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Research Article

Left Ventricular Diastolic Dysfunction: A Comparative Cross-Sectional Study among HIV Infected Children and Controls in Ilorin Nigeria

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Abstract

Background: Sub-Saharan Africa accounted for 10% of the world's population is home to over two-thirds of the world HIV patients. Improved survival of these patients, is accompanied by challenges of cardiovascular manifestation. Hence, we determined the left ventricular diastolic dysfunction of HIV infected children and controls using the reliable tissue Doppler imaging.

Methods: This was a comparative cross-sectional study among 100 HIV infected children and 100 HIV un-infected children as controls. The children were aged 2–14 years, recruited from both the Paediatric HIV and Paediatric outpatient clinics over 4months period. Data was analysed with SPSS® v 20. Mean and standard deviation of normally distributed data were determined. Categorical variables were compared using chi square test. Significant p was < 0.05.

Results: The mean age of subjects and controls was 9.42 ± 2.99 years. The prevalence of left ventricular diastolic dysfunction was 46% among subjects compared with 14% of controls. There was a significant association between occurrence of left ventricular dysfunction and degree of immune-suppression $p = 0.001$.

Conclusions: There is a high prevalence of left ventricular diastolic dysfunction among HIV infected children and more than thrice commoner in HIV compared with the controls. There was significant association between the degree of immune-suppression and the occurrence of left ventricular dysfunction in this study.

INTRODUCTION

Sub-Saharan Africa which has only 10% of the world's population, is home to more than two-thirds of the world HIV/AIDS patients [1,2]. With improved survival of patients with HIV, a higher proportion of these patients are manifesting varying degree of systemic involvement that includes the cardiovascular system [3].

Globally, HIV/AIDS has killed about 39 million people since its inception, among which 5.1 million are children [4]. As at 2019, there were 38 million people around the world living with HIV/AIDS and about 1.8 million of these were children [5]. In Nigeria, the National prevalence of HIV progressively increased from 1.8% to 5.8% in 2001 [6]. Thereafter, it declined to 5% in 2003 and was at its lowest (1.4%) in 2019 from the NAIIS sentinel survey [7]. Despite this reduction, it remained a disease of public Health importance due to our huge population. HIV/AIDS is taking an enormous toll on the health and psyche of its sufferers [8]. It has further reduced the quality of life of those living with the disease by worsening the social and economic indices [9]. It is the leading cause of death worldwide and 690,000 people died of AIDS in 2019 alone, with cardiovascular disease being one of the leading causes of death amongst them [10].

HIV transmission in children occur mostly (90% of cases) through vertical transmission from mother to child which could be during pregnancy, at the time of delivery or while breastfeeding [11]. It has adversely affected children as they take on more responsibility to earn an income, produce food, and care for family members. Hence it is more difficult for these children to access adequate nutrition, basic health, shelter and clothing [11,12]. Approximately 13.2 million children have been orphaned worldwide [13]. Nigeria the most populous African country with HIV has few studies on the effects of HIV on the heart, it's even worse in children [14].

Immunologic classification has been reported to have a direct relationship with LV dysfunction [15].This staging is categorized with the laboratory parameter (CD4) using either the absolute CD4 Counts or CD4 percentages [16]. A study by Ige *et al. [17],* in 2014 in Jos Nigeria is one of the very few published study known to the researchers on the subject matter. The said study reported 30.7% prevalence of left ventricular diastolic dysfunction among HIV infected children aged 7 months to 14 years compared with 12.7% among the age matched HIV negative control. The above study used the conventional method of diagnosing diastolic dysfunction (E/A ratio) which does not take care of those with pseudo normalization. A more recent study by Animasahun *et al. [18],* in 2018 reported 15% left ventricular systolic dysfunction among 39 HIV infected children. The study did not assess ventricular diastolic dysfunction and used a smaller (39) sample size. This study determined the left ventricular diastolic function among HIV infected children using the conventional and the more advanced Tissue Doppler Imaging (TDI) techniques.

MATERIALS AND METHODS

Study Design

This was a comparative cross-sectional study of children aged 2 – 14 years with HIV.

