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THE PREVALENCE LIVER FUNCTION AND IMMUNOLOGIC STATUS OF CHILDREN WITH HIV AND HEPATITIS B VIRUS COINFECTION IN ENUGU, NIGERIA

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Abstract

Background: Hepatitis B Virus (HBV) co-infection is prevalent among HIV infected individuals because of shared routes and mechanisms of transmission. The multidimensional immunosuppression from HIV infection causes impaired spontaneous recovery from an acute HBV infection, predisposing to chronic infection which is worsened by younger age at infection. Co-infection increases the risk of HBV replication, hepatotoxicity and liver related deaths from Highly Active Antiretroviral Therapy (HAART). The study was undertaken to highlight the burden of co-infection among HIV positive children in Enugu, determine the associated risk factors and compare the effect of co-infection between co-infected and non-co-infected children using liver enzyme and CD_4 counts.
Materials and Methods: A cross sectional study was carried out among HIV positive children attending the Paediatric ARV clinic of the University of Nigeria Teaching Hospital, Ituku-Ozalla. A total of 140 HIV infected children aged 18 months to 15 years were recruited. An interviewer questionnaire was administered. Hepatitis B surface antigen (HBsAg) was determined using Determine test Kit. Baseline and recent CD_4 counts/CD_4% were retrieved from the patients' folders.
Results: Fourteen (10%) were positive for HBsAg. The highest prevalence of HBsAg was observed among children aged 11- 15 years. The higher the socioeconomic class the less likely the HBsAg positivity. Seven (50%) of the co-infected children had elevated baseline ALT compared with 57 (45.2%) of non-co-infected children though the difference was not statistically significant (t = 0.6, $P = 0.56$). After the initiation of HAART, 10 (76.9%) of the co-infected and 18 (15.1%) of the non-co-infected children had elevated ALT. The baseline median CD_4 count among children ≥ 6 years was 230 cells/mm^3 and 360 cells/mm^3 respectively among the co-infected and non-co-infected, (P = 0.67). However, in children ≤ 5 years, it was 25% and 15 % respectively ($P = 0.06$).
Conclusion: HBV co-infection among HIV infected children is common in our environment, and co-infection is associated with impaired immunity and probably liver enzyme derangement.

Key words: HIV infection, Children, HBV co-infection, Liver function, Immunologic status

Introduction

Human Immunodeficiency Virus (HIV) is an RNA virus that mainly targets the T-lymphocytes bearing CD_4. Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) is a major cause of infant and childhood morbidity, hospitalization and mortality, has devastated families and complicated the efforts to fight poverty, improve health and promotion of development (ANECCA, 2005). In 2010, about 33.3 million people, worldwide, were living with HIV including 2.5 million children with an annual death rate of 1.8 million due to AIDS. Nigeria accounted for about 3.5-4 million people living with HIV including 360,000 children, with 340,000 new infections out of which 170,000 were children. There were also 220,000 AIDS-related deaths (WHO/UNAIDS, 2010).

Hepatitis B Virus (HBV), on the other hand, is a hepatotropic virus that replicates predominantly in the hepatocytes, lymphocytes, spleen, kidney and pancreas with areas of highest prevalence being the sub-Saharan Africa and South-East Asia (Yazigi,Balistrere, 2007, WHO/Hepatitis B). It is also a major public health problem with increased risk of chronicity in children and subsequent increase in morbidity and mortality. Younger age at acquisition of infection is the single most important predictor of chronic carriage (Yazigi, Balistrere, 2007, Uleanya, Obidike, 2015). Worldwide, an estimated two billion people are infected, with 350-400 million of them remaining chronic carriers of HBV, a leading cause of chronic liver diseases and liver-related mortality (WHO/Hepatitis B, Puoti et al, 2008, Sharma et al, 2008, Rouet et al, 2008, Mphahlele et al, 2002, Kire, 1996). It has also been estimated that 15 - 25% of the chronic carriers will die of these sequelae (WHO/Hepatitis B). Consequently, worldwide estimated annual mortality directly related to hepatitis B liver disease and cancer is between 600,000-1 million (Puoti et al, 2008, Sharma et al, 2008, Mphahlele et al, 2002). Nigeria is hyper-endemic with endemicity rate as high as 37-46% (Emechebe et al, 2009).

