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A study of cardiovascular abnormalities in newly diagnosed HIV infected children

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Abstract

Background: Children infected with HIV may develop a wide range of cardiovascular abnormalities, some of which are known to be associated with poor survival. With advances in the management of HIV patients, not only survival has increased but manifestations of late stage HIV infection are encountered more often including cardiovascular complications.

Aims: The present study was undertaken to determine the prevalence and nature of cardiovascular abnormalities in newly diagnosed HIV infected children.

Method: In this prospective, observational study, total 86 newly diagnosed HIV infected children, having age below 15 years and who were attending the PCOE at tertiary care institute were included in the study. All these recruited patients were subjected to chest radiograph, electrocardiography and 2D- echocardiography.

Results: There were six (7%) children with abnormal cardiovascular examination in form of tachycardia, tachypnea, increased precordial activity or murmur. Abnormal findings on chest radiograph were seen in 27 patients. Eight patients had right ventricular strain pattern and 3 patients had incomplete bundle branch block on electrocardiograph. On 2D echocardiography only 2 patients had thin rim of pericardial effusion. There was no significant correlation between these findings and clinical and immunological stage of patients. In patients with low CD4 counts or advanced stage there are higher chances of detecting a cardiovascular problem.

Conclusion: The study concluded that it is not cost effective to investigate for cardiovascular abnormalities in all newly diagnosed children at the onset. It can be done based on clinical examination, CD4 counts, stage of patients, and on follow up.

Keywords: Human immunodeficiency virus (HIV), Cardiovascular abnormalities, Chest radiograph, Electrocardiography, 2D- echocardiography, Tachycardia, Tachypnea, Murmur.

1. Introduction

HIV/AIDS is an important cause of morbidity and mortality, affecting 3.4 million children under 15 years of age [1]. HIV affects all the systems of the body which may be due to HIV infection itself or due to opportunistic infections or malignancies [2]. Common cardiac abnormalities noted in HIV infected individuals include cardiomyopathy, myocarditis, pericardial effusion and pulmonary hypertension [3]. These manifestations are due to prolonged immune suppression, opportunistic infections, viral infection, autoimmune response, drug related cardiotoxicity, or nutritional deficiencies [4].

The cardiac complications of HIV infection tend to occur late in the disease in those with acquired immunodeficiency syndrome (AIDS) or prolonged viral infection and are therefore becoming more prevalent as longevity improves [5]. However cardiac complications attributed to HIV infection vary, ranging from subclinical electrocardiographic (ECG) changes, to life-threatening cardiomyopathy, and sudden death [6-10]. Dilated cardiomyopathy is more common in HIV infected children than seroreverted ones and increases in frequency as disease progresses.

Also, it carries much worse prognosis than idiopathic dilated cardiomyopathy [4]. Studies published over past 3 years have tracked the incidence and course of HIV infection in relation to cardiac illness in both children and adults [11]. These studies show that subclinical echocardiographic abnormalities independently predict adverse outcomes and identify high risk groups to target for early intervention and therapy.

Considering the lack of data regarding cardiovascular abnormalities in newly diagnosed HIV-infected children in Indian subcontinent, the present study was undertaken with prime objective to determine the prevalence and nature of cardiovascular abnormalities in newly diagnosed HIV infected children and secondarily correlate these findings with clinical and immunological staging of HIV, also determine the need and feasibility of cardiovascular screening of newly diagnosed HIV infected children.

2. Materials and Methods

After obtaining Institutional Ethics Committee approvaland parent's written informed consent, this prospective, observational study was conducted in the Pediatric Centre of Excellence (PCOE) for HIV care, tertiary care hospital, fora period of 1 year. Total 86 newly diagnosed HIV infected children, having age below 15 years and who were attending the PCOE at tertiary care institute were included in the study. All children enrolled were assigned a study number and assent form was filled wherever applicable. History including demographic details, clinical symptoms as well as examinations was noted in a pre-designed proforma. Special attention was given to symptoms suggestive of cardiac origin like breathlessness, pedal edema, increased precordial activity, cyanosis etc.

