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ELECTRODIAGNOSTIC STUDY OF FOOT NEUROPATHY IN CORRELATION WITH DAS28 OF RHEUMATOID ARTHRITIS PATIENTS

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ARTICLE INFO	**ABSTRACT**

Introduction: Rheumatoid arthritis (RA) is described as a chronic systemic inflammatory immune-mediated disease characterized by symmetrical polyarthritis. **Objective:** We aimed in this study to evaluate neuropathic foot pain in patients with RA using electrophysiological studies to compare the occurrence and severity of neuropathic foot pain in RA activity, remission and to compare between seropositive and seronegative RA patients. **Methods:** A retrospective cohort study included sixty Patients selected from Rheumatology and Rehabilitation outpatient clinics, Aswan University Hospitals, Faculty of Medicine, Aswan University during the period from 1 May 2018 to 1 March 2020.Patients were diagnosed and classified as having RA by Rheumatologist, who fulfilled the ACR/EULAR 2010 criteria for classification of RA. **Results:** Regarding nerve conduction, the present study showed that Peroneal nerve mean +SD of latency, amplitude, velocity and F wave were (4.20+1.21, 4.62+2.33, 45.63+3.85 and 50.15+3.09 respectively), Post-tibial nerve mean +SD of latency, amplitude, velocity and F wave were (4.6+1.48, 8.36+4.15, 42+5.23 and 50.61+2.67 respectively) and Sural nerve mean +SD of latency, amplitude and velocity were (3.09+0.52, 11.8+5.90 and 36.25+5.82 respectively). Also, there was statistically significant difference between active and inactive RA groups as regard velocity of Post tibial nerve and amplitude of Sural nerve. There were no correlations between Disease Activity score in 28 joints and nerve conduction study /electromyographic results. **Conclusion:** Our study showed that there was non-significant correlation between neuropathy and disease duration, RF, DAS28 & HAQ-DI but there was significant correlation with SFAQ score.

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INTRODUCTION

Rheumatoid arthritis (RA) is described as a chronic systemic inflammatory immune-mediated disease characterized by symmetrical polyarthritis. Uncontrolled, the chronic joint inflammation leads to erosive joint destruction and disabling joint deformities. Its prevalence is estimated as 0.5 to 1% in whites, and women are affected three times more frequently than men. The initial presentation and the course of RA vary broadly within patients.[1] Clinical involvement of the peripheral nervous system may be asymptomatic in the early

stages of the RA or may present with a wide variety of symptoms such as pain, parathesias, and muscle weakness. These symptoms may mimic and overlap with those of arthritis. [2]In presence of severe joint disease, restriction, pain, and deformities, symptom of neuropathy may be overlooked or overestimated. [3] Although patients with RA complain of foot pain and disability because of foot problems, physicians generally overlook or neglect the feet in routine clinical examination. This is because feet and ankles are not included as part of the Disease Activity Scoring in 28 joints (DAS28) scoring system, which is generally used to assess disease activity and helps to define clinical remission of the disease. Hence, patients in remission may suffer from foot disease activity, as shown in the previous studies. [4] We aimed in this study to evaluate neuropathic foot pain in patients with RA using electrophysiological studies to compare the occurrence and severity of neuropathic foot pain in RA activity, remission

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and to compare between seropositive and seronegative RA patients.

PATIENTS AND METHODS

A retrospective cohort study included sixty Patients selected from Rheumatology and Rehabilitation outpatient clinics, Aswan University Hospitals, Faculty of Medicine, Aswan University during the period from 1 May 2018 to 1 March 2020. Patients were diagnosed and classified as having RA by Rheumatologist, who fulfilled the ACR/EULAR 2010 criteria for classification of RA. [5]

Exclusion Criteria: Patients with peripheral neuropathy due to any systemic or local disease 'other than RA e.g.

- Diabetes Mellitus
- Lumbar spine 5 and Sacral spine 1 radiculopathies.
- Space occupying lesions at the tarsal tunnel, foot trauma and fractures.
- Drug induced neuropathy.

Clinical evaluation: All the patients were subjected to a detailed history-taking, complete rheumatologic examination and neurological examination of the four extremities to exclude upper motor neuron lesions or lesions affecting any part of the lower motor neuron pathway other than the peripheral nerves.

