

CLINICAL STUDY OF CARDIAC AUTONOMIC DYSFUNCTION IN HIV PATIENTSH. Mallikarjun Swamy¹, S. R. Chandrashekar Patil², Sunil Gayad³**HOW TO CITE THIS ARTICLE:**

H. Mallikarjun Swamy, S. R. Chandrashekar Patil, Sunil Gayad. "Clinical Study of Cardiac Autonomic Dysfunction in HIV Patients". Journal of Evolution of Medical and Dental Sciences 2014; Vol. 3, Issue 46, September 22; Page: 11146-11159, DOI: 10.14260/jemds/2014/3454

ABSTRACT: BACKGROUND AND OBJECTIVES: Cardiovascular autonomic nervous dysfunction has been demonstrated to severely debilitate HIV infected patients, namely by postural hypotension and syncope. It has important implications in health care of HIV patients. **METHODS:** 50 patients (25 HIV +ve without AIDS and 25 HIV+ with AIDS) who fulfilled the inclusion and exclusion criteria and 50 healthy matched controls were enrolled in the study. Autonomic function was assessed by batteries of autonomic function tests. **RESULTS:** In the present study 16% of HIV +ve with the AIDS had abnormal autonomic dysfunction and 4% of HIV positive without AIDS had abnormal autonomic dysfunction. Abnormalities in autonomic function occurred at all levels of CD4 counts. More number of abnormal results was found below 200 CD4 range. But the difference was not statistically significant. **CONCLUSION:** Cardiac autonomic nervous dysfunction is a common and relevant clinical problem. It is significantly affected in both HIV positive without AIDS and HIV positive with AIDS groups. It may provide an alternative explanation for symptoms commonly observed in HIV infected individuals such as bowel and bladder dysfunction, impotence, syncope and sweating abnormalities.

KEYWORDS: HIV, AIDS, Autonomic Dysfunction, valsalva manoeuvre, heart rate.

INTRODUCTION: AIDS, (Acquired Immuno Deficiency Syndrome) is a fatal illness caused by a retrovirus known as Human Immunodeficiency virus (HIV) which breaks down the immune system, leaving the victim vulnerable to a host of opportunistic infections many of which are life threatening, neurological disorders, and unusual malignancies.¹

HIV involves almost all major organ systems including CNS. In addition to CNS and PNS, ANS also be involved. Autonomic nervous dysfunction has important implications in health care of HIV patients. It impairs the quality of life and can have fatal consequences.^{2,3} Because HIV affects various organ systems invasive procedures are often needed for diagnostic and therapeutic purposes. In late stages of HIV infection screening for autonomic dysfunction may be advisable before invasive procedures such as pericardiocentesis because of risk of cardiovascular collapse or sudden death.

Syncopal reactions have been reported in HIV patients with abnormal autonomic function during invasive procedure. It may identify HIV infected patients with particular risk beyond their immunological deterioration and thereby contribute to risk stratification.^{4,5} There is scanty literature on autonomic effects of HIV infection in Indian patients hence this study is being taken up to address question of cardiac autonomic dysfunction in the Indian scenario.

MATERIALS AND METHODS: SOURCE OF DATA: Patients admitted to Medical wards KIMS Hospital, Hubli, with HIV infection diagnosed as per NACO guidelines will be taken for study considering the inclusion and exclusion criteria.

INCLUSION CRITERIA:

- HIV infection diagnosed as per NACO guidelines.

EXCLUSION CRITERIA:

- H/o cardiovascular disease before testing.
- Very ill patients who are unable to perform the autonomic test manoeuvres.
- Patients with diabetes mellitus.
- Patients on Antiretroviral Therapy.
- Known alcoholics

CARDIAC AUTONOMIC DYSFUNCTION WAS TESTED BY VARIOUS MANOEURES AS FOLLOWS:

HEART RATE VARIATION TO VALSALVA MANOEUVRE: The test was performed by asking the patient to sit quietly and then to blow through mercury manometer up to 40mm Hg. and to maintain mercury column at that level by controlled blowing into mouthpiece connected to the manometer for 15 seconds, continuous ECG was recorded during the procedure and fifteen seconds after the release of pressure. This test was performed 3 times at 1 min interval. The ratio of longest R-R interval after the maneuver to shortest interval during maneuver was measured and the result was expressed as Valsalva ratio. A Valsalva ratio of 1.21 or greater was considered normal between 1.11 to 1.20 was borderline and 1.10 or less was taken as abnormal.