The age and sex of the patients, WHO clinical stage of HIV, immunological stage of HIV, symptoms at presentation, cardiac symptoms (dyspnoea, cough, pedal edema, chest pain, orthopnea, paroxysmal nocturnal dyspnea, syncope, suck rest suck cycle, increased precordial activity, palpitations, cyanosis), clinical features **(**General Examination, Pulse/HR RR BP, Anthropometry, Pallor / Icterus/ Edema feet /Clubbing/Cyanosis/Lymphadenopathy, Features s/o Infective Endocarditis) and investigations such as HB: TLC: DLC: PLT, CBC, CD4 etc were noted.All these recruited patients were subjected to chest radiograph, electrocardiography and 2D- echocardiography. The results were correlated with the clinical stage and CD4 counts of the patients. A conclusion was drawn according to the correlation analysis.

2.1 Statistical Analysis

Data were analyzed using SPSS, Version 15.0 package. Data were given as Mean±SD for quantitative variables and Number (Percentage %) for qualitative variables. Student's unpaired t test was applied to compare quantitative data between groups 1 and group 2. Chi square test was applied to compare percentages of qualitative data. Chi square test with continuity correction was applied to compare values in 2 by 2 Tables. If the cell values in 2 by 2 values were small, Fisher Exact Probability test was applied. Students paired t test was applied to compare means at two time points. All tests were 2 tailed. Level of significance was taken as $P<0.05$.

3. Observations and Results

A total of 86 newly diagnosed HIV positive patients were included in the study. Amongst them 50 (58.1%) patients were males and 36 (41.8%) were females. Male to female ratio was 1.38:1. Mean age of patients was 7.34+ 4.55 years. Maximum patients were in the age group of <5 years, (P=0.2). The weight of 44.2% children in our study group was below -3 SD (severely underweight), 25.6% had weight between -3 to -2 SD (moderately underweight), 17.4% had between -2SD to -1SD. Most of our children were underweight and 37.2 % children had height below -3 SD (severe stunting).The most common presenting symptom was fever (91.9%) followed by weight loss (36.0%), (Table 1).

Two children presented with acute immune thrombocytopenic purpura. Table 2 shows the opportunistic infection in study subjects. In about 12.7% patient's mode of transmission of disease was vertical i.e. from mother to child. In eleven patients, the mode of transmission could not be ascertained because parents were not alive. Some children were orphan where parents could not be traced.

Table 1: Presenting symptoms of study subjects at diagnosis

Presenting symptoms	Number (%)
Fever	79 (91.9 %)
Weight loss	31(36.0%)
Loose stools	18 (20.9 %)
Cold	16 (18.6 %)
Abdominal pain	15 (17.4 %)
Vomiting	13 (15.1 %)
Lymphadenopathy	11 (12.8 %)
Others	13 (15.1 %)

Table 2: Opportunistic infection in study subjects

Opportunistic infections		No. of patients (%)
Tuberculosis (Total 22)	Abdominal	10 (10.6 %)
	Pulmonary	09 (10.4 %)
	Lymphadenitis	02 (2.3 %)
	Pleural effusion	01 (1.1 %)
Other Opportunistic infection (Total 10)	Molluscum	02 (2.3 %)
	Scabies	01(1.1 %)
	Herpes zoster	01(1.1 %)
	Chronic diarrhea	01(1.1 %)
	External hordeolum	01(1.1 %)
	Varicella	01(1.1 %)
	Cryptoccocal meningitis	01(1.1 %)
	Candidiasis	01(1.1 %)
	Suspected PCP	01(1.1 %)

