

Cardiac Autonomic Dysfunction in Human Immunodeficiency Virus Infected Patients: A Cross Sectional Study

Sashindran VK¹, Nagesh IV^{1*}, Vivek Aggarwal¹ and Anadakrishnan U²

¹Department of Internal Medicine, AFMC, Pune, Maharashtra, India

²Armed Forces Medical College, Pune, Maharashtra, India

Abstract

Background: Neurological complications involving central and peripheral nervous system are well described but there is paucity of literature on involvement of autonomic nervous system. HIV patients on ART have a higher prevalence of symptoms due to dysautonomia in comparison to normal individuals.

Aims and objectives: To study the prevalence of cardiac autonomic dysfunction in PLHA (People living with HIV/AIDS) with and without antiretroviral treatment.

Methodology: It is a cross sectional study. The subjects are broadly divided into 3 categories with 25 patients in each group. PLHA on ART, PLHA not on ART and healthy controls.

Observation and results: Three patients from ART group two from ART naive group had symptoms of syncope. There was a significant difference between the autonomic parameters in the control population as compared to that of PLHA, but no difference between those on ART and not on ART. The resting heart rate was significantly higher in PLHA compared to controls. On testing for sympathetic response, there was no notable difference between the median values of fall in systolic blood pressure between PLHA patients and control population. Respiratory sinus arrhythmia, expiration to inspiration ratio, in the controls was higher when compared to PLHA. There is a significant difference in fall in systolic blood pressure between the HIV on ART and not on ART, however there was no significant difference in other autonomic parameters.

Conclusion: This study shows that deterioration of parasympathetic function is more common than sympathetic function decline in HIV infected subjects as compared to normal population.

Keywords: Autonomic nervous system; HIV infection; Antiretroviral therapy

Introduction

Neurological complications involving central and peripheral nervous systems in human immunodeficiency virus (HIV) infection are well characterized; but those involving autonomic nervous system are not adequately studied mainly due to difficulties in assessment. HIV patients on ART have a higher prevalence of symptoms due to dysautonomia in comparison to normal individuals [1]. Cardiovascular involvement with human immunodeficiency virus (HIV) infection is now well documented [2-4] but there is paucity of literature on autonomic dysfunction in HIV infection. The cardiovascular autonomic dysfunction is usually manifested as postural hypotension and syncope in HIV infected patients [5] and its prevalence in People living with HIV/AIDS (PLHA) has been reported to range from 5 to 77%. This data is however from the pre-HAART era [6]. PLHA receiving anti-retroviral therapy (ART) have better outcomes compared to those not on ART [7]. Cardiac autonomic dysfunction is seen both in early and late stages but more common in late stages when it is associated with cardiac manifestations. Since many of the autonomic symptoms resemble those of other systemic illnesses it is relevant to exclude autonomic nervous system involvement before extensive investigations are carried out. No studies on similar lines were found in the review of Indian literature. The aim of this study is to analyze the prevalence of cardiac autonomic dysfunction and to find out if there is any difference between patients with HIV on ART to that of ART naive.

Aims and Objectives

To study the prevalence of cardiac autonomic dysfunction in PLHA with and without antiretroviral treatment.

Methodology

Study setting

Tertiary care centre, western Maharashtra.

Study design

Cross sectional study.

Study population

HIV patients coming to the ART centre.

Inclusion criteria

- Group 1: HIV patients naive to ART.
- Group 2: HIV patients on ART at least for a period of 3 years.
- Group 3: Control: HIV negative individuals.

***Corresponding author:** Nagesh IV, Reader, Department of Internal Medicine, AFMC, Pune, Maharashtra, India, Tel: 9618024173 1857; E-mail: ivaturi_venkata@rediffmail.com

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Exclusion criteria

HIV patients younger than 18 years of age, known arrhythmias, smokers, Pregnancy, history of diabetes/alcohol consumption, or hypertension, Patients on antihypertensives or anti arrhythmics.

Sample size

Three sets of subjects were recruited.

- (a) PLHA on ART.
- (b) PLHA without ART.
- (c) HIV -ve controls.

Twenty-five subjects were enrolled in each group.

Methods

A detailed history was taken and clinical examination done. Investigations done included a complete hemogram, CD4 testing, and all biochemical markers of metabolic syndrome were tested. Autonomic function testing was done using CANWin (Windows based cardiac autonomic neuropathy) analyzer, manufactured by Genesis Medical System Pvt. Ltd. Hyderabad, India. The autonomic function tests included the following:

Parasympathetic function tests

- The Resting heart rate.
- **Deep breathing test:** ECG was recorded for 5 cycles of deep breathing. From this test the following parameters are obtained:
- **Expiration-Inspiration Ratio (E: I Ratio):** The longest R-R interval during expiration divided by the shortest R-R interval during inspiration. The E/I ratio varies depending on age. However, an E/I ratio less than 1.1 is abnormal at any age.
- **Respiratory sinus arrhythmia (RSA):** RSA is typically a benign, naturally occurring variation in heart rate that occurs during the breathing cycle. It is characterized by an increased heart rate during inhalation and a diminished heart rate during exhalation. On an electrocardiogram, RSA is detectable as changes in the P-P interval (or the distance between P waves).
- **Response to standing:** The subjects were allowed to take 5 minutes of rest and then asked to lie down comfortably on a couch. They were then asked to stand up. Their heart rates were recorded at the 15th and 30th beats immediately after standing to obtain 30:15 ratios. A 30/15 ratio of 1.04 or more considered significant.
- **Valsalva maneuver:** Heart rates at rest was recorded. Then the subjects were asked to blow air into the mouthpiece and the pressure was maintained at 40 mm hg for 15 seconds. ECG was continuously recorded. Valsalva ratio was then calculated. as the ratio of the longest RR interval after the strain to the shortest RR interval during the strain. A value of <1.21 was considered abnormal.

Sympathetic function tests

- **The Postural hypotension test (Postural challenge test):** It is expressed as the difference between the baseline supine and the minimal blood pressure after standing up immediately and after 01 minute and 03 minutes of standing. A decline in systolic blood pressure by more than 20 mmHg 1 minute or 3 minutes was considered abnormal.
- **The sustained hand grip test:** Subjects were asked to hold spring dynamo meters in his left hand and to compress it maximally. The values were noted. Then he was asked to hold the spring dynamo meters in their left hand and to compress it up to 30% of the maximum and to hold them for 4 minutes. The rise in the diastolic blood pressure at the point, just before the release of the hand grip, was noted. The increase in the diastolic BP was noted as the difference between the highest diastolic pressure during the examination and the average diastolic pressure at rest. A rise of ≥ 15 mm of Hg was considered normal.

Statistical analysis

The data obtained from the study was statistically analyzed using SPSS software. The descriptive analysis of the data was done and then Kolmogorov-Smirnov test, Mann-Whitney U test, Kruskal Wallis test were done.

Observation and Results

The study was conducted on 50 HIV positive subjects with 25 patients each in ART receiving and ART naïve group. Demographic data is given in Table 1. The age of PLHA on ART ranged from 20 yrs to 65yrs with a mean age 43.2 ± 11.49 yrs. In this group the lag time between detection of HIV status and institution of ART ranged from 4 years to 20 years with a mean duration of exposure 9 years. The CD4 count in this group ranged from 166 cells/ μ l to 640 cells/ μ l with a mean CD4 count 370.04 cells/ μ l. All the patients included in the group had taken ART for at least 3 years or more. The mean age of the patients who were naïve to ART treatment was 45.16 yrs. HIV infection duration in ART naïve group ranged from 1 year to 8 years and the CD4 count in the group ranges from 195 to 918 cells/ μ l with a mean CD4 count of 546 cells/ μ l. The age of the control population ranged from 22 yrs to 59 yrs with mean age 41.44 cells/ μ l. 3 patients from ART group and 2 patients of ART naïve group and none from the control group gave history suggestive of cardiac dysautonomia. Most of the symptomatic patients complained of dizziness on standing for a long time. The results of autonomic tests are given in Table 2. To know the significance of difference between the three study groups, the data was analyzed using One-sample Kolmogorov-Smirnov test to study the significance of difference between the mean values of all the parameters and the results are as shown in Table 3. It is evident that the variables in the data didn't follow a normal distribution pattern. This may be due to the small sample size. The data was therefore analysed using nonparametric methods. The Kruskal-Wallis test was performed for comparing the variables in the three study groups and results are shown in Table 4. The p values

Profile	HIV+ve on ART(n=25)	HIV+ve ART Naive(n=25)	Controls (n=25)
Mean age	43.2 \pm 11.9	45.6 \pm 12.3	41.1 \pm 11.4
Sex	Male: 17, Female: 08	Male: 14, Female: 11	Male: 15, Female: 10
Duration of HIV infection in yrs	9	4.48	--
Mean CD4 cells/ μ l	370	546	--
Symptoms	3	2	--

Table 1: Profile of patients.

Variable	HIV+ve on ART(n=25)	HIV+ve ART Naive(n=25)	Controls(n=25)
Mean HR bpm	78.9 ± 10.4	80.60 ± 17.55	67.04 ± 11.15
Mean respiratory sinus arrhythmia index	0.30 ± 0.63	0.18 ± 0.12	0.29 ± 0.11
Expiration to inspiration ratio	1.40 ± 1.20	1.18 ± 0.14	1.29 ± 0.13
30:15 ratio	1.09 ± 0.16	1.05 ± 0.14	1.24 ± 0.18
Mean valsalva ratio	3.85	3.94	1.57
Mean fall in Systolic BP	1.16 ±	7 ± 7.51	2.76 ± 7.66
Mean fall in diastolic BP	12.68 ± 6.89	12.44 ± 10.6	5.63 ± 9.3

Table 2: Results of cardiac autonomic tests.

