

Validity of high-resolution ultrasonographic measurement versus electrophysiological study in the detection of frequency of carpal tunnel syndrome in patients with rheumatoid arthritis

Rawhya R. El-Shereef^a, Ahmad Lotfi^a, Fatma Ali^a, Sammer F. El-Shayb^b

Departments of ^aRheumatology and Rehabilitation ^bNeurology, Faculty of Medicine, El Minia University, Minia, Egypt

Correspondence to Rawhya R. El-Shereef, MD, Department of Rheumatology and Rehabilitation, Faculty of Medicine, Minia University, Minia, Egypt
Tel: +0580744011; fax: 08 623 235 88; e-mail: rawhiaelshereef@yahoo.com

Received 20 February 2014

Accepted 18 April 2014

Egyptian Rheumatology & Rehabilitation
2014, 41:122–129

Objectives

This study aimed to determine the frequency of occurrence of carpal tunnel syndrome (CTS) in rheumatoid arthritis (RA) patients, determine its relation to disease activity, describe the ultrasonographic (US) finding of CTS, and compare the diagnostic value of US with the electrodiagnosis in the detection of CTS.

Patients and methods

This study was carried out on 54 adult RA patients (group II) compared with 20 healthy volunteers as controls (group I). The disease activity in all patients was assessed using DAS28. All patients and controls underwent complete rheumatological and neurological examinations. Nerve conduction study (NCS) and high-resolution sonography were assessed in a blinded manner to clinical data. The patients were subdivided into two groups according to the measurement of NCS (group IIA: RA patients with CTS and group IIB: RA patients without CTS).

Results

The frequency of CTS in RA patients was 40.7%. A strong positive correlation was found between group IIA and the disease activity scale ($P < 0.0001$). There was a significantly higher level of cross-sectional area at the carpal tunnel inlet in group IIA than in group IIB and the control group ($P < 0.0001$). There was a significant correlation between the mean cross-sectional area with the grades of CTS detected by the electrophysiological study. The area under the curve was large for all receiver operating characteristic curves for each measurement (0.800).

Conclusion

The frequency of CTS in RA patients is high. High-frequency US examination of the median nerve should be strongly considered as a new alternative diagnostic modality for the evaluation of CTS. Sonography is probably preferable because it is painless, fast, easily accessible, and preferred by the patients.

Keywords:

carpal tunnel syndrome, electrophysiological study, rheumatoid arthritis, ultrasonography

Egypt Rheumatol Rehabil 41:122–129

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1110-161X

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease of unknown etiology characterized by the involvement of the joints. RA is also associated with vasculopathy, peripheral, autonomic, and entrapment neuropathy resulting in distal sensory, and combined sensory and sensorimotor neuropathy [1,2]. Carpal tunnel syndrome (CTS) is the most common form of entrapment neuropathies, and the prototypical injury of the median nerve at the wrist is either an acute or a chronic compressive lesion. It is usually diagnosed by electrodiagnostic studies and clinical findings are variable and include symptoms of burning pain, tingling, numbness, and weakness or atrophy in the hands of the patients [3]. Tenosynovial proliferation of the flexor tendons, which increases pressure in the carpal tunnel, leads to CTS in patients with RA [2]. The most reliable method to confirm the clinical diagnosis of CTS is electrodiagnostic testing, but false negatives and false positives may

occur, even when the most sensitive methods are used [4,5].

MRI and ultrasonography (US) have been shown to be useful diagnostic tools in CTS, providing information on the median nerve and surrounding structures [6,7]. In the last few years, many reports have discussed the high sensitivity and specificity in CTS diagnosis, but many of these articles considered anomalous electrodiagnostic tests as the gold standard for inclusion criteria.

Patients and methods

This study included two groups: 20 healthy volunteers as a control group (group I) and 54 adult RA patients, 10 men (18.5%), 44 women (81.5%), in group II who were defined according to the revised criteria of the American college of rheumatology (ACR) [8]. All patients were subjected to a detailed assessment of

