Original Article

Ultrasonographic Measurement of the Peroneal and Tibial Nerves in Patients with Rheumatoid Arthritis with Symptoms or Signs of Polyneuropathy: A Cross-Sectional Study

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Received: 08-Oct-2019
Revision: 14-Jan-2020
Accepted: 21-Jan-2020
Published: 07-Apr-2020

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Abstract

Background: Drug toxicity, vasculitis, entrapment neuropathy, and amyloidosis are among the various different reasons of peripheral neuropathy in rheumatoid arthritis (RA). We aimed to determine the cross-sectional areas (CSA) of the peroneal and tibial nerves in patients with RA who had neuropathic symptoms, and to determine a cutoff value for peroneal and tibial nerves CSA by ultrasonography (USG) to diagnose polyneuropathy (PN) in patients with RA.

Materials and Methods: Sixty-nine patients with RA and thirty healthy controls were included in this cross-sectional study. According to nerve conduction study (NCS) test, patients with RA were divided into two groups, diagnosed as having PN or not. Demographic data, laboratory findings, CSA of bilateral peroneal and tibial nerves, NCS values, and painDETECT (PD-Q) scores of all patients were assessed. Disease duration, disease activity score 28, duration of neuropathic symptoms, and Health Assessment Questionnaire of patients with RA were also determined.

Results: No statistically significant difference was found among the groups in terms of age, gender, and laboratory findings. However, a statistically significant difference was found among these three groups in comparison with PD-Q, NCS values, and nerve CSA ($P < 0.05$). Seropositivity was statistically higher in the group with PN. When peroneal nerve CSA cutoff value was taken as 20 mm^2, sensitivity and specificity values were 96.6% and 79.6%, respectively, for the diagnosis of PN (area under the curve [AUC] = 0.962). When tibial nerve CSA cutoff value was taken as 8.5 mm^2, the sensitivity and specificity values were 93.1% and 71.6%, respectively, for the diagnosis of PN (AUC = 0.897).

Conclusion: USG can be used as a noninvasive diagnostic modality in the assessment of RA-associated PN.

Key Words: *Nerve conduction study, peripheral neuropathy, peroneal nerve, rheumatoid arthritis, tibial nerve, ultrasonography*

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory connective tissue disease affecting mainly synovial joints. Joint erosion, ligamentous laxity, and associated joint deformities secondary to synovial joint involvement may be seen and detected. However, extraarticular findings such as bursitis, tendinitis, fasciitis, neuropathy, and vasculitis may also be seen in 10%–20% of patients.[1] Peripheral nerve involvement is also reported up to 85% of patients with RA.[2] Neuropathy presents itself with extremely wide symptoms such as pain, paresthesia, and muscle weakness. As these symptoms may imitate arthritis, it is important to distinguish and separate neuropathy symptoms from arthritis symptoms.

Drug toxicity, vasculitis, entrapment neuropathy, and amyloidosis are among the various different reasons of neuropathy in RA.[3,4] A very few number of studies are arguing that neuropathy develops secondary to autoimmune phenomena.[5,6]

For the sake of early diagnosis of peripheral neuropathy in RA patients, even in the absence of clinical involvement,

Access this article online	
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DOI: 10.4103/injr.injr_151_19	

How to cite this article: Kaymaz S, Alkan H, Karasu U, Çobankara V. Ultrasonographic measurement of the peroneal and tibial nerves in patients with rheumatoid arthritis with symptoms or signs of polyneuropathy: A cross-sectional study. Indian J Rheumatol 2020;15:192-200.

electrophysiological studies are suggested to be used as a routine diagnostic method.[7] The main advantage of the musculoskeletal ultrasonography (USG) is its ability to produce dynamic images. This technique is ideal for imaging superficial musculoskeletal structures. Moreover, the technique is cost-effective, fast, and safe and does not involve ionizing radiation.

In RA patients, cross-sectional areas (CSA) of upper extremity peripheral nerves have been assessed by USG.[8,9] In this study, we aimed to determine the CSA of the peroneal and tibial nerves in patients with RA who had neuropathic symptoms and to determine a cutoff value for peroneal and tibial nerves CSA to diagnose PN in patients with RA.

