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Occult Hepatitis B virus infection in children

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ABSTRACT

Introduction. Occult hepatitis B virus infection (OBI) holds significant clinical importance, representing a unique phase of viral infection where HBsAg-negative individuals exhibit reduced viral DNA replication. This DNA may be undetectable or present in serum but is consistently found in the liver.

Materials and methods. A comprehensive review of the PubMed database, focusing on occult HBV infection in children from January 2013 to April 2023, was conducted.

Results. Out of 914 identified articles, 111 publications met the criteria for "occult HBV infection in children." During this phase, covalently closed circular DNA (cccDNA) exhibits low replication activity. The mechanisms underlying the suppression of HBV replication are associated with host immune responses and epigenetic factors. The prevalence of occult HBV infection in adults varies significantly across different geographic regions, influenced by risk factors for parenteral transmission and the sensitivity of assays used for detecting HBsAg and HBV DNA. Occult HBV infection in children is not well understood, with reported prevalence ranging from 20% to 54%. HBV transmission can occur parenterally, through blood transfusions, horizontal transmission, or liver transplantation, potentially leading to acute hepatitis. Reactivation can occur under immunosuppression, accelerating the progression from chronic hepatitis to cirrhosis, and contributing to the development of malignancies.

Conclusions. Occult HBV infection in children is a form of chronic HBV infection with a variable prevalence. Testing for anti-HBc is crucial for diagnosing hepatitis of unknown etiology in children, as it can help detect chronic HBV infection.

Keywords: HBsAg, occult HBV infection, cccADN

INTRODUCTION

Occult hepatitis B virus infection (OBI) is a specific phase of the viral infectious process, occurring in individuals negative for HBsAg with detectable HBV DNA in the blood at minimal or undetectable concentrations, where it persists in hepatocytes in the form of cccDNA (covalently closed circular DNA). During this phase, cccDNA exhibits minimal replication properties in the liver. Scientific research on the pathogenetic mechanism of HBV-induced viral processes and its replication suppression has demonstrated its dependence on host immune factors and the epidemiological and genetic factors of the virus, which can induce mutations in the pre-S or S gene [1-4]. These viral genomic mutations induce the synthesis of modified HBsAg that cannot currently be detected by sensitive commercial methods, while HBV DNA in these individuals can be present at very high concentrations in the blood, similar to those with positive HBsAg and viremia. HBV DNA also has the ability to integrate into the human genome; however, in this case, viral replication cannot occur, and the diagnosis of OBI is based on the presence of persistent replication components. Scientific studies demonstrate that HBV infection in humans can last throughout life, even in cases where viral replication is suppressed, and the absence of HBsAg in individuals with OBI alongside the presence of HBV cccDNA is considered an indication of suppression of viral replication as a result of the interaction of host immune factors and the epigenetic factors of the virus.

It is widely recognized that infection with the hepatitis B virus (HBV) can manifest in three clinical

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forms: acute viral hepatitis B (either icteric or anicteric), chronic viral hepatitis B (CVHB) characterized by persistent clinical symptoms and HBsAg, and long-term HBsAg persistence in the blood without characteristic clinical or paraclinical manifestations of hepatitis. HBV transmission can occur through various parenteral procedures involving inadequately sterilized medical instruments, blood transfusions, and liver transplantation. Under conditions of immunosuppression, the virus may undergo reactivation, leading to fulminant hepatitis, hastening the progression to cirrhosis in chronic cases of viral hepatitis B, or triggering the development of hepatocellular carcinoma [1,2]. The first documented case of post-transfusion HBV infection was reported in 1978, involving a recipient who received blood positive for anti-HBc antibodies but negative for HBs antigen and anti-HBs antibodies [4]. The scientific significance and practical importance of this phenomenon were confirmed in 1999 and subsequently in 2008 and 2018, with the publication of an article in the New England Journal of Medicine from Taormina, Italy, demonstrating the presence of the HBV genome in liver biopsies from individuals with chronic hepatitis C and negative HBs antigen [5]. Occult hepatitis B virus infection (OBI) was found in 20% of cases among gastroenterological patients with chronic liver diseases of unknown etiology [4]. In 2007, Castillo I. et.al. detected HBV DNA and HCV RNA in the liver tissue of 76 patients who were negative for HBs antigen, and presented with cytolysis syndrome while being followed up for 2 years [4,5]. OBI was confirmed in 22% of these patients, chronic infection with HCV in 46%, and occult coinfection with HBV and HCV in 32%, with both HBV DNA and HCV RNA detected simultaneously in liver tissue in 54% of cases [4,5]. OBI is classified into two evolutionary forms: seropositive (positive for anti-HBc antibodies and/or anti-HBs antibodies), observed in 80% of cases, and seronegative (negative for anti-HBc antibodies and anti-HBs antibodies), with HBV DNA detected solely in liver tissue [3-5].

