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Title: REVIEW OF OCCULT HEPATITIS B VIRUS INFECTION AMONG NIGERIANS: IMPLICATIONS FOR BLOOD TRANSFUSION MEDICINE

KENNETH OGAR INAKU (1), MARCUS ANIEKAN INYAMA (2), NATHANIEL ISONGUYO USORO (3), LAWSON EKPENI EKPE (1), OKOKON ITA ITA (4), HENRY CHIMA OKPARA (5).

1. Department of Chemical Pathology and Immunology, University of Calabar, Calabar, Nigeria
2. Department of Haematology and Blood Transfusion, University of Calabar, Calabar, Nigeria.
3. Department of Surgery, University of Calabar, Calabar, Nigeria.
4. Department of Medical Microbiology and Parasitology, University of Calabar, Calabar, Nigeria
5. Department of Chemical Pathology, Nnamdi Azikiwe University, Nnewi Campus, Nnewi, Nigeria.

Correspondence to: Dr. Kenneth Ogar Inaku MBBCh; FMCPath, Department of Chemical Pathology and Immunology, Faculty of Basic Clinical Sciences, University of Calabar, Calabar, Nigeria.
keninaku@unical.edu.ng

ABSTRACT

Occult hepatitis B virus infection (OBI) has been recognized for over 30 years as a culprit in the transmission of hepatitis B virus to blood transfusion recipients. It is usually not detected using routine screening methods involving simple chromatographic antibody testing. In hepatitis B virus endemic regions such as Nigeria where blood for transfusion is still screened by chromatographic detection of HBsAg, the chance of transmitting the disease among Nigerians may remain high. This review aims to determine the prevalence of OBI among Nigerians and its implication on blood transfusion. A search of various databases including PubMed, African Journals Online (AJOL), Google Scholar, and Research Gate was undertaken for all articles on occult hepatitis B virus infections among Nigerians. Each article was screened for content to ensure that it addressed the subject under consideration. Articles that were considered fit for inclusion were those that employed the acceptable diagnostic criteria for OBI. The use of nucleic acid testing to detect HBV DNA in subjects who tested negative for HBsAg was a compulsory criterion for inclusion of an article. Articles that used recommendations from the Taormina committee were also considered and included in the review. Eight articles met our inclusion criteria. Seven out of eight studies were carried out among blood donors in Nigeria. There were four articles from the South-West region and three were from South-East. One of the studies from the South-East included data from the Federal Capital Territory (FCT), Abuja. The rate of OBI among blood donors in Nigeria ranged from 5.4% to 36% with a pooled prevalence of 18.5%.One article reported the prevalence of OBI to be 11.2% among HIV positive patients in Nigeria. Hepatitis B virus genotype E was the most predominant as reported by three articles. Other genotypes were A, non-A and mixed HBV genotype A/non A by two studies. Anti-HBs prevalence among OBI patients was reported as 9.5% to 64.3% with a pooled prevalence of 33.7% (95% Confidence interval 4.16-63.23). We concluded that there is significant risk of transfusion of HBV among Nigerians and this risk may remain high if more sensitive screening methods such as HBV DNA detection are not employed.

Keywords: Hepatitis B virus; Occult hepatitis B virus infection; Blood donors; Nigerians; Hepatitis C virus; Hepatitis B virus genotype E

INTRODUCTION

Hepatitis B virus (HBV) infection shows variable clinical manifestations ranging from asymptomatic carrier state, acute, chronic, fulminant and occult HBV infection (OBI). It can progress from acute state to chronic and eventually to cirrhosis and hepatocellular carcinoma. It may also remain undetectable by routine screening methods. However, these clinical manifestations may vary depending on the age at infection. Symptoms are less in under 5 year old (<10%) than in adults (30-50%) [1]. The first report of occult silent hepatitis B virus infection dates back to about 30 years ago. It was reported in the context of blood transfusion which resulted in the transmission of HBV by a donor who was positive for anti-HBc as the only marker of HBV infection [2]. The prevalence of OBI varies according to geographical region. The variability also depends on the specificity and sensitivity of the routine serological assays and nucleic acid testing. The result is that some individuals who are positive for occult HBV may not show any serological evidence of exposure. This may make it difficult to diagnose OBI in Nigeria using currently available screening methods. Occult HBV infection is a risk factor for chronic liver disease and hepatocellular carcinoma (HCC). As the virus persist in the liver for a long time it may

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initiate a very mild but continuing necro-inflammation which may progress rapidly to cirrhosis in the presence of other causes of liver damage.

The risk of becoming infected with HBV from a single blood transfusion in sub Sahara Africa was put at 4.3% per 1000 units of blood, translating to 28, 595 infections with HBV if annual transfusion requirement projections by WHO were met [3]. Occult HBV infection will contribute a significant percentage of this risk. Occult HBV infection was defined in 2008 during an international workshop in Italy as "presence of HBV viral DNA in the liver (with or without detectable HBV DNA in serum) of HBsAg negative individuals tested with the currently available assays" [4]. The virus can also be demonstrated in the lymphatic (immune) system [5]. A cut-off of HBV DNA if present was expected to be less than 200 IU/ml as recommended by the Taormina expert committee [4]. The infection is found in a significant number of chronic hepatitis due to hepatitis C virus with hepatitis B viral DNA detectable in up to 30% of serum samples and 50% of liver biopsies [6].

Individuals with occult HBV infection can either be sero-positive or sero-negative. Those who are sero-positive will have detectable anti-hepatitis B core antibody (anti-HBc) with or without the presence of anti-hepatitis B surface antibodies (anti-HBs). Sero-positive OBIs are more common because often, occult HBV infection follows resolution of acute hepatitis and continues indefinitely after clearance of HBsAg and biochemical improvement of liver function [7]. In sero-negative OBI, both antibodies are absent. It has been suggested that up to 20% of individuals with occult HBV carriage evidenced by HBV DNA detection could be nonreactive for anti-HBc or any other serological evidence of exposure to HBV [7]. They usually do not have active liver disease but may show histological consequences of previous damage with variable amounts of residual fibrosis. HBV reactivation may be caused by immunosuppression leading to severe exacerbation of liver disease with HBsAg, HBV DNA, and even HBeAg rebound [8].

