Original Article

Prevalence and patterns of peripheral neuropathy in patients of rheumatoid arthritis

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Abstract

Background: Rheumatoid arthritis (RA) is an autoimmune disorder characterized by involvement of multiple small and large joints with multisystem extra-articular manifestations. Peripheral neuropathy is known extra-articular manifestation of RA with the incidence of around 39.19% as per previous studies. Early diagnosis and treatment of peripheral neuropathy has been shown to improve both physical and functional disabilities of patients with RA. **Objectives:** The primary objective was to study prevalence and patterns of peripheral neuropathy in patients with RA. The secondary objective was to study demographic, clinical parameters, disease severity, and extra- articular manifestations in patients with RA with and without peripheral neuropathy. **Materials and Methods:** Consecutive patients of RA were recruited. Detailed clinical examination and electrophysiological tests were done to diagnose peripheral neuropathy. The demographic and clinical parameters were noted and tabulated. Student's *t*-test was used to analyze continuous variable, whereas Chi-square test was used for analysis of categorical variables. **Results:** Of 89 patients with RA, 75.28% (n = 67) patients had peripheral neuropathy electrophysiologically, whereas 20.89% (14 patients of 67) had superficial touch sensory loss on examination. Subclinical neuropathy was present in 50.74% (n = 34) of patients. Statistically significant association between the presence of neuropathy and age of the patients, disease duration, use of disease-modifying antirheumatoid drugs, disease severity (disease activity score-28), and presence of subcutaneous nodules ($P < 0.05$). **Conclusion:** Patients with RA, especially elderly patients, should undergo electrophysiological testing to rule out peripheral neuropathy. Electrophysiological study is a diagnostic and gold standard tool to diagnose subclinical neuropathy in patients with RA. Presence of peripheral neuropathy in these patients has been found to be significantly associated with deteriorating health status, pain scores, and presence of extra-articular manifestations.

Keywords: Axonal, neuropathy, sensorimotor, subcutaneous nodules

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune multisystem disorder with symmetrical involvement of small and large joints. It has multiple extra-articular manifestations such as interstitial lung disease, peripheral neuropathy, and ocular involvement such as episcleritis, scleritis, and vasculitis. The prevalence of clinical neuropathy varies from 0.5% to 85% in patients with RA.[1] Presence of peripheral neuropathy exacerbates to functional disability in patients with RA. A previous study by Hart and Goldin was the first case series of patients wit RA with peripheral neuropathy.[2] The types of peripheral neuropathy in patients with RA are pure sensory, distal axonal sensory motor, mono-neuritis multiplex, and entrapment neuropathy. Patients with peripheral neuropathy present with diverse signs and symptoms such as pain, numbness, pins and needle sensation, and muscle weakness.[1,3] Thus, it is difficult to differentiate between signs and symptoms of peripheral neuropathy and that of arthritis. RA leads to joint and cartilage destruction. The etiology of peripheral neuropathy is poorly understood. Previous studies have attributed nerve entrapment, drug toxicity, vasculitis, amyloidosis, and autoimmune phenomenon as possible causes of peripheral neuropathy in

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patients with RA.[4-6] It is responsible for deteriorating quality of life and life expectancy rates.[7,8] The purpose of this study was to determine the prevalence, types, and clinical determinants of peripheral neuropathy in patients with RA.

Materials and Methods

This study was conducted at a tertiary care hospital of Uttrakhand. Eighty-nine newly diagnosed patients with RA age more than 18 years attending medicine clinic were recruited from May 2017 to December 2017 over a period of 6 months. The patients were diagnosed as per American Rheumatology Association (ARA) criteria, 2010.[9] Detailed demographic, clinical, and drug history was obtained from all patients. Detailed history of sensory symptoms such as pins and needle sensation, burning, numbness, and motor symptoms such as weakness of distal extremities was compiled 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 was done.

For testing superficial touch sensation, a 5.07 Semmes Weinstein monofilament was used. Pain sensation was tested using the blunt end of the needle. A 256-Hz turning fork was used to test vibration sense. Disease activity score (DAS)-28 was used to assess the severity of RA. Score more than 3.2 was considered to be active disease. Patients who were unconscious or had presented in altered sensorium were excluded from the study. Also, patients suffering from diabetes mellitus, hypothyroidism, hyperthyroidism, malignancy, and with alcohol or toxic exposure were excluded from the study.

Electrophysiological testing

Sensory nerve conduction study was done for bilateral sural nerves at mid- calf level. Similarly, sensory neuropathy was checked on bilateral median and ulnar nerves at wrist levels.

