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Original Article

Hepatitis D virus antibodies and liver function profile among patients with chronic hepatitis B infection in Abuja, Nigeria

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Abstract

Introduction: Hepatitis D virus (HDV) is a satellite virus of hepatitis B virus (HBV). An estimated 5% of HBV infected individuals worldwide have HDV infection. There is paucity of studies in Nigeria on the burden of HDV infection. This study aimed at determining the prevalence rate of HDV antibodies among individuals with chronic hepatitis B (CHB) infection and comparing the liver function test (LFT) and disease severity among the anti-HDV positive (anti-HDV+) and anti-HDV negative (anti-HDV-) individuals.

Methodology: A cross-sectional study of 180 CHB infected individuals who were clinically evaluated and tested for HDV antibodies using the Enzyme-linked Immunoassay method. Their LFT profile and Child-Turcotte-Pugh (CTP) were also assessed. Data were analyzed using the SPSS version 17.

Results: Their mean age was 35.2 ± 10.4 years. There were 150 (83.3%) and 30 (16.7%) individuals with uncomplicated and complicated CHB infection respectively. Thirty-four (18.9%) of the participants were anti-HDV+. The mean serum ALT, AST, albumin and INR of the anti-HDV+ subjects were 16.5 ± 13.8 IU/L, 26.3 ± 32.6 IU/L, 38.9 ± 7.6 g/L, and 1.2 ± 0.2 respectively. The mean values for the same parameters of the anti-HDV- subjects were 10.8 ± 9.5 IU/L, 13.4 ± 11.2 IU/L, 41.4 ± 6.0 g/L and 1.1 ± 0.2 respectively ($p < 0.05$). The mean CTP scores in the anti-HDV+ and anti-HDV- subjects were 6.1 ± 2.1 and 5.5 ± 1.2 respectively ($p= 0.03$).

Conclusions: Anti-HDV sero-prevalence rate was 18.9% and anti-HDV+ CHB patients had worse LFT results compared to those who were anti-HDV–.

Key words: hepatitis D; hepatitis B; antibodies; liver function; Nigeria.

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Introduction

Hepatitis D virus (HDV) is a defective single stranded RNA virus that requires the helper function of Hepatitis B virus (HBV) to assemble new virion particles and become infectious. It was first identified in Italy among patients with chronic hepatitis B (CHB) infection in 1977 [1]. CHB infection remains a global burden with an estimated 257 million individuals infected worldwide of which about 5% are also infected with HDV [2,3]. The global distribution of HDV tends to follow that of HBV, although with geographical differences [4]. Individuals with acute HDV/HBV co-infection are at risk of severe acute clinical outcomes (e.g. liver failure) compared to those with acute HBV infection alone. On the other hand, individuals with chronic HBV/HDV infection are at greater risk of developing chronic sequelae such as liver cirrhosis and hepatocellular carcinoma compared to those with chronic HBV mono-infection.

HBV infection is hyper-endemic in sub-Saharan Africa [5]. In Nigeria, several studies have reported high prevalence rates of HBV infection in different cohorts [6-8]. A national survey estimates the prevalence rate of HBV infection to be 12.2% [9]. There are only few studies on HDV infection from the southern part of Nigeria and paucity of data from the northern part of Nigeria where this study was done. Thus the potential impact of HDV infection on the morbidity and mortality associated with HBV infection is yet to be properly assessed in Nigeria.

The aim of this study was to determine the sero-prevalence rate of HDV antibodies (IgM and IgG) among CHBV infected individuals seen in a tertiary institution. The other objectives were to compare the LFT profiles and severity of liver disease, using the Child-Turcotte-Pugh (CTP) score, of the anti-HDV positive (anti-HDV+) and anti-HDV negative (anti-HDV-) individuals.

Methodology

The was a cross-sectional descriptive study, conducted from September to December, 2014 at the Gastroenterology Unit of the University of Abuja Teaching Hospital, Abuja, located in the North Central Geo-political zone of Nigeria.