Many reasons have been put forward to explain the aetiopathogenesis of OBI. The frequent detection of OBI in anti-HBc positive individuals is an indication that OBI develops after resolution of infection with HBV [6]. Infection caused by wild-type viruses with replication deficit has also been used to explain theoretically the development of OBI. This has been supported by the findings of intrahepatic persistence of covalently closed circular DNA (cccDNA), RNA transcripts and pregenomic replicative RNA intermediates in a large proportion of patients with OBI [9, 10]. This theory is however refuted by observation that patients with OBI are able to transmit the virus via liver transplant or blood product transfusion [2, 11, 12]. The concomitant presence of HBV and HCV infection has also been shown to facilitate clearance of HBsAg and progression to OBI [13]. Said et al reported that HCV RNA was a significant predictor for OBI with an increased frequency of HBV DNA in those who were HBsAg negative and HCV RNA positive (63.2%) compared with patients negative for HCV RNA (25%) [14]. It has also been observed that prior vaccination against HBV may only solve the problem of overt HBV infection but may favour the development of OBI if these individuals are later exposed [11]. In all, available data suggest that the development of occult status is determined by (a) the host immune response, (b) co-infection with other infectious agents, and (c) epigenic factors [8].

The probability of developing OBI is higher in HBV endemic areas [14, 15]. Prevalence of 0.1% to 2.4% has been reported among HBsAg negative and anti-HBc positive blood donors in Western countries such as the United States where only 5% of its population are exposed to HBV. A rate of up to 6% has been reported in a similar cohort in endemic areas where 70% to 90% of the population have been exposed to HBV [16, 17]. The true prevalence of the infection will depend on the nature of biological material tested with a higher yield from liver compared to serum specimens [18] and the sensitivity of the HBV DNA detection method employed [17].

Nigeria is an endemic region for HBV infection with a prevalence of 12.2% in the general population [19]. The most common method used to screen for HBV infection is HBsAg detection using immunochromatographic technique [20]. This is also employed during screening of donor blood for transfusion. There are published reports of OBI among Nigerians by some researchers [21-28]. We found it pertinent to review those studies to clarify the pooled prevalence of OBI and determine the magnitude of the problem in Nigeria and its impact on the safety of blood transfusions in our environment.

GEOGRAPHIC DISTRIBUTION OF OBI IN NIGERIA

We found eight [21-28] out of 25 studies on OBI in Nigeria after an extensive search of various data bases including AJOL, Pub Med, Google scholar, Research Gate etc. The studies included in the review were carried out in the Southern part of the country with just one study containing data from the Federal Capital Territory (FCT), Abuja located in the Northern part of Nigeria [21]. (Table 1) We were unable to compare OBI prevalence between different geographical regions such as North versus South. However, of the six geopolitical zones of Nigeria and the Federal Capital Territory (FCT) only 2 zones were represented in this review namely South-East, South-West and the Federal Capital Territory. (Table 1) The prevalence of OBI in the South-East ranged from 6.0% to 8.0% while that of the South-West was 5.4 to 36.0%. The reported prevalence from the FCT was 22.0% with the overall prevalence from all the studies being 5.4% to 36% and a pooled prevalence rate of 18.2%. This was lower than the highest reported rate in Egypt (58.3%) among patients with chronic liver

disease (CLD) [29]. A study among Nigerians involving a similar cohort of acute and CLD patients reported a prevalence of 7.2% [28].

OBI AMONG NIGERIAN BLOOD DONORS

Seven out of 8 studies were carried out among blood donors in Nigeria. (Table 1) There were four reports from the South-West region and three were from South-East. One of the studies from the South-East included data from the Federal Capital Territory (FCT), Abuja. The rate of OBI among blood donors in Nigeria ranged from 5.4% to 36% with a pooled prevalence of 18.5%. This is a disturbing reality for blood transfusion recipients. The rate of OBI among blood donors is far higher than what was reported among Egyptian blood donors. Elbahrawy et al in a review reported a prevalence of 4.16 among Egyptian blood donors without known anti-HBc serological status. A relatively higher prevalence of 14.3% was reported among donors who were anti-HBc positive [29]. The highest reported incidence among blood donors in Nigeria was 36% and the authors identified 3 categories of OBI among blood donors: 1) those positive for all of anti-HBc, anti-HBs, and HBV DNA, 2) those positive for anti-HBc and HBV DNA and 3) those positive for HBV DNA only [25]. It has been demonstrated that some persons with undetectable HBV DNA in serum may show positive HBV DNA in liver tissue [4, 7], and some individuals with OBI may have no demonstrable evidence of the infection in serum [30]. This fourth group was not captured in this classification. The prevalence of OBI reported among Nigerians in the studies may therefore be lower than the true prevalence of OBI in the general population. This is because all the studies made diagnosis of OBI from examination of blood specimen.

Blood transfusion is a major risk factor for OBI especially when the screening of potential blood donors is done with minimal screening methods [31]. There is at present no study conducted to estimate the percentage of people who become infected from transfusions with OBI positive blood in Nigeria. However, the overall infectivity rate of OBI after a blood transfusion was reported by a European study to be 28% [32]. Similar studies have reported lower prevalence of 18.2% among Taiwanese, [33] 3% among Japanese, [34] 0% among

Table 1—General and Epidemiological Characteristics of Included Studies

Reference	Study period	Study population	Location of study	Age group	Total number	OBI rate (%)
Osuji et al[21] (2018)	June- Oct 2016	Blood donors	South-East and FCT‡	Adults	212	14.0
Akintule et al[22] (2018)	ND†	Blood donors	South-West	Adults	206	8.7
Olotu et al[23] (2016)	June 2013-Jan 2014	Blood donors with Anti-HBc	South-West	Adults	356	5.4
Oluyinka et al[24] (2015)	ND	Blood donors	South West	Adults	492	17.0
Oluyinka et al[25] (2014)	ND	Blood donors	South-West	Adults	429	36.0
Opaleye et al [26] (2014)	Oct 2012-April 2013	ART naïve HIV positive patients	South-West	Children/ Adults	188	11.2
Nna et al[27] (2014)	ND	Blood donors	South-East	Adults	100	8.0
Ola et al[28](2009)	ND	Acute and chronic hepatitis	South-West	Adults	56	7.2