Recent scientific research has shown that HBV DNA can be detected in the blood of individuals with chronic infection in very low amounts or in hepatic tissue in those who test negative for HBsAg. This occurrence is referred to as occult HBV infection [1-4]. During this specific phase of chronic viral HBV infection, when active replication is minimal and cccDNA is detectable only at the hepatic tissue level, HBV DNA in blood or plasma may not be detectable or may be present at very low levels (below 200 IU/mL) [4,5]. The prevalence of HBV infection via HBV DNA detection in blood varies in certain geographic regions and depends on the sensitivity of the diagnostic tests used and the population studies conducted.

The purpose of the research was to identify and systematize the scientific results obtained by researchers on the topic of occult viral HBV infection in children, with reference to the most recent studies and bibliographic sources published in this field, in order to justify the importance of the issue for public health.

MATERIALS AND METHODS

To achieve the purpose of the current research, a database search was performed on PubMed, focusing on publications between January 2013 and April 2023. The PubMed database was last accessed on July 7, 2023. The following keywords and terms were employed: (1) Occult Hepatitis B Virus (HBV) infection; (2) Occult HBV infection in pediatric patients; (3) Prevalence of occult HBV infection in children; (4) Diagnostic methods; and (5) Management strategies. Original articles were included, conference abstracts, and study projects relevant to the topic in both adults and children who tested negative for HBsAg but positive for HBV DNA (i.e., individuals with occult HBV infection). A total of 914 papers were identified after duplicate removal, of which 111 (12%) were selected from sources referring exclusively to children and adolescents (Figure 1). Of these, only 18 articles met the following criterion: "Occult HBV infection in children", which included meta-analyses and systematic review. A total of 267 papers were excluded from the analysis since these were not relevant to any of the criteria specified above. The results of scientific studies are pre-

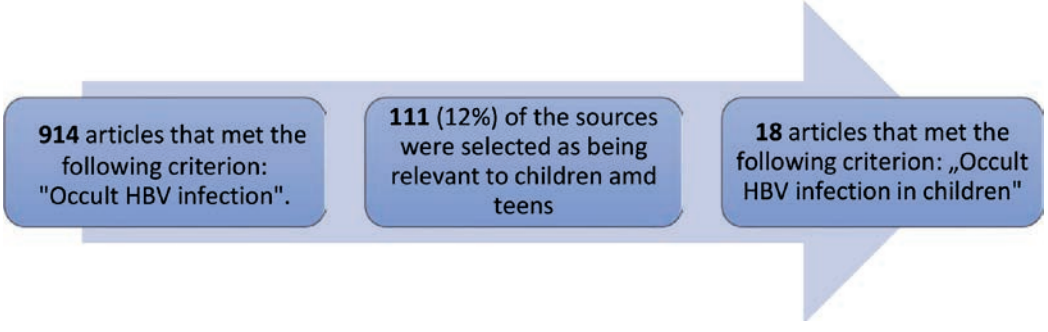

FIGURE 1. The algorithm for reviewing the PubMed database regarding pediatric HBV

sented in various sections, each containing a concise introduction to the addressed topic along with references derived from supporting evidence based on guidelines and other relevant studies.

