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ORIGINAL RESEARCH

CARDIAC MANIFESTATIONS IN HUMAN IMMUNODEFICIENCY VIRUS-INFECTED PATIENTS: AN ELECTRO- AND ECHOCARDIOGRAPHIC STUDY

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ABSTRACT

Background: Advanced novel therapies and antiretroviral medications for the treatment of human immunodeficiency virus (HIV) infection have led to the improved management and survival of the infected patients. However, I [i]t manifestations in late-stage diseases such as cardiac deformities, which are the major cause of fatality in HIV-infected patients. Hence the current study was undertaken to derive the association of cardiac dysfunctions in HIV-infected patients using electrocardiograph (ECG)and echocardiography (ECHO).

Methodology: The study included a total of 100 consecutive patients with HIV infection and was performed during January–December 2016 in the Department of General Medicine. Prior to the commencement of the study, ethical clearance was obtained from the Institutional Ethical Committee. Patients underwent complete blood count, ECG, and ECHO. Data were analyzed using Microsoft Excel spreadsheet and R-3.4.1 software.

Results: Majority of the patients were males (79) and 40–49 years was the most common age group. The duration of HIV infection in most of the patients (73) was 1–10 years. Among the study population, 79 patients received antiretroviral drugs. Chi-square test was used to find the association of clinical symptoms and cardiac abnormalities with CD4 count. Cardiac manifestations were observed in 62% patients; sinus tachycardia (29%) was found to be the most common cardiac manifestation on ECG. Diastolic and systolic dysfunctions were observed in 35 patients and 49 patients, respectively.

Conclusion: Patients with HIV infection are at a higher risk of developing cardiac dysfunctions. Early identification through ECG and ECHO-revealed abnormalities might assist in cardiac-targeted interventions, which can significantly reduce the fatal outcomes in HIV-infected patients.

KEY WORDS: Human immunodeficiency virus, Left ventricular dysfunction, Acquired immunodeficiency syndrome, Echocardiogram, Electrocardiogram.

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INTRODUCTION

Human immunodeficiency virus (HIV) that causes acquired immunodeficiency syndrome (AIDS) has claimed approximately 35 million fatalities, worldwide. Till date HIV-infected population have increased up to 70 million.[1] The emergence of antiretroviral drugs significantly altered the course of HIV infection by improving the patient's survival and quality of life.[2] However, currently, even with antiretroviral drugs, HIV-related mortality rate is scaling up and is invariably attributed to the manifestations of late-stage diseases such as cardiac-related complications.

Prevalence of cardiac dysfunctions in HIV-positive patients ranges between 28%–73%.[3] Contemporary investigations reported that cardiovascular diseases(CVD) are the major contributing factors in HIV-related mortalities.[4] CVD significantly intensifies the HIV-associated mortality rate with a 1.5–2.0 fold when compared to the common population.[4] Various cardiac dysfunctions associated with HIV infection include

pericardial effusion, left ventricular dysfunction, myocarditis, dilated cardiomyopathy, coronary artery disease, pulmonary hypertension, and malignant neoplasm.

Although the antiretroviral drugs are effective, the longevity of the antiretroviral therapy itself may predispose the patients to cardiac complications. Despite the benefits, the treatment stimulates metabolic abnormalities such as hyperlipidemia, hyperglycemia, and insulin resistance, which in turn induce the risk of developing coronary dysfunctions.[2] Malnutrition is frequently reported in HIV infection, especially during late stage, which may also contribute to cardiac dysfunctions such as ventricular disorder, independent of antiretroviral drugs usage.[2] Other independent factors that act as stimulants for cardiac dysfunctions are irrepressible HIV replication and inflammatory cytokines.[5] Greater attention towards the patients, especially those receiving antiretroviral drugs and, most importantly, regular screening and monitoring for cardiac dysfunctions through echocardiographic techniques may significantly improve the management of HIV-infected patients.[5]

Electrocardiogram (ECG) is an inexpensive and clinically implemented device used to evaluate the cardiac complications. ECG is recognized for its rapid diagnosis of cardiac complications, such as pericardial effusion, ventricular dysfunction, valve disorder, and cardiomyopathy even under unsuspected situations as well as clinically unapparent manifestations.[6] Cardiac output is one of the predominant cardiac events required for the flow of blood, along with blood quantity, contraction durability, and regular relaxation and contraction cycle. This is associated with various electrophysiological events in the cardiac cells, which can be monitored and deformities can be assessed using ECG.[7]

Echocardiography (ECHO) is an ultrasonic, noninvasive, and real time effective device, which is mainly known for the early detection of cardiac disorders. ECHO is employed to screen the cardiac functions and their deformities, which manifest in the presence of or progress before the apparent clinical symptoms appear.[5] ECHO employs sound frequency that has a range of 1.5–7.5 MHz and is considered as “ultrasound”; such ultrasound beams are allowed to pass through the cardiovascular system and reflected signals are visualized on the oscillograph creating a two-dimensional image.[8]

Detection of cardiac involvement during early stages in HIV cases is crucial and impacts on the prognosis of HIV infections. Hence, the current study intended to evaluate the cardiac involvement and its deformities in HIV-infected patients using ECG and ECHO.

