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Original Article

Internal Medicine Section

Electrophysiological Profile of Neuropathy in Rheumatoid Arthritis Patients: A Cross-sectional Study

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ABSTRACT

Introduction: Rheumatoid Arthritis (RA) is a chronic inflammatory condition that mainly affects the small joints of hands and legs. Peripheral neuropathy is one of the most common manifestations of Rheumatic disease.

Aim: To describe the electrophysiological profile of neuropathy in RA patients attending the Rheumatology Clinic of a Medical College in Southern India.

Materials and Methods: The present cross-sectional study was conducted in Department of Rheumatology, Coimbatore medical college, Coimbatore, Tamil Nadu, India, between September 2019 and September 2020. A total of 50 consecutive patients diagnosed with RA based on American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) criteria 2010, with disease duration more than two years were included in the study. Clinical examination, Erythrocyte Sedimentation Rate (ESR), Rheumatoid Factor (RF), Renal Function Tests (RFT), Liver Function Tests (LFT), Complete Blood Count (CBC), Human Immunodeficiency Virus (HIV) antibody testing, blood sugar and Nerve Conduction Studies (NCS) were performed in patients satisfying inclusion and exclusion criteria. Chi-square test was used to compare proportions of categorical variables and t-test was used to compare means across groups with various types of axonal neuropathy.

Results: Of 50 patients with RA, 37 (74%) patients had peripheral neuropathy electrophysiologically, whereas 27% (10 patients of 37) had sensory symptoms. Subclinical neuropathy was present in 73% (27 patients out of 37) of patients. Mixed non-compressive neuropathy of the lower limb was most common 25 (50%) Statistically significant association was found between the presence of neuropathy and RF positivity and also with duration of illness. No association was found with age, sex, ESR levels.

Conclusion: Prevalence of subclinical peripheral neuropathy is very common among patients with RA. Electrophysiological studies can detect peripheral neuropathy earlier. Hence, all RA patients should undergo NCS periodically to detect neuropathy early and to prevent development of complication related to it.

Keywords: Carpal tunnel syndrome, Nerve compression syndromes, Nerve conduction studies, Rheumatoid factor, Rheumatoid vasculitis

INTRODUCTION

The RA is a chronic inflammatory condition affecting mainly the small joints of hands and legs [1]. It is a systemic disorder with Extra-Articular Manifestations (EAM), and these may be the first presenting symptom in patients with RA. Prevalence of EAM in RA patient ranges between 40-70% [2-4]. EAMs can involve skin, eyes, heart, lungs and nervous system. Severity of the EAM depends on various factors like RF positivity, ANA positivity, smoking and early onset of the disease [5].

Rheumatoid vasculitis is the cause for EAM in a majority of the cases. It can lead to various cutaneous and organ specific manifestations. Vasculitides mainly affects the skin and peripheral nerves [6,7]. In RA patients, the most common neurological manifestation is peripheral neuropathy. Both compressive and non-compressive neuropathies are seen in RA patients. Compressive neuropathy is reported as most common type of neuropathy in RA patients. Studies report that the most common compressive type of neuropathy seen in RA patient is Carpel Tunnel Syndrome (CTS) [8-10]. Various literatures shows the prevalence of CTS as 3.5 to 23.3% [11,12]. Neuropathy in RA may result secondary to entrapment, vasculitis, and drug toxicity [1]. The prevalence of peripheral neuropathy in patients with RA ranges from 0.5-85% [13]. Pain, paresthesia and muscle weakness are common manifestations of peripheral neuropathy in patients with RA [8,14].

