

Evaluation of Cardiac Autonomic Dysfunction in Human Immunodeficiency Virus Infection and its Correlation with CD4 Levels

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Abstract

Introduction: The occurrence of autonomic dysfunction in human immunodeficiency virus (HIV) patients impacts their health care in several ways. Extra precaution is needed during invasive surgical procedures are to be done. Whether dys-autonomia is related to severity of HIV disease is still a matter of controversy.

Materials and Methods: This was a prospective, hospital-based study. 50 patients (25 HIV without AIDS and 25 HIV with AIDS) and 50 healthy age- and sex-matched controls were enrolled. Autonomic function was assessed by the following autonomic function tests. (1) Systolic blood pressure (BP) response to standing, (2) Diastolic BP response to the persistent handgrip, (3) Heart rate response to standing, (4) Heart rate response to Valsalva maneuver - Valsalva ratio, and (5) Heart rate variation to deep breathing. Grading was given for each autonomic function test. Results were classified into normal, borderline, and abnormal (scored 0.1 and 2, respectively).

Results: Mean age of patients in the study group was 35.08 ± 8.2 years and that of the control group was 35.12 ± 8.6 years. The majority of patients were in the age group of 26-35 years. Total number of males was 42 (84%) and females 8 (16%). 30% of HIV with AIDS had autonomic dysfunction and 12% of HIV without AIDS had an abnormal autonomic function. Abnormal Valsalva response was present in 60% of HIV with AIDS and in 40% of HIV without AIDS. Abnormal diastolic BP response to sustained handgrip was present in 36% of HIV with AIDS and in 20% of HIV without AIDS. Abnormal heart rate response to deep breathing was present in 48% of HIV with AIDS and in 36% of HIV without AIDS.

Conclusions: There was significant autonomic nervous system dysfunction in both HIV without AIDS and HIV with AIDS. Reduced heart rate variability was the most common manifestation of autonomic dysfunction noted in both HIV groups.

Key words: Autonomic dysfunction, Cardiac dysfunction, CD4 counts, Human immunodeficiency virus

INTRODUCTION

Human immunodeficiency virus (HIV) involves all organ systems including the nervous system. In addition to the central nervous system and peripheral nervous system, the autonomic nervous system can also be involved which has several implications in health care of HIV patients.¹ In the presence of autonomic neuropathy, additional precautions

have to be taken when invasive procedures are performed on HIV patients. Some of the antiretroviral drugs are also capable of causing autonomic neuropathy and hence presence or absence of preexisting neuropathy poses a problem in therapy also. Early detection of autonomic dysfunction helps in rehabilitation of HIV patients. Some of the changes appear to reverse on antiretroviral treatment (ART).²

Autonomic dysfunction occurs more frequently and with greater severity in patients with AIDS. However, it may be present in the early stages of HIV infection and appears to progress during the illness.³

In one of the earliest studies on this topic, Ronstadt *et al.* examined autonomic function in HIV patients at various

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stages of infection. They found evidence of substantial impairment with worsening as HIV progressed. Various studies have reported the prevalence of autonomic nervous system dysfunction from 4% to 76.5%.

There is scanty literature on autonomic effects of HIV infection in Indian patients; hence, this study was being taken up to address question of HIV and autonomic dysfunction in the Indian scenario.⁴

Aim of the Study

To evaluate the presence and extent of autonomic dysfunction in HIV/AIDS patients and to correlate autonomic neuropathy with levels of CD4.

MATERIALS AND METHODS

About 50 HIV-infected patients both outpatient and inpatient (25 without AIDS and 25 with AIDS) of both sexes aged between 15 years and 65 years were enrolled. 50 healthy age- and sex-matched healthy volunteers were recruited as controls. The study was carried out at JSS Medical College Hospital Mysuru, South India, between October 2007 and August 2009 (2 years). The Ethical Committee clearance was obtained from the JSS Institutional Ethical Committee. Informed written consent was obtained from all the all patients were evaluated according to a detailed proforma. Symptoms and signs of autonomic dysfunction were analyzed.

Inclusion Criteria

Patients with HIV infection patients of both sexes aged between 15 years and 65 years.

Exclusion Criteria

1. Patients with cardiovascular disease
2. Patients with uremia, diabetes mellitus, and severe anemia
3. Patients who were very ill
4. Patients with a history of current and chronic alcohol abuse.

Cardiac Autonomic Function was Tested by Various Maneuvers as Follows

Heart rate variation to Valsalva maneuver

The test was performed by asking the patient to blow through the tubing of the mercury manometer up to 40 mm Hg and to maintain mercury column at that level by blowing for 15 s. Continuous ECG was recorded during the procedure and fifteen seconds after the release of pressure.

