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OCCULT HBV INFECTION

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Resume. The review is devoted to terminology, causes of development, epidemiology, and clinical significance of occult HBV infection (OVI). Attention is focused on the differences in the definitions of OVI given by the European, American and Asian-Pacific Associations for the Study of Liver Diseases. Modern data on various types of mutations that can lead to the development of OVI are presented. The issue of the presence of specific mutations that distinguish OVI from other forms of HBV infection, in which the hepatitis B virus antigen (HBsAg) may not be detected, is being discussed. The importance of OVI patients as sources of infection in transplantology and transfusiology is considered. Much attention is paid to the possibility of OVI reactivation in patients with immunosuppression, as well as in cases of coinfection with hepatitis C and HIV viruses. Data on the possible role of OVI in the development of liver cirrhosis and hepatocellular carcinoma are presented.

Keywords: occult HBV infection; HBsAg; mutation; epidemiology; liver cirrhosis; hepatocellular carcinoma.

The importance of determining the hepatitis B virus antigen (HBsAg) in clinical practice cannot be overestimated. In fact, this is the most reliable marker indicating the presence of HBV infection in a patient, and, along with the detection of antibodies to the core antigen of the virus (anti-HBc), the determination of HBsAg is widely used as the first test if a patient is suspected of having hepatitis B.

HBsAg is the main envelope protein and includes regions responsible for virus attachment to hepatocytes, as well as the main epitope recognized by neutralizing antibodies (determinant "a" containing two amino acid loops 124-147). Determinant "a" is located in the core of HBsAg, called an even larger hydrophilic region [1]. Mutations of the virus in the PreS/S region of the genome alter the "a" determinant in such a way that HBsAg ceases to be detected using commercial test systems ("eluding diagnosis" of the mutant virus) or is capable of causing infection in those immunized with a vaccine or the introduction of a specific immunoglobulin ("vaccine-eluding" mutant virus). Another consequence of the mutation in the PreS/S region may be the development of occult HBV infection (OVI), which will be the focus of this review.

In a broad sense, OVI is defined as an infection caused by the hepatitis B virus, in which HBsAg is not detected in the blood, and the DNA of the virus can be detected either in blood serum or in a liver biopsy [2, 3]. If antibodies to HBsAg/HBcAg are detected, this form of OVI is called seropositive. If antibodies cannot be detected, they are seronegative [4]. Some authors call the seropositive variant secondary OVI, and the seronegative variant primary [5]. Such a pathogenetic approach to classification is not always supported by anamnestic data: most patients with both primary and secondary acute respiratory viral infections do not have a history of overt HBV infection. In this regard, "seropositive" and "seronegative" are more acceptable terms that characterize at least the diagnostic features of these two forms of OVI. According to M. Torbenson et al., who summarized a large number of literature data, the

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secondary or seropositive form of infection is more common, accounting for 78% of all OVI cases [5].

It is believed that the development of OVI is based on HBV mutations, which lead to a decrease in the replicative ability of the virus as a whole or only to a violation of S-protein synthesis [6]. A good argument in favor of this hypothesis is the low viral load recorded in most patients with OVI: almost all patients (about 90%) have a viral load of less than 20 IU/ml [7, 8]. Therefore, in most cases, the presence of OVI can only be confirmed using highly sensitive test systems or in the material obtained by biopsy of liver tissue [6, 9-11]. Since the ratio of subviral particles (HBsAg) to virions (HBV DNA) is 1000 to 100,000, the low replicative activity of the virus a priori results in an extremely low concentration of HBsAg or its complete absence in peripheral blood [12].

Svicher et al. 20 mutations (Y100S, Q101R, P105R, T115N, T116N, P120L, R122P, T123N, T126I, P127H/L, Q129P, M133T, Y134C, S143L, S167L, R169H, S174N, L175S, V177A) were described, mainly in the "a" determinant of the PreS/S gene, the frequency of which was strictly correlated with the presence of OVI in patients infected with genotype D virus [16]. Interestingly, in patients with OVI caused by genotypes B and C of the virus, the most frequently detected mutation was G145R/A, while those listed above practically did not occur [13-15]. This confirms the hypothesis that OVI-associated mutations are unique for each genotype of the virus [14].

