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What is the role of sensitization in carpal tunnel syndrome where pain impacts functional capacity?

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ABSTRACT

Aims: Expression of carpal tunnel syndrome (CTS) caused by the entrapped median nerve includes pain, paraesthesia and numbness. Extra median spread of pain can furthermore be seen as a clinical requirement defined by neuro inflammation. Central sensitization (CS) constructs a similar mechanism. This study aims to evaluate sensitization in patients diagnosed with CTS.

Methods: A total number of 152 patients diagnosed with CTS were evaluated, prospectively. Patients data such as gender, age, body mass index (BMI), disease duration, pain severity (NRS), painDETECT questionnaire, Boston CTS symptom severity scale (SSS) and functional status scale (FSS), CS scale, electroneuromyography results have been collected by the author and then the patients are divided into three groups.

Results: Regarding the age, BMI and CS rate, there was no statistical difference between the three patient groups ($p>0.05$). However, a statistically significant difference was found between these groups in disease duration, day-time and night-time NRS, Boston SSS, FSS, and pain DETECT scores ($p<0.05$). A statistically significant correlation between age, BMI, NRS daytime scores, Boston SSS, FSS, and CS existence was not found ($p>0.05$). Yet, statistically significant differences were found in a comparison of the patients with and without CS, in disease duration, NRS night scores, and painDETECT scores ($p<0.05$).

Conclusion: We conclude that the rate of CS is often undervalued in patients with CTS. CS should be considered in CTS patients with extra-median spread of pain.

Keywords: Carpal tunnel syndrome, functional capacity, central sensitization

INTRODUCTION

Carpal tunnel syndrome (CTS) is one of the common entrapment neuropathy that may be accompanied by neuropathic symptoms.[1]

Initially, pain and paresthesia occur due to compression of the median nerve in the wrist, and in the following period, loss of strength develops in the muscles innervated by the median nerve. However, some patients complain about the spread of the pain and paresthesia toward the proximal upper extremity, which does not follow the median nerve tracing. This clinical picture expressed as extra-median spread has been tried to be explained by peripheral and central sensitivity mechanisms.[2] Furthermore, Zanette et al.[2] noted that pain follows the median nerve trace in only 35% of the patients with CTS, while it occurs in the ulnar nerve trace at 5%. In another study, 45% of CTS patients had pain radiating to the elbow and shoulder region.[3] They explained this finding with neurogenic inflammation in the median nerve, sensitization mechanisms, and plasticity in the nociceptive pathways. This study also stated that neuropathic pain accompanied nociceptive pain, and the CTS patients with sensitization complained about increased pain at night and significantly reduced quality of life.[3]

Sensitization develops in many chronic painful musculoskeletal disorders.[4] It was postulated that increased nociceptive receptor sensitivity after long-term pain, peripheral sensitization due to neuroinflammation, the increased response of the nociceptive central nervous system neurons to normal or sub-threshold afferent inputs, or dysfunction of the endogenous opioid system causes central sensitization (CS). During the evaluation of CS, several methods, such as quantitative sensory tests, thermal sensitivity, and perception of vibration sensors, are used. However, these methods are difficult to apply

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in clinical practice and the evaluation process takes a long time. The CS inventory developed by Mayer et al.[5] is easy to use and provides rapid assessment, which has increased its use in clinical practice.

Delineation of the association between CS and CTS is essential for better understanding of the mechanisms of pain in CTS patients and during the decision-making processes regarding their therapeutic management. This study aimed to investigate the presence of sensitization in patients diagnosed with CTS.

METHODS

The study was initiated with the approval of Sivas Cumhuriyet University Non-interventional Clinical Researches Ethics Committee (Date: 17/11/2021, Decision No: 2021-11/02). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The current study was conducted as cross-sectional, at the medicine department of physical therapy and rehabilitation in a tertiary care centre. CTS patients aged between 18 and 75, with clinical symptoms and electroneuromyography (EMG) included in the study. Exclusion criteria were as follows: mental disability, pregnancy, cervical radiculopathy or plexopathy. Furthermore, since the conditions that are frequently accompanied by CS, patients with a previous diagnosis of migraine, fibromyalgia syndrome, chronic fatigue syndrome, restless legs syndrome, anxiety and depression, irritable bowel syndrome, multiple chemical allergies, and temporomandibular joint disorder were excluded from the study. All participants have signed informed consent documents before being included in the study.

