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Editorial

When can it be useful to look for occult HBV in haemodialysis patients?☆

¿Cuándo puede ser útil buscar VHB oculto en pacientesen hemodiálisis?

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Hepatitis B virus (HBV) is a serious world health problem. In year 2015, the estimated prevalence in the general population was 3.5%.[1] The morbidity and mortality associated with HBV-related chronic hepatitis is linked to the persistence of viral replication and progression to cirrhosis and/or hepatocellular carcinoma. One difficulty with HBV is the high risk of contamination, which magnifies the problem.[2]

Patients on haemodialysis (HD) are at risk of HBV infection ; they are frequently transfused, and they are immunocompromised and subjected to invasive procedures with blood manipulation. They should therefore have serology testing and all seronegative patients need to be vaccinated.[3,4] Thanks to this measure and isolation in the HD units according to the recommendations in Spain, the prevalence of HBV has dropped significantly to 1.03% in recent years.[5]

The improvement in sensitivity and specificity of the polymerase chain reaction (PCR) method for detecting HBV DNA, with a limit of detection ≤10 IU/mL, has led to the identification of patients with occult HBV infection (OBI).[6]

Definition of occult HBV infection

OBI is defined as persistent detectable HBV-DNA in serum or hepatocytes in patients with undetectable HBsAg, with or without serological markers of previous infection (anti-HBc

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and/or anti-HBs positive).[7] Most cases are asymptomatic and the clinical features are not well defined.

At the Taormina expert meeting, the diagnosis and classification were established according to the serological pattern: seropositive patients (80%) if they have a marker of previous contact with HBV, and seronegative patients, less common (20%), with no marker of previous contact with HBV.

Detection of HBV DNA by real-time PCR is therefore the only reliable diagnostic marker of OBI with a viral load below 200 IU/mL.

Many different mechanisms have been suggested to explain OBI profiles. The first is a loss of circulating HBsAg antigenicity caused by specific mutations in the S gene, which makes it difficult to be recognised by the anti-HBs antibodies. These ëscape mutantsc̈an be associated to HBV viral load levels comparable to overt infections and, according to some authors, they would be f̈alse OBI.̈ Other mechanisms would be a real decrease in the hepatic expression of the protein HBs, with undetectable levels of HBsAg associated with low levels of HBV replication, mutations in HBV genome regions, included the pre-S, pre-C and Core regions, phenomena of interference with HCV or HIV, or other factors related to the host's immune response.[8–10]

Measurement of HBV viral load

The methods currently used for quantification have greater sensitivity, reproducibility and specificity than the qualitative methods for detecting HBV DNA by PCR. There are commercial real-time PCR assays on the market with different detection limits, they vary from 10 IU/mL in QIAGEN (artus HBV QS-RGD kit) or Abbott (Abbott Real Time HBV) to 20 IU/mL in Roche (COBAS AmpliPrep/COBAS TaqMan HBV v2.0) and up to 64 IU/mL in Siemens (VERSANT HBV DNA 1.0 Assay kPCR).[11]

Anti-HBc as risk marker

The detection of anti-HBc may be useful to increase overall sensitivity to assess the risk of OBI. The risk associated with seropositivity for anti-HBc has been demonstrated, and its presence can be considered an alert marker of OBI. The Taormina group recommends its use if HBV DNA determination is not available. In a series with almost 4000 patients, all cases detected corresponded to patients with anti-HBc.[12]

Prevalence and risk groups

The reported prevalence of OBI ranges from 1% to 87%.[13] The variability is based on the sensitivity of the assays, the sample size, the study population and detection in liver tissue or serum. It seems to be higher among those at risk for HBV infection.

The identification of cases and the description of the prevalence are important to prevent the two main problems associated with OBI: the risk of reactivation and the risk of transmission.

Up to now the groups considered at risk are: HD patients ; patients co-infected with HCV or HIV; patients on chemotherapy or immunosuppressants; organ transplant recipients and donors; people with thalassaemia or haemophilia; healthcare professionals; and individuals with cryptogenic hepatitis.

In HD patients, the reported prevalence ranges from 0% to 58%.[14–25]

Risk of reactivation

Cases of reactivation have been described in patients on immunosuppressants, mainly with rituximab.