HEART RATE RESPONSE TO DEEP BREATHING: The subject sits quietly and breaths deeply and evenly at six breaths per minute, five seconds inspiration and five seconds expiration. ECG was continuously recorded during the procedure. The longest and shortest R-R intervals during expiration and inspiration were measured and corresponding heart rates calculated. The difference between maximum and minimum heart rates was calculated. A difference of more than 15 beats per minute was taken as normal. A difference of 11- 15 beats per minute was considered border line and difference of less than 10 beats per minute was considered as abnormal.

HEART RATE RESPONSE TO STANDING FROM SUPINE 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 was noted. The ratio of 1.04 or greater was considered normal between 1.01 to 1.03 was borderline and 1 or less taken as abnormal.

BLOOD PRESSURE RESPONSE TO STANDING UP: This test was performed by measuring the blood pressure while subject was in supine posture and later by making the patient to stand up and the blood pressure was recorded after 3 minutes. A difference in systolic blood pressure after patient stands up is less than 10 mm. of Hg. is considered normal and fall of 11 to 29 m. of Hg. taken as borderline and a fall of more than 30 mm. of Hg. taken as abnormal.

BLOOD PRESSURE RESPONSE TO SUSTAINED HANDGRIP: Here two sphygmomanometers were used. The cuff was inflated to 10 mm. of Hg. basal level kept at 10mm of Hg. Then patient was asked to compress the cuff to the maximum extent with the hand. The patient was asked to maintain pressure on the cuff at 30% of maximum effort for 3 minutes.

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The blood pressure was recorded at the beginning and at the end of the procedure. Normal rise of diastolic pressure at the end of procedure is more than 16 mm of Hg. A value between 11 to 15 mm is considered as borderline and a reading of less than 10 mm of Hg was taken as abnormal.

Sl. No.	Tests	Normal	Borderline	Abnormal
1.	Valsalva ratio	>1.21	1.11-1.20	<1.10
2.	HR to deep breathing	>15	11-14	<10
3.	HR to standing 30/15	>1.04	1.01-1.03	<1.00
4.	Blood pressure response to standing (Orthostatic hypotension)	<10 (mm.Hg)	11-29 (mm-Hg)	>30 (mm.Hg)
5.	Blood pressure response to sustained hand grip	>16 (mm.Hg)	11-15 (mm.Hg)	<10 (mm.Hg)

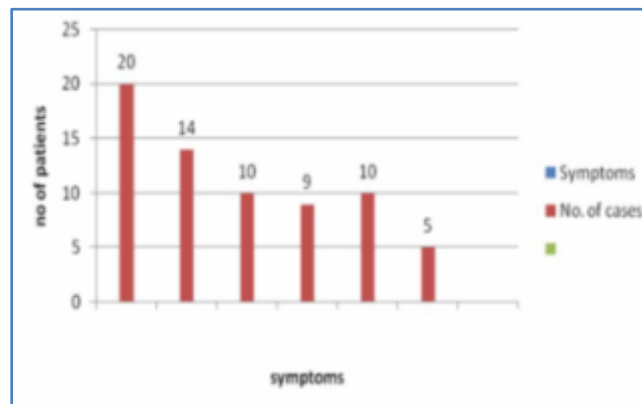
For grading of cardiovascular autonomic function, results were classified as normal, borderline, and abnormal (scored 0, 1 and 2 respectively). An overall score ≤ 3 considered to indicate normal autonomic function. Scores > 3 and < 8 were considered borderline and scores ≥ 8 were judged abnormal.

OBSERVATION:

COMMON MODE OF PRESENTATION AND SYMPTOMS OF THE PATIENTS.
DISTRIBUTION OF SUBJECTS BY CD4 COUNT.