Study Site

The study was conducted at the Antiretroviral therapy clinic of the University of Ilorin Teaching Hospital (UITH), located in Ilorin East Local Government Area of Kwara State in Nigeria. The hospital is a tertiary health facility that serves as a referral centre for patients from Kwara and neighbouring States of Osun, Niger, Kogi and Ekiti [19]. There were 180 children on HIV treatment and care, with 130 of them on HAART [20].The study lasted for four months from August to November 2017.

Study Population

Ilorin is the capital of Kwara State in the North Central geo-political zone of Nigeria. Kwara State has a population of 2.37 million from 2006 census [21].The Nigeria HIV/AIDS indicator and impact survey (NAIIS) reported a National prevalence of HIV as 0.2% and 1.5% among children and adults respectively (2019) with the South – south and North – west zones having the highest (3.1%) and the lowest (0.6%) prevalence respectively. The North – central zone had prevalence of 2.1% [7].

Sample size determination

The minimum sample size was determined using the formula [22],

$$n = \frac{Cpower \times P1[1-P] + P2[1-P2]}{[P1-P2]^2}$$

Where n = minimum sample size, Cpower is 13.0, made up of Zα (probability of type I error) at 5% and Zβ (probability of type II error) at 95%

P1 = Prevalence of diastolic dysfunction among HIV infected children is 30.7% and P2 = Prevalence of diastolic dysfunction among controls is 12.7% as reported by Ige *et al. [17],*

$$n = \frac{13.0 \times 0.307[1-0.307] + 0.127[1-0.127]}{[0.307-0.127]^2}$$

$$n = \frac{2.765763 + 0.110871}{0.0324}$$

n = 88.8

`Allowing for 10% attrition rate, a total of 100 HIV infected children was recruited as the study subjects and another 100 HIV negative children as control.

Ethical approval

Ethical approval was obtained from the University of Ilorin Teaching Hospital Research Ethics Committee. A written informed consent was obtained from the parents / care-givers and assent from subjects aged seven years and above, after a clear explanation of the study objectives.

Subject recruitment

Recruitment of subjects for the study was done at the HIV clinic, UITH. Known HIV-infected children attending the clinic that fulfilled the inclusion and exclusion criteria were recruited consecutively into the study after obtaining a valid written informed consent from the parents / care-givers and assent where applicable. The controls were age and sex matched HIV-uninfected children who fulfilled the criteria below, among children attending the paediatric out-patient clinic.

Inclusion and exclusion Criteria

Confirmed HIV positive in subjects aged 2-14 years who either gave assent or parental consent given for the study. Excluded from the study were; Children with pre-existing congenital and/or acquired heart diseases, chronic diseases like sickle cell disease (SCD) and nephrotic syndrome. Others are children with connective tissue diseases such as systemic lupus erythematosus (SLE), those receiving medications (non-antiretroviral) with cardiac related complications such as doxorubicin, as well as those with severe anaemia (packed cell volume PCV ≤15% or any PCV with cardiac decompensation).

Funding of Research: The researchers provided funds necessary for this study.

Recruitment Procedure

The parents/care-givers of eligible subjects were approached and details of the study explained to them in a language they understand. A semi-structured questionnaire was administered by the researchers at the clinic and responses filled in immediately. A detailed history that includes biodata, duration since HIV was diagnosis, current medications and symptoms were taken. A complete general physical and cardiovascular examination in a well-lit room.

Echocardiography

The procedure was explained to the subjects / controls and they were assured of the safety of the procedure. They were made to lie on an examination couch in the echocardiographic laboratory and were made to stay calm as much as possible. The intracardiac anatomy was determined according to the standard guidelines [23]. Measurements of ventricular inflow (The mitral and tricuspid valves) were done in diastole.

The left ventricular diastolic function was assessed using Pulsed Doppler of the trans-mitral flow which was performed immediately after the 2D echocardiogram; the apical 4-chamber view was used in order to place the pulsed Doppler sample volume at the tips of the mitral valve. Rapid filling (E-wave) and atrial contraction (A-wave) peak velocities were measured in cm/s and peak pressure gradient in mmHg [24].