RESULTS

Viral hepatitis B (HBV) is an infection induced by the hepatitis B virus, which affects the liver and is one of the most significant health issues, both in adults and children worldwide. According to the World Health Organization (WHO), in 2019 approximately 296 million people were chronically infected with HBV, characterized by the presence of HBsAg [6]. WHO estimates suggest that in 2019, hepatitis B resulted in around 820,000 deaths, primarily due to hepatic cirrhosis and hepatocellular carcinoma. HBV infection acquired during infancy and early childhood leads to chronic hepatitis in approximately 95% of cases [7]. Due to advanced scientific progress and the implementation of global and national non-specific and specific prophylactic programs through HBV vaccination, transmission of HBV has substantially decreased in the early years of life, resulting in a significant reduction in HBV infection prevalence among children to 1.3% [8]. The epidemiological and clinical significance of HBV infection is particularly relevant to latent (occult) forms of chronic viral infection. Until recently, it was considered that the screening marker of acute and chronic HBV infection is HBsAg, and its disappearance in chronically infected patients was thought to indicate the completion of the HBV replication phase and leading to spontaneous or drug-induced remission [9]. However, recent scientific investigations have revealed that even after HBsAg negativity in the blood, HBV DNA at low titers persists and can be detected in both blood and hepatic tissue of chronically infected individuals, even after the negation of HBsAg in the blood, regardless of effective antiviral therapy or spontaneous recovery following acute HBV infection. [7,10]. The concept of occult HBV infection was initially reported in 1978 [9,11], but it gained significant scientific attention only in 1999 following the publication of a landmark paper in the New England Journal of Medicine [10]. This study demonstrated the presence of HBV genomes in liver biopsy samples from HBsAg-negative patients with chronic liver disease. These findings led to the recognition of occult (silent or latent) forms of HBV infection in 2008 [7,10].

The definition of occult hepatitis B virus (OHB). The current definition was first formulated by the European Association for the Study of the Liver (EASL) in Taormina, Italy, in 2008 and revised in 2018. OHB is defined as the presence of replicative competent HBV DNA (covalently closed circular episomal HBV DNA - cccDNA) in the liver, in the presence or absence of HBV DNA in the blood in individuals who test negative for HBsAg by currently available commercial tests. At this stage of chronic HBV infection, HBV genomes are in the form of cccDNA with reduced replicative capacity, leading to intermittent detectability of HBV DNA in serum/plasma, typically at low viremic levels (<200 IU/mL). According to the 2017 EASL recommendations, occult chronic hepatitis B infection is typical of the fifth phase of HBV-induced chronic infection, characterized by negative HBsAg, and is referred to as "occult HBV infection" (Table 1).

Occult Hepatitis B Infection (OBI) is characterized by negative HBsAg in blood, negative HBeAg, overall negative or positive anti-HBc, HBV DNA in blood below 200 IU/mL or undetectable in serum and detectable cccDNA in liver tissue. ALT levels may be normal or slightly elevated, and histologically changes can range from minimal to severe. Each phase of the chronic viral hepatic process induced by HBV has significant clinical implications for the practicing physician (Table 2).

There are two clinical forms of occult HBV infection: seropositive and seronegative [9,10]. In the case of seropositive occult HBV infection, both anti-HBc and HBV DNA are concurrently detected in the patient's serum, with or without detectable anti-HBs antibodies, accounting for approximately 80% of all

TABLE 1. The new nomenclature of chronic HBV infection (2017 EASL)

