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Original Article

Frequency of Autonomic Neuropathy in Patients with Rheumatoid Arthritis

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Abstract

Objective: To assess the frequency of autonomic neuropathy (AN) in patients with rheumatoid arthritis.

Methods: This Cross sectional study was carried out at Department of Medicine, Mayo Hospital, Lahore, Pakistan, from March 2020 to February 2022. A total of 100 patients were registered in the study through Outpatient Department of Medicine, Mayo Hospital, Lahore. To assess cardiac autonomic neuropathy, the five cardiovascular reflex examinations listed by Ewing were performed that includes the effect of deep breathing, Valsalva maneuver as well as standing on the measurement of heart rate (HR),also blood pressure (BP) response to sustained handgrip and standing was noted. Grading of the cardiac AN was carried out in accordance with Agarwal D et al's description.

Results: The mean age of patients was 44.09 ± 10.06 years. There were 29 (29%) males and 71 (71%) females. The mean duration of disease was 7.88 ± 1.76 years with minimum duration of 5.5 years and maximum duration of 11 years. A total of 77 (77%) cases had autonomic neuropathy while rest of 23 (23%) cases did not have autonomic neuropathy. There were 23 (23%) cases who had mild, 32 (32%) had moderate and 16 (16%) cases had severe autonomic neuropathy.

Conclusion: It is concluded that more than in the 3rd quarter i.e. 77% cases of RA had Autonomic Neuropathy.

Keywords: Rheumatoid Arthritis, Autonomic dysfunction, Chronic inflammatory disorder, Extra-articular manifestations.

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder that mostly affects small joints. Usually, it causes swollen, warm, and painful joints. Pain and stiffness frequently get worse after resting. Common sites of involvement include wrists and hands, and the same joints frequently affect both sides of the body. Other areas of the body could also be impacted by the condition. Low red blood cell count and inflammation around the heart and lungs can also occur. Decreased energy levels and fever can also be its menifestations.[1,2] In the developed world, RA affects between 0.5 and 1% of adults, with 5 to 50 new cases per 100,000 individuals every year.[3] An extensive study conducted across France estimated that 0.47% of the population had RA in 2019—0.66% of women and 0.28% of males. Although numerous efficient treatments have been created in recent years, RA still has a high death rate of over 20% compared to the general population, making it a dangerous illness.[4] The most prevalent inflammatory joint condition, rheumatoid arthritis affects 1-2% of people worldwide.[5]

Rheumatoid arthritis predominantly affects the joints, but it also has extra articular manifestations like rheumatoid nodules, neuropathy and normochromic normocytic anemia. The most common neurological extra-articular characteristic is thought to be neuropathies. Mononeuritis multiplex, autonomic neuropathy (AN), peripheral polyneuropathy, and mononeuropathy (such as carpal tunnel syndrome, which is entrapment neuropathy,) are among the neuropathic implications of RA. The sympathetic and/or parasympathetic nerve fibers are affected in RA which leads to autonomic neuropathy. Clinical signs of autonomic neuropathy include chilly, clammy, and cyanotic extremities, as well as orthostatic hypotension, palpitations, sexual dysfunction and syncopal episodes.[1,2,4,5]

Autonomic dysfunction brought on by chronic inflammation increases the risk of cardiovascular diseases (CVD) in rheumatoid arthritis patients. Rheumatoid arthritis patients display symptoms of autonomic dys-

function, which may be related to the condition's established vascular and myocardial affection and elevated risk of CVD.[5,6]

A sympatho-vagal imbalance and altered autonomic nerve function may both result from RA. Although the participation of the peripheral as well as central nervous systems in RA has been widely documented, there are very few published research that discuss the involvement of the autonomic nervous system in RA.[7] The autonomic nervous system's inability to effectively adapt to internal and external environmental changes may make RA patients more susceptible to arrhythmias, which would raise cardiovascular mortality.[5,8]

Aggarwal D et al[9] observed that 80.65% of RA cases had autonomic neuropathy. According to a study by Jahan K. et al.5 78.3% of RA patients had autonomic neuropathy at various stages of development, and RA patients also had a high prevalence of AN. However, according to Maule et al.[10] Louthrenoo et al.[11] and Adlan AM et al.[12], autonomic neuropathy affects 15%, 47%, and 60% of RA patients, respectively and the frequency of occurrence of autonomic dysfunction was significantly less than that discovered by Aggarwal D et al. and Jahan K et al.

The reason of this study is to assess the frequency of autonomic neuropathy in patients suffering from RA. Studies have shown that the frequency of autonomic neuropathy was <50% but controversial results have been observed in literature. Therefore, we carried out this research to obtain data regarding the severity of the AN in our people as no study has been found in the literature that could assist us in estimating the severity of RA the local community. In the future, we will be able to screen the patients of RA for autonomic neuropathy in order to manage early and prevent the harmful consequences of this condition and also improve quality of life of patients by early treatment. This study will help us to get local evidence and improve our practice.

