ELECTROCARDIOGRAPHIC AND ECHOCARDIOGRAPHIC CHARACTERISTICS IN HIV-1 AND NON-HIV-1 INFECTED CHILDREN AT MUHIMBILI NATIONAL HOSPITAL DAR ES SALAAM, TANZANIA

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Summary

Objective: The objective of the study was to describe the electrocardiographic and echocardiographic characteristics of HIV–1 infected children. aged 18 months to 7years.at Muhimbili National Hospital.

Methods: A cross sectional comparative study was carried out between April 2001 and January 2002. All consecutive children aged between 18 months to 7 years admitted in the paediatric wards and those attending the out patient department between April 2001 and January2002 were enrolled for the study. Children who tested HIV-1 positive comprised the study group and those who tested HIV-1 negative formed the comparative group.

Results: The study population consisted of 280 children, 160 males and 120 females. The overall prevalence of cardiovascular disorders was (83/280) 29.6%.The prevalence of cardiovascular disorders was significantly higher in HIV infected than non-HIV infected children,(46.2% versus 23.3%, p< 0.0001).The common cardiac disorders strongly associated with HIV infection were pericardial effusion, (26.9%) (p< 0.0002), Left ventricular dysfunction (LVD) 24.7% (p< 0.0004),Dilated cardiomyopathy (DCM) 24.4% (p< 0.0001), and sinus tarchycardia 20.5% (p< 0.0001). Endocarditis was not detected.

Conclusion: Cardiac diseases are common in HIV infected children. ECG detectable sinus tachycardia prompts further investigation by Echocardiogram to detect the cardiac abnormalities in HIV-1 infected children.

Introduction

Human immunodeficiency virus infection is a multisystemic disease clinically presenting with a wide variety of manifestations.(1) Earlier studies arising from autopsy adult studies indicated the heart to be involved. The findings included, pericardial effusion, dilated cardiomyopathy (DCM), left ventricular dysfunction (LVD), non-bacterial endocarditis, Infarction and direct infections or neoplastic involvement of the heart.(2,.3.4).

In most studies the heart diseases in HIV infected patients have been reported to be silent becoming more apparent in advanced stages.(2.3.4) However, in some studies the opposite was observed (5,6). When non-invasive electrocardiogram(ECG) and ECHO studies were used heart diseases were found to be fairly common. The common heart conditions observed were pericardial effusions with or without tamponade, dilated cardiomyopathy , left ventricular dysfunction/dilatation , and non-specific ECG changes.(7.8.9) A few studies that have been carried out in children have shown that heart diseases found in HIV infected children are clinically without overt signs. In these studies pericardial diseases, myocardial diseases and conductive system abnormalities have been described. The prevalence of pericardial effusion ranged between 16-26%, dilated cardiomyopathy 10-25%, and LVD 20-25%.(10.11.12) Unlike the situation observed in adults, endocardial diseases have not been frequently observed.

The previous studies that addressed cardiac disorders in HIV-1 infected patients. particularly in Sub Saharan Africa are few and have been carried out in adults involving small numbers of patient. This study was carried out to describe the electrocardiographic and echocardiographic characteristics of HIV-1 infected patients using a large sample size of children in a hospital setting of a developing country .

Materials and Methods

This was a cross sectional comparative study done at the department of Paediastrics and Child Health of Muhimbili National Hospital, Dar es Salaam, Tanzania. Muhimbili National Hospital serves as Tertiary Referral Hospital and a Teaching University Hospital. The paediatric services at the hospital caters for children from infancy to 7 years of age. On average 700 children are admitted per month with an average outpatient clinic attendance of about 200 children per week. All children aged between 18 months and 7 years who were either admitted or attended the outpatient clinic between April 2001 and January 2002 were eligible for the study. All parents/guardians of eligible children gave a written informed consent after having been explained and counseled about the study. Blood samples from the children were collected in EDTA vacutainer tubes and sent to the laboratory within 6 hours. Plasma was separated for HIV testing and stored at -20 C until the time of assay. Plasma was tested with Behring enzygnost anti-HIV-1/2 plus ELISA (Behring, Marburg, Germany); and by Welcozyme anti-HIV-1 ELISA (Murex Diagnostics Ltd.,Dartford,UK). Samples reactive on both assays were considered positive for HIV-1 antibody.Samples with discordant reactivity were tested by Western blot (WB) assay (HIV Blot 2.2, Diagnostic Biotechnology LTD, Singapore).

