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Neuropathic Pain in Carpal Tunnel Syndrome: Association with Electrophysiological Findings and Functional Status

Karpal Tünel Sendromunda Nöropatik Ağrı: Elektrofizyolojik Bulgular ve Fonksiyonel Durumla İlişkisi

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This study was presented as a poster at the 26th National Congress of Physical Medicine and Rehabilitation, April 25-29 2017, Antalya, Türkiye.

BSTRACT Objective: Aims of the present study are to determine the presence of neuropathic pain according to The Leeds Assessment of Neuropathic Symptoms and Sign (LANSS) in patients with electrophysiologically confirmed carpal tunnel syndrome (CTS) and investigate the association of neuropathic pain with clinical and electrophysiological findings and hand functionality. **Material and Methods:** One hundred and seventy five patients (234 hands) whose electrophysiological test results were compatible with CTS were included. Standard electrophysiological tests, LANSS and Quick Disability of the Arm, Shoulder, and Hand (Q-DASH) were applied to each patient. Patients with LANSS score 12 formed Group 1 and <12 formed Group 2. **Results:** Of patients, 58.11% (136 hands) had a LANSS score ≥12 (Group 1) and 41.89% (98 hands) had a LANSS score <12 (Group 2). Female sex, symptom duration, sensory loss detected in the hand innervated by the median nerve, abductor pollicis muscle strength, thenar atrophy, phalen sign positivity and Q-DASH scores were higher in Group 1 ($p<0.05$). Electrophysiological severity was found to be higher in Group 1 ($p<0.005$). Median nerve motor distal latency and median nerve 2nd digit-wrist sensory distal latency were longer ($p<0.05$) in Group 1. Median nerve 2nd digit-wrist sensory amplitude and median nerve 2nd digit-wrist sensory velocity were found to be significantly lower in Group 1 ($p<0.05$). **Conclusion:** It has been shown that median nerve motor distal latency and sensory nerve conduction studies can be used to determine the presence of neuropathic pain in patients with CTS. Knowing the presence and mechanism of neuropathic pain in patients with CTS will guide the clinician in determining the appropriate treatment strategy.

Keywords: Carpal tunnel syndrome; electroneuromyography; neuropathic pain

ÖZET Amaç: Bu çalışmanın amacı, elektrofizyolojik olarak doğrulanmış karpal tünel sendromu (KTS) olan hastalarda Leeds Nöropatik Semptom ve Bulgu Değerlendirmesine [The Leeds Assessment of Neuropathic Semptom and Sign (LANSS)] göre nöropatik ağrının varlığının belirlenmesi ve nöropatik ağrının klinik ve elektrofizyolojik bulgular ve el işlevselliği ile ilişkisinin araştırılmasıdır. **Gereç ve Yöntemler:** Elektrofizyolojik test sonuçları KTS ile uyumlu olan 175 hasta (234 el) çalışmaya dâhil edildi. Her hastaya standart elektrofizyolojik testler, LANSS ve Kol, Omuz ve El Özürlülük Skalası [Quick Disability of the Arm, Shoulder, and Hand (Q-DASH)] uygulandı. LANSS skoru 12 olan hastalar Grup 1'i ve <12 olan hastalar Grup 2'yi oluşturdu. **Bulgular:** Hastaların %58,11'inin (136 el) LANSS skoru ≥12 (Grup 1) ve %41,89'unun (98 el) LANSS skoru <12 (Grup 2) idi. Kadın cinsiyet, semptom süresi, medyan sinir tarafından innerve edilen elde saptanan duyu kaybı, abdüktör pollisis kas kuvveti, tenar atrofi, phalen işaret pozitifliği ve Q-DASH skorları Grup 1'de daha yüksekti ($p<0,05$). Elektrofizyolojik şiddet Grup 1'de daha yüksek bulundu ($p<0,005$). Medyan sinir motor distal latansı ve medyan sinir 2. parmak-el bileği duyusal distal latansı Grup 1'de daha uzundu ($p<0,05$). Medyan sinir 2. parmak-el bileği duyusal amplitüdü ve medyan sinir 2. parmak-el bileği duyusal hızı Grup 1'de anlamlı olarak daha düşük bulundu ($p<0,05$). **Sonuç:** KTS'li hastalarda nöropatik ağrı varlığını belirlemek için medyan sinir motor distal latansı ve duyusal sinir iletim çalışmalarının kullanılabileceği gösterildi. KTS'li hastalarda nöropatik ağrının varlığının ve mekanizmasının bilinmesi uygun tedavi stratejisinin belirlenmesinde klinisyene yol gösterecektir.