The ratio of longest R-R interval after manoeuvre to the shortest interval during maneuver was measured and expressed as Valsalva ratio. A ratio of 1.21 or greater was taken as normal (no autonomic dysfunction). A ratio

of 1.11-1.20 as borderline and 1.10 or less as abnormal (autonomic dysfunction present).

Heart rate response to deep breathing

The subject was asked to breathe deeply and evenly at 6 breaths per minute, taking 5 s for inspiration and 5 s for expiration. ECG was continuously recorded. The longest and shortest R-R intervals during expiration and inspiration were measured and corresponding heart rates calculated. The difference between the maximum and minimum heart rates was calculated. A difference of more than 15 beats per minute was labeled as normal (no autonomic dysfunction) 11-15 beats per minute as borderline dysfunction. 10 beats per minute was considered as abnormal (autonomic dysfunction present).

Heart rate response on assuming standing posture from lying position

The ratio of the longest R-R interval to the shortest R-R interval after the patient moved quickly from supine to upright posture. The ratio of 1.04 or greater was taken as normal (no autonomic dysfunction). 1.01-1.03 as borderline and 1 or less as abnormal (autonomic dysfunction present).

Blood pressure (BP) response to standing up

BP response to standing up was performed by measuring the BP while the subject was lying quietly and then by making the patient to stand up and recording the BP after 3 min. A difference in systolic BP of <10 mm of Hg after patient standing up was taken as no autonomic dysfunction (normal). A fall of 11-29 mm of Hg as borderline dysfunction and a fall of more than 30 mm of Hg as abnormal (autonomic dysfunction present).

BP response to sustained handgrip

Two sphygmomanometers were used. The cuff of one was inflated to 10 mm of Hg then patient/subject was asked to compress the cuff with his hand was asked to maintain pressure for 3 min. BP was recorded with the other sphygmomanometer at the beginning and at the end. A rise of diastolic pressure at the end of procedure more than 16 mm of Hg was taken as no autonomic dysfunction (normal). A value of 11-15 mm as borderline and a reading of <10 mm of Hg as abnormal (autonomic dysfunction present).

For grading of cardiovascular autonomic function, results were classified as normal (no autonomic dysfunction), borderline, and abnormal (scored 0, 1, and 2, respectively). An overall score ≤ 3 considered to indicate normal autonomic function. Scores >3 and <8 were considered borderline and scores ≥ 8 were judged abnormal (autonomic dysfunction present).

CD4 count was done for all the patients and controls by flow cytometry.

Statistical Methods

The descriptive procedure was used to display univariate summary statistics for several variables in a single table and to calculate standardized values (z-scores).

The Independent-Samples “t” test was used to compare means for two groups of cases. All the statistical methods were carried out through the SPSS for Windows (version 16.0).

RESULTS

Mean age of patients in the study group was 35.08 ± 8.2 years and that of the control group was 35.12 ± 8.6 years. The majority of patients were in the age group of 26-35 years. Total number of males was 42% and females 8%. Male:female ratio was 8.4:1.6. The majority of the patients in the HIV without AIDS group had CD4 counts of above 500 cells/mm³ and the majority of the HIV with AIDS patients had CD4 counts in the range of 101-200 cells/mm³.

On analysis of heart rate response to standing between HIV with AIDS and HIV without AIDS group and control group, it was seen that there was a significant difference between HIV/AIDS patients group and control group (P = 0.002) (Table 1).

Analysis of Valsalva ratio in HIV without AIDS/HIV with AIDS and controls revealed that here was a significant difference between HIV/AIDS group and control group (P = 0.000) (Table 2).

Analysis of heart rate response to deep breathing between HIV without AIDS/HIV with AIDS and control group revealed that there was significant differences between HIV/AIDS patients group and control group (P = 0.000) (Table 3).

Analysis of systolic bp response to standing between HIV positive/AIDS and control group revealed that here was significant differences between HIV/AIDS patients group and control group (P < 0.00) (Table 4).

Analysis of diastolic bp response to sustained handgrip between HIV/AIDS and control group revealed significant differences between HIV/AIDS patients group and control group (P = 0.000) (Tables 5 and 6).