These mutations are considered to be the cause of OVI on the grounds that they are more often detected in patients with OVI than in patients with other (clinically obvious) forms of HBV infection (in 8.3-20.8 and 0-3.7% of cases, respectively) [16]. And although mutations can be detected in no more than 20.8% of OVI patients, this does not mean that they are absent in the rest of the patients: only a limited part of the virus genome is examined for mutations, therefore, it is impossible to guarantee the absence of mutations in the region that has not been studied.

The cause of OVI may be other mutations other than those described above. For example, a C695T nucleotide mutation leads to the formation of a stop codon. In such patients, HBsAg production is sharply reduced and, consequently, its detection in the blood is difficult [17]. It has recently been shown that deletions in the Pre-S region can also play an important role in the development of OVI, as they affect the expression, synthesis, and secretion of S-protein [18]. Since the polymerase gene of the virus is completely overlapped by the S-gene, mutations of the first one that have arisen under the influence of antiviral therapy can cause secondary mutations of the S-protein, thereby reducing its antigenic properties [19-23].

Some authors attribute cases of the disease caused by the HBV mutant virus that "eludes diagnosis" to OVI [9]. The most common mutations that make it impossible to detect HBsAg using 7 known commercial test systems are amino acid substitutions at positions C124R, C124Y, K141E, or D144A of the main hydrophilic region [13]. Another 10 known mutations (G119R, C124Y, I126S, Q129R, S136P, C139R, T140I, K141E, D144A, G145R) reduce the secretion of virion and/or S-protein in vitro.

Other researchers identify OVI with infection by "vaccine-elusive" viral mutants. The first and, as it turned out later, the most common mutation of this kind is the replacement of

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arginine with glycine at position 145 (G145R) [24]. This mutation is stable over time, and such a virus can also be transmitted horizontally [25, 26]. Other substitutions in the "a" determinant have been described, characterized as "vaccine-elusive" mutations (T116N, P120S/E, I/T126A/N/I/S, Q129H/R, M133L, K141E, P142S, D144A/E, G145R/A) [27]. Far from all "vaccine-elusive" mutations are "elusive from diagnosis," however, primarily among vaccinated subjects, the replicative activity of the mutated virus may be low, which makes it difficult to diagnose infection by determining HBsAg. A low viral load in about 20% of patients may result in a lack of an immune response to infection in the form of antibody formation (obviously, this is a seronegative form of OVI) [28, 36]. It would be wrong to discount the genetically determined features of the immune response to infection as the cause of the development of chronic forms of HBV infection, and OVI in particular. Gene polymorphism, primarily in the HLA DP region, may result in more frequent development of chronic forms of HBV infection, determine disease activity and the possibility of HBsAg clearance [29-31].

Such a broad interpretation of the causes of OVI (a specific mutation, "eluding diagnosis", "eluding vaccination" mutations) is reflected in the very significant differences in the definition of OVI, which is given to this form of infection by various hepatology manuals.

So, in the latest edition of the guidelines of the European Association for the Study of the Liver (EASL) OVI is considered as the 5th phase of HBV infection, calling it HBsAg-negative [32]. Thus, it is assumed that OVI is one of the possible outcomes of chronic HBV infection. It is emphasized that in some patients, the absence of HBsAg may be due to the use of insufficiently sensitive detection methods [33]. The presence of antibodies to HBcAg (anti-HBc) is mandatory, and antibodies to HBsAg (anti-HBs) are optional. HBV DNA is usually, but not always, absent in serum, but it can be detected in a biopsy sample as integrated circular covalently closed DNA (cccDNA) [34]. Thus, according to these guidelines, OVI is either the outcome of a chronic infection or the result of a virus mutation that "eludes diagnosis," which is obviously far from the same thing.