Nerve Conduction Studies have been widely used currently in determining peripheral nervous system dysfunction. The three main mechanisms known to affect peripheral nerves are: 1) Axonal degeneration - detected by measuring the reduction in amplitude of Sensory Nerve Action Potential (SNAP) and Compound Muscle Action Potential (CMAP); 2. Demyelination - detected by measuring the reduction in conduction velocity; and 3) Conduction block - detected by recording a drop in the CMAP amplitude. NCS can only evaluate large myelinated fiber functions and hence cannot be utilized in polyneuropathies affecting predominantly the small fibres. Since the neuropathic changes observed in RA patients are seen predominantly in large myelinated fibres, NCS are extensively used in the evaluation of peripheral neuropathy in RA patients. Electrophysiological NCSs can detect and classify neuropathy in patients with RA. As peripheral neuropathy is one of the most common morbidity in RA patients [15]; early detection and management of neuropathy can reduce the morbidity and increase functionality of the RA patients there by improving the quality of life [8]. Peripheral Neuropathy in RA is less studied in South Indian population [3]. The present study aimed to describe the electrophysiological profile of neuropathy in RA patients and secondary objective was to determine the factors associated with peripheral neuropathy in South Indian population by conducting cross-sectional study in a tertiary care hospital in Coimbatore, Tamil Nadu, India.

MATERIALS AND METHODS

The present cross-sectional study was undertaken in 50 RA patients attending the Outpatient Department (OPD) of Rheumatology, in collaboration with the Department of Neurology in Coimbatore Medical

College Hospital, Coimbatore, Tamil Nadu, India from September 2019 to September 2020. Informed consent from obtained from the study participants. The current study posed minimal risk to study participants. The data collected was anonymised to ensure privacy of study participants. The study was approved by the Institutional Ethics Committee of Coimbatore Medical College Hospital (IEC/2019/M230).

Sample size calculation: Sample size was calculated using the software "Sample size tables for Clinical studies" [16]. With a predicted approximate prevalence rate of peripheral neuropathy as 35% in RA [17-19] with a 95% confidence interval and absolute precision of 10%, the estimated sample size for this study was 48. Hence, around 50 patients were included for analysis for determining statistical significance ($p<0.05$) in this cross-sectional study.

Inclusion criteria: Patients satisfying ACR/ EULAR criteria 2010 and disease duration more than or equal to 2 years were included in the study.

Exclusion criteria: Minors (below the age of consent), patients not capable of giving consent (psychiatric and mentally challenged patients), patients with diabetes mellitus, HIV infection, leprosy, hypothyroidism, amyloidosis, liver disease, chronic renal failure, malignancy and alcohol intake. Patients who underwent orthopedic surgery Patients not willing to undergo study were excluded from the study.

Study Procedure

Detailed history of sensory symptoms such as pins and needle sensation, burning, numbness, and motor symptoms such as weakness of distal extremities was taken in the form of structured questionnaire. Detailed sensory examination in the form of testing for loss of superficial touch sensation, pain, temperature, vibration sense, and two-point discrimination were done. Laboratory investigations like ESR, RF, RFT, LFT, CBC, HIV antibody testing and blood sugar were performed. Patients selected were further subjected to NCS - electrophysiological study.

Nerve Conduction Study (NCS): NCS was performed in the Neurology Department, Coimbatore Medical College Hospital. NCS was done bilaterally on both upper and lower limbs. Both motor and sensory nerve conduction parameters were tested. It was done by peripheral nerve stimulation. Peripheral nerves were activated by placement of stimulating cathode and anode over the nerve, generating an electrical impulse. Duration and strength of stimulus can be adjusted, of which 0.1-0.2 milliseconds were utilized in the study. Greater was the strength of the stimulus, more the number of nerve fiber were recruited and thus action potential was increased until it reached the maximum. Recording of the electrical activity resulting from nerve excitation was done using surface electrodes. Electrodes were placed over a distal muscle, sensory nerve or cutaneous nerve distribution. Motor nerve studies were recorded from muscles. In motor NCSs, CMAP is recorded. Motor conduction was recorded by orthodromic method. (The stimulus is conducted from nerve to muscle in the direction of physiologic conduction). Sensory nerve conduction can be recorded in either orthodromic or antidromic method. For sensory recording, antidromic method was utilised.