Methods

After getting approval from the institutional review board of King Edward Medical University Lahore, this cross-sectional study was carried out at Mayo Hospital in Lahore, Pakistan, from March 2020 to February 2022. Sample size of 100 cases was determined with 95% confidence level, 8% margin of error and taking estimated percentage of autonomic neuropathy i.e.80.65% in patients of RA.[9] According to 2010ACR EULAR classification criteria for rheumatoid arthritis13adult patients aged 20 to 60 years of either gender who had rheumatoid arthritis for more than 5 years were included in the research. While Diabetic patients and patients already taking medication for neuropathy were excluded. Through Outpatient Department of Medicine of Mayo Hospital Lahore, 100 patients who fulfilled the inclusion criteria were recruited in the study with a written consent. Demographic data (name, gender, age, BMI duration of RA) were also gathered. Then five cardiovascular reflex tests were checked for assessment of autonomic neuropathy. Reports were assessed and patients were labeled for autonomic neuropathy. A survey of autonomic symptoms was used to subjectively evaluate autonomic neuropathy (AN). The cardiovascular reflexes were assessed using a battery of five non-invasive tests as described earlier by Ewing DJ and Clark BF.[14]

The definition of reporting for the tests is in Table l. According to Aggarwal D et al.'s report,[9] the cardiac AN indicated in Table 2 was graded. All data was entered and analyzed using SPSS version 26. Age, BMI, and the length of RA were quantitative factors for which mean, and SD were calculated. In order to account for qualitative factors like gender and autonomic neuropathy, frequency and percentage were determined. Data was segregated based on age, sex, BMI, and duration of RA. After stratification, the chi-square test was used when comparing autonomic neuropathy between stratified groups. P-value of 0.05 or less was considered as significant.

Results

This trial involved 100 patients. The mean age of patients was 44.09 ± 10.06 years with minimum and maximum age as 20 and 60 years. There were 32(32%) cases aged 20-40 years and 68(68%) cases were 41-60 years old. There were 29(29%) male and 71(71%) female case, with higher female to male ratio. The mean duration of disease was 7.88 ± 1.76 years with minimum and maximum duration as 5.5 and 11 years. A total of 61(61%) cases had 5.1-8 years and 39(39%) cases had > 8 years of duration. The mean BMI was 30.07 ± 4.30 kg/m^2 with minimum and maximum BMI as 23.20 and 37 kg/m^2. There were 60(60%) obese and 40(40%) non-obese cases. A total of 77(77%) cases had autonomic neuropathy while rests of 23(23%) cases did not have autonomic neuropathy (Figure l). There were 23(23%) cases who had mild, 32(32%) had moderate and 16(16%) cases had severe autonomic neuropathy (Figure II).

When data was stratified for age, among 20-40 years old and 41-60 years old cases 25(78.1%) cases and 52(76.5%) cases had autonomic neuropathy, the frequency of autonomic neuropathy in both age groups was statistically same, p-value > 0.05 (Table 3). There were 24(82.8%) male and 53(74.6%) female cases that had autonomic neuropathy; the frequency of autonomic neuropathy was statistically same in male and female cases, p-value > 0.05 (Table 3). In cases with duration of disease as 5.1 – 8 years, 47(77%) cases had autonomic neuropathy and among cases who had duration since

>8 years, 30(76.9%) cases had autonomic neuropathy. The frequency of autonomic neuropathy was statistically same in both groups of duration, p-value > 0.05 (Table 3).

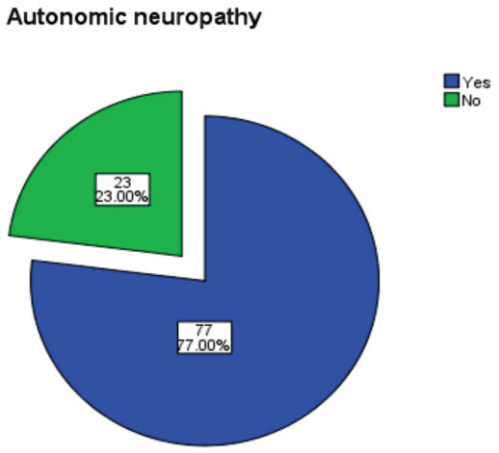

Fig-l: *Distribution of autonomic neuropathy*

A total of 43(71.7%) obese and 34(85%) non-obese cases had autonomic neuropathy, the frequency of autonomic neuropathy was statistically same in both obese and non-obese cases, p-value > 0.50 (Table 3).