Chronic Hepatitis B Infection	HBeAg-positive		HBeAg-negative		
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Chronic HBV hepatitis	Chronic HBV infection	Chronic HBV hepatitis	Chronic HBV infection	Chronic HBV hepatitis	Resolved HBV infection
HBsAg	high	high/ moderate	low	moderate	negative
HBeAg	positive	positive	negative	negative	negative
HBV DNA	>107 IU/mL	104-107 IU/mL	<2,000 IU/mL	>2,000 IU/mL	<10 IU/mL
ALT	normal	increased	normal	increased	normal
Liver changes	abs/minimal	moderate/ severe	abs	moderate/ severe	abs
Old terminology	immunotolerance	immune reactivation with positive HBeAg	Inactive carrier	Chronic hepatitis with negative HBeAg	negative HBsAg / anti-HBc positive

cases of occult HBV infection. In seronegative occult HBV infection, only positive HBV DNA is detected in the blood and/or liver tissue, while anti-HBc or anti-HBs are negative [15]. Seropositive occult HBV infection cases are more frequently encountered, while seronegative cases may account for up to 20% of all occult HBV infections.

Epidemiology

Recent studies indicate that the prevalence of occult hepatitis B virus (HBV) infection varies significantly across different regions for both adult and pediatric populations. This variability is influenced by several factors, including the sensitivity of HBsAg and HBV DNA diagnostic tests. Additionally, factors such as the prevalence of HBV in the general population, the implementation of anti-HBV vaccination programs in various countries, and the presence and severity of liver disease in the studied populations contribute to this variation [16]. In pediatric populations, the prevalence of occult HBV infection shows considerable fluctuation, with reported rates ranging from 0.1% to 87.5% in different scientific studies (Table 2).

In 2020, Yokoyama K. et al. reported a 1.3% rate of occult hepatitis B virus (HBV) infection among vaccinated children born to HBV carrier mothers in Japan [17]. Surprisingly, in Alborz province, Iran, among 660 examined children and their parents, 91 (16%) children tested positive for occult HBV infection (OBI) [18]. Furthermore, studies conducted on the prevalence of OBI among children in Mexico revealed that out of 215 children examined for clinical hepatitis, HBV infection was detected in 11.2% of cases. Among the children who tested positive for HBV DNA, 87.5% (n = 21/24) were diagnosed with OBI, while 12.5% (n = 3/24) tested positive for both HBV

TABLE 2. Characteristics of pediatric patients diagnosed with viral hepatitis B infection (PubMed database) [17,18,20-35]

Nº	Groups of pediatric population	The number of participants (children)	Children's age	Nº of patients diagnosed with occult HBV infection	The country of the research	Publication year
1	Vaccinated children born to HBsAg-positive mothers	222	2 y.o.	42%	India	2013
2	HIV-diseased children	254	-	6/254 (2,4%)	Spain	2013
3	Vaccinated children born to HBsAg-positive mothers	183	1 y.o.	9/183 (4,92%)	Wuwei town (China)	2013
4	Children with type I diabetes mellitus	170	<18 y.o.	0	Egypt	2014
5	Children with positive HCV in oncology patients	50	-	16/50 (31%)	Egypt	2014
6	Children with acute lymphoblastic leukemia	105	5	39%	India	2014
7	Children with clinical hepatitis	215	1-15 y.o.	24 with HBV DNA+; 87.5% (21/24) with HBV DNA+ and HBsAg-; 12.5% (3/24) with HBV (HBV DNA+/HBsAg+)	Mexico	2014
8	Children born to mothers with positive AgHBs	210	9 months – 3 y.o.	9/210 (4.28%)	Jiangsu, China	2014
9	Healthy children	3299	<18 y.o.	8/90 (8,9%)	Taiwan	2014
10	Children with chronic liver disease	115	9 months – 3,6 y.o.	45/115 (39,1%)	India	2015
11	Children born to mothers with positive AgHBs	64	6-132 months	2/64 (3,12%)	Egypt	2015
12	Children born to AgHBs positive mothers	158	7 months	32 (20,3%)	China	2016
13	Healthy, vaccinated children	1192 cu HBsAg-, ADN VHB investigated	<12 y.o.	15/1192 (1,26%)	Northwest China	2017
14	Children born to HBV-carrier mothers	158	12 y.o.	2/158 (1,3%)	Japan	2017
15	Children born to HBsAg positive mothers	44	12 months	3/44 (6,8%)	Weden	2019
16	Children in the general population, vaccinated	660	-	91 (16%)	Iran	2020
17	Vaccinated children born to HBsAg positive mothers	327	Mean age - 2.5 y.o.	10/327 (3,1%)	China	2020
18	Children born to HBsAg positive mothers	236	< 8 y.o.	78/21 (37,14%)	Jiangsu, China	2023

DNA and hepatitis B surface antigen. Importantly, the prevalence of OBI was significantly higher in non-vaccinated children compared to those who had received the hepatitis B vaccine ($p < 0.05$) [19].