According to the definition of the Asia-Pacific Association for the Study of the Liver (APASL), occult hepatitis is considered to be cases when HBsAg is not detected by most commercial test systems [35]. In this regard, the occult form is not considered as an exclusively final phase of infection (as in the EASL guidelines). The authors identify three variants of OVI. The first is when patients have recently been infected and HBV infection is in the so—called window period. HBsAg is no longer detected in the blood. Some patients will be classified as having a past infection upon follow-up, while others will have a chronic HBV infection. The second variant (the so-called primary OVI) is diagnosed in patients who had no history of HBsAg being detected. The third option is OVI in patients with documented chronic HBV infection who have spontaneous clearance of HBsAg. Up to 50-60% of such patients are positive for anti-HBs.

As for the Guidelines of the American Association for the Study of Liver Diseases (AASLD), the latest edition does not mention occult hepatitis, and the penultimate version only mentions it as a variant of the disease course in HBV/HIV coinfected [36, 37].

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Since the formal definition of OVI as the absence of HBsAg in the presence of DNA in serum or liver biopsy includes a fairly wide range of clinical conditions, it is not surprising that data on the prevalence of OVI in the world vary widely (from 1 to 87%) [38, 39].

G. Escobedo-Melendez et al., who conducted a study in Mexico, where the H HBV genotype prevails, identified OVI in 87% (!) children with clinical criteria for hepatitis (hepatomegaly, fever above 38 °C and/or jaundice with elevated serum transaminase levels (AST > 38 IU/L, ALT > 35 IU/L)). However, in fact, we are talking about a sample of 215 patients with a hepatitis clinic, 24 of whom were diagnosed with HBV infection (11.2%), including 21 of them (this is the desired 87.5%) with OVI. Moreover, it should be noted that occult infection was not always the cause of clinically obvious hepatitis: 54% of HBV-positive children (13 people) had markers of acute hepatitis A.

In China, where the prevalence of OVI is expected to be higher, HBV DNA was detected in 45.5% of the examined patients who had HBV infection caused by genotypes B or C of the virus [40, 41]. In South Korea, the rate of those infected with genotype C was significantly lower — 1.7–6.6% [42]. In Taiwan, OVI is detected in 10.9% of children vaccinated against hepatitis B and 0.11% of donors [43, 44]. In Egypt, among patients undergoing hemodialysis, its prevalence varies from 4.1 to 26.8% [45]. An interesting study from the USA, where in a sample of 487 people the frequency of seropositive forms of OVI was 18%, seronegative forms - 8.1%. However, these rather high figures for the United States should not be surprising, since the study was conducted in the Innuit community (one of the northern peoples), where the prevalence of HBV infection is traditionally high [39].

In the European region, the incidence of OVI is likely to also be proportional to the prevalence of HBV infection. For example, in Italy, a country with one of the highest levels of HBV infection, markers of past infection are detected in 8-9% of primary blood donors. When analyzing a representative sample (31,190 primary donors), L. Romano et al. 100 HBsAg-positive, anti-HBc-positive patients (0.32%), 2 HBsAg—positive patients (0.01%), and 2,593 anti-HBc-positive patients (8.3%) were identified [46]. Among the latter, 86.7% also had anti-HBs (with or without anti-HBe). HBV DNA was detected in 96.8% of HBsAg-positive patients and only in 0.55% (12/2186) anti-HBc-positive/HBsAg-negative, with a higher frequency among anti-HBs-negative than anti-HBs-positive subjects (1.68 vs. 0.37%; $p < 0.01$). The viral load was significantly higher in HBsAg-positive patients than in HBsAg-negative patients (median 456 IU/ml versus 38 IU/ml). The authors estimate the prevalence of OVI as low (1 in 2,599 blood donors), although in fairness it should be noted that they did not estimate the frequency of OVI among anti-HBc-negative donors.

In Denmark, the frequency of OVI among donors is extremely low and continues to decrease. Screening of 4.4 million blood samples identified 23 patients with OVI (1 : 191 304). The authors note that the low viral load allowed the identification of the virus genome in only 14 of the 23 donors. The authors identified 4 types of OVI in these patients: early stage infection (before the appearance of HBsAg), infection that developed after vaccination, infection caused by genotype G virus with reduced HBsAg production, and chronic OVI. Donors with OVI caused by genotype D of the virus demonstrated numerous "elusive" HBsAg mutations in the "a" determinant and CTL epitope, while no mutations were detected in OVI caused by genotype A [47].

