Original Article

To detect presence and severity of cardiac dysfunction in HIV infected children in central India

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Abstract

Objective: Evaluate cardiac dysfunction in HIV infected children and to assess the severity of disease with cardiac dysfunction **Design:** Longitudinal observational study. **Setting:** Pediatric wards, Pediatric intensive care unit and ART clinic of high resource tertiary care centre. **Method:** A study enrolled 144 HIV positive subjects between the age group of 18 months to 12 years. Clinical and immunological evaluation was done to classify cases according to WHO clinical and immunological classification. Children with congenital and acquired heart diseases were excluded from the study. Detail history of duration of illness, duration of therapy and ART drug was obtained. Detail general and systemic evaluation was performed. Electrocardiogram, chest radiograph, 2D echocardiography and CD4 count were done in all patients. **Result:** In this study, male to female ratio was 1.18:1. ECG abnormality was detected in 42.36% cases. Abnormal chest X ray was reported in 33.33% cases. 2 D Echocardiography showed diastolic dysfunction in 19.44%, pericardial effusion in 11.8%, systolic dysfunction in 5.5%, pulmonary hypertension in 7.64%, dilated cardiomyopathy in 5.5%, mitral regurgitation in 3.5% and hypertrophic cardiomyopathy in 0.7% cases. Maximum number of cases with echo abnormality was observed in WHO clinical stage III and stage IV disease. **Conclusion:** Echocardiography is a useful technique for the early recognitation and treatment of cardiac dysfunction in HIV positive patient. Echocardigraphic measures of left ventricular structure and function are independent and potentially useful long-term and short-term predictors of overall mortality in such children.

Keywords: AIDS, CD4 count, Echocardiogram, HIV.

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INTRODUCTION

Acquired immunodeficiency syndrome is characterized by an acquired profound irreversible immune suppression that predisposes the patient to multiple opportunistic infections, malignant neoplasms and progressive dysfunctions of multiple organ systems[1]. The prevalence of cardiac involvement in AIDS patients have been reported to range between 28% and 73%[2]. Cardiovascular complications results from complex interplay of events ranging from direct myocardial invasion by HIV, chronic inflammatory immune response, endothelial dysfunction, autoimmunity to HIV virus, co-infection with cardiotrophic viruses, cardiotoxicity from pharmacological agents and inflammatory cytokines. Pulmonary hypertension results from recurrent parenchymal lung disease. Children and adolescence offer a unique opportunity to study physiological mechanisms of HIV associated cardiac dysfunction because they are less likely than adults to be exposed to long term confounding factors like hypertension, diabetes, smoking, obesity and coronary atherosclerosis[3,4, 5,6]

Echocardiography is very useful in detecting cardiac dysfunction at early stage much before overt clinical manifestation develops. Early recognition and prompt interventions are important to prevent significant morbidity due to cardiac involvement. There is paucity of data related to cardiovascular dysfunction in HIV infected

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children from India. Thus this present study was planned to evaluate cardiovascular manifestation in HIV infected children as well as association of disease severity with cardiac dysfunction.

MATERIAL AND METHODS

This is a longitudinal observational study was carried out at department of pediatrics Government Medical College, Nagpur from October 2013 to September 2015. All HIV positive patients of age between 18 months to 12 years of either sex attending ART clinic, admitted to pediatrics ward and PICU were enrolled after obtaining informed written consent from parents or guardians and after approval from Institutional Ethical Board. Information obtained during the study was kept confidential. Patients with congenital or acquired heart disease or dysfunction were excluded. A sample size of 144 cases was calculated considering the expected incidence of cardiovascular dysfunction in HIV positive children as 60% with absolute precision 8% and desired confidence level (1-α)= 95%. At the time of enrollment detailed history of duration of illness, duration of therapy, ART drug and family history was obtained. General examination in form of vitals, lymphaednopathy, pallor and growth parameters were noted. Detail systemic evaluation was done. Investigations like electrocardiogram, chest radiograph, CD4 count and 2D echocardiography was carried out on a standard Philips IE33 2D echo machine by cardiologist. Following parameters of cardiac functions were determined. 1) Fractional shortening 2) peak aortic velocity 3) mean acceleration 4) stroke distance. Left ventricular systolic function was determined by calculating the fractional shortening is as follows.