CD4 count cells/ μ l	AIDS Patients	HIV+ve Patients
0-50	4	-
51-100	5	-
101-200	10	-
201-300	3	3
301-400	2	10
401-500	1	4
>500	0	8
Total	25	25

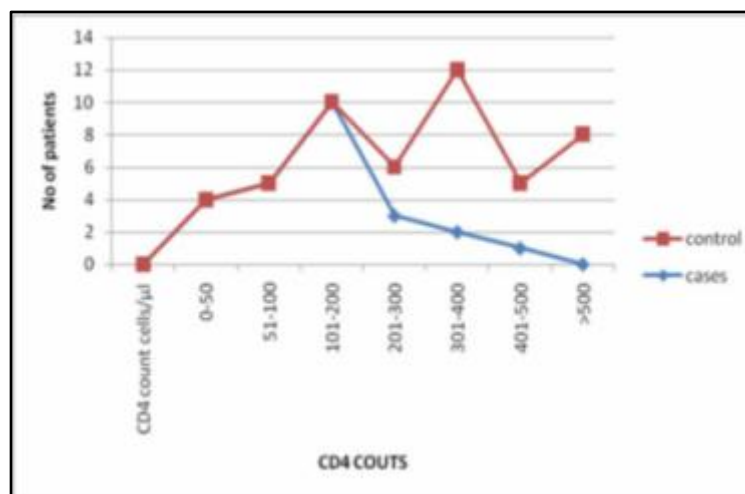
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The most common symptoms were dizziness and lower GI symptoms and least common were sexual disturbances.

DISTRIBUTION OF SUBJECTS BY CD4 COUNT

CD4 count cells/ μ l	AIDS Patients	HIV+ve Patients
0-50	4	-
51-100	5	-
101-200	10	-
201-300	3	3
301-400	2	10
401-500	1	4
>500	0	8
Total	25	25



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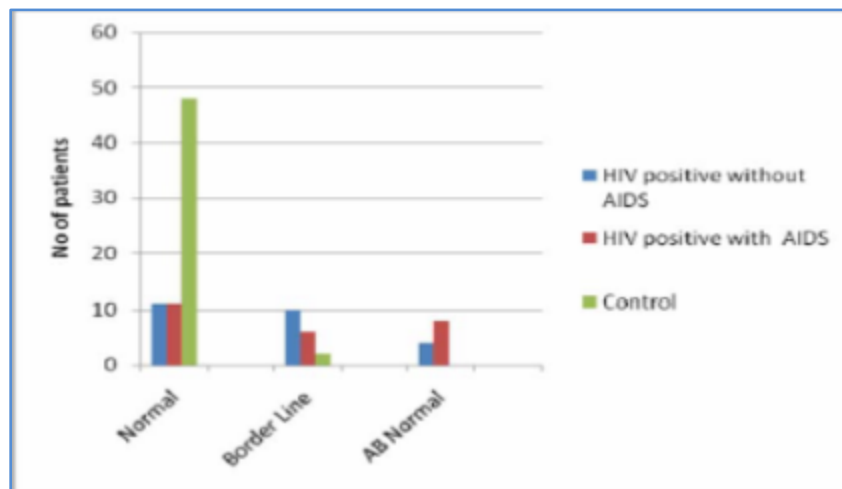
The present study showed majority of the AIDS patients had a CD4 range of 101-200 and majority of the HIV positive patients had a CD4 count in the range of 301-400.

SHOWING THE ANALYSIS OF HEART RATE RESPONSE TO STANDING BETWEEN HIV POSITIVE GROUP, AIDS GROUP AND CONTROL GROUP

Heart rate response to standing	HIV positive without AIDS	HIV positive with AIDS	Control	Total
Normal	11	11	48	70
	44.0%	44.0%	96.0%	70.0%
Border Line	10	6	2	18
	40.0%	24.0%	4.0%	18.0%
Abnormal	4	8		12
	16.0%	32.0%	0	12.0%
Total	25	25	50	100
	100.0%	100.0%	100.0%	100.0%

Chi-square-32.19, p value <0.001, Highly significant, df-1

Showing the analysis of heart rate response to standing between HIV positive group, AIDS group and control group



When the result of heart rate variation to standing was analyzed. It was found that there was significant differences between HIV/AIDS patients group and control group ($P = 0.000$).