Anahtar Kelimeler: Karpal tünel sendromu; elektronöromiyografi; nöropatik ağrı

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Carpal tunnel syndrome (CTS) is an entrapment neuropathy caused by compression of the median nerve at the wrist and is the most common of all entrapment neuropathies with a prevalence of 4.9% in the general population.[1] It has been suggested that pathological processes such as flexor tenosynovitis, vascular sclerosis, fibrous hypertrophy and synovial edema may cause the development of idiopathic CTS.[2,3] Neuropathic pain is defined as the pain that occurs as a result of a disease or lesion affecting the somatosensory system.[4] In addition to nociceptive mechanisms associated with underlying connective tissue disorders, neuropathic mechanisms due to median nerve involvement are thought to play a role in pain associated with CTS.

The aims of our study are to evaluate the presence of neuropathic pain according to the Leeds Assessment of Neuropathic Symptoms and Sign (LANSS) in patients with electrophysiologically confirmed CTS and to investigate the relation of neuropathic pain on clinical, electrophysiological parameters and hand functionality.

MATERIAL AND METHODS

A total of 175 patients (234 hands) applied to the electroneuromyography laboratory with a pre-diagnosis of CTS, whose electrophysiological test results were compatible with CTS were included in the study.

Electrodiagnostic studies were performed with Neuropack 2-MEB 7102-K (Nihon Kohden Corporation, Japan) device. Standard electrophysiological tests were applied to all of the patients for both hands by the same researcher, according to the electrodiagnosis guidelines of the American Academy of Electrodiagnostic Medicine (AAEM).[5] Ulnar motor and sensory nerve conduction studies were performed to exclude the diagnosis of polyneuropathy. During the studies, the room temperature was between 22-24˚C and the skin temperature was above 32˚C. All stimulations and recordings were made using bipolar superficial electrodes.

A superficial bar electrode was used in motor nerve conduction studies. The active electrode was placed at the belly of abductor pollicis brevis muscle. Median nerve distal stimulation was applied at the wrist, 5 cm proximal to the active electrode, and proximal stimulation at the elbow. Supramaximal stimulation was applied to obtain the compound muscle action potential (CMAP). Median nerve motor distal latency (MNMDL) was calculated as the time from the onset of stimulation to the beginning of the first deflection of CMAP, and median nerve motor amplitude (MNMA) as the distance between the peaks. Median nerve motor velocity (MNMV) was also calculated.

Sensory action potential (SAP) values were obtained by stimulating the median and ulnar nerves orthodromically. Median nerve sensory conduction study was performed by stimulating from thumb (D1), index (D2), middle digit (D3), lateral side of the ring finger (D4) and palm and those of the ulnar nerve were performed by stimulating from medial side of the ring (D4) and little digit (D5). All responses were recorded from the wrist. SAPs were obtained by a stimulation applied from an 8 cm distance in the palm-wrist and a 13 cm in D2-wrist. Median nerve 2nd digit-wrist sensory distal latency (MNSDL), median nerve 2nd digit-wrist sensorial amplitude (MNSA) and median nerve 2nd digit-wrist sensorial velocity (MNSV) values were calculated.