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Evaluating the data provided, it is necessary to pay attention to some patterns. Firstly, the incidence of OVI is higher in those regions where the prevalence of HBV is higher (South-East Asia, North Africa, Southern Europe). Here, the frequency of "elusive" mutations of both types is higher, if we still assume that the infection caused by them is one of the forms of OVI. Secondly, the possibility of diagnosing OVI directly depends on the sensitivity of the test systems used (i.e.— their availability), since 90% of OVI patients have a viral load of less than 20 IU/ml [7, 8]. Thirdly, the definition of a virus mutation that would help determine the OVI variant is currently available exclusively in scientific research and cannot be used in everyday practice.

The clinical significance of occult infection is the subject of constant study and is periodically updated with new data. Since classical OVI is by definition a low-replicative form of infection, clinically manifest forms of infection are unlikely. First of all, we are talking about truly occult forms of the disease, when the patient does not know about the presence of an infection and the diagnosis is established, if at all, then by chance, during laboratory examination. It is unclear whether OVI can lead to the development of CP or be the cause of HCC, but there is no doubt that patients with OVI are potential sources of infection. Therefore, OVI is currently primarily a problem of transfusiology and transplantology.Exclusion of anti-HCv-positive patients from the list of donors significantly reduces the risk of infection, but it cannot exclude it at the expense of patients with seronegative forms of infection. In this regard, attempts have been repeatedly made to use polymerase chain reactions (PCR) for screening donated blood [36]. The widespread use of this method is usually limited by its high cost and is unacceptable for countries with limited financial resources. On the other hand, the use of PCR in transplantation for screening donors may be economically feasible. In general, if we consider the situation in relation to our region, we should assume that the risk of infection from a blood transfusion from a patient with OVI is purely theoretical. This is due to two reasons. Firstly, Ukraine does not belong to countries with a high level of hepatitis B infection, and, as mentioned above, the incidence of OVI is proportional to the prevalence of other forms of HBV infection. Secondly, as noted above, 80% of patients with OVI are anti-HCv-positive. In Ukraine, unlike in many other countries, donated blood is tested for anti-HCv and such individuals are excluded from donation. Therefore, potential sources of infection can only be seronegative donors with OVI, the number of which should be very small.

There is also no doubt about the possibility of reactivation of occult infection with the development of immunosuppression, most often iatrogenic. In this regard, all anti-HCv-positive patients receiving immunosuppressants should be monitored for possible reactivation of hepatitis B. There are no precise recommendations regarding the timing, frequency of follow-up and methods used to control reactivation, which is mainly due to the lack of a clear definition of the cost of monitoring and its benefits.

The cause of reactivation of HBV infection in patients coinfected with hepatitis B and C viruses may be the successful treatment of hepatitis C with direct-acting antiviral drugs (PPD). In a study by S.J. Bersoff-Matcha et al. data on 24 cases of HBV infection reactivation in the treatment of chronic hepatitis C (HCV) are summarized PPD [48]. The data source was the FDA side effects database (FAERS) with a search depth of 11/22/13 — 07/18/16. The authors defined the case of reactivation as an increase in the viral load of HBV DNA or the appearance of HBsAg in previously ill (read — patients with occult

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infection). Most often, reactivation occurred during the first 4-8 weeks of treatment. In 2 cases, it caused death, and in one case, urgent liver transplantation. 6 patients required hospitalization. In 10 patients, reactivation caused the discontinuation of PPD therapy. The risk of reactivation was in no way related to the HCV genotype, the clinical form of HBV infection preceding the onset of HTP, or the combination of antiviral drugs used to treat HCV. Before starting treatment, HBV DNA was detected in 7 patients, 4 patients were HBsAg-positive, HBV-negative, and three had neither HBsAg nor HBV DNA. In all other cases, the initial status of HBV infection was unknown or the available data could not be interpreted. Thus, the frequency of reactivation of occult infection in this study was very significant (12.5%).