- Clinically, we stratified patients based on their disease activity assessed using the disease activity score assessing 28 joints (DAS-28), the number of tender joints (TJC) and swollen joints (SJC) out of 28 were calculated.
- Neurologically, superficial sensations using a pinprick were examined and an altered pinprick response was used to infer a possible neuropathic pain. [6]
- In this study, the Medical Research Council grading scale (0–5) was used for muscle strength assessment[7],muscle weakness was assumed to be present if any muscle in the lower limb had a score less than 5. Abnormal muscle mass index indicated muscle wasting. [8]
- Also, eliciting Tinel's sign was considered as an objective clinical sign for possible tibial or peroneal nerve entrapments. [3]
- In addition,assessment of foot function was carried out using the Swindon Foot and Ankle Questionnaire (SFAQ), which is a simply worded 10-point foot-and-ankle screening questionnaire with diagrams for rapid screening in routine rheumatology outpatients. [9]
- Assessment of functional disability was performed using the Stanford Health Assessment Questionnaire Disability Index (HAQ-DI), which consists of eight questions regarding the limitations that the patients experience in performing daily physical activities. [10]

Laboratory assessment:

- C-reactive protein (CRP).
- Erythrocyte sedimentation rate (ESR).
- Presence of rheumatoid factor (RF) and anti-citrullinated cyclic peptides antibodies (ACPA) by ELISA.
- fasting blood sugar.
- HBA1c.

Electrophysiological testing: All 60 patients were tested by the Neuropack M1 electromyograph (EMG) apparatus (Nihon Kohden, Tokyo, Japan). Nerve conduction (motor and sensory) studies were conducted to bilateral medial plantar, lateral plantar, deep peroneal, superficial peroneal and sural nerves. This was be done as described in a study by Kim and colleagues. Findings were presented as the mean value of both sides.

Data Management and Analysis: The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 25). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

Descriptive statistics

- Mean and Standard deviation (± SD) for parametric numerical data, while Median and Interquartile range (IQR) for non-parametric numerical data.
- Frequency and percentage of non-numerical data.

Analytical statistics

- Student T Test was used to assess the statistical significance of the difference between two study group means.
- Mann Whitney Test (U test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups.
- Chi-Square test was used to examine the relationship between two qualitative variables
- Fisher's exact test was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells
- Correlation analysis (using Pearson's and Spearman's method) to assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically "r" defines the strength (magnitude) and direction (positive or negative) of the linear relationship between two variables.

- r= 0-0.19 is regarded as very weak correlation
- r=0.2-0.39 as weak correlation
- r=0.40-0.59 as moderate correlation
- r=0.6-0.79 as strong correlation
- r= 0.8-1 as very strong correlation.

P- value: level of significance

- P>0.05: Non significant (NS).
- P< 0.05: Significant (S)
- P<0.01: Highly significant (HS).

RESULTS

In our study there were 42 females (70%) and 18 males (30 %). There were 30 active RA patients and 30 inactive RA patients and mean of disease duration was 8.32 years. As regardingDAS28, SFAQ and HAQ-DI scores, the mean ±SD in active RA group were(2.12 ± 0.17, 3.67 ± 1.32 and 0.25 ± 0.02 respectively), while in active RA group were (4.02 ± 0.98, 6.03 ± 1.4 and 0.55 ± 0.14 respectively) with statistically significant difference between active and inactive RA groups as regard DAS28, SFAQ Score & HAQ-DI Score (Table 1).

Table 1. Comparative analysis of DAS28, SFAQ and HAQ-DI scores between RA groups

		Groups of RA		Student t- test of sig.	
		Inactive RA N (%) Mean ± SD	Active RA N (%) Mean ± SD	P-value	Sig.
DAS28		2.12 ± 0.17	4.02 ± 0.98	<0.001	S
DAS28	Remission	30 (100%)	0 (0%)	<0.001[(F)]	S
	Low (2.6-3.2)	0 (0%)	9 (30%)		
	Moderate (>3.2-<5.1)	0 (0%)	16 (53.33%)		
	High (>5.1)	0 (0%)	5 (16.67%)		
SFAQ Score		3.67 ± 1.32	6.03 ± 1.4	<0.001	S
HAQ-DI Score		0.25 ± 0.02	0.55 ± 0.14	<0.001	S

[(F)] Monte-Carlo Fisher's Exact test of significance.

Table 2. Correlations coefficients between neuropathy and RA scores

RA patients (n=60)		Disease duration	RF	DAS28	SFAQ Score	HAQ-DI Score
Neuropathy	Spearman's rho	-0.061	0.082	0.138	0.294	0.102
	P-value	0.641	0.535	0.294	0.023	0.436
	Sig.	NS	NS	NS	S	NS

$P>0.05$: Non significant (NS). $P< 0.05$: Significant (S). $P<0.01$: Highly significant (HS).

Also, there was non-significant correlation between neuropathy and disease duration, RF, DAS28 & HAQ-DI and significant correlation with SFAQ score (Table 2). Rheumatoid Factor was positive in 40patients (66.7%) and negative in 20 patients (33.3%),anti-CCP was positive in 40 patients and negative in 20 patients, ESR mean ±SD was 412±2.86 and CRP was positive in 33 patients (55%) and negative in 27 patients (45%) (Table 3).