All hands with CTS were grouped as mild, moderate and severe CTS based on electrophysiological severity. Mild disease was accepted as a reduction in MNSV and/or SAP amplitude, moderate as additionally prolonged MNMDL and severe as the absence of SAP and/or reduction in thenar M-response amplitude and/or delay in sensorial and motor distal latencies and/or partial denervation findings in electromyography (EMG) examination of thenar muscles.[5]

After the clinical and electrophysiological diagnosis of CTS, all hands were evaluated by the Turkish version of the LANSS.[6] LANSS consists of two parts. The first part is a patient-administered questionnaire which assesses the patient's experiences related to neuropathic pain (dysesthesia, autonomic dysfunction, induced pain, paroxysmal pain, thermal pain) by five questions (maximum 16 points). In the second part, the presence of allodynia is tested by touching the painful and painless area with a cotton

ball (maximum 5 points). In addition, pinprick perception is evaluated in the same areas using a 23 gauge needle (maximum 3 points). Total score changes between 0 and 24. Scores ≥12 indicate neuropathic pain.

The functional evaluation of the patients was made using the Turkish version of Quick Disability of the Arm, Shoulder, and Hand (Q-DASH).[7] There are 11 questions in this scale and it questions the level of the patient's ability to do daily activities, the limitation of daily activities, symptoms, and sleep patterns. Each question is scored on a 5-point scale and the final score is calculated, ranging from 0 (no disability) to 100 (severe disability).

Ankara Numune Training and Research Hospital Ethics Committee approved the study (date: August 16, 2015/number: 1016). The study conforms to the provisions of the World Medical Association's Declaration of Helsinki. Written informed consent was obtained from all of the participants.

STATISTICAL ANALYSIS

SPSS for Windows 20 (IBM, Chicago, USA) package program was used for statistical analysis. The Shapiro-Wilk test was used to examine if the numerical data were normally distributed. Continuous variables were given as mean, standard deviation, median, and minimum-maximum values, and categorical variables as number and percentage values. When examining the difference of continuous variables between two groups, the independent samples t-test was used for normally distributed data, and the Mann-Whitney U test for non-normally distributed data. The Pearson chi-square test and the Fisher's exact chi-square test were used for intergroup comparisons of categorical variables. The correlation of the LANSS score with demographic characteristics, symptom duration, Q-DASH and electrophysiological parameters was assessed by the Spearman's correlation analysis since data were not normally distributed. Results were evaluated at 95% confidence interval and significance level of $p<0.05$.

RESULTS

The mean age of the patients was 50.89±10.95 (22-79). Female sex was predominant (89.7%). The mean body mass index (BMI) was 30.8±5.6 (18.10-48.65) kg/m². The demographic characteristics, professions and hobbies of the patients are given in Table 1.

TABLE 1: Demographic characteristics, professions and hobbies of the patients.

Age (years-$\bar{X}$±SD)	50.9±10.6
Sex, n (%)	
Female	157 (89.7)
Male	18 (10.3)
Body mass index (kg/m²-$\bar{X}$±SD)	30.8±5.6
Occupation, n (%)	
Housewife	118 (67.4)
Worker	17 (9.7)
Cleaning staff	16 (9.1)
Officer	15 (8.6)
Kitchen staff	6 (3.4)
Driver	2 (1.2)
Student	1 (0.6)
Hobbies, n (%)	
Handicraft	64 (36.6)
Garden work	18 (10.2)
Use of vibrating tools	9 (5.1)
More than one (handicraft+garden work)	16 (9.1)
None	16 (9.1)

SD: Standard deviation.

The mean duration of the symptoms was found to be 31.5±44.7 months. In 167 (95.4%) of 175 patients, the dominant hand was the right hand. The symptomatic hand was right in 75 (42.9%) patients, left in 41 (23.4%) patients, and bilateral in 59 (33.7%) patients. The severity of CTS was evaluated separately in 234 hands in total, and it was found as mild in 55 (23.5%) hands, moderate in 151 (64.5%) hands, and severe in 28 (12%) hands.

Neuropathic pain according to the LANSS was detected in 103 patients (42 right hand, 28 left hand, 33 bilateral involvement). Patients were grouped as 136 (58.11%) hands with LANSS score ≥12 (Group 1) and 98 (41.89%) hands with LANSS score <12 (Group 2). Female/male ratio was significantly higher in Group 1 ($p<0.05$). There was no significant difference between the groups in terms of age and BMI ($p>0.05$) (Table 2).

