ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 04 | April - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

CARDIOVASCULAR AUTONOMIC DYSFUNCTION IN HIV-POSITIVE PATIENTS AND ITS CORRELATION WITH CD4 CELL COUNT

Internal Medicine

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KEYWORDS

INTRODUCTION

According to Global human immunodeficiency virus and acquired immunodeficiency disease syndrome statistics, 38.4 million(33.9 million-43.8 million) people live globally with HIV in 2021, and 1.5 million people became newly infected with HIV in 2021(1). As per India HIV estimation report 2020, national adult (15–49 years) HIV prevalence was estimated at 0.22% (0.17%–0.29%) in 2020, 0.23% (0.18%–0.31%) among males and 0.20% (0.15%– 0.26%) among females(2). HIV is a condition which can progressively affect almost all body organs and systems due to immune system failure. Infection with HIV is well known to cause peripheral neuropathy and other neurological complication thus affecting the quality of life(3). Autonomic nervous system involvement can affect heart rate, vasomotor tone, sexual function, gastrointestinal motility, urination, thermoregulation and production of tears and saliva. This can lead to diverse symptoms like postural syncope, impotence, sweating, diarrhea/constipation, dry eyes and mouth, urinary incontinence and changes in skin temperature. Abnormalities in cardiac autonomic function occur at all CD4 levels(4,5). The aim of our study is to assess autonomic dysfunction in HIV-positive patients and to show the correlation between decreasing CD4 + T cell counts with increasing severity of disease in the form of autonomic dysfunction.

MATERIALS AND METHODS

A cross-sectional study was conducted over 17 months at a tertiary care hospital. Adult population(>18 years of age) of either sex with confirmed HIV seropositivity(HIV patients diagnosed as per WHO/NACO guidelines)(6). In the study group, 60 patients with confirmed HIV serology were recruited. The study group was divided into two subgroups. One with patients whose CD4 cell count was >200/ µl and the other group whose CD4 cell count was<200 µl.

Inclusion/exclusion Criteria

All adults(>18 years) with confirmed HIV infection by two different ELISA/Rapid/Simple ERS with different antigen preparation in patients who co-operated. The patients with the following medical conditions were excluded from the study- Diabetes Mellitus, Advanced Hepatic disease, Advanced kidney disease, advanced chronic lung disease, leprosy, multiple system atrophy, known case of autoimmune disease like celiac disease, Sjogren syndrome, rheumatoid arthritis, SLE, inflammatory bowel disease. Other than this patients who could not perform cardiac autonomic neuropathy function test, patients on medication that cause neuropathy and history of prolonged alcohol intake were also not included in the study.

Methodology

For all patients, a complete clinical history including physical examination and routine investigation like complete blood count, Liver function test, kidney function test, serum proteins, fasting and postprandial plasma glucose, chest x-ray, ultrasound abdomen, viral markers (HbsAg, anti-HCV), VDRL were done. HIV testing was done using 3 different kits: SD BIOLINE HIV-1/2 3.0 Test, PAREEKSHAK HIV-1/2 TRILINE Card Test and AIDSCAN HIV-1/2 TRISPOT Test Kit. CD4 T- cell count was done using Becton-Dickinson FACS flow cytometer. Evaluation of cardiac dysautonomia was done by cardiovascular responses to non-invasive autonomic function tests(ANF) as recommended by Ewing et al(7) and subjects were asked for symptoms such as dizziness or light headedness on standing up, dysphagia, abnormal sweating pattern, impotence and retention/ incontinence/ frequency of urine/fecal incontinence.

For assessment of parasympathetic function- heart rate response to Valsalva maneuver (Valsalva ratio) ,heart rate variation during deep breathing and immediate heart rate response to standing on 15th and 30th beat ratio were done.

For assessment of sympathetic function- Blood pressure response to standing up(fall in systolic BP), Blood pressure response to sustained hand grip(increase in diastolic blood pressure), Cold pressure test in which subjects were asked to immerse his/her hand in cold water with the temperature maintained at 4-6^{0}C and BP was measured from the other arm at 30 second interval for 3 times were done. The results were compared with normal values and findings were recorded in terms of normal, borderline or abnormal(Table-1)

Blood pressure was recorded by sphygmomanometer after person seated quietly for at least five minutes, with feet on the floor and arm at heart level. An appropriate-sized cuff (cuff bladder encircling at least 80% of arm) was used. Two measurements were taken. Heart rate was be measured in supine position after 5 min of rest by auscultation for 1 minute according to the consensus statement of the European Society of Hypertension(8).

Clinical characteristics were evaluated and Classified according to WHO clinical staging.

