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Research Article

Comparing Serological Markers of Hepatitis B Virus Infection among People Living with HIV/AIDS and HIV Seronegative Individuals

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Abstract

Background: HIV has a negative effect on the course/progression of Hepatitis B infection making chronicity more likely in acute infections, with increased risk of cirrhosis, Hepatocellular Carcinoma (HCC) and decompensated liver disease in chronic infections.

Objective: The study was conducted to show the prevalence of Hepatitis B infection in HIV positive individuals compared to HIV negative individuals.

Methods: Two hundred subjects consisting of 100 HIV infected individuals and 100 HIV negative healthy controls were recruited. Serological markers of Hepatitis B infection (HBsAg, HBeAg, Anti-HBe, Anti-HBc and Anti-HBs) using a rapid immunoassay test kit (ACON) were tested for in all of them.

Results: Fifteen (15%) of the HIV infected cases compared to 10% of the healthy controls were positive for HBsAg (P =0.393). HBeAg was positive in 10% of the cases and 4% of the controls (P = 0.164). Anti-HBs positivity was found in 8%of the HIV infected cases while 25% of the healthy controls were positive (P = 0.002). Twenty-two (22%) of the HIV infected cases were positive for Anti-HBe compared to 56%of the healthy controls (P = 0.000) . Anti-HBc was positive in 82%of the cases and73% of the healthy controls (P = 0.175).

Conclusion: HIV infected persons are less likely to clear HBV infection and develop natural immunity to it compared to the HIV negative controls. The very high level of Anti-HBc seen in both groups showed Nigeria is a highly endemic society for hepatitis B infection.

Keywords: HBsAg; Anti-HBs; HBeAg; Anti-HBe; Anti-HBc; HIV; HBV

Abbreviations

HBsAg: Hepatitis B Surface Antigen; Anti-HBs: Antibody to Hepatitis B Surface Antigen; HBeAg: Hepatitis B e Antigen; Anti-HBe: Antibody to Hepatitis B e Antigen; Anti-HBc: Antibody to Hepatitis B core Antigen; HIV: Human Immunodeficiency Virus; HBV: Hepatitis B Virus; PLWHA: People Living With HIV and Acquired Immune Deficiency Syndrome; HCC: Hepatocellular Carcinoma; HAART: Highly Active Antiretroviral Therapy; STI: Sexually Transmitted Disease; IRIS: Immune Reconstituition Syndrome; ELISA: Enzyme Linked Immunoadsorbent Assay

Introduction

Human Immunodeficiency Virus (HIV) and Hepatitis B Virus (HBV) infection share similar routes of transmission and hence readily co-exist in the same individual.

HIV has a negative impact on the course of Hepatitis B Infection i.e increased tendency to chronicity [1], increased liver related morbidity and mortality [2]. HIV and HBV co-infection also increases HBV replication, hepatitis flares and risk of progression to cirrhosis and Hepatocellular Carcinoma (HCC) [3].

There is therefore, a need to screen People Living with HIV and Acquired Immune Deficiency Syndrome (PLWHA) for possible HBV infection.

Screening for HBV infection in HIV positive individuals using HBsAg alone may not be enough because of the known risk of reverse seroconversion and occult hepatitis B infection in such individuals [4]. Studies have shown increased prevalence of HBV infection, both past and active infection in PLWHA when additional markers i.e antibody to the surface antigen (Anti-HBs) and antibody to the core antigen (Anti-HBc) were screened for in conjunction with HBsAg [5,6].

With the use of Highly Active Antiretroviral Therapy (HAART) , liver failure has emerged as a major cause of death in HIV/HBV co-infected individuals [7] especially in HBV endemic areas (areas with HBV prevalence greater than 8%). It is likely that decompensated liver disease in the setting of chronic hepatitis B will emerge as a greater problem due to Immune Reconstituition Syndrome (IRIS). Thus, it is important to understand HIV/HBV co-infection in HBV endemic regions because of the expanding role of antiretroviral programmes especially in view of the implications of using HAART agents that also possess anti-HBV activity.

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Table 1: Distribution of age, sex and marital status in the study group.

