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Serum Immunoglobulin E levels and Atopic Diseases in Human Immunodeficiency Virus-Infected and Non-Infected Children and Their Association with the Severity of HIV Infection at a Tertiary Hospital, South-West Nigeria

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ABSTRACT

Human immunodeficiency virus (HIV) infection had been reported to increase serum Immunoglobulin E (IgE) and the prevalence of atopic diseases. However, there is a paucity of data in the literature on the association between the severity of HIV infection and serum IgE and atopic diseases among children in the Sub-Sahara African region, particularly Nigeria.

OBJECTIVES: To assess serum IgE levels, prevalence and pattern of atopic diseases, and their association with the severity of HIV infection in children on antiretroviral therapy.

METHODS: One hundred HIV-infected children on antiretroviral therapy recruited consecutively into a cross-sectional study were age and sex-matched with 100 non-infected. International study of asthma and allergy in childhood (ISAAC) proforma was used to obtain information from all the participants. Serum IgE levels and Cluster of differentiation (CD) 4+ counts of all the participants were determined, as well as, HIV viral load of the infected participants. HIV viral load, CD 4 counts and WHO clinical staging were used to classified HIV severity. Data analysis was done using statistical package for social sciences (SPSS) version 21, and statistic significant level was put at $p<0.05$.

RESULTS: Mean (SD) serum IgE of the HIV-infected and non HIV-infected children were 150.6 (12.7)iμ/ml and 94.8 (5.6)iμ/ml respectively ($p=0.001$). The overall prevalence of atopic diseases among HIV-infected and non-infected children were 15.0% and 6.0% respectively, $p=0.031$. Among HIV-infected, allergic conjunctivitis accounted for 11.0% and allergic rhinitis 4.0%, while among non-infected allergic conjunctivitis, atopic dermatitis and asthma accounted for 4.0%, 1.0% and 1.0% respectively. Based on WHO clinical staging, serum IgE level was significantly higher in advanced disease than in early ($p<0.001$), and likewise the prevalence of atopic diseases ($p=0.011$).

CONCLUSION: An elevated level of serum IgE and a higher prevalence of atopic diseases were observed among infected children compared to non-infected counterparts. HIV disease severity was associated with elevated serum IgE and the prevalence of atopic disease. Atopic diseases should therefore be routinely sought for in HIV-infected children.

Keywords: Serum immunoglobulin E, Atopic diseases, HIV severity, Children

INTRODUCTION

Human immunodeficiency virus (HIV) infection is one of the infections of public health importance ravaging the world, most especially sub-Saharan Africa.[1-3] Nigeria; a country ranked 7th among the 10 countries of the world with highest population has the 2nd biggest HIV epidemic in the world.[4,5]

Immunoglobulin E (IgE) is one of the immunoglobulins found in human being. It is produced by the B-cells and has the lowest concentration in human serum when compared to the concentration of the other immunoglobulins (<0.001%).[6] IgE plays a key role in the control of infections (bacteria, viruses and parasites) and it is an important mediator of allergic reactions.[6,7]Atopic diseases (asthma, atopic dermatitis, allergic rhinitis or conjunctivitis) are clinical syndromes each characterized by constellations of symptoms and signs.[8] They have been reported to be associated with HIV infection and, in fact, they have been found to exhibit their clinical symptoms and signs in individuals living with HIV.[9]

Increase in serum IgE levels in HIV-infected individuals had been reported in some studies. [10,11] This increased level has been attributed to be impaired T-cell suppressive control on the B-cell antibody synthesis (immune dysregulation) leading to hypergammaglobulinaemia.[12] Similarly increased prevalence of atopic diseases in HIV-infected patients had also been documented.[9,13]

However, in Nigeria, there still exists a paucity of data on the serum IgE levels and the prevalence of atopic diseases in HIV-infected children compared to their non-infected counterparts. Also and to the best of the authors' knowledge, only one study in Nigeria assessed the association between the levels of serum immunoglobulin classes except for IgE levels and the severity of HIV infection in children in terms of Cluster of differentiation (CD) 4+ T-lymphocyte count. [14] In addition, only one study also assessed the association between the prevalence of atopic diseases and the severity of HIV infection in terms of World Health Organization (WHO) HIV clinical staging. [13]