% LVFS=LVDD-LVSD x100 LVDD LVDD-Left ventricular end diastolic dimension,

LVSD--Left ventricular end systolic dimension. Children with left ventricular fractional shortening <28% was classified as having left ventricular dysfunction. Estimation of pulmonary arterial systolic pressure was derived from measuring a tricuspid regurgitant jet using Bernoulli's equation. Pulmonary hypertension was defined as Systolic pulmonary arterial pressure >30mmHg at rest. Diastolic function was analyzed by following parameters of mitral valve flow1) E wave velocity 2) A wave velocity 3) E/A ratio 4) Deacceleration time of E wave 5) Isovolumic relaxation time. Ejection fraction was automatically calculated by existing software in equipment. ECG was performed on a standard Schiller CARDIOVIT AT-101 12 lead machine. Cases were classified according to revised WHO clinical and immunological staging[7].

Statistical Analysis

Data was collected in structured data sheet. All the categorical variables (gender, systolic dysfunction etc) were expressed in actual numbers and percentage. Categorical variables were compared performing chi squre test. P value of less than 0.05 was considered significant. Statistical software SPSS 16 was used for statistical analysis.

RESULTS

Study enrolled 144 HIV positive cases, maximum (47.91%) cases was between age group 6-12 years, 18.75% cases between age of 18 months to 2 years and 33.33% in age group of 2-6years. Male to female ratio was 1.18:1. Maximum number of cases (40.27%) cases belonged to WHO 'none', 23.6% mild, 24.30% advanced and 11.80% cases belonged to severe immunological classification. A 32.63% stage I, 26.38% stage II, 27.08% stage III, and 13.88% cases belonged stage IV disease of WHO clinical classification. ECG abnormalities were detected in 42.36% cases and sinus tachycardia was commonest abnormality followed by ST-T changes. Low voltage ECG was observed in 12 cases of which 9 cases belonged to advanced disease. Left ventricular hypertrophy was noted in 10 cases of which 6 belonged to advance stage. (Table1).

Table 1: ECG finding in study population

ECG abnormalities	n	%
Sinus tachycardia	40	27.77
ST-T changes	22	15.27
Low voltage	14	9.27
Left ventricular hypertrophy	10	6.94
Broad P wave	04	2.77

Abnormal chest radiograph was reported in 33.33% cases, non homogenous opacity was commonest finding seen in 13.88% cases, bronciectatic changes in 4 and diffuse reticular infiltration and pleural effusion in 2 each cases (Table 2).

Table 2: Chest radiographic finding in study population

Radiographic finding	n	%
Non homogenous opacities	20	13.88
cardiomegaly	15	10.41
Hilar Lymphadenopathy	12	8.33
Others	08	5.55

A 2D echocardiography revealed diastolic dysfunction as most commonest cardiac manifestation in 19.44% cases followed by pericardial effusion in11.8%, systolic dysfunction in 9%, pulmonary hypertension in 7.64%, dilated cardiomyopathy in 5.5%, mitral regurgitation in 3.5%cases. Only one case had hypertrophic cardiomyopathy recorded in study.

Table 3: Association of 2 D Echo findings with immunological classification

Cardiac Dysfunction	None	Mild	Advanced	Severe
Systolic dysfunction	00	01 (2.85%)	07 (20.59%	05 (29.41%)
Diastolic dysfunction	01 (1.72%)	02 (5.71%)	18 (52.94%)	07 (41.17%)
Mitral regurgitation	00	00	03 (8.82%)	02 (11.76%)
Pericardial effusion	00	01 (2.85%)	09 (26.47%)	07 (41.17%)
Dilated cardiomyopathy	00	02 (5.71%)	04 (11.76%)	02 (11.76%)
Hypertrophic cardiomyopathy	00	00	01(2.94%)	00
Pulmonary hypertension	01(1.72%)	01 (2.85%)	06 (17.64%	03 (17.64%)

Association of cardiac dysfunction with immunological classification based on age and CD4 count showed that diastolic dysfunctions was present in advanced and severe stage of disease and difference was statistically significant (P <0.001) while systolic dysfunction being observed in12 cases of advanced and severe disease and only in one case with mild disease, it was statistically significant (P<0.027). Mitral regurgitation was revealed in one case from mild stage and 5 from advanced and severe stage of disease and statistical difference was not significant. Pericardial effusion was seen in one case with mild stage and 16 from advance and severe stage of disease and the difference was statistically significant (P <0.001). Pulmonary hypertension was seen in 2 cases with mild and none stage and 9 cases from advanced and severe stage and statistical difference was significant (P 0.048) Table 3.