ND†= Not Determined, FCT‡ = Federal Capital Territory

Egyptians [35] and 7.9% among Sudanese blood donors [36]. The prevalence of OBI infectivity after a blood transfusion will vary directly with sensitivity of the nucleic acid testing method used. To increase the detection of OBI, it has been recommended that more sensitive methods with lower limits of detection (LLOD) of 5 IU/mL be employed [17]. All the studies included in this review that reported the sensitivity of the nucleic acid testing (NAT) had LLOD of ≥10 IU/L. (Table 2)

The detection of anti-HBc in serum has been recommended as a good test for tracking OBI detecting up to 80% of OBI cases [17, 37, 38]. The reported prevalence of anti-HBc among OBI patients in Nigeria ranged from 19% to 70.5% (Table 2). This means that the introduction of anti-HBc as a second screening tool will reduce the possibility of HBV transmission through blood transfusion [37, 38]. However, in HBV endemic region like Nigeria, rejecting all blood samples that test positive for anti-HBc will mean rejection of a lot of potential blood for transfusion considering that up to 70.5% of donors may test positive even though most of the blood would have tested negative for HBV [3, 37]. Another drawback is that sero-negative window period HBV infections will go undetected [37]. In Japan, some measures were adopted in 1989 to prevent HBV transfusion from anti-HBc positive donors. Anti-HBc positive blood with titres <1:32 or ≥1:32 with anti-HBs ≥200 mIU/L are accepted for transfusion [40]. Some countries will accept blood units for transfusion only when the anti-HBs

titre is higher than 100 IU/L [41]. Implementing some of these measures in our transfusion practices may not be feasible due to the high HBV endemicity and cost of screening involved. The priority in resource poor setting like ours should be to determine the prevalence of OBI in blood donors on a large scale and to establish the cost-effectiveness of adopting sensitive HBV NAT blood screening as a routine [37] or a gradual shift towards the use of transfusion alternatives which are devoid of infections.

OBI GENOTYPES AMONG NIGERIANS

At present a total of ten HBV genotypes (A-J) have been identified [42]. Hepatitis B virus genotype E was the most frequently reported by 3 articles reviewed with the other reported genotypes being A, non-A and mixed HBV genotype A/non A by two studies. (Table 2) Studies have shown that HBV genotype E is more prevalent in Nigeria [43] and it is said to be endemic in West Africa albeit with a low genetic diversity [44, 45]. Hepatitis B virus genotype E was reported to be more likely to become chronic in about 3 to 25% of infected individuals as compared to genotype A with less than 1% likelihood [46]. Genotype A was also reported to be widespread in Sub-Sahara Africa, Northern Europe and West Africa [47]. Some researchers found that infection with HBV genotype A has a higher risk of developing chronic infection [48, 49] relative to genotype B or C. Suzuki et al reported a higher persistence of hepatitis B infection after acute infection among individuals infected with genotype A (23%) compared to genotype B (11%) or genotype C (7%) infection [49]. The relative persistence among individuals with genotype E was not reported in this study. This is probably because genotype E is not prevalent in Japan. Studies conducted in India [42] and Egypt [29] reported that genotype D with subtypes D1 and D3 were accompanied by chronic and occult infections respectively while another study among Koreans found a correlation between occult hepatitis B and genotype C [42]. Another Indian study which reported an OBI prevalence of 10.1% among family members of HBV positive individuals reported genotypes A, C and D as the most prevalent HBV genotypes encountered among the OBI patients studied. Majority were found to belong to sub-genotypes A2, C2 and D3 respectively [50]. The high prevalence of occult hepatitis B reported by studies in this review is an indication that the most common genotypes A and E in Nigeria are also associated with occult hepatitis B virus infections. It does appear that OBI prevalence is not very much influenced by genotype as almost all genotypes have been implicated among individuals with OBI.

The distinction in the distribution of the different HBV genotypes is getting blurred owing to factors such as immigration of persons from regions of high endemicity to regions of low endemicity and recombination of different strains to produce subgenotypes [51]. Recombination is favoured in particular geographical regions by 3 factors including (1) the presence of 2 or more different HBV genotypes in circulation in the population; (2) high level of chronicity of HBV in the population; and (3) low public health awareness level in the population [52]. Mixed genotype in the same population was reported by one study among blood donors in South West Nigeria [22]. The mixed genotype was simply identified as HBV genotype A/non-A with no further sub-genotype classification. The non-A genotype also required proper classification. Over 30 related sub-genotypes belonging to HBV genotypes A-D and F have been identified to date [42]. Since HBV genotype and subgenotpes may predict outcome of HBV infection including response to treatment, [47] it is important that more research is done in the area of phylogenetic analysis to further characterize the subgenotype of the predominant HBV genotypes A and E among Nigerians.

DIAGNOSIS OF OBI

The diagnosis of OBI was made by detecting HBV DNA in serum of individuals with negative HBsAg using real time quantitative polymerase chain reaction (PCR) in almost all the studies reported. Two studies reported the use of nested [27] and semi nested [22] PCR. The LLOD of the method used was reported by only 3 studies (Table 2). None had a sensitivity of 5 IU/mL which is the recommended LLOD of HBV DNA in OBI patients [17]. Nature of specimen used was blood in all the studies reviewed even though the absence of HBV DNA in serum does not automatically rule out the presence of OBI since some individuals will show evidence of HBV DNA in liver tissue only [4, 7, 30] or in the lymphatic tissue [5]. In individuals who have HBV DNA in serum, the level is expected to be less than 200 IU/mL [6]. The HBV DNA among the subjects in this review range from undetectable to128 copies/mL as expected among patients with OBI. The diagnosis of OBI among blood donors will continue to be made using serum and methods with sensitivity above the recommended LLOD in the foreseeable future. However, there is need to adopt more sensitive methods and have a high index of suspicion when screening potential blood donors.