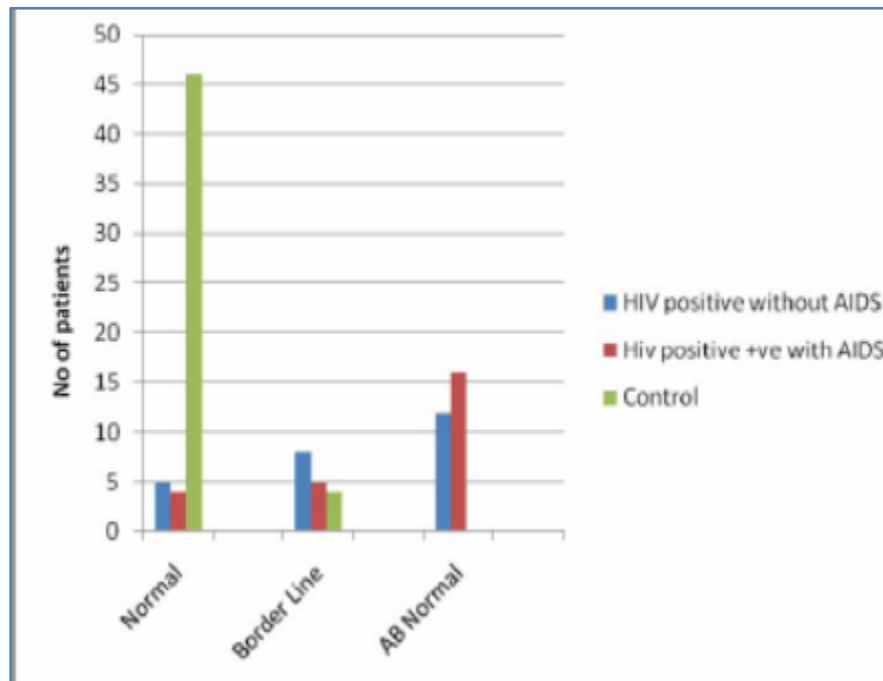
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Showing Analysis of valsalva ratio in HIV positive/aids group and Contro Group

Valsalva Ratio	HIV positive without AIDS	HIV positive +ve with AIDS	Control	Total
Normal	5	4	46	55
	20.0%	16.0%	92.0%	55.0%
Border Line	8	5	4	17
	32.0%	20.0%	8.0%	17%
AB Normal	12	16		28
	48.0%	64.0%		28.0%
Total	25	25	50	100
	100.0%	100.0%	100.0%	100.0%

Chi-square-55.31, p value-<0.001, Highly significant, df-1

Analysis of valsalva ratio in HIV positive/AIDS group and control group



When the results of valsalva ratio was analyzed it was found that there was significant difference between HIV/AIDS group and control group (p value <0.001).

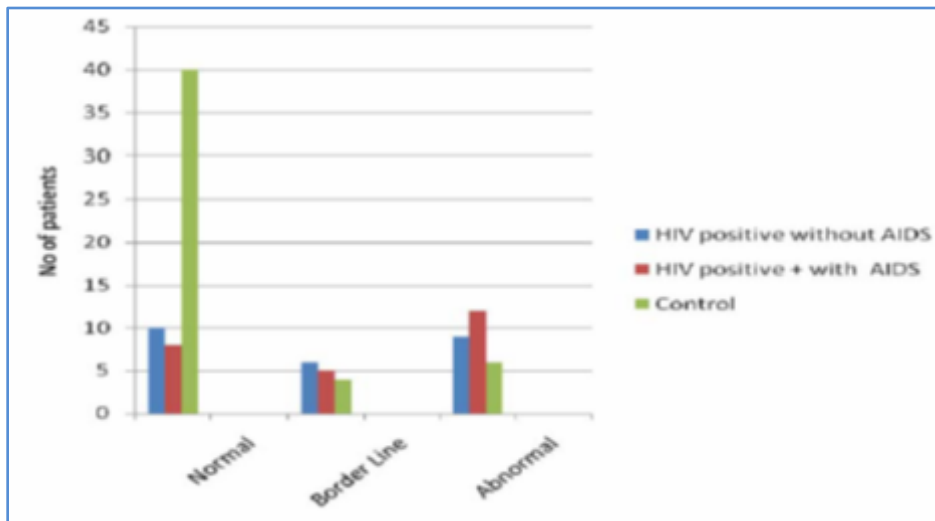
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Showing analysis of heart rate response to deep breathing between HIV positive/aids and control group.