Table 2: *Grading/Severity of cardiac Autonomic Neuropathy.*

Grade	Criteria	Severity of Cardiac Autonomic Neuropathy (CAN)
0	No abnormality in test	Nil
I	Only 1 test showed abnormality	Mild
II	2 tests showed abnormality	Moderate
III	≥3 tests showed abnormality	Severe

Table 1: *Reporting of cardiovascular autonomic reflexes tests.*

	Normal	Borderline	Abnormal
1. HR response to Valsalva maneuver (Valsalva ratio)	>1.21	1.11-1.20	<1.10
2. HR variation when inhaling deeply	>15 beats/min	11-14 beats/min	<10 beats/min
3. Response of HR when standing (30:15 ratio)	>1.04	1.01-1.03	<1.00
4. Reaction of HR to standing i.e. BP fall in systolic BP in response to standing (mmHg)	<10	11-29	>30
5. Rise in Diastolic blood pressure as a result of prolonged hand grasp (mmHg)	>16	11-15	<10

Table 3: *Comparison of frequency of Autonomic neuropathy in both age groups, male and female cases, with respect to duration of symptoms (years) and Body Mass Index (BMI).*

		Autonomic neuropathy		Total	
		Yes	No		
Age groups	20-40	25(78.1%)	7(21.9%)	32(100.0%)	Chi-square = 0.034
(years)	41-60	52(76.5%)	16(23.5%)	68(100.0%)	P-value = 0.854
Total		77(77.0%)	23(23.0%)	100(100.0%)	
Gender	Male	24(82.8%)	29(100.0%)	29(100.0%)	Chi-square = 0.765
	Female	53(74.6%)	71(100.0%)	71(100.0%)	p-value = 0.382
Total		77(77%)	23(23%)	100(100.0%)	
Duration (years)	5.1-8	47(77%)	14(23%)	61(100.0%)	Chi-square = 0.000
	> 8	30(76.9%)	9(23.1%)	39(100.0%)	P-value = 0.988
Total		77(77%)	23(23%)	100(100.0%)	
BMI	Obese	43(71.7%)	17(28.3%)	60(100.0%)	Chi-square = 2.409
(kilogram/square meter)	Non-Obese	34(85.0%)	6(15.0%)	40(100.0%)	P-value = 0.121
Total		77(77.0%)	23(23%)	100(100.0%)	

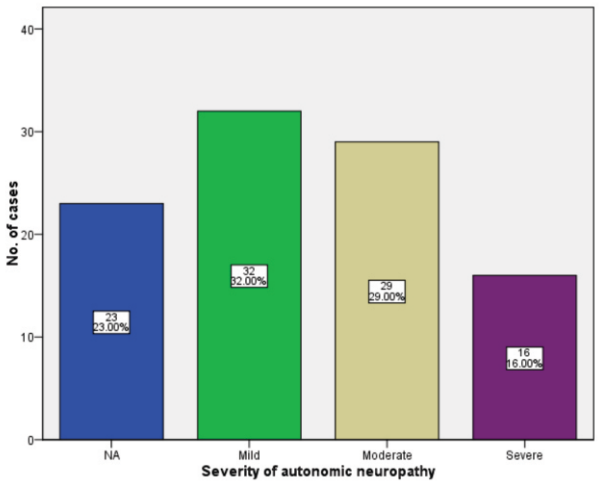

Fig ll: *Distribution of severity of autonomic neuropathy*

Discussion

An essential regulating system that helps to maintain homeostasis is the autonomic nerve system (ANS). For the immune system to effectively respond to disruptions of the internal and external surroundings, accurate coordination of the ANS with other organ systems is crucial.[15-16]

A study was conducted by Syngle V17 to see the relationship between RA and autonomic dysfunction. A total of 25 RA patients and 25 age- and sex-matched healthy controls were enrolled in this research. According to Ewing, five cardiovascular reflex tests can be used to evaluate autonomic function. Three tests—the heart rate response to deep breathing (HRD), heart rate response when standing (HRS), and the Valsalva maneuver —were used to diagnose parasympathetic dysfunction. Two tests—the handgrip test and the BP response to standing—were used to investigate sympathetic dysfunction. Sudoscan evaluated the function of the peripheral sympathetic autonomic nervous system. Measures specific to RA including inflammatory markers (DAS 28, ESR, C-reactive protein, TNF-, IL-1 and IL-6) were investigated. In comparison to healthy controls, it was discovered that RA patients had considerably reduced HRS, HRD, response of BP to hand grip, and sudomotor function. Pro-inflammatory cytokines were found to be considerably greater ($p<0.05$) in patients of RA when compared to controls who are considered to be healthy. DAS 28 and HRD in RA had a strong correlation. HRS and HRD have a strong correlation with ESR. Significant correlations have been shown between TNF- and sudomotor function, BP response to standing, HRD, and HRS. The relationship between IL-6 and HRS was shown to be significant. Patients who were seropositive displayed sudomotor impairment. Thus, it was determined that seropositivity, severity of disease, and pro-inflammatory cytokines are all linked in RA. Our research, however, focuses solely on the frequency of autonomic dysfunction in RA. Further research is required to determine the link between dysfunction of autonomic nervous system in RA and disease severity, seropositivity, and pro-inflammatory cytokines.