Materials and Methods

Patients

Patients diagnosed with RA according to the American College of Rheumatology 1987 criteria who were admitted to Rheumatology outpatient clinic with neuropathic complaints between May 2019 and September 2019 were included in this cross-sectional study.[10] In addition, thirty healthy controls who accompanied the RA patients in clinic and did not have any comorbidity, history of any drug use, alcohol abuse, and peripheral nerve lesion history were included in this study. On the other hand, healthy controls who occasionally had neuropathic complaints were not excluded from the study. The study protocol was approved by the institutional review board of the university, and each patient provided written informed consent to participate in this study. Patients who had comorbidities such as diabetes mellitus (DM), hypothyroidism, Vitamin B12 deficiency, alcohol abuse, liver failure, and chronic renal failure (CRF) which cause peripheral nerve lesion or PN; history of lepromatous leprosy; chronic inflammatory demyelinating PN (CIDP); and those with neurological disorders such as cerebrovascular disease and multiple sclerosis which lead to neuropathic symptoms were excluded from the study. Patients with organ dysfunction (cardiac conduction defect, erectile dysfunction, cachexia, malnutrition, renal insufficiency, proteinuria, and vitreous amyloid) due to amyloid deposition or patients diagnosed amyloidosis by performing tissue biopsy (abdominal fat pad, salivary gland, and heart, kidney) were also excluded from the study. Age, gender, and laboratory findings such as sedimentation and C-reactive protein were recorded. Disease duration, disease activity score (DAS28), Health Assessment Questionnaire (HAQ), rheumatoid factor (RF), anti-citrullinated protein antibody (ACPA) positivity, medical treatments, and duration of neuropathic symptoms were determined in patients with RA. For diagnosing of PN, a nerve conduction velocity (NCV) test which was a gold standard for the diagnosis of neuropathy was conducted on all patients and all healthy controls included in the study. Nerve conduction study (NCS) was conducted by a medical doctor blinded to the clinical findings of the patients. Bilateral CSA of peroneal and tibial nerves was determined by musculoskeletal USG in all the participants.

Neuropathic symptom measurement

PainDETECT (PD-Q) neuropathic pain questionnaire was used to screen the existence of neuropathic pain. It consists of four sections in total. The final score is obtained summing up the scores of the last three sections with a total score of 1–38.[11] Two cutoff values were used by the developer of PD-Q for the presence of neuropathic pain. Scores ≤12 state that a neuropathic pain component is unlikely, but PD-Q values ≥19 should indicate neuropathic component. The Turkish version of the PD-Q was shown to be reliable and valid.[12]

Functional status

HAQ was used in order to assess physical disability situation in RA patients.[13] It is a scale assessing the daily life activities, comprised of twenty questions in eight different sections. Each question is scored between 0 and 3 (0: I am doing without any difficulty; 1: I am doing with slight difficulty; 2: I am doing with great difficulty; and 3: I cannot do). Sections of the scale are dressing up, straightening up, eating, walking, hygiene, lying, grasping, and daily affairs, and each section contains two or three questions. Each section is separately scored, and the average of the scores of the eight sections is taken to determine a single HAQ score which may vary between 0 and 3. In the scoring of sections, the highest score obtained in the questions of that section is accepted and used as the section score. Turkish reliability and validity testing of the scale was also performed.[14]

Disease Activity Score

DAS 28 was calculated for the assessment of DAS.[15] This score is obtained by global assessment of patients, examination of 28 joints for swelling and tenderness, and erythrocyte sedimentation rate.

Nerve conduction study

NCS is a gold standard for the diagnosis of neuropathy. It was performed by the Keypoint DANTEC device (Skovlunde, Denmark). Stimulation duration was 0.2 ms for motor and 0.1 ms for sensory stimuli. All stimulations were performed supramaximally. Bipolar stimulus electrodes were used for all stimuli. Sensory examinations were all performed using the antiradical method. The band of frequencies was 20 Hz–10 kHz in the sensory, motor, and F-wave examinations. NCV under limit for the upper extremity was accepted as 50 m/s for motor conduction velocity (MCV) and 43 m/s for sensory conduction velocity (SCV). In addition, NCV under limit for the lower extremity was 42 m/s for both MCV and SCV. Under limit, the amplitude of motor unit potential (MUP) was taken as 6 mV for the median and ulnar nerve, 3 mV for peroneal

nerve, and 4 mV for tibial nerve.[16] The amplitude of the sensory nerve action potential was accepted as 10 μV for the median and ulnar nerves and as 6 μV for the sural nerve. Prolongation of motor distal latency >30% of normal, decrease of conduction velocity >25% of normal, prolongation of F wave >55 ms conduction block (so that the rate of proximal/distal amplitude MUP is under 50%) were evaluated as demyelination PN. Decrease of motor and sensorial amplitude >40% of normal value was evaluated as axonal PN.[17]

USG assessment

USG scans were performed with the use of a broadband linear array transducer (7–14 MHz, using 18 MHz band) of MyLab 70/Esaote (Italy).

