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Treatment Penetration and Correlates of Diagnostic Parameters among Hepatitis B Seropositive Individuals in Ondo State, Nigeria

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ABSTRACT

Our aim is to determine Hepatitis B Virus (HBV) infection's treatment penetration among infected patients and levels of correlation between serologic, biochemical and molecular tests. Serologic tests considered were, Hepatitis B surface Antigen (HBsAg), Hepatitis B surface Antibody (HBsAb), Hepatitis B 'e' Antigen (HBeAg), Hepatitis B core Antibody (HBcAb) and Hepatitis B 'e' Antibody (HBeAb); biochemical tests included alanine transaminase (ALT) and the molecular test was HBV viral DNA load. These parameters were considered among Hepatitis B seropositive patients so as to evaluate individual relevance of these tests to disease management in an endemic population. In this retrospective study, data of patients who attended Viral Hepatitis Clinics in University of Medical Sciences Teaching Hospital Complex, Ondo, Nigeria from 2014 to 2019 were extracted. Serological profiles (HBsAg, HBsAb, HBeAg, hepatitis B core antibody; HBcAb), antibody against HBeAg (HBeAb); biochemical markers (alanine transaminase; ALT); and HBV viral DNA loads were collated. Data were analyzed using the Statistical Package for Social Sciences (SPSS) software version 23.0. Among a total of 630 HBsAg sero-positive patients, 48 completed the three series of tests and commenced treatment; giving a treatment penetration rate of 7.6%. Among these, 28 were males and 20 were females (1.4:1) with mean age of 34years. All had detectable viral load above 20 iu/mL and were all HBcAb positive; 26 (54.2%) had viral load below 2,000 iu/mL. Among the total of 48 patients 2 were HBeAg positive while 46 were negative. Among 46 which were HBeAg seronegative, 20 (43.5%) had viral load above 2,000 iu/mL. The 2 patients with HBeAg had viral load above 20,000 iu/mL and were also positive for HBeAb. Among the 19 (39.6%) which had ALT values greater than 20iu/L, nine (47.4%) had viral load above 2,000

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iu/mL, while among 29 (60.4%) with ALT below 20 iu/L, 13 (44.8%) had viral load greater than 2,000iu/L. We concluded that wide gaps exist between HBsAg sero-positivity and treatment penetration in our environment. Neither serology, ALT nor viral loads can single handedly predict needs for patients' treatment. The presence of HBeAb was not protective against HBeAg. The need for special national hepatitis programs for adequate provision of treatment and follow-up services cannot be overemphasized.

Keyword: Treatment penetration, Hepatitis B surface antigen, HBV, DNA viral load, Alanine transaminase enzyme, Correlation.

INTRODUCTION

Hepatitis B surface antigen (HBsAg) is pathognomonic for hepatitis B viral infection and it is the earliest serological marker to appear in acute hepatitis B virus (HBV) infection[1]. National survey in Nigeria found hepatitis B infection of 12.2% prevalence in 2016[2]. However, the prevalence of HBV varies in different parts of Nigeria where 5-13 % was seen[3] and other countries such as Kenya 5-14%, Rwanda (3.9%), US (2%) and Britain (0.1 to 0.2%)[4,5]. The high prevalence of chronic Hepatitis has made it technically difficult to achieve eradication of HBV by means of universal vaccination[6]. And it has been estimated that 15%25% of chronic HBV carriers will die from complications of progressive diseases such as liver cirrhosis, hepatocellular carcinoma, and hepatic decompensation[1]. Overt and occult infections increase the complexity of the diagnostic algorithms, however, accurate and continuously improved diagnostic policies will identify the infections for appropriate treatment[7].

