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ORIGINAL RESEARCH

Central Sensitization in Patients with Chronic Pain Secondary to Carpal Tunnel Syndrome and Determinants

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Purpose: Central sensitization (CS) is commonly seen in chronic pain disorders, including neuropathic pain. However, there exist inconsistencies concerning the presence of CS in chronic pain secondary to carpal tunnel syndrome (CTS). CS and neuropathic pain manifestations in CTS remain not well established. Therefore, this study aims to investigate the CS and pain profiles in patients with CTS and to explore the potential determinants associated with CS.

Patients and Methods: Patients with suspected CTS symptoms lasting 3 months or above and healthy controls were enrolled. History, physical examinations, and nerve conduction studies were employed to confirm the diagnosis and severity of median nerve dysfunction. The central sensitization inventory (CSI) was used to screen CS. Other outcomes included neuropathic pain, CTS-specific symptom severity and functions, emotion, and health-related quality of life. Between-group comparisons were conducted in terms of the CS presence. Logistic regression analysis was performed to identify determinants associated with CS.

Results: Over 60% of participants with CTS were found with clinical CS, significantly higher than that in the control group. More than 70% of the CTS participants were identified to have possible or very likely neuropathic pain components. In addition, one-fourth of CTS cases had depression or anxiety. Anxiety was associated with an increased risk of developing CS in CTS (adjusted OR=1.31, 95% CI 1.08–1.59), whereas higher self-perceived general health rating was negatively associated with the presence of CS (adjusted OR=0.92, 95% CI 0.88–0.97) in the multivariate adjusted regression model.

Conclusion: CS is prevalent in patients with CTS. Predominant neuropathic pain characteristics were uncovered in CTS patients as well as comorbid psychological distress. Significant association was found between anxiety and CS presence. Self-perceived general health was inversely related to CS. Further research is warranted to explore the mechanisms of anxiety and central pain processing in painful entrapment neuropathy.

Keywords: central sensitization, chronic pain, carpal tunnel syndrome, determinants

Introduction

Central sensitization (CS), an abnormal condition of the central nervous system, is characterized by pain hypersensitivity manifestations such as hyperalgesia and allodynia, which is usually associated with the persistence of chronic pain.[1–3] The presence of CS has been reported to be related to augmented neural signal processing in the cortex and spinal cord.[1,2] CS is frequently reported in population with various chronic pain disorders, including osteoarthritis, low back pain, and

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peripheral neuropathies, and it may explain the widespread pain beyond the affected lesions, and worse still, place an adverse effect on the efficacy of pain management strategies.[4–8]

Carpal tunnel syndrome (CTS) is regarded as the most common type of peripheral nerve entrapment disorder that inflicts a number of people in the world.[9–11] Patients with CTS often complain of numbness, tingling, and pain symptoms in areas innervated by the median nerve, especially during the nighttime that may affect their normal sleep, and some may even experience weakness at hand with thenar muscle atrophy in severe cases.[9–11] CS has been identified in patients with CTS by previous relevant studies, which could be associated with a poorer functional recovery after carpal-release surgeries or other conservative interventions.[7,12–16] Aberrant pain sensitivity was found in CTS patients, with signatures of CS such as extraterritorial pain, lowered pain threshold, hyperalgesia to temperature and mechanical stimuli.[14,17–20]

Although few studies were conducted previously to examine the presence of CS in CTS, there exist several inconsistencies in the findings on sensory phenotypes of CS among CTS patients.[18–25] Several trials revealed differences in parameters including cold, mechanical, and vibration detection thresholds, heat pain threshold, and pressure pain threshold in CTS patients, compared with normal controls.[20,24,25] However, no significant between-group differences were discovered in other reports with regard to cold, heat, mechanical, or pressure pain thresholds between participants with and without CTS.[23,26] Furthermore, different psychophysiological factors may play a role in the development of CS among those with CTS, namely clinical pain patterns and magnitudes, body mass index (BMI), depression and/or anxiety, and so forth, however, few studies have considered these factors and controlled the possible confounding effects.[14,15]

The overall pain and CS profiles of patients with CTS have not been fully understood thus far, given the heterogeneous findings in previous studies. Also, the determinants of CS in CTS have yet to be well established. Therefore, the present study aimed to first detect the presence of CS in CTS by the validated Chinese Central Sensitization Inventory (CSI-C)[27] as well as to investigate the overall neuropathic pain profiles and clinical characteristics of participants with CTS. Moreover, this study would also like to explore the determinants associated with the CS presence among CTS patients.