Tibial nerve

Ultrasonographic images were taken when patients were in the lateral decubitus position with their ankle neutral position. During tibial nerve assessment, by positioning the probe axially so as to be parallel to medial malleoli and talus, tibial nerve was ensured to be viewed behind the flexor digitorum longus tendon [Figure 1]. For the sake of verification, alignment of tibial tendon, flexor digitorum longus, and posterior tibial vein-artery was viewed.[18]

Peroneal nerve

Ultrasonographic images were taken when patients were in the lateral decubitus position with their knees semiflexed (20°–30°). At least 5 cm of bilateral peroneal nerves just proximal to the level of fibular head was evaluated by USG.[19] The CSA of the nerve in transverse views was measured using continuous manual tracing, excluding the hyperechoic epineurial rim [Figure 2].

In both lower extremities, CSA of peroneal and tibial nerves was measured three times with time intervals of ½ h each. Then, the average of these three findings was taken.

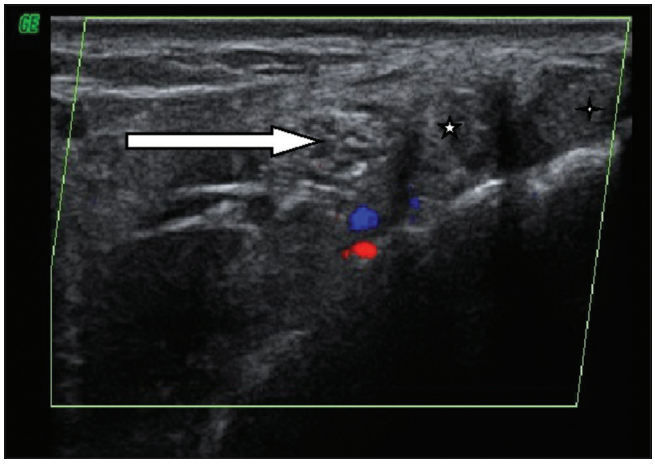

Figure 1: Cross-sectional view of the tibial nerve (thick arrow) at the ankle level in a volunteer. Asterisks: Flexor digitorum longus, square sign; posterior tibial tendon

Statistical analysis

The sample size was calculated as thirty patients in each group to determine the significance of the differences on clinical parameters and to find a cutoff value when RA patients were compared according to having PN or not with a power 85% or above based on the data obtained from the other studies.[9] All statistical analyses were performed using SPSS version 22.0 for Windows (Statistical Package for the Social Sciences Inc., Chicago, IL, USA). Descriptive statistics were used to describe demographic characteristics. The Kolmogorov–Smirnov test was used to analyze normal distribution assumption of the data. As the distributions were not normal, nonparametric tests were used in statistical evaluation. For continuous variables, the significance of the differences was analyzed using the Kruskal–Wallis variance analysis, whereas categorical variables were analyzed with Chi-squared test at baseline. Spearman's correlation analysis was used to assess correlation between nonparametric variables. A value > 0.6 was defined as indicative of a good correlation, with moderate correlation between 0.4 and 0.6 and poor correlation < 0.4. For each total nerve CSA, sensitivity and specificity were computed and graphed in a receiver operating characteristic (ROC) curve according to the diagnosis of PN. The ROC curve was used to select optimal cutoff nerve CSA scores for screening patients who had PN. Discriminant statistics such as sensitivity, specificity, and Youden index, for each possible nerve CSA cutoff score, were also obtained. The Kruskal–Wallis variance analysis and *post hoc* Bonferroni correction (Mann–Whitney U-test) were used for intergroup comparisons. In the *post hoc* Bonferroni correction analyses, $P < 0.0167$ was considered statistically significant, while in all the other analyses, $P < 0.05$ was considered statistically significant.

Results

Eighty-two RA patients were assessed for eligibility and 13 patients were excluded from the study; seven of

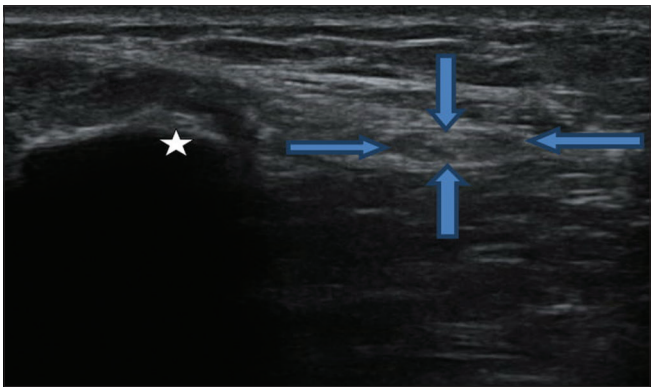

Figure 2: Cross-sectional view of the peroneal nerve (thick arrow) 5 cm proximal to the fibular head in a volunteer. Asterisks: Fibular head

them due to DM, four of them due to CRF, and two of them due to alcohol abuse. Thus, 69 RA patients and 30 healthy controls were included in the study. Thirty-two RA patients with sensory motor PN according to NCS results constituted Group 1, whereas 37 RA patients without PN constituted Group 2. Nearly 47.4% (47) of the patients had numbness, 37.3% (37) of patients had burning, 29.3% (29) of patients had tingling or prickling, 19.2% (19) of patients had paresthesias/hyperalgesia, and 17.2% (17) of patients had electric shock-like sensations.

