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Research Article

Study of cardiovascular manifestations in patients of HIV- its correlation with CD4 count and the ART regimen prescribed

Sarita Bajaj, T. Nisha Mol*, Piyush Saxena, Rakesh Kumar Yadav, Sujit Verma

Department of Medicine, MLN Medical College, Allahabad, Uttar Pradesh, India

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***Correspondence:**
Dr. T. Nisha Mol,
E-mail: nishanestle88@gmail.com

ABSTRACT

Background: In patients of HIV, there is correlation of CD4 count with severity of cardiac involvement. Some HAART regimens are associated with increased risk for cardiovascular events. This study was undertaken to detect occurrence of symptomatic or asymptomatic cardiac involvement in HIV/AIDS cases. Correlation with CD4+Tcell count and the ART regimen prescribed was also studied.
Methods: This single point cross sectional case control study of 103 patients with HIV infection on HAART therapy was studied from April 2014 to August 2015. The study population was investigated for routine blood tests, X-Ray chest PA view, ECG, CD4 count and 2D transthoracic echocardiography.
Results: The cases comprised of 43 females (41.75%) and 60 males (62.0%). Mean CD4 count was 205.48±150.06/µL and on X-ray chest PA view cardiomegaly was found in 40.78% of cases. The ECG findings were sinus tachycardia (19.42%), left axis deviation (5.82%), low voltage complexes (16.5%), right axis deviation (16.5%) intraventricular conduction delay (5.82%) and ST-T changes (8.7%) The echocardiographic findings were left ventricular diastolic dysfunction (60.24%), pericardial effusion (15.53%), dilated cardiomyopathy (23.03%), pulmonary artery hypertension (17.47%) and valvular lesions (33%).
Conclusions: Declining CD4 count was associated with increased cardiac manifestations but no statistically significant difference was found in both the (TLE and ZLN) subgroups.

Keywords: HIV, Cardiac manifestations, CD4 count, HAART

INTRODUCTION

According to global summary of the AIDS epidemic 2013, number of people living with HIV in 2013, total 35.0 million in whom adults are 31.8 million ; women were 16.0 million. People newly infected with HIV in 2013 are 2.1 million in whom adults are 1.9 million. No of deaths due to AIDS in 2013 are total 1.5 million; adults are 1.3 million 1. Infection with Human immunodeficiency virus (HIV) is a leading cause of acquired heart disease worldwide and specifically of accelerated atherosclerosis, symptomatic heart failure, and pulmonary arterial hypertension (PAH).[2-5] 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.[2] The introduction of highly active antiretroviral therapy (HAART) has significantly improved the clinical evolution of human immunodeficiency virus (HIV)/AIDS disease, with an increased survival of infected patients. However, the introduction of HAART has generated contrasting aspects in the clinical manifestation of cardiovascular complications. In developed countries, a reduction has been observed in the prevalence of HIV-associated cardiomyopathy, possibly related to the

reduction in the incidence of opportunistic infections and myocarditis. In developing countries, where HAART is not widely available, an increase has been noted in the prevalence of cardiomyopathy and pericardial effusion, with a related high mortality rate for congestive heart failure.[3] In the context of these new clinical findings, it has been observed in developed countries that some HAART regimens, especially those including protease inhibitors, may cause an iatrogenic metabolic syndrome (HIV-associated lipodystrophy syndrome) that is associated with an increased risk for cardiovascular events (myocardial infarction and stroke) because of a process of accelerated atherosclerosis. The most important clinical application of HIV-related immunology is measurement and interpretation of the absolute CD4 cell count. It is currently recommended that patients have this test performed at the time of HIV diagnosis and then again approximately every 3 to 4 months, usually in conjunction with an HIV RNA (viral load) test. Recovery of the CD4+T cell count in response to anti-retroviral treatment has been shown to be the most important predictor of clinical outcome, even more so than the virologic response. The wide range of cardiac abnormalities associated with HIV infection has been suggested by autopsy studies. The various abnormalities include pericardial effusion, lymphocytic interstitial myocarditis, dilated cardiomyopathy (frequently with myocarditis), infective endocarditis, and malignancy (myocardial Kaposi sarcoma and B-cell immunoblasic lymphoma).[6]

METHODS

103 patients with HIV infection admitted to the Post Graduate Department of Medicine and attending ART centre at S.R.N. Hospital were studied from April 2014 to August 2015.

