

Evaluation of Neuropathic Pain in Rheumatoid Arthritis Patients: Relation to Clinical and Laboratory findings

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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 with the incidence of around 39.19% as per previous studies. The presence of peripheral neuropathy in patients with rheumatoid arthritis contributes significantly to the functional limitation in patients with rheumatoid arthritis. Early diagnosis and treatment of peripheral neuropathy has been shown to improve both physical and functional disabilities of patients with RA.

Objectives: The objective was to assess neuropathic pain in patients with rheumatoid arthritis (RA) having neuropathic symptoms and to evaluate the relationship between electrophysiological findings and clinical & laboratory findings of RA.

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 60 patients with RA, 75.28% (n = 45) patients had peripheral neuropathy electro-physiologically. Statistically significant association between the presence of neuropathy and age of the patients, disease duration, use of disease-modifying antirheumatic drugs, disease severity (disease activity score-28), and activity in ultrasonography (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.

Keywords: Rheumatoid arthritis, Neuropathic pain, Peripheral neuropathy.

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune systemic disease of inflammatory nature, it affects synovial joints with extra articular manifestations [1]. RA prevalence is approximately around 39.19% of population worldwide as per previous studies [2].

RA is primarily a joint disease, but extraarticular manifestations can be detected in any organ system and may occasionally precede the onset of arthritis. Most common neurological manifestation in rheumatoid arthritis is entrapment neuropathy which is secondary to proliferative synovitis[3]

About 33.2% of the patients develop neurological problems during their lifetime. Peripheral nerve involvement in rheumatoid arthritis includes compressive neuropathy, distal sensory and combined sensorimotor neuropathy which is by far the commonest (4).

Although the underlying pathology resulting in rheumatoid neuropathy is not clear, ischemia secondary to vasculitis with

characteristic axonal loss and humoral mechanisms such as the deposition of immune complexes and fixation of complement are thought to be important factors[5]. The arteritis of small vessels commonly fibrinoid type and immune globins are demonstrated in walls of the vessels[6].

The presence of peripheral neuropathy in patients with rheumatoid arthritis is difficult to recognize as

patients often related neurological symptoms to joint disease. It is also difficult to assess neurological system in the presence of severe joint disease[5].

2. Objective

To assess neuropathic pain in patients with rheumatoid arthritis (RA) having neuropathic symptoms

Methods:

3. Patients

Inclusion criteria:

This study was carried out on sixty RA patients. All included patients full filled the 2010 ACR/EULAR criteria for classification of RA and aged >18 years.

They were recruited from the outpatients' clinic of Rheumatology, Rehabilitation, Benha university hospitals.

Controls:

Twenty apparently healthy volunteers of matched age and sex to patients were enrolled as a control group.

All patients and controls were subjected to full history taking, a thorough clinical examination and electrophysiological evaluation in the form of nerve conduction study of median nerve, ulnar nerve, common peroneal nerve and sural nerves[7,8].

Investigations Needed For The Study

- ESR, CRP, CBC, Liver, kidney functions.
- RF, FBS, 2h PPBS.

Past and current treatment history including prior use of steroids and disease-modifying antirheumatic drugs (DMARDS) was noted. X-rays of bilateral hands

were done in all the patients to detect joint erosions using Larsen score which gave a total score in the range 0–160 [9]. 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]

4. Results

Sixty patients with RA were included in our study. About forty-four (74.3%) patients showed peripheral neuropathy detected electrophysiologically. Out of 44 patients with RA with peripheral neuropathy, Phalen's sign was positive in 5 (8.3%), whereas Tinsel's sign was positive in 13 (29.5%). [Table1].

Eight (18.2%) patients with RA with peripheral neuropathy had motor abnormalities. The mean age of the patients with RA with peripheral neuropathy was 57.5 years which was significantly higher than those without peripheral neuropathy. The mean duration of illness of patients with neuropathy was significantly (17years) longer than that without neuropathy (5 years) [Table 2].