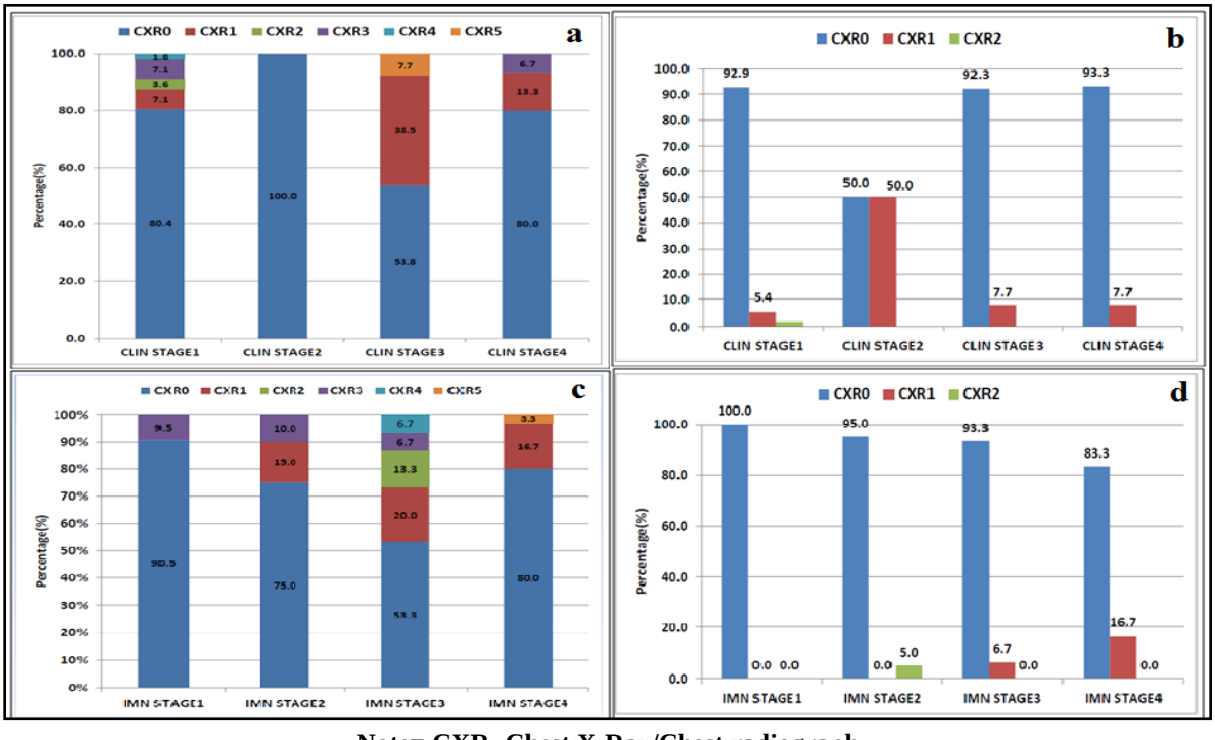
Maximum (65.1%) patients were in WHO clinical stage I followed by 2.3% in stage II while 15.1% and 17.1% in stage III and IV respectively. Immunologically, the CD4 count of 81.4% patients was above 200cells/µL suggestive of good immunity. Only 4.7 % had CD4 counts below 50cells/µL. The most common presenting symptom of probable cardiac etiology was cough (48.50 %) followed by breathlessness (23.30%) and chest pain (8.1 %), (Table 3).

Table 3: Cardiac symptoms in study subjects

Symptoms	Present (%)
Cough	42 (48.5 %)
Breathlessness	20 (23.3 %)
Chest pain	07 (8.1 %)
Palpitation	04 (4.7 %)
Syncope	03 (3.5 %)
Pedal edema	03 (3.5 %)
Increased precordial activity	03 (3.5 %)
Suck rest suck cycle	02 (2.3 %)
Cyanosis	00 (0)

Out of the 86 study subjects, six patients had abnormal cardiovascular examination in form of tachycardia, tachypnea, increased precordial activity or murmur while rest had normal findings. Abnormal findings on chest radiograph were seen in 27 patients. But there was no correlation between these findings and clinical and immunological stage of patients, (Figure 1).