Classification	Cases 100	Control 100	Total 200	X^2 chi-square	*P*-value
18- 30yrs	30 (30%)	26 (26%)	56 (28%)		
30- 39yrs	35 (35%)	60 (60%)	95 (47.5%)		
40- 49yrs	27 (27%)	12 (12%)	39 (19.5%)		
50yrs and above	8 (8%)	2 (2%)	10 (5%)		
Mean age ± standard Deviation	35.81 ± 9.31133	32.70 ± 6.88212			0.08
Male	43 (43%)	56 (56%)	99 (49.5%)	3.380	0.066
Female	57 (57%)	44 (44%)	101 (50.5%)		
Married	66 (66%)	59 (59%)	125 (62.5%)	1.878	0.391
Single	34 (34%)	40 (40%)	74 (37%)		
Widow	0	1 (1%)	1 (0.5%)		
Widower	0	0	0		

Objective

The aim of this study is to know the prevalence of HBV infection in PLWHA as compared to HIV negative individuals using other serological markers of HBV infection in addition to Hepatitis B Surface Antigen (HBsAg).

Materials and Methods

This was a comparative observational study, carried out at the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife, Osun State, Nigeria.

The study was done using people who were18years and above, who were seropositive for HIV 1 and/or 2 (ELISA method) and were treatment naive as at the time of recruitment. They were recruited at the Sexually Transmitted Infection (STI) Clinic of OAUTHC. Age and sex matched controls (HIV negative individuals) of equal number were also recruited for the study. These controls were recruited amongst pregnant women at the Antenatal Clinic and amongst blood donors at the Hematology Department, OAUTHC Ile-Ife. They all gave informed consent. Individuals with previous active immunization against hepatitis B virus infection were excluded from the study.

Eligible patients were serially recruited until sample size was exhausted.

The sample size was 100 each (making a total of 200) for both the HIV infected cases and HIV uninfected controls.

Each of the subjects was interviewed using a questionnaire focusing on demographic data and relevant history to the study. Each of the subjects had 5mls of blood (peripheral venous blood) drawn from them (venepuncture) using 5cc needle and syringe via a peripheral vein. The blood was centrifuged and the serum separated from the cells, few drops were placed on each of the five small holes on each test kit plate representing the five parameters that were being tested [the hepatitis B test kit is a one step Hepatitis B Virus Combo Test Device, trade name ACON, (CAT: IHB-355 LOT: HBV 0050004 EXP 2012-05) it works by the rapid immunoassay method]. The serum moved along a chromatographic column connected to each of the five small holes and the results were then read. The chromatographic column had two regions, a control and a test region from where the results were read. The investigations done on the subjects were HBsAg, Anti-HBs, Anti-HBc, HBeAg, and Anti- HBe.

The appearance of two lines in the chromatographic column, one in the control region and the other in the test region signified a positive test result for HBsAg, Anti-HBs and HBeAg (presence of the markers in the plasma of the subject) while the appearance of only one line in the control region signified a negative test result (absence of the markers in the plasma of the subject). The appearance of just a single line in the control region signified a positive test result for Anti-HBe and Anti-HBc while appearance of two lines both in the control and test region signified a negative test result.

Data was represented using descriptive statistics such as table and inferential statistics such as the chi square test ($\times^2$). Means and standard deviation were also used for continuous variables. Presence of all the serological markers of hepatitis B infection were compared between HIV positive and HIV negative subjects. P value less than or equal to 0.05 was taken as statistical significance.

Results

The study population comprised of 100 HIV positive subjects (cases) and 100 HIV negative subjects (controls) (Table 1). One hundred and ninety (95%) of the study population were under the age of 50 years, only 10 (5%) were 50years and above. The modal age range was 30years to 39years. The age range amongst the cases was 24years to 64years with a mean age of 35.81 ± 9.311 while the age range amongst the control was 18years to 55years with a mean age of 32.70 ± 6.882. (P value was 0.08).

The study population comprised of 99 (49.5%) males and 101 (50.5%) females. There were 43 (43%) males and 57 (57%) females amongst the cases, and 56 (56%) males and 44 (44%) female amongst the controls (P =0.066).

A total number of 125 (62.5%) of the subjects were married compared to 74 (37%) unmarried subjects, there was 1 (0.5%) widow among the subjects.

