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The Relationship Between Fatigue, Neuropathic Pain, and Neurophysiological Features in Carpal Tunnel Syndrome

Karpal Tünel Sendromunda Yorgunluk, Nöropatik Ağrı ve Nörofizyolojik Özellikler Arasındaki İlişki

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Abstract

Introduction: Carpal tunnel syndrome (CTS) is the most common entrapment mononeuropathy and can affect patients' daily living activities. In this study, it was aimed to find out whether there is a relationship between fatigue, neuropathic pain and neurophysiological features in CTS.

Material and Method: Patients with clinical features compatible with CTS were included in this retrospective study. Median nerve compound muscle action potential (CMAP) and compound nerve action potential (CNAP) of the patients were analyzed. The Turkish version of the Fatigue Severity Scale (FSS) was administered to all patients. Patients with a mean FSS score of ≥4 were considered to have fatigue. In addition, Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) was applied to some patients. If the LANSS score was 12 or higher, these patients were considered to have neuropathic pain.

Results: Thirty-two female and eight male CTS patients were included in the study. Thirty-two patients had clinically bilateral CTS and eight patients had right-sided CTS. FSS and LANSS were administered to 40 and 18 patients, respectively. There were 29 CTS patients (72.5%) with an FSS score ≥4. CNAP/CMAP amplitudes and sensory/motor nerve conduction velocities of patients with fatigue were lower than those without fatigue ($p<0.05$). Neuropathic pain was present in 9 (100%) and 4 (44%) patients with and without fatigue, respectively ($p=0.029$).

Conclusion: This study indicated that there may be an association between fatigue, neuropathic pain and nerve conduction study findings in CTS.

Keywords: Carpal tunnel syndrome, fatigue, nerve conduction study, neuropathic pain.

Öz

Giriş: Karpal tünel sendromu (KTS) en sık görülen tuzak mononöropatidir ve hastaların günlük yaşam aktivitelerini etkileyebilir. Bu çalışmada KTS'de yorgunluk, nöropatik ağrı ve nörofizyolojik özellikler arasında bir ilişki olup olmadığının ortaya çıkarılması amaçlanmıştır.

Gereç ve Yöntem: Bu retrospektif çalışmaya klinik özellikleri KTS ile uyumlu olan hastalar dahil edildi. Hastaların median sinir bileşik kas aksiyon potansiyeli (BKAP) ve bileşik sinir aksiyon potansiyeli (BSAP) analiz edildi. Tüm hastalara Yorgunluk Şiddet Ölçeği'nin (YŞÖ) Türkçe versiyonu uygulandı. Ortalama YŞÖ skoru ≥4 olan hastalarda yorgunluk olduğu kabul edildi. Ayrıca bazı hastalara Leeds Nöropatik Semptom ve Belirti Değerlendirmesi (LANSS) uygulandı. LANSS skoru 12 ve üzeri ise bu hastalarda nöropatik ağrı olduğu kabul edildi.

Bulgular: Çalışmaya 32 kadın ve sekiz erkek KTS hastası dahil edildi. Otuz iki hastada klinik olarak bilateral KTS ve sekiz hastada sağ taraflı KTS vardı. Sırasıyla 40 ve 18 hastaya YŞÖ ve LANSS uygulandı. YŞÖ skoru ≥4 olan 29 KTS hastası (%72,5) vardı. Yorgunluğu olan hastaların BSAP/BKAP amplitüdleri ve duyu/motor sinir iletim hızları, olmayanlara göre daha düşüktü ($p<0,05$). Nöropatik ağrı, yorgunluk olan ve olmayan sırasıyla 9 (%100) ve 4 (%44) hastada mevcuttu ($p=0,029$).

Sonuç: Bu çalışma, KTS'de yorgunluk, nöropatik ağrı ve sinir iletim çalışması bulguları arasında bir ilişki olabileceğini göstermiştir.

Anahtar Kelimeler: Karpal tünel sendromu, yorgunluk, sinir iletim çalışması, nöropatik ağrı.