clinical history; a careful rheumatological examination and extended neurological evaluation were performed. Demographic data in the form of age, sex, disease duration, and concomitant medications were obtained from the patients. DAS28 is a validated index of RA disease activity. It consists of four measures: 28 tender and swollen joints count, erythrocyte sedimentation rate (ESR), and the patient's general health measured on a 100 mm visual analog scale. It is calculated using the formula $0.56 \times (\text{square root of TJC28}) + 0.28 \times (\text{square root of SJC28}) + 0.70 \times \ln(\text{ESR}) + 0.014 \times \text{general health}$ [9]. The preliminary criteria for clinical remission in RA were used to evaluate the remission of the patients and the results showed that four of the patients were in remission [10]. Assessment of disability of RA patients was performed by health assessment questionnaire (HAQ). The Arabic version of the Boston Carpal Tunnel Questionnaire (BCTQ) was used [11]. A patient-oriented measurement was used (the Arabic version of the BCTQ) [12]. The BCTQ evaluates two domains of CTS, namely, 'symptoms', assessed using an 11-item scale (pain, paresthesia, numbness, weakness, and nocturnal symptoms), and 'functional status', assessed using an eight-item scale (writing, buttoning, holding, gripping, bathing, and dressing). The questionnaire was presented in a multiple-choice format, and scores were assigned ranging from 1 point (mildest) to 5 points (most severe). No response to a certain question was assigned 0 points. Each score is calculated as the mean of the responses of the individual items. Patients were divided into five groups according to their mean score: extreme (4.1–5 points), severe (3.1–4 points), moderate (2.1–3 points), mild (1.1–2 points), and minimal (0.1–1 point) [11]. It evaluates symptoms (11-item) and functional status (eight-item). Scores were assigned ranging from 1 point (mildest) to 5 points (most severe). Patients were divided into five groups according to their mean score: extreme (4.1–5 points), severe (3.1–4 points), moderate (2.1–3 points), mild (1.1–2 points), and minimal (0.1–1 point).

Investigations

The following investigations were performed in all patients: routine investigations such as ESR, complete blood count, and rheumatoid factor (RF), radiographs of the hands and wrists [anteroposterior (AP)]. Investigations to diagnose any secondary cause for CTS were performed, which included random blood sugar (RBS), thyroid function tests, radiograph of cervical spine, and special investigations including the following:

Nerve conduction studies

Nerve conduction studies were carried out for 108 hands; the electrodiagnosis protocol recommended

by the American Association of Electrodiagnostic Medicine (AAEM) was used [13]. The nerve conduction studies included determination of the sensory and motor conduction velocities of median and ulnar nerves in the upper limbs. In addition, comparative tests were performed in the fourth digit for ulnar–median nerve stimulation in the wrist. The temperature of the room was maintained at 22–24°C during all the processes. Standardized nerve conduction velocity techniques were used. Nerve conduction velocities were measured with conventional methods using surface electrodes. For motor nerve conduction studies, an active surface electrode was placed on the motor point of the appropriate muscle and reference 3 cm apart. Median and ulnar nerve compound muscle action potentials were recorded from the abductor pollicis brevis and the abductor digiti minimi muscles, and stimulation was delivered at the wrist and at the elbow. Sensorial nerve conduction studies were performed antidromically and a minimum of 10 responses were averaged. Ring electrodes were placed on the second digit for the median nerve and on the fifth digit for the ulnar nerve. In addition, the comparative test was performed in the fourth digit for ulnar–median nerve stimulation in the wrist. Latencies were measured at the initial deflection of the action potential in motor studies and at the peak of the negative spike in sensor studies. Amplitudes represent the distance between the isoelectric trace and the negative peak in sensory and peak-to-peak in motor conduction studies [14].

Description of diagnostic criteria for carpal tunnel syndrome

Measurements performed and cutoff points or normal values used in our study were as follows:

- (i) Median nerve distal sensory latency, upper limit of normal 3.6 ms;
- (ii) Difference between the median and ulnar nerve distal sensory latencies, upper limit of normal 0.4 ms;
- (iii) Distal motor latency over the thenar, upper limit of normal 4.3 ms;
- (iv) Median motor nerve conduction velocity, lower limit of normal 49 m/s;
- (v) Median sensory nerve conduction velocity, lower limit of normal 49 m/s [15,16].

The severity of CTS was assessed using the previously reported neurophysiological classification [17]:

- (i) Extreme (absence of motor and sensory responses);
- (ii) severe (absence of sensory response and abnormal distal motor latency);

- (iii) Moderate (abnormal digit–wrist sensory nerve conduction velocity and abnormal distal motor latency);
- (iv) Mild (abnormal digit–wrist sensory nerve conduction velocity and normal distal motor latency);
- (v) Minimal (abnormal comparative tests only); and
- (vi) Negative (normal findings in all tests).