Children who had documented laboratory evidence of HIV-1 seropositivity prior to current admission/clinic attendance and all those who tested HIV positive became the study group. Children who tested HIV negative became the comparable group.

Children aged less than 18 months and those whose parents/guardian did not consent were excluded from the study. Ethical clearance was obtained from the College Research and Ethical Clearance Committee.

All the study patients had a standard12 lead Electrocardiogram (ECG) done using a Schiller CARDIOVIT AT-4 recorder. Where necessary the child had to be sedated with Diazepam 1-2 mg/kg body weight during

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the procedure. Interpretation of the ECG was done by experienced Cardiologist/Paediatrician.

All the study patients had an Echocardiographic(ECHO) study done using a TOSHIBA system. A 3.5 mega hertz transducer was used. In some cases children had to be sedated with Diazepam 1-2m g. /kg. body weight during the study. Standard 2 dimensional.(2D) M-mode and Doppler studies were done obtaining spatial cardiac anatomy and standard M mode recordings for measurements.

Four echocardiographic views (parasternal long axis, parasternal short axis, apical four chamber and apical long axis) were obtained for each patient. In some patients a subcostal view was obtained to improve the diagnostic view.

The M-mode echocardiograms were obtained by positioning a cursor line on a 2 dimensional echocardiogram through the structure to be interrogated. This was done either using parasternal long axis or short axis views. Measurements were done as recommended by the American Society of Echocardiography.

For each patient, left ventricular end diastolic diameter (LVD) and left ventricular end systolic diameter (LVS) were obtained.Fractional shortening (FS) and Ejection Fraction (EF) were obtained as calculated by the computer software package of the recording TOSHIBA system. Doppler studies were done to assess the severity of the lesions and assessing LV diastolic function by standard technique. The findings were recorded on videocassettes and raw data entered on a structured data collection sheet. Left ventricular Fractional shortening (FS) less than 28% was taken to indicate cardiac dysfunction.

Data analysis

Data was analyzed using SPSS/Epiinfo version 6 programmes. All results were reported as a percentage of patients found to have the given abnormality.A 2x2 table was used to determine the chi-square, p-value, sensitivity and the specifity. A p-value of <0.05 was considered significant. The influence of potential risk factors for HIV infection on cardiac lesion was determined by the Odds ratio (OR) and the determined positive predictive value.

Results

A total of 2486 children were screened during recruitment. Those aged between 18 months and 7 years were 1104. Of these 312 (28.3%) fulfilled the inclusion criteria and formed the study and the comparable group. Six children were excluded (one from HIV infected group and five from the comparative group) due to inadequate left ventricular measurements(ventricular free wall abnormalities, paradoxical septal motion) and presence of congenital heart disease. Seven parents (5.4%) refused to consent for the study and 15 patients (4.8%) had incomplete data and therefore excluded from the analysis. Thus ,data for 280 patients was available for final analysis.

Table 1 shows the demographic features of the studied children in relation to their HIVserostatus The sex distribution was not statistically significant among the two groups (p=0.18).The mean age for HIV-1 positive children was 41.6 months (±20.55) and the mean age for HIV-1 negative children was 44.59 months (±22.2). The difference was not statistically significant (p=0.24).

Table1. Distribution of children according to sex, age and HIV serostatus.

Patient characteristics	HIV positive n (%)	HIV negative n (%)	Total n (%)	P-value
Sex Male	43 (26.9)	117 (73.1)	160 (57.1)	
Female	35 (29.2)	85 (70.8)	120 (42.9)	0.18
Total	78	202	280	
Age (Months)				
18-30	35 (30.4)	80 (69.6)	115 (41.0)	
31-42	10 (25.6)	29 (74.4)	39 (14.0)	
43-54	11 (26.2)	31 (73.8)	42 (15.0)	
55-66	9 (33.3)	18 (66.7)	27 (9.6)	
67-78	9 (31)	20 (69.0)	29 (10.4)	
79-84	4 (14.3)	24 (85.7)	28 (10.0)	0.60
Mean age ± SD	41.167 ± 20.559	44.594 ± 22.202		0.24

ECG Findings

Twenty-six (9.3%) children had sinus tachycardia. Among children with sinus tachycardia sixteen children (20,5%) were HIV infected versus ten (5.0%) who were non-HIV infected. The difference was statistically significant (p<0.000057). There was also a strong association between HIV infection and sinus tachycardia P<0.001 and the OR=4.95, [95% CI, 1.98-12.77]. All six children with sinus bradycardia were HIV sero-negative,but the difference was not statistically significant. (Table 2).