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INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common entrapment mononeuropathy and patients often present with sensory abnormalities in the fingers innervated by the sensory branch of the median nerve and/or weakness in the hand muscles innervated by the median nerve.[1-6] The diagnosis of CTS can be made by clinical features, neurophysiological findings, and imaging tests. Imaging tests can reflect a lesion that may cause median nerve neuropathy, or the anatomy of the median nerve, but cannot provide information about the physiology of the median nerve. Neurophysiological tests can reveal the physiological features of the median nerve.[1-4] Neurophysiological tests play a key role both in determining the severity of CTS and in the differential diagnosis, as well as making the diagnosis.[2-4] Nerve conduction studies are an important neurophysiological test required for the diagnosis of CTS. Slowing of median sensory nerve conduction velocity (NCV) and delayed median nerve compound muscle action potential (CMAP) latency are important neurophysiological findings in CTS patients.[2,3]

The complaints of CTS patients can be very mild or very severe. In some patients, muscle weakness or neuropathic pain may be very severe, so patients have difficulty using their hands. [1-6] Neuropathic pain can be so severe to weakness or sensory abnormalities that patients may have difficulty performing activities of daily living.[1-6] There is evidence suggesting that patients may not have symptoms related only to the extremities such as neuropathic pain or weakness or sensory abnormality and also that patients with CTS may have symptoms associated with depression or anxiety.[7,8] In this study, it was aimed to find out whether there is a relationship between neurophysiological features, neuropathic pain, and fatigue in CTS.

MATERIAL AND METHOD

The study was carried out with the permission of University of Health Sciences Adana Training and Research Hospital, Clinical Research Ethics Committee (Date: 23.06.2022, Decision No: 108/2008). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Subjects

Patients with clinical diagnosis of CTS who applied to Adana Training and Research Hospital Clinical Neurophysiology Laboratory between December 2021 and May 2022 were included in this retrospective study. The clinical features, height, weight and body mass index (BMI) values of the patients were recorded. The patient was considered to have CTS clinically if one of the following features was present:[1,3,5,6] 1) Paresthesia in the first/second/third digits 2) Sensory abnormality in the first/second/third digits or weakness in the hand muscles innervated by the median nerve confirmed by neurological examination. Patients with the following characteristics were excluded from the study: 1) Mononeuropathy other than CTS 2) Cervical or lumbosacral radiculopathy 3) Brachial or lumbosacral plexopathy 4) Neurodegenerative disease 5) Polyneuropathy or a disease that may cause polyneuropathy such as diabetes mellitus 6) Anemia 7) Liver or kidney disease 8) Psychiatric illness 9) Fibromyalgia. The clinical classification of CTS was made as follows:[2,3,5,6] 1) Nocturnal paresthesia in first/second/third digits (Very mild) 2) Diurnal paresthesia in first/second/third digits (Mild) 3) Hypoesthesia in first/second/third digits confirmed by neurological examination (Moderate) 4) Hand muscles innervated by median nerve weakness or atrophy confirmed by neurological examination 5) Plegia in hand muscles innervated by the median nerve. The Turkish version of the Fatigue Severity Scale (FSS) was administered to all patients.[9] Patients with a mean FSS score of ≥4 were considered to have fatigue. In addition, Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) was applied to some patients. If the LANSS score was 12 or higher, these patients were considered to have neuropathic pain.[10,11]