Figure 1: Correlation of lung and heart abnormalities in chest radiograph with clinical (a- Lung and b- Heart) and immunological stage (Lung-c and Heart-d)



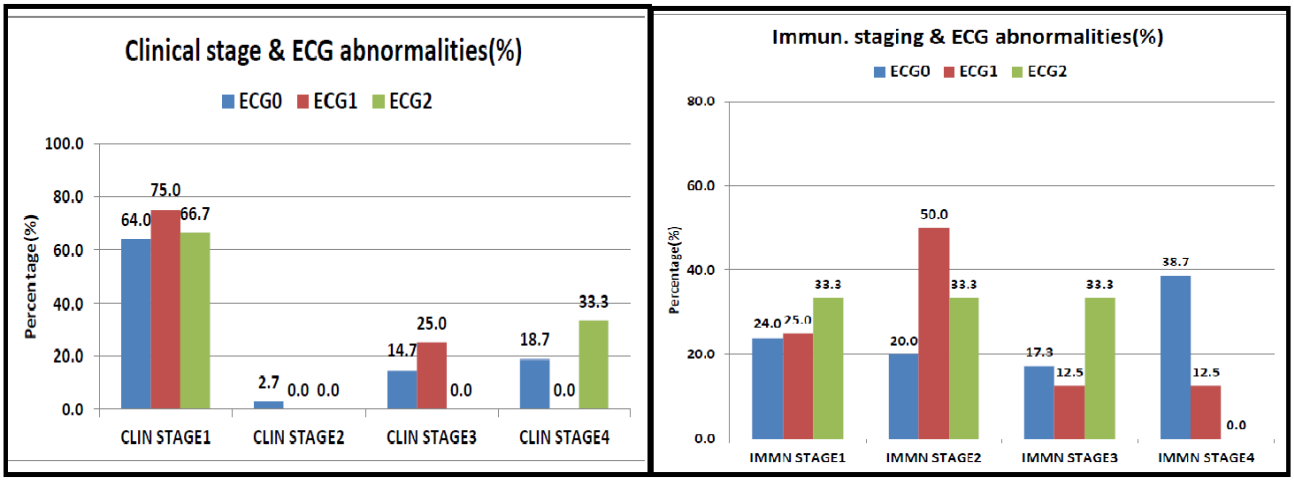
Note= CXR- Chest X-Ray/Chest radiograph

Key for charts a and c (Lung shadows on CXR):
CXR0: Normal;
CXR1: Hilar shadows;
CXR2: Reticulonodular shadows;
CXR3: Patch;
CXR4: Airbronchogram;
CXR5: Hilar shadows+Patch

Key for charts b and d (Heart shadows on CXR):
CXR0: Normal**;**
CXR1: Cardiomegaly**;**
CXR2: Straightened left border of heart

Eight patients have right ventricular strain pattern and three patients had incomplete bundle branch block on electrocardiograph. However, these findings were not correlating with the clinical and immunological stage of patients (Figure 2).