According to the data presented in Table 2, research conducted on various age groups of children vaccinated against Hepatitis B Virus (HBV) and born to AgHBs-positive mothers show varying degrees of presence of occult Hepatitis B viral infection (OHBV): 4.92% in Wuwei, China (2013); 32%-37.14% in China (2016) and Jiangsu, China (2023); 42% in India (2013); 3.1% in Japan (2017); 3.12%, Egypt, 2015.

There are conflicting data on OBI diagnosed in children with chronic liver disease, reported in 39.1% of cases in India in 2015. Studies conducted on cohorts of healthy children vaccinated against HBV have shown the presence of OBI in 1.26% of cases in China in 2017, 8.9% in Taiwan in 2014, and 16% in Iran in 2020 [20,21]. It has been demonstrated that occult HBV infection diagnosed among young adults with a positive anti-hepatitis B core antigen (anti-HBc) in Qidong, Jiangsu, Eastern China, was present in up to 76.42% of cases [22]. On the other hand, the rate of OBI in children in Northeast and Northwest China was only 0.77% and 4.92%, respectively [23]. Obviously, these significant variations reported data suggest that the real OBI rate in children remains underestimated and dependent on regional scientific studies. There is a notable lack of multicentered scientific studies across various geographic regions, which could provide further insights into the true prevalence rate of OBI among children.

Transmission routes of OBI in children

Blood transfusions. Over the past three decades, advancements in diagnostic technologies and the availability of specific and sensitive diagnostic tests have substantially reduced the risk of Hepatitis B virus transmission via blood transfusion among children. However, the transmission of Hepatitis B virus from blood donors with OBI continues to be a major public health concern in low- and middle-income countries, where the use of anti-HBc and Hepatitis B virus DNA tests is not widespread. [14,36]. However, there is still a minimal risk of OBI transmission to children via blood transfusion in developed countries. This is due to the fact that the recommended lower limit of HBV DNA detection established is below 2-4 IU/mL, while the commercial tests commonly employed in clinical practice have a higher virus detection threshold of over 50 IU/mL [12].

Transmission of HBV through blood or plasma transfusions can occur under 3 circumstances:

1. blood transfusion from a donor with occult HBV infection;
2. blood transfusion from patients in the infectious phase of HBV-induced inflammation; *or*
3. blood transfusion from a donor infected with mutant virus-induced HBV infection in the S region, which has not been detected by routine diagnostic tests for detecting HBsAg [37].

If the blood donor is HBV-positive, the likelihood of HBV transmission is influenced by several factors, including the volume of plasma transfused, the recipient's immune status, and the immunoserological status of both the donor and the recipient. HBV transmission could be maximally reduced by implementing the standard examination protocol and practical implementation of anti-HBc screening in patients with clinical and paraclinical signs of hepatitis of unknown cause and/or detecting HBV DNA by real-time PCR with specific and sensitive tests with a lower limit of virus detection of under 2-4 IU/mL.

Liver transplant transmission. HBV transmission can occur from a clinically seropositive OBI donor to a recipient who is HbsAg-negative, anti-HBc-negative, and anti-HBs-negative pretransplant, possibly further developing acute viral hepatitis B in the posttransplant period [38]. The transmission of HBV during liver transplantation is an evident outcome since hepatocytes serve as reservoirs for viral cccDNA. Importantly, the rate of HBV transmission is notably higher in liver transplants compared to other organ and tissue transplants, such as those involving the kidney, bone marrow, and heart [39]. To avert the reactivation of HBV in the transplanted liver, recipients should be administered lifelong prophylactic antiviral therapy with nucleoside analogues [38]. The transmission rates of HBV infection from HBsAg-negative but anti-HBc-positive donors have been reported to range between 17% and 94% [38,40].