HBSAG POSITIVITY AMONG NIGERIAN BLOOD DONORS

The detection of HBsAg is the most commonly used marker to identify persons with HBV in our environment [20]. Therefore, those who test negative are considered free of the infection and are even allowed to donate blood. Since the most common screening method employed is immunochromatographic technique, the possibility of missing positive cases is high. The prevalence of HBsAg reported by some of the authors range from 0% to 11.5% among donors previously tested negative for HBsAg using routine immunochromatographic techniques. (Table 2) In Nigeria a pooled prevalence of HBV infection was estimated to be 13.6% (95%

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confidence interval CI: 11.5 – 15.7%) and 14% among the general public and voluntary blood donors respectively [53]. Akintule et al observed that 3.9% of HBsAg previously negative blood donors tested positive with a more sensitive enzyme linked immunosorbent assay (ELISA) and 8.7% of the total samples were HBV DNA positive by a semi-nested PCR using HBV specific primer pairs [22]. This emphasises the need for the improvement of currently available methods used to screen for HBV infection among blood donors and the general public [54]. Nna et al reported a prevalence of 11.5% among regular blood donors as positive for HBsAg using an immunochromatographic strip with an analytical sensitivity of 1.0 ng/mL [27]. This is very disturbing because there is possibility that the number would be higher if a more sensitive method such as ELISA was used to screen them nstrated by Olotu et al who rescreened 507 HBsAg negative persons using immunochromatographic rapid test kit but found 5 of them to be positive for HBsAg when rescreened using ELISA [23] It is therefore recommended that HBsAg screening should be carried out using enzyme immunoassays (EIA) including enzyme-linked immonosorbent assay (ELISA) and chemiluminescence immunoassays (CLIAs)[31]. These different assays have sensitivity ranging between <0.1 and 0.62 ng of HBsAg per mL (1ng/mL corresponds to approximately 2 IU/mL) [31, 55]. There is therefore every need to adopt the recommended EIAs methodology to reduce cases of misdiagnoses and transfusion mishaps. However, nucleic acid amplification test (NAT) remains the method of choice in excluding infected donors in the pre- and post-HBsAg window period including OBI [17, 56, 57]

ANTI-HBS POSITIVITY AMONG OBI BLOOD DONORS

The presence of anti-HBs is believed to confer immunity against infection with HBV. However, it has been shown that OBI individuals who do not show evidence of anti-HBs could ~~be~~ transmit the infection [58]. The prevalence of anti-HBs reported in the studies
included ranged from 9.5% to 64.3%. (Table 2) The pooled prevalence was 33.7% (95% CI 4.16-63.23). Some authors reported anti-HBs prevalence of 35% among patients with OBI [59]. Studies have also shown that 50% of OBI occurs in asymptomatic, apparently healthy blood donors carrying ant-HBs [60]. This is probably the reason behind the decision in some developed countries like Germany, Austria and Japan, to allowed only blood units with anti-HBs higher than 100 IU/L before such blood is used for transfusion [61]. Applying this criterion in Nigeria will triple the cost of screening a unit of blood for transfusion.

Table 2—Serological Markers Present in Blood Donors and OBI Patients Studied

Reference	HBV DNA Mean [Range] (copies/mL)	DNA LLOD‡ (IU/mL)	HBs Ag (%)	Anti-HBs (%)	HBe Ag (%)	Anti-HBe (%)	Anti-HBc (%)	Anti-HCV (%)	Sero-negative OBI (%)	Genotype (%)
Osuji et al[21] (2018)	93 [≤20-128]	≥20	ND	64.3	0	0	35.7	ND	14.3	E (100)
Akintule et al[22] (2018)	ND†	ND	3.9	ND	ND	ND	ND	ND	ND	A (83.3), non A (10.2), A/non A (5.6)
Olotu et al[23] (2016)	ND[<20-68]	<20	1	ND	ND	ND	70.5	ND	ND	ND
Oluyinka et al[24] (2015)	5.7 [0-58]	ND	0	34.7	2.8	ND	66.7	3	28%	E (93) and A (7)
Oluyinka et al[25] (2014)	<50[ND]	ND	0	36	2	ND	68	ND	0.65	E (ND)
Opaleye et al[26] (2014)	<50 [ND]	ND	ND	25	ND	ND	29.2	2.1	ND	ND
Nna et al[27] (2014)	51* [30-80]	≥10	11.5	ND	ND	ND	19	0	ND	ND
Ola et al[28] (2009)	ND	ND	ND	9.5	0	9.5	14.3	0	0	ND

ND† = Not determined, LLOD‡ = Lower Limit of Detection, (*) = Median

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OBI DISTRIBUTION AMONG DIFFERENT AGE GROUPS

The studies reviewed only involved adults who were old enough to donate blood for transfusion. Children were excluded because by law, persons below the age of 18 years are not allowed to donate blood. The only study that included children involved antiretroviral naïve HIV patients [26]. But the authors did not stratify their subjects into different age groups. Hence it was not possible to tell if the prevalence is higher among children than adults. It is in order to expect that the prevalence should be lower among children than adults in our environment due to the introduction of the Hepatitis B vaccine into the National Program on Immunization (NPI) in 2004 [62, 63]. Although it has been observed that vaccination can only protect against acute HBV infection but favours the development of OBI, [11] this is yet to be proven in our populations. The evidence shows that the prevalence of OBI is proportional to the burden of HBV infection in the environment [64]. There is a stepwise increase in the burden of the disease with age as demonstrated by many researchers. [65-67]. The relatively low prevalence among children in our environment is probably due to the effect of the vaccines given at birth as was observed among Egyptian children [29]. A rather unexpectedly high prevalence of OBI was observed among Egyptian Children who had multiple risk factors for HBV including poly-transfusion, immunosuppression and a higher rate of coinfection with HCV [29]. Vaccinated children who were healthy with no similar risk factors did not show any evidence of the presence of OBI or past infection with HBV (anti-HBc) [68]. There is however a need to conduct research to establish the true prevalence of OBI among the different age groups in Nigeria.