High-resolution ultrasonography

The US examination was performed by a rheumatologist who had 15 years of experience in musculoskeletal US and who was blinded to the clinical and nerve conduction test [a linear array 7.5 MHz transducer (ultrasound machine, Logic 3 The LOGIQ e Ultrasound from GE Healthcare, General Electric Company) was used]. Patients were sitting with their forearm resting in a supinated position on a small table. The US probe was held as lightly as possible to avoid disturbing the anatomy of the nerve. The median nerve was examined at the entrance of the carpal tunnel, between the pisiform bone and the tubercle of the scaphoid bone, where the distal volar crease is an external pisiform landmark. A continuous trace was made just within the hyperechogenic boundary of the nerve. Both wrists were examined; we examined the following structures.

The cross-sectional area (CSA) of the median nerve was calculated directly using the software of the US equipment. Each median nerve was measured three times and the mean value was used for further analyses.

Flattening ratio (FR) of median nerve during passive flexion and extension of the index finger.

Bowing of FR, AP dimension of carpal tunnel.

Transverse sliding of the median nerve at the inlet and outlet of the tunnel.

These two last investigations were performed in a blinded manner by two observers.

Statistical analysis

Data were analyzed using the statistical package for the social sciences (SPSS, version 11.0) [18] for Windows. Two-tailed tests were used throughout and statistical significance was set at conventional 0.05 levels. The following statistics were obtained: descriptive statistics: the ranges, means, and SDs were calculated for interval, ordinal variables, and the frequencies and percentages for categorical variables. Comparisons were carried out using several procedures depending on the type of variable; Students' *t*-test was used to compare the difference

between two group means in interval and ordinal variables. The χ^2 -test is a nonparametric measure of the statistical independence of the categories of the two variables measured on a nominal or a dichotomous scale. When the percentage of the expected frequencies less than 5 exceeded 20%, Fisher's exact test was used. Sensitivity and specificity were used to quantify the diagnostic utility of US measurement in adult patients with CTS; in RA patients, we constructed a receiver operating characteristic (ROC) curve, using, for this analysis, the value of the CSA and the FR in patients with CTS (the current gold standard) and patients without CTS.

Results

Characteristics of RA patients: 54 (44 women, 10 men) patients fulfilled the updated revised criteria for the classification of RA, 81.5% women and 18.5% men. The mean age of the patients was 45.6 ± 13.1 years (range 23–77 years), whereas that of the controls was 44.5 ± 13.3 years. The mean age at onset and disease duration among RA patients was 37.7 ± 12.03 (range 10–62 years), and 8.5 ± 6.3 (range 1–25 years), respectively (Table 1). In terms of the drug history, 75.9% received methotrexate, 63% received antimalarial, 14.8% received steroid, and 68.5% received NSAIDs as a single drug or combined. The RA patients were subdivided into two groups; the first one, group IIA, included RA patients with CTS, and the second one, group IIB, included RA patients without CTS according to the measurement of the nerve conduction study.

Clinical picture

The rheumatoid factor was positive in 42 (77.8%) patients. Erosions of the hands were present at the time of examination in 35 (64.8%) patients of the study group. The maximum disease activity score was defined in 40 (74%) patients of the study group. Mean \pm SD of ESR was 67.0 ± 16.9 (range 42–93). Mean \pm SD of HAQ was 1.7 ± 0.4 (range 1.1–2.6). Mean \pm SD of ACR criteria was 5.2 ± 0.7 (range 4–6). Family history was positive in three (5.5%) patients.

Table 1 Demographic data of rheumatoid arthritis patients and controls

Demographic data	Group II		Group I	
	Range	Mean \pm SD	Range	Mean \pm SD
Age (years)	23–77	45.6 ± 13.1	22–70	44.5 ± 13.3
Age at onset (years)	10–62	37.7 ± 12.03		
Duration of disease (years)	1–25	8.5 ± 6.3		
Sex [<i>n</i> (%)]				
Male	10 (18.5)		4 (20)	
Female	44 (81.5)		16 (80)	

Frequency of carpal tunnel syndrome

One hundred and eight hands of 54 adult patients with RA (44 women, 10 men) were included in the study. Forty hands of 20 healthy volunteers (15 women, 5 men) who had a normal neurological examination were included in the control group. There was a highly statistically significant difference between patients and controls in CTS ($P < 0.0001$); no CTS was present in the control group clinically and by the nerve conduction study.