Most of the subjects had more than one risk factor (Table 2). Multiple sexual partnership was the commonest risk factor, it was present in 119 (59.5%) subjects amongst the study population. Sixty (60%) subjects amongst the cases and 59 (59%) amongst the controls

Table 2: Distribution of risk factors for HIV/HBV infection in the study group.

Classification	Cases 100	Control 100	Total 200	X^2 Chi-square	P-value
Multiple sexual partner	60 (60%)	59 (59%)	119(59.5%)	0.021	1.000
Injection from quacks	37(37%)	40 (40%)	77(38.5%)	0.190	0.771
Scarification marks	34 (34%)	30 (30%)	64(32%)	0.368	0.649
Blood transfusion	5 (5%)	4(4%)	9 (4.5%)	0.116	1.000

had a history of multiple sexual partner (P = 1.000).

The number of subjects that tested positive to HBsAg was found to be 25 (12.5%) with 15 (15%) being amongst the cases compared with 10 (10%) amongst the controls (P =0.285) (Table 3). Fourteen (7%) subjects tested positive to HBeAg, and amongst them were 10 (10%) subjects from the cases and 4 (4%) subjects from the controls (P =0.096). The number of subjects who tested positive to anti-HBe in the study group was 78 (39%), 22 (22%) subjects amongst the cases compared with 56 (56%) subjects amongst the controls (P = 0.000). The frequency of anti-Hbe was more than 2-fold higher in controls compared to the cases. Anti-HBs positivity was found in 33 (16.5%) subjects of which 8(8%) subjects were amongst the cases while 25 (25%) subjects were amongst the controls(P = 0.002). The frequency of anti-HBs amongst the controls was more than 3-fold higher than amongst the cases. The frequency of anti-HBc amongst the cases was 82% and amongst the controls was 73% (P = 0.128). Isolated anti-HBc/anti-Hbe was also found in the study group. The frequency of isolated anti-HBc/anti-Hbe amongst the cases was15% compared to 30% amongst the controls (P = 0.011).Isolated anti-HBc was found in44% of the cases and 8% of the controls (P = 0.000).

Discussion

Most of the subjects were younger than forty years. These might be due to majority of HIV infections occurring mostly in younger age [8,9], and also younger age commonest amongst blood donors [10] and women of reproductive age, both of whom were used as controls.

Multiple sexual partnership and injections from quack doctors were found to be the most common risk factors in the study. The risk factor profile is however same in both population.

The prevalence of HBsAg and HbeAg in the HIV positive cases was higher than in the HIV negative population although these differences were not found to be significant. However, they were both higher in HIV infected subjects. This may be explained by the possible low/impaired immunity in HIV infected people making them unable to clear HBV infection [4], although a comparative CD4 count level between the cases and controls was not done as part of this study. HIV infected individuals with low immunity are mostly unable to mount a response to the envelope and surface antigen making them to persist longer than in the HIV uninfected population [4]. The findings are also comparable to those from other studies done in other areas of Nigeria, Olokooba et al. [11] showed HBsAg prevalence of 15% in HIV/HBV co-infection in North-Eastern Nigeria, Ejele Nwauche et al. [12] showed a HBsAg prevalence of 9.7% in HIV/HBV co-infection in the Niger Delta.

Anti-HBe and anti–HBs were found to be more than two fold and three fold prevalent in the HIV negative population than the HIV positive population respectively. These were significant differences between the cases and controls, and they may also be due to the reduced immunity seen in untreated HIV infection as a result of the progressive lowering of the CD4 count. Eventually, resulting in either the loss of the existing anti-HBe/anti-HBs (reverse seroconversion) or failure of HBsAg seroconversion in the first place. Isolated antiHBe / AntiHbc positivity was also more prevalent in the HIV negative population compared to the HIV positive population. Isolated anti-Hbe/anti-HBc positivity in the absence of other serological markers is a situation that has not been widely recognized but has been described by some studies to mean occult hepatitis B infection as well [13,14]. Mutant viruses not producing HBsAg is an explanation for this situation or it might be that Anti-HBe persists longer than previously thought in population with resolved infection (as this was mostly found among the HIV negative controls in this study).

