Science Research
2015; 3(6): 324-328
Published online December 9, 2015 (http://www.sciencepublishinggroup.com/j/sr)
doi: 10.11648/j.sr.20150306.19
ISSN: 2329-0935 (Print); ISSN: 2329-0927 (Online)

Seroprevalence and Associated Risk Factors of HBV Co-infection Among HIV Infected Children Enrolled into Care at Kilimanjaro Christian Medical Centre, Tanzania

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To cite this article:

Rose H. Mende, Blandina T. Mmbaga, Rahim K. Damji, Ben C. J. Hamel, Ann M. Buchanan. Seroprevalence and Associated Risk Factors of HBV Co-infection Among HIV Infected Children Enrolled into Care at Kilimanjaro Christian Medical Centre, Tanzania. *Science Research.* Vol. 3, No. 6, 2015, pp. 324-328. doi: 10.11648/j.sr.20150306.19

Abstract: Sub-Saharan Africa remains the region most affected with HIV. The wide use of highly active anti-retroviral therapy has led to improvement in life expectancy among HIV infected individuals. However, hepatitis B virus related complications like liver cirrhosis and liver failure are now becoming common causes of morbidity and mortality in this group. The aim of this study was to determine the seroprevalence and risk factors of HBV/HIV co-infection among HIV infected children enrolled into care at Kilimanjaro Christian Medical Centre (KCMC). This cross sectional analytical study was conducted among 323 HIV infected children at KCMC between February 2013 and May 2013. Investigations included interviews, physical examination and HBsAg analysis. HIV serostatus and CD4 counts/percentages were obtained from patients records. In addition, information on hepatitis vaccine status was recorded. Among 323 HIV-infected children enrolled, 177 (54.8%) were males. The prevalence of hepatitis B virus and HIV co-infection was found to be 1.2% (n=4). Hepatitis B virus co-infection was not significantly associated with any of the sociodemographic or behaviour risk factors which were assessed. CD4 counts were significantly associated with hepatitis B virus status whereby children with CD4 counts less than 350 cells/mm3 were 14 times more likely to have hepatitis B virus co- infection as compared to those who had CD4 counts greater than 350 cells/mm3. All of the hepatitis B virus co-infected children had no records of hepatitis B virus immunization, though one was born during the period of universal infant's hepatitis B vaccination (<4 years old). The frequency of hepatitis B virus co-infection with HIV infection was low among HIV infected children in our set up. It is important to strengthen the implementation of the universal infant's hepatitis B virus vaccination. The screening of HIV infected children for hepatitis B virus co-infection is still important whenever possible with immunization of all HIV infected children and adolescents with negative HBsAg.

Keywords: Hepatitis B, HIV, Prevalence, Co-infection, Children

1. Introduction

Both hepatitis B virus (HBV) and HIV are known to be major global public health problems. Worldwide more than 400 million people are estimated to have chronic HBV infection and about 34 million people have HIV infection [1, 2]. Sub-Saharan Africa constitutes about 69% of HIV infected individuals [2]. HBV and HIV share common routes of transmission, but they differ in their efficiency by which

certain types of exposures transmit them [3]. Individuals with HBV and HIV co-infection have an increased risk of developing complications such as lamivudine resistance, liver cirrhosis, hepatocellular carcinoma and death [4]. To our knowledge, only two studies were published documenting the seroprevalence of HBV co-infection among HIV infected children in Tanzania [5, 6], and more over there are no existing guidelines on the management of these children. This study was conducted to determine the seroprevalence and risk factors of HBV/HIV co-infection among HIV infected children enrolled into care at Kilimanjaro Christian Medical Centre (KCMC).