Motor conduction studies: Nerves selected for study in upper limb were ulnar and median and measurement was taken from elbow and wrist. In lower limbs, tibial and peroneal nerves were used for study and electrodes were placed on knee and ankle. Conduction velocities, latency and amplitudes were measured and compared with normal values.

Sensory conduction studies: Nerves studied for sensory conduction studies in upper limb were ulnar and median nerves. Electrode was placed in wrist for measurement. In lower limb, sural nerve was used, and the electrode was placed in mid-calf. Conduction velocities, amplitude, latency were recorded by antidromic method. Following electrophysiological parameters (CMAP's, SNAP's and conduction velocity, latency and amplitude) were measured and interpreted to determine the type of neuropathy. Data obtained from the NCS was compared to age, sex, duration of the disease RF and ESR levels.

STATISTICAL ANALYSIS

Chi-square test was used to compare the association between dependent variables and Levene's T test was used to compare the association between independent variables. All statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software version 27. All analysis were arrived at 5% level of significance and p value <0.05 were considered as significant.

RESULTS

During the study period, 50 patients participated in the study. Out of 50 patients, 37 (74%) had peripheral neuropathy electrophysiologically, whereas only 27% (10 patients of 37) had sensory symptoms. Subclinical neuropathy was present in 73% (27 patients out of 37) of patients. Axonal neuropathy was detected by NCS in all 37 (74%) neuropathy patients. Non-compressive type of neuropathy was seen in all 37 patients and 2 (4%) among them also had compressive neuropathy. Various patterns of axonal neuropathy were observed in the NCS. Mixed non-compressive neuropathy of the lower limb was most common (n=25; 50%) followed by mixed non-compressive neuropathy of the upper limb (n=15; 30%), sensory non-compressive neuropathy of upper limb (n=13; 26%), motor non compressive neuropathy of lower limb (n=12; 24%) and compressive neuropathy (carpal tunnel syndrome (n=2; 4%). No demyelinating neuropathy pattern was detected in the study population. Study participants had a mean (SD) age of 49.7±11.9 years of the study participants, 38 (76%) were female. RF was positive in 20 (40%) of study population [Table/Fig-1].

Characteristics	Values
Age (years); mean *(SD)*	49.7 (11.9)
Gender	n (%)
Female	38 (76)
Male	12 (24)
Rheumatoid Factor (RF)	
Positive	20 (40)
Axonal neuropathy	
Present	37 (74)
Pattern of axonal neuropathy	
Sensory non-compressive neuropathy	
Upper limb	13 (26)
Lower limb	0 (0)
Motor non-compressive neuropathy	
Upper limb	2 (4)
Lower limb	12 (24)
Mixed non-compressive neuropathy	
Upper limb	15 (30)
Lower limb	25 (50)
Carpal tunnel syndrome - compressive neuropathy	2 (4)

[Table/Fig-1]: Characteristics of study participants.

There was no significant difference in mean age, and mean ESR between those with peripheral neuropathy and those without peripheral neuropathy [Table/Fig-2]. No significant association was found between sex and RF positivity (p-value=0.417). We found statistically significant (p-value=0.03) difference in proportion of patients with RF positivity between those with peripheral neuropathy (n=18; 48.6%) and those without peripheral neuropathy (n=2; 15.4%). Significant association was observed between the occurrence of axonal neuropathic changes and duration of illness (p-value=0.01) [Table/Fig-2].

Characteristics	Axonal neuropathy		p-value
	Present (N=37)	Absent (N=13)	
	Mean (sd)	Mean (sd)	
Age in years	50.6 (12.6)	47.2 (9.8)	0.40
Duration of Rheumatoid Arthritis (RA) in (years)	5.7 (3.5)	3.1 (2.4)	0.01
Erythrocyte Sedimentation Rate (ESR) in (millimeter)	32.0 (7.0)	33.0 (5.4)	0.49
Rheumatoid Factor (RF)	**n (%)**	**n (%)**	
Positive	18 (48.6)	2 (15.4)	0.03
Negative	19 (51.4)	11 (84.6)	

[Table/Fig-2]: Factors associated with axonal neuropathy.

