Sonographic measurements can be misleading for diagnosing carpal tunnel syndrome in patients with rheumatoid arthritis

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ABSTRACT

Objectives: To compare the nerve cross sectional areas (CSA) of patients with RA, without any sign of peripheral neuropathy, to healthy controls.
Methods: Clinical, electrophysiological and sonographic assessments were done by three blinded researchers. The patients who had an electrodiagnostic or manifestations of peripheral neuropathy were excluded from the study. Nerve CSA were measured at various levels; hamatum hook, pisiform bone, radio-ulnar joint, distal 1/3 of forearm, and elbow for median nerve; radio--ulnar joint, pisiform bone, distal 1/3 of forearm, and medial epicondyle for ulnar nerve.
Results: The study was completed with 30 women with RA and 30 healthy women. Despite both groups had neither clinical nor electrophysiological neuropathy, the sonographic measurements showed that median nerve CSA at radioulnar joint, pisiform and hamatum levels of patients with RA were larger in rheumatoid arthritis patients than healthy controls. Ulnar nerve CSA at radioulnar joint, pisiform and distal 1/3 forearm and medial epicondyle levels of patients with RA were also increased ($p<0.05$). If the pisiform level median nerve CSA>10 mm^2 was used as sonographic carpal tunnel syndrome (CTS) criterion, 23/60 hands of 30 patients with RA and 5/60 hands of 30 healthy controls could be diagnosed as CTS.
Conclusion: Median and ulnar nerve CSA were larger than healthy control in patients with rheumatoid arthritis, without clinical and electrophysiological peripheral neuropathy. The rheumatologists should be careful to diagnose CTS in patients with RA while using US.

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INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common upper limb compression neuropathies in general population and also in patients with rheumatoid arthritis (RA)[1,2,3]. CTS is a clinical diagnosis based on the patient's history and physical examination[4]. In recent years musculoskeletal ultrasound (US) has become popular for diagnosing CTS and there are also studies suggesting the use of US in patients with RA[5-8]. However, the pathogenesis of CTS or another peripheral neuropathy in RA can be other besides the idiopathic compression neuropathies. In this study we aimed to compare the nerve cross sectional area (CSA) of median and ulnar nerves in patients with RA, who didn't have any sign of clinical and electrophysiological peripheral neuropathy, to healthy controls.

MATERIAL AND METHODS

The study group was generated from referrals to Rheumatic Diseases Outpatient Clinics, during January 2013 to March 2014. The patients and the control group were assessed by three independent researchers. After clinical assessment of the clinician (IY), the patients were referred to the electrodiagnosis laboratory. Nerve conduction studies (NCS) were performed by the same electrodiagnostician (BMK) who was blinded to clinical findings. The electromyographer excluded the patients who had an electrodiagnostic abnormality and referred patients to ultrasonographic assessment, which was done by a third blinded researcher (MAL).

The sample size was calculated based on pisiform level CSA of the median nerve, which was the most sensitive parameter according to literature[9,10]. The minimum subject number was found to be 14 in each group, which would be necessary to detect a difference at the 5% level (=0.05) with an 80% chance (=0.2). The study protocol was approved by the local ethics committee (MAR-09.2013.0063) and all patients gave written consent for participating in the study.

CLINICAL ASSESSMENT

Age, gender, occupation, marital status, height, weight, body mass index, concomitant disorders including thyroid, renal, cardiovascular, and liver disorders, previous surgery, alcohol consumption and smoking were assessed with a standardized patient assessment form. Neurological examination was performed with standard assessment including muscle strength, sensory testing (light touch, pinprick, position, temperature, vibration senses), knee and ankle stretch reflexes.

Patients and controls were examined for the presence of Tinnel's sign, Phalen test, tenar atrophy, and Flick sign. KATZ hand diagram was used for diagnosing clinical CTS[11]. Patients were asked to mark as accurately as possible the areas of pain, paresthesia and/or numbness. KATZ hand diagram classified patients into four groups: classic pattern, probable pattern, possible pattern and unlikely pattern. The specificity and sensitivity of KATZ hand diagram was found to be 70% and 79% percent in Turkish population, in a previous study[12]. The patients with classic, probable and possible pattern were accepted as clinical CTS and excluded from the study.

All patients filled the Boston Questionnaire which is a self-administered disease specific questionnaire for the assessment of the severity of symptoms and functional status in CTS based on two scales. The symptom severity scale is comprised of 11 questions, and the functional status scale includes 8 questions. The assessment of each question was on a scale of 1 to 5 points, in which 1 indicates no symptom, and 5 indicates severe symptoms[13].

Patients with RA had been managed by first clinician with a strict scheduled follow-up program. The patients had been evaluated with DAS-28 scores in 1st, 3rd, 6th, 9th month and 1st year after initial diagnosis. The patients who had mild or moderate disease activity were enrolled to the study. The exclusion criteria were, concomitant endocrine disorders such as hypothyroidism or diabetes mellitus, previous carpal tunnel release, DAS 28 score greater than 5.1, clinical or electrophysiological peripheral neuropathy.