Autonomic function tests were abnormal in 8 (32%) HIV with AIDS patients but in only 3 (12%) HIV without

Table 1: Heart rate response to standing: HIV with AIDS and HIV without AIDS group and control group

Heart rate response to standing	HIV without AIDS (%)	HIV with AIDS (%)	Control (%)	Total (%)
Normal	13 (52.0)	15 (60.0)	44 (88.0)	72 (72.0)
Border line	9 (36.0)	5 (20.0)	6 (12.0)	20 (20.0)
AB normal	3 (12.0)	5 (20.0)	-	8 (8.0)
Total	25 (100.0)	25 (100.0)	50 (100.0)	100 (100.0)

P=0.002, HIV: Human immunodeficiency virus

Table 2: Valsalva ratio in HIV without AIDS/HIV with AIDS and controls

Valsalva ratio	HIV positive without AIDS (%)	Hiv positive +ve with AIDS (%)	Control (%)	Total (%)
Normal	6 (24.0)	5 (20.0)	40 (80.0)	51 (51.0)
Border line	9 (36.0)	5 (20.0)	10 (20.0)	24 (24.0)
AB normal	10 (40.0)	15 (60.0)	-	25 (25.0)
Total	25 (100.0)	25 (100.0)	50 (100.0)	100 (100.0)

P=0.000, HIV: Human immunodeficiency virus

Table 3: Analysis of heart rate response to deep breathing between HIV without AIDS/HIV with AIDS and control group

Heart rate response to deep breathing	HIV without AIDS (%)	HIV with AIDS (%)	Control (%)	Total (%)
Normal	10 (40.0)	8 (32.0)	40 (80.0)	58 (58.0)
Border line	6 (24.0)	5 (20.0)	4 (8.0)	15 (15.0)
Abnormal	9 (36.0)	12 (48.0)	6 (12.0)	27 (27.0)
Total	25 (100.0)	25 (100.0)	50 (100.0)	100 (100.0)

P=0.000, HIV: Human immunodeficiency virus

Table 4: Analysis of systolic BP response to standing between HIV positive/AIDS and control group

Systolic BP response to standing	HIV without AIDS (%)	HIV with AIDS (%)	Control (%)	Total (%)
Normal	21 (84.0)	8 (32.0)	46 (92.0)	75 (75.0)
Border Line	4 (16.0)	12 (48.0)	4 (8.0)	20 (20.0)
Abnormal	-	5 (20.0)	-	5 (5.0)
Total	25 (100.0)	25 (100.0)	50 (100.0)	100 (100.0)

P=0.000, BP: Blood pressure, HIV: Human immunodeficiency virus

Table 5: The analysis of diastolic BP response to sustained handgrip between HIV without AIDS, HIV with AIDS and control group

Diastolic BP response to sustained handgrip	HIV with AIDS (%)	HIV with AIDS (%)	Control (%)	Total (%)
Normal	9 (36.0)	3 (12.0)	43 (86.0)	55 (55.0)
Border line	11 (44.0)	13 (52.0)	7 (14.0)	31 (31.0)
Abnormal	5 (20.0)	9 (36.0)	-	14 (14.0)
Total	25 (100.0)	25 (100.0)	50 (100.0)	100 (100.0)

BP: Blood pressure, P=0.000, HIV: Human immunodeficiency virus

AIDS patients. None of the controls had abnormal function. Only 2 (8%) of 25 HIV with AIDS patients had a completely normal autonomic function. More than 55% of HIV-infected patients had borderline results. The results were statistically significant ($P = 0.000$) (Tables 7-9).

33.3% of those with CD4 counts between 201 and 400 had autonomic dysfunction.

Only 9.1% of those with CD4 counts between 401 and 600 had autonomic dysfunction.

35.3% of those with CD4 counts <200 had autonomic dysfunction. 20% of those with CD4 count between 201 and 400 CD4 had autonomic dysfunction. 50% of those with CD4 count between 401 and 600 CD4 level had autonomic dysfunction. The differences were not statistically significant $P = 0.866$ (Table 10).

In the HIV with AIDS on ART group, 57.1% had abnormal results, whereas only 22.2% of patients in the HIV with AIDS not on ART group had abnormal results. Antiretroviral therapy did not have a significant effect on autonomic function tests results ($P = 0.204$) (Table 11).

Analysis of autonomic function test results in HIV with AIDS and HIV with AIDS with opportunistic infections revealed that whereas 29.4% of patients in the former had abnormal results 37.5% of patients in the latter group had abnormal results. The presence of opportunistic

infection did not have significant effect on autonomic function ($P = 0.587$)

DISCUSSION

About 50 HIV/AIDS patients were studied to evaluate the presence and extent of autonomic dysfunction and to correlate autonomic neuropathy with levels of CD4.