Pattern of neuropathy was compared with various parameters like age, sex, duration of illness, ESR and no statistical significant association was seen [Table/Fig-3]. In the present study, no significant association was seen between symptoms of neuropathy and various parameters like age, duration of illness, sex of the patient and RF [Table/Fig-4].

S. No	Clinical parameters	Axonal neuropathy pattern	Frequency	Mean±2SD	p-value
1	Age when neuropathy diagnosed (years)	Sensory NCN-UL	Present	49±16	0.06
			Absent	50±10	
		Sensory NCN-LL	Present	-	-
			Absent	50±12	
		Motor NCN - UL	Present	43±7	0.41
			Absent	50±12	
		Motor NCN - LL	Present	47±17	0.10
			Absent	50±10	
		Mixed NCN - UL	Present	54±10	0.13
			Absent	48±12	
		Mixed NCN - LL	Present	52±10	0.31
			Absent	47±13	
		CTS - CN	Present	58±3	0.17
			Absent	49±12	
2.	Duration since neuropathy diagnosed (years)	Sensory NCN-UL	Present	5.77±3.6	0.86
			Absent	5.51±3.2	
		Sensory NCN-LL	Present	-	-
			Absent	5.58±3.2	
		Motor NCN - UL	Present	12.5±3.5	0.94
			Absent	5.29±2.9	
		Motor NCN - LL	Present	5.92±4	0.23
			Absent	5.47±3	
		Mixed NCN - UL	Present	5.27±3	0.82
			Absent	5.71±3.4	
		Mixed NCN - LL	Present	5.64±3.4	0.68
			Absent	5.52±3.2	
		CTS - CN	Present	4±1.4	0.21
			Absent	5.65±3.3	
3.	Erythrocyte Sedimentation Rate (ESR) in mm	Sensory NCN-UL	Present	32±7.9	0.42
			Absent	32.3±6.2	
		Sensory NCN-LL	Present	-	-
			Absent	32.2±6.6	
		Motor NCN - UL	Present	28.5±2.1	0.20
			Absent	32.7±6.7	
		Motor NCN - LL	Present	31.8±6	0.41
			Absent	32.4±6.9	
		Mixed NCN - UL	Present	31.2±6.9	0.86
			Absent	32.7±6.5	
		Mixed NCN - LL	Present	32.1±7.6	0.26
			Absent	32.4±5.6	
		CTS - CN	Present	32.5±4.9	0.54
			Absent	32.2±6.7	
4.	Sex (Male/ Female)	Sensory NCN-UL	Present	5/8	0.15
			Absent	7/30	
		Sensory NCN-LL	Present	-	-
			Absent	12/38	
		Motor NCN - UL	Present	0/2	0.41
			Absent	12/36	
		Motor NCN - LL	Present	3/9	0.92
			Absent	9/29	
		Mixed NCN - UL	Present	4/11	0.77
			Absent	8/27	
		Mixed NCN - LL	Present	8/17	0.18
			Absent	4/21	
		CTS - CN	Present	1/1	0.38
			Absent	11/37	

[Table/Fig-3]: Association between axonal neuropathy patterns and various clinical parameters.

S. No	Clinical parameters	Category	Peripheral neuropathy symptom		p-value
			Present	Absent	
1.	Sex	Male	18	2	0.74
		Female	19	11	
2.	Rheumatoid Factor (RF)	Present	4	16	1
		Absent	6	24	
3.	Mean age (years) ± 2 SD	-	58±7	49±13	0.09
4.	Mean illness duration (years) ± 2 SD	-	5.1±2.8	5.7±3.4	0.37

[Table/Fig-4]: Association between peripheral neuropathy symptoms and various clinical parameters.