The sample size was derived using the Fisher's Formula based on the closest available prevalence rate in Nigeria [10]. One hundred and eighty (180) chronic hepatitis B infected patients were recruited for this study to cover for a 5% attrition rate.

Inclusion criteria**:** All patients who had CHBV infection attending the Gastroenterology Clinic and gave a written consent to participate in the study. This included patients with liver cirrhosis and hepatocellular carcinoma.

Inclusion criteria**:** Patients with hepatitis C virus (HCV) or Human immunodeficiency virus (HIV) infection as well as patients with history of significant alcohol consumption were excluded. Patients already taking anti-viral chemotherapy for chronic hepatitis B infection were also excluded.

Data collection: A semi-structured interviewer administered questionnaire was administered to each participant. The questionnaire was pre-tested in the Local Government Area Council Health Centre before the commencement of the study. A detailed history was taken from each participant focusing on symptoms related to the hepato-biliary system, symptoms suggestive of hepatic encephalopathy, history of alcohol consumption (and quantity), drug history (including HBV anti-viral drugs) and co-morbidities. Each participant underwent a detailed physical examination with focus on general physical examination, stigmata of chronic liver disease, abdominal and neurological examination. Hepatic encephalopathy was graded using the West Haven staging criteria [11].

Ten millilitres of venous blood sample was taken from the antecubital fossa of each participant under aseptic conditions - 5mls was taken in a plain sample bottle and another 5mls in a sodium citrate bottle for prothrombin time test. Samples taken in plain bottles were left to clot and then centrifuged at 4000 rpm for 5 minutes to extract serum. All samples were properly labeled with the serial number on the questionnaire and stored at -20^{o}C in a freezer. HBsAg, HBcAb-IgM, HBcAb-total and HCV-Ab tests were done using the *CTK onsite* rapid test kit (manufactured by CTK Biotech Inc., Poway, USA) which is an immunochromatographic based test. HIV screening was done using Determine® HIV-1/2 kit (manufactured by Alere Medical Co, Tokyo, Japan). Liver function tests (LFTs) were done by the use of spectrophotometer manufactured by Erba Mennhein Diagnostics, Mennheim, Germany and reagents manufactured by Randox Laboratories Ltd, U.K. IgG anti-HDV and IgM anti-HDV tests were done using test kits manufactured by Creative Diagnostics, New York, U.S.A which is based on the enzyme-linked immunoassay (ELISA) method. All tests were done based on the manufacturers' protocols. Results of the tests were recorded in the respective questionnaires for each participant. All participants underwent an abdominal ultrasonography to assess for evidence of liver cirrhosis, portal hypertension or hepatic masses.

Based on the history obtained, physical examination and abdominal ultrasound scan report, patients were grouped into two diagnostic categories, viz: uncomplicated chronic hepatitis B infection (individuals with no clinical or radiologic evidence of liver cirrhosis or hepatocellular carcinoma) and complicated chronic hepatitis B infection (individuals with clinical and/or radiologic evidence of liver cirrhosis or hepatocellular carcinoma). Severity of liver disease was assessed using the Child-Turcotte-Pugh (CTP) Score using serum total bilirubin, albumin, INR and assessment of ascites and hepatic encephalopathy [12].

Ethical consideration**:** Approval of the Health Research and Ethics Committee of The University of Abuja Teaching Hospital was obtained before the commencement of the study. Written informed consent was obtained from patients willing to participate in the study. The purpose of the study was explained to each prospective participant in the language best understood by the participant. Consent was, however, also obtained from parents of participants who were less than 18years of age (16-18 years) and from the next of kin or caregivers of patients who had hepatic encephalopathy.