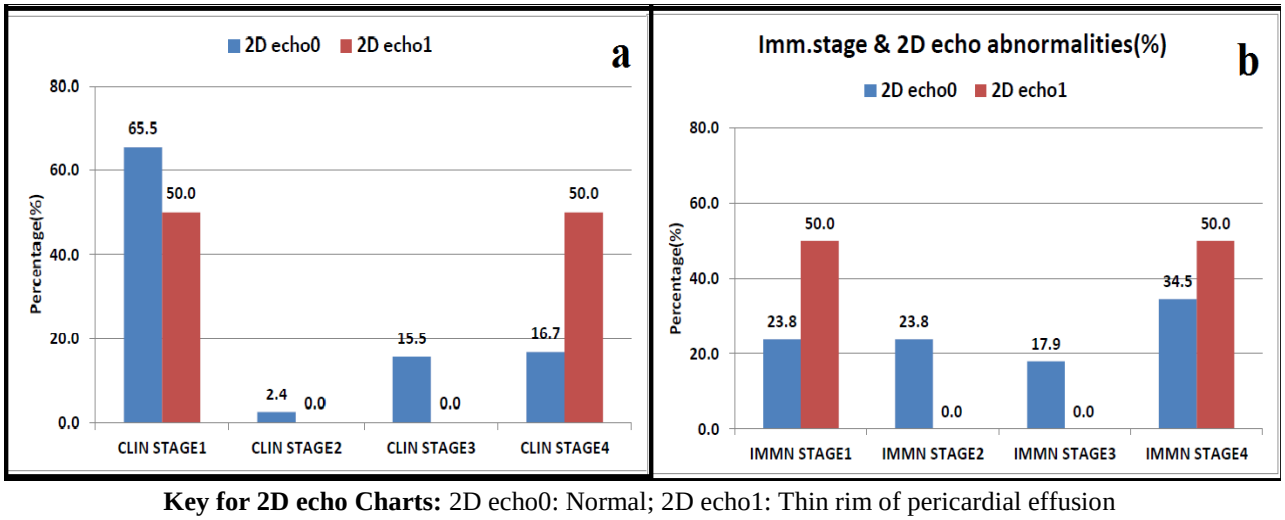
Figure 2: Correlation of ECG abnormalities with clinical and immunological stage



Key for ECG charts: ECG0: Normal; ECG1: Right ventricular strain pattern; ECG2: Incomplete bundle branch block

On 2D echocardiography only two patients had thin rim of pericardial effusion. There was no significant correlation between these findings and the clinical and immunological stage of patients (Figure 3). There was no evidence of cardiovascular abnormalities on echocardiography in our study. This could be attributed to recently diagnosed HIV infection, good immunity, clinical stage 1 in most of the patients and they being naive to ART. In patients with low CD4 counts or advanced stage there are higher chances of detecting a cardiovascular problem.

Table 3: Correlation of Clinical (a) and immunological (b) staging with 2D echo abnormalities



Key for 2D echo Charts: 2D echo0: Normal; 2D echo1: Thin rim of pericardial effusion

4. Discussion

HIV-infected adults are known to have cardiac involvement in the form of diseases of the pericardium, myocardium and the endocardium [12]. Cardiac involvement in HIV infected children is sub-clinical. Clinical examination, chest radiographs and electrocardiography may pick up subclinical cardiac disease. Sub-clinical manifestations such as left ventricular dilatation hypertrophy and decreased systolic function can be detected only by echocardiography. Majority of studies have reported cardiac abnormalities in HIV infected children who were terminally ill, had advanced AIDS or AIDS related complex, or had symptomatic HIV disease with severe immunosuppression [13-15]. In present study, majority of children were in WHO clinical stage 1 and 2, this was congruent to the studies done by Kumar *et al*[16] and Singh *et al* [17]. The maximum number of patients in our study had CD4 more than 200 indicating good immunity. In the study conducted by Singh *et al* [17] majority of children (65 %) did not have significant

immune suppression while 8% of them had mild immune suppression, 16% and 11 % cases had advanced and severe immune suppression, respectively. In study by Bishnu *et al* [18], the overall mean CD4 count was 176.04± 163.49 cells/µl. In contrast to this in our study the mean CD4 count was 710.28±661.31.