Heart rate response to deep breathing	HIV positive without AIDS	HIV positive + with AIDS	Control	Total
Normal	9	5	46	60
	36.0%	20.0%	92.0%	60.0%
Border Line	6	6	2	14
	24.0%	24.0%	4.0%	14.0%
Abnormal	10	14	2	26
	40.0%	56.0%	4.0%	26.0%
Total	25	25	50	100
	100.0%	100.0%	100.0%	100.0%

Chi-square=42.04, p value-<0.001, Highly significant, df-1

Showing the analysis of heart rate response to deep breathing between HIV positive/AIDS in control group



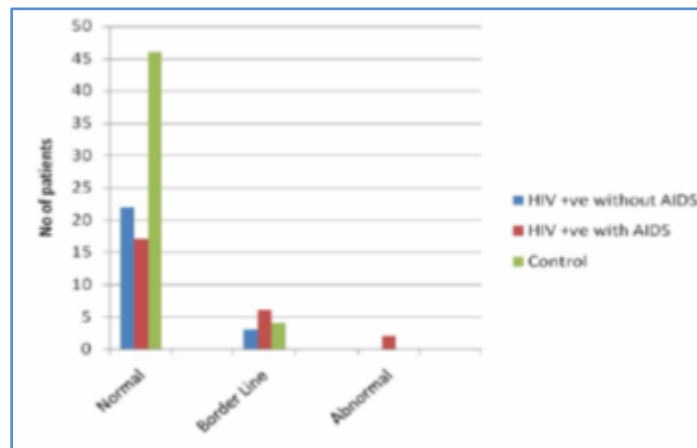
The results of heart rate response to deep breathing variation to standing were analyzed. It was found that there was significant differences between HIV/AIDS patients group and control group (P= 0.000) Showing the analysis of systolic BP response to standing between HIV positive/AIDS and control group.

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Systolic BP response to standing	HIV +ve without AIDS	HIV +ve with AIDS	Control	Total
Normal	22	17	46	85
	88%	68%	92%	85%
Border Line	3	6	4	13
	12%	24%	8.0%	13%
Abnormal	-	2	-	2
	-	8%	-	2.0%
Total	25	25	50	100
	100.0%	100.0%	100.0%	100.0%

By applying Fisher's Exact test p value <0.05, significant

Showing the analysis of systolic BP response to standing between HIV positive/AIDS and control group



When the results of systolic BP response to standing was analyzed. It was found that there was significant differences between HIV/AIDS patients group and control group ($P < 0.05$).

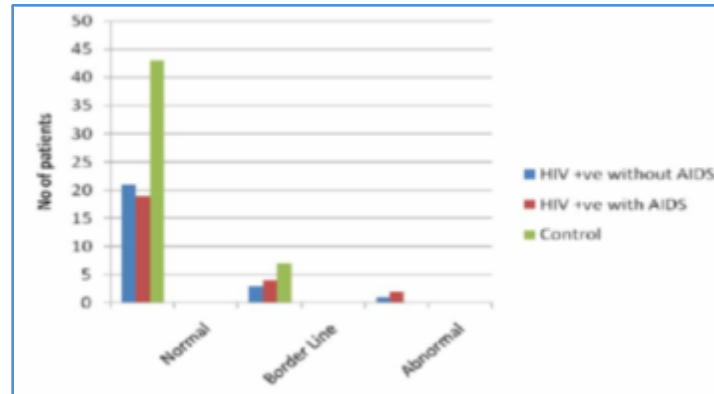
Showing the Analysis of Diastolic BP response to Sustained Hand Grip between HIV/AIDS and Control.

Diastolic BP response to sustained hand grip	HIV +ve without AIDS	HIV +ve with AIDS	Control	Total
Normal	21	19	44	55
	84%	76%	88%	55.0%
Border Line	3	4	6	31
	12%	16%	12%	31.0%
Abnormal	1	2	0	14
	4%	8%	0%	14.0%
Total	25	25	50	100
	100.0%	100.0%	100.0%	100.0%

Chi-square-1.19, p 0.05, not significant, df-1

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Showing the analysis of diastolic BP response to sustained hand grip between HIV/AIDS and control group