A statistically significant difference was not detected in terms of disease duration, medical treatment, and DAS28 between RA patients with or without PN ($P > 0.05$), but nevertheless, there was a statistically significant difference between these two groups in terms of HAQ, neuropathic symptoms duration, RF, and ACPA positivity as shown in Table 1 ($P < 0.05$).

Laboratory findings, bilateral lower extremity NCS results, and nerve CSA are shown in Table 2. No statistically significant difference was found among these three groups in terms of age, gender, and laboratory findings ($P > 0.05$). However, a statistically significant difference was found among these three groups in terms of NCS values and nerve CSA ($P < 0.05$) [Table 2]. Intergroup comparison revealed that peroneal and tibial nerve CSA were statistically significantly higher in RA patients with PN when compared to RA patients without PN and healthy controls and also higher in RA patients without PN when compared to healthy controls ($P < 0.0167$). Intergroup comparison in terms of NCS values revealed that amplitudes of all the three nerves were statistically significantly lower in RA patients with PN when compared to RA patients without PN and healthy controls and also lower in RA patients without PN when compared to healthy controls ($P < 0.0167$). PD-Q values were found to be statistically significantly higher in RA patients with PN when compared to other two groups and also higher in RA patients without PN when compared to healthy controls ($P < 0.0167$) [Table 2].

CSA of both peroneal nerves had a significant relationship with amplitude, latency, and velocity of peroneal nerve ($P < 0.05$). Similarly, CSA of right and left tibial nerves had a statistically significant relationship with amplitude, latency, and velocity of tibial nerve ($P < 0.05$). In RA patients, a statistically significant and a strong positive correlation was detected between PD-Q values and CSA of both nerves ($P < 0.05$) [Table 3].

When tibial nerve CSA cutoff value was taken as 8.5 mm^2, sensitivity and specificity values were 93.1% and 71.6%, respectively, for the diagnosis of PN (area under the curve [AUC] = 0.897) [Figure 3]. When peroneal nerve CSA cutoff value was taken as 20 mm^2, the sensitivity and specificity values were 96.6% and 79.6%, respectively, for the diagnosis of PN (AUC = 0.962) [Figure 4]. Figures 3 and 4 demonstrate the ROC curves used in the determination of cutoff values of nerve CSA.

Table 1: Comparison of two groups with rheumatoid arthritis in terms of medical treatment, disease duration, disease activity score 28, and Health Assessment Questionnaire criteria

Clinical parameters and laboratory findings	Group 1 (*n*=32) RA with PN	Group 2 (*n*=37) RA without PN	*P*
HAQ, median (IQR)	1.52 (0.5)	1.05 (0.35)	0.004*
RF positivity, *n* (%)	27 (84.3)	17 (45.9)	0.001*
ACPA positivity, *n* (%)	27 (84.3)	16 (43.9)	<0.001
Disease duration, median (IQR), year	15 (12)	14 (8)	0.558
Medical treatment, *n* (%)			
MTX	8 (25)	12 (32.4)	0.221
MTX + LEF	16 (50)	11 (29.7)	
Biologic agent	8 (25)	14 (37.8)	
DAS28, median (IQR)	3.5 (1.5)	3.5 (1.2)	0.823
Neuropathic symptom duration (months), median (IQR)	16 (12.5)	10.5 (9)	0.025*

Mann–Whitney U-test was used. *P<0.05, statistically significant. IQR: Interquartile range, MTX: Methotrexate, LEF: Leflunamide, DAS28: Disease activity score 28, HAQ: Health Assessment Questionnaire, RF: Rheumatoid factor, ACPA: Anti-citrullinated peptide antibodies, PN: Polyneuropathy, RA: Rheumatoid arthritis

Discussion

In this cross-sectional study, we aimed to determine a cutoff value for peroneal and tibial nerve CSA to diagnose PN in patients with RA. Our results demonstrated that the cutoff values derived from ROC curve supported the diagnosis of PN with high sensitivity and specificity when peroneal nerve CSA cutoff value at the fibular head was taken as 20 mm^2 and when tibial nerve CSA cutoff value at the ankle level was taken as 8.5 mm^2in our study. Moreover, nerve CSA had a significant relationship with NCS.