NERVE CONDUCTION STUDIES

NCS were performed with Medtronic-Keypoint (Denmark, 2007) device by the same physician. All studies were done under standard room temperature of 25ºC. Hand temperature was maintained at 32ºC or greater. Median motor NCS was recorded with surface electrodes from abductor pollicis brevis muscle. The standard distance between stimulation at wrist and recording electrode was 8 cm. Median, ulnar and tibial motor nerve proximal and distal latencies, motor nerve conduction velocities and compound muscle action potential amplitudes were measured. Median sensory NCS were recorded with wire electrodes from 3rd digit antidromically with standard distance of 14 cm. Ulnar sensory NCS were recorded from 5th digit with standard distance of 13 cm. Sural nerve sensory NCS was recorded at the lateral malleolus with midcalf stimulation with standard distance of 14 cm. For all sensory NCS, distal latency, sensory nerve action potential amplitude and sensory nerve conduction velocity were measured. The latencies were marked at the onset of first negative peak and the amplitudes were determined from peak to peak. Median and ulnar motor NCS were recorded with cup electrodes from 2nd lumbrical-interosseous muscle. The stimulation points were over the carpal tunnel for median nerve and Guyon canal for ulnar nerve with standard distance of 9 cm.

Electrophysiological diagnosis of any neuropathy was obtained according to normative values of our laboratory. The measures greater than 3.7 ms for median motor nerve distal latency, and median sensory nerve velocity slower than 50 m/s for wrist-3rd digit segment were used for median nerve demyelinitation criteria. Differences more than 0.4 ms for latency of median nerve and ulnar nerve recorded from 2nd lumbrical-interosseous was another criterion for median neuropathy. Ulnar sensory nerve velocity slower than 50 m/s and sural sensory nerve velocity slower than 40 m/s, tibial motor nerve distal latency greater than 5 ms were used to detect polyneuropathy. The electrophysiological testing was extended if there was a suspicious condition such as polyneuropathy, radiculopathy or other peripheral nerve system disorders. The electrodiagnostic studies should be completely normal for inclusion to the study.

SONOGRAPHIC ASSESSMENT

Sonographic assessments were performed by a well

TABLE I. DEMOGRAPHIC DATA AND CLINICAL CHARACTERISTICS OF THE GROUPS

	Patients with RA	Control Group	Statistical analysis
Age (years)	45.56 ± 10.49	41.56 ± 10.40	F:0.106 p=0.14
BMI (kg/m^2)	28.43 ± 4.69	27.19 ± 3.88	F:0.88 p=0.26
Symptom severity score	1.86 ± 0.88	1.99 ± 1.04	F:4.22 p=0.88
Functional capacity score	1.86 ± 0.75	1.93 ± 1.1	F:9.92 P=0.76

TABLE II. MEDICAL TREATMENTS OF THE PATIENTS

Medical Therapy	Number of patients
DMARD monotherapy	13
Biologics	3
DMARD+corticosteroids	13
Biologics+DMARD+corticosteroids	1
Total	30

trained specialist who was blind to the participant's history and NCS results with using a 6-18 MHz linear array probe (Esaote Mylab 70, Italy). All examinations were performed with the participants in a supine position on a table. The nerves were viewed in axial plane. The transducer was kept perpendicular to median nerve. Nerve CSAs were measured in various levels: at hamatum hook, pisiform bone, radio-ulnar joint, distal 1/3 of forearm, and medial epicondyle for median nerve; radio-ulnar joint, pisiform bone, distal 1/3 of forearm, and medial epicondyle for ulnar nerve. The CSA was measured by tracing the nerve just inside its hyperechoic rim. Three different measurements were obtained and the average measure was used for each level.

STATISTICAL ANALYSES

The statistical analyses were performed with Statistical Package for the Social Science Program (SPSS Version 10.0). The main characteristics of patients were evaluated with descriptive studies. Comparison of the mean values of age, Boston Questionnaire and body mass index parameters were performed with t tests, CSA were compared with Mann Whitney U test. Categorical values were analysed with chi-square tests. *P* values lower than 0.05 were accepted as statistically significant.

RESULTS

The study included 30 female patients with RA and 30 healthy female. The demographic and clinical characteristics of patients were summarized in Table I. Both groups were similar according to age and body mass index.

The medical management of the patients with RA was demonstrated in Table II. Eight patients had low disease activity (DAS28: 2.6-3.2) and 22 patients were in remission (DAS28<2.6).

According to patient selection criteria none of the patient had an electrodiagnostic abnormality. The sonographic measurements of both groups are listed in Table III.

Despite both groups had no clinical and electrophysiological CTS, the sonographic measurements showed that ulnar and median nerve cross sectional area of patients with RA were larger than healthy age matched controls.