Data analysis**:** Information on the questionnaires was entered into the Statistical Package for Social Sciences (SPSS) software (SPSS version 17, Chicago, IL) which was used to analyze the data set for this study. Differences in categorical variables were analyzed using Chi square (χ^2) or Fisher's exact while differences in continuous variables were analyzed using Student's t test and Analysis of Variance (ANOVA) as appropriate. P value $\leq$ 0.05 was considered statistically significant.

Results

Of the 180 individuals who participated in the study, 116 (64.4%) were males, while 64 (35.5%) were females. The mean age was 35.2 (± 10.4) years. The

clinical diagnosis was uncomplicated CHB in 150 (83.3%) patients and complicated CHB in 30 (16.7%) patients (of which 14 had features of liver cirrhosis and 16 had features of HCC).

Thirty-four (18.9%) of the participants were positive for HDV antibodies (anti-HDV+) while the remaining 146 (81.1%) tested negative for HDV antibodies (anti-HDV-). This consisted of 6 (3.3%) who were positive for both IgM and IgG anti-HDV, 18 (10%) were positive for IgG anti-HDV alone and 10 (5.6%) were positive for IgM anti-HDV alone. Thus, a total of 24 (13.3%) were positive for IgG anti-HDV while 16 (8.9%) participants were positive for IgM anti-HDV.

The mean age (± SD) was 37.1 (± 10.1) years among those who were anti-HDV + and 34.8 (± 10.4) years among those who were anti-HDV -. (p = 0.25). The gender-specific prevalence rates were 16.4% for males and 23.4% for females (p = 0.25). IgG anti-HDV was positive in 13 (11.2%) of the males and 11 (17.2%) of the females (p = 0.26) while IgM anti-HDV was positive in 9 (7.8%) of the males and 7 (10.9%) of the females (p = 0.47). Both IgM and IgG were positive in 3 each of the male (2.6%) and female (4.7%) participants.

The proportion of patients positive for IgM and/or IgG anti-HDV in the different diagnostic groups is shown in Table 1.

The LFT profile showed a significantly higher mean ALT, AST and INR among all the individuals who were anti-HDV+ compared to those who were anti-HDV-. The mean serum albumin was significantly lower among all the individuals who were anti-HDV+ compared to those who were anti-HDV-. Table 2 shows the LFT profile among all the individuals who were anti-HDV+ compared to those who were anti-HDV–.

The mean CTP score was significantly higher among all the participants who were anti-HDV+ compared to those who were anti-HDV-. However, in the different diagnostic groups, the mean CTP scores were not significantly different in those who were anti-HDV+ compared to those who were anti-HDV– (Table 3).

Table 1. Prevalence rate of anti-HDV antibodies in the different clinical diagnostic groups.

HDV Antibodies	Uncomplicated CHB (N = 150)	Complicated CHB (N = 30)	P – value*
IgM positive	13 (8.7%)	3 (10.0%)	0.815
IgG positive	16 (10.7%)	8 (26.7%)	0.019
Both IgM and IgG positive	4 (2.7%)	2 (6.7%)	0.265
IgM and/or IgG positive	25 (16.7%)	9 (30.0%)	0.089

*chi square.

Table 2. Liver function test profile and HDV sero-status among all the 180 patients with CHB infection.

	All Participants (n = 180)		
LFT profile	Anti-HDV positive Mean (± S.D)	Anti-HDV negative Mean (± S.D)	P – value*
T. Bil (μmol/L)	25.9 (± 33.4)	21.0 (± 56.2)	0.628
C. Bil (μmol/L)	16.5 (± 28.4)	10.4 (± 33.5)	0.329
ALP (IU/L)	115.3 (± 77.5)	120.8 (± 107.5)	0.775
ALT (IU/L)	16.5 (± 13.8)	10.8 (± 9.5)	0.005
AST (IU/L)	26.3 (± 32.6)	13.4 (± 11.2)	< 0.0005
T. Protein (g/L)	67.8 (± 8.2)	70.6 (± 7.8)	0.062
Albumin (g/L)	38.9 (± 7.6)	41.4 (± 6.0)	0.042
INR	1.2 (± 0.2)	1.1 (± 0.2)	0.018

* Student's t- test.