Hepatitis B virus co-infection is common among patients with HIV, because of shared routes and mechanisms of transmission (Thio et al, 2002, Levy et al, 2006). It has been estimated that about 6 to 15% of the 33.3 million people living with HIV infection are also chronically infected with HBV (Psevdos et al, 2010). The multidimensional immunosuppression caused by HIV can: compromise

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one's ability to recover spontaneously from an acute HBV infection thus leading to a chronic infection; lower incidence of spontaneous loss of HB e antigen (HBeAg) or HBsAg and cause more rapid decline in hepatitis B surface antibody over time (Thio et al, 2002, Psevdos et al, 2010, Mgonda, 2004). Co-infection increases the risk for HBV-related liver disease progression and also the risk for antiretroviral drug related hepatotoxicity (Thio et al, 2005). This high risk of hepatotoxicity may then imply an increased risk of death from the liver disease in co-infected people (Thio et al, 2002). In viral hepatitis and drug induced hepatotoxicity, alanine transaminase is the most specific marker of hepatotoxicity (Baron et al 1994). Paradoxically, there is low serum alanine transferase concentration but high HBV DNA and HBe Ag levels found in the serum of co-infected persons (Puoti et al, 2008, Kellerman et al 2003, Thio et al, 2002). Such co-infected persons are at higher risk for a more rapid progression to chronic hepatitis, HBV-related cirrhosis and hepatic de-compensation than are only HBV infected persons (Puoti et al, 2008, Kellerman et al, 2003). It has also been documented that the rate of liver-related deaths from progressive liver disease are highest among those with lowest CD_4 count, which also increases after the introduction of HAART. It is noted that CD_4 depletion alter the intrahepatic cytokine milieu contributing to increased fibrosis (Thio et al, 2002). Co-infection therefore poses a treatment challenge. With increasing access to HAART, it is expected that AIDS-related mortality will become reduced (Puoti et al, 2008, Rouet et al, 2008). However, it is most likely that liver disease related to chronic HBV infection or drug-induced hepatotoxicity will increase and liver failure may emerge as a major cause of death whether amongst the treated or untreated co-infected patients.

This study was, therefore, undertaken to highlight the burden of co-infection in our environment, determine the associated risk factors and compare the effect of co-infection as determined by derangement in liver enzyme and CD_4 counts of co-infected children with that of surface antigen negative HIV infected children. Such information will be of help to health policy makers in generating guidelines for effective management and/or prevention of both infections.

Methods

This was a cross sectional study carried out among HIV positive children attending the paediatric antiretroviral (ARV) clinic of the University of Nigeria Teaching Hospital (UNTH), a tertiary medical institution in Enugu. The clinic provides care for about 240 HIV positive children from Enugu and its environs.

A total of 140 Western Blot confirmed HIV positive children aged 18 months to 15 years were studied with HIV positive HBsAg negative children serving as controls. Exclusion criteria were those aged less than 18 months or older than 15 years, unconfirmed HIV status and those whose parent(s)/guardian did not consent.

Ethical clearance was given by the University of Nigeria Teaching Hospital Health Research and Ethics committee. Informed consent (both verbal and written) was obtained from the child and the parent(s) or guardian. They were duly educated on the need for, and benefits of the study. The specimen to be collected and how it was to be collected was explained to them before collection. A structured interviewer administered questionnaire was designed for this study. Information sought included bio-data, occupation and educational status of both parents/guardian for the determination of socioeconomic class, risk factors for HBV infection including previous history and frequency of blood transfusion, histories and instruments of scarification, tattooing, ear piercing, circumcision, use of contaminated needles and syringes for injection (either used or reused needle or syringe considered as contaminated), intravenous drug use, histories of sex (where necessary), and sharing of tooth brush were obtained. In this study, co-infection was defined by the presence of HBsAg positivity in HIV positive children.