Neurophysiological Tests

Neurophysiological tests were performed using the Cadwell Sierra Summit electromyography (EMG) unit (Cadwell Laboratories, Kennewick, Washington, USA). Nerve conduction study was performed if the temperature of the extremities was >32°C, otherwise cold extremities were warmed. Previously suggested methods and reference values were used for nerve conduction study.[12,13] Superficial electrodes were used for stimulation and recording. Stimulation was done supramaximally. For motor and sensory nerve conduction studies, low-high band filters were set as 20Hz-10kHz and 20Hz-2kHz, respectively. Sensory NCV was calculated using peak latency. Both CMAP and compound nerve action potential (CNAP) amplitudes measured from peak to peak. Sensory nerve conduction study was performed antidromically. For motor nerve conduction studies, the distance between the stimulation point of the median/ulnar nerve at the wrist and the recording electrode was 5 cm. Lower reference limits for CNAP amplitude and NCV across the 2nd finger-wrist segment were 15 µV and 40.9 m/s, respectively.[12,13] The lower reference limit for median nerve CMAP amplitude and the upper reference limit for median nerve CMAP distal latency were 4.3 mV and 3.7 ms, respectively.[13] The neurophysiological classification of CTS was as follows:[2,3,5,6] Mild CTS- slowing of median sensory NCV across the 2nd finger-wrist segment, Moderate CTS- slowing of the median sensory NCV across the 2nd finger wrist segment, and delayed median nerve CMAP distal latency, Severe CTS- Absence of median nerve CNAP and delayed median nerve CMAP distal latency, Very severe CTS- Absence of median nerve CNAP and CMAP.

Statistical Analysis

Categorical variables were expressed as numbers and percentages, and numerical variables as mean standard deviation, median, min-max. Pearson's chi-square test or Fisher's exact test was used to compare categorical variables between the two groups, and Mann-Whitney U test was used

to compare numerical variables. Correlation analysis was performed with the Spearman test. If $p < 0.05$, it was considered significant. SPSS 22.0 program was used for statistical analysis.

RESULTS

Forty patients (32 female, eight male) were included in the study. The mean age of the patients was 50.1±12.6 (min-max 29-78) years. The mean height, weight and BMI of the patients were 164.6±7.0 cm, 80.1±13.3 kg and 29.6±4.6 kg/m2, respectively. The mean duration of the patients' complaints was 11.6±6.5 (min-max 1-120) months. Thirty-two of the patients had clinically bilateral CTS and eight had right-sided CTS. Seventy-two extremities with CTS were included in the analyses. **Table 1** shows the characteristics of patients' nerve conduction study, clinical and neurophysiological CTS classification, LANSS and FSS scores.

The number of patients with an FSS mean score ≥4 and <4 were 29 (72.5%) and 11 (27.5%), respectively. Four (13.8%) of patients with FSS score ≥4 and four (36.4%) patients with FSS score <4 were male (p=0.182). The number of patients according to clinical and neurophysiological classifications among patients with FSS mean score ≥4 and FSS mean score <4 are shown in **Table 2**. Comparison of clinical features and nerve conduction study findings between patients with FSS mean score ≥4 and FSS mean score <4 is given in **Table 3**. **Figure 1** shows comparison of right median sense NCV between patients with FSS mean score ≥4 and FSS mean score <4. The comparison of number of patients with neuropathic pain between patients with an FSS mean score ≥4 and patients with an FSS mean score <4 is shown in **Figure 2**. **Table 4** shows the correlation of FSS mean score and clinical features/nerve conduction study findings. **Figure 3** shows the negative correlation found between the FSS mean score and the left median sense NCV.

Table 1. The characteristics of patients' nerve conduction study, clinical and neurophysiological CTS classification, LANSS and FSS scores

Clinical/Neurophysiological features	Mean±SD (median)
Right/Left median sensory NCV (m/s)	34.6±6.1 (35) (n=37*)/33.8±4.5 (33) (n=29*)
Right/Left median CNAP amplitude (μV)	24.9±14.4 (22.1)/27.7±17.0 (26.2)
Right/Left median nerve distal CMAP latency (ms)	4.1±1.9 (3.7)/4.1±1.2 (3.9)
Right/Left median nerve distal CMAP amplitude (mV)	12.9±4.4 (12.9)/13.3±4.1 (13.9)
Clinical classification of Right/Left-sided CTS patients	2.8±0.9 (3)/2.9±1.0 (3)
Neurophysiological classification of Right/Left-sided CTS patients	1.2±0.8 (1)/1.5±0.8 (1.5)
FSS scores of the CTS patients	41.3±14.2 (42.5)
FSS mean scores of the CTS patients	4.6±1.6 (4.7)
LANSS score	15.2±5.6 (18.0)

*: CNAP could not be obtained in 3 patients. CTS: Carpal tunnel syndrome. LANSS: Leeds Assessment of Neuropathic Symptoms and Signs. FSS: Fatigue Severity Scala. NCV: nerve conduction velocity. CNAP: compound nerve action potential. CMAP: compound muscle action potential. BMI: body mass index.