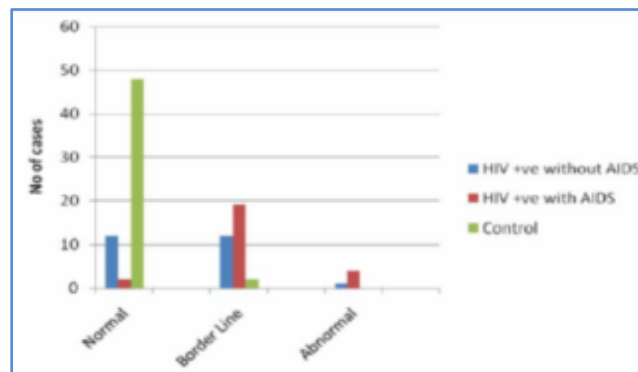
When the results of diastolic BP response to sustained handgrip was analyzed. It was found that there was no statistical differences between HIV/AIDS patients group and control group ($P > 0.05$).

SHOWING FREQUENCY DISTRIBUTION OF NORMAL BORDERLINE, ABNORMAL AUTONOMIC FUNCTION BETWEEN HIV POSITIVE, AIDS AND CONTROL GROUP

		HIV +ve without AIDS	HIV +ve with AIDS	Control	Total
RESULT	Normal	12	2	48	55
		48.0%	8.0%	96.0%	55.0%
	Border Line	12	19	2	34
		48.0%	76.0%	04.0%	34.0%
	Abnormal	1	4	-	11
		4.0%	16.0%	-	11.0%
Total		25	25	50	100
		100.0%	100.0%	100.0%	100.0%

p value = 0.000

Showing frequency distribution of normal borderline, abnormal autonomic function between HIV positive, AIDS and control group



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When the results of autonomic function tests was analyzed in HIV positive, AIDS and control group. It was found that autonomic function tests was abnormal in 4(16%), AIDS patients, but in only 1(4%) HIV positive patients without AIDS. None of the HIV negative patients had abnormal function. Only 2 (8%), of 25 AIDS patients had completely normal autonomic function. More than 45% of HIV infected patients and 76% of AIDS had borderline results. The results were statistically significant (p value.000).

COMPARATIVE STUDY OF ABNORMAL AUTONOMIC FUNCTION BETWEEN AIDS GROUP AND HIV POSITIVE GROUP

a) VALSALVA RATIO:

VALSALVA RATIO:	HIV +ve with AIDS	HIV +ve without AIDS
Normal	4	5
	16%	20%
Border Line	5	8
	20%	32%
Abnormal	16	12
	64%	48%
Total	25	25
	100.0%	100.0%

Fisher's Exact Test-p value>0.05,Not significant, df-1.

b) HEART RATE RESPONSE TO DEEP BREATHING

Heart rate response to deep breathing	HIV +ve with AIDS	HIV +ve without AIDS
Normal	5	9
	20%	36%
Border Line	6	6
	24%	24%
Abnormal	14	10
	56%	40%
Total	25	25
	100.0%	100.0%

Chi-square test-1.59,p value>0.05, Not significant, df -1.

c) HEART RATE RESPONSE TO STANDING

Heart rate response to standing	HIV +ve with AIDS	HIV +ve without AIDS
Normal	17	22
	68%	88%
Border Line	6	3
	24%	12%
Abnormal	2	0
	8%	0%
Total	25	25
	100.0%	100.0%

d) SYSTOLIC FALL IN BP ON STANDING

Systolic fall in BP on standing	HIV +ve with AIDS	HIV +ve without AIDS
Normal	17	22
	68%	88%
Border Line	6	3
	24%	12%
Abnormal	2	0
	8%	0%
Total	25	25
	100.0%	100.0%

Chi-square test-2.91;p value>0.05, Not significant,df-1.

e) DIASTOLIC RISE IN BP ON SUSTAINED HAND GRIP

Diastolic rise in BP on sustained hand grip	HIV +ve with AIDS	HIV +ve without AIDS
Normal	19	21
	76%	84%
Border Line	4	3
	16%	12%
Abnormal	2	1
	8%	4%
Total	25	25
	100.0%	100.0%

Chi-square test-0.5,p value>0.05;Not significant;df-1.

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When the results of abnormal autonomic function tests were analyzed there is no significant difference between AIDS group and HIV group. However the most pronounced abnormalities were found in patients with AIDS, but across groups there was a trend towards increasing autonomic dysfunction, from asymptomatic HIV disease to AIDS. This shows that dysfunction can occur at any stage of the disease.

