Predictors of cardiac dysfunction in children with HIV/AIDS attending University of Nigeria Teaching Hospital Enugu

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Abstract

Cardiac dysfunction, though common as a primary effect of HIV infection or its treatment in HIV-infected children, is often clinically masked by pulmonary disease in patients with HIV infection and AIDS. The objective of the study was to determine the prevalence and predictors of cardiac dysfunction in children with HIV/AIDS infection. This was a cross-sectional comparative case - control study of clinical and echocardiographic findings in 90 pediatric HIV/AIDS children aged 18 months to 14years and their age and gender - matched HIV – negative controls attending the University of Nigeria Teaching Hospital, Enugu. Relevant clinical information including demographics, investigations including echocardiography and treatment, were captured using a datasheet designed for the study. Data analysis was done using SPSS version 20.0. A p value of <0.05 was considered significant. The majority of the subjects had cardiac abnormalities and was on HAART. The pattern of cardiac abnormalities in HIV – infected and AIDS groups were left ventricular diastolic dysfunction (33.8% and 36.4% in the HIV – infected and the AIDS groups respectively, followed by dilated cardiomyopathy (6.8%) seen only in AIDS group (p=0.03). A strong linear relationship between cardiac dysfunction and $CD4^+$ counts (R^2=0.8642) and age (R^2=0.4203) among the patients were observed. Cardiac dysfunction is common in children with HIV/AIDS and predicted by $CD4^+$ count and increasing age. Need exists to monitor the development of cardiac dysfunction using appropriate clinical details and echocardiography is recommended to improve their quality of life.

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Informed consent: All patients participating in this study signed a written informed consent form for participating in this study. This were obtained from parents /guardians of the children while assent was also obtained from children aged 7years and above respectively. Also a legally authorized representative(s) for anonymized patient information to be published in this article.

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Introduction

Human Immunodeficiency Virus (HIV) infection and its effect, Acquired Immune Deficiency Syndrome (AIDS) constitutes a global health challenge. With improved clinical surveillance and treatment, using Highly Active Antiretroviral Therapy (HAART), survival is improved with progressive dysfunction of organ systems and the burden of resulting cardiac dysfunctions posing great challenge.[1,2] The World Health Organization has estimated that 38-110 million people will be living with AIDS by 2025.[1] In Sub - Saharan Africa it is an epidemics, with prevalence rate of >1%; cardiac dysfunctions has become a clinical problem and a leading cause of mortality in this region.[2-4]

The first report of cardiac dysfunction in HIV infection was by Austran *et al.* in Haiti in 1983.[5] Recent studies showed that HIV may exhibit a cardiac tropism.[6,7] However on the predictors of cardiac dysfunction in children with HIV/AIDS, few controlled studies have been published.[7-9]

Cardiac dysfunction, though common as a primary effect of HIV infection or its treatment, is often clinically masked or attributed to pulmonary disease in patients with HIV infection and AIDS.[9,10] Therefore, there is a need for predictors of cardiac dysfunctions be studied, as these may be useful in identifying or monitoring patients for intervention.[11,12] Some studies had noted that

age, a low CD4+ cell counts, use of HAART, HIV – associated encephalopathy and malnutrition and wasting may predict cardiac dysfunction.[11,13-16]

This study looked at these predictors of cardiac dysfunction in HIV/AIDS in our environment.

Materials and Methods

This was a cross-sectional comparative case controlled study of clinical and echocardiographic findings of 90 pediatrics HIV and AIDS children and adolescents aged between 18 months and 14 years with age and gender matched HIV-negative controls. The patients were seen at the University of Nigeria Teaching Hospital (UNTH) Enugu from February to December 2017.

Ethical clearance was obtained from the Health Ethics Research Committee (HERC) of the University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu.

Subjects included were HIV 1 and/or 2 positive patients, who were or were not on HAART while the controls were HIV negative age and sex-matched children attending the children's Outpatient Clinics who had minor illnesses which were mainly uncomplicated malaria or upper respiratory infections.

The patients with positive HIV serology and a clinical diagnosis of HIV infection according to CDC criteria were classified into two groups: HIV-infected group with 74 (82.2%) patients and AIDS group with 16 (17.7%) patients. Patients on medications with known cardiovascular effects, children with pre-existing cardiac diseases, chronic diseases associated with demonstrable wasting or edema were excluded.