Therefore, this study assessed the serum IgE levels, prevalence, and pattern of atopic diseases in HIV-infected and non-infected children aged 1-16 years at a Nigerian tertiary hospital. Also, the association between the severity of HIV infection and the serum IgE levels and the prevalence of atopic diseases was assessed in terms of WHO HIV clinical staging, CD 4+ count, and HIV viral load.

MATERIALS & METHODS

STUDY LOCATION

The study location was Ladoke Akintola University of Technology (LAUTECH) Teaching Hospital (LTH), Osogbo, South-West Nigeria. Osogbo occupies an area of 47Km^2. It is situated at 1,043 feet above sea level and on coordinate 7^0 4^1 North 4^0 34^1 East. LTH Osogbo offers tertiary-level of health care and serves as a referral centre for various communities in and outside the state. It is also one of the treatment centres for HIV/AIDS in South-West Nigeria. The study was conducted at the Paediatric Emergency Unit, Paediatric Welfare Clinic and Paediatric antiretroviral clinic of the hospital over a 5-month period (28th September 2018 to 28th February 2019).

STUDY DESIGN AND POPULATION

The study was cross-sectional. Age and sex-matched 100 HIV-infected (on antiretroviral

therapy) and 100 non-infected children aged 1-16years were consecutively recruited. Excluded from the study were HIV-infected and non-infected children on corticosteroids, or had parasite(s)/ oval of parasite in the stool or consent/assent could not be obtained. Ethical approval was obtained from the Ethics and Research Committee of the hospital (LTH/EC/2017/09/331).

DATA COLLECTION

Socio-demographic and socioeconomic characteristics of the participants were obtained using a pre-tested questionnaire. Parental socioeconomic index scores were awarded to each participant according to Oyedeji's classification of social class. [15] The diagnosis of atopic diseases (asthma, eczema, rhino-conjunctivitis) was based on validated International study of asthma and allergy in childhood (ISAAC) questionnaire. [16] HIV disease severity was assessed by WHO HIV clinical staging, CD4+ T-lymphocyte count and HIV viral load for the HIV-infected participants. Suppressed and unsuppressed viral loads were defined as viral copies: <1000/ml and >1000/ml, [17] respectively. Significant immunosuppression and not significant immunosuppression were defined as CD4 counts <500 cells/μL and > 500 cells/μL, [17] respectively.

LABORATORY DATA

HIV screening was conducted on all the non HIV-infected children to justify their inclusion into the study using the HIV Determine™ Enzyme-linked immunosorbent assay (ELISA) Kit (Alere Medical, Co; Japan). Retroviral screenings were not repeated for the HIV-infected participants since their statuses had been known earlier and were already on antiretroviral therapy. Serum IgE assay and CD4+ T-lymphocyte counts were determined for all the participants using Human IgE ELISA kit (Rayto RT-2100C, Rayto Life and Analytical Sciences, Co., Ltd. Shanghai, China) and flow cytometric analytical machine (Sysmex Partec ®, Sysmex Co., Kobe, Japan) respectively. HIV viral load of the infected participants was determined using Amplicor HIV-1 monitor ™ test version 1.5 (Roche diagnostics system Inc; USA).

STATISTICAL ANALYSIS

Data from the questionnaire were manually sorted out for errors and omissions. They were entered into the computer and analyzed using statistical package for social sciences (SPSS) version 21 (SPSS Chicago Inc; IL, USA). Categorical variables were summarized using proportions and percentages. Categorical variables were compared using chi-square, Fisher's Exact and Analysis of covariance (ANOVA) where appropriate. Continuous variable were summarized using mean (standard deviation (SD) for normally distributed variables and median and interquartile range (IQR) for non- normally distributed variables. Differences between the mean (SD) and median (IQR) were compared using T-test and Mann-Whitney U-tests respectively. Statistical significance was set at p-value <0.05 for all values of statistical tests.