Regarding nerve conduction, the present study showed that Peroneal nerve mean ±SD of latency, amplitude, velocity and F wave were (4.20±1.21, 4.62±2.33, 45.63±3.85 and 50.15±3.09respectively), Post-tibial nerve mean ±SD of latency, amplitude, velocity and F wave were (4.6±1.48, 8.36±4.15, 42±5.23 and 50.61±2.67 respectively) and Sural nerve mean +SD of latency, amplitude and velocity were (3.09±0.52, 11.8±5.90 and 36.25±5.82 respectively).

Table 3. Lab investigations for whole study group

		RA patients (n=60)	
		N	%
RF	Negative	20	33.3%
	Positive	40	66.7%
Anti-CCP	Negative	20	33.3%
	Positive	40	66.7%
ESR$_{mean +SD}$		41.00	22.86
CRP	Negative	27	45.0%
	Positive	33	55.0%

Table 4. Nerve conduction study for whole study group

		RA patients (n=60)	
		Mean	SD
Peroneal nerve	Latency	4.20	1.21
	Amplitude (mv)	4.62	2.33
	Velocity (m/s)	45.63	3.85
	F wave	50.15	3.09
Post-tibial nerve	Latency	4.61	1.48
	Amplitude (mv)	8.39	4.15
	Velocity (m/s)	42.00	5.23
	F wave	50.61	2.67
Sural nerve	Latency	3.09	0.52
	Amplitude (mv)	11.82	5.90
	Velocity (m/s)	36.25	5.82

Also, there was statistically significant difference between active and inactive RA groups as regard velocity of Post tibial nerve and amplitude of Sural nerve (Table 4).There were no correlations between Disease Activity score in 28 joints and nerve conduction study /electromyographic results (Table 5).

DISCUSSION

Rheumatoid arthritis (RA) is a systemic disease of unknown etiology that primarily affects the joints, but involves nonarticular sites, including the skin, heart, lungs, eyes and the nervous system. Nervous system involvement can be variable in RA patients. The most common lesion is peripheral neuropathy, including entrapment neuropathy, distal axonal predominantly sensory polyneuropathy, mononeuropathy or multiple mononeuropathy, as well as fulminant sensorimotor polyneuropathy. [(12)] The current study showed that as regarding Rheumatoid Factor was positive in 40patients (66.7%) and negative in 20 patients (33.3%),anti-CCP was positive in 40 patients and negative in 20 patients, ESR mean ±SD was 412±2.86 and CRP was positive in 33 patients (55%) and negative in 27 patients (45%). There was statistically significant difference between active and inactive RA groups as regard RF, ESR and CRP. Findings of our results were not coincided with study of Kaymaz*et al.*[(13)]as they found no statistically significant difference among their studied groups as regard ESR and CRP. In the study of Umay*et al.*[(14)], the mean of RF in their studied group was 74.2 ± 65.3, the mean of ESR was 27.9 ± 16.6 and the mean of CRP was 20.02 ± 14.3.

In the study in our hands, As regarding DAS28, SFAQ and HAQ-DI scores, the mean ±SD in in active RA group were (2.12 ± 0.17, 3.67 ± 1.32 and 0.25 ± 0.02 respectively), while in active RA group were (4.02 ± 0.98, 6.03 ± 1.4 and 0.55 ± 0.14 respectively) with statistically significant difference between active and inactive RA groups as regard DAS28, SFAQ Score & HAQ-DI Score. Also, there was non-significant correlation between neuropathy and disease duration, RF, DAS28 & HAQ-DI and significant correlation with SFAQ score. Our results were in line with study of El-Hewala *et al.*[(15)] as they found a highly significant SFAQ scoring ($P \leq 0.001$) was encountered more among the active patients than among the inactive ones.

Table 5. Correlations coefficients between Disease Activity score in 28 joints and nerve conduction study/electromyographic results

	Active RA			Inactive RA		
	r	P-Value	Sig.	r	P-Value	Sig.
Peroneal n. DML	0.38	0.038	S	-0.096	0.615	NS
Peroneal n. CMAP amplitude	0.172	0.363	NS	0.079	0.679	NS
Peroneal n. motor conduction velocity	-0.033	0.862	NS	0.087	0.647	NS
Peroneal n. DSL	0.042	0.824	NS	-0.098	0.608	NS
Peroneal n. SNAP Amplitude	-0.080	0.674	NS	-0.166	0.382	NS
Sural n. DSL	0.207	0.272	NS	-0.215	0.254	NS
Sural n. SNAP Amplitude	0.026	0.890	NS	-0.254	0.176	NS
Post tibial n. DML	-0.211	0.263	NS	-0.145	0.446	NS
Post tibial n. CMAP amplitude	0.190	0.315	NS	-0.009	0.964	NS
Post-tibial n. motor conduction velocity	-0.073	0.700	NS	-0.020	0.918	NS

P>0.05: Non significant (NS). P< 0.05: Significant (S). P<0.01: Highly significant (HS).

