

# Prevalence, types, clinical associations, and determinants of peripheral neuropathy in rheumatoid patients

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## Abstract

**Background:** Rheumatoid arthritis is a multi-system autoimmune disorder predominantly involving multiple small and large joints along with certain extra-articular manifestations. The presence of peripheral neuropathy in patients with rheumatoid arthritis contributes significantly to the functional limitation in patients with rheumatoid arthritis. **Objectives:** To study the prevalence, types, and determinants of peripheral neuropathy in patients with rheumatoid arthritis. **Materials and Methods:** We studied 74 patients with rheumatoid arthritis of at least 2 year duration for the presence of peripheral neuropathy both clinically and electrophysiologically. The data obtained were entered into a database and continuous variables were analyzed using the Student t test and categorical variables were analyzed using the chi-square test. **Results:** Peripheral neuropathy was detected in 39.19% (29 out of 74 patients) patients on electrophysiologic testing and 82.76% (24 out of 29 patients) of the patients were asymptomatic. There was significant association between the presence of peripheral neuropathy and disease duration and rheumatoid factor positivity by the latex agglutination method. Sensory neuropathy was the most common form detected. **Conclusions:** Our study shows that subclinical peripheral neuropathy particularly sensory neuropathy which is not related to disease severity is very common in patients with prolonged disease duration.

## Key Words

Mononeuritis, neuropathy, peripheral, rheumatoid, sensory, sensorimotor

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## Introduction

Rheumatoid arthritis (RA) is a multisystem autoimmune disorder characterized by chronic deforming arthritis of predominantly small and large joints along with extra-articular manifestations such as interstitial lung disease, rheumatoid nodules, and ophthalmic involvement like scleritis, vasculitis, and neurological manifestations including various forms of peripheral neuropathy. The disability and functional limitation of patients with long-standing RA result in lost work days and significant impairment with far reaching social and economic impacts. The presence of peripheral neuropathy in patients with RA is an often overlooked aspect; however, it contributes significantly to the functional limitation in patients with RA. Hart and Goldin<sup>[1]</sup> were the first to describe a definitive series

of patients with neuropathy and rheumatoid disease. The peripheral neuropathy commonly encountered in patients with RA are- (a) distal sensory, (b) distal sensorimotor, (c) mononeuritis multiplex, (d) entrapment.<sup>[2-8]</sup> The present study was conducted at the rheumatology out-patient clinic of the hospital and aimed to find out the prevalence and types of peripheral neuropathy (symptomatic as well as asymptomatic) in patients as well as to study the clinical characteristics, determinants, and associations of peripheral neuropathy.

## Materials and Methods

A detailed clinical history was obtained (as per a structured questionnaire which specifically included symptoms like numbness, tingling, burning feeling, sensation of pins and needles of the extremities as well as motor symptoms like wasting, weakness of extremities) and a physical examination was done in the 74 patients attending rheumatology clinic, between May 2007 and November 2008 with diagnosed RA of at least 2 year duration (as per the American Rheumatological Association/ARA criteria 1987)<sup>[9]</sup> to find out any evidence of peripheral neuropathy. The severity of RA was assessed as per the disease activity score (DAS of greater than 3.2 was considered as active disease) of 28 joints. The patients were also examined for the presence of extraarticular involvement

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in the form of subcutaneous nodules, interstitial lung disease, and features of vasculitis like Raynaud's phenomenon, digital infarctions, and palpable purpura. The past treatment records were examined and all the patients were asked about prior history of intake of steroids and disease-modifying anti-rheumatic drugs (DMARDs) including methotrexate intermittently or continuously for at least 1 year. X-rays of hand were done in the patients to look for evidence of joint-space erosions, and all patients underwent chest x-ray and pulmonary function test to look for the presence of interstitial lung disease. The patients with suggestions of restrictive lung disease (five patients) underwent high resolution computerized tomogram (HRCT) scan of chest for confirmation. Rheumatoid factor was tested for qualitatively with latex agglutination test.