2. Methods

2.1. Study Design, Setting and Population

This cross sectional analytical study was conducted at the Child Centred Family Care Clinic (CCFCC) in KCMC between February 2013 and May 2013. KCMC is the referral and consultant hospital in northern Tanzania. The CCFCC clinic was established in 2007 to attend children and families with HIV infection, with the child as the entry point to care and treatment for other family members who are HIV infected. The CD4 counts/percentages are monitored on a 6-monthly basis, HBV is not routinely screened. There is also adolescents HIV clinic taking place once a month within CCFCC. The clinic is being attended by physician, paediatrician and gynaecologist so as to give opportunity for families, parents/caretakers who are HIV infected with their children to receive care at the same clinic and on the same day. Confirmed HIV infected children below the age of 18 years who were attending the CCFCC at KCMC during the study period were included in this study. Children from orphanage centres and those whose parents/caretakers refused to consent were excluded from the study.

2.2. Data Collection

Parents/caretakers were interviewed using a data extraction sheet to obtain information concerning child's demographics, age, sex, HBV vaccination status, presence of any house hold member with liver problems including cancer of the liver, history of blood transfusions, surgery/circumcision and history of piercing/scarification. Those who had a history of piercing/cutting/scarification were asked about sharing of instruments. Patient record files were used to obtain information concerning HIV status and CD4 counts. HIV status included date of diagnosis, World Health Organization clinical stage, Highly Active Antiretroviral Therapy (HAART) and co-trimoxazole use. Only recent CD4 counts (within six months) were recorded. Those who had no recent CD4 counts were tested during the time of enrolment to the study.

2.3. Physical Examination

A thorough physical examination was done according to standard clinical methods [7]. General examination, followed by systemic examination was performed, with special attention for jaundice, enlargement of the liver and the presence of any piercing or scarification.

2.4. Laboratory Investigations

2.4.1. Detection of HBsAg

Laboratory analysis was done at the KCRI Biotechnology laboratory where a qualified laboratory technician as per manufacturer's instructions conducted laboratory analyses for HBsAg. HBsAg was detected by using Monolisa HBsAg ULTRA kit manufactured by Bio-Rad, which is approved by the US Food and Drug Authority. ELISA reader ELX80814 SN205774 and ELISA washer EXL50 SN206202 machines both manufactured by Bioteck were used in the analysis. The kits, which were used, have a tested specificity and sensitivity of 99.9% and 100% respectively.

2.4.2. CD4 Counts/Percentage Testing

For the analysis of CD4 counts/percentages, Facs callibur immunocytometry machine manufactured in San Jose CA – USA was used.

2.4.3. Statistical Analysis

Data were entered, cleaned, and analysed using Statistical Package for Social Sciences (SPSS) software version 22. Data were presented by frequency tables and contingency tables. Chi-square test and odds ratio at 95% confidence interval (CI) was used to test for statistical significance. The association was considered significant at $p \leq 0.05$.

2.4.4. Ethical Consideration

Ethical approval for the study was obtained from the Kilimanjaro Christian Medical University College Research Ethics Committee. The parents/caretakers were requested to read and sign a written informed consent prior to enrolment and assent was obtained for those children aged 12 years and above. Those who refused to participate in the study were given equal services and care.

3. Results

The study involved 323 HIV-infected children recruited between February and May 2013. Among them 177 (54.8%) were males. Children older than 10 years (>120 months) were 143 (44.3%) while under-fives (<60 months) were 67 (20.7%) (Table 1).

Table 1. *Characteristics of the study participants (n = 323).*

Variable	n (%)
Sex	
Male	177 (54.8)
Female	146 (45.2)
Age (months)	
Less than 60	67 (20.7)
60-120	113 (35.0)
Greater than 120	143 (44.3)
Median(Interquartile range (IQR)	*112 (68-150)*
WHO clinical stage	
I	23 (7.1)

Variable	n (%)
II	68 (21.1)
III	135 (41.8)
IV	97 (30.0)
HAART status:	
On HAART	296 (91.6)
Not on HAART	27 (8.4)
Line of regimen(n=296)	
First line	230 (77.7)
Second line	66 (22.3)
CD4 percent:*	
Children under-five (n=63)	
25% or lower	22 (34.9)
Above 25%	41 (65.1)
Median(IQR)	*32.0 (22.0-370)*
CD4 count (cells/μL)*	
Children ≥ 5 years (n=244)	
350 or lower	34 (13.9)
Above 350	210 (86.1)

* CD4 count/percent missing in 16 patients due to occasional absence of reagents.