Rheumatologists and physiatrists actively using the musculoskeletal USG have recently started to be interested in USG for the assessment of peripheral nerve system. de Miguel *et al*. expressed as a result of their study that rheumatologists may use USG in peripheral neuropathy diagnosis.[20] Also, in our study, USG was employed for the assessment of peripheral neuropathy in RA patients. CSA of upper extremity peripheral nerves has been assessed previously in RA patients.[8,9,21] Yagci *et al*. assessed CSA of median and ulnar nerves by USG in RA patients. It was demonstrated that CSA of both of these nerves was higher than that of healthy controls in their study.[9] In another study, it was also determined that median nerve CSA was higher in RA patients than healthy controls.[21] In accordance with these studies, we also found that lower extremity nerve CSAs of RA patients were higher than that of healthy controls. On the other hand, the tibial

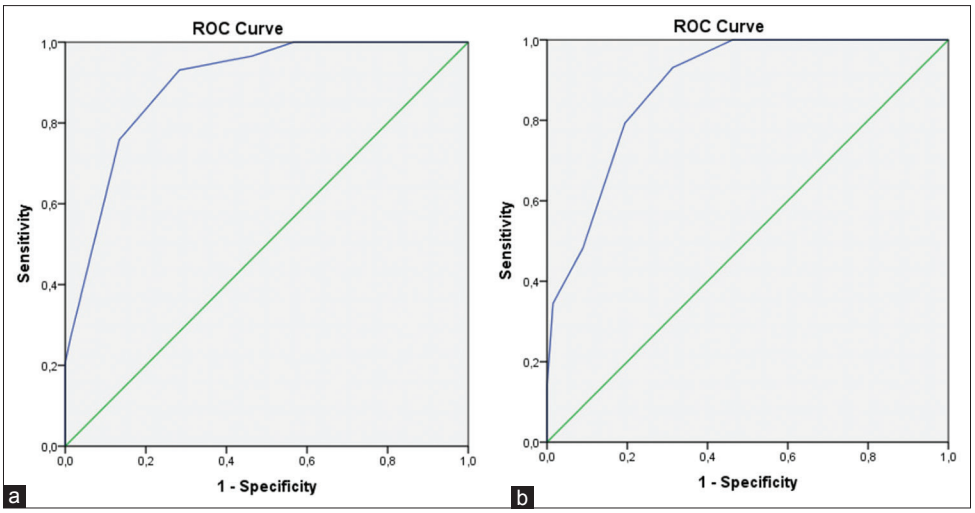

Figure 3: (a) Receiver operating characteristic curve for right tibial nerve cross-sectional area according to the diagnosis of polyneuropathy. Area under the curve: 0.897 (b) Receiver operating characteristic curve for left tibial nerve cross-sectional area according to the diagnosis of polyneuropathy. Area under the curve: 0.885

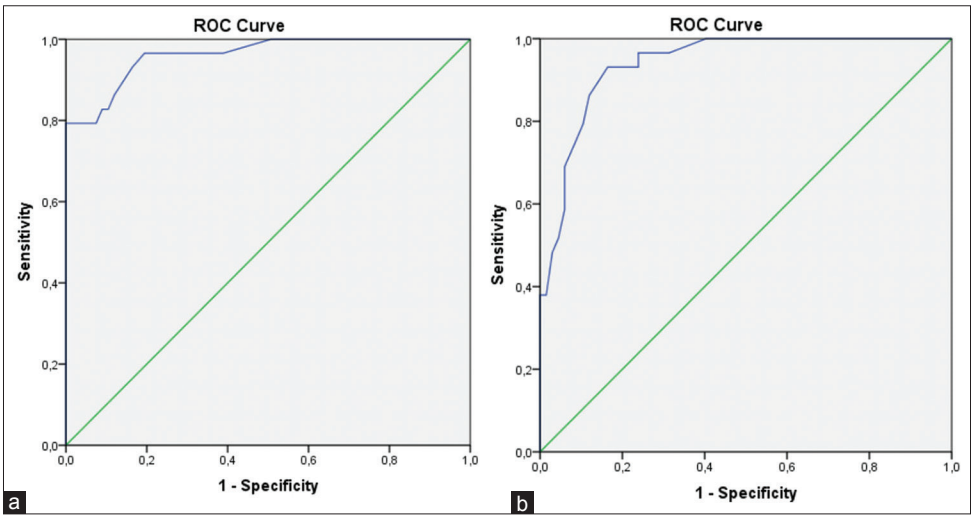

Figure 4: (a) Receiver operating characteristic curve for right peroneal nerve cross-sectional area according to the diagnosis of polyneuropathy. Area under the curve: 0.962 (b) Receiver operating characteristic curve for left peroneal nerve cross-sectional area according to the diagnosis of polyneuropathy. Area under the curve: 0.962

and peroneal nerve CSA results obtained from previous studies in healthy controls were similar to those obtained in our study.[18,19] However, to our knowledge, there was no literature assessing the lower extremity peripheral CSA in patients with RA.