Material and Methods

This study was part of a prospective cohort trial, with consecutive sampling from public cluster hospitals in Hong Kong. Ethics approval was obtained from Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster, and it was preregistered at the clinical trial registry of The University of Hong Kong (HKUCTR-2828) prior to the start of the study. Participants were fully informed about the purpose of the study, and their written consent was obtained before joining the study. All procedures in the study were conducted in accord with the Declaration of Helsinki.

Participants

Patients with suspected CTS symptoms, which lasted at least 3 months were enrolled in two public hospitals in Hong Kong from December 2020 to February 2022. The inclusion criteria for the CTS group were as follows: a) clinically diagnosed as CTS confirmed by nerve conduction study (distal motor latency of the median nerve >3.8 m/s and/or sensory or motor conduction velocity of the median nerve <50 m/s) with positive clinical provocative tests such as Phalen's test and Tinel Sign;[28–30] b) duration of the clinical symptoms lasting no less than 3 months; c) symptom severity score on the visual analogue scale (VAS) greater than 4/10 points; d) willing to join and able to comply with the study protocol.

Those patients who met any of the following conditions were excluded from the study: a) with a history of a wrist or hand surgery or trauma within the past 6 months or intra-articular injection of corticosteroids within the past 3 months; b) having severe or unstable comorbidities including stroke, spinal cord injury, Parkinson's disease, gout, diabetes mellitus, ischemic heart disease, hypertension, chronic kidney disease, cancer, and so on; c) having other concurrent chronic central or peripheral neuropathic pain conditions; d) having other concurrent chronic musculoskeletal pain disorders; e) abnormal cognitive or mental status, unable to cooperate with the procedures; f) other reasons leading to a failure to comply with the experimental procedures.

A pain-free healthy control group with age- and gender-matched was also recruited in this study. The inclusion criteria for the healthy control group: a) having no pain complaints in the past 3 months; b) having no history of arthritis, fibromyalgia,

CTS, or other nerve injuries or dysfunction or other chronic musculoskeletal pain disorders; c) reporting no anxiety or depression in the past 3 months. The exclusion criteria for the healthy control group were similar to that mentioned for the CTS group. Besides, the healthy controls were excluded if they presented acute pain at the screening visit.

Electro-Diagnostic Examination

Nerve conduction studies were employed for a confirmation of the diagnosis of CTS among the participants. The nerve conduction study was conducted in the following standardized steps previously validated by our team at the Clinical Electro-diagnostic Unit, Tung Wah Hospital.[31] First, the median sensory nerve conduction was tested. Participants were asked to wash their hands with warm water and dry up. The stimulating ring electrode is placed over the proximal interphalangeal joint of the index finger, and the reference ring electrode over the distal interphalangeal joint of the index finger. The recording electrodes were placed between the flexor carpi radialis and the palmaris longus tendons at the wrist, which is about 12 cm proximal to the ring electrode, as well as at a point just proximal to the distal wrist crease. The ground electrode was positioned between the stimulation and the recording sites. Then, supramaximal electrical stimulation to the median nerve was applied through the stimulating electrode over the index finger for ten times.[31] For a better comparison, the ulnar sensory nerve was also measured.