In his work, Peçanha T et al18showed that RA is a chronic autoimmune inflammatory disease that damages the heart and vasculature in addition to the synovial joints, compounding the negative effects of the illness. In fact, cardiovascular disease (CVD) is the main factor contributing to morbidity and mortality in RA. Traditional risk factors such as diabetes, dyslipidemia, hypertension, and inactivity can help to explain some of the higher risks of CVD in RA. Recent research has, however, shown additional elements that have a role in the pathophysiology of CVD in RA. Among them, cardiovascular autonomic dysfunction, also known as impairment in autonomic cardiovascular regulation, has drawn more attention recently.

In order to look for the association of autonomic dysfunction in RA patients and its severity, Aggarwal D.[9] conducted a study. He investigated autonomic symptoms in order to subjectively assess ANS. Heart rate (HR) reaction to deep breathing, standing, and the Valsalva maneuver, as well as blood pressure (BP) response to standing and sustained handgrip, were used to measure cardiac autonomic involvement. 31 healthy volunteers and 31 RA patients with matched ages and sexes were recruited. Study revealed that patients (80.65%) had a substantially higher prevalence of cardiac autonomic neuropathy than controls (51.61%) ($p=0.016$). This is consistent with our study, which found that autonomic dysfunction affected 77% of the patients.

Ingegnoli F.[19] measured heart rate (HR) as well as variability in heart rate (HRV) to examine cardiovascular autonomic dysfunction in RA. It was discovered that the association between RA's imbalance of the autonomic nervous system and the cardiovascular system could partially account for the well-documented increase in cardiovascular disease and RA-related mortality, which could not be fully explained by conventional risk factors like diabetes, hypertension, hyperlipidemia, etc.

Research was conducted on Cardiac Autonomic Neuropathy in RA by N. K. Thulaseedharan.[20] He claims that an excellent bedside tool for identifying people with cardiac autonomic neuropathy is resting tachycardia. He discovered that significant cardiac autonomic neuropathy affected 54.5% of the subjects with resting tachycardia. In contrast, our study found that 16 (16%) cases had severe autonomic neuropathy, whereas 32 (32%) cases had moderate autonomic neuropathy.

In a study by Nejad ZJ et al[21] cardiovascular autonomic neuropathy (CAN) in RA patients were evaluated using

measures of cardiovascular autonomic function. 44 RA patients were enrolled. Cardiovascular reflex tests were used to evaluate CAN. This included BP reaction to standing up, sustained handgrip, and heart rate disparity during deep breathing. They also included heart rate response to the Valsalva maneuver and to standing up. The results did not display a statistically significant deterioration in the cardio-vascular autonomic function of RA patients. Which is contrary to our study which showed, 77% of RA cases (more than the third quarter) exhibited cardiac autonomic neuropathy.

In order to evaluate the frequency and severity of autonomic dysfunction in RA as well as the association between inflammatory indicators, illness severity, and serological variables, Jahan K and colleagues[7] did a cross-sectional study on 60 RA patients. Additionally, they checked for cardiovascular autonomic neuropathy using the five cardiovascular reflex tests that Ewing listed. According to the findings, 78% of RA patients had CAN. They came to the conclusion that RA and autonomic neuropathy were significantly related. Our study's findings are quite consistent with these conclusions. In our study, autonomic neuropathy was present in 77% of RA patients.

Our study is constrained in various ways by a number of issues. We were only able to enroll participants from one academic institution in our study. The sample size was rather small, which is another drawback. Another flaw in this research was its cross-sectional design, which does not demonstrate a causal connection. The final drawback is that the more subtle abnormalities in cardiovascular autonomic function may be difficult to detect with the existing cardiovascular reflex test methods. Therefore, extensive prospective cohort studies with more sensitive diagnostics are needed to emphasize the changes in the cardiovascular autonomic function of RA patients.

Conclusion

Autonomic neuropathy is a common, sub clinical extra-articular manifestation of RA. Our study revealed that 77% cases of RA patient had Autonomic Neuropathy. The sympathetic as well as parasympathetic components of ANS are often affected by autonomic neuropathy in RA which can be the predictor of sudden cardiac death. Thus autonomic dysfunction must be taken into account and diagnosed using specialized clinical and electrophysiological testing for better patient management and to reduce the related risk of disease severity and death in patients of RA.

Conflict of Interest: *None*

Funding Source: *None*

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