Motor nerve conduction studies were done for bilateral median and ulnar nerves at wrist and elbow levels and also for bilateral peroneal and tibial nerve at ankle and knee level. F waves were calculated for bilateral tibial and peroneal nerves. The polyneuropathy was pathophysiologically differentiated as axonal or demyelinating type. Detailed physical examination was done to look for extra-articular manifestations such as subcutaneous nodules, interstitial lung disease, and features suggestive of vasculitis in the form of palpable purpura and digital infarcts. Routine investigations in the form of liver function tests, renal function tests, and inflammatory markers in the form of erythrocyte sedimentation rate (ESR), and C-reactive protein were done in all the patients with RA.

Past and current treatment history including prior use of steroids and disease-modifying antirheumatoid drugs (DMARDS) was noted. X-rays of bilateral hands were done in all the patients to detect joint erosions. Pulmonary function tests and HRCT thorax were done in 17 patients with RA who had symptoms and signs suggesting interstitial lung disease. Quantitative assessment of rheumatoid factor was done using latex agglutination test. Stanford Health Assessment Questionnaire Disability Index (HAQ-D1) was used to assess functional disability of patients with RA.[10] It is a set of eight questions based on daily physical activities. Tinsel's sign was elicited to detect possible tibial and peroneal neuropathies. Phalen's sign was elicited to detect median neuropathy. Pain assessment was done using visual analog scale (VAS).[11] Ethical clearance was taken from institutional ethics committee. Written informed consent was taken from all the patients participating in this study.

Results

Eighty-nine patients with RA were included in the study. Sixty-seven (75.28%) patients showed peripheral neuropathy detected electrophysiologically. Out of 67 patients with RA with peripheral neuropathy, only 20.89%[14] had clinical loss of superficial touch sensation, 14.42%[10] had loss of temperature sensation, and only 4.1%[3] patients had loss of joint position and vibration sense [Table 1]. Phalen's sign was positive in 8 (8.9%), whereas Tinsel's sign was positive in 24 (26.9%). Six (8.95%) patients with RA with peripheral neuropathy had motor abnormalities. Subclinical neuropathy was present in 34 (50.74%). The mean age of the patients with RA with peripheral neuropathy was 54.34 ± 11.64 years which was significantly higher than those without peripheral neuropathy. The mean duration of illness of patients with neuropathy was significantly (15 ± 7.29 years) longer than that without neuropathy (5.32 ± 5.51) [Table 2].

Five (7.46%) patients out of 67 patients had foot deformities, 3 (4.47%) had hammer toes, 2 (2.98%) had claw toes, whereas

Table 1: Demographic, clinical, and extra-articular manifestation of patients of rheumatoid arthritis

Parameter	Frequency (%), *n*=89
Gender (F/M)	78/11 (87.6%/12.4%)
Married	80 (89.9%)
Unmarried	9 (10.1%)
NSAIDS	87/2 (97.8%/2.2%)
Sulfasalazine (y/n)	51/38 (57.3%/42.7%)
Methotrexate (y/n)	70/19 (78.7%/21.3%)
Hydroxychloroquine (y/n)	58/31 (65.21%/34.8%)
Leflunomide (y/n)	26/63 (29.2%/70.8%)
Neuropathy	67 (75.3%)
Sensory superficial touch loss	14 (20.89%)
Temperature loss	10 (14.92%)
Vibration and joint position loss	3 (4.1%)
Motor abnormalities.	6 (8.95%)
Interstitial lung disease	17 (19.19%)
Subcutaneous nodules	13 (14.6%)
Muscle wasting (upper limb)	17 (19.1%)
Muscle wasting (lower limb)	13 (14.6%)
Tinel's sign	24 (26.9%)
Phalen's sign	8 (8.9%)
Subclinical neuropathy	34 (50.74%)

HCQS: Hydroxychloroquine; ILD: Interstitial lung disease

only one (1.49%) patient had hallus valgus deformity. Four (5.97%) patients had Achilles tendonitis and two (2.98%) had plantar fasciitis. The majority ($n = 30$, 22.38%) of the patients with RA had asymmetrical sensorimotor axonal neuropathy followed by pure motor neuropathy ($n = 15$, 22.38%), 6 (8.95%) patients had sensory neuropathy, 8 (11.94%) had entrapment neuropathy, and 8 (11.94%) had mononeuritis multiplex on nerve conduction study. Out of eight patients with entrapment neuropathy, two had bilateral median nerve involvement, four had unilateral median nerve, whereas only two had unilateral ulnar nerve entrapment. The majority of the patients with RA with peripheral neuropathy were receiving DMARDS (methotrexate 94.02%, hydoxychloroquine 80.59, sulfasalazine 70.14%. leflunamide 38.80%) when compared with the other group. The mean DAS-28 score was higher (6.63% ± 0.544%) in the group of patients with peripheral neuropathy. The values of phase reactants (ESR, CRP) were also higher in the group with peripheral neuropathy (ESR = 75.16 ± 18.33) compared with the other group (50.54 ± 2.50).