Median motor nerve conduction was evaluated as follows: The recording electrode was placed at the motor point of the abductor pollicis brevis at the thenar area, and the referencing electrode was placed over the proximal phalanx of the thumb. Electrical stimuli were given at several different sites, including the middle of palm, which is about 3–4 cm distal to the distal wrist crease, 6.5 cm proximal to the recording point at the wrist between flexor carpi radialis and palmaris longus tendons, as well as the medial aspect of the antecubital space of the elbow, respectively. The distal motor latency, CMAP amplitude, and conduction velocities of the median nerve were collected. Similarly, the ulnar motor nerve conduction was also measured for a contrast. The recording electrode was placed over the belly of the abductor digiti minimi, and the reference electrode to the distal phalanx of the little finger. Electrical stimulation was performed at the wrist, 7cm proximal to the recording electrode, as well as below and above the elbow, 5cm distal and proximal to the ulnar groove.

The diagnosis of CTS was determined based on the nerve conduction studies of the median nerve, as well as the clinical history and the specific provocative physical examinations such as the Tinel sign and Phalen's test, in accord with the internationally established guidelines.[9,29,30] The severity grading of CTS ranging from very mild to severe was made depending on the neurophysiological results, including the distal motor latency of the median motor nerve and/or the conduction velocity and amplitude of median sensory nerve.[29,30]

Self-Reported Clinical Outcomes

Several self-reported outcome measures were adopted in the present study to investigate the pain sensitization, neuropathic pain features, pain magnitude and related functions and quality of life, as well as mental status of the participants, which will be elaborated as below.

Central Sensitization Inventory

Central sensitization inventory (CSI) was employed in this study to detect signs of central pain sensitization in patients with CTS.[27,32,33] CSI is comprised of two parts. The first part includes 25 questions related to the sensitization symptom severity. For each item, five levels of options including "never, rarely, sometimes, often, and always" are provided. A cutoff score of 30 is commonly used to differentiate between subclinical and clinical central sensitization.[34] The second part provides a checklist of several central sensitivity syndromes as well as depression and anxiety. Cultural adaptation and validation of Chinese CSI were conducted prior to implementation in the present study, which demonstrated good reliability and validity.[27]

PainDETECT Instrument

The neuropathic pain component among the participants was identified by the PainDETECT instrument (PD), which is an efficient screening tool in clinical practice with a recognized sensitivity (85%) and specificity (80%).[35–37] PD embodies seven specific questions concerning typical neuropathic pain symptoms, including numbness, burning sensation, tingling

or pricking, electric shock pain, pain sensitivity to light touch, temperature, and pressure. Each question was rated in a 6-point Likert scale, namely "never", "hardly noticed", "slightly", "moderately", "strongly", and "very strongly". In addition, pain radiation and the pattern of pain symptoms on a body chart were also recorded. The presence of a neuropathic-like pain component by PD is determined by the final scoring, that is, 0–12 points indicate an unlikely neuropathic pain component; 13–18 points mean possible neuropathic pain, and 19 points or above imply a very likely neuropathic pain component.

Visual Analogue Scale

Visual analogue scale was used to assess the pain intensity, which employs a 100-mm line to allow participants to rate their pain intensity across a continuum from "no pain at all" to "extremely intolerable pain".[38] Participants enrolled were asked to give three pain ratings based on their actual experiences, namely current pain intensity and the worst, and average pain intensities experienced over the past 1 month.

Boston Carpal Tunnel Syndrome Questionnaire

Boston carpal tunnel questionnaire (BCTQ) was adopted in this study to evaluate the specific disease-related symptom severity and function for CTS.[9,39,40] It consists of two subscales, namely symptom severity scale (SSS) and functional scale (FS).[40] The former has 11 questions concerning the severity of clinical presentations of hand/wrist symptoms such as numbness, tingling, pain, and weakness, while the latter includes eight items related to hand functions. The BCTQ used in this study was the validated Chinese version by Fok, Leung, and Lee.[41]

Hospital Anxiety and Depression Scale

Mental states of anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HADS).[42] HADS contains 14 items assessing anxiety and depression, respectively. Each item on the questionnaire can be scored from 0 to 3 on a 4-point Likert scale. The subscales of anxiety and depression were calculated independently. The rating criteria are as follows: 0–7 points means no anxiety or depression, while 8 points or above represents a positive case of anxiety or depression.[42]

EQ-5D-5L

EQ-5D-5L, a popular generic and standardized measure of health status, was utilized to evaluate health-related quality of life.[43,44] The EQ-5D-5L includes five dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression with five rating levels (ranging from "no difficulty" to "extremely difficult"). An overall grading of self-perceived health status through a 0–100 scale is also included.[44] Official permission of the Chinese version of EQ-5D-5L was obtained from EuroQol.org before using it in the study.