DISCUSSION

Among the 50 patients, 12 (24%) were males and 38 (76%) were females. The female to male ratio in the present study was 3:1, similar to the study reported by Shi W et al., [20]. Higher number of females can be due to the genetic and hormonal difference where oestrogen is found to have a role in causation as it increases immunogenicity. In the present study, the age of the study population was between 20-80 years and the mean age of the study population falls in the 5th decade (49.7 yrs) as similarly reported by Turesson C et al., [21]. Recently, there is a shift in the RA incidence to older age group [22]. As the age of onset is delayed, the chances for development of complications are also increased.

The prevalence of peripheral neuropathy among RA patients in our study was 74% which is similar to the study conducted by Nidhi Kaeley et al., [23]. In the study conducted by Sharma G et al., an incidence as high as 84% was reported [24]. On the contrary, studies conducted by Biswas M et al., and Aneja R et al., reported the prevalence of neuropathy in RA patients as 39.19% and 37.87%, respectively [17,18]. Prevalence varies widely among the reported studies between 37.87% and 84%. [17,18,23,24].

All patients with peripheral neuropathy in the current study had axonal type of neuropathy and no demyelination type of neuropathy observed. Non-compressive neuropathy was the most common type of axonal neuropathy in the present study (74%) which is in agreement with the study conducted by Kaeley N et al., [23]. Among the axonal neuropathy patterns, mixed sensory motor neuropathy affecting the lower limbs (50%) was the most common type of neuropathy recorded in this study, followed by the pure sensory neuropathy of upper limbs (26%). Other studies conducted

by Lanzillo *B* et al., Yazdchi M et al., and Agarwal V et al., also reported mixed sensory motor neuropathy as most common type of neuropathy type in RA patients [13,25,26]. As against the present study, sensory neuropathy was found to be common in reports of Albani G et al., and Biswas M et al., [17,27]. In the present study, 2 people (4%) were found to have Carpel tunnel Syndrome that was similar to the studies reported by M Biswas et al and a Turkish study by Aktekin L et al., [17,28]. As regard to the occurrence of CTS various studies show varying percentage ranging between 3.5-23.3% [11,12,29].

In the present study, no association was found between the age of onset and the occurrence of peripheral neuropathy in RA patients. No gender predilection was also found in the development of neuropathy changes in RA patients. There was no association found between ESR levels and development of neuropathic changes. Significant association was found between the duration of the disease and development of peripheral neuropathy. The findings of the present study agreed with the findings of Sim MK et al., [19]. In the present study, type of neuropathy was compared with various parameters like age, sex, duration of the disease, ESR, and did not find statistically significant difference.

A 40% of study participants were positive for RF. This result questions the use of RF as a diagnostic marker for RA. This finding agrees with the study of Shmerling RH and Delbanco TL, and Thomas MJ et al., [30,31]. From the present study we could not make out any association between sex and RF positivity. Significance was found between RF positivity and peripheral neuropathy which was similar to the study findings of Kaeley N et al., Biswas M et al., and Albani G et al., [17,23,27]. No association was found between RF positivity with any particular pattern of neuropathy.

In the present study, symptoms of peripheral neuropathy like pins and needle sensation, numbness were present in 27% of the RA patients with neuropathic changes. Rest of the 73% of RA patients with neuropathy was asymptomatic. Lanzillo B et al., reported a similar figure in relation to the percentage of RA patients with neuropathy presenting with symptoms of peripheral neuropathy [25]. There was no significant association seen between symptoms of neuropathy and age, or with duration of the disease or with gender of the patient.

Limitation(s)

The present study was single centric study involving South Indian population. This limitation can be addressed in future by designing a multicentric study across Indian subcontinent to understand the true prevalence of peripheral neuropathy and their patterns with risk factors, in patients with RA.

CONCLUSION(S)

Subclinical peripheral neuropathy is common in patients with RA. NCS can detect peripheral neuropathy and its various types. Among various pattern of axonal neuropathy the mixed non-compressive neuropathy involving the lower limbs was the commonest pattern observed.We recommend using NCS for screening of patients with RA during routine follow-up visits for early detection of neuropathy to prevent development of debilitating co-morbidities and thereby improving quality of life.

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