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Human Immuno-Deficiency Virus and Hepatitis B Virus coinfection in pregnancy at the University College Hospital, Ibadan

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Summary

Human Immuno-deficiency virus (HIV) and Hepatitis B Virus (HBV) share common modes of transmission which include blood borne and the vertical routes. Although, the natural course of HIV does not appear altered by HBV, the rate of liver-related deaths is several times higher among HIV/HBV co-infected persons. Clinicians providing care for HIV positive individuals, including pregnant women, need to be aware of this problem. This is a 2-year cross-sectional study that commenced in January 2006, among HIV positive pregnant women seen at the University College Hospital, Ibadan. During the study period, 721 HIV positive pregnant women were screened for hepatitis B virus infection. Sixty-four women (8.9%) were positive for HBsAg, 14(1.9%) were HCV positive and 642 (89.2%) were negative for both HBV and HCV. One patient was positive for both HBV and HCV. There were no remarkable differences between HIV infected and HIV-HBV co-infected patients in terms of the hematological, albumin and bilirubin measurements. Alanine transaminase was however higher in the HIV-HBV co-infected patients than HIV patients and this was statistically significant (17.5 iu/ml vs. 15.0 iu/ml, *p value- 0.009*). In addition, the CD4 cell count was lower and the viral load marginally higher in the hepatitis B virus positive patients. The differences were however not statistically significant (*p value- 0.114 and 0.644 respectively*). HIV- HBV co-infection in HIV positive pregnant women is not of negligible proportions as demonstrated in this study. Thus, HIV positive pregnant women should be screened for HBV and assisted to access care targeted at preventing morbidity and vertical transmission.

Keywords: *HIV, hepatitis B, pregnancy, Nigeria*

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Résumé

LE VIH et VHB partagent les mêmes modes de transmission qui incluent le sang et les routes verticales. Bien que, le parcours naturel du VIH n'alterne pas le VHB, le taux des décès lies au foi est plusieurs fois plus élevé parmi les personnes Co-infectes du HIV/ VHB. Les médecins apportent des soins aux individus séropositifs incluant les femmes enceintes, ont besoin de la sensibilisation de ce fléau. Ces deux années d'étude commença en Janvier 2006, parmi les femmes enceintes séropositives vues au Centre Universitaire Hospitalier, Ibadan, Nigeria. Durant cette étude, 721 Cas ont été détectés ayant l'infection du virus de l'hépatite B. Soixante quatre cas des femmes (8.9%) étaient positives pour le HBsAg, 14(1.9%) étaient positive au VHC et 642 (89.2%) étaient négative au VHB et VHC. Un patient était positif au VHB et VHC. Ils n'y avaient pas de différences remarquables entre les infectées du VIH et co-infection du HIV-VHB dans les mesures hématologiques, albumine et bilirubine. Alanine transaminase était cependant élevé chez les VIH-VHB patients Co-infectés que les VIH seulement et ceci était statistiquement significatif (17.5 iu/ml vs. 15.0 iu/ml, *p - 0.009*). En Plus, Le taux des cellules CD4 étaient plus bas et la masse virale était bas marginalement plus élevé chez les patients positif au virus de l'hépatite B. Les différences n'étaient pas statistiquement significatives (*p - 0.114 et 0.644 respectivement*). La co-infection VIH- VHB chez les femmes enceintes séropositives n'est pas de proportions négligeables comme démontré dans cette étude. Ainsi, Les femmes enceintes séropositives doivent être examines pour le VHB et assistées pour évaluer les soins désirés a prévenir la souffrance et la transmission verticale.

Introduction

Hepatitis B virus infection (HBV) is a global health problem [1,2]. It is estimated that 2 billion people are infected worldwide with 350 million suffering from chronic hepatitis B virus infection and about 1.2 million deaths annually due to its various complications [3]. It

is most prevalent in Asia, Africa, southern Europe and Latin America, where the prevalence of hepatitis B surface antigen (HBsAg) carriers in the general population ranges from 2 – 20% [1]. HBV infection occurs mainly during infancy and early childhood in these hyper-endemic areas including Nigeria [1,4,5,6].

Hepatitis B virus and the Human Immunodeficiency Virus (HIV) have several common features. They have similar transmission routes including the potential for vertical transmission; thus, all HIV infected patients should be tested for HBV infection [7]. Both viruses are capable of integrating into target host cell genome via the process of reverse transcription, which prevents their eradication [8]. However, this process may be inhibited by nucleosi(ti)des reverse transcriptase inhibitors [8]. Finally the mechanisms for development of resistance are very similar for both viruses [8].