Conventional treatment criteria for HBV are based on Levels of viral replication, degree of host response and extent of liver damage. Levels of viral replication has been done using viral load, HBsAg quatification or HBeAg serum status; degree of host response has been determined using liver biopsy and alanine aminotransferase (ALT) levels and extent of liver damage have been based on fibrosis staging by histopathology, liver stiffness measurement or serum bilirubin levels[8-10]. HBV DNA load is the most reliable marker of active viral replication and correlates with levels of circulating viral particles[11]. It is also of prognostic values in acute and chronic HBV infections. However, HBV viral load is expensive[12] and the impact on treatment penetration may hinder the attainment of global viral hepatitis control[13]. The highly endemic nature of HBV in low income countries along with the dwindling economic fortunes underscores the need for development of cost effective management modalities for HepB hepatitis and calls for cheaper tests that can be used to monitor viral replication and responses to antiviral therapy.

Proper correlation of serologic, molecular markers in combination with clinical assessment and biochemical tests is a focus in right direction in the assessment of the natural history and individual risks of progressive liver disease. It may also provide a background for modified international and local HBV treatment guidelines[11].

We aim at determining HBV treatment penetration and levels of correlation of serological, biochemical and molecular parameters among HBsAg positive patients in a tertiary care centre in Ondo, Nigeria, in order to evaluate individual relevance of these tests to disease management in an endemic population.

MATERIALS AND METHODS

In this retrospective study, data of patients with hepatitis B viral infection from 2014 to 2019 were extracted from the database of laboratory and viral

hepatitis clinics of UNIMEDTH Complex, Ondo, Nigeria. Three series of tests namely serological profiles for HBV (HBsAg, HBsAb, HBeAg, anti-HBc, anti-HBe); alanine transaminase (ALT); and HBV DNA Quantification done were collated. Data generated were analyzed using the SPSS software version 23.0. Liver biopsy result which could have also included were removed because only 5 patients did the test.

Analysis for serological markers for HBV was by means of the Enzyme Linked Immunosorbent Assay (ELISA) (DiaPro Diagnostic Bioprobes; Milano, Italy and Biokit, Spain) in accordance with the manufacturer's instructions.

Alanine aminotransferase (ALT) was quantitatively measured using Pars Azmoon kit (Tehran, Iran) based on the kit instruction. HBV DNA was extracted from serum samples followng manufacturer's instructions using QIAmp DNA mini-extraction kit (Qiagen, Hilden, Germany and quantification of HBV DNA were done by real-time PCR using the Artus Light Cycler HBV DNA kit (Qiagen; Hilden, Germany); as per kit instructions and Light Cycler 2.0 instrument Real-Time PCR (Roche, Germany).

Data collected were manually inputted into the computer system and checked for data consistency manually by double entry; and analyzed using the SPSS version 23.0. Univariate data were represented in tables and charts. P-values <0.05 were considered significant at 95.0% confidence level for all inferential analysis.

RESULTS

Among a total of 630 patients that were HBsAg sero-positive during the period under review, forty-eight (48) completed the three series of tests in order to commence treatment; giving a treatment penetration rate of 7.6%. Among these, 28 were males and 20 were females (1.4:1) with mean age of 34years.

All (48) had detectable viral load above 20 IU/mL. The distribution of viral loads (<2000 and >2000 copies/ml) according to age range of the subjects were shown. The peak (47.8%) age group was 30-39 years while least (2.3%) age group was 19 years and below. The Patients' Age range of 10 -19, 20-29, 30-39, 40-49, 50-59 and 60-69 years were distributed with 48 Serum samples (1,6,24,8,7 & 2) accordingly with their Viral loads cut off levels <2000 & > 2000 IU/mL respectively (Figure 1). Serologic markers, viral loads and ALT levels were distributed along HBeAg status in Table1. HBeAg was detectable in only 2 (4.2%) and the two patients were the only ones with HepB viral load above 20,000 IU/mL Among the remaining 46 patients, 26 (56.5%) who were HBeAg negative, had viral loads less than 2,000 IU/mL while 20 (43.5%) had viral load above 2,000 iu/mL and the difference was not statistically significant. We found 38 patients (including those with HBeAg), positive for HBeAb; showing that HBeAb does not protect against aggressive HepB viral replication.

Among the 5 (11.9%) with ALT values greater than 45 IU/L, three (60%) had viral loads above 2,000 IU/mL, while among those with ALT below 45 IU/L, 14 (37.8%) had viral loads greater than 2,000 IUm/L and the difference was not statistically significant. HBcAb was detected in all (100%) of which all had viral above 20 IU/mL.