The following investigations were done in all the patients – (1) hemoglobin, total and differential leucocyte count, platelet count, and peripheral blood smear, erythrocyte sedimentation rate (ESR), prothrombin time (PT), and partial thromboplastin time (PTT); (2) fasting blood sugar, blood urea nitrogen, and creatinine; (3) liver function tests for bilirubin, albumin, globulin, transaminases, and alkaline phosphatase; (4) thyroid function tests; and (5) anti-nuclear antibody (ANA).

All the 74 patients were tested by a nerve conduction velocity (NCV) study in the Neurology Department of our Institute. The NCV study was carried out on bilateral median, ulnar, radial, peroneal, tibial, and sural nerves as described by Misra and Kalita<sup>[10]</sup> and the findings were compared. The NCV study was carried out at room temperature. The palm-wrist conduction studies were done on the patients to detect carpal tunnel syndrome.

Unconscious and severely ill patients were excluded from the study. Persons who were mentally impaired or unable to give consent or suffering from diabetes, hypothyroidism, uremia, cirrhosis of liver, malignancy, and those on neurotoxic drug, alcohol, toxic exposure, or other autoimmune disease were excluded. Approval was taken from institutional ethics committee and informed consent was obtained from all the patients.

The data obtained were entered into a database and continuous variables were analyzed using the Student t test and categorical variables were analyzed using the chi-square test. The statistical analysis was done using the microsoft excel (MS office) work sheet. A P value less than 0.05 was considered statistically significant.

## Results

There were 29 patients (39.19%) who were diagnosed as having peripheral neuropathy after electro physiologic testing. Five patients (17.24%) had some clinical evidence of peripheral neuropathy. (Two patients had paresthesias or pins and needle sensations on both lower limbs and on clinical examination they had impaired vibration sense in lower limbs as well as loss of ankle and knee jerk on motor examination and other three patients had pain over thenar eminence which was particularly worse at night, the patients had carpal tunnel syndrome). The other 24 patients (82.76%) had no clinical evidence of peripheral neuropathy. Fifteen (51.72%) patients with peripheral neuropathy had pure sensory neuropathy on the NCV study. Three patients (10.34%) had carpal tunnel syndrome. The other

types of peripheral neuropathy detected are shown in Table 1. All the patients had axonal type of peripheral neuropathy and six patients (20.69%) had predominantly sensory impairment in the sensorimotor group of peripheral neuropathy and two patient (6.90%) had predominantly motor involvement.

The demographic analysis of patients with RA showed that maximum number of patients (18 or 62.07%) with peripheral neuropathy was in age group 41-50 years and 13 patients (44.83%) were female in the same age group. Fifty seven patients (77.03%) of the entire patient population with RA were female.

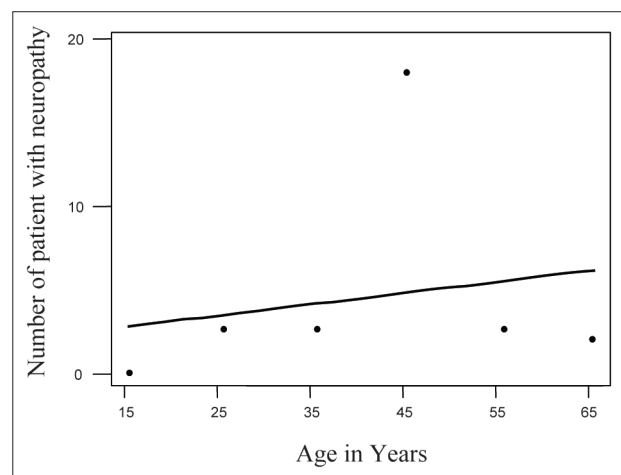
The correlation coefficient of age and number of patients with peripheral neuropathy was +0.204 and that between age and number of patients without peripheral neuropathy was +0.029. Even though there was a stronger positive correlation between age and patients with peripheral neuropathy, the difference was not statistically significant by the F test [Figure 1].