Table (1)Demographic and clinical findings of patients of rheumatoid arthritis

Parameter	Frequency (%), n=60
Gender (F/M)	54/6 (90%/10%)
NSAIDS	58 (96.7%)
Sulfasalazine (y/n)	1(1.7%)
Methotrexate (y/n)	52 (86.7%/21.3%)
Hydroxychloroquine (y/n)	33 (55%)
Leflunomide (y/n)	32 (53.3%)
Neuropathy	44 (74.3%)
Motor abnormalities.	12 (20%)
Tinel's sign	21 (35%)
Phalen's sign	5(8.3%)
Tendon reflex	48(80%)

Table (2)Comparison of parameters of patients with RA with and without neuropathy

Parameter	Patients with neuropathy (n=44)	Patients without neuropathy (n=16)	P	Parameter
Age (years)	57.5 (50.25-60.0)	24.0 (29.0-30.0)	0.001	Age (years)
Disease duration (years)	18.0 (16.0-19.0)	5.0 (4.0-6.75)	0.000	Disease duration (years)
RF positivity	37(48.1)	2(33.3%)	0.001	RF positivity
ESR	55.0(55.0-75.0)	45.0 (41.25-70.0)	0.001	ESR
Absence of tendon reflexes	8 (18.2%)	4 (25%)	0.048	Absence of tendon reflexes
Muscle weakness	8 (18,2%)	4 (25%)	0.72	UL, LL weakness
Tinel's sign	13 (29.5%)	8 (50%)	0.14	Tinel's sign
Phalen's sign	5(9%)	0 (0%)	0.001	Phalen's sign
HAQ-D1 (mean±SD)	0.5 (0.5-1.0)	1.0 (1.0-2.0)	0.007	HAQ-D1 (mean±SD)
Pain sensitivity (VAS: 0-10)	5.0 (5.0-7.0)	8.0 (6.0-9.0)	0.001	Pain sensitivity (VAS: 0-10)
Steroids	26(59.1%)	13(18.2%)	0.11	
NSAIDS	44(100%)	14(87.5%)	0.068	
Biological	1(2.3%)	0(0%)	0.54	
Hydroquine	32(72.7%)	1(6.3%)	0.001	
Leflunamide	30(68.2%)	2(12.5)	0.001	
Mtx	40(90.9%)	12(75.2%)	0.11	
salazopyrine	0(0%)	1(6.3%)	0.093	

RA: Rheumatoid arthritis; 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, NSS: Neuropathy Symptoms Score.

The majority of the patients with RA with peripheral neuropathy were receiving DMARDS (methotrexate 90.9%, hydroxychloroquine72,7,

biological 2,3% sulfasalazine 0%. Leflunamide (68,2%) when compared with the other group.

However, no significant correlation was found between presence neuropathy and prior use of steroids or NSAID with the presence of neuropathy.

However, no significant correlation was found between presence neuropathy, and NSS with the presence of neuropathy. Health assessment score (HAQ-D1) and VAS were significantly higher in patients with RA with neuropathy.

5. Discussion

This study aimed to assess neuropathic pain in patients with rheumatoid arthritis (RA) having neuropathic symptoms. We also assessed the effect of peripheral neuropathy on general well-being as well as pain scores of patients with RA. Our study revealed forty-four (74.3%) patients out of sixty patients with RA showed peripheral neuropathy detected electrophysiologically.

In our study we have found a significant correlation between presence of Peripheral neuropathy and age, gender and the duration of illness, Females outnumbered males (7.3:1.1) in our study. This could be due to the fact that RA is a female-dominant disease Deformity, Phalen's test were significantly higher in patient with neuropathy than in patients without neuropathy, there was no significance of weakness, Tinel test or loss of tendon reflex in our study.

No significant association was found between presence of neuropathy and prior use of steroids, and NSAIDS in our study, while the majority of the patients with RA with peripheral neuropathy were receiving DMARDS.

peripheral neuropathy in our study was found to be significantly associated with rheumatoid factor positivity.

A significant association was found between inflammatory markers of disease activity (ESR) and peripheral neuropathy in our study.

In our study we 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, 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

The presence of peripheral neuropathy in our study was (74.3%) 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]

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.[13,14] Interestingly, Albani et al. reported that male gender was significantly associated with the presence of peripheral neuropathy.[15,16,17]

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[18]. 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.[19,20,21] 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. found significant association was found between inflammatory markers of disease activity (ESR) 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] .

No significant association was found between presence of neuropathy and prior use of steroids or NSAIDS 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.[27]

6. Conclusion

- Peripheral nerve involvement seems to be one of the different aspects of rheumatoid arthritis. Electrophysiological testing should be included in the routine evaluation of rheumatoid arthritis as subclinical cases predominate.
- Peripheral neuropathy in RA is common among higher age, longer disease duration. This adds to the functional disabilities especially in geriatric population.

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