Table 3. Mean Child-Turcotte-Pugh score and HDV sero-status among the different groups of patients with CHB.

Clinical Diagnosis	Mean CTP score (± S.D)		P – value*
	Anti-HDV positive	Anti-HDV negative	
Uncomplicated CHB infection (n = 150)	5.1 (± 0.3)	5.1 (± 0.2)	0.647
Complicated CHB infection (n = 30)	8.9 (± 2.3)	8.0 (± 1.8)	0.245
All participants (n = 180)	6.1 (± 0.0)	5.5 (± 1.2)	0.025

* Student's t- test.

Discussion

HBV infection is hyper-endemic in sub-Saharan Africa. National sero-prevalence rate of HBV infection is estimated to be 12.2% in Nigeria where acquisition of HBV is mainly through horizontal transmission amongst unimmunized children and vertical transmission from infected mothers [2,9]. The burden of HBV infection in Nigeria cannot be underestimated as it accounts for significant morbidity and mortality. It is a major cause of liver cirrhosis and HCC with resultant increased burden of healthcare cost particularly in a third world country like Nigeria. A hospital-based study reported HCC and liver cirrhosis to be responsible for 44.3% and 20.4% of liver diseases respectively [13]. The study reported HBV infection as the risk factor in 61.4% of the HCC cases and 45.9% of the liver cirrhosis. The prognosis of HCC tends to be poorer in this region compared to the western world due to late presentation, poor healthcare infrastructure and lack of access to expensive treatment [14]. The contribution of HDV to the severity and progression of HBV-related liver disease in Nigeria has not been widely studied, particularly in the Northern region where this study took place.

The prevalence rate of anti-HDV in this study was 18.9% (16.7% among patients with uncomplicated CHB and 30.0% among patients with complicated CHB). These findings are comparable to the prevalence rates reported among HBV carriers in Cameroon (17.6%) [15] but lower than reported prevalence rates in Niger Republic – 29.3% and 40.2 % among asymptomatic HBV infected individuals and complicated CHBV patients respectively [16,17]. These countries share border with Nigeria to the East and North respectively. In Nigeria, the prevalence rate of anti-HDV in this study is comparable to 15.5% among HBV carriers that was reported about two decades ago in the South-Eastern part of Nigeria [18], but higher than more recent reports from the same region – 6.7% among asymptomatic HBV carriers and 15.0% among advanced CHB patients [10]. Much lower prevalence rates have been reported in the South-Western part of Nigeria – 2% among CHB patients [19] and 4.9% in a multi-centre study done in the South-Western Nigeria among HBV infected individuals [20]. It is uncertain if the differences in prevalence rates reported in the different regions of Nigeria are due to differences in sample size, characteristics of the study population or a reflection of regional variation in the prevalence of HDV. This regional variation may be due to differences in traditional and cultural practices or climatic variation in different regions of Nigeria. Nigeria has three major tribes located in the south-eastern, south-western and northern parts of the country. The tribes have different cultural practices relating to tribal and scarification marks, circumcision, marriage practices, etc. The southern and northern parts on Nigeria are mainly tropical rainforest and savannah respectively with the South having higher humidity and lower average temperature compared to the North. These may presumably affect the prevalence rates however, there is no conclusive evidence of this. There have been reports of regional variation in the prevalence of HDV in Senegal and Kenya which were attributed to different cultural practices [21,22].