The prevalence of Hepatitis B surface Antigen (HBsAg) among HIV infected children was 1.2% (4 children). HBsAg was found in 3 children aged above 10 years and in 1 child aged 5 to 10 years. No child less than 5 years old had HBsAg.

HBV co-infection was not associated with any of the assessed demographic or behaviour risk factors. Those who had surgery/circumcision, were two times more likely to be infected by HBV compared to those who had no surgery/circumcision; however, the association between HBV status and surgery/circumcision was not statistically significant (OR=1.80, 95% CI, 0.25-12.94, p=0.620) (Table 2).

CD4 counts were significantly associated with HBV status. Children with CD4 counts of less than 350 cells/mm^3 were 14 times more likely to have HBV infection as compared to those who had CD4 counts of greater than 350 cells/mm^3. However, the confidence interval was very wide showing low precision of the association (OR=14.42, 95% CI=1.47-141.41, p=0.019) (Table 2).

4. Discussion

The prevalence of HBV infection in the studied group of HIV infected children was low (1.2%). This was in accordance with the prevalence of 1.2% which was reported by Telatela et al. in 2007 in Tanzania and a prevalence of 2.0% reported by Abera et al. in 2014 in Ethiopia [5, 8]. However, the prevalence in these 3 studies was significantly lower than the respective seroprevalences in Nigeria, Ivory Coast, Zambia, India and China [9-13] (Table 3).

Table 2. *Association between risk factors and HBV co-infection among HIV infected children (n=323) enrolled in care at CCFCC of KCMC.*

	total	HBV status n (%)		OR (95%CI)	p-value
		positive	negative		
House hold member with liver disease	2	0 (0)	2 (100.0)	1.01 (0.10-1.02)	0.975
History of blood transfusion	19	0 (0)	19 (100.0)	1.06 (1.03-1.09)	1.000
History of surgery or circumcision	116	2 (1.7)	114 (98.3)	1.80 (0.25-12.94)	0.620
Cuts/piercing/scarification	87	1 (1.1)	86 (98.9)	0.90 (0.09-8.80)	1.000
CD4 count					
High	251	1 (0.4)	250 (99.6)	1	0.019
Low	55	3 (5.5)	52 (94.5)	14.42 (1.47-141.41)	

Out of 323 enrolled children, 150 (46.4%) had no records of HBV vaccination. All four children with positive HBsAg results had no records of HBV vaccination.

Table 3. *Seroprevalence of HBV co-infection among HIV infected children in different countries.*

Author	Country	Study design	Prevalence (%)	When sampled	HBV vacc started (included in the national schedule)	Coverage when study performed
This study	Tanzania	Prospective cross sectional	1.2 (4/323)	2013	2002	>90%
Telatela et al, 2007 [5]	Tanzania	Prospective cross sectional	1.2 (2/167)	2005	2002	>90%
Muro et al, 2013 [6]	Tanzania	Retrospective cross sectional	7.0 (11/157)	Dec. 2006 to June 2009	2002	>90%
Sadoh et al, 2011 [9]	Nigeria	Prospective cross secional	7.7 (12/155)	2009	2004	27% in 2008
Rouet et al, 2008 [10]	Ivory coast	Retrospective cross sectional	12.1 (34/280)	2000 to 2003	2001	48% in 2002
Abera et al, 2014 [8]	Ethiopia	Prospective cross sectional	2.0 (5/253)	2014	2007	Around 85%
Peebles et al, 2015 [11]	Zambia	Retrospective cross sectional	10.4 (43/411)	2011 to 2014	2005	Around 85%
Bhargava et al, 2009 [12]	India	Prospective cross sectional	29.7 (30/101)	2005 to 2007	2007	58% in 2008
Zhou et al, 2009 [13]	China	Retrospective cross sectional	4.9 (53/1082)	2005 to 2009	2002	92% in 2006