The mean duration of RA in patients with neuropathy (61.17 months, standard deviation = 17.25 months) was significantly different from patients without peripheral neuropathy (43.38 months, standard deviation-11.97 months). Twenty four patients (82.76%) with peripheral neuropathy showed rheumatoid factor positivity and it was significantly different from the patients without peripheral neuropathy. The other clinical characteristics were same in both the patient groups [Table 2]. All the patients with mononeuritis multiplex had

**Table 1: Different types of peripheral neuropathy in rheumatoid arthritis patients**

Types of neuropathy	Sex distribution		Total no. of cases	Percentage of total cases
	M	F		
Pure sensory	2	13	15	51.7
Sensorimotor	3	5	8	27.7
Mononeuritis multiplex	1	2	3	10.3
Only entrapment neuropathy (CTS)	1	2	3	10.3
Total	7	22	29	100

CTS = Carpal tunnel syndrome; M = Male; F = Female



**Figure 1: Showing a regression plot depicting relationship of age with the number of patients with neuropathy ( $y = 1.94048 + 7.14E-02x$ ,  $R-sq = 0.042$ )**

features of vasculitis (Two patients had digital infarcts and one patient had purpuric spots). The standard indicators of severity of rheumatoid patients such as disease activity score, extra-articular manifestations, usage of DMARDs and corticosteroids and erosions in hand X-ray were not significantly related to peripheral neuropathy.

## Discussion

The present study conducted over a period of one and half years showed that pure sensory form of peripheral neuropathy was the most common type detected in rheumatoid patients and peripheral neuropathy was significantly related to disease duration and rheumatoid factor positivity. The neuropathies detected were all non-demyelinating in nature.

In this study, we found electrophysiological evidence of peripheral neuropathy in 29 out of 74, i.e. 39.19% of rheumatoid patients. This finding is quite similar to those of Aneja *et al.*<sup>[11]</sup> (2007) who found it to be 37.87% in their study group. Dani *et al.*<sup>[12]</sup> (2005) found subclinical neuropathy in 50% of patients and 10% had clinical feature of peripheral neuropathy. The prevalence of peripheral neuropathy varies widely in different studies. [Table 3] The variability in selection criteria, duration

**Table 2: Clinical characteristics of patients with and without peripheral neuropathy**

	With peripheral neuropathy	Without peripheral neuropathy	P value
Mean duration in months	61.17 (SD = 17.25)	48.38 (SD = 11.97)	0.001
Duration ≥ 60 months	22	7	0.000
Male: Female	7:22	10:35	0.848
RF positivity	24	20	0.001
DAS (mean value)	4.19 (SD = 0.783)	4.29 (SD = 0.815)	0.56
ILD	3	2	0.32
SCN	8	11	0.763
Features of vasculitis <sup>§</sup>	5	2	0.07
Prior use of corticosteroids	25	37	0.649
Prior use of DMARDs	20	31	0.994
Joint-space erosions in hand X-ray	20	28	0.55

DAS = Disease activity score; DMARD = Disease-modifying anti-rheumatic drugs; ILD = Interstitial lung disease; RF = Rheumatoid factor; SCN = Subcutaneous nodule, SD = Standard deviation. <sup>§</sup>digital infarcts, palpable purpura, and Raynaud's phenomenon were taken as features of vasculitis

**Table 3: Comparative analysis of different studies undertaken for detection of peripheral neuropathy in rheumatoid patients**

Study and year	Prevalence of peripheral neuropathy	Subclinical neuropathy	Sensory	Motor	Sensorimotor	Mononeuritis multiplex	Entrapment
Present study	29/74	24	15		8	3	3
Agarwal <sup>[4]</sup> <i>et al.</i> (2008)	62/108	46	28		25	7	11
Bharadwaj <sup>[5]</sup> <i>et al.</i> (2005)	12/140	0					
Nadkar <sup>[6]</sup> <i>et al.</i> (2001)	10/31	5		4	6	4	1
Sivri <sup>[2]</sup> <i>et al.</i> (1999)	8/33	8				6	2
Lanzillo <sup>[7]</sup> <i>et al.</i> (1998)	26/40	26			26		5
Lang <sup>[8]</sup> <i>et al.</i> (1981)	10/23	2					5

of disease, and method of diagnosis may be the explanation of such wide variation.

In the study by Bharadwaj *et al.*,<sup>[5]</sup> neuropathy was seen in 8.57% of RA patients. In their study, they have discussed leflunomide as a confounding factor, not excluding patients with diabetes or alcoholism. Moreover, nerve conduction studies were performed only in patients with some clinical features of neuropathy; hence the subclinical cases were missed.