Inclusion criteria

All patients diagnosed for HIV infection after ELISA test being positive and on HAART regimen were included in the study. The control group comprised of age and sex matched normal healthy volunteers.

Exclusion criteria

Cases with congenital heart disease, rheumatic heart disease, hypertension, ischemic heart disease, diabetes mellitus and chronic kidney disease were excluded from the study.

The study population was investigated for complete blood count, liver function test, serum urea & creatinine, fasting lipid profile, CD4 count-Ray chest PA view, ECG, 2D transthoracic echocardiography.

All patients were assessed clinically by detailed history taking, general and systemic physical examination. CD4 count was done using kits supplied by the National AIDS control organization of India (NACO) to anti-retroviral therapy (ART) Centre; Allahabad. CD4 count was done for all patients using flow cytometry using a BD FACS count system.

Statistical analysis

The statistical tools employed to analyze the results were mean, standard deviation,'t' test for independent samples, chi-square test and degree of freedom for $\chi 2$ test. The Chi-square test procedure tabulates a variable into categories and computes a chi-square statistics.

RESULTS

Table 1: Echocardiographic dimensions in cases and controls.

Parameter	Cases (n = 103)	Controls (n = 51)	P value T test
LA (cm)	3.44±0.43	3.22±0.3	0.0013
AO (cm)	3.35±0.38	2.606±0.285	<0.0001
IVST (cm)	0.78±0.14	0.78±0.2	1.0
LVPWT (cm)	0.79±0.15	0.783±0.13	0.728
RV dimension (cm)	3.14±0.46	2.98±0.25	0.0218
Fractional shortening (%)	29.18±8.05	41.10±6.53	<0.0001

LA: left atrial diameter; AO: aortic root diameter; IVS: interventricular septum; LVPWT: posterior wall thickness; FS: Fractional shortening.

Table 2: Echocardiographic abnormalities in cases and controls.

Echocardiographic abnormalities	Cases (n = 103)	Controls (n = 51)	P value
Pericardial effusion	16 (15.53%)	0	0.0071
LVDD grade 1	27 (26.21%)	0	0.0001
LVDD grade 2	33 (32.03%)	0	<0.0001
Dilated cardiomyopathy	24 (23.03%)	0	0.0004
Pulmonary artery hypertension	18 (17.47%)	0	0.0036
Valvular lesions	34 (33%)	0	<0.0001

This single point cross sectional case control study comprised majority of males in both cases (62.0%) and controls (83.0%).The mean age of cases was 36.05±6.79 years and that of control group was 35.52±6.47 years

The CD4 count ranged from 16 to 608/µL with a mean of 205.48±150.06/µL. In 27.18%of cases CD4 count was less than 50/µL. 30.1% of cases had CD4 count between 50 and 200/µL, 25.24% of cases had CD4 count between 200 and 349/µL and 17.48% cases had CD4 count ≥350/µL. Echocardiographic dimensions in cases and controls are shown in Table 1 and Echocardiographic

abnormalities in cases and controls are mentioned in Table 2. Cardiovascular manifestations were increased with declining CD4 count in cases as shown in Table 3.

Table 3: Association of 2D echocardiographic findings with CD4 count in cases.

Cardiac manifestations	CD4 count in /µL				Total
	<50 (n=28)	50-199 (n=31)	200-349 (n=26)	≥350 (n=18)	
Pericardial effusion	6	7	2	1	16
LVDD grade 1	4	16	4	3	27
LVDD grade 2	22	4	6	1	33
Dilated cardiomyopathy	15	2	5	2	24
PAH	7	5	5	1	18
Valvular lesions	17	7	8	2	34

Table 4: Mean pattern of study parameters with cardiac dysfunction and their correlation.

Parameter	Group with echo findings Mean±SD (n = 66)	Group without echo findings Mean±SD (n = 37)	Statistical significance P value
Mean age	37.7±7.4	34.84±6.37	0.051
Hemoglobin	9.08±1.52	9.1±1.31	0.95
Total leucocyte count	4194±1642	5403±1418	0.0003
Total cholesterol	230.24±29.01	238.73±26.28	0.143
CD 4 Count	150±126.5	305±140	<0.0001
Triglycerides	239.65±49.71	220.53±36.4	0.043
LV Mass	90.65±18.77	71.27±13.0	<0.0001
LVEF	44.55±10.17	58.24±2.93	<0.0001
LV Posterior wall thickness	0.8±0.15	0.76±0.13	0.176
Fractional shortening	25±6.14	36.68 ± 5.05	<0.001

On CXR PA view, cardiomegaly was found among 40.78% of cases and normal cardiac shadow was seen in 59.22% of cases. Also, cardiac shadow was normal in control group.