The duration of symptoms was higher in Group 1 ($p<0.05$). In the physical examination, sensory

TABLE 2: Comparison of demographic characteristics among groups.

	Group 1 (LANSS≥12) (n=103)	Group 2 (LANSS<12) (n=72)
Sex (F/M)	98/5	59/13
Age (years)	49.9±10.7	52.3±11.1
BMI (kg/m^2)	30.9±5.9	30.7±5.1

LANSS: Leeds Assessment of Neuropathic Symptoms and Sign; F: Female; M: Male; BMI: Body mass index.

deficit was significantly higher in the areas innervated by the median nerve, abductor pollicis muscle strength decreased, thenar atrophy and phalen sign were positive in Group 1 ($p<0.05$). MNMDL and MNSDL were longer ($p<0.05$) in Group 1. In addition, the MNSA and MNSV were found to be significantly lower in Group 1 ($p<0.05$). There was no significant difference between the groups in terms of MNMA and MNMV ($p>0.05$). Q-DASH score was found to be significantly higher in Group 1 ($p<0.05$) (Table 3). In addition, all items of the LANSS were found to be significantly more frequently in Group 1 than in Group 2 (Table 4).

The electrophysiological severity was found to be statistically significantly higher in Group 1 ($p<0.001$) (Table 5).

DISCUSSION

In the pathogenesis of CTS, it is thought that there is a dysfunction in the median nerve as a result of increased intra-canal pressure and mechanical compression. However, recent studies based on scoring indicate that the subjective symptoms do not comply with the pathology in the nerve fibers.[8,9] Processes such as flexor tenosynovitis, vascular sclerosis, fibrous hypertrophy and synovial edema have also been reported to play a role in the pathogenesis of idiopathic CTS.[4,5] Therefore, neuropathic mechanisms due to median nerve involvement may cause pain in CTS, as well as nociceptive mechanisms associated with underlying connective tissue disorders. Differentiation of neuropathic and nociceptive pain in patients with CTS is important in determining the correct treatment strategy. In addition, in the presence of neuropathic pain, early surgery may be considered in order to prevent central sensitization that may develop over time.[10]

In 58.1% of the hands with CTS, whom we included in the study and diagnosed electrophysiologically, the LANSS score was ≥12, indicating that the pain was of neuropathic origin. No significant difference was observed between the two groups which

TABLE 3: Comparison of symptom duration, clinical and electrophysiological findings of hands with CTS in Group 1 (LANSS≥12) and Group 2 (LANSS<12).

	Group 1 (n=136)	Group 2 (n=98)	p value
Symptom duration ($\bar{X}$±SD)	42.1±52.2	19.8±28.8	<0.001*
Tinel sign, n (%)	114 (83.8)	72 (73.5)	0.06
Phalen sign, n (%)	114 (83.8)	54 (55.1)	<0.001*
Sensorial deficit, n (%)	83 (61)	20 (20.4)	<0.001*
Motor deficit, n (%)	56 (41.2)	23 (23.5)	0.005*
Thenar atrophy, n (%)	53 (39)	20 (20.4)	0.002*
MNMDL (ms) ($\bar{X}$±SD)	4.9±1.6	4.1±0.8	<0.001*
MNMA (mV) ($\bar{X}$±SD)	10.2±7.6	10.5±3.2	0.8
MNMV (m/sn) ($\bar{X}$±SD)	52.7±10.1	54.7±3.8	0.07
MNSDL (ms) ($\bar{X}$±SD)	3.7±1.1	3.4±0.5	0.03*
MNSA (μV) ($\bar{X}$±SD)	8.9±7.4	12.6±7.3	<0.001*
MNSV (m/sn) ($\bar{X}$±SD)	26.8±13.4	34.7±7.7	<0.001*
Q-DASH ($\bar{X}$±SD)	49.2±18.1	24.4±15.9	<0.001*

*p<0.05 (significant); CTS: Carpal tunnel syndrome; LANSS: Leeds Assessment of Neuropathic Symptoms and Signs; SD: Standard deviation; MNMDL: Median nerve motor distal latency; MNMA: Median nerve motor amplitude; MNMV: Median nerve motor velocity; MNSDL: Median nerve 2nd digit-wrist sensory distal latency; MNSA: Median nerve 2nd digit-wrist sensorial amplitude; MNSV: Median nerve 2nd digit-wrist sensorial velocity; Q-DASH: The Quick Disability of the Arm, Shoulder, and Hand.