OBI AMONG HIV POSITIVE PATIENTS IN NIGERIA

We found only one article published on the prevalence of OBI among HIV positive patients in Nigeria. (27) The study involved 188 HIV infected (ART-naïve) HBsAg negative patients enrolled in the HAART clinic. The ages ranged from 3 to 67 years with a mean of 33 years. The reported prevalence of OBI was 11.2% which is higher than the prevalence reported among OBI blood donors by other researchers in Nigeria [22, 23, 27, 28] It is however lower than the OBI prevalence rate among other blood donors without HIV [21, 24, 25]. The clinical role of OBI among HIV positive individuals is not clear and its prevalence is controversial [69]. Bell et al [70] reported a prevalence of 63.4% (45/71) of HBsAg negative/HBV DNA positive among HIV infected individuals in South Africa. But majority did not meet the Taormina criterion for OBI that HBV DNA count is expected to be below <200 IU/ in true OBI [4]. Only 6.7% (3/45) persons met the criteria as true OBI with HIV. Similar studies conducted in Ivory Coast and Sudan reported OBI prevalence of 10% and 15% respectively among HIV patients [71, 72]. The evidence suggests that the detection of HBV DNA may be higher in liver tissue and peripheral blood mononuclear cells (PMNC) than in circulating blood [73]. However, OBI has been observed to occur more frequently among HIV/HCV co-infected individuals with a prevalence of less than 1% to 40% [69]. The reported prevalence of HCV/HIV co-infection among Nigerians was 1.6% [27]. HCV genome has a strong inhibitory effect on HBV replication and this is thought to be responsible for the clearance of HBsAg in serum [74].

OBI/HCV COINFECTION AMONG NIGERIANS

Hepatitis B and C viruses' co-infection is a common finding in clinical practice. The concomitant presence of both viruses in the blood of an individual has been shown to facilitate clearance of HBsAg and progression to OBI [13, 74]. The prevalence of HCV infection among Nigerians with OBI ranged from 0.0% to 3.0% according to available data [24, 26-28]. (Table 2) This is far lower than the prevalence of 1.85% to 38.3% reported among Egyptians [29]. The wide range in prevalence rate among the Egyptians was attributed to a possible difference in the study design as well as the sensitivities of the method of detection. Although Ola et al [28] did not find any HCV positive patient among those who were diagnosed with OBI, they reported a prevalence of 33.3% HCV rate among their cohort of acute and chronic liver disease individuals who were all negative for HBsAg. This was the highest prevalence of HCV infection reported among Nigerians. The high rate of HCV infection among this cohort goes to confirm that HBV/HCV frequently coexists and this may favour the development of clearance of HBsAg and possibly favour the development of OBI [13]. An even higher prevalence of 50% was reported among chronic HBV infected Egyptians with OBI/HCV co-infection [75]. There is a general consensus based on available data that patients infected with HCV should be considered as a category of individuals with a high prevalence of OBI [14, 76]. This review has not demonstrated a high prevalence of HCV among Nigerians with OBI as can be seen from lower and comparable rate of 2.1% and 3.0% reported among HIV positive patients [26] and blood donors [24] respectively.

Clinically, OBI/HCV co-infection has been observed to impact adversely on HCV outcomes [77]. There is an associated alkaline phosphatase (ALT) flare which is thought to be due to HBV replication [78]. There is also decreased response to interferon therapy when used in patients with OBI/HCV co-infected individuals than in mono infection with HCV [79], and an acceleration of cirrhosis, hepatic decompensation and liver cancer [78, 80].

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CONCLUSION

There are few articles on OBI among Nigerians as seen in this review with just one study on OBI among HIV positive patients. The evidence in this review indicates that OBI is common among Nigerians who routinely donate blood for transfusion. The high prevalence of OBI among blood donors portends a high risk of possible transfusion of HBV infected blood. There is therefore urgent need to introduce more sensitive screening methods of blood before transfusion. The screening of blood for HBV and HCV using rapid immunochromatographic methods as is the practice now should be discouraged and discontinued. The minimum allowable screening of blood should be HBcAb and HBV DNA using sensitive methods like ELISA or chemiluminiscence. HBsAb detection and quantification should be introduced as part of screening of potential blood donors. Ultimately, the use of blood transfusion alternatives should be considered as it is safe and effective. This will go a long way to reduce the incidence of HBV infection by blood transfusion and prevent its complications.

More research is needed to determine the prevalence of OBI in the Northern part of Nigeria as no data was found. There is also need to determine the true prevalence rate of OBI/HCV co-infection and the possible impact on the response of patients to therapy. Further evaluation of OBI among Nigerian young population is needed especially those born after the introduction of protective childhood HBV vaccination in 2004.