The data of patients such as age, gender, body mass index (BMI), disease duration, and pain severity (numerical rating scale-NRS), has been recorded in the system. Neuropathic pain assessment has been performed through the painDETECT scale, and CS has been evaluated with the CS questionnaire. The Boston CTS rating scale was used to evaluate the impact of the disease on functional capacity. During the evaluation of CTS severity and electrophysiological examinations, American Electro diagnostic Medical Association guidance and diagnostic criteria were assessed.6 Patients who had prolonged distal latency in the median nerve sensory branch and reduced sensory nerve action potential amplitude were accepted as mild CTS. Yet, patients who had prolonged distal latency of the motor branch, according to these findings, were defined as having moderate CTS. Patients who had prolonged distal latency in both motor and sensory branches and reduced or absent compound muscle amplitude were defined as having severe CTS.

Levine-Katz (Boston) Questionnaire analysis (CTS Rating Scale): The scale has been developed by Levine et al., for functional and symptomatic assessment7.8 For symptomatology, the scale includes 11 questions; and for functional status, it includes 8 questions. Each question is scored on a scale of vary between 1 to 5 (i.e., mild to severe). The patient's functional and symptomatic complaints count on the higher score; if the score is high that refers to it is more severe. The outcome of the Boston Symptom Severity Scale (SSS) demonstrates symptomatic severity, yet, Boston Functional Status Scale (FSS) demonstrates its impact on functionality.

PainDETECT Questionnaire: The questionnaire is utilised for specifying the pain type.9, 10 Regarding the total questionnaire score of patients, 12 or fewer points are accepted as nociceptive pain. In contrast to this, patients with scores in the range of 13 to 18 were accepted to have a mixed type of pain with a neuropathic component, and pain scores of 19 and above reveal neuropathic pain.

Central Sensitization (CS) Inventory

This inventory consists of two sections: Section A is the CS-related symptoms, and Section B is the part regarding CS syndromes and questions whether the patient was diagnosed before or not.5 Section A contains 25 items and is scored between 0 and 100 points. In addition, each symptom is scored on a scale of 1 to 5 as never (0), rarely (1), sometimes (2), frequently (3), and always (4). Thus, relatively higher scores indicate more severe CS-related symptoms.[11]

Numerical rating scale (NRS) for pain: The scale has numerical values between 0 and 10 and the patient is requested to select the number that represents pain clearly. While a score of 0 indicates "no pain", a score of 10 indicates "unbearable pain". NRS assessments have been performed in both daytime and nighttime. These questionnaires were conducted for research goals in a face-to-face approach. All questionnaires and scales had Turkish validation.

Statistical Analysis

The SPSS (version: 22, 0) IBM SPSS statistical package program was executed through all statistical analyses in this study. Numerical data delivered as means and standard deviations revealed normal distribution. For the variables that are not offered the normal distribution, medians and interquartile ranges (IQR) were provided. Percentages and frequencies were operated for categorical variables. The results of the Shapiro-Wilk test, histogram, and q-q plots were analysed to assess the normality of data. Bonferroni, which is one of the Post Hoc tests has been employed to conduct pairwise comparisons. To compare multiple groups that did not show normal distribution, the Kruskal-Wallis test has been operated.

The Mann-Whitney U test and two-sided independent samples t-test have been performed to compare the differences between continuous variables.

The Pearson Chi-square test or Fisher's exact test has been conducted for comparing differences between categorical variables. Yet, the Phi correlation test was utilized to compare the categorical and continuous variables. For the p-value, the accepted significance level was lower than 0.05.

RESULTS

A total number of 152 participants met the inclusion criteria. The mean age of these patients was 43.35±12.71 years and 124 (81.6%) were women. The severity assessment revealed that CTS was mild in 55 (36.1%), moderate in 65 (42.8%), and severe in 32 (21.1%) patients. The CS inventory evaluation demonstrated that CS was current in 118 (77.6%) patients, and there was no CS in 34 (22.4%) patients. When the difference between the patients with and without CS regarding gender and the CTS severity (p>0.05) was examined, there was no statistically significant found. In **Table 1**, patients' demographic and clinical characteristics were presented.

Table 1. The demographic and clinical characteristics of the patients

Female/male	124 (81.6)/28 (18.4)
Age, (years)	43.35±12.71
BMI, (kg/m2)	29.48±4.62
Disease duration,(years) (years)	5.00±3.86
NRS	
Daytime	4.08±2.04
Night-time	5.76±2.65
Boston-SSS	3.00±0.73
Boston-FSS	2.38±0.86
CS scale	50.46±14.87
PainDETECT	16.02±4.44

Date presented as mean ± standard deviation or number (%)
BMI: Body masss index, NRS: Numerical pain scale, Boston SSS: Boston symptoms Severity scale, Boston-FSS: Boston functional status scale, CS: Central sensitization

Daytime and night-time NRS values of the patients were 4.0 (0.0- 8.0) and 6.00 (0.0-10.0). According to the outcome of the pain DETECT questionnaire, 28 (18.4%) patients had nociceptive pain; 99 (65.1%) patients had mixed-type pain and 25 (16.4%) patients had neuropathic pain.