The frequency of CTS was 40.7% among RA patients (14.8% unilateral and 25.9% bilateral) (Figs. 1 and 2). The classification of CTS diagnosed by electrophysiological study is summarized in Figs. 3 and 4.

Clinical feature of carpal tunnel syndrome

Clinical findings are variable and include symptoms of burning pain, tingling, numbness and weakness,

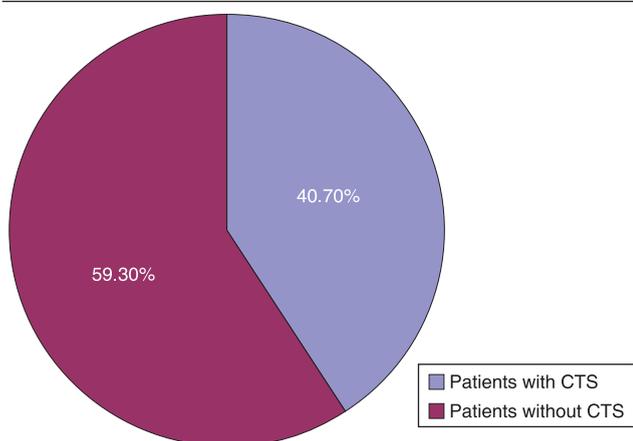
or atrophy in the hands of the patients. Twenty-four (44.4%) patients had symptoms of CTS; of these, only 14 had CTS by electrophysiological study and US. These symptoms of CTS can be divided into motor in 20.4%, sensory in 13%, and motor and sensory in 11.1% of our patients (Figs. 5 and 6). The mean duration of CTS symptoms was 3.4 ± 2.9 months (range 0.5–12 months). Phalen’s and Tinel’s signs were positive in 20 (37%) and 22 (40.7%) patients, respectively. There was a statistically significant relation

Table 2 Relation of symptom of carpal tunnel syndrome with abnormal electrodiagnostic tests in rheumatoid arthritis patients

Clinical features	RA with CTS (22)	RA without CTS (32)	χ^2	P
Asymptomatic	8	22	5.53	0.02*
Symptomatic	14	10		

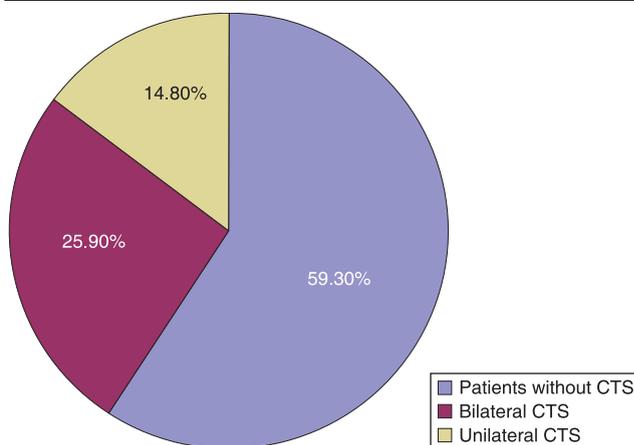
CTS, carpal tunnel syndrome; RA, rheumatoid arthritis; *statistically significant.

Figure 1



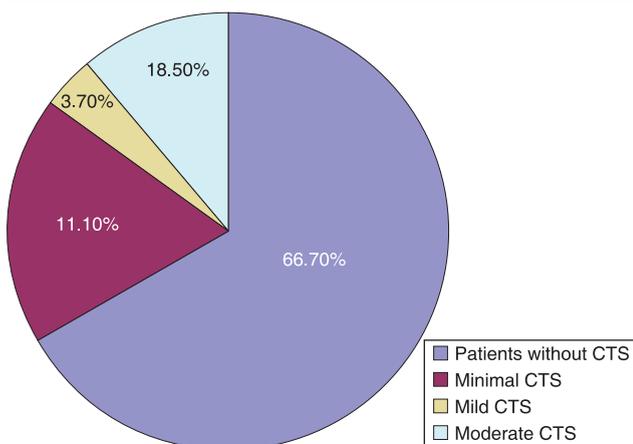
Frequency of carpal tunnel syndrome (CTS) in rheumatoid arthritis patients.

