult hepatitis B is associated with various serological markers of hepatitis B. But according to studies, 20% of cases are reported to be negative for hepatitis B antibodies. There are 2 possibilities for it. Either these antibodies were present initially after

hepatitis B infection but then they progressively disappeared years after recovery or these antibodies were absent from the start of infection.³⁹

A study conducted in Brazil recruited 752 hemodialysis patients. Out of 752 patients, 201 (26.7%) patients were anti-HBc positive. Hepatitis B virus DNA was detected in 3/201 patients. It was reported that isolated anti-HBc may reveal undiagnosed occult hepatitis B.⁴⁰ Another study was conducted in which out of 100 anti-HBc positive liver transplant donors, 52% had occult hepatitis B.⁴¹

A study carried out in 2018 by Caviglia et al. demonstrated high levels of anti-HBc in patients with occult hepatitis B. According to this study, serum anti-HBc levels can be used as a screening test to exclude occult hepatitis B.⁴¹ Studies have indicated that vaccination in patients with occult hepatitis B might lead to the disappearance of HBV DNA from their blood/serum. Therefore, the possible role of vaccination must be considered in these patients.⁴² The benefit of antivirals in occult hepatitis B has not been documented. According to a study, the benefit of antiviral therapy is expected to be low because these patients have low HBV DNA levels.²⁸ About one-third of the occult hepatitis B patients die from HBV reactivation. Akram et al. in 2018 reported in his study that the administration of antiviral therapy to prevent HBV reactivation is the best method to decrease the mortality rate. However, there are no recommendations for routine antiviral prophylaxis except in those taking immunosuppressive therapy. Serial monitoring of HBV DNA can detect viral reactivation and is recommended by Japanese guidelines.² In another study conducted in 2017, it is stated that prophylactic antiviral therapy is only recommended in occult hepatitis B patients who are going to start immunosuppressive drugs.^{1,2}

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