All the study participants were black children with at least one parent or guardian who gave informed consent. Ethical clearance was also obtained from UNTH ethics committee.

Clinical assessment using a questionnaire was obtained. Important demographic characteristics including age and sex, relevant clinical information (HAART naïve or on HAARTS, duration of treatment with HAARTS) physical examination- respiratory rate, heart rate, blood pressure, anthropometry (weight, length/height and subsequently BMI in kg/m^2) was determined while 5mL of venous blood was drawn for full blood count, HIV serology, and CD4+ cell count [performed by a slide technique with APAAP mouse monoclonal antibody (Dako, glostrup, Denmark)]. Antibody level against HIV were measured by an enzyme linked immunosorbent assay and confirmed by western blotting and 2D Echo examination was done using standard protocol with Hewlett-Packard SONO 2000 machine. The machine has a transducer with multi-frequency in the range 5.5-12MHz.

Definition of terms

Depressed LV systolic function = Fractional Shortening (FS) of ≤28% or ejection fraction (EF) of less than <40%. LV diastolic dysfunction was diagnosed in the presence of any of: impaired relaxation with an E/A ratio <1, IVRT>100 m/s and DT>220 m/s, restrictive pattern with E/A ratio >2, IVRT <70m/s and DT<150m/s or Pseudo normalization with normal configuration of E/A but low DT. Dilated cardiomyopathy was defined as systolic dysfunction with LV dilatation (LVEDD>5.6cm and LVESD>4.1cm).

Statistical analysis

Analysis was done using Statistical Package for Social Sciences (SPSS) version 20.0.

Results were presented as mean and Standard Deviation (SD).

Table 1. Demographic and clinical characteristics of HIV/AIDS patients with and without cardiac abnormality.

Features	Cardiac abnormality n=68	No cardiac abnormality n = 22	t- value	p-value
Sex				
Male	33	15	0.98(χ^2)	0.61
Female	35	7		
Age in years (mean ± SD)	6.33 ± 2.30	12.00 ± 4.20	0.29	0.04*
Weight(kg)	25.50 ± 7.9	31.23 ± 9.00	0.79	0.02*
BMI for- age	M F	M F		
2 – 4 years	16.9±2.0 16.8±2.2	18.5±2.0 18.9±1.9	6.02(χ2) 5.26	0.11
5 – 9 years	15.9±0.8 15.7±1.0	19.3±1.5 19.5±1.0	4. 54	0.06
10 – 14 years	17.5±1.8 17.0±2.5	19.0±1.3 19.3±1.8		0.13
Pulse rate/min	120.50 ± 3.21	86.50 ± 10.01	2.18	0.03*
Respiratory rate/min	35.02 ± 3.21	25.34 ± 4.00	1.13	0.19
SBP(mmHg)	85.00 ± 10.48	88.34 ± 4.52	0.70	0.35
DBP(mmHg)	48.33 ± 11.69	48.54 ± 8.14	0.08	0.87
Hb (g/dL)	7.34±1.78	9.10± 0.67	0.45	0.12
WBC (Total)µL	3783 ± 1896.75	5543.78 ± 2590.43	1.12	0.42
CD4+ count	950.87 ± 137.16	1250 ± 146.32	2.10	0.04*
Clinical stage				
HIV-Infection	56	18	1.98	0.42
AIDS	12	4	0.92	0.09
Total	68 (75.6%)	22 (24.4%)	2.50	0.02*
Treatment with HAART				
Yes	54	10	5.82	0.01*
No	10	16		
Mean duration on HAART (years)	6.33 ± 5.07	2.38 ± 4.18	0.45	0.67

Figures shown are mean ± one standard deviation (±1SD) of the mean. BMI: body mass index. * = Statistically significant.

The nonparametric chi-squared (χ^2) test was used to test comparable categorical variables, while one - way ANOVA was used for continuous variables. Pearson's correlation and multiple linear regression analysis were used to assess correlation for predictors. A p-value of <0.05 was considered significant.