Nerve CSAs were assessed in patients with DM who had diabetic PN (DPN). In a recent study, it was stated that tibial nerve CSA was higher in patients with DPN than that of healthy controls.[22] In another study, it was reported that CSA was higher in diabetic patients with DPN than diabetic patients without DPN.[23] One small study also demonstrated that CSA of tibial and peroneal nerves was higher in DPN patients than healthy controls.[24] Similar to these studies, nerve CSAs of RA patients were studied, and the CSA was found to be higher in RA patients with PN than RA patients without PN in the present study.

In a case–control study, significant correlation was determined between NCS and CSA of tibial nerve in diabetic patients.[24] In another study, it was stated that there was a negative correlation between nerve latency and nerve CSA.[25] Furthermore, Kim *et al*. determined a significant association between median nerve CSA and latency, amplitude, and velocity of median nerve in diabetic patients.[26] Also, in our study, similarly, a significant relationship was determined between nerve CSA on one side, and latency, velocity, and amplitude on the other side. However, to our knowledge, there was no study in the literature which evaluates the relationship between CSA of lower extremity peripheral nerves and NCS in patients with RA.

Visser *et al*. stated that if the peroneal nerve CSA at fibular head level is >8 mm^2, then the sensitivity and specificity of common fibular entrapment neuropathy diagnosis

Table 2: Comparison of demographic, clinic, laboratory, and nerve conduction values and nerve cross-sectional areas of groups

Clinical parameters and laboratory values	Group 1 (*n*=32) RA with PN	Group 2 (*n*=37) RA without PN	Group 3 (*n*=30) Healthy controls	*P*	Mann-Whitney U-test with Bonferroni correction
Gender, *n* (%)					
Male	9 (28.1)	10 (27)	10 (33.3)		
Female	23 (71.9)	27 (73)	20 (66.6)	0.850	
Age, median (IQR), year	65 (7)	61 (11)	62 (12)	0.056	
ESR, median (IQR), mm/h	27 (17)	29 (18)	28 (17)	0.834	
CRP, median (IQR), mg/d	1.5 (1)	1.3 (1)	1.5 (1.5)	0.852	
PainDETECT, median (IQR)	21 (4)	17 (5)	2 (1)	<0.001*	Group 1 >Group 2, *P*<0.001
					Group 2 >Group 3, *P*<0.001
					Group 1 >Group 3, *P*<0.001
PainDETECT, >19, *n* (%)	25 (78.1%)	9 (24.3%)	0	<0.001*	
Right peroneal					
Amplitude, median (IQR), mV	1 (2)	3 (2)	4 (1)	<0.001*	Group 1 <Group 2, *P*<0.001
					Group 2 <Group 3, *P*=0.001
					Group 1 <Group 3, *P*<0.001
Latency, median (IQR), ms	5 (2)	4 (1)	3 (1)	<0.001*	Group 1 >Group 2, *P*<0.001
					Group 2 >Group 3, *P*<0.001
					Group 1 >Group 3, *P*<0.001
Velocity, median (IQR), m/s	32 (15.5)	44 (6)	50 (11)	<0.001*	Group 1 <Group 2, *P*<0.001
					Group 2 <Group 3, *P*=0.015
					Group 1 <Group 3, *P*<0.001
Right tibial					
Amplitude, median (IQR), mV	2.5 (2)	5 (6)	9 (6)	<0.001*	Group 1 <Group 2, *P*<0.001
					Group 2 <Group 3, *P*=0.001
					Group 1 <Group 3, *P*<0.001
Latency, median (IQR), ms	6 (2)	4 (1)	3 (1)	<0.001*	Group 1 >Group 2, *P*<0.001
					Group 2 >Group 3, *P*<0.001
					Group 1 >Group 3, *P*<0.001
Velocity, median (IQR), m/s	39 (8)	43 (4)	51 (8)	<0.0001*	Group 1 <Group 2, *P*<0.001
					Group 2 <Group 3, *P*<0.001
					Group 1 <Group 3, *P*<0.001
Right sural					
Amplitude, median (IQR), µV	0	7 (6)	10 (11)	<0.0001*	Group 1 <Group 2, *P*<0.001
					Group 2 <Group 3, *P*<0.001
					Group 1 <Group 3, *P*<0.001
Left peroneal					
Amplitude, median (IQR), mV	1.5 (2)	3 (2)	5 (2)	<0.001*	Group 1 <Group 2, *P*<0.001
					Group 2 <Group 3, *P*<0.001
					Group 1 <Group 3, *P*<0.001
Latency, median (IQR), ms	5 (3)	4 (2)	4 (0)	<0.001*	Group 1 >Group 2, *P*<0.001
					Group 2 >Group 3, *P*<0.001
Velocity, median (IQR), m/s	38 (12)	45 (8)	49 (10)	<0.001*	Group 1 <Group 2, *P*<0.001
					Group 2 <Group 3, *P*=0.054
					Group 1 <Group 3, *P*<0.001
Left tibial					
Amplitude, median (IQR), mV	1.5 (1)	5 (6)	9 (5)	<0.001*	Group 1 <Group 2, *P*<0.001
					Group 2 <Group 3, *P*=0.009
					Group 1 <Group 3, *P*<0.001