Statistical Analyses

Shapiro–Wilk test was used to assess the normality of data distribution. For data that were not normally distributed, median and interquartile range (IQR) are presented for continuous variables and categorical variables are reported with a frequency distribution. Non-parametric statistical tests were employed for the relevant statistical analyses. The presence rate of central sensitization by CSI was calculated for both the CTS and control group. Kruskal–Wallis test was used to compare the demographic and clinical outcomes between the two groups. Cross tabulation and chi-square statistics were used to detect associations between nominal and categorical variables. Binary logistic regression was performed to estimate the odds ratio (OR) and 95% confidence interval (95% CI) for the presence of a central sensitization component in CTS patients. Univariate logistic regression analysis was carried out for the initial selection of potential predictors associated with the presence of central sensitization. Those predictors screened in univariate regression with significance and met the theoretical hypotheses underlying central sensitization in CTS and are then incorporated in the multivariate regression model. Prior to running the multivariate logistic regression, correlations between the candidate variables were examined to avoid multicollinearity. In addition, the multivariate model was adjusted for the covariate of age and gender. All data analyses were conducted using IBM SPSS Statistics for Macintosh, Version 28.0 (Chicago: SPSS Inc.) and the significance level was set at 0.05.

Results

Demographic and Clinical Characteristics

Totally 168 patients with wrist/hand complaints were screened in the outpatient clinic. Of them, 155 were confirmed with diagnosis of CTS after physical examinations and nerve conduction studies, and eligible for enrollment. In addition, 57 healthy controls were recruited. The average age of the CTS group was 63 years, and the majority of them were female. Similarly, the control group had a mean age of 59 years and over 90% were women. Participants with CTS complained of wrist/hand symptoms for more than 30 months on average. According to the grading system of CTS severity, over 70% of the CTS participants were classified as moderate or severe CTS.[29,30]

The demographic and clinical characteristics of CTS participants and healthy controls are displayed in Table 1.

Table 1 Demographic and Clinical Characteristics of Participants

	CTS (n=155)	HC (n=57)	*P* value
Age (year, mean (SD))	63.0 (10.49)	59.1 (6.13)	0.053
Sex (Female, n (%))	130 (83.87%)	55 (96.49%)	0.018
BMI (mean (SD))	25.1(4.39)	22.0 (3.21)	<0.001
Right-handed, n (%)	147 (94.84%)	57 (100%)	0.193
Marital status, n (%)			
Married	128 (82.58%)	42 (73.68%)	0.001
Single	19 (12.26%)	9 (15.79%)	
Divorced	0 (0.0)	5 (8.77%)	
Prefer not to answer	8 (5.16%)	1 (1.75%)	
Employment, n (%)			
Employed	66 (42.58%)	25 (43.86%)	0.200
Unemployed	8 (5.16%)	0 (0)	
Retired	50 (32.26%)	16 (28.07%)	
Housewife	31 (20%)	16 (28.07%)	
Smoker, n (%)	8 (5.16%)	0	0.141
Alcohol drinker, n (%)	3 (1.94%)	0	0.564
Pain duration (month, mean (SD))	31.5 (31.34)	NA	NA
CSI total score (mean (SD))	33.8 (13.34)	14.8 (9.59)	<0.001
PainDETECT total score (mean (SD))	14.9 (3.63)	0.4 (1.39)	<0.001
Current pain intensity (mean (SD))	4.7 (2.08)	NA	NA
Maximal pain intensity in past month (mean (SD))	7.1 (2.09)	NA	NA
Average pain intensity in past month (mean (SD))	5.5 (1.74)	NA	NA
Depression score (mean (SD))	5.9 (4.26)	1.7 (1.77)	<0.001
Anxiety score (mean (SD))	5.7 (3.88)	1.8 (2.22)	<0.001
BCTQ-SSS total score (mean (SD))	26.7 (7.13)	NA	NA

(*Continued*)

Table 1 (Continued).