The ECG findings among cases were sinus tachycardia (19.42%), left axis deviation (5.82%), low voltage complexes (16.5%), right axis deviation (16.5%) intraventricular conduction delay (5.82%) and ST-T changes (8.7%). Most commonly seen finding was sinus tachycardia followed by right axis deviation and low voltage complexes.

Mean pattern of study parameters with cardiac dysfunction and their correlation are shown in Table 4.The cardiac manifestations in both subgroups of study population with ZLN and TLE regimen were similar without any statistically significant difference (Table 5).

Table 5: Echocardiographic findings in ZLN and TLE group.

Echo findings	ZLN group (n=39)	TLE group (n=64)	P value
PE	5	11	0.7542
LVDD grade 1	13	14	0.2930
LVDD grade 2	9	24	0.1923
DCMP	9	15	0.9665
PAH	6	12	0.8660
Valvular lesions	12	22	0.8717

DISCUSSION

103 patients with HIV infection and registered in ART centre and 51 controls of HIV negative are included in this study. The age of the patients studied ranged between 22 and 58 years with a mean age of 36.68 (±7.18) years and 35.53(±6.41) years among cases and controls respectively. Majority of the patients were young and were in the age group of 20 to 40 years (69.9% and 78.43% among cases and controls. The NACO report has shown that most HIV patients in India were young adults. Men were more affected than females by a ratio of 1.61:1. The cases comprised of 43 females (41.75%) and 60males (62.0%), while the controls comprised of 19 females (17.0%) and 32 males (83.0%). The gender difference was also at par with NACO report, where 39% of the total HIV patients in India were females, 3.5% were children and the rest 57.5% were males.[7]

The CD4 count ranged from 16 to 608/µL with a mean of 205.48±150.06/µL. In 27.18% of cases CD4 count was less than 50/µL. 30.1% of cases had CD4 count between 50 and 200/µL, 25.24% had CD4 Count 200 and 349/µL and 17.48% cases had CD4 count ≥350/µL. Thus most of the cases studied had CD4 count less than 200/µL and categorized under WHO revised clinical stage 4 and clinical stage 3.

In the present study, out of 103 cases studied 61 (59.22%) patients had normal X-ray chest. Cardiomegaly was present in 42 (40.78%) cases patients. Shrinivas et al noticed that out of 50 cases, 33 patients (66%) had normal chest x-ray.[9] Commonest abnormality noted in chest x-ray in HIV individuals were cardiomegaly (14%) and pleural effusion (12%).

In this study, out of 103 cases, 62% patients had normal ECG. Commonest abnormalities were sinus tachycardia

in 19.42% of cases, low voltage complexes in 16.5% of cases only. ST-T changes were found in 8.7% of cases and intraventricular conduction delay in 5.82% of cases. Hamide et al noticed sinus tachycardia in 40% cases, low voltage complex in 10% cases, ischemic heart disease in 3% cases & left ventricular hypertrophy in 4% cases.[10] The sinus tachycardia might suggest an early evidence of cardiac failure or left ventricular diastolic dysfunction.

It was observed that 2D echocardiography was normal in 37 out of 103 cases (35.92%), while various abnormalities were observed in 66 (64.08%) cases. Left ventricular diastolic dysfunction was the commonest findings being noticed in 58.24%. Other abnormal findings were pericardial effusion in 15.53% cases and pulmonary artery hypertension in 17.47% of cases.

The finding of left ventricular diastolic dysfunction was much higher in the present work compared to previous workers. Basavraj et al noticed it in 10% cases, Hamide et al[10] in 7% cases.[8,10] A very high prevalence of 64% was noticed by Schuster et al The left ventricular diastolic dysfunction is one of the earliest evidence of myocardial involvement and may be an asymptomatic in early stages.[30]

In our study, it was observed that in 76.67% cases with left ventricular diastolic dysfunction had CD4 +T cell count was less than 200 cells/mm^3.