Contd...

Table 2: Contd...

	Group 1 (*n*=32) RA with PN	Group 2 (*n*=37) RA without PN	Group 3 (*n*=30) Healthy controls	*P*	Mann-Whitney U-test with Bonferroni correction
Latency, median (IQR), ms	6 (2)	4 (1)	4 (0)	<0.001*	Group 1 >Group 2, *P*<0.001
					Group 2 >Group 3, *P*<0.001
					Group 1 >Group 3, *P*<0.001
Velocity, median (IQR), m/s	38 (7)	43 (6)	52 (7)	<0.001*	Group 1 <Group 2, *P*<0.001
					Group 2 <Group 3, *P*<0.001
					Group 1 <Group 3, *P*<0.001
Left sural					
Amplitude, median (IQR), μV	0	6 (7)	11 (10)	<0.001*	Group 1 <Group 2, *P*<0.001
					Group 2 <Group 3, *P*<0.001
					Group 1 <Group 3, *P*<0.001
Right peroneal CSA, median (IQR) mm^2	32.5 (12)	15 (10)	12 (3)	<0.001*	Group 1 >Group 2, *P*<0.001
					Group 2 >Group 3, *P*<0.001
					Group 1 >Group 3, *P*<0.001
Right tibial CSA, median (IQR) mm^2	11 (2)	8 (2)	4 (1)	<0.001*	Group 1 >Group 2, *P*<0.001
					Group 2 >Group 3, *P*<0.001
					Group 1 >Group 3, *P*<0.001
Left peroneal CSA, median (IQR) mm^2	28 (18)	15 (9)	12 (3)	<0.001*	Group 1 >Group 2, *P*<0.001
					Group 2 >Group 3, *P*<0.001
					Group 1 >Group 3, *P*<0.001
Left tibial CSA, median (IQR) mm^2	10.5 (2)	8 (3)	5 (1)	<0.001*	Group 1 >Group 2, *P*<0.001
					Group 2 >Group 3, *P*<0.001
					Group 1 >Group 3, *P*<0.001

**P*<0.05 statistically significant. IQR: Interquartile range, PN: Polyneuropathy; CSA: Cross-sectional area; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate, RA: Rheumatoid arthritis

were 90% and 69%, respectively.[27] In a recent study, it was determined that the CSA cutoff value for diagnosing peroneal neuropathy at the fibular head was found to be 11.5 mm^2 with 80% sensitivity and 99% specificity.[19] In this study, it was found that when the CSA of peroneal was taken as 20 mm^2, the sensitivity and specificity of PN diagnosis were 96.6% and 79.6%, respectively. The higher cutoff value obtained in our study differently from the other two studies mentioned herein above may be related or attributed to RA diagnosis of patients in our study because even in the absence of a clinic symptom in a study, RA patients had a higher CSA than healthy controls.[9] Thus, assessment of nerves at a single level constituted the most important limitation of our study because in a study, it was determined that in patients with peripheral neuropathy, CSA of nerves was widening diffusely.[23]

In the literature, the relationship between neuropathic pain and nerve CSA was examined in patients with DPN. In a recent study, a statistically significant correlation was found between the Toronto Clinical Neuropathy Score and tibial nerves CSA in patients with DPN.[22] In our study, PD-Q scale was used to evaluate neuropathic pain in RA patients. We also demonstrated a statistically significant association between lower extremity nerve CSAs and PD-Q questionnaire.