MATERIALS AND METHODS

The current observational study was carried out in the Department of General Medicine for a period of one year. A total of 100 patients symptomatic or asymptomatic for cardiac diseases were included in the study. Patients with hypertension, diabetes mellitus, rheumatic heart disease, congenital heart disease, or ischemic heart disease were excluded from the study.

Institutional ethical clearance was obtained and signature of the patient on a consent form was taken after explaining about the study and the procedures involved. The patients underwent laboratory investigations, such as complete blood count, HIV test by ELISA kit (Bio-Rad, United States), CD4/CD8 cell count, ECG, and ECHO. All the patients underwent 12-lead ECG and were subjected to two-dimensional ECHO.

The cardiac functions were considered abnormal if the ECG detected abnormal rather than normal sinus rhythms and if ECHO detected abnormalities such as ejection fraction, systolic and diastolic dysfunction, pulmonary hypertension, valvular lesions, dilated cardiomyopathy, hyperkinesia, and pericardial effusion. ECG detected the following cardiac complications: sinus tachycardia, left ventricular hypertrophy, acute anterior wall myocardial infarction, and atrial fibrillation.

Left ventricular hypertrophy was diagnosed if changes were observed on ECG, as per the criteria given by Romhilt-Estes point score system.[9] Two-dimensional and M-mode ECHO were carried out using Philips HD 72D-echocardiography machine (Philips, Netherlands).

Dilated cardiomyopathy was diagnosed if the left ventricular ejection fraction (LVEF) was < 55% and if the left ventricular end diastolic diameter was > 3.2 cm/m2. Pericardial effusion was graded as mild (< 500 ml), if it was localized posteriorly and the atrio-ventricular sulcus is not cranially obscure; moderate (500–1000 ml), if it was uniformly distributed in the pericardial cavity; severe (1000 ml), if it was diffusely detected (posterio-medially, laterally, and anteriorly) and around the apex. Myocarditis was detected on the basis of clinical data and was later confirmed by necropsy, according to Dallas criteria.[10] ST elevation at J-point in two leads with ≥0.2 mV and ≥0.15 mV in mean and women, respectively V2–V3 and/or ≥ 0.1 mV in other leads. ST depression and T-wave changes; new horizontal or down-sloping ST depression in >0.05 mV two contagious leads and T inversion ≥0.1 mV in two contagious leads with ≥ 1 R/S ratio.

Abnormal wall motion was assessed by evaluating the shifts and changes in thickness of the left ventricular walls by means of computer digitization of systolic and diastolic endocardial borders. The endocardial outlines were divided into 24 equivalent segments and the motion of the individual radians or areas were expressed as a bar graph.

Statistical analysis

R version 3.4.1 software was used to analyse the data. The categorical data were expressed as rates, ratios, and proportions. Chi-square test was used to find the association between clinical symptoms and cardiac abnormalities with CD4 count. P value < 0.05 was considered statistically significant.

RESULTS

Among the study population, majority (39) of the patients belonged to the age group of 40–49 years. Male preponderance with 3.6:1 male to female ratio was observed. Out of 100 patients, CD4 count > 200 cells/mm3 was observed in 33 patients, followed by 100-150 cells/mm3 in 22 patients, 50–100 cells/mm3 in 18 patients, and < 50 cells/mm3 in 11 patients (Table 1). Among the 62 patients with cardiac abnormalities, 44 patients had CD4 count < 200 cells/mm3 and the remaining patients had CD4 count > 200 cells/mm3. Majority of the patients (51) had chest pain, followed by fever in 39 patients (Table 2).

Table 1: Distribution of HIV-infected patients based on CD4 count

CD4 count (cells/mm^3)	HIV-infected patients
< 50	16
50–100	18
100–150	22
150–200	11
≥ 200	33
Total	**100**

Table 2: Clinical symptoms in HIV-infected patients

Clinical symptoms		CD4 count(cells/mm^3)		*P* value
		≤ 200	> 200	
Chest pain	**Yes**	15	4	0.3
	No	54	27	
Breathlessness	**Yes**	35	16	0.93
	No	34	15	
Edema	**Yes**	18	10	0.53
	No	51	21	
Fever	**Yes**	29	10	0.36
	No	40	21	
Cough	**Yes**	24	11	0.95
	No	45	20	

Out of 100 patients, 73 patients had HIV infection with a duration of 1-10 years; of these, 45 patients were diagnosed with cardiac abnormalities. Four among the five patients who had HIV infection for > 10 years had cardiac abnormalities. Out of 22 patients infected with HIV for less than a year, 13 patients were diagnosed with cardiac abnormalities.