Statistical Evaluation

The data analysis was done by SPSS software for windows, version 20. Quantitative variables were reported as mean ± standard deviation and were compared by student t test or chi- square and Kruskal- Wallis test.

RESULTS

A total of 60 patients were recruited between 19-65 years with Mean age 33.1833 $\pm$ 8.73429. They were further categorized into case group 1 with 22 patients whose CD4 count was less than 200 and Case group 2 with 48 patients whose CD4 count more than 200. The patient characteristics in our study are elaborated in table 3

Neurological involvement was present in 4 patients out of the total 60 patients in study population. In patients with CD4 cell count less than 200/µl, out of the 22 patients,2 patients had cryptococcal meningitis and one had tubercular meningitis. Among the second group of CD4 cell count more than 200/µl only one patient had tuberculoma of the brain.

A questionnaire evaluating the autonomic dysfunction was asked to the patient and the data was divided based on CD4 count. Among the study population, out of 60 patients, 16 patients had complaints of dizziness, of which 13 patients had CD4 +T cell count < 200/µl and three patients had CD4 + T cell count > 200/µl. The association of dizziness with CD+T cell count was statistically significant ($p<0.05$).

5 patients complained of dysphagia, of which 2 patients had CD4 +T cell count < 200/µl and 3 patients had CD4 + T cell count > 200/µl. However, dysphagia was not associated with the CD4 +T cell count ($p=0.384$).

8 patients complained of impotence, of which 6 patients had CD4 +T cell count < 200/µl and 2 had CD4+ T cell count> 200/µl. The association of impotence with the CD4 +T cell count was statistically significant ($p<0.05$).

6 patients had Bowel and bladder dysfunction out of which 5 patients had CD4+T cell count <200/µl and 1 had CD4+ T cell count> 200/µl. The association of bowel and bladder dysfunction with the CD4 +T cell count was statistically significant ($p<0.05$).

Abnormal sweating was not seen in any patient. It was evident that patients with CD4 + T cell count <200/µl had more symptoms of autonomic dysfunction as compared to those with CD4 + T cell count >200/µl. Six bedside non-invasive autonomic function tests were done in all the subjects and the results elaborated in Table 4

Each cardiovascular autonomic function test had significant association with CD4 + T cell count ($p<0.05$). These patients were further classified and graded into 4 categories based on the number of positive test(s). Out of 60, 26 patients had normal autonomic function tests. 8 patients with CD4 count < 200/µl with mean CD4 147.75 $\pm$ 32.936 and 13 patients had CD4 + T cell count > 200/µl with mean CD4 293.00 $\pm$ 77.77 had early autonomic dysfunction. 3 patients with count < 200/µl with mean CD4 66.00 $\pm$ 48.59 and 10 patients with count <200/µl with mean CD4 51.4 $\pm$ 28.547 had definitive and severe respectively autonomic dysfunction whereas there was no patient with CD4 count > 200/µl in these two categories(Figure1). On applying the Kruskal Wallis Test for the correlation of CD4 + T cell count and the degree of dysautonomia, it was observed that there was a highly significant association between the variables ($p=<0.05$), with a degree of freedom of 3.

DISCUSSION

HIV-infected patients commonly develop autonomic neuropathy (HIV-AN), a heterogeneous disorder characterized by varying degrees of sympathetic and vagal dysfunction. Among the various immunological parameters CD4 +T cell counts have been found to be the most reliable marker as a predictor of HIV disease progression. Thus the assessment of autonomic nervous system dysfunction with non-invasive tests and its correlation with CD4 levels can allow early detection and provide window to manage symptoms during early stages.

All subjects in the study were evaluated for autonomic dysfunction. They were asked for symptoms suggestive of autonomic neuropathy/ dysfunction and non-invasive bedside cardiovascular autonomic function tests were done on them. Dizziness and light headedness on standing was present in 22 patients with CD4 cell count <200/µland 3 patients with CD4 cell count >200/µl. This was in the absence of dehydration, cardiac failure or anaemia. However, adrenal insufficiency was not ruled out in these patients. The association with CD4 count was statistically significant. It was the most common symptom of our study and was consistent with the study done by Compostella et al(10). However, Sigmund Ruttimann et al(11) had reported a lower value of 24% in their study They had not found any significant difference between the study group and control group. No controls were taken in our study since it was an observational study. Hyperhidrosis and anhidrosis was not seen in any patient.

Impotence, yet another symptom of autonomic dysfunction was present in 8(13.33%) patients of the study population. In the group of CD4 +T cell count <200/µl (n=22) which included 15 males, of which 6(27.27%) patients reported impotence.

