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A Study on Cardiac Autonomic Neuropathy in Rheumatoid Arthritis Patients in Cuddalore District

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Abstract

Autonomic Neuropathy (AN), found to be a strong predictor of sudden cardiac death, has been reported variably in patients with Rheumatoid Arthritis (RA). Being an inflammatory condition, RA affects the cardiovascular system in the form of increased intima-medial thickness, endothelial dysfunction, and in general, a higher prevalence of atherosclerosis. These extra-articular manifestations are strong predictors of decreased survival in patients of RA. AIM OF THE STUDY: To study the correlation between cardiac autonomic neuropathy and Age, Sex, Duration of disease, Rheumatoid factor positivity, and the DAS 28 score.METHODS: This is a cross-sectional- case-control study conducted for a period of 6 months from 2021 February to July 2021. The study patients were below 60 years of age so that the neurological problems due to aging were minimized. . Informed consent was taken from both patients and control before assigning them to study. Five standard cardiovascular autonomic reflex tests which assess the integrity of the sympathetic and parasympathetic system on cardiovascular system were done.RESULTS: Among the 53 cases 39 were Rheumatoid factor positive and 35 were CRP positive. The majority of the cases ie, 77 % in our study comes under the DAS28 category is >5. Most of the definite cardiac autonomic neuropathy patients come under the age group of 41-50 ie (39.1%) but p = 0.596, suggesting that definite can and age have no statistically significant relation. For definite cardiac autonomic neuropathy and CRP positivity p = 0.8127, suggesting that definite can and CRP positivity has no statistically significant relation. For definite cardiac autonomic neuropathy and Hb p = 0.8279. suggesting that definite CAN and Hb have no statistically significant relation. Heart rate variability during deep breathing, Valsalva ratio, and rise in diastolic BP during sustained handgrip is more significantly decreased in the study. CONCLUSION. As autonomic dysfunction has been linked to a reduced quality of life and serious and potentially life-threatening cardiovascular complications, further research must be carried out to get a better understanding of the condition. Longitudinal follow-up studies involving a larger number of patients will help in getting a clearer picture of the pathogenesis, influences, and long-term effects of AN in patients of RA.

Keywords: Autonomic Function Test, Neuropathy CRP, Valsalva Ratio

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic multisystem disease of autoimmune etiology. The characteristic feature is the persistent inflammatory synovitis usually involving peripheral joints in asymmetric distribution. [1]Though it is considered a disease predominantly involving the joints it can cause a variety of extra-articular manifestations. It can affect skin, eye, cardiovascular, respiratory, and nervous systems and may produce hematological complications including an increase in the risk of

Hodgkin's disease, non-Hodgkin's lymphomas, leukemias independent of the immunosuppressive drugs. [2]One of the important extra-articular manifestations is the involvement of the nervous system. Neurological manifestations may be due to the involvement of the central nervous system, peripheral nervous system, or autonomic nervous system. [3]They may be either due to vascular involvement, direct compression, or immune-mediated mechanism. Autonomic neuropathy in Rheumatoid arthritis is rare. But recent studies have shown variable results and it varied from 0-70% symptomatic or asymptomatic.[4] It can affect parasympathetic only or sympathetic only or both. The most common is parasympathetic involvement. An important adverse effect of autonomic neuropathy is cardiac autonomic neuropathy, as it can lead to an increase in morbidity and mortality.[5] Cardiac autonomic neuropathy can lead to sudden cardiac death, various arrhythmias, adverse effects on drugs, increase in the incidence of frequent falls especially in the elderly further aggravating the morbidity.[6]