Left ventricular diastolic dysfunction was defined;

i. when the E/A ratio is < 1 (impaired relaxation),

ii. the E/A ratio is > 2.5 (restrictive filling) and a

iii. deceleration time (DT) of either > 240ms or < 160ms.

Tissue Doppler imaging was done to determine the e´ wave, a´ wave (which are measurements taken 1-2 cm proximal to the mitral valve annulus using the average from the lateral and the medial wall mitral annular velocity) and E / e´ ratio (a measure of ventricular filling pressure) [25].The E / e´ ratio is relatively independent of preload and it is the best marker of diastolic dysfunction [23]. The tissue Doppler measurement of mitral annular velocity was done using the apical 4-chamber view to determine e´ (considered normal at > 12) and E / e´ (considered normal at 5 – 15) [23,24]

Left Ventricular Diastolic Dysfunction

The left ventricular diastolic dysfunction was diagnosed with the following, depending on the stage of the dysfunction;

E /A ratio < 1, at the stage of slowed / impaired relaxation pattern [24]. Or either of the following at the other stages;

E / A ratio > 2.5.

e´ / a´ ratio < 1

E / e´ ratio < 5 and/or > 15 (the most sensitive).

Others that complement the diagnosis of left ventricular diastolic dysfunction includes IVRT and DT which were reduced in all except for the stage of slowed / impaired relaxation pattern.

Data Analysis

The results were entered into a microcomputer using numerical codes. Data analysis was done using SPSS®20. Tables and charts were used to report descriptive statistics. Mean, standard deviation (SD) of normally distributed data was done. Categorical variables were compared using the chi square test (Yates correction done as appropriate) while continuous variables were analysed using the student t-test. The level of significance was established at p value < 0.05.

RESULTS

HIV staging and ART status of study participants

Of the 100 HIV – infected participants in this study, most are at the asymptomatic stage with 15% at the severe stage. Only 6% of this study participants were yet to be commenced on Antiretroviral therapy as at the time of their recruitment, with most of those on treatment on first line medications Table 1.

A total number of 200 children aged 2 – 14 years were recruited over 4 months period, 100 HIV positive subjects and an equal number of HIV negative children served as control. The mean age of subjects was 9.42 ± 2.99 years, males were 58 with M: F of 1.4:1.

Prevalence of Left Ventricular Diastolic Dysfunction among Cases and Controls

The prevalence of left ventricular diastolic dysfunction of HIV infected children using the most sensitive parameter of measurements (E/e') was 46% compared with 14% of the controls. There were significant differences between the left ventricular diastolic dysfunction among HIV positive children and control $p = 0.001$ (Table 2).

Table 1: HIV staging and ART status of study participants

Variables		Frequency n (%)		
Staging (CD4 count based)	Asymptomatic		73 (73%)	
	Mild		6 (6%)	
	Moderate		7 (7%)	
	Severe		14 (14%)	
ART			1st Line	2nd Line
	Yes	94 (94%)	84 (84%)	10 (10%)
	No	6 (6%)		

Table 2: Prevalence of Left Ventricular Diastolic Dysfunction among cases and controls

	HIV Positive	HIV Negative	Total	χ^2	*p*-value
Variable	n (%)	n (%)	N (%)		
Left Ventricular Diastolic Dysfunction					
E/A ratio					
Abnormal	9 (9.0)	4 (4.0)	13 (6.5)	12.064	0.001
Normal	91 (91.0)	96 (96.0)	187 (93.5)		
e´/a´					
< 1	19 (19.0)	4 (4.0)	23 (11.5)	11.054	0.001
≥ 1	81 (81.0)	96 (96.0)	177 (88.5)		
E/e´					
< 5	33 (33.0)	9 (9.0)	42 (21.0)	9.384	0.006
5 – 15	54 (54.0)	86 (86.0)	140 (70.0)		
> 15	13 (13.0)	5 (5.0)	18 (9.0)		

χ^2: Chi square test; *: *p* value <0.05

Mean Left Ventricular Parameters in Subjects and Controls

The LVM was also found to be higher among subjects than the controls but no significant difference $p = 0.899$. The variables for left ventricular diastolic function (E/A, e', a', e'/a', E/e' etc) were higher among HIV positive children compared with HIV negative children but there was no significant difference save for the Ejection time (p=0.0001) (Table 3) (Figure 1).