HBV reactivation has been identified in patients co-infected with HBV/HCV on treatment for HCV with direct-acting antivirals (DAA). Several authors warn about this and insist on monitoring HBV load to start early antiviral therapy.

The Food and Drug Administration (FDA) published information warning on the possibility of reactivation of HBV in subjects co-infected with HBV/HCV and receiving treatment with DAA.[26] A recent meta-analysis[27] evaluates the risk of reactivation in patients who received therapy based on DAA or with interferon (IFN). The HBV reactivation rate in patients who were HBsAg-negative and anti-HBc positive was 0.6% for those who received DAA and 0% for those who received IFN; none of these patients had an outbreak of hepatitis in relation to virus reactivation. The authors conclude that the reactivation rate is lower in patients without HBsAg, while stressing the importance of preventive treatment to avoid reactivation.

Another recent study[28] investigated the risk of reactivation of HBV during follow-up of 108 patients with resolved HBV infection treated for chronic hepatitis C; no replication or seroconversion of the HBsAg was detected.

Some authors postulate that the rapid suppression of HCV viral load with DAA boosts HBV replication, while others consider that, the IFN exerts an antiviral action against HBV.

The reactivation may result in the reappearance of hepatitis ranging from acute or fulminant to various forms of chronic infection, including asymptomatic carriers, chronic hepatitis, cirrhosis and hepatocellular carcinoma.

It has been clearly established that in patients with OBI the objective should be to prevent reactivation. There are recommendations from the European[29] and American[30] Gastroenterology Societies and the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) [Spanish Agency of Medicines and Medical Devices] for treatment in patients who are going to receive immunosuppression.

These same recommendations are valid for patients on the kidney, heart or lung transplant lists, and they should also be tested for HBV serology to rule out OBI.[31,32] In kidney transplant recipients since they are on immunosuppressive therapy, it is recommended that, although HBsAg−/anti-HBc+ patients have a low risk of developing HBV reactivation, HBV viral load should be determined. If it is detectable, prophylaxis should be given as if it were HBsAg+; if the viral load is negative, monitoring of transaminase, HBV DNA and HBsAg is recommended to detect reactivation early, and, if close monitoring cannot be guaranteed, indefinite prophylaxis with lamivudine is recommended. The risk of developing *de novo* HBV infection after receiving a kidney transplant from an anti-HBc+ donor in unprotected patients is very low, and systematic

prophylaxis is not indicated, but it is recommended monitoring of transaminases and HBsAg.[33]

Detection of OBI

There is no question that patients on HD who are already taking or are going to receive immunosuppression therapy need to be tested for OBI with the same criteria as in the general population, and that means requesting viral load. In patients who will not receive immunosuppression, the SEN (Sociedad Española de Nefrología [Spanish Society of Nephrology]) Guidelines on viral diseases recommend in the initial study of HBV with anti-HBc and DNA determination to rule out the window period. It is necessary to determine real time quantitative PCR to detect low viral load levels.

Until now, patients simultaneously positive for anti-HBc and anti-HBs IgG were considered protected and not contagious, but that is not what is being described in cases of OBI. In one of the published series with the largest number of patients, surprisingly, almost half of the cases were patients significantly positive for anti-HBs. The titres observed in this subgroup of patients with OBI were in the considered protection range (median 155 [40–396] IU/mL).[12] Therefore, based on what has been published, the risk is associated to a positive anti-HBc and the protection of anti-HBs does not seem safe in these patients.

Would periodic HBV viral load testing be justified for all HD patients to check for seropositive or seronegative OBI? That is a difficult question to answer because of lack of evidence. In seronegative patients the best practice is to follow guidelines recommendations regarding vaccination and periodic serology determinations. Since the OBI cases described are mostly seropositive patients, in our centre, based on the detection of cases reported at the 2016 SEN Congress in Oviedo,[34] viral load determinations are currently performed in all anti-HBc-positive patients, regardless of the anti-HBs levels, when they start HD and every 3 months. The extremely low viral load described may fluctuate and sometimes is undetectable, and therefore it is advisable to perform several determinations. Monitoring of liver enzymes does not seem to be related to the detection of OBI, and monitoring of diagnosed liver disease according to aminotransferase levels in patients with HD is difficult; uraemia could reduce inflammatory responses in the liver and, consequently, there would be no hepatocyte destruction.[35]

Risk of spread and transmission

There is no clear information about the risk of transmission in patients with OBI. There are published cases of transmission from blood transfusion with OBI from the 1970s and later, in chimpanzees inoculated with sera from HBsAg-negative individuals.[36,37] It has been reported that the risk of transmission of HBV infection in liver recipients from donors HBsAg-negative and anti-HBc-positive serological profiles is reported as 17–94%,[38] but there is no data about transmission in HD centres or among other groups affected.