In terms of age and BMI, it was determined that there was no significant difference between the groups. However, there were significant differences between these patient groups regarding disease duration, daytime and night-time NRS scores, Boston SSS, FSS, and painDETECT scores. In addition, there was a positive correlation between disease severity and all other parameters, as shown in **Table 2**.

Table 2. Relationship between CTS severity, demographics data, and clinical evaluation results

	CTS severity			r	p
	Mild	Moderate	Severe		
Age, (years)	42.0 (19.0)	43.0 (19.0)	41.0 (21.5)		0.781
BMI, (kg/m2)	28.07 (7.05)	29.97 (6.97)	30.43 (4.51)		0.151
Disease duration, (years)	3.0 (5.0)	9.0 (6.0)	5.5 (4.75)	.279	0.002
NRS					
Daytime	3.0 (2.0)	4.0 (2.5)	5.0 (2.75)	.314	0.000
Night	4.0 (2.0)	8.0 (3.0)	7.0 (3.0)	.483	0.000
Boston-SSS	2.36 (0.71)	3.09 (0.8)	3.71 (.78)	.636	0.000
Boston-FSS	1.87 (1.0)	2.5 (1.0)	3.6 (1.0)	.738	0.000
Pain DETECT	14.0 (4.0)	17.0 (3.5)	17.0 (6.75)	.485	0.000

Data presented as median (interquartile range), *p<0.05 is significant
CTS: Carpal tunnel syndrome BMI: Body mass index, NRS: Numerical pain scale, Boston SSS: Boston symptoms severity scale, Boston-FSS: Boston functional status scale,

Age, BMI, NRS daytime scores, Boston-SSS, FSS, and the presence of CS (p>0.05) was examined and, no statistically significant correlation was found. However, patients' comparison with and without CS revealed statistically significant differences in disease duration, NRS night scores, and painDETECT scores (p<0.05). The relationship of CS with demographic data and other variables is presented in **Table 3**.

Table 3. Relationship between CS inventory results and clinical variables

	Presence of CS		r	p
	Absence of CS	Presence of CS		
Age, (years)	43.0 (19.50)	43.0 (18.25)		0.464
BMI, (kg/m2)	28.30 (7.37)	29.01 (6.18)		0.430
Disease duration, (years)	2.5 (6.0)	5.0 (5.0)	.163	0.045
NRS				
Daytime	4.0 (3.0)	4.0 (2.25)	.226	0.153
Night	4.0 (1.25)	6.0 (3.25)		0.005
Boston-SSS	2.81 (0.62)	3.0 (1.0)		0.076
Boston-FSS	2.0 (0.90)	2.0 (1.13)		0.995
Pain DETECT	13.50 (6.0)	16.0 (3.0)	.347	0.000

Data presented as median (interquartile range), *p<0.05 is significant
BMI: Body mass index, NRS: Numerical pain scale, Boston SSS: Boston symptoms Severity scale, Boston-FSS: Boston functional status scale, CS: Central sensitization

In the numerical evaluation of the CS scale, there was a weakly positive correlation with disease severity (r=0.170). However, a statistically significant difference was not found between the mild, moderate, and severe CTS groups regarding the presence or absence of CS as per categorical evaluation (p>0.05). The data regarding the relationship between CTS severity and CS are shown in **Table 4**.

Table 4. Relationship between CTS and CS inventory results

	CTS severity			p
	Mild	Moderate	Severe	
Absence of CS	10	20	4	0.082
Presence of CS	45	45	28	

*p<0.05 is significant, CTS: Carpal tunnel syndrome, CS: Central sensitization

DISCUSSION

In musculoskeletal diseases that cause chronic pain, long-term nociceptive input leads to changes in pain transmission pathways and activation of peripheral and central sensitization mechanisms. Therefore, multi-dimensional evaluation is required in managing these diseases in addition to standard medical treatment.[12]

A positive correlation and significant difference were found between disease duration, the severity of nocturnal pain, neuropathic pain scores, and the presence of CS. However, no statistically significant difference was found between the disease severity and the presence of CS.