In another, larger study, C. Wang et al. An attempt was made to establish the risk of reactivation of HBV infection in a cohort of 327 HCV patients treated with PPD (SOF + DCV; PrOD; LDV/SOF) in a highly endemic hepatitis region in China [49]. The study on hepatitis B markers revealed 10 HBsAg-positive patients and 124 patients with occult HBV infection among them. Active hepatitis (the criterion was a 2-fold increase in transaminase activity) developed in 10 patients (3.1%) treated with PPD, but in only 3 cases it was associated with reactivation of HBV infection (all previously HBsAg-positive patients: 1 case without jaundice, 1 with jaundice and 1 case with development of fulminant hepatitis). In the remaining patients (7 cases), alcohol and traditional Chinese medicine drugs were the cause of hepatitis. The authors found that the presence of HBsAg before starting PPD therapy was a strong predictor of HBV infection reactivation (risk ratio 15.0; $P < 0.001$). No reactivation was recorded in any patients with occult HBV infection.

This study, unlike the first one, seems to negate the importance of occult infection as a risk factor for hepatitis reactivation in the treatment of PPD. However, the problem lies in the fact that the authors of the study do not provide criteria on the basis of which this form of the disease was diagnosed. Moreover, in the same article, they characterize these patients as patients with past infection, implying that they lack HBsAg and have antibodies to HCV. The article does not contain any indication of the isolation of HBV DNA from the blood or liver biopsy of these patients.

In general, summarizing the data presented, it can be considered that reactivation of occult infection is possible, although unlikely, in the treatment of hepatitis C PD in coinfected patients. Nevertheless, monitoring of reactivation should be carried out. And if everything is clear for patients with overt HBV infection (according to the latest edition of the AASLD guidelines, they need to monitor their viral load every 4 weeks during treatment with hepatitis C PD), then for patients with pastinfection, they are only encouraged to remember about the theoretical possibility of reactivation and, in case of an unexpected increase in transaminase activity, conduct a serum test for HBV DNA [50].

The risk of reactivation of HBV infection in patients receiving immunosuppressive therapy is disproportionately higher [51-55]. It depends on the underlying disease, the type and duration of immunosuppressive therapy. The risk is particularly high and is estimated at 21-67% in patients with oncohematological profile who have undergone stem cell transplantation or who are receiving biological drugs such as anti-CD20 monoclonal antibodies (rituximab) or anti-CD52 (alemtuzimab) [52, 56-59]. The probability of death due to reactivation of HBV infection in such patients is about 20% [60, 61]. The risk of tumor

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chemotherapy is somewhat lower, but it is significant if the combined treatment regimen includes glucocorticoids. The latter affect the glucocorticoid-sensitive receptors of the virus, enhancing the production of HBeAg and the expression of DNA and i-RNA of the virus by stimulating HBV transcription [62, 63]. The frequency of reactivation after cycles of chemotherapy, including and not including corticosteroids, is 47 and 8%, respectively. Severe course of the disease is observed in 10-22% of cases. The mortality rate ranges from 4 to 41% [64-66].

Since cytolysis in HBV infection is immuno-mediated, clinically significant reactivation (with the development of active, including fulminant hepatitis) is most often observed after discontinuation of immunosuppressive therapy, when the body returns to an immunocompetent state [67-70]. This dictates the need to use preventive antiviral treatment not only during chemotherapy, but also after its termination.