Group	RSA	RHR	E:I ratio	30:15 Ratio	VR	Systolic fall	Diastolic increase
HIV patients on ART	0.000 ^c	0.200 ^{c,d}	0.000 ^c	0.002 ^c	0.000 ^c	0.200 ^{c,d}	0.077 ^c
HIV patients naive to ART	0.134 ^c	0.033 ^c	0.200 ^{c,d}	0.200 ^{c,d}	0.000 ^c	0.200 ^{c,d}	0.137 ^c
Control population	0.200 ^{c,d}	0.200 ^{c,d}	0.200 ^{c,d}	0.200 ^{c,d}	0.000 ^c	0.015 ^c	0.200 ^{c,d}

Table 3: One-sample Kolmogorov-Smirnov Test-Asymp. Sig. (2-tailed).

Group	Mean Rank
RHR	1 45.20
	2 43.14
	3 25.66
RSA	1 30.28
	2 32.12
	3 51.60
E:I ratio	1 32.60
	2 31.28
	3 50.12
30:15 Ratio	1 32.16
	2 29.50
	3 52.34
VR	1 33.78
	2 40.68
	3 39.54
Systolic fall	1 31.14
	2 47.44
	3 35.42
Diastolic increase	1 43.08
	2 43.46
	3 27.46

Table 4: Study of all the variables in three groups using Kruskal Wallis test.

of all dependent variables were less than 0.05 except for Valsalva ratio. So there was a significant difference between the autonomic parameters in the control population as compared to that of PLHA. However there was no difference between those on ART and not on ART. On testing for parasympathetic function, the resting heart rate was significantly higher in HIV infected groups compared to that of the controls, who had a lower value. Respiratory sinus arrhythmia, expiration to inspiration ratio, 30:15 ratio in response to standing in the controls was higher when compared to PLHA. On testing for sympathetic response, there was no notable difference between the median values of fall in systolic blood pressure between PLHA and control population.

Mann-Whitney U test was performed to look for differences in autonomic response amongst PLHA on ART and those not on ART. The test showed a significant difference in fall in systolic blood pressure between the PLHA on ART and not on ART, however there was no significant difference in other autonomic parameters.

Discussion

This study was a cross sectional observational study for comparing

the prevalence of cardiac autonomic dysfunction among HIV infected patients on ART, and those not on ART and in the HIV negative healthy individuals. Autonomic dysfunction in PLHA was brought to attention by Craddock et al. [8] in 1987 when they noticed sudden cardiac arrest following lung needle aspiration. Literature search revealed very few studies from India. The prevalence of autonomic nervous system symptoms in our study is 12% among people on ART and 10% in patients not on ART. Relevance of autonomic nervous system derangement is 28% among people with ART and 24% patients not on ART. Parasympathetic nervous system was more commonly than sympathetic nervous system and it was more common in patients on ART. The symptomatic subjects in the study were significantly less compared to that of study done by Robinson et al. [9] who observed that the that symptoms of orthostatic intolerance were higher in HIV infected patients. The resting heart rate of the HIV infected subjects were higher than that of HIV negative controls.

The higher resting heart rate may have been due to impaired parasympathetic activity rather than increased sympathetic activity as resting heart rate is predominantly regulated by the parasympathetic nervous system.

These finding point to impaired parasympathetic activity in HIV+ve vis - a- vis HIV-ve subjects. This has been shown in other studies also [10], Using heart rate variability, Lebech et al. [11] demonstrated that cardiac autonomic dysfunction gradually occurs with HIV disease progression. A study on African subjects found that a significant difference between the groups for the Valsalva test and blood pressure but did not show any significant difference in heart rate variability test. In this study, significant difference in resting heart rate, and heart rate response to deep breathing, standing, valsalva maneuver was observed along with rise in diastolic blood pressure after sustained hand grip amongst those who were on ART and those were not on ART. However the median fall in systolic blood pressure was higher in patients who were ART naive compared to patients on ART. Similar results were shown by Dominic chow et al. [12]. which may suggest that ART doesn't contribute to short term changes in autonomic function. Probably a larger sample size and a larger follow on ART may be required to conclusively comment on the effect of ART on autonomic function. Autonomic dysfunction in PLHA assumes great relevance in the Indian setting due to high prevalence of TB co infection &thence adrenal involvement.

Conclusion

This study shows that deterioration of parasympathetic function is more common than sympathetic function decline in HIV infected subjects as compared to normal population. In the late stages of HIV

infection, screening for autonomic dysfunction may be advisable before diagnosis of adrenal suppression in PLHA people. The effect of ART on autonomic dysfunction in PLHA requires more studies.

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