Table 2 compares viral loads with ALT, HBcAb and HBsAb in the study population. Among the 19 (39.6%) which had ALT values greater than 20iu/L, nine (47.4%) had viral load above 2,000 iu/mL, while among 29 (60.4%) with ALT below 20 iu/L, 13 (44.8%) had viral load greater than 2,000iu/L. This was not statistically significant. None had detectable HBsAb. All had detectable core antibody.

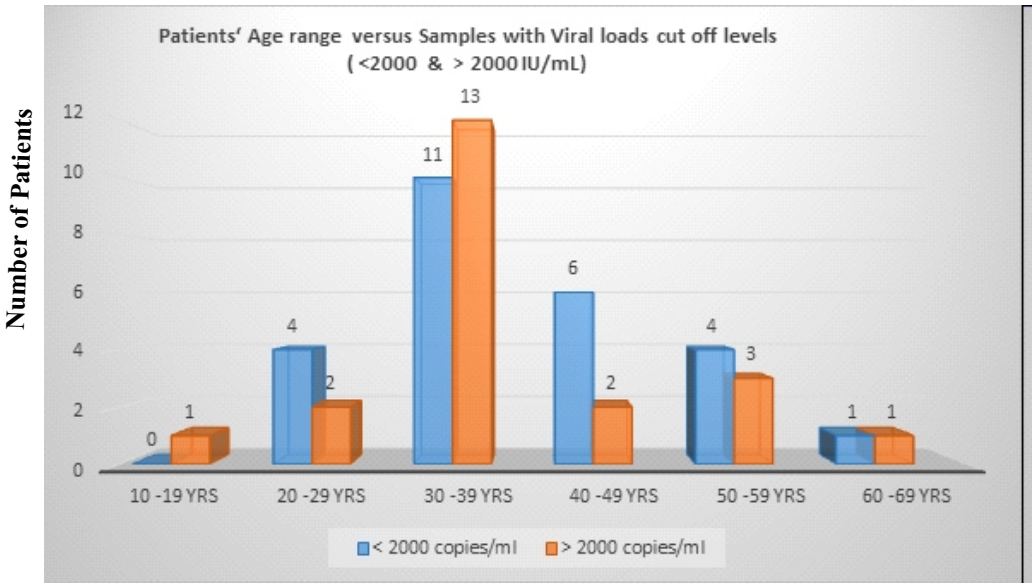

Figure 1: Patterns of viral load distribution vis-à-vis the ages of the subjects studied

Table 1: Distribution of viral diagnostic tests according to HBeAg status in subjects

Variables	No. Tested	HBeAg + ɳ(%)	HBeAg - n(%)	P-value
Anti -HBc	**48**	**2**	**46**	
Positive		2 (100)	46(100)	<0.05
Negative		0 (0.0)	0 (0.0)	
Anti - HBe	**48**	**2**	**46**	
Positive		2 (100)	36(78.3)	<0.05
negative		0(0.0)	10 (21.7)	
HepB viral Loads(IU/mL)	**48**	**2**	**46**	
< 20		0 (0.0)	0 (0.0)	<0.05
20 – 2000		0 (0.0)	26 (56.5%)	
2000 -20,000		0 (0.0)	20 (43.5)	
>20,000		2 (100)	0 (0.0)	
ALT(IU/L	**42**	**2**	**40**	0.1190
<45	37	1 (68.4)	36 (12.5)	
>45	5	1 (31.6)	4 (87.5)	

Table 2: Comparison of viral loadswith ALT, HBcAb and HBsAb amongsubjects

Variables Viral loads (iu/mL)	No. Tested	n(%) ALT <20	n(%) ALT >20	Total	P value
20 – 2000	**48**	16 (62.2)	10 (40.0)	**26**	0.343
2000 -20,000		13(37.8)	9 (60.0)	**22**	
		29	**19**	**48**	
		HBcAb +	**HBcAb –**		
20 – 2000	**48**	26 (54.2)	0 (0.0)	**26**	0.5
≥2000		22 (45.8)	0 (0.0)	**22**	
		48	**0**	**48**	
		HBsAb -	**HBsAb +**		
20 – 2000	**48**	26 (54.2)	0 (0.0)	**26**	0.5
≥2000		22 (45.8)	0 (0.0)	**22**	
		48	**0**	**48**	