RESULTS

A total of 200 children - 100 HIV-infected and 100 non HIV-infected were studied. Out of the 100 HIV-infected children, 57 (57.0%) were males and 43 (43.0%) females giving a male to female ratio of 1.2:1; the same ratio applied to their non-infected counterparts. Table 1 shows the socio-demographic and socioeconomic characteristics of the children studied.

Table 1: Sociodemographic and socioeconomic characteristic of the study participants

	Study participants			
	HIV-Infected N (%)	**Non-HIV-Infected N (%)**	χ^2	***p*-value**
Age groups (years)				
1-5	29 (29.0)	29 (29.0)		
6-10	43 (43.0)	43 (43.0)		
11-16	28 (28.0)	28 (28.0)		
Total	*100(100.0)*	*100(100.0)*		
Family structure				
Monogamous	79 (79.0)	84 (84.0)		
Polygamous	11 (11.0)	15 (15.0	8.000♦	**0.046***
Separated	10 (10.0)	1 (1.0)		
Total	*100(100.0)*	*100(100.0)*		
Socioeconomics class				
Low	54 (54.0	20 (20.0)		
Middle	13 (13.0)	15 (15.0)	26.21+	**0.001***
High	33 (33.0)	65 (65.0)		
Total	*100(100.0)*	*100(100.0)*		

****Significant*** **+*Pearson's chi square*** **♦*Fisher's Exact Chi-square***

Serum IgE levels and atopic diseases in the participants

Means (SD) serum IgE levels of the HIV-infected and non-infected participants were 150.5 (12.7) IU/ml and 94.8 (5.6) IU/ml respectively (p = 0.001). The prevalence of atopic diseases among the HIV-infected participants was15.0% (15 out of 100) and 6% (6 out of 100) among the non-infected. The difference was statistically significant (p = 0.031). Table II shows the prevalence and pattern of atopic diseases among all the participants.

Table II: Prevalence and pattern of atopic diseases among participants

	HIV-Infected	**Non-HIV-Infected**	**Total**
Atopic diseases	**N (%)**	**N (%)**	**N (%)**
Asthma	0 (0.0)	1 (1.0)	1 (0.5)
Atopic dermatitis	0 (0.0)	1(1.0)	1 (0.5)
Allergic Rhinitis	4(4.0)	0(0.0)	4(2.0)
Allergic conjunctivitis	11(11.0)	4(4.0)	15(7.5)
Non- atopic	85(85.0)	94(94.0)	179(89.5)
Total	100(100.0)	100(100.0)	200(100)

Serum IgE levels and HIV disease severity

Out of the 100 HIV-infected participants studied, 97 (97%) of the infected participants had early disease (WHO clinical stage I and II) while 3 (3%) advanced disease (stage III and IV) with the means (SD) IgE levels of 146.8 (18.5) IU/ml and 267.65 (5.45) IU/ml, respectively. When the means serum IgE levels of the participants with early and advanced diseases were compared there was a statistically significant difference, (t = 11.249 p <0.001).

Thirty-four (34.0%) HIV-infected participants had significant immuno-suppression (CD4 <500 cells/UL) with mean (SD) serum IgE level of 153.3 (22.4%) IU/ml, while 66 (66.0%) had no significant immunosuppression (CD4 >500 cells/UL) with mean (SD) IgE level of 149.2 (15.3) IU/ml. There was no statistically significant difference when the means (SD) IgE of the two groups were compared (p =0.880).

Sixty-four (64.0%) HIV-infected participants had suppressed viral load (<1000copies/ml) and had mean (SD) IgE of 150.3 (16.1) IU/ml, while 36 (36.0%) who had unsuppressed viral load (>1000 copies/ml) had mean (SD) IgE level of 151. (21.1) IU/ml. Comparison of the two means of the serum IgE levels yielded no statistically significant difference (p = 0.977).