TABLE 4: Presence of LANSS items in hands with CTS in Group 1 (LANSS≥12) and Group 2 (LANSS<12).

	Group 1 (n=136)	Group 2 (n=98)	p value
Dysesthesia (Item 1)	136 (100%)	87 (88.8%)	<0.001*
Autonomic dysfunction (Item 2)	65 (47.8%)	5 (5.1%)	<0.001*
Evoked pain (Item 3)	103 (75.7%)	26 (26.5%)	<0.001*
Paroxysmal pain (Item 4)	117 (86.0%)	55 (56.1%)	<0.001*
Thermal pain (Item 5)	77 (56.6%)	29 (29.6%)	<0.001*
Allodynia (Item 6)	90 (66.2%)	7 (7.1%)	<0.001*
PPT change (Item 7)	103 (75.7%)	15 (15.3%)	<0.001*

*p<0.05 (significant); LANSS: Leeds Assessment of Neuropathic Symptoms and Signs; CTS: Carpal tunnel syndrome; PPT: Pin prick threshold.

TABLE 5: Comparison of electrophysiological severity among hands with CTS in Group 1 (LANSS≥12) and Group 2 (LANSS<12).

	Mild disease	Moderate disease	Severe disease	p value
Group 1 (n=136)	22 (16.2%)	89 (65.4%)	25 (18.4%)	<0.001*
Group 2 (n=98)	33 (33.7%)	62 (63.3%)	3 (3.1%)	

*p<0.05 (significant); CTS: Carpal tunnel syndrome; LANSS: Leeds Assessment of Neuropathic Symptoms and Signs.

have LANSS score ≥12 and <12 in terms of age and BMI. In the study conducted by Gürsoy et al. including 124 hands of 72 patients with CTS, the LANSS score was found to be ≥12 in 47.6% of hands with CTS.[11] In the study of Truini et al. where they investigated the neuropathic pain mechanism in CTS, 65% of the symptomatic hands were found as neuropathic according to the Douleur Neuropathique en 4 (DN4) questionnaire in 70 patients with 117 CTS hands.[12]

In our study, neuropathic pain was more common in female sex. Similarly, in a study conducted by Torrance et al. where 6,000 adults were assessed by using LANSS for the prevalence of neuropathic pain in England, neuropathic pain was found to be more common in women.[13] It is thought that "biological" and "psychosocial" mechanisms, contributed by gonadal hormones, endogenous pain modulating systems, sex and cognitive/emotional factors, play a role in the pain response.[14]

Recent studies have shown the contribution of peripheral and central sensitization mechanisms in pain in CTS. After peripheral damage, excessive and repeated sensory stimuli reach the central nervous system, causing changes in the dorsal horn receptor area and resulting neuroplastic reorganization.[15] In this central sensitization process, the duration and severity of the peripheral input are important. In the study conducted by Fernández-de-las-Peñas et al. investigating central sensitization in the patients with unilateral CTS, a significant decrease was found in the pain threshold due to diffuse pressure in the bilateral upper extremities and this decrease was associated with symptom severity and duration.[16] In our study, we found that the duration of symptoms was significantly higher in the patients with neuropathic pain according to the LANSS compared to the group without neuropathic pain. This suggests that central sensitization resulting from increased peripheral input due to prolonged symptom duration in CTS plays a role in the development of neuropathic pain parameters such as allodynia and decreased pin prick threshold (PPT).