Table 4: Association of 2D echo finding with Clinical classification

Cardiac Dysfunction	I	II	III	IV
Systolic dysfunction	00	01 (2.56%)	08 (21.05%)	04 (20%)
Diastolic dysfunction	01 (2.12%)	03 (7.69%)	19 (50%)	05 (25%)
Mitral regurgitation	00	01 (2.56%)	02 2.56%)	02 (10%)
Pericardial effusion	00	01 (2.56%)	10 (26.31%)	06 (30%)
Dilated cardiomyopathy	00	01 (2.56%)	04 (10.52%)	03 (15%)
Hypertrophic cardiomyopathy	00	00	01(2.63%)	00
Pulmonary hypertension	01(1.72%)	01 (2.56%)	05 (13.15%	04 (20%)

Diastolic dysfunction was commonest abnormality reported in 75% of cases belonged to stage III and IV and only in 9.81% cases of stage I and II. Systolic dysfunction was reported in 41.05% cases of stage III and IV and 2.56% of stage I and II (Table 4). The statistical difference was highly significant for diastolic dysfunction between clinical classification stage III and IV disease compared to stage I and stage II disease (P<0.001) while it was significant for systolic dysfunction, pericardial effusion, pulmonary hypertension between early (stage I, II) and advance (stage III, IV) disease.

DISCUSSION

In the present study, population comprised of 144 HIV positive cases, among that 47.91% cases were between 6-12 years, 33.33% between 2-6 years and 18.75% between the age group 18 months -2 years with male to female ratio 1.18:1. Similar type of sex distribution pattern was reported by Badal S *et al*[8] while slightly higher male to female ratio were observed by Singh A *et al*[9] in their study. In our study, maximum number of cases (40.27%) belonged to WHO immunological 'none' classification followed by 'mild' then 'advanced' and least number of cases in 'severe' classification while 32.63% cases in stage I,26.38% in stage II, 27.08% in stage III and 13.88% cases in stage IV WHO clinical classification. Similar type of observation was noted by Rajeshwari K *et al*[10] and Badal *et al* in their study but Singh A *et al* noted 28.6% cases in severe and 32.9% cases in advance classification. In present study, 42.36% cases showed ECG abnormality, sinus tachycardia was the most commonest (27.77%) followed by ST-T changes. Badal *et al* reported ECG abnormality in 47% of which most commonest was sinus tachycardia while Pongprot Y *et al*[11] revealed 52% cases with right axis deviation and right ventricular hypertrophy and in 39% cases with non specific ST-T changes. The prevalence of ECG abnormality was much lower in present study compared to study conducted by Lipshultz *et al* from United States of America who reported abnormal ECG in 93% cases, possibly because of 24-hour ambulatory ECG was utilized in addition to the standard 12 lead ECG. Out of 61 cases with ECG abnormalities maximum number of cases (23) belonged to WHO advanced, 16 in mild, 11 in none and 17 in severe classification. The statistical difference was found to be significant only for ST-T changes (P=0.035) and low voltage complex (P=0.018) between mild and advanced immunological classification likewise the statistical difference was found to be significant for sinus tachycardia between stage II and stage III clinical classification (P=0.025) and was also significant for ST-T changes between stage II and stage IV clinical classification (P=0.02). Badal *et al* did not