Prevalence of atopic diseases and HIV disease severity

Table III displays the association between the prevalence of atopic diseases and HIV disease severity as assessed by WHO HIV clinical staging, CD4+ count and HIV RNA viral load. Statistically, a significant difference was observed only in WHO HIV clinical staging (p= 0.011), where the prevalence of atopic diseases was significantly higher among advanced disease participants than in early disease.

Table III: Association between atopic diseases and HIV disease severity

HIV severity classifications	Atopic diseases			
	Present N (%)	Absent N (%)	Total N (%)	χ^2 p-value
CD4+ T-lymphocyte (cells/µl)				
Significant immunosuppression (>500 cells/µl)	4 (11.8)	30 (88.2)	34 (100)	
No significant immunosuppression (>500 cells/µl)	11 (16.7)	55 (83.3)	66 (100)	0.423 0.370
Total	*15(100.0)*	*85(100.0)*	*100 (100.0)*	
HIV RNA Viral load copies/ml)				
Suppressed (<1000copies/ml)	9 (14.1)	55 (85.9)	64 (100)	0.123 0.469
Unsuppressed (>1000copies/ml)	6 (16.7)	30 (83.3)	36 (100)	
Total	*15(15)*	*85(85)*	*100 (100.0)*	
WHO HIV clinical staging				
Early disease (Stage I& II)	13 (13.4)	84 (86.6)	97 (100)	
Advanced disease (Stage II&IV)	2 (66.7)	1 (33.3)	3 (100)	6.475 **0.011***
Total	15 (15)	85 (85)	100 (100)	

****Significant***

DISCUSSION

The mean serum IgE level of the HIV-infected participants was significantly higher compared to the value obtained from the non-infected in this study. This finding agrees with Lyamuya et al [18] study at Dares Salaam, Tanzania. The reason for this consistency may be due to similarity in the systemic response to the viral particles of HIV in view of the genetic make-up of being Africans. More so, similar principle of IgE quantification assay was deployed. In addition, similar results were also reported by Zar et al [19] among South African HIV-infected children and Park et al [11] among Koreans with the infection.

The causes of elevated IgE levels could be multifactorial. Various hypotheses had been postulated by previous researchers and they included antigenic challenges from infectious agents such as viruses and parasites. [20-23] It has also been documented that abnormal activation of B-cells in HIV-infected individuals leads to spontaneous proliferation and secretion of all immunoglobulins (hypergamma-globulinemia) with the gradient of increase being more with IgE than the other immunoglobulins. [24] This hypergammaglobulinemia has been reported to be loss of the oversight function of T-cells on the B-cell synthesis of the immunoglobulins. [12]

Marone et al [20] revealed that HIV glycoproteins, Tat proteins and Nef protein activate human high-affinity IgE receptor (FCER1)-expressing basophils and mast cells by acting as superantigens. Pate et al [25] further hypothesized that when such superantigens are presented to B-cells, a cascade of reactions ensue which ultimately results in immunoglobulin switching to IgE production.

The prevalence of atopic diseases in this study was higher among the infected than the non-infected. This was not a surprise because clinical manifestations of atopic diseases have been documented in individuals with HIV infection. [9,13] A possible disequilibrium in the Th1-Th2 cytokines with Th2 taking pre-eminence suggests a predilection for atopic diseases in these patients. [26] Th2 cytokines play important roles in the pathogenesis of

asthma, atopic dermatitis, and allergic rhinoconjunctivitis. They include interleukines (IL) - 4, 5, 6, 9, 10 and 13. While IL-4 and 13 play vital function in immunoglobulin isotype switching to IgE, IL-5 and 9 enhance IgE synthesis and contribute immensely to the development of eosinophils. Eosinophils release intracellular granules which are sources of inflammatory proteins which cause damage to epithelial cells, induce airway hyperreactivity and hyperresponsiveness. [27]