The etiology of peripheral neuropathy has not been understood exactly yet. In previous studies, drug toxicity, vasculitis, amyloidosis, and autoimmune phenomena have been regarded as possible causes of PN in patients with RA.[3-5] Kaeley *et al*. and Rajesh *et al*. reported that there was a strong relationship between PN and RF positivity, ACPA positivity, and DAS 28.[28,29] In another study, it was found that the duration of RA diagnosis was associated with PN.[30] There was no statistically significant difference between Group 1 and Group 2 in terms of amyloidosis, duration of disease diagnosis, DAS28, and the medical treatment, but seropositivity was significantly higher in the first group than in the second group in our study. This may have caused a higher incidence of PN and nerve CSAs in the first group compared to the second group because seropositivity is a risk factor for neuropathy.[28,29]

Systemic diseases such as DM, lepromatous leprosy, CIDP, and amyloidosis may also cause an enlargement in CSAs of peripheral nerves.[19,31-33] Although it was paid attention to the absence of the mentioned diseases in patients with RA included in the study, not performing nerve biopsy to determine amyloid accumulation was an important limitation of our study because amyloid fibrils may cause compression and ischemia in the vascular structures of

Table 3: Relationship of nerve cross-sectional areas with clinic and nerve conduction values

Clinical parameters and laboratory values	Right peroneal CSA		Right tibial CSA	
	r	*P*	*r*	*P*
PainDETECT	0.666	<0.001*	0.770	<0.001*
DAS28	0.297	0.003*	0.456	<0.001*
HAQ	0.591	<0.001*	0.654	<0.001*
Right peroneal				
Amplitude	−0.523	<0.001*	-	-
Velocity	−0.500	<0.001*	-	-
Latency	0.543	<0.001*	-	-
Right tibial				
Amplitude	-	-	−0.383	0.04
Velocity	-	-	−0.587	<0.001*
Latency	-	-	0.561	<0.001*
Clinical parameters and laboratory values	**Left peroneal CSA**		**Left tibial CSA**	
	r	*P*	*r*	*P*
PainDETECT	0.616	<0.001*	0.761	<0.001*
DAS28	0.292	0.004*	0.475	<0.001*
HAQ	0.518	<0.001*	0.641	<0.001*
Left peroneal				
Amplitude	−0.571	<0.001*	-	-
Velocity	−0.458	<0.001*	-	-
Latency	0.480	<0.001*	-	-
Left tibial				
Amplitude	-	-	−0.413	0.038
Velocity	-	-	−0.691	<0.001*
Latency	-	-	0.493	<0.001*

*P<0.05, statistically significant. HAQ: Health assessment score, DAS28: Disease activity score 28, CSA: Cross-sectional area

the nerve. As a result of this physiopathology, nerve CSA enlarges in amyloidosis.[32]

Pure sensory, pure motor, sensory motor, small fiber neuropathy, mononeuritis multiplex, carpal tunnel syndrome, and subclinical neuropathy are among the neuropathy forms seen in patients with RA.[28,34] Agarwal *et al*. found that subclinical neuropathy was the most common form of neuropathy in patients with RA.[35] In two studies, subclinical neuropathy was reported to be the most common form after sensory motor PN.[2,28] However, there are few studies on the role of ultrasound in the diagnosis of PN, especially subclinical neuropathy in patients with RA. In a study conducted by Yagci *et al*., it was found that patients with the diagnosis of RA but without PN had higher nerve CSAs than healthy controls. They stated that this may be related to subclinical neuropathy.[9] In our study, the higher nerve CSAs in the patients with the diagnosis of RA without PN may be related to subclinical neuropathy. In addition to subclinical neuropathy, small fiber neuropathy that cannot be detected by USG and NCS but causes neuropathic complaints is one of the neuropathy forms that should be taken into consideration.[34] This form can be determined by skin biopsy. As indicated previously, not performing biopsy was the most important limitation of our study.

Vasculitis plays a role in the etiology of neuropathy in patients with RA.[35] Ito *et al*. showed that ultrasonographic measurement of tibial nerve CSA had a role in the diagnosis of vasculitic neuropathy (VN).[36] Grimm *et al*. stated that focal CSA enlargement in one or more nerves could be a hint for VN and thus facilitate diagnostic procedures.[37] In another study, it was observed that evaluating vascularity of nerves and CSAs at multiple levels might be beneficial in the diagnosis of VN.[38] Further studies of biopsy-proven VN are required to define the USG findings of peripheral nerves in this setting. In our study, not evaluating vascularity of the nerves and CSAs at multiple level were limitations of our study that should be taken into consideration.

In this cross-sectional study, as also mentioned herein above, assessment of nerves at a single level, not performing nerve biopsy, operator-dependent nature of USG, and failure in elimination of incidental relationship in cross-sectional studies can be listed as the major limitations of our study.

Conclusion

USG can be used as a noninvasive diagnostic modality in the assessment of RA-associated PN. In addition to clinical and NCV findings, USG may improve the diagnostic performance of PN in patients with RA.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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