Patient's baseline and recent CD_4 count/CD_4% and alanine aminotransferase results were retrieved from their folders. Assays for HBsAg was done using Abbott DETERMINE HBsAg test kits - an enzyme immunoassay (specificity of 99.85% and a sensitivity of 94.64%). The test was then read after a waiting interval of 15 minutes to 24 hours (as specified by the manufacturer).

The data was analysed using SPSS version 15. Measures of central tendencies – mean and median were used to summarize quantitative and qualitative variables where applicable. Frequency tables were constructed as appropriate and analytical tests of significance were done using the Student t- test for continuous variables, Chi square and Fischer's exact tests for non-continuous variables and p value at the level of < 0.05 was accepted as significant. Odds ratios for the risk factors were calculated. Socioeconomic class was determined using the method proposed by Oyedeji (Oyedeji, 1985).

Results

A total of 140 questionnaires were administered with a 100% response rate. Blood samples were collected and analysed from all 140 subjects for HBsAg. Eight and seven subjects had only baseline ALT and CD_4 results respectively. These were confirmed HIV positives but were new to the clinic.

The age and sex distribution of the study populations is as shown in Table 1. The mean age of subjects was 7.3 ± 3.6 years. There were 74 males and 66 females with a male to female ratio of 1.1: 1. The majority of the subjects 61 (43.6%) were in the age range of 6-10 years and the least represented age range was 11-15 years – 29 (20.7%). The socioeconomic class of the subjects is also as shown in Table 1. Most were in the lower class.

Of the 140 children studied, 14 were positive for HBsAg, giving a prevalence rate of 10%. Ten (9.1%) of the HBsAg positive subjects were from the lower socioeconomic class, four (18.2%) from the middle class while none among the upper class was positive for HBsAg. Ten (13.5%) out of the 74 HIV positive males and 4 (6.1%) of the 66 HIV positive females were also positive for HBsAg. The prevalence of HBsAg increased with age among the subjects (Table 2). However, the highest prevalence was found among four children (13.8%) aged 11-15 years, ($\chi 2 = 1.5$, $p = 0.47$)

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None of the subjects was involved with intravenous drug injection though all had received intramuscular injections for one reason or the other as shown in Table 3. However, 19 (13.6%) used contaminated needle/syringes, 42 (30%) had past history of blood transfusion, 76 (54.3%) were circumcised, 33 (23.6%) had scarification marks, 3 (2.1%) had a history of tattoo /ritual marks, 65 (46.4%) had ear piercing, while 9 (6.4%) shared toothbrushes. One subject (0.7%) was involved in unprotected sex (a victim of sexual assault). The observed differences between the risk factors and HBsAg positivity were not statistically significant. However, the odds ratio of the risk of transmission of HBV through these risk factors is as shown in table 3.

Among the 14 co-infected children, 7 (50.0%) had elevated baseline alanine amino-transaminase (ALT) above the upper limit of normal while 7 (50.0%) had baseline ALT within normal limits. Of the 126 HIV positive but HBsAg negative children, a total of 57 (45.2%) had elevated baseline ALT while most (69 [54.8%]) had baseline ALT within normal limits. Having been initiated on antiretroviral drugs for varying periods, among the co-infected children, 10 (76.9%) now had elevated ALT while three (23.1%) had normal ALT. Eighteen (15.1%) of the HBsAg negative HIV positive children had normal ALT while 101 (84.9%) had elevated ALT above the upper limit of normal. The mean of baseline ALT among the HBV co-infected subjects was 17.9 ± 11.6 iu/l while it was 19.3 ± 17.6 iu/l among the surface antigen negative subjects (126) ($t = 0.3$, $p = 0.76$). The mean value of the most recent ALT of the co-infected children (13) was 24.7 ± 14.2 iu/l while that of the HBsAg negative children (119) was 28.6 ± 23.7 iu/l ($t = 0.6$, $p = 0.56$). The differences were not statistically significant (Table 4).