Sensory neuropathy was the most frequent subtype followed by sensorimotor in the current study. The finding is similar to studies by Albani *et al.*<sup>[13]</sup> but certain other studies<sup>[6,14]</sup> found sensorimotor neuropathy to be the most frequent subtype. A very important benefit of electrophysiological study in patients with RA is early detection of entrapment neuropathy (detected in 4% of our patients) as it is amenable to treatment. The prevalence of entrapment neuropathy in various studies<sup>[2,4,7,14]</sup> varies from 4% to 54.6%. The majority of the cases in the current study were subclinical detected only by electrophysiological study and similar results were obtained in other studies.<sup>[7,11]</sup>

In this study, 7 out of total 17 male patients and 22 out of 57 female patients showed electrophysiological evidence of peripheral neuropathy. So, 41.18% (7/17) of the male patients and 38.60% (22/57) of the female patients had peripheral neuropathy. The male to female ratio of rheumatoid patients with neuropathy (1: 3.14) was similar to that of our study population (1: 3.35). No statistical significance was found between the two attributes i.e. sex of the patient and presence of neuropathy in this study. Albani *et al.*<sup>[13]</sup> found male gender to be significantly related to peripheral neuropathy ( $P < 0.04$ ) but Sivri *et al.*,<sup>[2]</sup> Bharadwaj *et al.*,<sup>[5]</sup> and Lang *et al.*<sup>[8]</sup> found gender not to be correlated to peripheral neuropathy.

The current study found no correlation between age and peripheral neuropathy and it is similar to some other studies,<sup>[8]</sup> but certain studies<sup>[4,5,14]</sup> have found a relationship between the two. Albani *et al.*<sup>[13]</sup> on the basis of multivariate analysis found that age is the most important independent predictor of peripheral neuropathy ( $P < 0.002$ ) with probability increasing steadily after age 50. The small sample size of the present study may account for not obtaining a significant relationship between the two.

We found rheumatoid factor positivity to be significantly associated with the presence of peripheral neuropathy in patients with RA. Our findings are similar to the studies conducted by Albani *et al.*<sup>[13]</sup> However most studies<sup>[2,5,6,8,11,15]</sup>

found no significant relationship between the two attributes. The single center, tertiary referral center-based patient population and small number of subjects might explain the result.

The disease duration was significantly related to the presence of peripheral neuropathy in our study and it is similar to the findings by other studies.<sup>[5,14,16]</sup> However, certain other studies<sup>[11,8]</sup> found no relationship between the two.

We found no significant association between the presence of peripheral neuropathy and any of the conventional markers of severe rheumatoid disease such as 28 joint disease activity score, presence of erosions in hand X-ray, extra-articular manifestations such as subcutaneous nodules, interstitial lung disease, and features of vasculitis. Our findings are similar to the study conducted by Agarwal *et al.*,<sup>[4]</sup> Nadkar *et al.*,<sup>[6]</sup> and Lanzillo *et al.*<sup>[7]</sup> Prior use of corticosteroids or DMARDs had no bearing with the presence of peripheral neuropathy in rheumatoid patients. The findings are in agreement with that of Agarwal *et al.*,<sup>[4]</sup> however Lanzillo *et al.*<sup>[7]</sup> found that prior use corticosteroids had a protective effect on progression of peripheral neuropathy.

Our study had several practical limitations. The major weakness of the study was the lack of a pathological gold standard namely "nerve biopsy" studies to confirm our electrophysiologic findings. As a matter of fact none of the patients consented to a nerve biopsy. As the study was conducted in a tertiary care university hospital so mostly the severe, deforming variants of the disease were encountered. Most of the patients had history of intake of DMARDs and this might have confounded the study results, as certain drugs are known to affect peripheral nerves.<sup>[17,18]</sup> A multi-centric study would have made the patient population more heterogeneous. Our study shows that subclinical peripheral neuropathy which is not related to disease severity is very common in patients with prolonged disease duration and regular electroneurophysiologic studies need to be done for early detection in patients with disease duration more than 5 years.

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