Figure 2



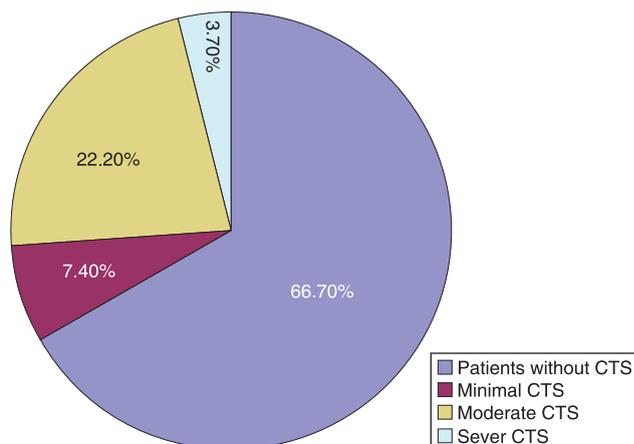
Frequency of types of carpal tunnel syndrome (CTS) in rheumatoid arthritis patients.

Figure 3



Frequency of abnormal nerve conduction of the right side. CTS, carpal tunnel syndrome.

Figure 4



Frequency of abnormal nerve conduction of the left side. CTS, carpal tunnel syndrome.

between the symptom of CTS and the presence of CTS by electrophysiological study and US ($P < 0.02$) (Table 2). There was no statistically significant relationship between the presence of CTS and the grades of the CTS questionnaire (Table 3). There is no significant correlation was present between the presence of CTS and duration of the disease (Table 4).

Relationship of the presence of carpal tunnel syndrome in rheumatoid arthritis patients with outcomes and disease features

No significant correlation was present between the presence of CTS and demographic data of the patients in group IIA in terms of age, age at onset, sex, and duration of the disease. No significant correlation was found between the mean of US finding or electrophysiological study and laboratory results for RF, hemoglobin, white blood cells, platelets, and first hour ESR among the RA patients in group IIA. Also, there was no significant correlation between the mean and clinical manifestations of RA among patients of group IIA.

The mean and SD of DAS28 of all patients was 4.4 ± 1.6 . The mean DAS28 in patients with and without CTS was 5.9 ± 1.1 and 3.4 ± 0.89 , respectively. There was a highly statistically significant difference between these groups of patients in the disease activity index ($P < 0.0001$) (Fig. 7).

Ultrasonographic measurement of carpal tunnel syndrome in rheumatoid arthritis patients

Our results showed a significantly higher level of CSA in group IIA than in group IIB and group I; however, no significant difference was found between the three groups (groups I, IIA, and IIB) in the FR, bowing of FR, and AP of carpal tunnel (CT) (Tables 5 and 6 and Figs. 8 and 9). Eighteen (33.3%) RA patients presented

Table 3 Relation between the abnormal electrodiagnostic tests in rheumatoid arthritis patients and the questionnaire of carpal tunnel syndrome

CTSs	Severe	Moderate	Mild	Minimal	Asymptomatic	χ^2	P
No CTS	2	3	8	13	6	7.44	0.49
Unilateral CTS	1	2	2	2	1		
Bilateral CTS	1	4	1	3	5		
Total	4	9	11	18	12		

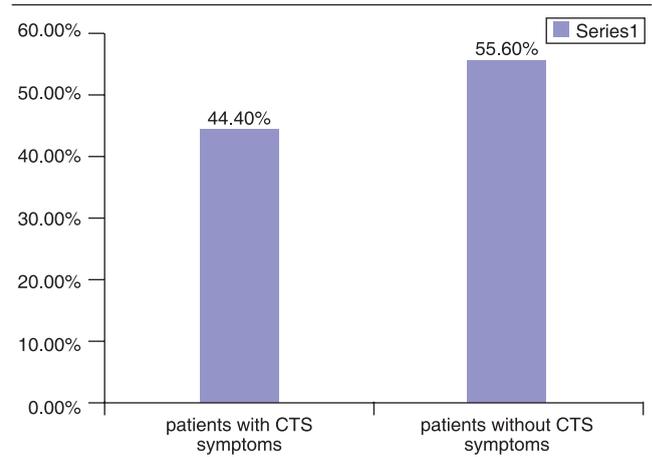
CTS, carpal tunnel syndrome.