Table 1: Socio-demographic characteristics of HIV positive Children**.**

Age Range (years)	HIV Positive N (%)
1-5	50 (35.7)
6-10	61 (43.6)
11-15	29 (20.7)
Gender	
Male	74 (52.9)
Female	66 (47.1)
Social class	
Upper class	8 (5.7)
Middle class	22 (15.7)
Lower class	110 (78.6)

* The lowest age in this study was 18 months

Table 2: Age distribution of HBsAg among HIV positive children

Age range (Years)	HIV positive	
	HBs (+) N (%)	HBs (-) N (%)
1-5	3 (6.0)	47 (94.0)
6 -10	7 (11.5)	54 (88.5)
11-15	4 (13.8)	25 (86.2)

$\chi 2 = 1.5$, $p = 0.47$

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Table 3: Showing the relative risk of HBsAg positivity among HIV positive children

Risk factors	Total Sample	HBsAg positive N (%)	χ^2	p	OR
Blood transfusion					
Present	42	7 (16.7)	3.0	0.12	2.6
Absent	98	7 (7.1)			
Scarification marks					
Present	33	2 (6.1)	0.75	0.52	0.5
Absent	107	12 (11.2)			
Tattooing					
Present	3	0 (0.0)	-	-	-
Absent	137	14 (10.2)			
Circumcision					
Present	76	10 (13.2)	1.76	0.26	2.2
Absent	64	4 (6.3)			
Intravenous drug use					
Absent	140	14 (10.0)	-	-	-
Contaminated syringe/needle use					
Present	19	1 (5.3)	0.55	0.69	0.5
Absent	121	13 (10.7)			
Ear piercing					
Present	65	4 (6.2)	1.99	0.26	0.4
Absent	75	10 (13.3)			
Sharing of toothbrush					
Present	9	1 (11.1)	0.01	0.91	1.1
Absent	131	13 (9.9)			
Unprotected sex					
Present	1	0 (0.0)	-	-	-
Absent	139	14 (10.1)			

Table 4: Baseline and Recent ALT of HIV infected children

Mean (SD)	HBsAg status	
	Positive	**Negative**
	(N)	**(N)**
Baseline (ALT (iu/L)	17.9 (±11.6)	19.3 (±17.6)
	(14)	(126)
	t = 0.3,	p = 0.76
Recent ALT (iu/L)	24.7 (± 14.2)	28.6 (± 23.7)
	(13)	(119)
	t = 0.6,	$P = 0.56$

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Table 5: Median and Mean CD_4 count/CD_4% of HIV infected children

	Baseline (Mean ± SD)	**Median**	**Recent (Mean± SD)**	**Median**
	HBsAg positive	**HBsAg negative**	**HBsAg Positive**	**HBsAg negative**
CD_4 count (cells/mm^3)	230.50	360	682	723
	(386.7 ± 419.8)	(458.3 ±352.2)	(712.2 ± 610.5)	(741.2± 447.2)
Number of children	11	79	10	78
	t = 0.6	p = 0.54	t = 0.19	p = 0.85
CD_4%	25	15	21.8	30.2
	(28.2 ±13.0)	(16.3 ± 10.3)	(20.8 ± 9.8)	(29.5 ± 10.7)
Number of children	3	47	3	42
	t = 1.9	P = 0.06	t = 1.4	P = 0.18

Table 6: Immunologic classification of HIV positive children ≥ 6 years

CD_4 range (Cells/mm^3)	**Baseline HBsAg positive N (%)**	**CD_4 HBsAg negative N (%)**	**Recent HBsAg positive N (%)**	**CD_4 HBsAg negative N (%)**
<200	5 (45.5)	22 (27.8)	4 (40.0)	7 (9.0)
201- 349	1 (9.1)	15 (19.0)	0 (0.0)	8 (10.3)
350- 499	2 (18.2)	15 (19.0)	0 (0.0)	10 (12.8)
≥ 500	3 (27.3)	27 (34.2)	6 (60.0)	53 (67.9)
	Fischer's exact test	P=0.67	Fischer's	exact test P = 0.027

Table 7: Immunologic classification of HIV positive subjects ≤ 5 years.