After exposure to HBV, many patients mount strong immunologic response which culminates in clearance of HBV viraemia, and development of immunity-conferring HBV surface antibody (anti HBS). The ability to clear HBV depends on the degree of host cytotoxic T lymphocyte (CTL) response. HIV infected patients are more likely to have defective CTL response and increased risk of viral persistence. Chronic infection is approximately 5 times more likely in HIV/HBV co-infected patients compared to those with HBV infection only [7]. Though the natural course of HIV does not appear to be altered by HBV, the hepatic cytolysis that antiretroviral compounds (especially protease inhibitors and non- nucleoside reverse transcriptase inhibitors) may induce may be accelerated by HIV/HBV co-infection [9]. In addition, the rate of liver –related death has been estimated to be several times higher in HIV/HBV co-infected persons compared with those who had HIV infection or HBV infection alone [10]. It is thus imperative that clinicians providing care for HIV positive individuals including pregnant women are aware of the burden of this problem.

Objectives

The aim of this study is to determine the prevalence of HIV-HBV co-infection in a group of HIV positive pregnant Nigerian women and document the degree of morbidity associated with the co-infection state as demonstrated with some selected laboratory parameters.

Materials and methods

This is a retrospective cross-sectional study that examined the records of every woman newly diagnosed for HIV and presenting for prevention of mother-to-child transmission services (PMTCT), between January 1st 2006 and December 31st 2007, at the University College Hospital, Ibadan. These PMTCT services are as outlined by the national PMTCT policy and provided in the context of the President's Emergency Plan for AIDS Relief (PEPFAR) sponsored care and support program.

Data obtained from the patients' records included socio-demographic information, baseline CD4 T lymphocyte counts and viral load. Other laboratory results obtained include Hepatitis B virus surface antigen (HBsAg) and hepatitis C antibodies status, serum liver alanine transaminase, bilirubin level, and total leukocyte and lymphocyte enumeration.

Laboratory diagnosis of HBV

HBsAg detection assay was used for diagnosis of HBV infection in the study population. A commercially available direct Enzyme Linked Immunosorbent Assay (ELISA), Monolisa (Biorad, Paris, France) was used. About 5mls of blood was collected from each HIV positive pregnant woman into an EDTA containing sterile tube. The blood samples were then transported to the laboratory in the Department of Virology of the hospital, where they were spun, plasma separated and used for the test. The test procedure and interpretation of results were done according to the manufacturer's recommendations.

Ethical approval

Ethical approval was obtained from the University of Ibadan/ University College Hospital ethical review committee.

Statistical analyses

Data were analyzed as means ± standard deviation, percentages and median. Disparity between the mean and median values of measured parameters in HIV infected and HIV/HBV co-infected patients were analyzed by T-test and Mann-Whitney test respectively. Data entry and analysis was done using SPSS statistical package. P value less than 0.05 was considered significant.

Results

Detection of Hepatitis B surface antigen (HBsAg) among HIV -1 infected pregnant women

During the study period, seven hundred and seventy-one (771) women presented for care including three

Table 1: Selected Maternal Socio-Demographic Characteristics

Socio-demographic variable	Hep. B positive n=(64)	Hep. B negative (n=642)	Total (n = 706)
Age of patient (years)			
<25	6 (9.4%)	134 (21.2%)	140 (19.8%)
25-34	52 (81.3%)	427 (67.1%)	479 (67.9%)
≥ 35	6 (9.4%)	81 (11.7%)	87 (12.3%)
Educational level			
No formal education	3 (4.6%)	39 (5.9%)	42 (5.9%)
Primary school	22 (34.4%)	179 (27.9%)	201 (28.5%)
Secondary school	25 (39.1%)	291 (45.5%)	316 (44.8%)
Tertiary	14 (21.9%)	133 (20.7%)	147 (20.8%)
GA at presentation			
≤ 13weeks	2 (3.1%)	42 (6.5%)	44 (6.2%)
14-26 weeks	22 (34.4%)	207 (32.2%)	229 (32.4%)
≥27 weeks	40 (62.5%)	393 (61.3%)	433 (61.3%)
Marital status			
Single	3 (4.6%)	24 (3.7%)	27 (3.9%)
Married	60 (93.8%)	593 (92.4%)	653 (92.4%)
Separated/ divorced	0 (0%)	18 (2.8%)	18 (2.5%)
Widowed	1 (1.6%)	7 (1.1%)	8 (1.1%)