Table 2. The number of patients according to clinical and neurophysiological classifications among patients with and without fatigue

Clinical/ Neurophysiological classification	The number of right-sided CTS patients with a FSS mean score ≥ 4 (%)	The number of right-sided patients with a FSS mean score < 4 (%)	The number of left-sided CTS patients with a FSS mean score ≥ 4 (%)	The number of left-sided patients with a FSS mean score < 4 (%)
Clinical classification				
Very mild	1	2	0	3
Mild	9	5	4	2
Moderate	8	4	11	1
Severe	11	0	11	0
Neurophysiological classification				
Normal	1	6	0	4
Mild	16	4	10	2
Moderate	9	1	13	0
Severe	3	0	3	0

CTS: Carpal tunnel syndrome. FSS: Fatigue Severity Scala.

Table 3. Comparison of clinical features and nerve conduction study findings between patients with and without fatigue

Clinical and neurophysiological features	The number of patients FSS mean score ≥ 4 Mean±SD (median) (number)	The number of patients FSS mean score < 4 Mean±SD (median) (number)	P value
Age (years)	52.8±12.5 (55.0) (n=29)	42.8±9.9 (46.0) (n=11)	0.025
BMI (kg/m2)	29.3±4.1 (29.9) (n=29)	30.4±6.1 (29.5) (n=11)	0.988
Duration of the complaints (months)	13.8±21.7 (7.0) (n=29)	5.8±3.7 (5.0) (n=11)	0.048
LANSS score	18.6±2.7 (18) (n=9)	11.9±5.9 (11) (n=9)	0.011
Right/Left median sensory NCV (m/s)	32.5±5.1 (34.0) (n=26)/32.1±3.0 (32.0) (n=23)	39.5±5.7 (41.0) (n=11)/40.5±2.7 (42.0) (n=6)	0.003/<0.001
Right/Left median CNAP amplitude (μV)	20.5±12.2 (21.0) (n=29)/24.4±16.4 (23.8) (n=26)	36.5±13.5 (35.5) (n=11)/41.8±12.4 (38.5) (n=6)	0.004/0.014
Right/Left median nerve distal CMAP latency (ms)	4.4±2.1 (3.8) (n=29)/4.3±1.3 (4.2) (n=26)	3.2±0.6 (3.3) (n=11)/3.2±4.1 (3.4) (n=6)	0.009/0.002
Right/Left median nerve distal CMAP amplitude (mV)	12.4±4.9 (13.9) (n=29) /12.6±4.2 (12.8) (n=26)	14.2±2.2 (14.6) (n=11)/16.7±0.6 (16.9) (n=6)	0.237/0.008
Clinical classification of Right/Left-sided CTS patients	3.0±0.9 (3,0) (n=29)/3.3±0.7 (3.0) (n=26)	2.2±0.8 (2.0) (n=11)/1.7±0.8 (1.5) (n=6)	0.017/0.001
Neurophysiological classification of Right/ Left-sided CTS patients	1.5±0.7 (1.0) (n=29)/1.8±0.7 (2.0) (n=26)	0.6±0.7 (0) (n=11)/0.3±0.5 (0) (n=6)	0.001/<0.001

FSS: Fatigue Severity Scala. BMI: body mass index. LANSS: Leeds Assessment of Neuropathic Symptoms and Signs. NCV: nerve conduction velocity. CNAP: compound nerve action potential. CMAP: compound muscle action potential. CTS: Carpal tunnel syndrome.