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REFERENCES

1. McMahon BJ, Alward WL, Hall DB, Heyward WL, Bender TR, Francis DP, *et al.* Acute hepatitis B virus infection: relation of age to the clinical expression of disease and subsequent development of the carrier state. J Infect Dis. 1985; 151:599-603.
2. Tabor E, Hoofnagle JH, Smallwood LA, Drucker JA, Pineda-Tamondong GC, Ni LY, *et al.* Studies of donors who transmit post-transfusion hepatitis. Transfusion. 1979; 19: 725-731.
3. Jayaraman S, Chalab Z, Perel P, Guerriero C, Robert I. The risk of transfusion-transmitted infections in sub-Sahara Africa. Transfusion. 2010; 50(2):433-442.
4. Raimondo G, Allain JP, Brunetto MR, Buendia MA, Chen DS, Colombo M, *et al.* Statements from the Taormina expert meeting on occult hepatitis B virus infection. J. Hepatol. 2008; 49: 652–657.
5. Michalack TI. Occult persistent and lymphotropism of hepadnaviral infection: insights from the woodchuck viral hepatitis model. Immunol Rev. 2000; 174:98-111.
6. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007; 45: 507-539.
7. Torbenson M, Thomas DL. Occult hepatitis B. Lancet Infect Dis 2002; 2: 479-486.
8. Aller de la Fuente R, Guitierrez ML, Garcia-Samaniego J, Fernandez-Rodriguez C, Lledo R, Castellano G. Pathogenesis of occult hepatitis B virus infection. World Journal of Gastroenterology. 2011; 17(12): 1543-1548.
9. Marusawa H, Uemoto S, Hijikata M, Ueda Y, Tanaka K, Shimotohno K, Chiba T. Latent hepatitis B virus infection in healthy individuals with antibodies to hepatitis B core antigen. Hepatology 2000; 31: 488-495.
10. Mason AL, Xu L, Guo L, Kuhns M, Perrillo RP. Molecular basis for persistent hepatitis B virus infection in the liver after clearance of serum hepatitis B surface antigen. Hepatology 1998; 27: 1736-1742.
11. Gerlich WH, Bremer C, Saniewski M, Schüttler CG, Wend UC, Willems WR, Glebe D. Occult hepatitis B virus infection: detection and significance. Dig Dis 2010; 28: 116-125
12. Liu CJ, Lo SC, Kao JH, Tseng PT, Lai MY, Ni YH, Yeh SH, Chen PJ, Chen DS. Transmission of occult hepatitis B virus by transfusion to adult and pediatric recipients in Taiwan. J Hepatol 2006; 44: 39-46
13. Sheen IS, Liaw YF, Lin DY, Chu CM. Role of hepatitis C and delta viruses in the termination of chronic hepatitis B surface antigen carrier state: a multivariate analysis in a longitudinal follow-up study. J Infect Dis 1994; 170: 358-361
14. Said ZN, El-Sayed MH, El-Bishbishi IA, El-Fouhil DF, Abdel-Rheem SE, El-Abedin MZ, Salama II. High prevalence of occult hepatitis B in hepatitis C-infected Egyptian children with haematological disorders and malignancies. Liver Int 2009; 29: 518-524
15. Bréchot C, Thiers V, Kremsdorf D, Nalpas B, Pol S, Paterlini-Bréchot P. Persistent hepatitis B virus infection in subjects without hepatitis B surface antigen: clinically significant or purely "occult"? Hepatology 2001; 34: 194-203
16. Hollinger FB. Hepatitis B virus infection and transfusion medicine: science and the occult. Transfusion 2008; 48: 1001-1026.
17. Hollinger FB, Sood G. Occult hepatitis B virus infection: a covert operation. J Viral Hepat 2010; 17: 1-15.
18. Chemin I, Trépo C. Clinical impact of occult HBV infections. J Clin Virol 2005; 34 Suppl 1: S15-S21.

19. Olayinka AT, Oyemakinde A, Balogun MS, Ajudua A, Nguku P, Aderinola M, et al. Seroprevalence of Hepatitis B Infection in Nigeria : A National Survey. 2016; 95(4): 902–907.
20. Salawu L, Murainah HA. Pre-donation screening of intending blood donors for antibodies to infectious agents in a Nigerian tertiary institution: a pilot study. Afr J Med med Sci. 2006; 35: 453–456.
21. Osuji A, Agbakba NR, Ifeanyichukwu MO, Tatfeng M. Occult hepatitis B virus infection among blood donors at two teaching hospitals in Nigeria: implications for blood transfusion. American Journal of Infectious Diseases and Microbiology. 2018; 6(1):16-25.
22. Akintule OA, Olusola BA, Odaibo GN, Olayeye DO. Occult HBV infection in Nigeria. Archives of Basic and Applied Medicine. 2018; 6:87-93.
23. Olotu AA, Oyelese AO, Lateef S, Audu RA, Okwuraiwe AP, Aboderin AO. Occult Hepatitis B virus infection in previously screened, blood donors in Ile-Ife, Nigeria: implications for blood transfusions and stem cell transplantation. Virology Journal. 2016; 13:76.
24. Oluyinka OO, Tong HV, Tien SB, Fagbemi OA,Tien SB, Fagbami AH et al. Occult hepatitis B virus infection in Nigerian blood donors and hepatitis B virus transmission risks. PLoS ONE. 2015; 10(7): e0131912.
25. Opaleye OO, Fagbemi AH, Bolaji AH. Occult hepatitis B virus infection in fully screeened blood units in Nigeria. 2014; 16th ICID Abstract/International Journal of Infectious diseases 21S:1-460.
26. Opaleye OO, Oluremi AS, Atiba AB, Adewumi MO, Mabayoje OV, Donbraye E, et al. Occult hepatitis B virus infection among HIV positive patients in Nigeria. Journal of Tropical Medicine. 2014. Available at http://dx.doi.org.10.1155/2014/796121
27. Nna E, Mbamalu C, Ekejindu I. Occult hepatitis B viral infection among blood donors in South-East Nigeria. Pathogens and Global Health. 2014. 108:223-228.
28. Ola SO, Otegbayo JA, Odaibo GN, Olayele DO, Olubuyide IO, Summerton CB, et al. Occult HBV infection among a cohort of Nigerian adults. J Infect Dev Ctries. 2009; 3(6):442-446.
29. Elbahrawy A, Alaboudy A, El Moghazy W, Elwassief A, Alashker A, Abdallah AM. Occult hepatitis B virus infection in Egypt. World J Hepatol. 2015; 7(12): 1671-1678.
30. Inaku KO, Ita OI, Ogar FA, Inaku LA. Fulminant hepatitis with negative viral serological markers: a possible case of occult hepatitis B infection. Ann. Trop Pathol. 2019; 10:100-103
31. Candotti D, Allain JP. Transfusion-transmitted hepatitis B virus infection. J Hepatol 2009; 51: 798-809.
32. Allain JP, Mihaljevic I, Gonzalez-Fraile MI, Gubbe K, HolmHarritshøj L, Garcia JM, Brojer E, Erikstrup C, Saniewski M, Wernish L, Bianco L, Ullum H, Candotti D, Lelie N, Gerlich WH, Chudy M. Infectivity of blood products from donors with occult hepatitis B virus infection. Transfusion 2013; 53: 1405-1415.
33. Wang JT, Lee CZ, Chen PJ, Wang TH, Chen DS. Transfusiontransmitted HBV infection in an endemic area: the necessity of more sensitive screening for HBV carriers. Transfusion 2002; 42: 1592-1597.
34. Satake M, Taira R, Yugi H, Hino S, Kanemitsu K, Ikeda H, Tadokoro K. Infectivity of blood components with low hepatitis B virus DNA levels identified in a lookback program. Transfusion. 2007; 47: 1197-1205.
35. Said ZN, Sayed MH, Salama II, Aboel-Magd EK, Mahmoud MH, Setouhy ME, Mouftah F, Azzab MB, Goubran H, Bassili A, Esmat GE. Occult hepatitis B virus infection among Egyptian blood donors. World J Hepatol. 2013; 5: 64-73.
36. Hassan AG, Yassin ME, Mohammed AB, Bush NM. Molecular Detection and Sero-frequency Rate of Occult Hepatitis B Virus among Blood Donors in Southern Darfur State (Sudan). African Journal of Medical Sciences. 2017, 2 (9).
37. Hollinger FB, Sood G. Occult hepatitis B virus infection: A covert operation. J Viral Hepat 2010;17:1-5.
38. Liu CJ, Chen DS, Chen PJ. Epidemiology of HBV infection in Asian blood donors: emphasis on occult hepatitis B infection and the role of NAT. J Clin Virol. 2006; 36 Suppl 1:S33-S34.
39. El-Sherif AM, Abou-Shady MA, Al-Hiatmy MA, Al-Bahrawy AM, Motawea EA. Screening for hepatitis B virus infection in Egyptian blood donors negative for hepatitis B surface antigen. Hepatol Int. 2007; 1: 469-470.
40. Seo DH, Whang DH, Song EY, Han KS. Occult hepatitis B B virus infection and blood transfusion. World Journal of Hepatotlogy. 2015;7(3):600-606.
41. Tani Y, Aso H, Matsukura H, Tadokoro K, Tamori A, Nishiguchi S, Yoshizawa H, Shibata H. Significant background rates of HBV and HCV infections in patients and risks of blood transfusion from donors with low anti-HBc titres or high anti-HBc titres with high anti-HBs titres in Japan: a prospective, individual NAT study of transfusion-transmitted HBV, HCV and HIV infections. Vox Sang 2012; 102: 285-293.
42. Minuk GY, Sun DF, Uhanova J, Zhang M, Caouette S, Nicolle LE, Gutkin A, Doucette K, Martin B, Giulivi A. Occult hepatitis B virus infection in a North American community-based population. J Hepatol. 2005; 42: 480-485.
43. Sunbul M. Hepatitis B virus genotype: Global distribution and clinical importance. World J Gastroenterol. 2014; 20(8):5427-5432.