	CTS (n=155)	HC (n=57)	*P* value
BCTQ-FS total score (mean (SD))	15.3 (5.02)	NA	NA
CTS severity grade			
Severe	8 (5.16%)	NA	NA
Very Mild	38 (24.52%)	NA	NA
Mild	52 (33.55%)	NA	NA
Moderate	57 (36.77%)	NA	NA

Abbreviations: CTS, carpal tunnel syndrome; HC, healthy control; SD, standard deviation; BMI, body mass index; CSI, central sensitization inventory; BCTQ, Boston carpal tunnel questionnaire; SSS, symptom severity scale; FS, functional scale.

Presence of Central Sensitization

The presence of central sensitization is determined by the CSI-C.[27] A threshold score of 30 was used to discriminate between subclinical and clinical central sensitizations.[45] As seen in Table 2, over 60% of participants with CTS in the study were present with clinical central sensitization, compared to that of 8.7% in the control group ($p<0.001$). Moreover, severity levels of central sensitization among the CTS population ranged from mild to extreme (Table 2), with regard to previously established classification system.[34]

Neuropathic Pain Features

The neuropathic pain components classified by PainDETECT between patients with CTS and healthy controls were compared. Table 3 demonstrates that approximately three-quarters of CTS patients experienced possible or very likely neuropathic pain components in this study, while all participants in the control group were classified as having unlikely neuropathic pain.

Prevalence of Depression and Anxiety

Abnormal mental status including depression and anxiety by HADS was detected among the participants enrolled in the study. As shown in Table 4, over 25% of CTS patients were presented with depression and about 28% with anxiety. No depression or anxiety was reported in the healthy control group.

Table 2 The Presence of Clinical Central Sensitization of Participants

	CTS (n=155)	HC (n=57)	*P* value
Subclinical CS, n (%)	58 (37.42%)	52 (91.22%)	<0.001
Clinical CS, n (%)	97 (62.58%)	5 (8.77%)	<0.001
Mild	41 (26.45%)	5 (8.77%)	
Moderate	39 (25.16%)	0	
Severe	12 (7.74%)	0	
Extreme	5 (3.23%)	0	

Abbreviations: CTS, carpal tunnel syndrome; HC, healthy control; CS, central sensitization.

Table 3 Neuropathic Pain Components Among Participants

	CTS (n=155)	HC (n=57)	*P* value
Unlikely NP, n (%)	38 (24.52%)	57 (100%)	<0.001
Possible NP, n (%)	88 (56.77%)	0	<0.001
Very likely NP, n (%)	29 (18.7%)	0	<0.001

Abbreviations: CTS, carpal tunnel syndrome; HC, healthy control; NP, neuropathic pain.

Table 4 Depression and Anxiety Status of Participants

	CTS (n=155)	HC (n=57)	*P* value
Depression, n (%)			
Depression case	41 (26.45%)	0	<0.001
Normal case	114 (73.55%)	57 (100%)	
Anxiety, n (%)			
Anxiety case	44 (28.39%)	0	<0.001
Normal case	111 (71.61%)	57(100%)	

Abbreviations: CTS, carpal tunnel syndrome; HC, healthy control.

Determinants of Central Sensitization

The predictors associated with the presence of central sensitization in participants with CTS were explored using logistic regression. Univariate regression analyses showed several factors associated with the presence of central sensitization (see Table 5). Potential variables with statistical significance in univariate regression model included sex, employment status, maximal pain intensity in the past month, neuropathic pain features by PD, depression and anxiety, BCTQ scoring, as well as self-perceived general health rating. The severity level of CTS was with a borderline significance value.