According to previous studies the most sensitive and specific parameter for sonographic diagnosis of CTS was pisiform level CSA of median nerve. In general practice 10 mm^2 is used as a cutoff value[6,7]. The study showed that 23/60 hands of 30 patients with RA and 5/60 hands of 30 healthy controls were above 10 mm2 and could be diagnosed easily as CTS and statistical significance was found between groups with chi-square test (p<0.001) (Table IV).

DISCUSSION

Rheumatologists, and also other physicians, who are working on musculoskeletal system are showing increasing interest in high frequency ultrasound. According to a recent survey; rheumatologists also use ultrasound for diagnosing peripheral neuropathies[14]. In fact, there are numerous studies that prove ultrasound is a valuable diagnosing tool for compression neuropathies particularly in CTS. Local swelling of the median nerve and increased cross sectional area is highly correlated with clinical symptoms[15,16]. According to literature areas of 10-13 mm^2 have been reported in

TABLE III. SONOGRAPHIC MEASUREMENTS

	Patients with RA (mean ± standard deviation) [median/interquertile range]	Control group (mean ± standard deviation) [median/interquertile range]	Statistical analysis
Median nerve cross sectional area at radio-ulnar joint	(8.8±1.53) [9/2]	(7.85±1.02) [8/1]	p=0.001
Median nerve cross sectional area at pisiform level	(9.16±1.71) [9/2]	(8.03±0.94) [8/1]	p=0.002
Median nerve cross sectional area at hamatum level	(9.61±1.92) [9.5/3]	(8.48±1.08) [9/1]	p=0.001
Median nerve cross sectional area at distal 1/3 forearm	(8.26±1.11) [8/1]	(8±1) [8/2]	p=0.132
Median nerve cross sectional area at elbow	(9.6±1.78) [9.5/2]	(9.6±1.78) [9/2]	p=0.724
Ulnar nerve cross sectional area at radio-ulnar joint	(6.75±0.89) [7/1]	(6.08±0.88) [6/1.75]	p=0.001
Ulnar nerve cross sectional area at pisiform level	(6.8±1) [7/1]	(6.18±0.91) [6/1]	p=0.001
Ulnar nerve cross sectional area at distal 1/3 forearm	(8.11±1) [8/1]	(7.45±0.94) [7/1]	p=0.001
Ulnar nerve cross sectional area at medial epicondyle level	(8.61±1.32) [9/2]	(8.21±1.22) [8/2]	p=0.034

TABLE IV. NUMBER OF PATIENTS WITH SONOGRAPHIC CTS

	RA	Control	Statistics
Median CSA<10 mm^2	37 (61,7%)	5591,7%	χ^2:15,093 p<0.001
Median CSA≥10 mm^2	23 (38,3%)	5 (8,3%)	

patients with mild symptoms, 13-15 mm^2 showed moderate symptoms and areas >15 mm^2 were found in patients with severe CTS[9]. However, there may be other factors causing increase in the CSA such as body weight and other systemic diseases[17,18] and the usage of CSA in some patient groups may be challenging.

CTS is a well known neurological involvement in patients with rheumatoid arthritis. Karadag *et al*[10] found that CTS frequency was 17% in RA. This study suggested that CSA between 10 and 13 mm^2 and using Boston Questionnaire could raise the suspicion of CTS in patients with RA[10]. However, there are some controversy studies on the diagnostic utility of ultrasound for diagnosing CTS in RA. In a previous study, Hammer *et al*[19] investigated CSA of median nerve in 30 patients with RA and health controls and they found higher CSA in patients with RA than healthy controls and suggested the use of ultrasound in patients with RA when CTS was clinically suspected. On the other hand in their later study they found that without symptoms or signs CSA of patients with RA were similar to healthy controls. They reported 10% increased values in patients with RA. In both studies there were no ultrasound measurements of ulnar nerve. Therefore we hypothesized that, RA is a systemic disease causing local nerve swelling without any compression and we measured median and ulnar nerve CSA at various levels. We also used strict inclusion criteria by using electrodiagnosis and standardized clinical assessment to obtain a homogenous sample size without any clinical and electrophysiological sign and symptoms of CTS. We found that median nerve CSA of patients with RA were larger than healthy age matched controls at wrist level. None of the previous studies had evaluated the ulnar nerve. We showed that ulnar nerve CSA of the all levels were significantly increased in patients with RA. As routinely used, if a CSA 10 mm^2 at pisi-

form level is defined as a cut off value for diagnosing CTS, 23/60 hands of 30 patients with RA and 5/60 hands of 30 healthy controls could be misdiagnosed as CTS in our study population. The results also suggested that there may be subclinical neuropoathy in patients with RA which can not be detect by conventional electrodiagnostic studies.

CONCLUSIONS

Median and ulnar nerve CSA were larger in rheumatoid arthritis patients than healthy controls, being both groups without clinical and electrophysiological peripheral neuropathy. An increased CSA can be misleading in the diagnosis of CTS, in patients with rheumatoid arthritis and without clinical or electrophysiological abnormality.

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