Among the study population, 79 patients were receiving antiretroviral drugs; of these, 48 patients had cardiac abnormalities. Among the 21 patients who were not receiving antiretroviral drugs, 14 had cardiac abnormalities. Opportunistic infections were found in 38 patients and of these, 22 patients had cardiac abnormalities.

ECG findings were normal in majority (54) of the patients, however sinus tachycardia (29), left ventricular hypertrophy (7), anterior wall myocardial infarction (6), inferior wall myocardial infarction (3), and atrial fibrillation (1) were observed in these patients (Table 3).

ECHO findings such as systolic (13) and diastolic dysfunction (35) (P = 0.2) were observed. Among the diastolic dysfunction patients, 27 had CD4 count < 200 cells/mm,3 and among systolic dysfunction, 10 patients had less than 200 cells/mm3 CD4 count. Pulmonary hypertension was observed in 13 patients and among these nine patients had CD4 count less than 200 cells/mm3. Followed by valvular lesions (18) of these 11 patients had CD4 count more than 200 cells/mm3, dilated cardiomyopathy (9), hypokinesia (15), and pericardial effusion (6); however, statistical significance was not observed when these parameters were associated with the CD4 count (Table 3).

Table 3: Association of cardiac manifestations with CD4 count in HIV-infected patients

Diagnosis		CD4 count(cells/mm^3)		*P* value
		≤ 200	> 200	
ECG	Normal	39	15	0.45
	Abnormal	30	16	
Ejection fraction	< 60	30	15	0.65
	≥ 60	39	16	
Systolic dysfunction	Yes	10	3	0.51
	No	59	28	
Diastolic dysfunction	Yes	27	8	0.2
	No	42	23	
Pulmonary hypertension	Yes	9	4	0.98
	No	60	27	
Valvular lesion	Yes	11	7	0.43
	No	58	24	
Dilated cardiomyopathy	Yes	8	1	0.18
	No	61	30	
Hypokinesia	Yes	11	4	0.69
	No	58	27	
Pericardial effusion	Yes	4	2	0.9
	No	65	29	

ECG, Electrocardiogram

DISCUSSION

HIV infection diminishes the immunity to a level where the patient becomes highly susceptible to various infectious and noninfectious health complications. CD4 count is well recognized as the surrogate marker for the prediction of HIV disease progression, and especially, determines the requirement of antiretroviral therapy.[11]

In the initial stages of HIV exposure, the infection is generally asymptomatic and is mainly accompanied by minor alterations in the immune system.[12] Gradually, the viral load increases and HIV-specific antibodies become apparent in the blood stream after 90 days of initial exposure. As the disease progresses, the consequences and the clinical symptoms stretch out and greatly vary from one individual to another.[12] Clinical symptoms such as fever, cough, breathlessness, edema, and chest pain were the common presentations observed in our study. In a study by Antwal et al., clinical features such as fever, breathlessness, cough, and weight loss were observed to be significant with HIV-positivity.[13] Higher CD4 count and clinical manifestations were found to be statistically insignificant in our study. Similarly, a study conducted by Wal et al.[14] observed negative association between higher CD4 count and clinical symptoms as well.

HIV-related opportunistic infections, which are prominent and frequent due to suppressed immunity, were surprisingly less in the current study than expected. Despite the frequency, most of the patients with opportunistic infections had CD4 count < 200 cells/mm3. It is postulated that HIV-infected patients with decreasedCD4 count are at a greater risk of developing AIDS-related opportunistic infections as well as AIDS-related carcinomas, which is in agreement with our findings.[11]

Majority of the patients in our study received antiretroviral drugs and most of them were predisposed to cardiac abnormalities. It has been documented that the protein inhibitors, which are the most essential components of antiretroviral regimens, result in reduced triglyceride deposition and elevated lipid discharge. Protease inhibitors also result in fluctuation of hepatic functions and impair endothelial triglyceride clearance leading to hyperlipidemia and insulin resistance,[2] which suggests that antiretroviral drugs might also be responsible for the development of cardiac-related complications.