Table 4. The correlation between FSS mean scores and clinical features/nerve conduction study findings

Clinical/Neurophysiological features	FSS mean score	
	p	R (n)
Age (years)	0.580	0.090 (n=40)
BMI (kg/m2)	0.381	-0.142 (n=40)
Duration of the complaints (months)	0.278	0.176 (n=40)
LANSS score	0.060	0.451 (n=18)
Right/Left median sensory NCV (m/s)	0.014/0.004	-0.402 (n=37)/-0.521 (n=29)
Right/Left median CNAP amplitude (mV)	0.215/0.826	-0.201 (n=40)/-0.040
Right/Left median nerve distal CMAP latency (ms)	0.214/0.265	0.201 (n=40)/0.203 (n=32)
Right/Left median nerve distal CMAP amplitude (mV)	0.797/0.233	0.042 (n=40)/-0.217 (n=32)
Clinical classification of Right/Left-sided CTS patients	0.262/0.765	0.182 (n=40)/0.049 (n=32)
Neurophysiological classification of Right/Left-sided CTS patients	0.268/0.167	0.180 (n=40) /0.251 (n=32)

FSS: Fatigue Severity Scala. BMI: body mass index. LANSS: Leeds Assessment of Neuropathic Symptoms and Signs. NCV: nerve conduction velocity. CNAP: compound nerve action potential. CMAP: compound muscle action potential. CTS: Carpal tunnel syndrome.

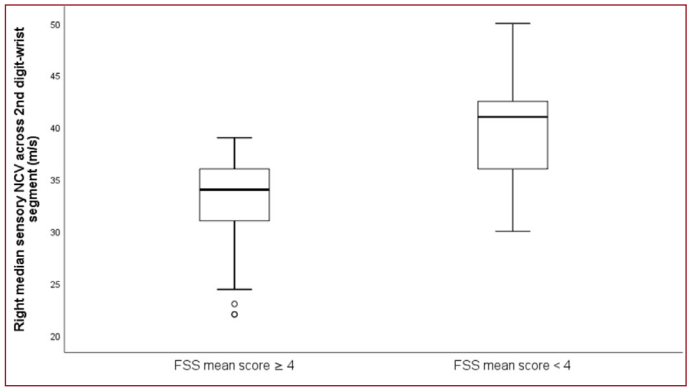

Figure 1. Comparison of right median sensory NCV between CTS patients with and without fatigue

CTS: carpal tunnel syndrome; FSS: fatigue severity scale; NCV: nerve conduction velocity.

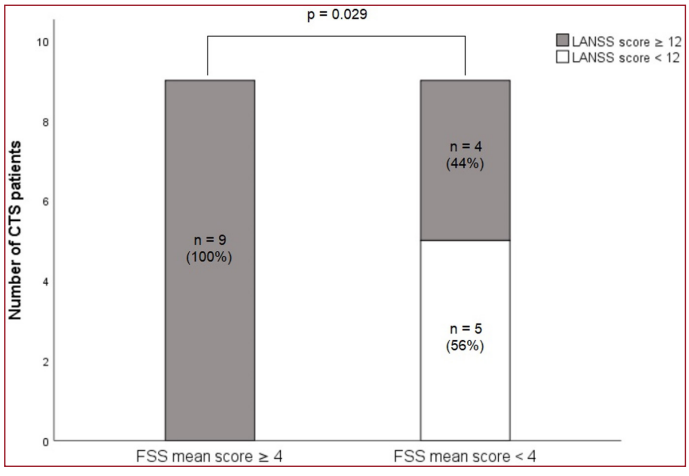

Figure 2. Comparison of CTS patients with neuropathic pain between CTS patients with and without fatigue

CTS: carpal tunnel syndrome; FSS: fatigue severity scale; NCV: nerve conduction velocity.