Table 4 Relationship between patients with carpal tunnel syndrome and duration of the disease

Duration of disease	Patient with CTS (22)	Patients without CTS (32)	χ^2	P
<2 years	4	7	0.115	0.94
	11	15		
>10 years	7	10		

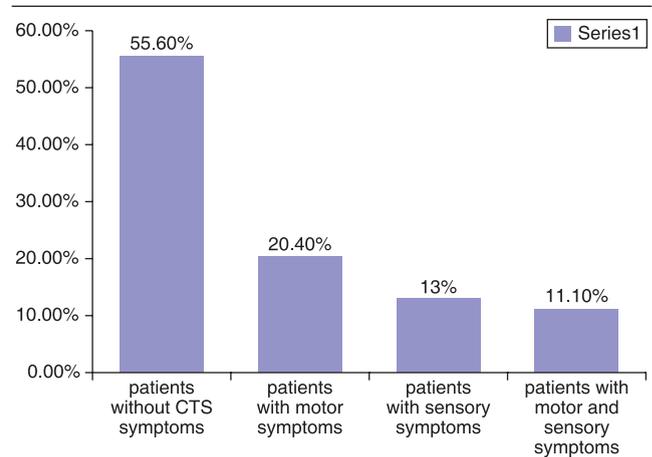
CTS, carpal tunnel syndrome.

Figure 5



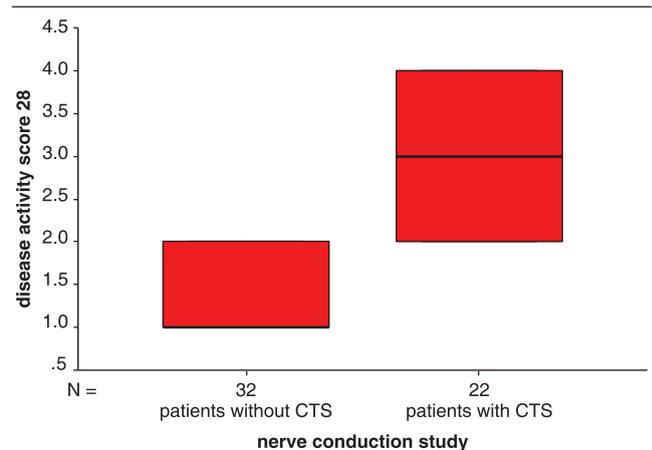
Frequency of symptoms and signs of carpal tunnel syndrome (CTS) in rheumatoid arthritis patients.

Figure 6



Frequency of patients complaining of symptoms and signs of carpal tunnel syndrome (CTS).

Figure 7



Comparison between patients with carpal tunnel syndrome (CTS) and patients without CTS with DAS28 in rheumatoid arthritis patients.

with tenosynovitis. Thirty-five (64.8%) patients had synovitis/localized swelling in the tendons in the area of the carpal tunnel. US yielded confident results for diagnosis, treatment planning, and follow-up of the patients with CTS.

There was a positive correlation between the mean CSA level in relation to DAS28 ($P < 0.0001$), with no significant correlation between its means and disease duration ($P < 0.12$).

Table 5 Comparison of ultrasonographic measurements between patients groups and control group on left hand

US variables	Control (20)	RA with CTS group IIA	RA without CTS group IIB	P
Cross-sectional area	2.53 ± 0.51	11.8 ± 1.5	2.62 ± 0.24	0.0001****
Flattened ratio	1.41 ± 0.048	1.9 ± 0.61	1.41 ± 0.05	0.07
Bowing of FR	0.85 ± 0.46	1.05 ± 0.2	0.86 ± 0.46	NS
AP of CT	11.9 ± 0.91	11.9 ± 1.3	11.9 ± 0.91	NS

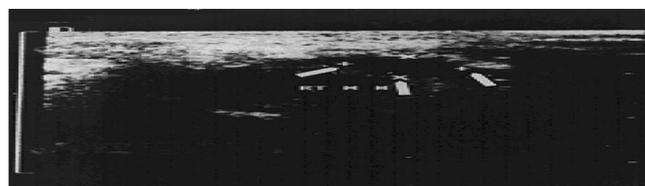
AP, anteroposterior; CTS, carpal tunnel syndrome; FR, flattening ratio; RA, rheumatoid arthritis; US, ultrasonography; ****highly statistically significant.