Hemodialysis-associated transmission. Pediatric patients undergoing hemodialysis procedures are at increased risk of parenteral infection with hepatotropic viruses, including HBV or HCV, due to their immunosuppressed condition and exposure to repeated invasive procedures over many years, prolonged use of the same dialysis machine, and receiving more blood and plasma transfusions than the general population. The prevalence of occult HBV infection among hemodialysis patients ranges from 0% to 54%, contingent on the sensitivity of the diagnostic techniques used to detect HBV markers [37,40]. Several studies suggest that OBI among hemodialysis patients could be a source of transmission to other patients as well as to healthcare personnel in hemodialysis units [37].

Perinatal transmission from mother to child. Perinatal transmission, viz. from mother to child, of HBV is one of the main routes of HBV infection in

children. Recent advancements in immunization strategies, including the introduction of revolutionary antiviral therapies in pediatric medical practice, national programs for managing chronic HBV infection in pregnant women with high levels of HBV DNA in their blood, combined with effective vaccination protocols for newborns and timely administration of specific anti-HBV immunoglobulin within 12 hours of birth for high-risk infants, have substantially reduced the transmission of HBV from viremic mothers to their offsprings [41-43]. Nevertheless, the introduction of high-sensitivity HBV DNA detection technology has revealed through numerous studies that some children born to mothers positive for AgHBs still test positive for HBV DNA in their blood, even after successful specific immunoprophylaxis measures have been administered. In other words, in some of these children, despite adherence to specific anti-HBV immunoprophylaxis as per guidelines, occult HBV infection persisted [25-28, 44-48]. The incidence of OBI in children who have been vaccinated against HBV but become infected by their viremic mothers varies significantly across different geographic regions and scientific studies, ranging from 3.1% to 64.0% of cases [25-28, 44-48]. Some studies suggest that a weak post-immunization specific anti-HBV response is a risk factor for OBI in childhood [41,43].

It's crucial for the medical system to identify groups of children at higher risk for occult HBV infection, including:

a) blood and solid organ donors;
b) patients who are at risk of reactivation after undergoing immunosuppressive therapy;
c) patients with autoimmune liver diseases;
d) patients undergoing hemodialysis;
e) patients with chronic HCV infection;
f) patients with hepatocellular carcinoma;
g) patients with cryptogenic liver disease;
h) children born to pregnant women with HBV viremia detected in the last 3 months of pregnancy, due to an icreased risk of vertical transmission of OBI through umbilical cord blood.

OBI diagnosis. While the definition of OBI is clear enough, today medical practitioners do not have a globally approved diagnostic algorithm by consensus for a staged detection of OBI cases in children. The diagnosis of OBI is based on the detection of HBV DNA in the blood or liver along with anti-HBc in individuals found negative for HBsAg. The diagnosis of OBI depends on the sensitivity of the commercial tests used and the diagnostic techniques, the medical equipment used in medical laboratories and the expertise of the professionals involved in detecting HBV DNA and AgHBs. Tests with low sensitivity can yield false negatives, leading to underdiagnosis. Highly sensitive commercial tests, with a lower detection limit for HBsAg of 0.05 IU/mL, are available globally. Recent studies have shown that 1%-48% of blood samples initially tested negative for HBsAg with standard commercial tests used and retested with highly sensitive tests with a cutoff of 0.005 IU/ml were positive for HBsAg. Additionally, commercial tests vary in their ability to detect S-escape variants [24].

The lower detection limit of the most commonly used commercial HBV DNA tests currently available is 10-20 IU/mL. However, considering that HBV DNA is present at very low concentrations, it is important for HBV DNA tests to be highly sensitive with a lower detection limit of HBV DNA of 2-4 IU/mL. A study using highly sensitive HBV DNA testing systems with a detection limit of 3.4 IU/mL identified 3 blood donors who were previously tested as negative for HBsAg and HBV DNA, but later demonstrated the presence of HBV infection [49].