Table 2: Selected laboratory parameters

Selected lab. parameter	Hep. B positive n=(64) Median	Hep. B negative (n=642) Median	p-value@	Total (n = 706) Median
CD4 cells/μl	260	328	0.114	321
ALT iu/ml	17.5	15.0	0.009	16.0
Bil mg/ml	0.3	0.4	0.252	0.4
	Mean ± SD	*Mean ± SD*	*p-value**	*Mean ± SD*
Albumin	3.21± 0.52	3.41± 0.56	0.179	3.39 ±0.56
Log_{10} (Viral load)	4.15± 0.99	4.09± 1.09	0.644	4.10±1.08
White blood cell count	5765.5± 1568.1	5793± 1991.1	0.919	5,800.8±1930.4
Lymphocytes	27.09± 8.0	27.88± 9.56	0.502	28.01 ± 8.57

@ from Mahn Whitney test comparing the median values of selected parameters for Hepatitis B positive and Hepatitis B negative women

**From student t-test comparing the mean values of selected parameters for Hepatitis B positive and Hepatitis B negative women*

hundred and forty- eight (348) and four hundred and twenty- three (423) in 2006 and 2007 respectively. Fifty of the women had no result available for screening tests for either HBV or HCV and so were excluded from the analysis. Sixty-four (8.9%) women were positive for HBsAg, 14(1.9%) for HCV positive and 642(89.2%) were negative for both HBV and HCV. One patient was positive for both HBV and HCV. This patient and the hepatitis C positive pregnant women were also excluded from further analysis because the presence of HCV could confound the results obtained.

Socio demographic characteristics

Table 1 shows the distribution of the socio demographic characteristics. The mean age of all the women, HBsAg positive and HBsAg negative women was 28.86years±5.85, 28.8 years ±3.9 and 28.8 years ± 5.9 respectively. There were no remarkable differences in

the socio demographic characteristics, between the HIV infected and HIV-HBV co-infected patients.

Selected laboratory parameters

Table 2 shows the value of selected laboratory parameters evaluated for this study. There were no significant differences in the haematological measurements of HBV negative and the HIV-HBV co-infected women. Although, serum albumin and bilirubin did not show any remarkable differences, serum alanine transaminase levels were higher in the HIV-HBV co-infected patients. The difference was statistically significant *(p value- 0.009)*. In addition, the CD4 count was lower and the viral load marginally higher in the HIV-HBV co-infected patients. These differences were however not statistically significant.

Discussion

HIV and HBV are both blood borne pathogens with similar risk factors and high propensity to co-infect humans [11]. In the present study, we found 8.9% sero-prevalence of HBsAg among these HIV positive pregnant women. Various HBsAg sero-prevalence values have been reported by previous workers in different clinical settings in the general population in Nigeria. Obi *et al* [12] working in the early 1990s reported a rate of 4.4% among a group of apparently healthy Nigerian pregnant women. While Otuonye *et al* [13] working in Lagos reported a rate of 40.0% among attendees of a STD clinic, Iwalokun *et al* [14] found a rate of 51.9% among a group of HIV positive individuals in Lagos. In a recent study, Otegbayo *et al* [15] reported a rate of 11.9% among adult non-pregnant HIV positive individuals but more common among males than females (15.4% vs 10.1%, respectively). The prevalence in the present study is much higher than that of Obi *et al.*, lower than that of Otuonye *et al.*, and Iwalokun *et al.*, but similar to that of Otegbayo *et al.* The population studied in this study was in the same clinic and locale as that reported by Otegbayo *et al.*

The CD4 T lymphocyte levels in the HIV-HBV co-infected patients in this study were lower than values observed in HIV infected patients. Iwalokun *et al.*, [14] working in Lagos reported a similar finding. These workers in Lagos suggested that HBV has a depressant effect on blood lymphocyte level in HIV patients [14]. However, these findings contradict other views that HBV infection neither leads to a more rapid decline of CD4+ T lymphocytes nor to an increased frequency of AIDS defining events [8].