report significant association between ECG finding and immunological classification. In our study, 33.33% cases showed abnormal chest X ray, non homogenous opacity was commonest finding followed by cardiomegaly. Similar types of observation were reported by Badal S *et al* and Pongprot Y *et al*. A 2D echocardiography abnormality was observed in 30.55% cases. Similar results (in 36.9% cases) were reported by Badal *et al*. Okoshi and Montenegro[12] studied etiology of cardiac lesions in patients with AIDS in retrospective study of 73 necropsies. Microscopy showed inflammatory cells, myofibrillar atrophy, and myocardial necrosis in 51% cases. A Brazillian study by Herdy Gutt *et al*[13] of clinicopathological correlation aimed at analyzing myocardial abnormality in 50 AIDS patients reported myocarditis in 33 cases, degenerative histological changes in 17 cases. Etiological agents was toxoplasma in 11 cases, Cryptococcus in 7 cases, cytomegalovirus in 3 cases. No etiological agent was found in 12 cases and 15 others had evidence of endocarditis and pericarditis. Commonest Echo abnormality in present study was diastolic dysfunction in 19.44%. Most of these cases belonged to clinical stage III and IV and immunological stage of advanced and severe HIV infection. Study done by Singh A *et al* reported diastolic dysfunction in 8.5% cases. Another study by Rajeshwari K *et al* found diastolic dysfunction in 5% cases. Left ventricular diastolic dysfunction has been described as first abnormality of cardiovascular dysfunction in HIV patient in research conducted by Coudray N *et al*[14]. They reported increase in isovolumetric relaxation time and decrease in E wave velocity in a study of 60 patients with AIDS. Thuesen L *et al*[15] reported significant reduction in E/A ratio in patient with advanced infection. The second most common echo abnormality was pericardial effusion present in 11.8% cases. A study conducted by Cheny *et al*[16] reported pericardial effusion in 33% cases and Mycobacterium tuberculosis was the most common cause of tamponade[17]. Pericarditis and pericardial effusion are the most frequently recognized heart disease in AIDS patients[18,19]. Etiology can vary and can be related to infection by HIV virus itself or to opportunistic agents such as coxsackievirus or cytomegalovirus. Study conducted by Singh A *et al* reported pericardial effusion in 17.4% of cases and Werneck GL *et al*[20] reported pericardial effusion in 8% cases with advanced disease. In present study systolic dysfunction was found in 9% cases, mostly these cases belonged to advanced and severe stage. Study done by Werneck *et al* reported left ventricular dysfunction in 31.5% in patients with advanced disease and in 37%cases reported by Singh P *et al*[21]. The fractional shortening of left ventricle was significantly lower in these patients indicating decrease in left ventricular global systolic function. Study by Mondy KE *et al*[22] reported left ventricular systolic dysfunction in 18% cases. Pulmonary hypertension was reported in 7.64% cases, possible causes are recurrent bronchopulmonary disease, left ventricular dysfunction and primary pulmonary hypertension. In a study conducted by Pongprot Y *et al*, 41% cases had evidence of pulmonary hypertension while Singh A *et al* reported 11.42% cases and Singh RBS *et al*[23] with pulmonary hypertension. It is hypothesized that this increased incidence of pulmonary hypertension in HIV might be secondary to increased production of platelet derived growth factor, but exact mechanism is still not clear[24] In present study dilated cardiomyopathy was found in 5.55 of cases. A study by Singh a *et al* detected dilated cardiomyopathy in 8.5% cases. Study by Giuseppe B *et al* on a 52 HIV infected patients were followed up to determine incidence of dilated cardiomyopathy 8% of patients developed DCM. Incidence was higher in patients with CD4 cell count<400per cumm and those receiving Zidovudine. Authors concluded that dilated cardiomyopathy can be caused by direct action of virus on myocardium, other cardiotrophic viruses or by autoimmune process. Various studies agree that most important factor in development of cardiac abnormalities is level of immunosupression and there is strong correlation between CD4 count and echo abnormalities which is also demonstrated in present study. Myocardial damage can also result from direct action of HIV on myocardium, other opportunistic agents, cardiotrophic viruses, cytokines released by HIV infected lymphocytes or monocytes, nutritional deficiency, autoimmuno dysfunctions and action of antiretroviral drug such as Zidovudine.

CONCLUSION

Asymptomatic patients with HIV infection did not show significant 2 D Echocardigraphic abnormalities while HIV infected children with advanced and severe stage of disease had high incidence of diastolic dysfunction, pericardial effusion, left ventricular systolic dysfunction and pulmonary hypertension. Echocardiography is a useful technique for early recognition of cardiac dysfunction in such patients.

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