METHODS: This is a cross-sectional- case-control study conducted for a period of 6 months from 2021 February to July 2021at Rajah Muthiah Medical College, Annamalai University, Chidambaram in collaboration with the General medicine department The study patients were below 60 years of age so that the neurological problems due to aging were minimized. . Informed consent was taken from both patients and control before assigning them to study. Five standard cardiovascular autonomic reflex tests which assess the integrity of sympathetic and parasympathetic system on cardiovascular system Few patients had difficulty in exerting maximum handgrip in the dynamometer. But they were able to achieve 30% of the maximum handgrip for the age and sex-matched control. The controls were selected from the healthy relatives of the patients and those who attended OPD with minor ailments like URTI. Informed consent was taken from both patients and control before assigning them to the study. Inclusion criteria: Patients who fulfilled 1987 revised AMERICAN RHEUMATOLOGY ASSOCIATION criteria for rheumatoid arthritis. Exclusion criteria: Age above 60 years, Endocrine and Metabolic disorders like Diabetes and Electrolyte imbalance like Hyponatremia and Hypokalemia, Hypertension, Liver, Renal, Respiratory and Cardiac diseases, Pregnancy, Severe anemia, Treatment with drugs influencing the adrenergic nervous system like beta-blockers, antiarrhythmic agents, diuretic, adrenergic inhibitor, vasodilator, sedative, hypnotic and antiepileptic drugs were also excluded from the study. All the selected patients were subjected to detailed clinical examination. The hematological evaluation included a complete hemogram, Biochemical parameters including blood urea, serum creatinine, serum sodium, serum potassium, Liver function test, TFT, Random blood sugar. The immunological evaluation included Rheumatoid factor and CRP by latex agglutination method. Cardiac autonomic neuropathy testing: 1. Heart rate response to deep breathing (E/I ratio) 2. Heart rate response to Valsalva manoeuvre. 3. Immediate heart rate response to standing(30:15) 4. Blood pressure response to sustained handgrip. 5. Blood pressure response to standing. The first three tests assessed the parasympathetic system and the rest two assessed sympathetic functions. Parasympathetic system assessment is done by taking continuous ECG monitoring with 8-channel Psyco-physiopac software and by calculating the heart rate and ratio by using the standard guidelines as described below. The sympathetic system was assessed by measuring the blood pressure in a standing and sustained handgrip using a dynamometer and mercury manometer. Patients were asked to relax in a quiet room for at least 10 minutes before testing. Then tests were conducted, in the following order. First supine BP is measured and maximum power in dynamometry assessed, then ECG limb leads connected and continuous ECG recording is done at lead 2 in 8-channel Psyco-physiopac software. Time is noted separately during the start of each phase like beginning and ending point of inspiration, beginning of strain phase of Valsalva and release phase,30^{th} and 15^{th} beat after immediate standing, etc, to calculate heart rate at various phases. Recording done at first during normal breathing for 30 seconds, then deep breathing for one minute instructed to take normal breathing again for 30seconds after this Valsalva maneuver done as described in a further section. After the Valsalva maneuver is over, the patient takes normal breathing for 30 seconds and is then asked to stand immediately. Once the 30^{th} QRS complex is over in ECG recording after standing,

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recording is stopped. Then Blood pressure was measured at 3rd minute of standing from a supine position. (Recording at normal breathing done in between to get a stable baseline heart rate between each event) .Then patient lies in the supine position, Blood pressure is measured, and after one-minute handgrip, BP is measured by using a grip dynamometer with 30% of maximum power.

STATISTICAL ANALYSIS

The information collected regarding all the selected cases was recorded in a Master Chart. Data analysis was done with the help of a computer using the Epidemiological Information Package (EPI 2020). Using this software, range, frequencies, percentages, means and standard deviations, and p-value were calculated.