A study by Welby et.al(12) who evaluated autonomic dysfunction in HIV/AIDS patients, reported impotence and decreased libido in 9(60%) of male patients & this was the commonest symptom of their study. The main reason for the discrepancy of data on impotence between the two studies may be due to the small sample size(n=17) of Welby et al(12) who studied sexual dysfunction in an sample which had advance disease of stage 4.Fin our study, the sociocultural inhibition of Indian population do account of low reporting of sexual behaviour. However there is significant association($p<0.05$) between the CD4 + T cell count and impotence.

Bladder & Bowel involvement (incontinence) was noted in 5(8.34%) out of the total 60 patients. This observation on statistical analysis proved to be significant ($p<0.05$) and the data was consistent with the study done by Sigmund Ruttimann et al(11)

Dysphagia was not a major symptom with only 5 patients. Among these 5patients, 2 patients had associated oral candidiasis and probably esophageal candidiasis as well. On correlation it was not statistically significant ($p=0.384$).None of the previous studies had accounted this symptom to autonomic dysfunction.

Six non-invasive cardiac autonomic tests were done on each patient in the two groups(CD4 count <200/µl and CD4 +T cell count >200/µl).The results of these tests in each subgroup were statistically significant ($p<0.05$), indicating that with the fall of CD4 cell count to <200cells/µl, there is a significant increase in cardiovascular dysautonomia. Heart rate response to Valsalva manoeuvre was the most frequently abnormal test, second being heart rate variability in our study. But in various other studies, as reported by Sakhuja et al(13), Chow et al(14,15)and Mittal et al(16) heart rate variability with deep breathing was found to be most sensitive for autonomic dysfunction.

In our study Autonomic nervous system involvement was more frequent 21(95.45%) in the group of CD4 +T cell count <200/µl than the HIV patients with CD4 +T cell count >200/µl. Autonomic dysfunction that is noted is consistent with the other authors. Shahmanesh et.al(17) observed 15(48.3%) (n=31) patients with abnormal autonomic tests. IN THEIR STUDY, Jeffery A Cohen et.al(18) had autonomic dysfunction in 50% of cases (n=10). In contrast to our study S B Welby et.al(12) had noted 11(76.5%) patients of 13 patients studied with abnormal tests. The reason behind the high prevalence in their study was due to the skewed composition of their study population. In their study group of 17 patients, 13 were in stage 4 of the disease, whereas in our study we had a large population of 60 patients which had 22 patients with CD4 +T cell count <200/µl and 38 with CD4 +T cell count <200/µl. But if we take the group with CD4 +T cell count <200/µl, it is similar to the study group of S B Welby and the results could be observed highly skewed.

In a case study done by Mathew et al(19) 16% of HIV positive with the AIDS had abnormal autonomic dysfunction and 4% of HIV positive without AIDS had abnormal autonomic dysfunction. Reduced heart rate variability is the commonest manifestation of autonomic dysfunction noted in both HIV positive without AIDS and HIV positive with AIDS groups. However, There was no statistically significant correlation between the CD4 level and autonomic nervous system dysfunction in both groups. Our study was one step further as we were able to show a correlation between decreasing CD4 cell count with increasing occurrence of autonomic dysfunction.

A study done by Chaddock et.al(20) described syncopal attacks in 5 patients after fine needle aspiration of lung, with many others who reported symptoms suggestive of dysautonomia, even cardiorespiratory arrest in HIV patients. Therefore, in view of possible occurrence of life threatening syncopal attacks and cardiorespiratory arrest, if autonomic abnormalities are present, it may be wise to subject HIV/AIDS patients, particularly with other neurological abnormalities and with lower CD4 +T cell counts to simple bed-side non-invasive tests before they undergo any invasive procedure and general anaesthesia.

The limitation of our study is that the duration of the disease was not taken into account and the study comprised of a heterogeneous group which included the patients who are on anti-retroviral therapy and who were naïve HIV patients. Further the duration of treatment and compliance to treatment was not taken into consideration. Since there were no controls and sample size of only 60 patients, therefore extrapolation of the results to the general population is not effectively possible.