Table 5 Univariate Analyses of Central Sensitization in Participants with Carpal Tunnel Syndrome

Variable	OR	95% CI	*P*-value
Age	1.003	0.972, 1.034	0.865
Sex			
Female	3.035	1.259, 7.314	0.013
Male	1		
BMI	1.022	0.948, 1.103	0.567
Employment status			
Employed	1		
Unemployed	6.588	0.767, 56.569	0.086
Retired	1.673	0.788, 3.552	0.180
Housewife	3.765	1.362, 10.404	0.011

(*Continued*)

Table 5 (Continued).

Variable	OR	95% CI	*P*-value
Marital status			
Married	1		
Single	0.995	0.366, 2.701	0.992
Smoking			
Yes	1		
No	0.323	0.074, 1.406	0.298
Alcohol drinking			
Yes	1		
No	0	0	0.999
CTS severity grade			
Very mild	1		
Mild	2.516	0.468, 13.542	0.060
Moderate	2.348	0.964, 5.722	0.451
Severe	1.342	0.625, 2.881	0.251
Pain duration	1.006	0.995, 1.017	0.323
Current pain intensity	1.161	0.987, 1.367	0.072
Maximal pain intensity in past month	1.269	1.078, 1.494	0.004
Average pain intensity in past month	1.149	0.949, 1.391	0.153
PainDETECT score	1.157	1.046, 1.279	0.004
Depression score	1.299	1.158, 1.458	<0.001
Anxiety score	1.453	1.265, 1.668	<0.001
BCTQ-SSS	1.126	1.062, 1.194	<0.001
BCTQ-FS	1.199	1.101, 1.306	<0.001
Self-perceived general health rating	0.897	0.863, 0.932	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; BMI, body mass index; CTS, carpal tunnel syndrome; BCTQ, Boston carpal tunnel questionnaire; SSS, symptom severity scale; FS, functional scale.

Taking into account the hypotheses underlying the presence of central sensitization as well as considering the issue of multicollinearity in multiple regression models, 10 predictors were incorporated into the multivariate logistic regression model, adjusted by age (Table 6). The multivariate analysis demonstrates that anxiety is a risk factor associated with the presence of central sensitization in CTS patients with an elevated OR value of 1.31 (p=0.007; 95% CI, 1.08 to 1.59). In addition, the self-perceived general health rating is a protective factor in the development of central sensitization among CTS participants (p=0.001, OR=0.92, 95% CI, 0.88 to 0.97).

Discussion

To the best of our knowledge, the present study firstly looked at the profiles of CS and neuropathic pain features using CSI among the Chinese population with the most prevalent entrapment neuropathy of CTS. More than 63% of the

Table 6 Multivariate Analyses of Central Sensitization in Participants with Carpal Tunnel Syndrome

Variable	Adjusted OR	95% CI	*P*-value
Age	1.02	0.96, 1.08	0.605
Sex			
Female	1.98	0.50, 7.90	0.335
Male	1		
Employment status			
Employed	1		
Unemployed	9.68	0.51 18.39	0.131
Retired	1.34	0.57, 5.19	0.675
Housewife	1.11	0.26, 4.78	0.891
Maximal pain intensity in past month	1.01	0.75, 1.30	0.940
PainDETECT score	1.05	0.88, 1.25	0.615
Depression score	1.04	0.87, 1.23	0.690
Anxiety score	1.31	1.08, 1.59	0.007
BCTQ-SSS	1.07	0.97, 1.18	0.175
BCTQ-FS	1.01	0.89, 1.16	0.839
Perceived general health rating	0.92	0.88, 0.97	0.001
CTS severity grade			
Very mild	1		
Mild	2.95	0.25, 34.98	0.392
Moderate	1.74	0.15, 20.52	0.658
Severe	0.58	0.06, 6.13	0.653

Abbreviations: OR, odds ratio; CI, confidence interval; BCTQ, Boston carpal tunnel questionnaire; SSS, symptom severity scale; FS, functional scale; CTS, carpal tunnel syndrome.

participants with CTS in this study were found to be present with clinical CS, significantly higher than that in the normal control group. A large majority of CTS participants were identified to have possible or very likely neuropathic pain components. In addition, quite a few CTS cases exhibited depression or anxiety. The multivariate regression model demonstrated that anxiety was associated with an increased risk of developing CS in CTS, while higher self-perceived general health rating was negatively associated with the occurrence of CS.