As the serum cardiac Troponin I increases so does the left ventricular diastolic dysfunction worsens, evidenced by the fit line and the equation y = 7.35-2,78*x.

Left Ventricular Diastolic Dysfunction and Socio-demographics characteristics of HIV participants

There is significant association between degree of immune suppression and presence of left ventricular diastolic dysfunction p = 0.001, but no significant relationship between age group, sex, social status and left ventricular diastolic dysfunction p = 0.778 (Table 4**).**

Table 3: Mean Left Ventricular Parameters in subjects and controls

	HIV STATUS			
	Positive	Negative		
Variables	Mean ± SD	Mean ± SD	T	p value
Left ventricular diastolic function				
Left Ventricular Mass (LVM)	86.67 ± 73.44	85.56 ± 58.75	0.128	0.899
Ratio of Early to late LV filling (E/A)	1.66 ± 0.64	1.57 ± 0.54	1.061	0.290
e´	10.64 ± 4.75	10.23 ± 4.21	0.647	0.518
a´	6.86 ± 3.08	6.67 ± 2.95	0.457	0.648
e´/a´	1.77 ± 0.97	1.72 ± 0.88	0.352	0.725
E/e´	7.07 ± 5.78	7.20 ± 7.00	-0.144	0.886
Deceleration Time (DT in sec)	135.36 ± 34.42	142.74 ± 34.44	-1.516	0.131
Isovolumic Contraction Time (IVCT)	0.43 ± 0.08	0.43 ± 0.09	0.363	0.717
Isovolumic Relaxation Time (IVRT)	0.64 ± 0.09	0.64 ± 0.08	0.032	0.975
Ejection Time (ET)	2.59 ± 0.53	2.79 ± 0.48	-2.889	0.004

t: Independent sample T test; *p* value <0.05

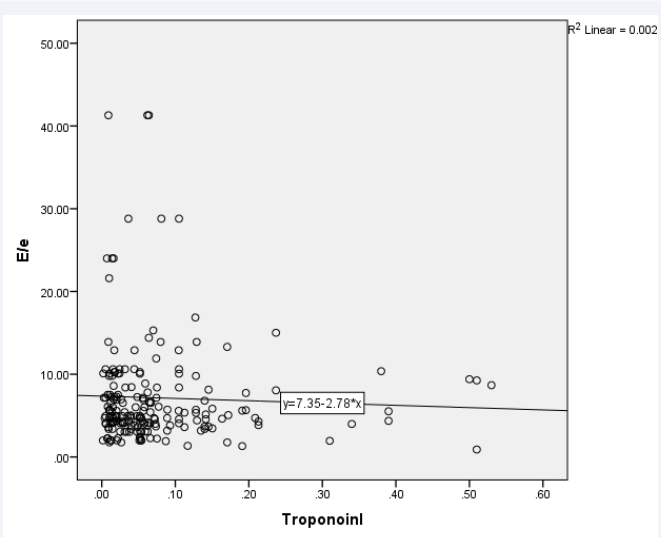

Figure 1: Scatter plot of the regression analysis between E/e' and serum Troponin I.

Relationship between Serum Troponin I Levels and Left Ventricular Dysfunction in HIV infected children

There is a strong relationship between elevated levels of serum Troponin I and the occurrence of left ventricular diastolic dysfunction. There is four times higher chances of an HIV infected child with a raised serum Troponin I of ≥ 0.10µg/L to have a left ventricular diastolic dysfunction compared with those with elevated Troponin I (OR = 4.44 CI 1.90 – 10.39) $p = <0.001$ (Table 5).

DISCUSSION

The prevalence of left ventricular diastolic dysfunction in this study was 46%, this may not be surprising as diastolic dysfunction often times precedes systolic dysfunction [25].This is comparable to the findings by Hsue *et al* [26], in San Francisco among who reported 50% left ventricular diastolic dysfunction.