Table 2: Comparison of parameters of patients with RA with and without neuropathy

Parameter	Patients with neuropathy (n=67)	Patients without neuropathy (n=22)	*P*
Age (years)	54.34±11.644	36.32±13.56	0.005
Morning stiffness	31.19±17.94	75.09±19.51	0.179
Disease duration (years)	15.07±7.29	5.32±5.51	0.000
DAS-28 score	6.32±0.544	4.79±0.83	0.000
RF positivity	89.39±54.24	10.711±1.78	0.35
Hemoglobin	10.71±1.78	12.861±0.98	0.000
ESR	75.16±18.33	50.54±2.50	0.000
Absence of tendon reflexes	27 (40.29%)	2 (9.09%)	0.001
Loss of knee jerk	3 (4.47%)	0	0.001
Erosions on X-ray	50 (74.62%)	8 (36.36%)	0.001
Superficial fine touch sensory loss	14 (20.89%)	0	0.001
Temperature loss	10 (14.92%)	0	0.001
Loss of joint position and vibration sense	3 (4.1%)	0	0.000
Motor abnormalities	6 (8.95%)	0	0.000
NSAIDS	67 (100%)	20 (90.09%)	0.13
Methotrexate	63 (94.02%)	7 (31.81%)	0.000
Hydroychloroquine	54 (80.59%)	4 (18.18%)	0.000
Sulfasalazine	47 (70.14%)	4 (18.18%)	0.000
Leflunomide	26 (38.80%)	0	0.000
ILD	10 (14.9%)	7 (31.81%)	0.1
Subcutaneous nodules	7 (10.4%)	6 (27.2%)	0.006
Muscle wasting (upper limb)	16 (23.8%)	1 (4.5%)	0.01
Muscle wasting (lower limb)	12 (17.9%)	1 (4.5%)	0.02
Anti-CCP antibody positive	44 (65.6%)	5 (22.7%)	0.000
Tinel's sign	22 (32.8%)	2 (9%)	0.01
Phalen's sign	7 (10.4%)	1 (4.5%)	0.045
HAQ-D1 (mean±SD)	0.63±0.24	0.21±0.3	0.02
Pain sensitivity (VAS: 0-100)	86.2±13.6	45.3±22.6	0.03

RA: Rheumatoid arthritis; DAS: Disease activity score; RF: Rheumatoid factor; ESR: Erythrocyte sedimentation rate; ILD: Interstitial lung disease; HAQ-D1: Health Assessment Questionnaire Disability Index; SD: Standard deviation; VAS: Visual analog scale

However, no significant correlation was found between presence neuropathy, interstitial lung disease, or prior use of steroids with the presence of neuropathy. Health assessment score (HAQ-D1) and VAS were significantly higher in patients with RA with neuropathy. Table 3 shows comparisons of peripheral neuropathy patterns between present and past studies.

Discussion

This study focuses on prevalence and types of peripheral neuropathy in patients with RA. It highlights the differences of various demographic, clinical, and extra-articular manifestations between patients with RA with and without peripheral neuropathy. We also assessed the effect of peripheral neuropathy on general well-being as well as pain scores of patients with RA.

The presence of peripheral neuropathy in our study was (75.28%) slightly higher than previous studies conducted by Sim *et al.* (33%) and Biswas *et al.* (39.19%). This difference could be explained by the fact that our study included all the old and newly diagnosed cases of RA. Previous studies have included either newly diagnosed cases of RA or only patients with signs and symptoms of peripheral neuropathy. Biswas *et al.* included 74 patients with RA, whereas Sim *et al.* included only 30 patients with RA who had symptoms of peripheral neuropathy.[12,13]

Interestingly, only 49.25% ($n = 33$) of patients with peripheral neuropathy detected electrophysiologically had sensory signs and symptoms of neuropathy. Around 50% patients were asymptomatic and had subclinical neuropathy. The most common diagnosis was loss of superficial fine touch followed by loss of ankle reflex. We used standard questionnaire to elicit symptoms

Table 3: Comparisons of peripheral neuropathy patterns between present and past studies