Anti-HBc is the Hepatitis B marker that persists longer than any other markers of infection. Anti-HBc in association with Anti-HBs is a sign of natural immunity and in association with HBsAg is a sign of current /ongoing infection [4]. The prevalence of Anti-HBc was 82% in HIV positive cases and 73% in HIV negative controls. This very high prevalence of anti-HBc confirms that Nigeria is a highly endemic society for HBV infection. This was also reported by Sirisena et al. [15] which showed 70% - 90% of Nigerians have evidence of HBV infection either active or previous. The prevalence of Anti-HBc alone (isolated Anti-HBc) in HIV positive cases was 44% compared with 8% in the HIV negative controls , this may signify occult hepatitis B infection which is a common finding in the setting of HIV infection although the presence of HBV DNA is required for confirmation. The overall prevalence of Anti-HBc was not found to be significantly different between the cases and controls.

The significance of the serological profiling done was that there were more HBeAg positive chronic hepatitis B individuals amongst the HIV positive cases compared to the HIV negative controls which mean fewer HBeAg negative chronic hepatitis B individuals amongst the cases compared to the controls. There were more people with serological evidence of natural immunity amongst the HIV negative controls compared to the HIV positive cases. The evidence of present or past infection was very high amongst both the cases and controls. The study was unable to differentiate those with active liver disease from those without active liver disease as both serum HBV DNA and serum alanine transaminase were not done as part of the study.

Conclusion

The prevalence of chronic hepatitis B infection in HIV positive population with respect to hepatitis B surface antigen is not significantly different between HIV positive and HIV negative subjects, however still slightly higher in HIV positive subjects. HBeAg positive chronic hepatitis B infection is higher among the HIV positive subjects compared to HIV negative subject but this was not found to be significantly different.

Natural immunity to hepatitis B infection as evidenced by the presence of Anti-HBs and Anti-HBc is much higher in HIV negative subjects than HIV positive subjects this can be attributed to the lowering of immunity in the setting of HIV infection.

A very high proportion of both HIV positive (82%) and HIV negative (73%) subjects had evidence of contact with hepatitis B virus

Table 3: Distribution of HBsAg, HBeAg, Anti-HBe, Anti-HBs and Anti-HBc in the study group.

Classification		Cases 100	Controls 100	Total 200	X^2 chi-square	P-value
HbsAg	Positive	15 (15%)	10 (10%)	25 (12.5%)	1.143	0.285
	Negative	85 (85%)	90 (90%)	175(87.5%)		
HbeAg	Positive	10 (10%)	4 (4%)	14 (7%)	2.765	0.096
	Negative	90 (90%)	96 (96%)	186 (93%)		
Anti-HBs	Positive	8 (8%)	25 (25%)	33 (16.5%)	10.488	0.002
	Negative	92 (92%)	75 (75%)	167(83.5%)		
Anti-Hbe	Positive	22 (22%)	56 (56%)	78 (39%)	24.296	0.000
	Negative	78 (78%)	44 (44%)	122 (61%)		
Anti-HBc	Positive	82 (82%)	73 (73%)	155(72.5%)	2.323	0.128
	Negative	18 (18%)	27 (27%)	45 (22.5%)		
Anti-HBc/Anti-Hbe	Positive	15 (15%)	30 (30%)	45 (22.5%)	6.452	0.011
	Negative	85 (85%)	70 (70%)	155(77.5%)		
Isolated Anti-HBc	Positive	44 (44%)	8 (8%)	52 (26%)	33.679	0.000
	Negative	56 (56%)	92 (92%)	148 (74%)		

either past infection or ongoing infection. This shows that Nigeria is a highly endemic environment of hepatitis B virus very much higher than the prevalence of HIV infection (4.4%) despite the common routes of transmission. Those subjects with isolated antiHBe/ antiHBc, majority of whom are amongst the controls probably have resolved infection with unusual persistence of the anti-HBe or may have an occult hepatitis B infection but further studies will be needed to adequately identify these group of individuals. Those subjects with anti-HBc alone (isolated anti-HBc) may have occult hepatitis B infection which is a common finding in the setting of HIV infection although the presence of HBV DNA is required for confirmation.

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