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RESEARCH ARTICLE

CARDIOVASCULAR ABNORMALITIES IN HIV INFECTED PEDIATRIC POPULATION IN KERALA.

Dr Usha Kumari S, Dr Lathika Nayyar, Dr Cibu Mathews

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Abstract

Cardiac abnormalities associated with HIV infection increase the risk of mortality and morbidity among patients. Literature on the prevalence of these abnormalities in HIV-infected children is negligible, particularly from India. This study was conducted to evaluate and describe the cardiac anomalies associated with HIV infection in pediatric population. This cross-sectional study was done at Pediatric HIV Clinic, Medical College, Thrissur, Kerala, for a period of one year. All 64 participants of the study underwent thorough clinical evaluation and echocardiography. Data collected was analyzed using appropriate statistical methods. The mean age of the participants was 9.62 ± 3.19 years. On physical examination, the symptoms noted were pallor (26.6%), lymph node enlargement (51.6%), opportunistic infections (79.7%), and clubbing (9.4%). Pulmonary artery hypertension (9.4%) and valvular regurgitations (26.6%) were the major echocardiographic findings among the participants. No significant association was noted between history of anti-retroviral therapy (ART) and pulmonary artery hypertension (PAH; $\chi^2=2.676$, $p=0.102$). Cardiac anomalies were not prevalent or were not of poor prognosis in the pediatric population in this study. Most of the cardiac anomalies seem to be subclinical in children with HIV infection. Main cardiac abnormalities noted were mild pulmonary hypertension and mild valvular regurgitations. None of the patients had cardiomyopathy. No association could be found between cardiac abnormalities and ART status.

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Introduction:-

The estimated number of people infected by HIV, worldwide, is around 34 million, out of which 3.4 million are children below the age of 15 years (WHO, 2014). Cardiac abnormalities in these children increase the risk of mortality, even when these symptoms are in subclinical stage. Early detection is the key for successful treatment of the condition (Lipshultz *et al.*, 2000). LV diastolic dysfunction, dilated cardiomyopathy, LV hypertrophy, LV systolic dysfunction, pulmonary hypertension, and pericardial effusion are the most frequently described cardiac problems in HIV-infected adult patients (Barbaro *et al.*, 2001; Khunnawat *et al.*, 2008). Earlier studies reported a high incidence of cardiac abnormalities in children infected with HIV (Lubega *et al.*, 2005). There are very few studies dealing with cardiac anomalies in HIV-infected pediatric population from India. This study was proposed to determine the prevalence of cardiac abnormalities in HIV-infected children and to describe the different cardiac symptoms using echocardiography, ECG, and x-ray. The study also aimed at finding the association of cardiac anomalies with anti-retroviral therapy (ART) status.

Methodology:-

This is a cross sectional descriptive study conducted at Pediatric HIV clinic, Medical College, Thrissur, Kerala, from July 2011 to June 2012. Demographic, clinical, and echocardiographic data were collected from 64 children infected by HIV who attended the clinic. The study population consisted of children less than or equal to 15 years, for whom at least one parent has given an informed consent. All patients were subjected to clinical examination and details were recorded in the prescribed proforma. Name, age, gender, and the clinical stages as per WHO classification were entered for each participant. Documents from ART center were verified for drug compliance, ART regimen, and recent CD4 count. CD4 count estimation was done for all patients by flow cytometry using a BD FACS count system.

After clinical examination all patients were subjected to the following investigations- X-ray chest, ECG and ECHO. A 12-lead scalar electrocardiogram was taken to evaluate abnormalities in rate, rhythm, chamber enlargement, conduction abnormalities and ST-T changes. X-ray chest posteroanterior view was taken to note cardiac size, enlargement of specific cardiac chambers, pulmonary edema or venous congestion, pulmonary arterial hypertension, and lung parenchymal abnormality. Review of the X-rays was done by the radiologist who was blinded to patient's identity. All patients were evaluated using M-mode transthoracic ECHO cardiography and colour-flow Doppler examination using GE VIVID 3 machines with 5 MHz probe. Parasternal long axis view and apical 4 chamber view were conducted by the cardiologist. Left atrial dimensions, left ventricular end systolic and diastolic dimensions, ejection fraction, TR gradient, presence of pulmonary artery hypertension (PAH), presence of any mass, clot or effusion, structural valvular lesions, and approximate RV pressure obtained from TR jet gradient were studied using echocardiography. LV function were classified as, normal if ejection fraction (EF) is >55%, mild impairment if EF 40-55%, moderate impairment if EF 30-40% or severe impairment if EF is <30%. RV pressure was calculated from TR jet gradient if there is significant TR. PAH was classified as mild if calculated RV pressure is 35-50 mm of Hg, moderate if RV pressure is 50-75, and severe if RV pressure is more than 75. Data analysis was conducted using appropriate statistical package and methods.