RESULTS

TABLE 1 AGE DISTRIBUTION IN CASES AND CONTROL

AGE IN YEARS	CASES		CONTROL	
	NO	%	NO	%
<30	4	7.5	5	16.1
30-39	19	35.8	12	38.7
40-49	23	43.4	10	32.3
50 & ABOVE	7	13.2	4	12.9
TOTAL	53	100	31	100
RANGE	21-56		25-58	
MEAN	40.5		38.8	
SD	7.7		8.7	
P-VALUE	0.2837 NOT SIGNIFICANT			

Table :1 Mean age is 40.5 among cases, and 38.8 among control. There is no statistically significant relationship between age distribution among cases and control (p = 0.2837) There is no statistically significant relationship between sex distributionamong cases and control (p= 0.8491)

TABLE 2 CRP PREDICTION

PARAMETER	POSITIVE		NEGATIVE	
	NO	%	NO	%
RF	39	73.6	14	26.4
CRP	35	66.1	18	33.9

Table: 2 Among the 53 cases 39 were Rheumatoid factor positive and 35 were CRPpositive.

TABLE 3: CAN SCORE DISTRIBUTION

CAN SCORE	CASES

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	NO	%
NO CAN	4	7.5
EARLY CAN	31	58.5
DEFINITE CAN	18	34
TOTAL	53	100

Table :3 Among 53 cases 18 (34%) had Definite cardiac autonomic neuropathy. Most of the definite cardiac autonomic neuropathy patients come under the age group of 41-50 ie (39.1%) but p = 0.596, suggesting that definite can and age have no statistically significant relation. Most of the definite cardiac autonomic neuropathy patients are ie (39.1%) females. but p = 0.702, suggesting that definite can and sex have no statistically significant relation. For definite cardiac autonomic neuropathy and duration of illness p = 0.88, suggesting that definite can and duration of disease has no statistically significant relation.

TABLE 4 DEFINITE CAN AND CRP

CRP	NO. OF CASES	DEFINITE CAN			
		POSITIVE		NEGATIVE	
		NO	%	NO	%
POSITIVE	35	12	34.3	23	65.7
NEGATIVE	18	6	33.3	12	66.7
P-VALUE	0.8127 NOT SIGNIFICANT				

Table:4 For definite cardiac autonomic neuropathy and CRP positivity p = 0.8127, suggesting that definite can and CRP positivity has no statistically significant relation

TABLE 5 DEFINITE CAN AND DAS28

DAS 28	DAS28			
	POSITIVE		NEGATIVE	
	NO	%	NO	%
<3	0	0	1	2.9
3.1-5	2	11.1	9	25.7
>5	16	88.9	25	71.4
TOTAL	18	34	35	66
MEAN DAS28	6.5		6	
S.D	1		1.3	
P-VALUE	0.62 NOT SIGNIFICANT			

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Table :5 For definite cardiac autonomic neuropathy and DAS28 p = 0.62. suggesting that definite can and DAS28 have no statistically significant relation. For definite cardiac autonomic neuropathy and Hb p = 0.8279. suggestingthat definite CAN and Hb have no statistically significant relation.

TABLE 6 EWINGS BATTERY OF TEST RESULTS IN PATIENTS AND CONTROL

PARAMETER	STUDY	CONTROL	P-VALUE
	MEAN±SD	MEAN±SD	
HR REST	79.9 ± 8.5	75.5± 4.9	0.0272
HR DB MAXIMUM	89.6±8.8	90±5.5	0.7872
HR DB MINIMUM	77.5±9.5	68.1±4.6	0.0001
HR VARIABILITY	12.1±6.9	21.9±3.7	0.0001
VAL MAX	99±11.7	98.1±4	0.6283
VAL MINI	76.4±9.4	66.1±4.4	0.0001
VAL RATIO	1.31±0.19	1.49±0.09	0.0001
30:15	1.03±0.06	1.08 ±0.02	0.0367
SYSTOLIC FALLIN BP ON STANDING	11.06±6.76	7.94 ± 3.67	0.048
HAND GRIP DBPDIFFERENCE	11.68±6.23	17.23±2.72	0.0001

Table:6 Heart rate variability during deep breathing, Valsalva ratio, and rise in diastolic BP during sustained handgrip is more significantly decreased in the study.