Table 2. Distribution of Electrocardiographic features in HIV-Infected and Non-HIV infected children.

ECG features	HIV positive N=78 n (%)	HIV negative N=202 n (%)	Total N=280 n (%)	P value
Sinus Tachycadia	**16 (20.5)**	**10 (5.0)**	**26 (9.3)**	**0.00005764**
		OR=4.95	**95% CI, 1.98-12.57**	
Sinus Bradycardia	**0 (0.0)**	**6 (2.1)**	**6 (2.1)**	**0.1908**
Ectopics	**1 (1.3)**	**3 (1.5)**	**4 (1.4)**	**1.0000**
Sinus Rhythm	**77 (98.7)**	**199 (98.5)**	**76 (98.6)**	**0.897**
Abnormal QRS	**14 (17.9)**	**32 (15.8)**	**46 (16.4)**	**0.6697**
Abnormal T-wave	**15 (19.2)**	**35 (17.3)**	**50 (17.9)**	**0.7092**
ST-segment changes	**11 (14.1)**	**27 (13.4)**	**38 (13.6)**	**0.8719**
LVH	**4 (5.1)**	**24 (11.9)**	**28 (0.1)**	**0.0913**
RVH	**4 (5.1)**	**17 (8.4)**	**21 (7.5)**	**0.3491**
Electrical Alterans	**7 (9.0)**	**13 (6.4)**	**20 (7.1)**	**0.45963**

Echocardiographic Findings

The prevalence of ECG and Echocardiographic abnormalities was higher in HIV infected patients than in HIV non-infected patients (p<0.0001). (Table 3).

Twenty nine (10.4%) children had pericardial effusion. Of these, twenty-seven had mild to moderate pericardial effusion and two patients has severe pericardial effusion with tamponade. Twenty one (26.9%) children with pericardial effusion were HIV positive compared to 8 (4.0%) who were HIV seronegative. The difference was statistically significant (p<0.0001). In addition a detection of pericardial effusion had a positive predictive value of 72.4% [OR=8.9, 95% CI, 4.19-41.14].

Twenty four (8.6%) children had dilated cardiomyopathy (DCM). Nineteen children were HIV infected versus five who were HIV non-infected. The difference was statistically significant (p < 0.00001).There was a strong association between HIV serostatus and DCM. [OR=12.5, 95% CI, 4.19-41.14,] p<0.001.

Fractional shortening of less than 28% reflecting impaired LV systolic function was notable significantly among HIV infected compared to non-infected children(p<0.0004).

Table 3. Echocardiographic features in HIV infected and non HIV infected children

ECHO diagnosis	HIV positive N=78	HIV negative N=202	Total N=100	OR	CI	p value
No.of patients	n(%)	n(%)	n(%)	95%		
Pericardial effusion Dilated	21(26.9)	8(4.0)	29(10.4)	8.9	4.61-39.9	0 .00002
Cardiomyopathy (DCM)	19(24.4)	5(2.5)	24(8.6)	12.5	4.19-41.14	0.00001
Fractional Shortening FS< 28%	19(24.7)	10(5.1)	29(10.6)			0.00004
Congenital Heart Disease	1(1.3)	25(12.4)	26(9.3)			0.00413
Rheumatic Heart Disaese	1(1.3)	9(4.5)	10(3.6)			0.2925
Endomyocardial Fibrosis (EMF)	0(0.0)	3(1.5)	3(1.1)		0.5625	

Discussion.

The most significant differentiating ECG abnormality among HIV infected and non -HIV patients detected in this study was sinus tarchycardia. This occurred in sixteen (20.5%) infected versus ten(5%) non- infected patients (p<0.00005). Okeahialam reported a frequency of tachycardia of 24% in 33 HIV-positive Nigerian adults [19]. Significant tachycardia has also been reported elsewhere with a frequency of 20-40%.[11.12.14.25.26]

It has been postulated that the tachycardia could be due to the HIV infection of the neuro-endocrine system with the associating viral myocarditis .The underlying mechanism could be excessive sympathetic stimulation from autonomic imbalance or stimulation of the b-receptors by the gp 120 protein of HIV[12.]