Results:-

There were 64 participants in the study with a male to female ratio of 1:1.1. The mean age group (mean±SD) of patients in the study was 9.62±3.19 years. About 50% of the patients belonged to the age group of 11-15 years. Mean weight grade (mean±SD) of the participants was 22.38±7.5 kg. About 21.9% of children had grade 1 and grade 2 protein-energy malnutrition (PEM), 11 had grade 3, and 4 had grade 4 PEM. About 26.6% (n=17) had first degree stunting, while 10 participants (15.6%) each had 2nd and 3rd degree stunting. More than 60% of the patients (n=39) had stage 2, 20.3% had stage 1, with relatively few in advanced disease stages, including 12.5% in stage 3 and 6.3% in stage 4 disease. Out of the 64 patients, 52% (n=33) were on ART, of which 65% were on zidovudine, lamivudine, nevirapine (ZLN) therapy. Four children (13%) in the study were in zidovudine, lamivudine, efavirenz (ZLE) therapy, while 16% (n=5) were on stavudine, lamivudine nevirapine combination therapy.

Among the different cardiac symptoms, 4 children had class 1 dyspnea on exertion. The different clinical features at presentation are given in **Table 1**. On clinical examination, the symptoms noted were pallor (26.6%), lymph node enlargement (51.6%), opportunistic infections (79.7%), and clubbing (9.4%). On x-ray examination, the symptoms observed were RA enlargement (15.6%), apex LV (85.9%), apex RV (14.1), and dilated hilar vessels (15.6%). No LA enlargement was present in any of the participants. The symptoms observed on x-ray examination and echocardiography are given in **Table 2**. PAH (9.4%) and valvular regurgitations (26.6%) were the major echocardiographic findings among the participants. ECG examination did not reveal significant changes in any of the features like ECG rate or rhythm, enlargement of chambers, ST or T wave, and conduction. Six patients (9.4%) had mild pulmonary hypertension. No significant association was noted between history of ART and pulmonary artery hypertension (PAH; $\chi^2=2.676$, $p=0.102$). Retroviral therapy did not have any significant association with echocardiographic mitral regurgitation (ECHO MR; $\chi^2=0.288$, $p=0.592$). Echocardiographic pulmonary regurgitation was also not significantly associated with ART in the patients (ECHO PR; $\chi^2=1.939$, $p=0.164$).

Table 1:- Clinical features at presentation in patients (PEM = Protein energy malnutrition; IAP = Indian Academy of Pediatrics, ZLN = zidovudine, lamivudine, nevirapine; ZLE = zidovudine, lamivudine, efavirenz; D4 T+3Tc +NVP = stavudine, lamivudine nevirapine)

	No: of cases	Percentage
WHO clinical stage		
Stage I	13	20.3
Stage II	39	60.9
Stage III	8	12.5
Stage IV	4	6.3
Antiretroviral therapy		
None	33	51.6
ZLN	20	31.25
ZLE	4	6.25
D4 T+3Tc +NVP	5	7.81
Others	2	3.12
PEM (IAP classification)		
No PEM	21	32.8
Grade 1	14	21.9
Grade 2	14	21.9
Grade 3	11	17.2
Grade 4	4	6.3
Height grade		
No stunting	27	42.2
Ist Degree	17	26.6
2 nd Degree	10	15.6
3 rd degree	10	15.6
Clinical examination		
Pallor	17	26.6
Clubbing	6	9.4
Lymph node enlargement	33	51.6
Opportunistic infections	51	79.7

Table 2:- Symptoms in x-ray examination and echocardiography.

Feature	No: of cases	Percentage
X-ray examination		
RA enlargement	10	15.6
Apex LV	55	85.9
Apex RV	9	14.1
Dilated Hilar Vessels	10	15.6
Echocardiographic findings		
Pulmonary artery hypertension	6	9.4
Valvular regurgitations	17	26.6

Discussion:-

The aim of the study was to analyze and describe the major cardiac abnormalities in a population of HIV-infected children. The various cardiac manifestations were determined by x-ray, ECG, and echocardiography. Out of the 64 children with HIV infection, 43.75% had grade 1 or 2 PEM. Analysis of symptoms that could result from cardiac anomalies showed that four participants had tachypnea and dyspnea on exertion. Out of these, one had underlying respiratory problem, while three had anemia. But there were no other symptoms suggestive of cardiac failure. Other studies have reported dyspnea, cough and tachycardia as prevalent clinical signs in pediatric patients with HIV infection (Cheloet *et al.*, 2015).

Radiological review of all the patients for significant symptoms revealed 10 cases suggestive of right atrial enlargement by criteria, and 9 cases of right ventricular type of apex. None of the participants had features of pulmonary venous congestion, pulmonary edema, or pulmonary hypertension. Moreover, there were no symptoms of cardiomegaly in any of the cases in the study. ECG abnormalities were also nil in all the cases, with evidence of chamber enlargement or ST-T changes totally lacking.