The results and observation of the present study are compared and discussed with other studies as follows.

The occurrence of autonomic dysfunction in HIV with AIDS group and HIV without AIDS group was 32% and 12%, respectively. The results correlate with study done by Nzuobontane *et al.*⁵ and Rogdstadt *et al.*⁶

In the present study, age range of the study group was 19-60 years with mean age of 35.16 ± 9.17 years and age range of control group was 20-58 years with mean age of 35.0 ± 8.69 years. Rogdstadt *et al.*⁶ observed age range of 26-58 years with mean age of 38 years for study group and age range of 26-60 years with a median age of 38.12 years for the control group. The findings in our study group correlate with the above studies.

The present study showed higher preponderance in males which is consistent with results seen in previous studies.

In the present study, 34% of cases had CD4 count <200. 22% of cases had CD4 count 201-400 range, 26% of cases had CD4 range of 401-600 range, and 18% had >600 CD4, which is consistent with the study of Becker *et al.*, wherein maximum number of patients had CD4 count below 200.

Resting Heart Rate

In the present study, resting heart rate of more than 100 beats/min was found in 28% of HIV-positive group and 56% of AIDS group indicating resting tachycardia due to unopposed cardiac sympathetic activity. This is consistent with the study of Becker *et al.*,⁷ wherein resting heart rate was higher in HIV-infected group than in healthy subjects

Table 6: Frequency distribution of normal borderline, abnormal autonomic function between HIV without AIDS, HIV with aids and control group

Result	HIV without AIDS (%)	HIV with AIDS (%)	Control (%)	Total (%)
Normal	8 (32.0)	2 (8.0)	45 (90.0)	55 (55.0)
Border line	14 (56.0)	15 (60.0)	5 (10.0)	34 (34.0)
Abnormal	3 (12.0)	8 (32.0)	-	11 (11.0)
Total	25 (100.0)	25 (100.0)	50 (100.0)	100 (100.0)

$P=0.000$, HIV: Human immunodeficiency virus

Table 7: Comparative study of abnormal autonomic function between HIV without AIDS group and HIV with AIDS group

Autonomic function test	HIV with AIDS (%)			HIV without AIDS (%)			P value
	Normal	Borderline	Abnormal	Normal	Borderline	Abnormal	
Valsalva	5 (20)	5 (20)	15 (60)	6 (24)	9 (36)	10 (40)	NS
Heart rate response to standing	15 (60)	5 (20)	5 (20)	13 (52)	9 (36)	3 (12)	NS
Heart rate response to deep breathing	8 (32)	5 (20)	12 (48)	10 (40)	6 (24)	9 (36)	NS
Systolic fall in blood pressure on standing	8 (32)	12 (48)	5 (20)	21 (84)	4 (16)	0	<0.007
Diastolic blood pressure rise on sustained handgrip	3 (12)	13 (52)	9 (36)	9 (36)	11 (44)	5 (20)	NS

NS: Non significant, HIV: Human immunodeficiency virus

Table 8: The correlation of CD4 cell count with autonomic dysfunction in HIV without AIDS group

Result	CD4 cell count (%)			
	<200	201-400	401-600	600+
Normal	-	-	3 (27.3)	5 (62.5)
Border line	-	4 (66.7)	7 (63.6)	3 (37.5)
AB normal	-	2 (33.3)	1 (9.1)	-

The results were not statistically significant. $P=0.079$, HIV: Human immunodeficiency virus

Table 9: The correlation of CD4 cell count with autonomic dysfunction in HIV with AIDS group

Result	CD4 cell count (%)			
	<200	201-400	401-600	600+
Normal (no autonomic dysfunction)	2 (11.8)	-	-	-
Border line autonomic D	9 (52.9)	4 (80)	1 (50)	1 (100)
Abnormal	6 (35.3)	1 (20)	1 (50)	-

HIV: Human immunodeficiency virus

Table 10: Correlation of effect of antiretroviral therapy with autonomic dysfunction in HIV with AIDS patients

Result	AIDS (%)		Total (%)
	AIDS without ART (%)	AIDS with ART (%)	
Normal	2 (11.1)	-	2 (8.0)
Border line	12 (66.7)	3 (42.9)	15 (60.0)
Abnormal	4 (22.2)	4 (57.1)	8 (32.0)
Total	18 (100.0)	7 (100.0)	25 (100.0)

$P=0.204$, ART: Antiretroviral treatment, HIV: Human immunodeficiency virus

Table 11: Effect of opportunistic infections with autonomic dysfunction in aids patients

Result	AIDS (%)		Total (%)
	AIDS without opportunistic infections	AIDS with opportunistic infections	
Normal	2 (11.8)	-	2 (8.0)
Border line	10 (58.8)	5 (62.5)	15 (60.0)
Abnormal	5 (29.4)	3 (37.5)	8 (32.0)
Total	17 (100.0)	8 (100.0)	25 (100.0)

$P=0.587$

although it did not differ among pre-AIDS and AIDS patients.