In our study the presence of HIV infection was significantly associated with tachycardia [OR=4.95, 95 CI. 1.98-12.57]. p<0.00005

In this study tachycardia had a sensitivity of 66% and a specificity of 85%.It could be argued that the presence of tachycardia in HIV-infected patients calls for echocardiographic examination to detect associating cardiovascular abnormalities in affected patients. Sinus tachycardia could therefore be used as a screening test for subsequent cardiovascular evaluation especially taking into account the high cost and un availability of ECHO facilities in developing countries.

The other ECG abnormalities that were found in HIV positive patients but not significantly different from non HIV infected patients included ectopics, abnormal QRS complexes, ST-T segment changes and T-wave abnormalities. Previous studies had indicated T-wave changes to be associated with myocarditis and pericarditis resulting from HIV infection [12. 15..]

ECG- T-wave and ST-T segment changes were noted in 36 HIV positive and 62 HIV-negative patients. In other studies the frequency of ECG abnormalities among HIV positives ranged between 49-70%. [14. 15.] Our study gave a prevalence rate of 34% which was lower than the rates previously reported in other hospital based cohort studies. The differences in the prevalence rates could probably be due to the differences in the sample size. Our sample size involved more patients probably reflecting a more realistic prevalence compared to previous studies.

Echocardiography was a gold standard test in detecting pericardial effusion and dilated cardiomyopathy with a predictive value of 72% and 79% respectively. LV fractional shortening of less than 28 % reflected the poor LV function, the prevalence of which was significantly different among HIV positive versus HIV negative patients (p<0.00004)

Echocardiography should be performed in all patients where there is a suspicion of cardiac disease in HIV/AIDS patients. This would pick asymptomatic cardiac manifestation for early cardiac treatment. In clinical practice, the ECG and Echocardiogram supplement each other in early detection of cardiac abnormalities in HIV patients.

Cardiac manifestations detectable by ECHO in HIV infected individuals include dilated cardiomyopathy, pericardial diseases, and LV dysfunction.

The cardiomyopathy of AIDS has been attributed to concurrent cardiac involvement of opportunistic organisms or neoplasms such as Karposi sarcoma and lymphomas and malnutrition. The prevalence of cardiac diseases in HIV infected children in this study was 46.2% compared to 23.3% in HIV uninfected children. This was in agreement with the few earlier studies done in hospital based cohort children that ranged between 14% and 45%.[10,11.12). The prevalence of cardiac diseases ware noted to increase with age.[16.17)

Al Attar et al (1995) and Langstone et al. (2001) found that 35% and 51% of HIV infected children studied with HIV related deaths had chronic cardiac diseases respectively diagnosed prior to death.[14.17) This study, however has

shown that cardiac diseases are fairly common in toddler years since 50% of HIV children studied were below 3 years. Similar results were noted in a study done in infants and children where most HIV studied children had cardiac diseases.[10].

This study showed that Pericardial disease particularly pericardial effusion is the commonest HIV associated heart disease. Twenty-seven percent of HIV infected patients had pericardial effusion ranging from mild to severe pericardial effusion compared to 4.0% of HIV non-infected children. The difference was statistically significant p<0.001 (OR=8.9 at 95% CI, 4.61-39.88). Pericardial effusion had a positive predictive value of 72.4%. Previous studies in children had indicated a prevalence rate of pericardial effusion to be between 16-26%[11,.12, 13]. Higher prevalence rates ranging between 30% and 45% were observed in a number of previous adult studies.[1..20.21. 23].

Myocardial disease was the second commonest cause of heart diseases accounting for 24.4% of the cases. However myocardial disease was more common in HIV infected children 24.4% (19/78) compared to 8.6% (24/202) in HIV uninfected group (p<0.0000, OR=12.5 at CI 95%, 4.19-41.14).

In one center, 25% of HIV infected children who died had cardiomyopathy[23]. Left ventricular dysfunction and Left Ventricular Dilatation (Dilated Cardiomyopathy) was reported in 20% of HIV infected patients in P2C2 HIV children study.[11 24].

In this study Left Ventricular Fractional Shortening (LVFS) less than 28% was taken to indicate Left Ventricular Dysfunction. Nineteen (24.7%) HIV infected children had Left Ventricular Dysfunction compared to 10 (5.1%) HIV uninfected children. The difference is highly statistically significant (p<0.001) Table 2. Previous studies reported the prevalence of Dilated Cardiomyopathy in HIV infected patients between 10-25% and Left Ventricular Dysfunction between 20-25%.[11.14] The Nigerian study done in adults reported patients to have normal ventricular dimensions but significantly reduced contractility indices and thick walls probably a starting point for dilated cardiomyopathy.[19] Other studies in non- African adults indicated a prevalence rate between 12.5% and 29.5%.[6,9,.10]. Dilated cardiomyopathy has been associated with advanced HIV/AIDs disease. Endocarditis appears not to be a common problem in HIV infected children. This experience has also been observed in previous adult studies. A few cases observed in these studies were seen in drug users.