SHOWING THE CORRELATION OF CD4 CELL COUNT WITH AUTONOMIC DYSFUNCTION.

		CD4 cell count				Total
		<200	201-400	401-600	600+	
RESULT	Normal	2	3	6	3	14
		10%	16.6%	100%	50%	28%
	Border Line	15	14	-	2	31
		75%	77.7%	-	33.3%	62%
	AB Normal	3	1	-	1	5
		15%	5.6%	-	16%	10%
Total		20	18	6	6	50

In the present study patients autonomic dysfunction occurred at wide range of CD4 cell count. However more number of abnormal results were found below 200 CD4 range and more number of normal results were found in CD4 Count range of 401-600.

DISCUSSION: It was observed in this study that there was evidence of substantial autonomic dysfunction in HIV and AIDS patients compared with controls. Incidence of cardiac autonomic nervous dysfunction increases with HIV disease progression.

HIV AND WITH AUTONOMIC NEUROPATHY: 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.⁶Early clinical features of autonomic dysfunction in HIV infected patients include syncope, pre syncope, diminished sweating, diarrhea, bladder dysfunction, impotence. Subclinical autonomic neuropathy has been found in up to 50% of HIV infected patients.

PATHOGENESIS OF THE AUTONOMIC NERVOUS SYSTEM:

DYSFUNCTION OF HIV INFECTIONS: HIV-1 enters the brain early in the course of the disease probably at the time of sero conversion. Entry is by way of blood borne infection and to a lesser extent by "spread" from chronic meningeal infection which in turn is likely related to low level infection of the choroid plexus.⁷Such low level infection is kept in check by a relatively intact immune system but as HIV-1 disease progresses, brain infection becomes unchecked and compensatory

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mechanisms are activated that result in the production of various cytokines that over a period of time lead to central nervous system dysfunction. Additionally, the low level brain infection is now capable of being amplified by the similarly unchecked systemic disease thereby accounting for the perivascular distribution.

The tissue damaged by the cytokines then becomes secondarily infected both by the now unchecked local brain infection and by the systemically circulating infected cells. Moreover, as HIV-1 disease advances there is a reduction in CD4 + cells and there is a selection towards macrophage tropic isolates of HIV-1 that further infect the brain: essentially the brain cells that are of macrophage lineage namely the microglial cells.^{8,9}

At the cellular level, the envelope glycoprotein of HIV-1 gp120 is toxic to rodent neurons and the neuronal killing is critically dependent upon the presence of cells of the macrophage lineage^{10,11}. Furthermore, the precise mechanism of neuronal damage is by way of activation of the N-methyl D-aspartate receptor with consequent influx into the cell of calcium and secondary synthesis of nitric oxide in those neurons containing nitric oxide synthetase.

Not only do macrophage lineage cells serve to facilitate neuronal damage but it appears that they release neuronotoxic factors as well. Some of these are as yet undefined, while others are arachidonic acid metabolites and platelet activating factor, that require cell-to-cell interactions for toxicity.^{12,13}

Peripheral nerves are also affected by the cytokines that are released by macrophage lineage cells in an attempt to control infection. Another possible mechanism is the documented methylation defect in HIV-1 infected individuals that may lead to changes similar to cyanocobalamin deficiency. The third possibility, namely direct infection of oligodendrocytes.¹⁴

CONCLUSION: Cardiac autonomic nervous dysfunction is a common and relevant clinical problem it is significantly affected in both HIV positive without AIDS and HIV positive with AIDS groups. It may provide an alternative explanation for symptoms commonly observed in HIV infected individuals such as bowel and bladder dysfunction, impotence, syncope and sweating abnormalities.

Reduced heart rate variability is the commonest manifestation of autonomic dysfunction noted in both HIV positive without AIDS and HIV positive with AIDS groups. Diastolic BP responses to sustained handgrip have a limited role in discriminating autonomic function in HIV infected patients. There is no statistically significant correlation with the CD4 level and the presence of autonomic nervous system dysfunction in both the groups.

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Date of Submission: 16/09/2014.
Date of Peer Review: 17/09/2014.
Date of Acceptance: 18/09/2014.
Date of Publishing: 19/09/2014.