Linhar et al [9] and Masekela et al [21] reported higher prevalence of atopic diseases among HIV-infected children in Sao Paulo, Brazil and Pretoria, South Africa respectively when compared to what was obtained in this study. This could partly be due to environmental factor of the study location (Osogbo, Nigeria), which is basically an agrarian community devoid of industrial pollution which may contribute to atopic manifestations. [28] Moscato et al, [29] in Pavia, Italy reported lower prevalence when compared to the prevalence from this present study. This could be attributed to the fact that the participants in Moscato study were highly active antiretroviral therapy (HAART)-naïve, while the participants in the present study were HAART-exposed. HAART use has been documented to be associated with immune reactivation and consequently predisposition to atopic diseases. [30]

Allergic conjunctivitis was the predominant atopic disease among both infected and non-infected groups but the prevalence was higher among the infected. Though the prevalence was within the range reported in previous studies, [13,31] It was lower than what Martin-Odoom et al [32] reported in Ghana. The difference may be due to the fact that many of the participants in the Ghanaian study were of older ages. The frequency of occurrence of allergic conjunctivitis has been reported to increase as age advances. [33]

Additionally, allergic rhinitis was reported among the infected participants but none among the non-infected. The prevalence obtained was lower than what was obtained by Masekela et al [21] and Porter et al [34]. The disparity could have been a result of different methodologies deployed in the diagnosis of allergic rhinitis. While Masekela et al [21] made use of ISAAC proforma and also subjected the participants' nasal smear to Hansel staining for eosinophils, the present study limited its diagnosis to findings from the ISAAC proforma only. Hansel staining of nasal smear for eosinophils offers diagnosis of allergic rhinitis to be made in those that may be missed using ISAAC proforma because of its self-reporting nature hence the difference in prevalence.

An association was observed between serum IgE and severity of HIV disease as measured by the WHO HIV clinical staging (mean IgE level was significantly higher in the advanced disease stage than in the early). This finding was in consonance with some previous reports. [35,36] In fact, Rancinan et al [36] deposited that serum IgE level is associated with a rapid progression to AIDS postulating that it could be used as a prognostic marker. Akinpelu et al [14] noted that immunoglobulins (IgA, G and M) levels were not associated with severity of HIV disease in children in terms of CD 4 counts. This assertion was corroborated in this study where IgE was observed not to have association with severity of HIV as classified by CD 4 counts.

Furthermore, serum IgE level was not associated with HIV viral load in this study. This finding was at variance to Nalto et al work [37] in which IgE level was found to be directly proportional to HIV viral load. The Nalto observed relationship was made in respect of a case study unlike the present study finding that made use of 100 participants in its analysis. A robust analysis using many study participants as in this present study may give more reliable and representative findings than a single case report.

Atopic diseases were observed to be associated with severity of HIV infection as measured by WHO HIV clinical staging in

this study, while Lin et al [38] observed severity association in term of CD4 counts. The prevalence of atopic diseases was found to be significantly more among participants with advanced disease than the early disease. This observation is not surprising as children in advanced disease stage exhibited significantly higher serum IgE levels than the study participants in early disease stage. IgE plays a central role in allergy sensitization and atopic disorders. Allergic and atopic disorders manifest due to Type I hypersensitivity reactions involving IgE and other immune cells to produce the clinical symptoms observed in atopic disorders. [39] It is a known fact that type one hypersensitivity reaction is the hallmark or the fundamental basis of atopic diseases.

Limitation

The findings of this study may need to be cautiously generalized because of the relatively smaller sample size of the study participants.

CONCLUSION

This study had demonstrated that serum IgE levels were markedly elevated in HIV-infected children compared to non HIV-infected, and atopic diseases were commoner among the HIV-infected than the non-infected, with allergic conjunctivitis being the commonest in both groups. Serum IgE was significantly elevated in advanced disease, and likewise the prevalence of atopic diseases was significantly higher in advanced disease than early disease stage. Thus, elevated serum IgE and the prevalence of atopic diseases were observed to be associated with HIV severity in term of WHO clinical staging. Atopic diseases should therefore be routinely and painstakingly sought for in HIV-infected children and management instituted.

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