DISCUSSION

In this study, treatment penetration rate of less than tenth (7.6%) was seen among HBsAg positive individuals. This is lower than WHO estimated 16.7% penetration among people diagnosed with HBV[13]. From our interactions with patients, we found that low penetration resulted from high cost of tests in our setting as many clients paid out of pocket and lack of a formidable health insurance cover. This agrees with findings of Lesi et al who related low treatment penetration to cost and inadequate availability of molecular technology[1]. In addition, most patients feel minimal symptoms until progression from chronic hepatitis to end stage liver cirrhosis and cancer, resulting in low commitment to pursue effective medical care by infected individuals. This calls for more patients' education and need for supports towards the establishment of hepatitis management programs with national and international supports.

HBeAg was detectable in only 4.2% of patients and these had viraemia above 20,000 IU/mL. This is similar to other findings in which association of HBsAg and HBeAg was infrequent and were associated with high level viremia [1, 3, 14, 15]. It is worthy of note that the two patients with HBeAg positivity had detectable anti-HBe antibodies. Confirming that HBeAb does not protect against aggressive HBV infection[1,16].

Our finding of 43.5% of 46 HBeAg negative patients having a viral load between 20- 2,000 IU/mL is similar to the findings of Atay et al, 2012[14], which showed that viral replication may persist in chronic HBV-infected patients who are HBeAg-negative. This HBeAg-negative hepatitis, is an important form of liver disease in Asia and sub-Saharan Africa and is usually associated with pre-core stop codon mutation at nucleotide-1896 mainly selected in non-A HBV genotypes. The diagnosis of HBeAg-negative CHB has been based on HBsAg positivity, HBeAg negativity, increased alanine aminotransferase (ALT) and serum HBV-DNA levels and exclusion of other causes of liver disease. It has been proposed that adults with normal ALT levels, which usually indicate no current liver inflammation, and undetectable or viral loads less than 2,000 IU/mL generally do not require treatment[17,18]. However, Bárcena & García, (2009)[19] found seropositivity for HBsAg as one of the most important risk factors for HCC and Seropositivity for HBeAg associated with an increased risk for HCC regardless of serum levels of ALT and status of liver cirrhosis. This therefore calls for proper clinical and laboratory evaluations moreso that National Institute of Health workshop on management of hepatitis B infection proposed that a serum HBV DNA level of 105 copies/mL (about 20iu/mL) be used to differentiate HBeAg-negative chronic hepatitis B from an inactive carrier state[20].

In this study only 5 (11.9%) had ALT values greater than 45 iu/L, and all were HBeAg negative. Three (60%) of which had viral load above 2,000 iu/mL, while among those with ALT below 45 iu/L, 14 (37.8%) had viral load greater than 2,000iu/L The presence of 100% HBcAb among this HBsAg sero-positive population with viral load above 20 IU/mL is a proof of penetrative infection and may be a major factor in the epidemiology of huge disease burden of hepatocellular carcinoma (HCC) in sub-Saharan Africa[21,22].

The small size of our study population occasioned by low treatment penetration among patients is an important limitation to this study.

CONCLUSION

This study showed a wide gap between HBV infection and treatment penetration among the study population. Neither serology, ALT nor viral loads can single handedly predict needs for patients' treatment. The presence of HBeAb was not protective against HBeAg.

Recommendation

The need for national hepatitis programs for adequate provision of treatment and follow-up services should be strengthened.

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None

Conflict of interest
Authors have no conflict of interest.

Role of authors
Odimayo M S. and Alabi B Y. conceptualized the work, Odimayo M S., Alabi B Y, Olatunji O A and Ogedengbe B O did the initial data collection, Adebimpe W O and Olatunji O A did the data analysis, Odimayo M S and Nwadioha S I developed the initial draft, all authors read, made input and agreed on the final manuscript.

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