CONCLUSION

With the emerging antiretroviral therapy, now we are able to manage HIV/AIDS patients in better way. Besides the treatment of HIV and treatment of opportunistic infection to improve the quality of life in these patients, symptomatic therapy is also important. Therefore any patient complaining of vague symptoms that are suggestive of autonomic dysfunction, should undergo active but less invasive monitoring first to give a clue about autonomic function. CD4 cell count can further help in predicting the severity of autonomic dysfunction in these patients and it can thus be used a screening marker for early diagnosis. There is a scope of improvement in future studies by using a control group and bigger sample size to in order to generalize the results to the population

Table 1- Normal,borderline and abnormal values in tests of cardiovascular autonomic function(9)

TESTS	NORMAL	BORDERLINE	ABNORMAL
Tests reflecting Parasympathetic function			
a)Heart rate response to Valsalva (Valsalva ratio)	>1.21	1.11-1.20	<1.10
b)Heart rate (R-R interval)variation during deep breathing (beat/min)	>15	11-14	<10
c)Immediate heart rate response to standing up	>1.04	1.01-1.03	<1.00
Tests reflecting sympathetic function			
a)Blood pressure response to standing up (fall in systolic blood pressure)	<10	10-29	>30
b)Blood pressure response to sustained hand grip	>16	11-15	<10
c)Cold pressure test	>16	11-15	<10

Based on the above, autonomic dysfunction was classified and graded as below:-

Table 2-Classification of Autonomic neuropathy

Absent	0	All five tests are normal or one test borderline
Early	1	One abnormal test or two more borderline tests
Definite	2	Two or more abnormal tests
Severe	3	Two or more heart rate tests abnormal and one abnormal or two borderline blood pressure tests

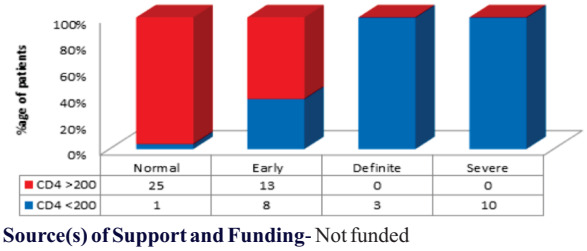
Table 3- Patient characteristics

PATIENT CHARACTERISTICS		No. of patients with CD4 COUNT <200/µl	No. of patients with CD4 COUNT>200/µl
Gender	Male	15(68.18%)	7(31.81%)
	Female	27(71.05%)	11(28.95%)
Stage of disease	Stage 1	2 (9.09%)	26 (68.42%)
	Stage 2	1 (4.545%)	2 (5.26%)
	Stage 3	14 (63.63%)	8 (21.05%)
	Stage 4	5 (22.72%)	2 (5.26%)
Clinical profile of study population	Abdominal TB	0 (0%)	1 (2.63%)
	Asymptomatic	2 (9.09%)	25 (65.79%)
	Chronic Diarrhoea	2 (9.09%)	0 (0%)
	Cryptococcal Meningitis	1 (5.54%)	0 (0%)
	Generalised Asthenia	1 (5.54%)	0 (0%)
	Lymphadenopathy	0 (0%)	1 (2.63%)
	Oral Candidiasis	4 (18.18%)	6(15.79%)
	Pulmonary TB	4 (18.18%)	1 (2.63%)
	Pulmonary TB/Oral Candidiasis	1 (5.54%)	0 (0%)
	Syphilis	0 (0%)	1 (2.63%)
	TB Lymphadenopathy	3 (13.63%)	0 (0%)
	TB Meningitis	2 (9.09%)	0 (0%)
	TB Pleural Effusion	0 (0%)	1 (2.63%)
	Tuberculoma	0 (0%)	1 (2.63%)
	UTI	0 (0%)	1 (2.63%)
	Vulvovaginal Candidiasis	2 (9.09%)	0 (0%)

Table 4:Normal, Borderline and abnormal values in tests of cardiovascular autonomic function

Tests	Patients with CD4 <200			Patients with CD4 <200		
	Normal	Borderline	Abnormal	Normal	Borderline	Abnormal
H. R response to valsalva	2(9.09%)	7(31.81%)	13(59.09%)	26(68.42%)	10(26.31%)	2(5.263%)
H. R variation during deep breathing	5(22.73%)	8(36.36%)	9(40.90%)	25(65.79%)	12(31.58%)	1(2.63%)
Immediate H.R response to standing (30:15)	10(45.45%)	5(22.73%)	7(31.81%)	35(92.10)	3(7.9%)	0(0%)
BP response to standing	10(45.45%)	11(50.0%)	1(4.545%)	28(73.68%)	10(26.31%)	0(0%)
B.P response to sustained hand grip	10(45.45%)	9(40.90%)	3(13.636%)	33(86.84%)	5(13.16%)	0(0%)
Cold Pressure test	10(45.45%)	10(45.45%)	2(9.09%)	32(84.21%)	6(15.79%)	0(0%)

Fig.1 percentage of patients with different category of autonomic dysfunction.



Source(s) of Support and Funding- Not funded

Conflict of Interest statement - No conflict of interest among the authors

Ethical Approval- Institutional Ethical approval was obtained before carrying out the study as it was done as a thesis for MD, Internal Medicine

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