Study	Number of patients	Sensorimotor	Pure sensory	Pure motor	Mononeuritis multiplex	Carpal tunnel syndrme	Subclinical neuropathy	Parameters significantly associated with peripheral neuropathy
Agarwal *et al.*	108	25	28	0	7	11	46	Evidence of vasculitis, absent deep tendon reflexes
Nadkar *et al.*	31	6	0	4	4	1	5	No association
Fleming *et al.*	102	0	15	3	0	52	17	No comparison done
Mi Kyung Sim *et al.*	30	2	1	0	0	7	No comment	Age and anti-CCP antibody
Present study	89	30	6	15	8	8	13	DMARDS, muscle wasting, anti-CCP, HAQ-D1, VAS

DMARDS: Disease-modifying antirheumatoid drugs; HAQ-D1: Health Assessment Questionnaire Disability Index; VAS: Visual analog scale

of peripheral neuropathy and specific tests to diagnose peripheral neuropathy clinically. Despite using a standard protocol of examination, we could only diagnose less than 50% cases of neuropathy clinically. The remaining cases were asymptomatic. Hence, it is difficult to diagnose peripheral neuropathy only by physical examination. Electrophysiological studies and further nerve biopsy studies are gold standard techniques. Aneja *et al.* observed that 24.2% of patients had sensory signs of peripheral neuropathy and 9.09% patients had motor signs.[14] In our study, the majority of the patients had asymmetrical sensory motor axonal neuropathy followed by pure motor neuropathy.

Nadkar *et al.* and Lanzillo *et al.* also found that sensorimotor axonal neuropathy was the most common type of peripheral neuropathy in patients with RA.[15,16] However, Biswas *et al.* and Albani *et al.* reported that pure sensory type was the most common type of peripheral neuropathy in the patients with RA.[13,17]

Females outnumbered males (7.3:1.1) in our study. This could be due to the fact that RA is a female-dominant disease. This association of gender and presence of peripheral neuropathy was not in accordance with the studies conducted by Sivri *et al.*[18] Interestingly, Albani *et al.* reported that male gender was significantly associated with the presence of peripheral neuropathy.[17] Our study described a significant association of increasing age and presence of peripheral neuropathy. Thus, one of the secondary causes of peripheral neuropathy in geriatric population is RA. Peripheral neuropathy in geriatric population is often underdiagnosed. Apart from the secondary causes, there are physiological deterioration in the anatomy and function of peripheral nerves with increasing age. These patients are more prone to falls. This could significantly limit their daily activities and functional decline in old age.[19-21] Bharadwaj *et al.* and Agarwal *et al.* reported this association to be significant.[1,3] On the contrary, certain studies in the past did not find this association to be significant. This could be attributed to smaller sample size in these studies.

Rheumatoid factor positivity was found to be significantly associated with presence of peripheral neuropathy. A similar result was reported by Albani *et al.* and Biswas *et al.*[13,17] However, multiple studies in the past have refuted this correlation.[22,23]

Studies conducted by Bhardwaj *et al.* and Hamed *et al.* have found a positive association between presence of neuropathy and disease duration.[3,24] Our study also showed a similar result. A significant association was found between inflammatory markers of disease activity (ESR, CRP) and peripheral neuropathy in our study. Similarly, significant association was found between DAS-28 and presence of peripheral neuropathy. This was also observed by Rajesh *et al.*[25] There was no significant association between presence of subcutaneous nodules and peripheral neuropathy in our study. Similar results were reported by previous studies.[13,15]

Significantly large number of patients with peripheral neuropathy in our study had radiological evidence of joint erosion of bilateral hands. Such an association was reported to be insignificant by Biswas *et al.*, Sivri *et al.*, and Nadkar *et al.* Smaller sample size could be the reason for this. No significant association was found between presence of neuropathy and prior use of steroids, and interstitial lung disease in our study. This was in accordance with previous studies.[13,15,18] Previous studies have found a significant correlation between presence of functional incapacity in patients with RA with neuropathy and disease activity. Also, pain score (VAS) was higher in patients with RA with neuropathy.[26] Our study also had higher HAQ-D1 score in patients with RA with neuropathy. Hence, overall well-being of the patient with RA can be correlated with presence of neuropathy especially in geriatric population.[27]

The treatment of peripheral neuropathy involves a multispecialty approach. Hence, the role of family medicine physician is pivotal in not only treating these patients but also improving their quality of life.

Conclusion

Peripheral neuropathy in RA is associated with increasing age, duration of Disease, and increased disease severity. This adds to the functional disabilities especially in geriatric population. Overt neuropathic symptoms can be detected clinically, whereas subclinical neuropathy can only be detected electrophysiologically. Hence, nerve conduction studies should be carried out in all the patients with RA. This will help in better management of these patients.

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Conflicts of interest

There are no conflicts of interest.

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