DISCUSSION

Among patients with cardiac autonomic neuropathy, only four patients (22%) have symptoms of cardiac autonomic neuropathy, and the remaining ie, 14 patients (78%) them are asymptomatic. Correlating our study results with the age, sex, duration of disease, DAS28, rheumatoid factor positivity, and CRP, it was found that there is no statistically significant relationship between CAN and these parameters. [7] Among the reflex tests Valsalva ratio, and Expiration: inspiration ratio, and diastolic BP in handgrip had the high significance value. [8] Similar studies conducted in various centers showed little variation inthe percentage of cardiac autonomic neuropathy in the study population but uniform finding in these studies is that cardiac autonomic neuropathy has no statistically significant relationship with age, sex, duration of disease, rheumatoid factor positivity, or DAS 28.[9] Gabriel SE, et al studied CAN IN RA among 34 RA patients with M: F 1:7.5, age group were 47.2±10.5 and duration of disease was 5.1±3.6[1] This study used standard Ewings test for assessing the cardiac autonomic status. In this study, 47% of the RA Patients have diminished cardiovascular ANS responses. It showed no correlation to the number of Swollen joints, ESR, RF titer, or Duration of disease. [10] Gary S et al studied Attenuated cardiovascular reflexes in established RA, in 62 patients with 41 healthy age and sex-matched control. In this study age was 38±8.4yrs[34]. This study showed that Valsalva ratio, Heart rate variation during deep breathing, 30:15 ratio, Diastolic blood pressure response to handgrip were significantly decreased in rheumatoid arthritis patients. The following are the p-value for the standard cardiovascular test The Valsalva ratio (VR)(p=0.03), The heart rate variation during deep breathing (HRV) was (p=0.01), The 30:15 ratio in the entire RA cohort (p=0.001).[11] The diastolic blood pressure response to handgrip in RA patients (p=0.001), No abnormalities were found in the systolic blood pressure response to standing.In RA patients in this study, the lowest values for VR, HRV, and 30:15 were recorded in those with the disease of greater than 10 years duration. However, on multivariate analysis, neither age nor duration of disease nor seropositivity[35] was found to be an independent variable predicting impaired

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cardiovascular reflexes.[12] .In a study conducted by Levine AB. et al.cardiac autonomic dysfunction was reported to be 60%. who demonstrated that 60% of their 50 RA patients had ANS dysfunction, defined by abnormal results on two of the three cardiovascular reflex tests. However, ANS dysfunction showed no correlation with the Duration of the disease, Inflammatory syndrome, RFtiter, or Articular destruction.40 healthy controls. Autonomic nervous system dysfunction was determined according to classical Ewing autonomic test battery and modified Ewings criteria. Both the classical and modified Ewing test batteries have revealed that the frequencies of autonomic neuropathy were significantly higher in inpatient groups compared with controls ($p < 0.001$). No relation was found between autonomic neuropathy and disease duration, disease activity, and autoantibody positivity.[13] Mc Gregor. et al j studied sympathetic nervous system involvement in fifty rheumatoid arthritis patients between the age group of 20 to 60 yrs by using standard tests and found out that 26% of rheumatoid arthritis patients had sympathetic dysfunction[14]. Mortensen et al. also showed impaired autonomic nervous function in patients with RA. They reported that autoantibodies directed against autonomic nervous system structures might play a role in the pathogenesis of autonomic dysfunction. Our study had only 53 patients and a study on a larger population could throw more light on the cardiac autonomic neuropathy in rheumatoid arthritis[15]

CONCLUSION

Cardiac autonomic neuropathy is a common manifestation in patients with rheumatoid arthritis. More than 3/4th of the cardiac autonomic neuropathy is asymptomatic. Cardiac autonomic neuropathy has no relation with age, sex, seropositivity, duration of illness, or DAS 28. This study emphasizes the need for early screening for cardiac autonomic neuropathy in rheumatoid arthritis to avoid morbidity and mortality and to anticipate cardiovascular responses in procedures like general anesthesia and surgical procedures

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