The differences observed in the serum alanine transaminase levels were significant. Again, Iwalokun *et al* [14] working in Lagos reported statistically significant higher levels of the amino-transaminases and bilirubin in the HIV-HBV co-infected patients. They suggested a strong correlation between HBsAg antigenaemia and hepatic cytolysis in HIV-HBV patients. Bessesen *et. al.*, [16] also suggested that HIV-HBV co-infection could cause marked rebound in viral replication causing hepatitis flare. Others have however reported the contrary, that lower transaminases are more frequently observed in HIV-HBV co-infected patients compared to HBV monoinfected individuals [17, 18]. Lower transaminases occur because hepatic inflammation in HBV infection is not caused by direct cytopathic effect of the hepatitis virus; rather it is a correlate of host immunologic response. Thus, the impairment of cellular immunity which may lead to an increase in viral replication is also associated with reduced hepatocyte damage. Therefore, transaminases in HBV/HIV co-infected patients are frequently only mildly raised. In contrast HBV DNA, a marker of viral replication is higher. Accordingly, despite less inflammatory activity, liver fibrosis and cirrhosis are more common in HIV/HBV co-infected individuals [8]. Thus, the elevated serum alanine transaminase in HIV-HBV infected pregnant women, as observed in this study requires further investigation to rule out hepatitis flare and thoroughly evaluated for features of liver fibrosis and cirrhosis.

Some of the adverse outcomes associated with the HIV-HBV co infection status such as increased risk of highly active antiretroviral therapy (HAART) - induced hepatotoxicity can be ameliorated by therapy for the HBV [8]. Some antiretrovirals (ARVs) that have demonstrated activity against the hepatitis B virus in HIV-HBV infected persons include emtricitabine, tenofovir, and lamivudine. However antiretroviral monotherapy is contraindicated in HIV infected persons because this usually leads to HIV resistance [8, 19]. If ARVs are used in a HIV patient, it should be administered as part of a triple combination therapy [20]. Some of these ARVs are commonly used in the Nigerian PMTCT program and will thus be of therapeutic benefits to HIV-HBV co-infected pregnant women. In addition, hepatitis A and B vaccination is recommended in non-immune HIV infected persons [21], and they should be screened for HCV infection as well [7].

Pregnancy neither increases maternal mortality or morbidity from hepatitis B nor is the risk of fetal complications, such as fetal death, abortion, or congenital anomalies increased [22]. Women with chronic hepatitis B (CHB) who become pregnant while on therapy can continue treatment, but the stage of the mother's liver disease and the potential benefit of treatment must be weighed against the risk to the fetus. Some of these ARVs (e.g. lamivudine) cross the placenta freely and can be found in colostrum and breast-milk [23]. However, the benefits of offering ARVs as a component of PMTCT services to the women studied here include their roles of preventing vertical transmission of HIV and HBV and may justify any potential risks.

Although vertical transmission is rarely symptomatic, 70 – 90% of babies infected from their mothers will remain chronically infected into adult life, if immuno-prophylaxis is not given [1]. The clinical benefits of including HBV in the expanded program on immunization (EPI) have been reported in many countries [24]. Various methods of immuno-prophylaxis are used worldwide, depending on the prevalence of HBV infection and the resources of the country. In high prevalence countries such as Nigeria, active immunization with HBV vaccines and passive immunization with hepatitis B immunoglobulin (HBIG) is advocated for all HBV exposed babies. While the primary hepatitis B immunization series conventionally consists of 3 doses of vaccine, 4 doses may be given for pragrammatic reasons [25, 26]. Since perinatal or early postnatal transmission is an important cause of chronic infections globally, the first dose of hepatitis B vaccine should be given as soon as possible (< 24 hours) after birth with other doses following with minimum intervals of 4 weeks [25, 26]. This post exposure immunization beginning at birth can prevent the spread of more than 90% of HBV infections from mother to baby [26]. It is also associated with a decline in the incidence of hepatocellular carcinoma in children, [27,28] a reduction in mortality rate of fulminant hepatitis in infants and a further decline in the incidence of HCC in adults [29]. Thus, pregnant women discovered to be HBsAg positive in this environment, HIV positive or negative, should be assisted to understand the need for infant immunization in the immediate postnatal period and access to these services ensured in the prenatal period.

Conclusion

HIV- HBV co infection in HIV positive pregnant women is not of negligible proportions as demonstrated in this study. Clinicians providing care to these women must make concerted efforts to determine their HBV status. As also noted, HIV-HBV pregnant women may be more likely to have deranged liver transaminases and so should be thoroughly evaluated. In addition, they must be assisted to access PMTCT and immunization programs to prevent vertical transmission of both viruses.

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