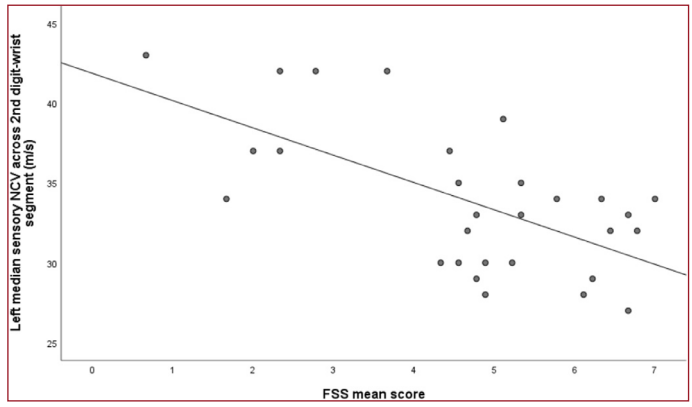

Figure 3. Correlation between FSS score and left median sense NCV in CTS patients

CTS: carpal tunnel syndrome; FSS: fatigue severity scale; NCV: nerve conduction velocity.

DISCUSSION

In this study, the relationship between fatigue, neuropathic pain and neurophysiological findings in CTS patients was investigated, and findings were obtained regarding fatigue as an important finding in CTS patients. It has been reported that CTS patients did not have complaints concerning only the upper extremities, and psychiatric disorders such as depression may be associated with CTS.[7,8] Fatigue was found in approximately 70% of CTS patients in this current study. Complaints such as neuropathic pain or weakness in the upper extremity may affect patients' activities of daily living, and as a result, psychiatric findings may be related to this. All these factors may have triggered fatigue in CTS patients. The fact that neuropathic pain was more common in CTS patients with fatigue was found in the present study, supporting that fatigue may be associated with neuropathic pain and similar complaints.

Most of the neurophysiological findings in CTS patients with fatigue were found to be worse than in CTS patients without fatigue. In addition, a negative correlation between median nerve sensory NCV/median nerve distal CMAP amplitude and FSS scores found in this study may indicate that fatigue worsens as neurophysiological findings worsen. Moreover, in the non-fatigue CTS group, there were no patients with severe CTS according to both neurophysiological and clinical classification. The reduced CMAP/CNAP amplitude indicates axonal degeneration.[14] Severe axonal degeneration is known to have a poor prognosis.[15,16] All these findings may lead to a poor clinical course. Therefore, all these findings also show that fatigue seen in CTS may be related to both neurophysiological and clinical findings.

Many factors such as age, BMI or gender have been reported to be associated with CTS.[1-3] In this current study, the fact that the age of CTS patients with fatigue was higher than that of CTS patients without fatigue may indicate that age is important for fatigue. However, no correlation was found between fatigue score and age in this study. For this reason,

it would be beneficial to conduct further studies on CTS and fatigue with more CTS patients. As the duration of symptoms increases in CTS patients, clinical and neurophysiological findings may worsen if appropriate treatment is not given.[17,18] Similarly, the relationship between FSS scores and duration of complaints found in this study suggests that appropriate treatment should be given as soon as possible in CTS patients.

There were several limitations of this study. First, the retrospective nature of this study was one of the limitations. Therefore, LANSS was not applied to every patient included in the study. In addition, we could not include healthy individuals in the study because it was a retrospective study, and therefore FSS values of healthy individuals are not available. This may be a limitation, but it should be noted that we determined fatigue in patients according to the Turkish validity study, which also included the cut-off value of FSS.[9] Secondly, nerve conduction studies cannot reflect the neurophysiology of small nerve fibers, which can be considered a limitation. Third, as we mentioned earlier, CTS patients with fatigue were older. This may have affected our results. However, it should be noted that there is no correlation between age and FSS scores. Finally, the number of patients was insufficient. However, it should be noted that CTS patients with fibromyalgia or polyneuropathy or other diseases such as multiple sclerosis that may cause fatigue were not included in the study.

CONCLUSION

This study showed that there may be a relationship between fatigue and clinical features/neurophysiological findings/neuropathic pain in CTS. Fatigue may be seen more frequently in patients with neuropathic pain. It was also concluded that fatigue may worsen as clinical and neurophysiological findings worsen.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of University of Health Sciences Adana Training and Research Hospital, Clinical Research Ethics Committee (Date: 23.06.2022, Decision No: 108/2008).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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