Characterized by amplified central processing of pain, CS has been popularly discovered in a variety of chronic disorders with ongoing pain.[4–8] Patients with CTS were also found to experience CS, who complained of extraterritorial pain apart from the typical symptoms of paraesthesia, tingling, as well as pain in areas innervated by the median nerve.[14,17–20] Although several previous studies have employed quantitative sensory testing to detect CS among CTS patients, controversial results are noted across different trials.[18–26] Our findings showed over 60% of CTS participants were recognized as having clinical CS through CSI classification.[27,34] In previous relevant reports, over a quarter of CTS patients were identified to be with CS using clinical rules of prediction based on quantitative sensory testing.[7] The high prevalence of CS found in the present study could be partly due to the subjective nature of the CSI questionnaire, which echoed similar reports on presence rate of neuropathic pain based on the individual perception of pain symptoms in

CTS.[25,46–48] Nonetheless, it was claimed that CSI scoring was not related to CS signs of different sensory thresholds.[49] The insignificant association between subjective and objective measurements for CS could be probably related to the variances in demographic and clinical features of participants involved, including the age range, the CTS symptom severity, as well as functional limitations. For instance, in that study, CTS patients were relatively younger and of less severe CTS symptomatology.[49] CSI is a convenient scale to screen for CS in clinical practice,[27] which would be a supplementary alternative to quantitative sensory testing. However, the lack of quantitative sensory testing in this study has limited a further comparison of the exact association between CSI scores and somatosensory profiles of CTS patients, which deserves additional efforts in the future.

Given the definition of neuropathic pain,[50] pain symptoms secondary to CTS, commonly with altered sensation, should be naturally identified as neuropathic pain. However, previous studies noted that some CTS patients' dominant presentations fell into the type of nociceptive pain rather than neuropathic pain.[51] The prevalence of neuropathic pain among patients with CTS varies across different trials, ranging from 30% to 80%.[25,46,48,52] In our study, as high as 75% of participants with CTS were classified as having possible or very likely neuropathic pain via the PainDETECT tool, which is consistent with previous study,[25] despite different measuring instruments used for classifying neuropathic pain. Moreover, those CTS of positive neuropathic pain character seemed more vulnerable to develop CS symptomatology, and negative correlations were found between the severity of neuropathic pain and sensory function as well as mental health status in CTS.[25] Our univariate analysis found that neuropathic pain by the PainDETECT score was significantly associated with CS presence; however, it was no longer a predictor of significance in the multivariate regression model with age and gender adjusted. Since neuropathic pain severity is related to an impaired emotional health such as anxiety or depression,[53,54] its predicting effect in the multiple regression model could probably be attenuated as anxiety turned out to be a significant risk factor for the presence of CS in CTS in the present study.

Negative emotions such as depression and anxiety have been found to be correlated with the persistence of chronic pain and abnormal pain sensitization.[14,15,54,55] In the present study, about 26% and 28% of CTS patients were classified as depression cases and anxiety cases, respectively. The average depression and anxiety scores of CTS participants were 5.9 and 5.7, which are significantly higher than the normal control group. Similarly, previous studies have demonstrated significantly higher rates of depression and anxiety in those with CTS, compared to the general population.[30,56] The population with CTS is reported to be associated with a heightened risk to develop anxiety and depressive symptoms.[30] The comorbidity of anxiety and/or depression with chronic pain is not uncommon,[54,57] and the underlying pathophysiological mechanisms may be due to overlapping regions and neural networks associated with chronic pain and psychological distress in the brain.[58–61] Those with anxiety or depression may be more likely to experience abnormal pain sensitization such as CS and less responsive to pain relieving treatments, which merits further attention in practice.[7,15,16]