The gender specific prevalence rates of anti-HDV were not significantly different among the males compared to the females. This is similar to the findings of another study in Southeast Nigeria [10], but at variance to the findings of a study conducted in Brazil where the gender specific prevalence rate of anti-HDV was significantly higher in males compared to females [23]. The mean age of the participants who were anti-HDV+ compared to those who were anti-HDV- was not statistically different, even in the different diagnostic groups. Similar finding was reported in a study in Cameroon [15]. This is in contrast to the findings in Niger Republic where cirrhosis patients with HDV infection were significantly younger than those without HDV infection [17]. Considering the association of HDV with faster disease progression, it is expected that cirrhosis and HCC may develop at a younger age in CHB patients who have HDV infection compared to those who do not.

Six (3.3%) of the participants in this study were found to be positive for both IgM and IgG anti-HDV while 10 (5.6%) and 18 (10.0%) of the participants had isolated IgM anti-HDV and IgG anti-HDV antibodies respectively. A similar trend was reported in a study of 153 HBV infected individuals in Turkey [24]. Unlike in other viral hepatitis infections, IgM anti-HDV may persist in chronic HDV infection [25]. The presence of IgM anti-HDV in chronic infection appears to correlate with levels of HDV replication [26]. The monomeric (7S) form of IgM anti-HDV is predominant in chronic HDV infection while the pentameric (19S) form is found in acute HDV infection [27]. Thus, tests for 7S and 19S IgM anti-HDV may be of value for differentiating between acute and chronic HDV infections [28]. The assay used in this study, however did not differentiate the type of IgM anti-HDV detected. The participants in this study with isolated IgM anti-HDV could have had an acute HDV super-infection or a chronic HDV infection. Our finding of a significantly

higher proportion of the patients with complicated CHB being IgG anti-HDV positive compared to the patients with uncomplicated CHB may corroborate the association of chronic HDV infection with faster disease progression as suggested by other authors [29,30]. Perhaps, early detection and treatment of HDV (and CHB) infection may slow down the rate of development of complications among CHB patients.

In this study, there was a significantly higher mean serum ALT, AST and INR among all the anti-HDV+ compared to the anti-HDV- individuals. The mean serum albumin was also significantly lower among the anti-HDV+ individuals.

Studies have demonstrated a significantly higher histological activity among HDV infected compared to HDV non-infected CHB patients [31,32]. AST Platelet Ratio Index (APRI) score has been validated as a good predictor of fibrosis among CHB patients [33]. Our study design did not include platelets in the laboratory test and this is a limitation to our use of the APRI score to predict fibrosis among our patients. However, assessment of severity of liver disease in this study was measured using the CTP score rather than histology, which is considered the gold-standard in assessing liver disease. The mean CTP score in this study was significantly higher among the anti-HDV+ compared to the anti-HDV- participants ($p = 0.03$). However, in the different diagnostic groups, the difference in CTP score was not statistically significantly different in the anti-HDV+ compared to the anti-HDV- participants. HDV may thus have contributed to disease severity in the entire study population, but this impact was not significant among the individual diagnostic groups. Further studies based on APRI score and histological assessment of liver disease would be required to evaluate the contribution of HDV to severity of liver disease in CHB patients in Nigeria.

Public enlightenment is necessary to stem the tide of transmission of both HBV and HDV. Currently there is no vaccine against HDV. Some countries however, recorded a decline in the prevalence of HDV due to vaccination against HBV as well as heightened public awareness on safe practices. With the widespread availability of HBV vaccine, the global burden of HBV, and thus HDV, can be controlled in the not too distant future. However, sustainability of HBV immunization programmes as well as its uptake remains a challenge in sub- Saharan Africa [2]. HDV screening should be routine among HBV infected individuals to allow HBV carriers know their status and to determine the best management for CHB patients.

Conclusions

The sero-prevalence rate of HDV antibodies in this study was 18.9%, which is higher than what was obtained in previous studies in Nigeria. The liver function parameter demonstrated significantly higher serum AST, ALT, INR and lower serum albumin among the anti-HDV+ compared to the anti-HDV- individuals. Screening for HDV should be encouraged for all individuals with CHB.

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