According to the EASL guidelines, patients with suspected past infection should be screened for HBV DNA in their serum by PCR before starting immunosuppressive therapy [35]. In the presence of viremia, antiviral therapy should be initiated, as well as in patients with overt HBV infection. In the group of patients with a high (more than 10%) risk of reactivation (this includes anti-HCv-positive patients who are to be treated with rituximab or alemtuzimab or stem cell transplantation), preventive antiviral treatment should be prescribed regardless of the presence of viremia and should last at least 18 months after discontinuation of biological or chemotherapy, followed by monitoring of reactivation. within 12 months [71-73]. In patients with a lower risk of reactivation, HBsAg and/or HBV DNA should be monitored every 1-3 months. The most likely event is HBsAg seroconversion or the appearance of HBV DNA, which is accompanied by hepatitis reactivation (increased transaminase activity) in about 50% of patients [74]. In this case, antiviral therapy should be initiated immediately, regardless of the level of transaminases, as the risk of developing fulminant hepatitis is very high. Reactivation of HBV infection in patients with OVI is accompanied by the appearance of HBsAg and a high viral load. Timely initiation of antiviral therapy may result in the disappearance of HBV replication markers, the disappearance of HBsAg, and the appearance of anti-HBs [74].

With much less certainty, we can talk about the role of OVI in the development of CP and HCC. Most studies have shown that almost all patients with OVI have normal serum transaminase levels, and biopsy shows no or minimal signs of necroinflammatory activity and fibrosis [75, 76]. However, the available data do not allow us to completely exclude the role of OVI in the development of liver cirrhosis and HCC. It is possible that the mentioned mild but persistent liver inflammation and the proven oncogenic potential of HBV can be attributed to the mechanisms that increase the chances of developing HCC [77]. OVI, as a possible cause of the development of these conditions, is well documented in patients with hepatitis C virus coinfection [78], and the established incidence of OVI in patients with cryptogenic CP varies from 4.8 to 40% [79, 80]. Evidence of the connection between HCC and OVI can be found in studies in which the HBV gene was detected in 45-80% of patients with an unidentified cause of HCC in the liver [81, 82]. A meta-analysis of 14 separate studies demonstrated that OVI increases the chance of developing HCC by almost 9 times [83]. The fact that OVI accelerates the progression of the disease is evidenced by the data of H. Koga et al.: the average age of patients with HCC and OVI was lower than in patients with HCC alone (63.0 and 68.1, respectively; $p < 0.05$). Other risk factors for developing

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HCC were more common in patients with OVI and HCC than in the group of patients without OVI (p = 0.0057). However, the presence of OVI has no effect on survival after surgical treatment of HCC [84].

The frequency of OVI in patients with cryptogenic cirrhosis of the liver (CP) varies depending on the geographical region. Thus, in Iran it ranges from 14 to 38%, in India — 38%, in Italy — 23.4%, in Egypt — 2.7%, in the USA — 19.4%, in China — 32 and 3.88% [85-89]. However, the presence of OVI in a CP patient does not prove that OVI was the cause of its development. CP could have formed as a result of active HBsAg-positive hepatitis B, and only after that spontaneous elimination of HBsAg with the development of OVI occurred (the 3rd variant of the OVI development scenario according to the APASL guidelines). Although there are some studies indicating a possible role of OVI in the progression of the disease. For example, among HIV-infected patients who did not receive ART, the proportion of patients with APRI > 2 and FIB-4 > 3.25 was higher in the presence of OVI compared with HBsAg, DNA HBV-negative, and anti-HBc-positive patients [90].

Thus, OVI is one of the forms of chronic HBV infection caused by various mutations, mainly in the PreS/S region of the viral genome. Despite the fact that patients with "diagnostic-evading" mutations of the virus formally fall under the definition of OVI, the latter still refers to low-replicative forms of infection and is caused by other OVI-specific mutations. A distinctive feature of OVI is the extremely low viral load, not exceeding 20 IU/ml in 90% of OVI patients. The clinical significance of OVI patients is determined by the possibility of reactivation of HBV infection if such patients receive immunosuppressive therapy. Sometimes reactivation occurs many months after discontinuation of treatment with immunosuppressants, which necessitates long-term monitoring of reactivation in these patients. OVI patients can be a potential source of infection if they act as blood donors or, to a much greater extent, as organ donors. The latter circumstance is associated with the risk of reactivation of HBV infection in recipients of donated organs during immunosuppressive therapy aimed at preventing transplant rejection. The importance of OVI in the development of CP and HCC is assumed, but cannot be considered proven. In this regard, there are no recommendations supporting the need to prescribe antiviral therapy to such patients.

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