The gold standard for diagnosing OBI is the detection of replication-competent HBV DNA in the liver (cccDNA), which remains in hepatocytes and can sometimes be identified in the liver even when absent in serum [4]. However, standardized and validated tests for HBV DNA detection in the liver are not yet widely accessible. The only method for detection of HBV DNA in liver tissue or blood is Real-Time PCR (Polymerase Chain Reaction), which identifies the virus in real-time by measuring emitted fluorescence from less than 10 copies of HBV DNA [50]. Recommended techniques include nested PCR to amplify at least three different viral genomic regions, real-time PCR assays, and digital droplet PCR assays [9,51]. Due to the low concentrations of HBV DNA in individuals with OBI, samples should be appropriately sized and freshly frozen liver tissue should be used instead of formalin-fixed tissue.

According to Hollinger F.B. and Sood G. [2], liver biopsy may not always be feasible for detecting HBV DNA in liver tissue. However, in most chronic HBV infections, biopsy is justified as it not only allows for the detection of HBV DNA in liver tissue but also helps clarify the etiology of liver disease through morphohistological studies and the application of immunomorphological and electron microscopy methods.

In cases where HBV DNA cannot be detected in liver tissue or tests for HBV DNA detection in blood are limited, detection of total anti-HBc in serum has diagnostic significance. Anti-HBc in serum appears rapidly after HBV infection and can be detected in anyone who has had exposure to HBV and is assumed to be in various stages of the B viral inflammatory process, even after the virus has been cleared. Therefore, following the meeting and reviews carried out by the EASL expert group in Taormina, Italy

[12], anti-HBc was considered to be an imperfect marker of HBV infection, but still recommended as a "surrogate" diagnostic marker in the case of blood donation /tissues or organs, in patients undergoing immunosuppressive therapy or in epidemiological studies. It should be noted that the absence of anti-HBc does not exclude the presence of OBI.

Clinical impact of OBI. The increasing interest in OBI stems from mounting evidence of its clinical significance. While clinical sequelae of HBV infection are largely underexplored, OBI can lead to:

- transmission of HBV infection to blood or tissue/organ transplant recipients, resulting in acute viral hepatitis B;
- reactivation and replication of HBV in patients undergoing cancer chemotherapy or other immunosuppressive therapies like high-dose corticosteroids or anti-rejection therapy for solid organ transplants;
- potentially exacerbation of chronic liver disease progression;
- fostering malignancy and hepatocellular carcinoma development in individuals with chronic liver disease.

Various studies also indicate that OBI infection might contribute to the progression of chronic inflammatory processes in viral hepatitis C and impede the expected antiviral treatment response.

CONCLUSION

The literature and scientific publication review from the last decade regarding the issue of HBV-induced occult infection confirms the existence of contradictions and data diversity regarding the prevalence, clinical significance, and diagnostic methods of occult B viral infection in children. This is especially true for the diagnostic value of anti-HBc. Limiting testing to patients in high-risk groups only for HBsAg and underestimating the importance of the anti-HBc marker, thus occult HBV infection in children remains undiagnosed. This poses a significant potential for maintaining perpetuating the epidemiological chain of HBV transmission among children.

The issue of Occult HBV infection in children remains a pertinent concern for clinicians and healthcare systems, as current international and national data underestimate its prevalence, and literature addressing this topic in pediatric populations is insufficient. Occult HBV infection carries a major risk of perinatal transmission of HBV to the newborn child from the infected and viremic pregnant mother, as well as through blood or plasma transfusions to recipients, and reactivation in individuals previously treated with immunosuppressive therapy. Undiagnosed children with occult HBV infection might be a source of HBV transmission and should be integrated into the epidemiological control measures for HBV infection.

Occult HBV infection poses a considerable challenge to the healthcare system and demands ongoing vigilance aimed at eliminating viral hepatitis B by 2030.

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