Congenital heart diseases were in this study found to be more prevalent in non HIV infected patients (12.4%) compared to (1.3%) of HIV infected patients p=0.00041 (Table 3). This might imply that the virus could have been acquired after the period of organogenesis. This finding has been reported in earlier studies.[11,.12,. 13].

Conclusion

Cardiac abnormalities are common in children with HIV infection. ECG Sinus tachycardia in HIV infected children is highly associated ECHO detectable cardiac abnormalities mainly pericardial effusion and dilated cardiomyopathy.

Recommendation

In poor resourse countries, HIV/AIDS patients with un explained clinical tachycardia should be subjected to ECG and ECHO examination.

References

1. **Fauci A.S, Masur H, Gelmann E P, Markam P D, Hahn B H, Lane HC.The acquired immunodeficiency Syndrome, an update. Ann.Intern.Med. 1985,102:800-813.**
2. **Kawo G, Karson K, Lyamuya E, Kalokola F M, et al Prevalence of HIV infection, associated clinical features and motality among hospitalized children in Dar es salaam, Tanzania. Scand.J.Inf.Dis. 2000,32:357-363.**
3. **Fink L, Reichek N, St.John-Sutton MG, Cardiac abnormalities in acquired immunodeficiency syndrome. Am. J.Cardiol. 1984,54:1161-1163.**
4. **Corallo S, Multinell M R, Lazzarin A, Celano V,Repassin A, Boroldi G. Echocardiography detects myocardial damage in AIDS. Prospective study of 102 patients. Eur. Heart J. 1988,9:887-892.**
5. **Reilly J M, Cinnion R E, Andreson D W, O'leary T J, Simon J T, Lane H Frequency of Myocarditis, Left ventricular dysfunction and ventricular tachycardia in the acquired immunodeficeincy syndrome. Am.J.Cardiol 1988,62:789-793.**
6. **Cohen I S, Anderson D W, Virmani R, Reen B M, Macher A M, Sennesh J, Dirlorenzo P, Redfield R R. Congestive cardiomyopathy in association with AIDS.N. Engl.J.Med. 1986,315:628-630.**
7. **Calabrase L H, Proffitt M R, Yen-Lieberman B, Hobbs R E, Ratiliff N B. Congestive cardiomyopathy and illness related to the acquired immunodeficiency syndrome. Associated with the retrovirus from the myocardium. Ann.Intern.Med. 1987, 107:691-692.**
8. **Monsuez J J, Kinney E L, Vittecog D, Kitzis M, Rozenb W, D'Agay F M et.al. Comparison among acquired immunodeficiency syndrome patients with and without clinical evidence of cardiac disease. Am.J.Cardiol.1988,62:1311-1313.**
9. **Levy S W, Simon L G, Rios C J, and Ross M A. Prevalence of cardiac abnormalities in Human immunodeficiency virus infection. Am.J.Cardiol.1989, 63:86-89.**
10. **Currie P F, Jacob A J, Foreman A R, Elton R A, Brettle P D, Boon N A. Heart muscle disease related to HIV infection. Prognostic implications. Br.M.J 1994,309(6969): 1605-1607.**
11. **Lipshultz S E, Chanock S, Sanders S P, Colan S D, Perez-Atayde A,Mc Intosh K. Cardiovascular manifestations of human immunodeficiency virus infection in infants and children. Am.J.Cardiol.1989, 63(20): 1489-1497.**
12. **Starc J T, Lipshultz S E, Kaplan S, Kik A, Easley M S et al. Cardiac complications in children with immunodeficiency virus infection. Peadiatr.1999, 104(2): 1-10.**
13. **Lai W W, Lipshultz S E, Easley K .A et.al. Prevalence of congenital malformations in children with immunodeficiency virus infected women. J.Am.Coll.Cardiol.1988, 32(6): 1749-1755.**
14. **Shearer W T, Lipshultz S E, Easley K A et.al. Alteration in cardiac and pulmonary function in rapid human deficiency virus type-1 disease progressors. Pead.2000, 105(1): 1-8.**