Our study showed that diastolic dysfunction was frequently seen in our HIV-infected patients, signifying ventricular filling abnormalities due to a non-compliant ventricle. Diastolic dysfunction was also observed to be more frequent and worsening with disease progression. Diastolic dysfunction had also been reported in other studies.[11,12]

DCM is a well-documented cardiac abnormality in HIV/AIDS and was found in 23.03% of our cases, with none in the control group.[13,14] Most patients with DCM had more advanced immunosuppression with a CD4 count of 50/µl. This result correlates well with several reports that dilated cardiomyopathy in HIV is associated with advanced immunosuppression and lower CD4 lymphocyte counts <100/µl.[15] Nzuobotane et al demonstrated a similar relationship between the degree of immunosuppression and the likelihood of cardiomyopathy.[16] Interestingly, a CD4 count of 100/µl proved to be the important threshold in that study as well. Whereas studies published by Moreno et al and Hakim et al had detected 6% and 5% respectively. Therefore the mean CD4 count of cases was much less in this study as compared to other studies.[17,18]

Pericardial effusion was seen in 15.53% of cases which is as par with Indian studies done by Aggarwal et al and studies done at United States by Himelman et al.[14,19] The pericardial effusion detected was often small in amount and without any hemodynamic significance. Pericardial effusion in HIV patients may be marker of end stage HIV infection because it is associated with very low CD4 count.

Majority of the existing evidence suggested that HIV infection could lead to cardiac dysfunction, either in its systolic or diastolic function. However data regarding the factors associated with HIV infection that could predict cardiac dysfunction in the patient population was inadequate. Again, like the incidence of CMP, CD4 cell count was one of the main factors that had been investigated, and controversial data had been reported. In this study, there was no significant linear correlation between CD4 count and parameter for cardiac manifestations. Herskowitz et al reported 9 patients experiencing symptomatic heart disease, all of them having CD4 T cell counts <200 mm^3, which represented a significant factor in predicting cardiac disease in HIV infected patents.[20] Cardoso et al also reported that HIV infected patients with CD4+ lymphocytes counts < or = 100/mm^3 had more frequent abnormal echocardiograms than those with CD4+ lymphocytes counts > 100/mm^3.[21] Similar findings had been reported by Herskowitz et al[22] demonstrating a greater proportion of prospective and referred patients with LV dysfunction to have CD4 counts < 100/mm^3 (62 and 79%, respectively) than did those without LV dysfunction (35%). All of HIV+ patients diagnosed with unexplained congestive heart failure had CD4 counts less than 100/mm^3 in a cross-sectional study. An Italian study revealed that left ventricular shortening fraction was lower in the subgroup with CD4 lymphocyte count less than 100/cubic mm.[23]

In this study, there was significant correlation present between CD4 count and echocardiography abnormality. Singh A et al showed that patients with CD4 count less than 200/ µL had a high prevalence of echocardiographic abnormalities than those with CD4 count more than 200/µL.[24] Some studies had reported no association between CD4 cell counts and cardiac dysfunction in HIV infected patients. Jain et al found no significant association between diastolic dysfunction and CD4 cell count.[25] Similar results have been reported by Guha et al reporting no association between CD4 cell count and either diastolic or systolic dysfunction.[26] Lipshultz et al also reported no association was seen between longitudinal changes in LV fractional shortening and CD4 count.[27] It is due to direct HIV virus involvement in myocarditis and not associated with immunosupression.

Thienemann F et al stated that HIV itself induced immune activation is considered to independently contribute to CVD and may partially explain the higher cardiovascular mortality in this patient group.[31] Moreover, ART via associated dyslipidaemia or insulin resistance may further enhance cardiovascular risk. In our study we found that the cardiac manifestations in both subgroups of study population with ZLN and TLE regimen were similar without any statistically different significance.

CONCLUSION

This study clearly revealed that the majority of patients with HIV infection had echocardiographic abnormalities which were clinically quiescent. This suggests echocardiography as a relevant tool for diagnosis of subclinical cardiac abnormalities, with the aim of instituting management early where necessary. Similar findings have been reported by other workers.[13,28,29]

Though echocardiography seems to be a useful technique for the early recognition and treatment of cardiac dysfunction in such patients; clinico-pathological studies may help to clarify the role of HIV virus and opportunistic infections in the pathogenesis of cardiac abnormalities found in HIV infected patients.

In view of the high frequency of cardiac abnormalities detected by echocardiography in the HIV/AIDS patients in this study, it is suggested that HIV positive patients should have a careful initial and periodic cardiac evaluation to detect the cardiac involvement earlier.

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