	HBsAg status	
Baseline CD_4%	**Positive N (%)**	**Negative N (%)**
< 15	0 (0.0)	21 (44.7)
15 – 20	1 (33.3)	15 (31.9)
20-25	1 (33.3)	3 (6.4)
> 25	1 (33.3)	8 (17.0)

Fischer's exact test P= 0.079

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The median of baseline CD_4 count of HBsAg negative children ≥ 6 years was 360 cells/mm^3, with a mean of 458.3 ± 352.2 cells/mm^3 while the co-infected children ≥ 6 years had a median baseline CD_4 count of 230 cells/mm^3 with a mean of 386.7 ± 419.8 cells/mm^3 (t = 0.6, p = 0.60) (Table 5). The median of their most recent CD_4 count (all having been on HAART for varying periods), of the children without HBV co-infection was 723 cells/mm^3 with a mean of 741.2 ± 447.2 cells/mm^3 while that of the co-infected was 682 cells/mm^3 with a mean of 712.2 ± 610.5 cells/mm^3 (t = 0.19, p = 0.85). Among the children ≤ 5 years, the baseline median CD_4% of HBsAg positive children was 25% with a mean of 28.2 ± 13.0 while surface antigen negative children had baseline median CD_4% of 15% with a mean of 16.3 ± 10.3. Having received HAART for varying periods, the median CD_4% of the co-infected children was 21.8% while that of surface antigen negative children rose to 30.2%.

From the baseline CD_4 count, 30 (33.3%) children ≥ 6 years studied did not have significant immunosuppression. Seventeen (18.9%) had mild immunosuppression, 16 (17.8%) had advanced immunosuppression and 27 (30%) had severe immunosuppression. Five (45.5%) of the co-infected subjects were severely immunosuppressed compared with 27.8% (22) of the non-co- infected subjects. However, there was no significant association between the levels of immunosuppression and HBsAg positivity (p = 0.64). Among the HIV positive HBsAg negative children, 34.2%, and 27.3% of the co-infected subjects had baseline CD_4 count ≥ 500 cells/mm^3 respectively. Having been on HAART for varying periods, their most recent CD_4 reveals that 40% of the co-infected children still had CD_4 count < 200 compared with 9% of the HIV positive HBsAg negative children (P = 0.027) (Table 6).

Among children ≤ 5 years, 44.7% (21) of the HIV positive HBsAg negative children had baseline CD_4% < 15% while none of the co-infection children had a CD_4% < 15%. However, 33.3% (1) of co-infected children had CD_4% > 25% while 17% (8) of those without HBsAg had CD_4% > 25% (Table 7).

Discussion

This study revealed a 10% prevalence rate of HBsAg among 140 HIV infected children, which is lower than the 19% and 12.1% among co-infected children in Maiduguri and Ivory Coast (Rouet et al 2008, Ashir et al, 2009) respectively. This difference may be due to higher prevalence of HIV and HBV infections in these areas compared to Enugu. It is higher than the seroprevalence of 7.7% in Benin (Sadoh et al, 2011) and 7.8% in Makurdi (Anigilaje,Olutola, 2013). It is also higher than the 1.2% in Dar-es-Salaam (Telatela et al, 2007). The role of universal HB immunization in Tanzania since 1999 may have accounted for this lower prevalence. Generally, this prevalence of 10% is higher than the estimated 8% for Africa (Puoti et al, 2008). This probably may be because Nigeria is hyper-endemic (Emechebe et al, 2009) and the fact that HIV infected children tends to have early exposure to HBV risk factors following repeated illnesses and hospitalizations. The large number of children co-infected with HBV can easily transmit the infection to other children, considering the fact that HBV is 100 times more infective than HIV (Mgonda, 2004). This makes the infection a major public health problem that requires enhanced measures of prevention and care in order to achieve eradication in sub-Saharan Africa.