The maximum number of our patients had normal findings on cardiovascular examination correlating with the outcome of our study. The abnormal findings observed in the six patients were later attributed to fever or anemia. Moving ahead to the investigations and their analysis**,** there were 20 patients who had abnormalities in the chest radiograph (lung field). But there was no correlation found between these findings and the clinical stage of patients. Similarly, there was no correlation between abnormal heart shadow found in 7 patients on chest radiograph and clinical stage of these subjects**.** Out of these seven patients six (6.9%) had cardiomegaly, of which two had thin rim of pericardial effusion. But no evidence of pulmonary hypertension was noted on echocardiography. Also there was no correlation between the immunological stage and findings on chest radiograph. In our study, we did not find any correlation of the abnormalities with clinical stage or immunological stage of patients. 8 patients had right ventricular strain pattern and 3 had incomplete bundle branch block. Also, we found few children having age related ST segment changes (not categorized as abnormal in the table). 80 percent of patients had normal ECG in study performed by Kumar P *et al* [2] and this was much same in our study where we had 75 normal ECG reports. In the study done by Kumar R *et al* [16], comparisons of various parameters of ECG in various stages were found to be statistically insignificant which was comparable with our study. In this study, most of the patients were newly diagnosed or received ART for than six months' duration until enrolment [16]. The only difference was our patients were ART naive.

In present study, two children had thin rim of pericardial effusion on 2D ECHO while no significant relationship with the clinical and immunological stage was observed. Maximum patients were in clinical stage 1 with normal 2D echo finding. Also comparison of cardiac parameters according to CD4 count (<200 and >200) were found to be statistically insignificant. In study done by Singh *et al* [17] 37% children had left ventricular systolic dysfunction (LVSD) (FS<28 %). Mild tricuspid regurgitation (TR) was present in 18 % children and mild mitral regurgitation (MR) in 6 % children. While two patients had dilated cardiomyopathy and two had pericardial effusion. Children in WHO stage 1 disease were less affected as compared to children in WHO stage 3. This can explain the results of our study as we had maximum (65%) number of patients in WHO clinical stage I. Echocardiographic studies have detected a pericardial effusion in approximately 20% (range 10- 40%) of these patients, and the effusion was large in 4% [19]. Pericarditis has also been reported as the first manifestation of AIDS [20]. Our study did not find significant results related to this probably because we had few patients in stage 4 and all were newly diagnosed. LVSD (left ventricular systolic dysfunction) was seen more commonly in children in WHO stage III as reported by Shah *et al* [21] and Lubego *et al* [22]. Reinsch *et al* [23] reported that the prevalence of diastolic dysfunction in HIV infected patients was 48%. Patients with diastolic dysfunction were characterized by older age, higher body mass index, arterial hypertension, dyslipidemia, and diabetes mellitus. Our study cohort did not have any of these co morbidities explaining the normal 2D echo findings.

It is likely that the cardiac problems might appear during later phase of disease. Likewise in our study group we had patients, who were newly diagnosed, naïve to ART, most of them in clinical stage I, with good CD4 count in around 81% patients. All these parameters support the fact that most of them had normal findings on cardiovascular investigations (ECG, Chest radiograph, 2D ECHO). Similar to our study Kumar R *et al* [16] also concluded that there was no overt increase in the cardiovascular abnormalities due to early disease stage, although their study age group was 10-65 years. As mentioned in study done by Reinsch *et al* [23] diastolic dysfunction is frequent in long-term survivors of HIV infection. Such dysfunction may be preceded by systolic dysfunction signaling an early manifestation of HIV associated cardiac disease.

Kumar P *et al* [2] mentions the mean CD4 count was significantly lower in patients with cardiac disorder than in patients without cardiac disorder. Also he commented that lower CD4 count was significantly associated with the presence of pericardial effusion. This supports the discovery of our study where we had patients with good CD4 count (81%) and hence normal findings in most of them.

5. Conclusion

The present study concluded that it is not cost effective to investigate for cardiovascular abnormalities in all newly diagnosed children at the onset. It can be done based on clinical examination, CD4 counts, clinical stage of patients and on follow up. However it would be good to have a baseline investigation to compare later on follow up. This would not miss out on asymptomatic patients.

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