Results

The characteristics of the study participants are as shown in Table 1; the mean age, weight, and CD4 cell count were significantly lower in patients with cardiac abnormalities, compared to patients without cardiac abnormalities, p=0.04, 0.02, and 0.04 respectively. Pulse rate was higher in those with cardiac abnormality compared with those without, p=0.03. The number of those with cardiac abnormality on HAART was significantly higher than those without cardiac abnormality who are HAART – naïve.

Table 2 shows the patterns and prevalence of cardiac abnormalities in HIV – infected and AIDS groups. Left Ventricular (LV) diastolic dysfunction was the most common abnormality seen in both groups. It accounted for 33.8% and 36.4% of the cardiac abnormalities noted in the HIV-infected and the AIDS groups respectively.

Dilated cardiomyopathy accounted for 6.8% of the cardiac abnormalities. This was seen only in AIDS group and showed a significant difference (p=0.03).

Pericardial effusion accounted for 1.3% in HIV-infected group and 4.5% in the AIDS group and showed a significant difference (p=0.01). Though recorded as separate abnormalities some patients however had multiple cardiac abnormalities in both groups.

Figures 1 and 2 show scatter diagrams of lines of best fit and regression equation for relationship between the two variables tested and cardiac abnormalities that were found in the study. A strong linear relationship between cardiac dysfunctions and $CD4^+$ cell counts and age of the patients is clearly depicted.

The highest coefficient of determination (R^2)=0.8642 was associated with CD4+ cell counts followed by the age of the patients R^2=0.4203 in that order. The points tightly clustered around the regression lines indicate a strong correlation pattern.

Discussion

Cardiac abnormalities in children with HIV/AIDS have been established as a clinical entity. This present study noted a high prevalence rate of 75.6%. This was implied but now reflected in Table 1. However, it has not attracted much attention in Africans due to dominance of chronic diarrhoea from opportunistic infection and severe malnutrition in HIV/AIDS.[10,11] So it is masked and need an index of suspicion for its diagnosis. Hence predictors to

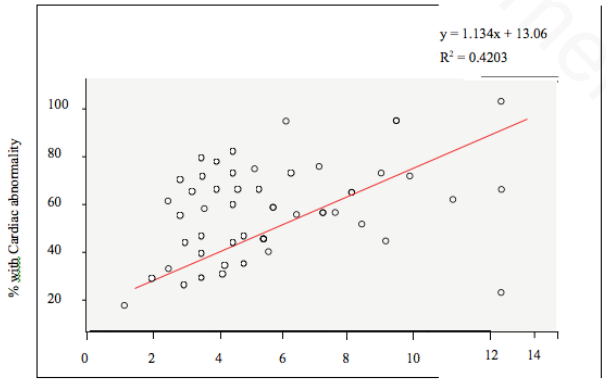

Figure 1. Partial Regression Plot of Cardiac abnormalities against age of patients.

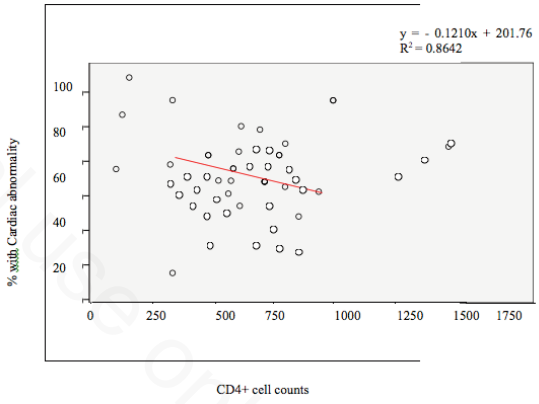

Figure 2. Partial regression plot of Cardiac abnormalities against CD4+ cell counts.

Table 2. Pattern and prevalence of cardiac abnormalities in HIV - infected and AIDS groups.