An increasing prevalence of HBsAg with age was observed among the HIV positive children in this study. Other studies have also noted a similar trend (Telatela et al, 2007, Emechebe et al, 2008). This pattern would suggest that there is a predominance of horizontal transmission of HBV infection among HIV infected children in our environment. Though the highest number of HBsAg positivity was found in those children aged 6 -10 years, the highest prevalence of HBsAg was found among those aged 11-15 years. The high prevalence of co-infected Nigerian children of this age may reflect their inability to lose HBsAg due to their impaired immunity (Levy et al, 2006). In this study also, zero prevalence was observed in the age group 18 months to 3 years, which implies that vertical transmission of HBV has remained low in Nigerian women. It may also be that the mothers were not co-infected with HBV, considering the fact that Ilboudo in Burkina Faso recorded that three co-infected mothers who were positive for HBeAg, HBsAg and HBV DNA vertically transmitted the virus to their children (Ilboudo et al, 2010). This finding is similar to that in Dar-es-salaam (Telatela et al, 2007).

The social class of the children in this study was not significantly associated with HBsAg positivity. However, it was observed that the higher the social class, the lower the number of children positive to HBsAg. This is similar to the findings in Bangui (Komas et al, 2010), and in Enugu (Emechebe et al, 2008). This could be because people in the upper socioeconomic class are less likely to patronize medical quacks, or indulge in activities that may promote infection with HBV such as alternative medicine.

Though the risk factors in this study were not statistically significant, those transfused were about three times more likely to have HBV infection than those not transfused. It is worthy to note that blood transfusion may have contributed to this high prevalence rate considering the fact that infectious HBV can be present in blood without detectable HBsAg (Alexander,Kowdley, 2006). Al-Fawaz had earlier adduced that even an HBsAg free blood obtained by the very sensitive 3rd generation screening techniques can not completely safeguard against HBV (Al-Fawaz,Ramia, 1993). Also, it had been noted that history of blood transfusion was a sufficient risk factor for chronic hepatitis B infection, a major aetiological factor for primary hepatocellular carcinoma in Africa and Southeast Asia (Ndububa et al, 2001).

Irrespective of age and sex, serum alanine (ALT) levels greater than the upper limits of normal (15 iu/l) is often considered abnormal. Though the difference in ALT between the co-infected and non-co-infected children was not statistically significant, it was higher in the study group when compared with normal values. It probably may imply in-apparent liver disease in these children. The observed higher values among HBsAg negative subjects could be as a result of the fact that seven of the subjects had moderate to severe hepatic derangement with values of 50-206 iu/l. It is also possible that the higher value is due to other causes of liver disease in HIV positive individuals considering that 50% of the co-infected children had elevated baseline ALT compared with 45.2% among HBsAg negative HIV infected children. This differed from findings in Maiduguri (Ashir et al, 2009), and in Dar-es-Salaam (Telatela et al, 2007). Having been on HAART for varying periods, the mean ALT increased among both the co-infected and non-co-infected children showing a worsening liver disease probably due to HAART.

The immune status of the co-infected children as depicted by the baseline median CD_4 count was lower than in those with HIV infection alone. They also had lower median CD_4 value even after being on HAART for a variable period. The improvement in immune

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status of this children compared with the co-infected was statistically significant. This implies that HBV co-infection significantly impairs the immune system of HIV positive children and that immunologic failure is commoner among co-infected subjects. This finding is consistent with those of Anigilaje, *et al*, Rouet *et al* Thio *et al* and Psevdos *et al*.

Conclusion

Hepatitis B virus infection is common among HIV infected children and co-infection is associated with impaired immunity (lower baseline CD_4 count), even more significantly after initiation of HAART. Hepatitis B Virus co-infection is also associated with liver enzyme derangement (liver disease) although the difference was not statistically significant and this is probably exacerbated by HAART.

Conflict Interest Statement: The authors of this work hereby declares that there is no competing interest among them and that there are also no financial or professional affiliations with any group or company.

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