Table 6 Comparison of ultrasonographic measurements between patients groups and control group on right hand

	Control (20)	RA with CTS group II A	RA without CTS group II B	P
Cross-sectional area	2.6 ± 0.4	11.6 ± 1.3	2.9 ± 0.6	0.0001****
Flattened ratio	1.3 ± 0.06	2 ± 0.4	1.5 ± 0.5	0.09
Bowing of FR	0.74 ± 0.36	1.05 ± 0.2	0.86 ± 0.54	NS
AP of CT	10.9 ± 0.82	11.9 ± 1.3	11.2 ± 0.76	NS

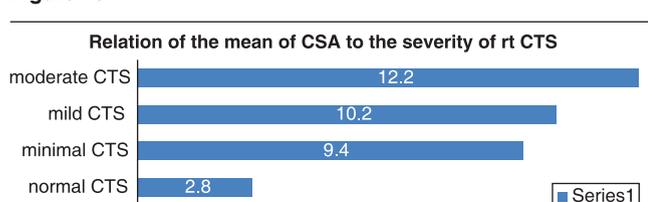
AP, anteroposterior; CTS, carpal tunnel syndrome; FR, flattening ratio; RA, rheumatoid arthritis; ****highly statistically significant.

Figure 8



Transverse scan showing an enlarged (swollen) median nerve.

Figure 10



Mean cross-sectional area in relation to electrophysiological carpal tunnel syndrome (CTS) grades in the right hand.

In our study, the various levels of disease severity were assessed by US. A significant statistical difference was found between the mean CSA, with minimal, mild CTS proved by electrophysiological study ($P < 0.013$), whereas a highly significant statistical difference was found between mild CTS and moderate CTS ($P < 0.001$). Although there was no significant difference between moderate CTS and severe CTS, the mean value of CSA was higher in severe CTS (Figs 10 and 11).

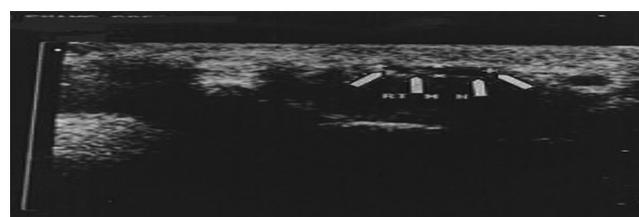
To quantify the diagnostic utility of US measurement of CTS in patients with RA, we constructed a ROC curve. Using a cutoff value of 6.7 mm, CSA had a sensitivity of 0.5 and a specificity of 0.8 for identification of RA patients with CTS. At a cutoff value of 10.9 mm, CSA had a sensitivity of 0.7 and a specificity of 0.9, and at a cutoff value of 13.5 mm, CSA had a sensitivity of 1 and a specificity of 1.0. The corresponding ROC curve is shown in (Figs 12 and 13). The area under the ROC curve was 0.800.

Discussion

In adults, the concurrence of CTS in patients with RA has been investigated in the literature. The frequency of CTS has been reported to range between 3.6 and 6% in RA patients [1,2,19]. Aluclu *et al.* [20] reported that the frequency of CTS was 25%.

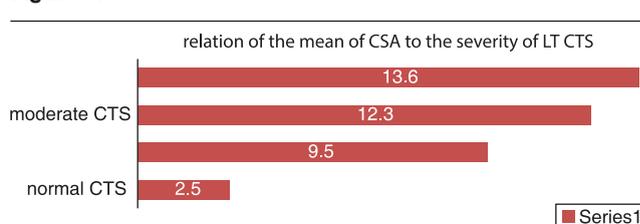
In this study, the prevalence of CTS in patients with RA was 40.7%; this high CTS rate can be attributed

Figure 9



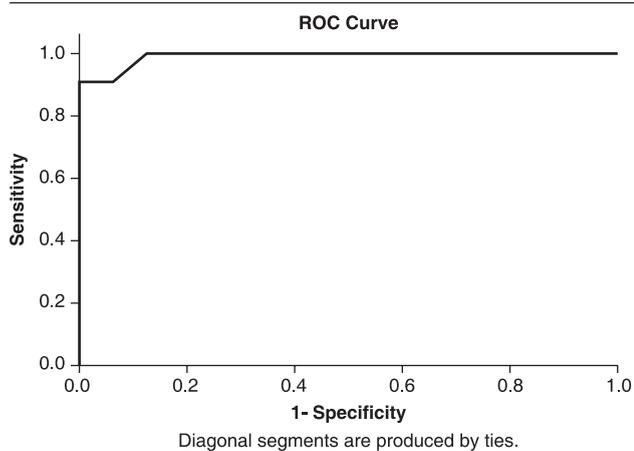
Transverse scan showing flattening of the median nerve.

Figure 11



Mean cross-sectional area in relation to electrophysiological carpal tunnel syndrome (CTS) grades in the left hand.