Cardiac abnormalities	HIV – infected Total abnormalities = 80 (%)	AIDS Total abnormalities = 44 (%)	χ^2	p-value
LV Diastolic dysfunction	27.0 (33.8)	16.0 (36.4)	9.23	0.01*
LV Systolic Dysfunction	20.0 (25.0)	13.0 (29.5)	7.95	0.03*
LV dilatation	18.0 (22.5)	0	8.30	0.02*
LV hypertrophy	6.0 (7.5)	4.0 (9.1)	2.78	0.15
Dilated cardiomyopathy	0.0	3.0 (6.8)	5.11	0.03*
Pericardial thickening	5 (6.3)	3.0 (6.8)	4.95	0.26
Pericardial effusion	1.0 (1.3)	4.0 (4.5)	3.76	0.01*
Mitral regurgitation	3.0 (3.8)	1.0 (2.8)	3.61	0.09
Multiple cardiac abnormalities**	18 (28.1)	5 (19.2)	6.32	0.14

*Statistically significant. **Multiple cardiac abnormalities are the involvement of more than one abnormality, so its number was not included in the total abnormalities.

aid this suspicion are what this work evaluated. Cardiac abnormalities observed in this study were diverse; ranging from innocuous abnormalities as mild pericardial effusion to life-threatening ones as dilated cardiomyopathy (DCM) as showed in Table 2.

Predictors of cardiac abnormalities

The variables found to have predictive value for cardiac abnormalities were age in years, pulse rate (shown in the result in Table 1) $CD4^+$ cell count and use of HAART. Gender and stage of the disease did not have any association with cardiac dysfunctions. Other workers have also similar findings.[17-20] This finding on gender is not surprising, considering the fact that there may be little scientific basis to expect a direct link between gender and cardiac abnormalities. Similarly, advanced stage of disease which is a known risk factor for cardiac involvement,[6,21] was not significantly associated with the presence of cardiac dysfunction in this study. This may be explained by the fact that most of the subjects with cardiac dysfunction were in early category A of the infection. It may also be connected with the population studied, as racial or genetic differences had been noted to influence predictors.[19-21]

Of the variables studied CD4+ cell count showed highest coefficient of determination (R^2)=0.8642. This implies that significant decrease in CD4+ cell count is the highest risk factor for the development of cardiac dysfunctions. This finding is at variance with Lipshultz *et al.*[22] and Lobato *et al.*[23] in 1995, who noted the presence of HIV encephalopathy as predictor of cardiac dysfunction despite the CD4+ cell count level. This difference may be due to their inclusion criteria of only perinatally infected children. Also the timing of the study may have influenced the finding, as this was when Prevention of Mother To Child Transmission (PMTCT) of HIV was not a priority.[23] Now encephalopathy are rare diagnosis in HIV – infected children due to PMTCT.

Lower CD4+ count and younger age were significantly associated with the development of cardiac dysfunction. This agrees with the report of Herskowitz *et al.*,[24] although in adults, who found a median CD4+ cell count of 30/µL in HIV infected patients with left ventricular dysfunction compared to a median count of 187/µL in those without ventricular dysfunction.[24] Younger aged children had been noted to have a rapid course of disease progression with end organ affectation.[17,22] We also noted similar finding with lower CD4+ count and increased cardiac dysfunction.

However, the Concorde trial showed that CD4+ count alone as a predictor of long- term prognosis and end- organ affectation is not absolute.[8] A decline in CD4 cell count correlates well with disease progression but a wide individual variation may exist, reducing its predictive power for patients. Therefore its use should be in combination with other serological results and the presence of heart muscle disease.[8]

This study noted an increase of cardiac dysfunctions in subjects on HAART (p=0.01). The links between HIV infection, HAART, and cardiac dysfunction have been studied by researchers.[25,23] These authors reported an increase in LV dysfunction with HAART, especially Zidovudine (AZT). Although the present study noted same, making a conclusive statement is beyond the scope of this study. A prospective study is a better study design.

Also a contrary finding on the relationship between HAART and cardiac dysfunction has been reported.[8,24] They noted that AZT had no effect on cardiac changes. This finding may be applicable to the 10 patients in this present study that had cardiac abnormalities in spite of being HAART-naive. It may also be there are yet unidentified factors which confound the relationship between HIV-induced cardiac dysfunction and the effects of HAART.

Therefore, this present work will help create awareness among heath-workers to watch with these predicators and implement early intervention.

Conclusions

The CD4+ cell count as the best predictor of cardiac abnormalities in our environment (R^2=0.8642), followed by age of ≤4.03 years of the patient (R^2=0.4203). These findings justify changes in policy and practice in the care of these children; for early identification through these predicators.

Limitation of the study

The study was cross-sectional in design; patients were assessed only once at presentation. There is a probability of changes in the predictors on further patient follow up. It was therefore not possible to study the possible progression of the observed abnormalities over time.

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