Table 4: Left Ventricular Diastolic Dysfunction and Socio-demographics characteristics

Left ventricular diastolic dysfunction of HIV subjects					
	Yes	No	Total	χ^2	*p* value
Variable	**n=46 (%)**	**n=54 (%)**	**N=100**		
Age (years)					
3 – 5	6 (6.0)	7 (7.0)	13 (13.0)	1.097	0.778
6 – 9	15 (15.0)	16 (16.0)	31 (31.0)		
10 – 14	25 (25.0)	31 (31.0)	56 (56.0)		
Sex					
Male	27 (27.0)	31 (31.0)	58 (58.0)	0.017	0.896
Female	19 (19.0)	23 (23.0)	42 (42.0)		
Social class					
Upper	2 (2.0)	2 (2.0)	04 (4.0)	1.079[F]	0.670
Middle	12 (12.0)	19 (19.0)	31 (31.0)		
Lower	32 (32.0)	33 (33.0)	65 (65.0)		
Immuno-deficiency classification					
Severe	12 (12.0)	2 (2.0)	14 (14.0)	14.025[F]	**0.001**
Moderate	5 (5.0)	2 (2.0)	7 (7.0)		
Mild	3 (3.0)	3 (3.0)	6 (6.0)		
Not Significant	26 (26.0)	47 (47.0)	73 (73.0)		

χ^2: Chi square test; F: Fisher's exact test; *: *p* value <0.05

Table 5: Relationship between Serum Troponin I Levels and Left Ventricular Diastolic Dysfunction in HIV infected children

	Left ventricular dysfunction					
	Yes	N o	Total	OR (95% CI)	χ^2	*p* value
Troponin µg/L	n (%)	n (%)	N (%)			
≥ 0.10	28 (60.9)	14 (25.9)	42 (42.0)	4.44 (1.90 – 10.39)	12.45	<0.001*
< 0.10	18 (39.1)	40 (74.1)	58 (58.0)			
Total	46 (100.0)	54 (100.0)	100 (100.0)			

χ^2: Chi square test; OR: Odds ratio; 95% CI: 95% Confidence Interval; *: *p* value <0.05

The similarity despite use of different study population may be attributed to their strong methodologies.

In contrast, the prevalence of left ventricular diastolic dysfunction in this study is higher than the 30.7% earlier reported by Ige *et al*. [17], in Jos. This observed variation may be due to the usage of the more efficient and sensitive tissue Doppler imaging technique in the current study. Similarly, it is equally higher than the 28.8% reported by Uwanuruochi and colleagues [27], among adults at Umuahia Nigeria as well as the 24.5% reported by Miller *et al* .[28], among Zimbabwean adolescents. The reasons for the discrepancies of the above-mentioned studies with the current study is not clear. However, the earlier advanced reason of the utilization of a more robust diagnostic tool (tissue Doppler imaging "TDI" studies) in the present study could also explain the differences noticed. The TDI measures cardiac wall motion by assessing the ventricular function as a whole and it is not influenced by the preload unlike the traditional E/A (rapid "early" ventricular filling [E] and the late "atrial contraction" ventricular filling [A] [25].

Most of the HIV infected children with severe immune suppression have left ventricular diastolic dysfunction compared with only about a third of those at the asymptomatic stage of HIV. Likewise, Arodiwe and colleagues [29], in Enugu Nigeria reported similar findings among children. The similarity probably arose from the utilization of similar study population. In contrast, study by Ige *et al.* [17], also among children but in Jos Nigeria found no association between the degree of immune-suppression and left ventricular diastolic dysfunction. The explanation for the disparity noticed may be due to the fact that one-sixth of our subjects were in stage IV of the disease as against only four subjects in the Jos study.

In addition, Namuyonga *et al*. [30], in Uganda also reported no association between the status of immune-suppression and the occurrence of left ventricular diastolic dysfunction. The exact reason for this observation is not known but may be that the Ugandan study participants have better immune status as they were all on HAART unlike the present study where some are HAART naïve. Furthermore, more than two-third (68%) of the Ugandan study participants were virally suppressed and with 94% adherence to ART implying better immune status, which were not assessed in the present study

CONCLUSIONS

The prevalence of left ventricular diastolic dysfunction among HIV infected children in this study was twice that of the controls (46% vs 14%). There was a significant association between the degree of immune-suppression and the occurrence of left ventricular diastolic dysfunction among subjects.

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