In our HD units during the recent years, there has not been new cases due to HBV transmission. The measures recommended by the guidelines regarding viral diseases are being followed, but guidelines make no recommendations on testing for OBI and few authors in Spain have reported results on this subject; there are two publications with totally opposing figures; one from 1997,[14] with HBV DNA detection by PCR in serum and peripheral blood mononuclear cells in a small group of patients and HD staff, with a prevalence of 58%; a second report is from 2005,[16] from a hospital, with a prevalence of 0%.

The fact that there is very limited information on the prevalence of OBI or cases of infection in our HD units poses a number of questions, including whether or not we should isolate these patients, because even if the viral load is low, there is still a potential risk of transmission.

Nevertheless as today there is no evidence to support the need of isolation of these patients and it is a measure that could generate financial and organisational problems for the centre and negative psychological influence to the patient.

HBV vaccination

One aspect not mentioned but worth to consider is the issue of vaccination: if the majority of patients are protected with a safe anti-HBs titre, the hypothetical risk of contagion by OBI cases should be preventedavoid

According to the data from the PIBHE study,[5] 27.2% of patients on HD had not been vaccinated. A considerable percentage of patients with prior contact with HBsAg– anti-HBc+ HBV lacked anti-HBs and had not been vaccinated (33.8%); these patients are more likely to have immunity due to immunological memory and, they are also at greater risk of reactivation in a situation of immunosuppression, so it is important to be vaccinated.

The Working Group on vaccination in Adult Population and Groups at Risk[39] recommends for in renal patients serological monitoring to ensure seroconversion and annual determination of HBsAg if there is no response.

Our opinion is that it is really important to actively insist on the recommendation for vaccination,[40] in the initial stages of the disease to improve the immune response. We consider that HD patients need to be immunised; novel drugs and treatments are being used and undoubtedly they are beneficial, but can make certain subjects potentially contagious.

Conclusions

Many aspects of OBI are still not fully understood and require clarification. It would be helpful to know the actual prevalence in our HD units and its relationship with possible cases of reactivation or transmission. Without ignoring that the most important recommendation to prevent transmission is to comply with Universal Precautions, in cases of OBI it would be helpful to have common guidelines. We suggest to the Virus Group of the Spanish Society of Nephrology (SEN) to conduct studies aiming identify the actual prevalence of OBI among our patients and reach a consensus on recommendations for detection, monitoring and management of these patients.

Recommendations for the detection of OBI and approach in HD units based on the opinions of this group:

- Determination of HBV viral load in all anti-HBc patients (considered a sentinel marker by the Taormina group), at the initiation of haemodialysis in incident patients, and at least once a year in prevalent patients.
- Determination of HBV viral load in all anti-HBc-positive patients that are going to receive cytostatics, immunosuppressants, monoclonal antibodies or immunomodulators in general, establishing a frequency of at least quarterly for viral load testing during the treatment period, and monthly monitoring of transaminases.
- Determination of HBV viral load in all patients on DAA therapy for HCV who are anti-HBc-positive at the start of treatment, and repeat testing in the middle of treatment, at 6 weeks (since the FDA warns about the risk of reactivation at 4–8 weeks).
- If OBI is detected, we do not universally recommend patient isolation, but it is recommended to refer to Gastroenterology and start treatment as soon as possible to neutralise DNA and prevent reactivation. If treatment cannot be started and the patient is at risk of reactivation due to immunosuppressive therapy, isolation could be indicated until DNA is neutralised.
- Always follow the recommendations for vaccination against HBV in the Clinical Guidelines and ensure strict compliance with Universal Precautions.

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