Analysis of the results reveals that heart rate variability is reduced in HIV-seropositive individuals in early stages of infection without AIDS.

Similar observation was made in the study by Mittal *et al.*⁸ They showed that heart rate variability was decreased in patients with HIV infection without AIDS and that incipient autonomic dysfunction was present even early in the course of HIV

infection. This was in contrast to the earlier study by Becker *et al.*⁷ where it was reported that cardiac autonomic nervous system dysfunction was not significant in pre-AIDS patients.

HIV patients without AIDS did not have any HRV parameters significantly different from healthy controls ($P > 0.017$), whereas HIV with AIDS patients demonstrated reduced HRV in 14 parameters ($P = 0.0341$). The study by Becker demonstrated that HIV with AIDS patients exhibits a high degree of cardiac autonomic nervous dysfunction, whereas HIV-infected subjects have an intermediate position between HIV negative and AIDS.⁹

The results of our study are different from the study by Becker *et al.*⁷ and the reasons for the same may be the faster progression of HIV infection and difference in subtype of HIV stain in an Indian setting.

Results of the present study suggest that autonomic dysfunction occurs in cases of AIDS and also in the early course of HIV infection. Similar observations were made in the study done by Nzuobontane *et al.*⁵ Rogstad *et al.*⁶ and Becker *et al.*⁷ The presence of abnormalities of various autonomic function test in present study is compared with studies of Nzuobontane *et al.*⁵ Most of the autonomic function tests were abnormal in present study, and the findings are similar to those reported by Nzuobontane *et al.*⁵

This study adopted a cross-sectional design and criteria for the diagnosis of autonomic dysfunction which was similar to the study by Nzubontane *et al.*⁵ However, this study did show significant differences in BP and heart rate tests, whereas they found only clear differences for BP tests. Probably, the divergence of results is related to differences in sample size, patient selection, fast progression of HIV infection, and difference in subtype of HIV strain in Indian setting.¹⁰

In the present study, 32% of patients of HIV with AIDS showed abnormal results which are comparable to the results of Nzuobontane *et al.*⁵ (27% AIDS) while it was less in the study of Rogstad *et al.*⁶ (20% AIDS). In the study, 12% of subjects of HIV without AIDS showed abnormal results which are comparable the study of Rogstad *et al.*⁶ (14% of HIV without AIDS) while it was less in the study of Nzubontane *et al.*⁵ (4.2% of HIV without AIDS). If borderline results are considered over 60-80% of HIV/AIDS patients did not have normal results.

In HIV-infected patients, simple tests such as BP responses to standing or handgrip can warn of cardiovascular autonomic dysfunction thus signaling the need for added precautions when invasive procedure are proposed.¹¹

The mean CD4 count range of the present study is higher than seen in the other studies. In our study, autonomic dysfunction occurred at a wide range of CD4 cell count. However, more number of abnormal results was found below 200 CD4 range and more number of normal results found in 600 CD4 counts 600 and above range. Although, results are statistically insignificant. *P* value - HIV without AIDS = 0.079 HIV with AIDS = 0.866.

In the present study as opposed to earlier other studies, we have included AIDS patients with opportunistic infections and those who were on ART to ascertain if the presence of opportunistic infection of ART had any effect on autonomic function.

37% of HIV with AIDS showed abnormal results, whereas HIV without AIDS patients showed 30% abnormal results. However, these results were statistically not significant (*P* = 0.587). Hence, it is concluded that the presence of opportunistic infection does not have any significant effects on autonomic function. Similarly, there was no statistically significant difference in prevalence of autonomic dysfunction between patients of HIV with AIDS who were on ART and HIV with AIDS without ART (*P* = 0.204).

CONCLUSION

It is concluded that there is significant autonomic nervous system dysfunction in both HIV without AIDS and HIV with AIDS. Reduced heart rate variability was found

to be the most common manifestation of autonomic dysfunction in both. There was no correlation between the CD4 level and the presence of autonomic nervous system dysfunction. Larger studies are needed to confirm the findings of this study.

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