Pulmonary hypertension is one of the most frequently described abnormalities in HIV-infected patients (Barbaro *et al.*, 2001; Khunnawat *et al.*, 2008). Radiological review did not reveal any cases of pulmonary hypertension, but echocardiography detected 9.4% (6 participants) as having this symptom. Our report is comforted by the fact that pulmonary hypertension was present only in 7% of the children in a more recent study conducted by Cheloet *et al.* (2015). And this is higher than 3.6% reported in Zimbabwe by Miller *et al.* (2013). This symptom is of significance as outcome of patients with right-ventricular dysfunction is related to the degree of pulmonary hypertension, varying from a mild symptomless condition to severe cardiac impairment with cor pulmonale and death (Pellicelli *et al.*, 1998). And, pulmonary hypertension found on screening echocardiography or right-heart catheterisation warrants an aggressive investigation for treatable pulmonary infections. Of the total of 6 children with pulmonary hypertension one with 2 yrs had previous history of 5mm ostium secundum atrial septal defect (ASD) at 6 months of age. Present ECHO or clinical review did not show any evidence of ASD. None others had underlying cardiac problem or chronic pulmonary problem to account for the pulmonary hypertension.

More than half of the patients (51.6%) were not on ART in this study. Majority of those on ART (31.25%) were on ART protocol containing ZLN (zidovudine, lamivudine, and nevirapine). Despite a good proportion being on this protocol, no significant association could be traced between ART and the presence of a cardiac abnormality. But, this study was cross sectional and not comparative, making it difficult to evaluate the influence of different treatment modules on cardiac anomalies. Echocardiographic studies did not reveal any case of LV dysfunction, and this does support the fact that ART containing Zidovudine has low risk for heart as mentioned in other studies (Miller *et al.*, 1993; Coodley *et al.*, 1994).

Earlier studies had reported high prevalence of LV systolic dysfunction and LV dilatation. Our study did not have any cases of these two symptoms. Study by Miller *et al.*, (1993) reported 10.9% of LV dilatation and 5% of LV systolic dysfunction. While in a Nigerian study, the prevalence of these symptoms were even higher – 33% and 33.7% of systolic dysfunction and dilated cardiomyopathy, respectively (Okoromah *et al.*, (2012). The large difference in findings could stem from the variation in the mean age of the participants in the study. In the Cohort chosen by Miller *et al.* (1993), the mean age of the participants was 15 years as against 9.2 years in our study. The Zimbabwe study also had late diagnosis and most of them were on late stages of infection at the time of diagnosis. In the Nigerian cohort, on the other hand, 83% of the children were in AIDS stage at the time of diagnosis. Thus, it is possible that prevalence of LV dysfunction increases with advanced stages of disease at the time diagnosis. Similarly in an Indian perspective, 64.2 % cases had left ventricular systolic dysfunction in a cross sectional observational study on 100 HIV infected children between 1 and 18 years of age (Singhet *et al.*, 2015). Larger sample size and advanced stage of the disease are the probable cause of the higher incidence of the symptom. Studies do show that early diagnosis and initiation of ART in HIV-infected children will reduce the incidence of anomalies of LV systolic dysfunction (Lubega *et al.*, 2005; Cheloet *et al.*, 2015).

High prevalence of LV dysfunction is reported in HIV-infected children who are malnourished. In Ugandan population of infected children, 50% were malnourished with growth retardation. This cohort showed a high prevalence of LV dysfunction (17%; Lubega *et al.*, 2005). Other studies too reported malnutrition as a worsening factor for LV abnormalities (Miller *et al.*, 1993). Malnutrition is also described as a worsening factor irrespective of ART in some of the studies. The nutritional status of the participants in the study was adequate. The incidence of

valvular regurgitations observed in the present study was high (26.6%) compared to that noted in general population, but all the cases were of trivial to mild type. This particular symptom needs follow up for a better understanding of its prevalence. Cardiomyopathy was not seen in any of the participants, although this is considered to be a prevalent cardiac abnormality in HIV-infected patients.

There was no statistically significant association between echocardiographic abnormalities and the clinical variables. One of the reasons for the difference might be earlier diagnosis of infection. Most of the participants in the study were in stage II (60.9%), when compared to the advanced stages of disease in participants of other studies (Lubega *et al.*, 2005; Singhet *et al.*, 2015). This study shows that most of the cardiac involvement is subclinical in HIV-infected children. Early diagnosis and treatment are thus the tools for reducing progression of the disease. This can prevent morbidity and mortality among the patients to a large extent.

Conclusions:-

Cardiac anomalies were not prevalent or were not of poor prognosis in the pediatric population in this study. Most of the abnormalities seem to be subclinical in children with HIV infection. Valvular regurgitations and pulmonary hypertension were the echocardiographic findings from the study. Early diagnosis and treatment may help in reducing the incidence of cardiac abnormalities.

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