Since centrally mediating pain mechanisms in CTS patients can have an adverse impact on the therapeutic efficacy of clinical treatments for CTS,[15,62] it is of crucial importance to identify relevant predictors of CS. Due to its complex pathophysiological mechanisms, several different factors could be influencing CS in CTS, including symptom intensity, severity of the median nerve dysfunction, emotional well-being, as well as BMI and smoking.[14,15] In this study, a multivariate regression analysis showed that anxiety scores were positively associated with CS presence in CTS, with an elevated OR of 1.31 (95% CI 1.08–1.59) adjusted for age and sex. As mentioned above, patients with CTS had a higher risk of developing negative emotions like depression and anxiety.[30,56] In return, those CTS patients with coexisting anxiety may be associated with an increased risk of experiencing abnormal pain sensitization. The interplay between affective distress such as anxiety and depressive symptoms and central sensitization is complicated and not well understood, which could play an important role in the chronification of refractory pain syndromes.[60,61] In addition, good self-perceived general health seems to be a protective factor to develop CS among those with CTS in the study, with an OR of 0.92 (95% CI 0.88–0.97). It can be explained that those patients without CS tend to have a more satisfactory health-related quality of life. Knowledge of the clinical predictors associated with CS in CTS may serve to supply first-line clinicians with evidence-based reference when making clinical decisions on management strategies for different patients with CTS, as the existence of CS should affect the responsiveness of clinical treatments.[62]

There are both strengths and limitations in this study. First, the study included a sample of more than 150 older people with CTS (mean age of 63 years), having a prolonged duration of pain symptoms. Of these, the majority are female, with

an increased BMI on average, which is in fact a risk factor for CTS. Furthermore, the CTS participants in the study presented with moderate-to-severe pain, and more than half of the patients were diagnosed as having moderate-to-severe CTS. Hence, the present study represented a clinical sample of Chinese CTS patients with medium to high severity and more afflicting pain magnitude lasting for a relatively long period of time. This study also employed the validated Chinese CSI to investigate the CS among the population of CTS, providing additional evidence for CS screening through the self-administered scale that is easily used in clinical practice. In addition, neuropathic pain features and mood disorders such as depression and anxiety of participants were also evaluated. Several limitations also exist. Since quantitative sensory testing was not incorporated in the study, no correlational analysis was done to compare the CS presence between two approaches via objective assessments and subjective measurements. However, as existing evidence has proved the presence of CS by quantitative sensory testing, the principal objective of this study was to investigate the utility of our validated CSI-C to screen CS in chronic pain related to the entrapment neuropathy of CTS. In addition, only two factors were significantly associated with CS presence in the multivariate regression model, though quite a few variables were of statistical significance in the univariate analyses. A larger sample size may be needed in the future for further validation.

Conclusion

We conclude that CS is prevalent in chronic pain secondary to CTS. Predominant neuropathic pain characteristics were uncovered in CTS patients as well as comorbid psychological distress. Significant association was found between anxiety score and the presence of CS in CTS. The self-perceived general health status was inversely related to CS. Future studies should be warranted to explore the underlying mechanisms of anxiety and central pain processing.

Abbreviation

BCTQ, Boston carpal tunnel questionnaire; BMI, body mass index; CI, confidence interval; CS, central sensitization; CSI, central sensitization inventory; CSI-C, the validated Chinese Central Sensitization Inventory; CTS, carpal tunnel syndrome; FS, functional scale; HC, healthy control; IQR, interquartile range; NP, neuropathic pain; OR, odds ratio; PD, the PainDETECT instrument; SD, standard deviation; SSS, symptom severity scale; VAS, the visual analogue scale.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the first author (Beibei Feng, fengbb@connect.hku.hk or fengbb@mail.sysu.edu.cn) on reasonable request for academic purpose.

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Author Contributions

All authors made a significant contribution to the current manuscript, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no conflicts of interest.

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