44. Ocana S, Casas ML, Buhigas I, Lledo JL. Diagnostic strategy for occult hepatitis B virus infection. World J Gastroenterol. 2011;17(12):1553-1557.
45. Odemuyiwa SO Mulders MN Oyedele OI Ola SO Odaibo GN Olaleye DO. Phylogenetic analysis of new hepatitis B virus isolates from Nigeria supports endemicity of genotype E in West Africa. Journal of Medical Virology. 2001; 65: 463-469.
46. Mulders MN Venard V Njayou M Edorh AP Oyefolu AOB Kehinde MO. Low genetic diversity despite hyperendemicity of hepatitis B virus genotype E throughout West Africa. Journal of Infectious Diseases. 2004;190: 400-408.
47. Allain JP. Epidemiology of Hepatitis B virus and genotype. Journal of Clinical Virology. 2006; 36(S1): S12-S17.
48. Liu CJ, Kao JH. Global pespective on the natural history of chronic hepatitis B virus genotypes A-J. Semin Liver Dis. 2013; 33:97-102
49. Ogawa M, Hasegawa K, Naritomi T, Torii N, Hayashi N. Clinical features and viral sequences of various genotypes of hepatitis B virus compared among patients with acute hepatitis B. Hepatol Res. 2002;23(3):167–177.
50. Suzuki Y, Kobayashi M, Ikeda K,etal. Persistence of acute infection with hepatitis B virus genotype A and treatment in Japan. J Med Virol 2005;76(1):33–39.
51. Datta S, Banerjee A, Chandra PK, Chowdhury A, Chakravarty R. Genotype, phylogenetic analysis and transmission pattern of occult hepatitis B virus (HBV) infection in families of assymptomatic HBsAg carriers. Journal of Medical Virology. 2006; 78: 53-59.
52. Poukarim MR, Amini-Bavil-Olayee S, Kabanov F, Ranst MV, Taske F. Molecular identification of hepatitis B virus genotypes/subgenotypes: Revised classification hurddles and updated resolutions. World J Gastroenterol. 2014; 20(32): 7152-7168.
53. Erhabor O, Kwaifa I, Bayawa AM, Isaac ZI, Dorcas I, et al. Comparison of ELISA and rapid screening technique for the detection of HBsAg among blood donors in Usmanu Danfodiyo University Teaching Hospital, Sokoto, North West Nigeria. J. Blood Lymph. 2014; 4:124.
54. Raouf HE, Yassin AS, Megahed SA, Ashour MS, Mansour TM. Seroprevalence of occult hepatitis B among Egyptian paediatric hepatitis C cancer patients. J Viral Hepat. 2015; 22: 103-111.
55. Kishk R, Atta HA, Ragheb M, Kamel M, Metwally L, Nemr N. Genotype characterization of occult hepatitis B virus strains among Egyptian chronic hepatitis C patients. East Mediterr Health J. 2014; 20: 130-138.
56. Kumar GT, Kazim SN, Kumar M, Hissar S, Chauhan R, Basir SF, Sarin SK. Hepatitis B virus genotypes and hepatitis B surface antigen mutations in family contacts of hepatitis B virus infected patients with occult hepatitis B virus infection. J Gastroenterol Hepatol. 2009; 24: 588-598.
57. Ding, X.; Park, Y.N.; Taltavull, T.C.; Thung, S.N.; Jin, X.; Jin, Y.; Trung, N.S.; Edamoto, Y.; Sata, T.; Abe, K. Geographic characterization of hepatitis virus infections, genotyping of hepatitis B virus, and p53 mutation in hepatocellular carcinoma analyzed by in situ detection of viral genomes from carcinoma tissues: Comparison among six different countries. Jpn. J. Infect. Dis. 2003; 56:12–18.
58. Katsoulidou A, Paraskevis D, Magiorkinis E, Moschidis Z, Haida C, Hatzitheodorou E, Varaklioti A, Karafoulidou A, Hatzitaki M, Kavallierou L, Mouzaki A, Andrioti E, Veneti C, Kaperoni A, Zervou E, Politis C, Hatzakis A. Molecular characterization of occult hepatitis B cases in Greek blood donors. J Med Virol. 2009; 81: 815-825,
59. Torbenson M, Thomas DL. Occult hepatitis B. Lancet Infect Dis. 2002; 2: 479-486.
60. Brojer E, Grabarczyk P, Liszewski G, Mikulska M, Allain JP, Letowska M. Characterization of HBV DNA+/HBsAg- blood donors in Poland identified by triplex NAT. Hepatology. 2006; 44: 1666-1674.
61. Minuk GY, Sun DF, Uhanova J, Zhang M, Caouette S, Nicolle LE, Gutkin A, Doucette K, Martin B, Giulivi A. Occult hepatitis B virus infection in a North American community-based population. J Hepatol. 2005; 42: 480-485
62. Abdulraheem IS, Onajole AT, Jimoh AAG OA. Reason for incomplete vaccination and factors for missed opportunities among rural Nigerian Children. J Pub Hlth Epid. 2011; 3:194–203.
63. Paediatric Association of Nigeria (PAN) recommended routine schedule for Nigerian Children. PAN Advisory Committee on Immunization. Niger J Paed. 2012; 39(4):152–158.
64. Schmeltzer P, Sherman KE. Occult hepatitis B: clinical implications and treatment decisions. Dig Dis Sci 2010; 55: 3328-3335
65. Inaku KO, Ita OI, Ogar FA, Inaku LA. Hepatitis B antigenaemia in Ogoja Local Government Area of Cross River State, Nigeria. Scolars Journal of Applied Medical Scienses. 2019; 7(1):323-326
66. Olayinka AT, Oyemakinde A, Balogun MS, Ajudua A, Nguku P, Aderinola M, EgwuenuOladejo A, Ajisegiri SW, Sha'aibu S, Musa BO, Gidado S. Seroprevalence of hepatitis B infection in Nigeria: A national survey. The American journal of tropical medicine and hygiene. 2016; 95(4):902-7.