İt was well-known that age and obesity are the risk factors for CTS, and CTS is most common in patients aged between 40 and 60.[13] In a case-control study, it was stated that morbid obesity was a risk factor for CTS,[14] in another study including total of 109 patients, no statistically significant association was found between CTS severity and obesity.[15] In obesity, an increase in inflammatory mediators such as interleukins and the calcitonin gene-related peptide has been detected.[16] These mediators also play a role in the pathogenesis of CS. Although the impact of obesity on pain perception was previously analysed, the relationship between obesity and CS has not been evaluated.[17]

In this study, it was determined that there was no statistically significant difference was found between age and obesity, the severity of CTS, and the presence of CS. In CTS, repetitive exposure to painful stimuli and the prolongation of the disease duration cause an increase in pain intensity.[18] The CS mechanisms have an impact on the pathogenesis of refractory and chronic pain. Prolongation of the disease duration and the persistence of neuro inflammation leads to chronic pain and modulate pain sensitivity.[19]

In this study, disease duration was positively correlated with CS. This finding aligns with the other studies advising that disease duration and sensitization mechanisms should be taking into consideration during management of the treatment.[12]

The Boston CTS scale has been utilized in a meta-analysis study before and after CTS treatment to evaluate symptom severity and functional capacity.[20] The authors emphasized the effectiveness of manual therapy techniques based on soft tissue and neurodynamic mobilizations on isolation, pain, physical function and nerve conduction studies in patients with CTS.

In this study, we found a positive correlation and significant difference between disease severity and CTS scale results. However, it was not found to be a significant difference between patients with or without CS regarding Boston CTS scale results.

In CTS, it has been reported that the incidence of neuropathic pain was in the range of 31-77%.[21] occurring during the development of neuropathic pain triggered both peripheral and CS mechanisms.[22] In many clinical conditions, such as post herpetic neuralgia, complex regional pain syndrome, or traumatic nerve injury, neuropathic pain is accompanied by CS in the later stages.[23] In our study, we uncovered a statistically significant positive correlation between the painDETECT questionnaire scores and the CS. Pathophysiological changes that occur in the formation of CS and neuro inflammation mechanisms that cause an extra median spread of pain deliver common features.

The CS should be assessed for CTS patients with severe pain, parenthetic complaints, and extra-median spread of pain, appropriate treatment must be chosen.

In a study including a total number of 53 patients with chronic pain due to knee osteoarthritis, the researchers worked on CS.[24] In addition to evaluating the functional capacity of the patients, these authors conducted pain distribution mapping by operating a unique device. In this study, the increased extent of knee pain was accepted as evidence of diffuse hyperalgesia and CS. In another study involving a total number of 91 patients with knee osteoarthritis who experienced total arthroplasty, CS was detected in 44 patients, and relatively less pain palliation was determined in patients with CS in the postoperative period.[25] In a study number of 31 patients with CS who originated myofascial trigger points after whiplash, local anaesthetic was injected in 15 patients, and saline was injected as a placebo in 16 patients. Consequently, an increased pain threshold was observed in the local anaesthetic group.[26] In addition, a review hypothesized that manual therapy may inhibit CS mechanisms by reducing abnormal afferent input, inflammation, and oxidative stress.[27]

In another study, including a number of 140 female patients with CTS, participants were requested to map the pain.[28] Among these patients, 124 reported extra-median symptoms; however, no relationship was determined between pain severity and clinical and psychological factors. In addition, no relationship was found between the lateralization and spread of pain and the pain severity. These authors clarified the extra-median spread of the pain with CS.

In this study, the diagnosis of CTS was revealed by clinical presentation and EMG outcomes, and the pain distribution pattern was not questioned. Being found CS in most of our patients (i.e., 77.6%) indicates that sensitization should be evaluated in these cases.

A small number of subjects, the absence of a control group, and the lack of pain distribution mapping can be considered as the limitations of our study.

CONCLUSION

The CS rate is often undervalued in patients with CTS. CS should be considered in CTS patients with atypical pain, pain intensity and extra-median spread of pain. We advise that the examination of the co-existence of CTS and CS will be required due to the relief of symptoms caused by CS that may contribute to CTS treatment. Large series of studies that evaluate the effects of CTS treatments on CS is required to reach definitive conclusions.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of Sivas Cumhuriyet University Non-interventional Clinical Researches Ethics Committee (Date: 17/11/2021, Decision No: 2021-11/02).

Informed Consent: Written consent was obtained from the patient participating in this study.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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