Figure 12



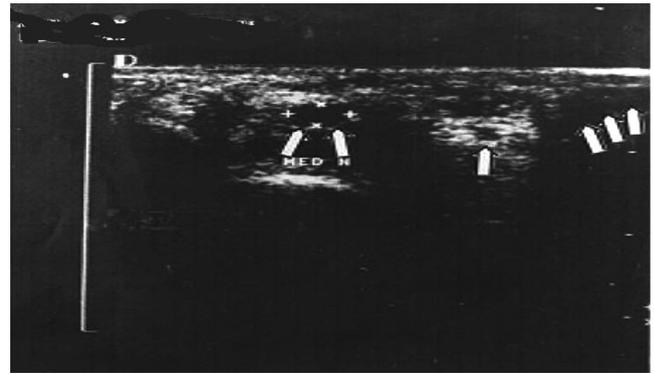
Presentation of the sensitivity and specificity of cross-sectional area. ROC, receiver operating characteristic.

to the fact that 89% of the patients were in the active period, of whom, 74% had severe RA. In our study, the symptom of CTS was present in 24 (44.4%) patients. Patients with CTS usually complain of numbness, paresthesias, and pain in the median nerve distribution. These symptoms are similar to those of RA patients and probably overlapped. Clinical evaluation of RA patients in the search for neuropathy is difficult as neuropathic symptoms may be confused with those for arthritis [21]. Various physical maneuvers designed to stress the median nerve in the carpal tunnel (e.g. Phalen's test, reverse Phalen's test) may exacerbate the symptoms. These tests have especially discriminatory values in the majority of patients with CTS [22]. However, hand-wrist impediments in all RA patients did not allow us to apply these tests correctly in the study. Therefore, the clinical diagnosis of CTS in RA patients is difficult because of such clinical findings.

In agreement with our study, Nadkar *et al.* [23] found that disease parameters of RA such as rheumatoid factor and functional and radiological grade do not correlate with neuropathy and CTS.

Also, our results showed a significantly higher level of CSA in RA patients with an abnormal electrophysiological study of CTS (group IIA) than in those without CTS (group IIB) and those of the control group (group I). The mean CSA ranged from 11.7 ± 1.5 in the left hand to 11.5 ± 1.3 in the right hand. Also, using a cutoff value of 6.7 mm, CSA had a sensitivity of 0.5 and a specificity of 0.8 for identification of RA patients with CTS. At a cutoff value of 10.5 mm, CSA had a sensitivity of 0.7 and a specificity of 0.9, and at a cutoff value of 13.5 mm, CSA had a sensitivity of 1 and a specificity of 1.0.

Figure 13



Transverse scan showing a normal median nerve (hypoechoic and ovoid in shape).

Similar to our study, previous studies showed that the nerve CSA indicating CTS ranged from 9 to 15 mm², and the sensitivity and specificity of CSA ranged from 57 to 97% [12,24–27].

Assessment of cutoff points for moderate and severe cases in comparison with electrodiagnostic measures showed that a CSA measurement greater than 13.5 mm² can be considered positive and corresponds to electrodiagnostic measures in the severe level, whereas a CSA at the level of greater than 12.2 mm² corresponds to a measure in the moderate level. These data are in agreement with the findings reported by Lee *et al.* [28], who found that one can be confident of determining the level of severity of median nerve neuropathy on the basis of US measurement of its CSA.

It has been reported that the FR is highly variable and thus poorly predictive [29,30]. The mean FRs for our patients and those in the control group were 2 ± 0.4 and 1.3 ± 0.06 , respectively. According to the Buchberger criterion of 3, these FRs were low [25]. The results of this study indicate that the inclusion of patients in the early phase of the disease probably led to such findings related to CTS. It has been reported that the role of nerve flattening varies among studies, with sensitivities of 38–65% [25]. In agreement with our study, many authors have shown that increased bowing of the flexor retinaculum was observed less frequently [31–33].

Conclusion

From this study, we can conclude that the frequency of CTS in patients with RA was 40.7%. The accuracy of sonography is comparable with that for electrodiagnostic tests, but sonography may be preferable because it is painless, easily accessible, and has a lower cost and a

shorter examination time, in addition to its diagnostic accuracy; it can define the cause of nerve compression and aids treatment planning.

Recommendation

We consider that the treatment of CTS by medical and/or surgical methods in RA patients will decrease complaints and improve life quality. Therefore, we recommend that an electroneurophysiologic examination or, preferably, US should be performed for all patients with RA as a routine diagnostic procedure.

Acknowledgements

Conflicts of interest

None declared.

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