Sinus tachycardia is considered as one of the poor prognostic factors as well as the most common symptom of heart failure.[15] ECG findings revealed sinus tachycardia as the common cardiac abnormality in our study and other similar studies,[16, 17] however it was statistically insignificant. ECG also showed that majority of the patients with ECG-revealed cardiac abnormalities had CD4 count < 200 cells/mm3.

Diastolic dysfunction is one of the early complications that manifests the existence of CVD in HIV-infected patients.[18] It has been characterized that the risk factors of CVD significantly induce the risk of developing diastolic dysfunctions.[19] The current study encountered more number of diastolic dysfunction patients than systolic dysfunction. Studies have found similar results, wherein, HIV-infected patients had greater preponderance of development of diastolic dysfunction, and are independently linked with HIV infection.[19, 20] Studies have reported that development of systolic and diastolic dysfunctions are not possibly induced by antiretroviral therapy.[18] Findings suggest that diastolic dysfunctions can also be the markers of CVD involvement in HIV-

infected patients, with or without antiretroviral therapy.[19,20]

HIV-infected patients receiving antiretroviral drugs are prone to various infections including pulmonary hypertension.[21] The pathogenesis of development of pulmonary hypertension in HIV-infected patients and the effect of antiretroviral drugs on it is still not clear.[22] However, HIV infection contributes to the hypercoagulable activity that results in thromboembolic disease, which is significantly associated with the development of pulmonary hypertension.[23] In the current study, pulmonary hypertension prevalence was found to be less and was statistically insignificant. In a study by Quezada M et al.,[24] among392 patients examined, 9.9% patients had pulmonary hypertension, which is in concordance with the current study.

The pericardial effusion is symptomless and the prevalence is found to be 11% in HIV-infected patients.[22] The reason behind pericardial effusion development is unknown and may be due to the persistence of opportunistic infections. In the present study, six patients had pericardial effusion and among these four patients had CD4 count < 200 cells/mm3. A study by Lind et al.[25] also observed pericardial effusion in few HIV-infected patients, wherein, among the 802 HIV-infected patients only two patients had pericardial effusion. These findings suggest that pericardial effusion is not a prevalent cardiac deformity in the antiretroviral era.

The current study observed valvular lesions in 18 patients, in a study by Reinsch et al.,[26] among 803 HIV-infected patients, clinical valvular disorders were observed in 4.7% patients. In a study by Twagirumukiza et al.,[27] among 416 HIV-infected patients only 71 patients had clinical features of cardiomyopathy. In the current study, only nine patients were found have dilated cardiomyopathy among that eight patients had CD4 count < 200 cells/mm3.[22] The prevalence of cardiomyopathy decreases with successful antiretroviral treatment similar to the findings of the current study, wherein, few patients were diagnosed with cardiomyopathy.

In the current study, although it was observed that there was no statistical significance between cardiac abnormalities and other factors like CD4 count and the duration of the disease, it was noticed that the cardiac abnormalities were more prevalent among the HIV-infected patients with a CD4 count < 200 cells/mm3. It was also observed that antiretroviral regimens alone might not be the significant contributors in the development of cardiovascular complications. Due to the longevity of antiretroviral drugs, careful management of HIV-infected patients with regular monitoring for cardiac deformities is essential, which might assist in reducing the mortality rates of HIV-infected patients.

Due to its cross-sectional design, the current study possesses several limitations. The sample size was small, hence, difficult to assess the correlation between cardiac abnormalities and other factors such as CD4 count. HIV infection wasn't confirmed by western blot, except for few patients in whom HIV couldn't be confirmed with ELISA. Diagnosis of diastolic dysfunction was based on the ratio of early to late (E/A) ventricular filling velocities and color doppler was not used. A longitudinal study in which all such factors are measured is currently needed with a larger sample size and longer follow-up.

CONCLUSION

In our study, overall cardiac abnormality was detected in 62 patients, where ECG revealed cardiac abnormalities in 46 patients, and among 54 ECG-normal patients ECHO revealed abnormalities in 16 more patients, which suggests that along with ECG, ECHO should be employed for accurate diagnosis. Even though current study observed no statistical significance between cardiac abnormalities and other factors such as CD4 count, the cardiac abnormalities were found more prevalent among the HIV-infected patients with a duration of more than one year. Higher percentage of patients reported CD4 count < 200 cells/mm3. Sinus tachycardia and left ventricular diastolic dysfunction were the most common complications observed on ECG and ECHO, respectively.

AUTHORS' CONTRIBUTIONS

The participation of each author corresponds to the criteria of authorship and contributorship emphasized in the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals of the International Committee of Medical Journal Editors. Indeed, all the authors have actively participated in the redaction, the revision of the manuscript and provided approval for this final revised version.

SPONSORSHIP

Declared none.

COMPETING INTERESTS

The authors declare no competing interests.

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