In our study, it was observed that physical examination findings and distal motor latency and sensory nerve conduction findings among electrophysiological parameters were more affected in the patients with neuropathic pain according to the LANSS scale. In addition, electrophysiological findings were more severe in the patients with neuropathic pain. In patients with predominant neuropathic pain, phalen test positivity, thenar atrophy, sensory and motor deficits were significantly higher than pa-

tients with predominant nociceptive pain. This situation indicates that the presence of motor and sensory disorders is mostly associated with neuropathic pain in the patients with CTS.

In the study conducted by Dandinoğlu et al. including patients with CTS, DN4 and LANSS scores were not correlated with electrophysiological severity.[17] It has been suggested that the treatment of neuropathic complaints should be managed regardless of electrophysiological findings.[17] Contrarily, in our study, we found that the LANSS score was associated with electrophysiological severity and electrophysiological findings except motor amplitude and motor velocity. This indicates that electrophysiological parameters, especially sensory nerve conduction studies and distal motor latency values, can be used in neuropathic pain evaluation.

In another study from our country, conducted in 80 patients with unilateral CTS, a correlation was observed between electrodiagnostic CTS severity and Washington neuropathic pain scale score.[18] Although different neuropathic pain scales were used, a similar relationship was also shown in our study. Therefore, we are in the opinion that LANSS will help the clinician in the evaluation of the clinical course in patients with CTS.

In the study of Sonohata et al., neuropathic pain assessment was performed with the PainDETECT, and no correlation was reported between the PainDETECT and MNMDL.[10] In our study, LANSS was found to be correlated with motor distal latency, motor amplitude and sensory nerve conduction parameters. In their study, unlike ours, sensory nerve conduction assessment was not performed.[10] However, the AAEM reported that sensory nerve conduction studies are more sensitive than motor nerve conduction studies in the diagnosis of CTS.[19]

In the study conducted by Sonohata et al., a significant correlation was observed between the PainDETECT and the DASH scores.[10] Similarly, in our study with Q-DASH, which is a modification of the DASH questionnaire that provides a short and rapid evaluation, a correlation was observed between the LANSS score and the Q-DASH score, and the Q-DASH score was found to be significantly higher in the neuropathic pain group. In other words, it was observed that the presence of neuropathic pain might further impair functionality in activities of daily living. In a study conducted by Padua et al. with 1,123 patients with idiopathic CTS, a strong correlation was found between DN4 scores and Boston Functional Capacity Scale.[20] All these studies show that the rate of daily living activities being affected by neuropathic pain is high.

In our study, the electrophysiological severity was found to be statistically significantly higher in the group with LANSS score ≥12. Since LANSS evaluates neuropathic components including dysesthesia, autonomic dysfunction, evoked pain, paroxysmal pain, thermal pain, allodynia and PPT change, these factors can be interpreted as being related to the severity of CTS. Allodynia occurs when the Aβ fibers, which physiologically conduct the touch-pressure sensation, begin to play a role in the transmission of painful stimuli. Evaluation of thickly myelinated Aβ fibers with EMG may explain the significant relationship between allodynia and electrophysiological.[17] Our study shows that Aβ fibers may have a role in the formation of allodynia, PPT change, thermal pain, evoked pain and paroxysmal pain. In neuropathic pain formation, not only allodynia but also other neuropathic components may occur, especially due to Aβ fiber involvement.

The limitation of our research is that moderate cases outnumber severe ones. This situation might cause an increase in the frequency of neuropathic pain in our patient group. The strength of our study is that it included both electrophysiological and functionality assessment of patients with CTS.

CONCLUSION

In conclusion, female gender, prolonged symptom duration, impaired sensory and motor examination were found to be associated with neuropathic pain in the patients with CTS. Among electrophysiological parameters, it has been shown that median nerve distal motor latency and median nerve sensory conduction examinations can be used to determine the presence of neuropathic pain. Based on assessment of hand functionality, it has been determined that

daily living activities were more impaired in the presence of neuropathic pain in the patients with CTS. Knowing the presence and mechanism of neuropathic pain in patients with CTS will guide the clinician in determining the appropriate treatment strategy.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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