This disagrees with the study conducted by Waller et al.[9] which reported that the SFAQ did not correlate with DAS28. However, a limitation of both studies, Waller's research and this study, is that feet and ankles are not included as part of the DAS28 scoring system. Similarly, a highly significant HAQ-DI was encountered more among the active patients than among the inactive ones (P ≤ 0.001). Keeping-up with this results, previous studies found a significant correlation between HAQ-DI and DAS28 in RA patients [16] suggesting that functional incapacity is most associated with disease activity in early RA. [17] In contrary with our results, study of Kaeley et al.[18] as they reported that rheumatoid factor positivity was found to be significantly associated with presence of peripheral neuropathy. A similar result was reported by Biswas et al.[19] However, multiple studies in the past have refuted this correlation. [20] Study conducted by Hamed et al.[21] has found a positive association between presence of neuropathy and disease duration. Regarding nerve conduction, the present study showed that Peroneal nerve mean ±SD of latency, amplitude, velocity and F wave were (4.20±1.21, 4.62±2.33, 45.63±3.85 and 50.15±3.09 respectively), Post-tibial nerve mean ±SD of latency, amplitude, velocity and F wave were (4.6±1.48, 8.36±4.15, 42±5.23 and 50.61±2.67 respectively) and Sural nerve mean +SD of latency, amplitude and velocity were (3.09±0.52, 11.8±5.90 and 36.25±5.82 respectively). Also, there was statistically significant difference between active and inactive RA groups as regard velocity of Post tibial nerve and amplitude of Sural nerve. There were no correlations between Disease Activity score in 28 joints and nerve conduction study /electromyographic results.

In the study of El-Hewala et al.[15] 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. They used standard questionnaire to elicit symptoms of peripheral neuropathy and specific tests to diagnose peripheral neuropathy clinically. Despite using a standard protocol of examination, they 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.[22] observed that 24.2% of patients had sensory signs of peripheral neuropathy and 9.09% patients had motor signs. In their study, the majority of the patients had asymmetrical sensory motor axonal neuropathy followed by pure motor neuropathy.

Nadkar et al.[23] also found that sensorimotor axonal neuropathy was the most common type of peripheral neuropathy in patients with RA. However, Biswas et al.[19] reported that pure sensory type was the most common type of peripheral neuropathy in the patients with RA. In the study of El-Hewala et al.[15], the electrophysiological diagnosis of posterior TTS (Tarsal Tunnel Syndrome) was encountered in 18 (36%) patients. Moreover, Ibrahim et al.[3] documented the electrodiagnosis of posterior TTS in 28 out of the 30 feet of RA patients. The electrophysiological findings of peroneal nerve entrapment at the fibular neck may be due to the compression of the nerve by a ganglion, rheumatoid nodule, an extension of synovial hypertrophy from the knee or even a large knee osteophyte. Data about incidence and prevalence of peroneal neuropathy in rheumatoid knees are insufficient. An increased peroneal neuropathy at the fibular head has been reported in RA. [24]

Similarly, none of the patients who were diagnosed with peroneal nerve entrapment at the fibular neck showed isolated superficial peroneal nerve lesion. It was reported that the superficial peroneal nerve is usually less involved than is the deep peroneal nerve. The most likely explanation was the selective vulnerability of different nerve fascicles to injury, which leads to differing degree of damage to individual fascicles within the common peroneal nerve. [25] According to Borman et al.[4], no correlation was observed between current foot pain and demographic parameters like age and gender but current foot pain was significantly associated with higher BMI and longer disease duration (r=0.24, p= 0.01, r=0.23, p=0.01). Corticosteroid therapy was correlated with current foot pain (r=0.24, p=0.01). The radiological scores did not correlate with duration of foot symptoms and current foot pain (p>0.05) but the total number of foot deformities was found to be correlated with Larsen scores (r=0.26, p=0.001). No correlation was observed between HAQ scores and deformities.

Conclusion

Our study showed that there was non-significant correlation between neuropathy and disease duration, RF, DAS28 & HAQ-DI but there was significant correlation with SFAQ score.

Data sharing: The data underlying this article will be shared on reasonable request to the corresponding author.

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