67. Huang P, Zhu LG, Zhu YF, Yue M, Su J, Zhu FC, Yang HT, Zhang Y, Shen HB, Yu RB, Zhai XJ. Seroepidemiology of hepatitis B virus infection and impact of vaccination. World Journal of Gastroenterology. 2015; 21(25):7842.
68. Elrashidy H, El-Didamony G, Elbahrawy A, Hashim A, Alashker A, Morsy MH, Elwassief A, Elmestikawy A, Abdallah AM, Mohammad AG, Mostafa M, George NM, Abdelhafeez H. Absence of occult hepatitis B virus infection in sera of diabetic children and adolescents following hepatitis B vaccination. Hum Vaccin Immunother 2014; 10: 2336-2341.
69. Sagnelli E, Pisaturo M, Martini S, Fillipino P, Sagnelli C, Coppola N. Clinical impact of occult hepatitis B virus infection in immunosupressed patients. World J Hepatol. 2014; 6(6):384-393.
70. Bell TG, Makondo E, Martinson NA, Kramvis A. Hepatitis B Virus Infection in Human Immunodeficiency Virus Infected Southern African Adults: Occult or Overt – That Is the Question. PLoS ONE. 2012; 7(10): e45750.
71. N'Dri-Yoman T, Anglaret X, Messou E, Attia A, Polneau S, Toni T (2010). Occult HBV infection in untreated HIV-infected adults in Cote d'Ivoire. Antiviral Therapy. 15: 1029–1034.
72. Mudawi H Hussein W Mukhtar M Yousif M Nemeri O Glebe D (2014). Overt and occult hepatitis B virus infection in adult Sudanese HIV patients. International Journal of Infectious Diseases. 29: 65-70.
73. Cassini R, De Mitri MS, Gibellini D, Urbinati L, Bagaglio S, Morsica G, Domenicali M, Verucchi G, Bernardi M. A novel stop codon mutation within the hepatitis B surface gene is detected in the liver but not in the peripheral blood mononuclear cells of HIV-infected individuals with occult HBV infection. J Viral Hepat. 2013; 20: 42-49.
74. Filippini P, Coppola N, Pisapia R, Martini S, Marrocco C, Di Martino F, Sagnelli C, Filippini A, Sagnelli E. Virological and clinical aspects of HBV-HCV coinfection in HIV positive patients. J Med Virol. 2007; 79: 1679-1685.
75. Mahmood OAEK, Ghazal AAER, Metwally DES, Shamseya MM, Hamdallah HM. Detection of hepatitis B virus among chronic hepatitis C patients. Alexanderia Journal of Medicine. 2016; 52:115-123.
76. Emara AH, El-Gammal NE, Mohammed LA, Bahgat MM. Occult hepatitis B infection among Egyptian Chronic hepatitis C patients: prevalence, impact on pegylated interferon/ribavarin therapy. Virol J. 2010; 7:324.
77. El-Sherif A, Abou-Shady M, Abou-Zeid H, Elwassief A, Elbahrawy A, Ueda Y, Chiba T, Hosney AM. Antibody to hepatitis B core antigen as a screening test for occult hepatitis B virus infection in Egyptian chronic hepatitis C patients. J Gastroenterol. 2009; 44: 359-364.
78. Chu CJ, Lee SD. Hepatitis B virus/hepatitis C virus coinfection: epidemiology, clinical features, viral interactions and treatment. J Gastroenterol Hepatol 2008; 23: 512-520.
79. Mrani S, Chemin I, Menouar K, Guillaud O, Pradat P, Borghi G, Trabaud MA, Chevallier P, Chevallier M, Zoulim F, Trépo C. Occult HBV infection may represent a major risk factor of non-response to antiviral therapy of chronic hepatitis C. J Med Virol 2007; 79: 1075-1081
80. Ikeda M, Kato N. Life style-related diseases of the digestive system: cell culture system for the screening of anti-hepatitis C virus (HCV) reagents: suppression of HCV replication by statins and synergistic action with interferon. J Pharmacol Sci. 2007; 105: 145-150.