Muro et al. at KCMC found a prevalence of 7.0% among HIV infected children [6]. The different results between our study and the Muro et al. study may be due to improvement of HBV vaccination coverage. Muro et al. studied samples which were collected 4 years after the HBV vaccination has been introduced in Tanzania. The Hepatitis B immunization started in 2002 in Tanzania and by 2005 the coverage was estimated to be above 90% [14]. This might have played a role in the lower prevalence due to good vaccination coverage in the current study, though the high official HBV vaccination coverage rates are not matched with the fact that 46.4% of the children enrolled in our study and all 253 children and adolescents in the Ethiopian study were not vaccinated [8]. By the year 2008, it was reported that the HBV vaccination coverages in Nigeria and Ivory Coast were 27% and 56%, respectively, while 42% of the children were unvaccinated in India [14]. The high HBsAg prevalences in Nigeria, Ivory Coast, India and China may also be explained by their lower vaccine immunization coverage, though this seems to be an unlikely explanation in Zambia and China. In our study the known risk factors for HBV co-infection, like blood transfusion and scarification did not show significant association. Similar findings were observed in the studies reported by Teletela et al. in Dar es Salaam, Tanzania and Shadoh et al. in Nigeria [5, 9], while Abera et al. in Ethiopia found no association with female genital mutilation, traditional uvulectomy and blood transfusion [8]. This could be explained by a high awareness of HIV which has improved knowledge and practices on prevention not only in hospital settings but also in the general population. Nwolisa et al. in 2013 in Nigeria also found no significant association between blood transfusion and HBV co-infection [15].

Our study demonstrated that children with CD4 counts of less than 350cells/mm^3 were more likely to have HBV infection compared to those who had CD4 counts above 350cells/mm^3 though the precision was low. Other studies reported also low CD4 counts in HBV/HIV co-infected individuals [16-18]. The study conducted in Nigeria reported lower CD4 count among HBV-HIV co-infected children compared to those who had HIV infection only [18], as was found by Peebles et al. in Zambia [11].

All four HBV co-infected children had no records on HBV immunization. For the 3 children who were 10 or more years old, this not surprising, since universal HBV vaccine was introduced in Tanzania in 2002. However, the one in the age group 5-10 years was staying with his aunt who had no information on the immunization history of the child. Therefore, it is possible that the mother had HBV infection leading to vertical transmission or the child was not vaccinated at all, or the child was vaccinated but there was a vaccine failure. In Nigeria in 2011, Sadoh et al. found that 83.3% of the HBV co-infected children below 5 years of age reported complete HBV vaccination [9].

5. Conclusion

The prevalence of hepatitis B virus co-infection among HIV infected children is low among HIV infected children enrolled into care at CCFCC of KCMC, but this should not be underestimated. It is important to strengthen the implementation of the universal infant's hepatitis B virus vaccination, as early as possible after birth to prevent mother to child transmission and introduction of immunization to all HIV infected children and adolescents with negative HBsAg [19]. The screening of HIV infected children for hepatitis B virus co-infection is still important whenever possible.

Study Strength and Limitation

Since this study was a cross sectional study, it was relatively easy to conduct over a short period of time and the variables were collected only once.

One of the study limitations included financial constrains which limited our investigation to HBsAg only. It was not possible to conduct HBcAb, anti HBsAb, HBeAg, HBV DNA and ALT tests. Other limitations were short duration and the fact that some CD4 counts/percentages were not done due to occasional lack of reagents.

Acknowledgments

We acknowledge the support provided by the specialists and residents in the Department of Paediatrics and Child Health of KCMC, health workers in CCFCC of KCMC, Mr. Gabriel Karia for collection of blood samples from the patients and health workers in KCRI Biotechnology Laboratory for performing HBsAg analyses. We acknowledge the statistical support provided by Mr. Gibson Kapanda and Mr. Jeremy Damian. We finally wish to thank all the parents, guardians and children for their willingness to participate in this study.

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