



Occult Hepatitis B and Other Unexplored Risk Factors for Hepatocellular Carcinoma in Latin America

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ABSTRACT

Occult hepatitis B infection (OBI) is the presence of hepatitis B virus (HBV) DNA in the liver and/or serum (< 200 IU/mL) in HBsAg-negative patients with or without serologic markers of previous viral exposure. The clinical significance of OBI is of concern in post-transfusional hepatitis B infection, hepatitis B reactivation, chronic liver disease and hepatocellular carcinoma (HCC). The diagnosis of OBI relies on the use of highly sensitive and specific laboratory techniques. Herein, comments derived from a study analyzing the frequency and characteristics of OBI in HCC Japanese patients are stated. While OBI and other causes of HCC have been highly studied in Asia and Europe, research in Latin America in these topics is limited. Several findings such as population risk groups with high prevalence of overt and OBI infection, HBV genotype F in Argentinean HCC patients, and the clinical impact of the foreign A-D genotypes suggest the need of further investigation. Additionally, alcoholism, obesity, NASH and type 2 diabetes may override the presence of OBI. Therefore, OBI diagnosis is essential. It is known that anti-HBc alone is a predictive signal of potential OBI and given the fluctuations of the HBV infection markers, testing for HBsAg and anti-HBc at baseline and follow-up is recommended. In conclusion, OBI and other causes involved in the epidemiology of HCC in Latin America are unexplored risk factors. Genome-based research is required to decipher the role of gene-environmental interactions associated with chronic liver disease. Novel algorithms to detect OBI supported by basic/applied/clinical research are also needed.

Key words. Risk factor. Epidemiology. Hepatocellular carcinoma. HBV genotypes. Diagnostics.

Occult HBV infection (OBI) refers to the appearance of HBV DNA in the liver and/or serum (< 200 IU/mL) in HBsAg-negative patients with or without serologic markers of previous viral exposure.^{1,2} OBI constitutes a phase of chronic hepatitis B infection in which replication-competent viruses are actively suppressed by genetic, epigenetic and post-transcriptional mechanisms.¹ The clinical significance of OBI is of concern in risk patients coursing with post-transfusional hepatitis B infection, hepatitis B reactivation, chronic hepatitis, and hepatocellular carcinoma (HCC).^{1,2}

One of the main challenges for the management of OBI is the diagnosis. The detection of both HBsAg and HBV DNA is substantially reliant on the availability of highly sensitive and specific serological and molecular techniques, respectively. Worldwide, the performance of these diagnostic assays varies widely, thus, affecting the rate of

prevalence of OBI among distinct risk groups.³ Consequently, conventional criteria and standardized protocols for the detection of serum/liver HBV DNA were agreed (Taormina meeting, 2008).² Thus, it was suggested that OBI positivity is confirmed by using nested polymerase chain reaction (PCR) primers annealing within at least two of the four open-reading frames of the HBV genome (S,C,P,X).

In this issue of *Annals of Hepatology*, Muto, *et al.* published the incidence and characteristics of OBI among 75 Japanese patients with HCC.⁴ In this study, OBI was detected in 38% of cryptogenic and 25.6% of hepatitis C patients with no other detectable risk factors (alcohol, steatosis), by using a highly sensitive, in-house PCR detection system for total HBV DNA and covalently-closed circular (ccc) DNA. Other HBV markers (HBsAg, anti-HBs, anti-HBc, Anti-HBe) were also measured.

The authors concluded: "There was no correlation between OBI and anti-HBV antibodies, but fewer patients with OBI [compared to the non-OBI cases] had, high inflammatory activity, suggesting that factors other than inflammation may be involved in HCC carcinogenesis in patients with OBI." This data suggests that the characteristics of OBI involved in HCC pathogenesis are variable; thus, creating the need of novel research and comparative analysis of the multiple risk factors interacting among different populations.

One starting point of analysis is the global variances in the prevalence pattern of HCC. Estimates show that the age-adjusted incidence rate (AAIR) for HCC (all causes combined) is relatively low in the North and Latin America (LA) (1.5-3.0/100,000) compared to Eastern Asia (27.6 to 36.6/100,000).⁵ One may ask what fraction of HCC is attributable to OBI. Another overlapping factor is the role of HBV genotype on the global epidemiology of OBI given their differential distribution among Asia, Europe and LA (B and C, A and D, F and H, respectively), as well as the degree of endemicity.³ Further analysis would lead us to ask, how much data do we have on OBI from each of these regions. In agreement with the prevalence of HCC, statistics on OBI is more abundant in areas with higher overt hepatitis B infection rates and less in lower endemic localities.^{3,6} In contrast, in LA, a region with a diverse prevalence pattern of hepatitis B infection,^{7,8} there have been relatively few articles published in the last decade (2008-2018) related to OBI per country. OBI has been studied in native populations, blood donors, chronic hepatitis B and C patients, HIV patients, hemodialysis and pediatric patients.⁸ Nonetheless, in regards to HCC and hepatitis B infection (overt or occult), this association is ultimately unexplored in LA, compared to Asia and Europe. This drawback may be due to limited in-depth research, lack of monitoring, the absence of high-sensitive detection assays, and unawareness among the medical community. Therefore, research aimed to diminish these limitations is warranted. In the case of Mexico, several studies have been performed to seek insight concerning the low incidence of HBV-related HCC. To date, it has been proposed that the endemic HBV genotype H may have imposed genetic adaptations on the host favoring a prompt suppression of HBV replication promoted by ethnic-related immune mechanisms.^{7,8} Environmental factors could be the alkaline neutralization of potentially aflatoxin-contaminated maize-derived food products, reducing the risk of HCC regardless of the high prevalence of past infection (anti-HBc).⁹ Other reasons may be the premature death of patients with liver cirrhosis before the detection of HCC. Nonetheless, these explanations may not apply to all countries alike because each may have its own set of risk factors.

Several reasons justify the need to study the risk factors involved in HCC in LA. One such evidence is the high OBI status among Mexican natives in high endemic regions (as in South America with HBV genotype F), blood donors, and patients with HIV or chronic liver disease.^{8,10} Additionally, the finding of genotype F (overt infection) in HCC cases in admixed populations of Argentina (or in others of Spain and Alaska) but not in South American natives reveals differential gene-environmental interactions.⁷ On the other hand, the influence of the non-endemic HBV genotypes A and D, (commonly found in European OBI cases) or of HBV genotypes B and C (related to the high rate of HCC in Asia) among the current population of LA requires further investigation. Other co-morbidities that override the presence of OBI are alcoholism, obesity, NASH and type 2 diabetes may impose further undetected liver damage.⁸ Therefore, OBI diagnosis is essential. It is known that anti-HBc alone is a predictive signal of potential OBI and given the fluctuations of the HBV infection markers, testing for both HBsAg and anti-HBc at baseline and follow-up is recommended.^{1,10,11}

In conclusion, the role of OBI and other causes involved in the epidemiology of HCC in LA are still unexplored risk factors. Genome-based research is required to decipher the role of genetics and interacting environmental risk factors in association with the natural history of HBV infection (including OBI) among the populations of LA, as well as the influence of other etiological agents that may cause chronic liver disease. Novel algorithms to detect OBI supported by basic/applied/clinical research are also necessary.

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