ORIGINAL ARTICLE

Combination of Pain Location and Pain Duration is Associated with Central Sensitization-Related Symptoms in Patients with Musculoskeletal Disorders: A Cross-Sectional Study

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■ **Abstract**

Objectives: Increased evidence indicates that pain location affects central sensitization (CS)-related symptoms. In addition, pain location and pain duration may be intricately related to CS-related symptoms. However, these factors have been investigated separately. This study aimed to investigate the association between CS-related symptoms and pain location and/or pain duration in patients with musculoskeletal disorders.

Methods: Six hundred thirty-five participants with musculoskeletal disorders were included in this cross-sectional study. All participants were assessed for pain location, pain duration, central sensitization inventory (CSI), EuroQol-5 dimension, and brief pain inventory. The participants were categorized into 3 groups based on pain location (spinal, limb, and both spinal and limb pain) and into 2 groups based on pain duration (acute and chronic pain).

Results: The interaction between pain location and pain duration were not significant on CSI score ($P > 0.05$). The odds ratio for higher CSI score (≥ 40) in patients with both spinal and limb pain vs. those with spinal or limb pain was 2.64 ($P < 0.01$) and that in patients with chronic pain vs. those with acute pain was 1.31 ($P = 0.52$). In addition, the prevalence of higher CSI scores in the combination of chronic and "both spinal and limb" pain was high (23.1%, adjusted residual = 4.48).

Conclusions: Pain location independently influenced CSI scores, and the combination of both spinal and limb pain and chronic pain indicated high CSI scores. The combination of pain location and pain duration is an important clue that points to CS-related symptoms. ■

Key Words: pain location, pain duration, central sensitization-related symptoms, musculoskeletal disorders

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INTRODUCTION

Central sensitization (CS) suggests augmentation of responsiveness of the central nervous system to normal or subthreshold afferent input, resulting in increased pain sensitivity.[1] Robust evidence exists regarding CS as one of the mechanisms of musculoskeletal pain, including chronic low back pain, osteoarthritis, shoulder pain, fibromyalgia, and whiplash-associated disorders, which are related to symptom severity.[2–5] The central sensitization inventory (CSI) was developed as a screening tool to help identify whether a patient's symptom may be related to CS.[6] CSI has been broadly used in a variety of musculoskeletal disorders.[7,8] In addition, a systematic review revealed that CSI has strong psychometric properties and adequate clinical utility.[9]

The CSI score is related to clinical symptoms, such as pain intensity, disability, depression, and catastrophization.[10,11] Moreover, several studies have investigated characteristics affecting the CSI score. Mibu et al.[12] reported that the CSI score of patients with chronic low back pain is higher than that of patients with knee osteoarthritis. Roldán et al.[13] also reported that the CSI score in chronic musculoskeletal pain disorders is more affected by factors such as low back and neck, sex, and age. IndividualS with fibromyalgia, characterized by widespread musculoskeletal pain, has higher CSI score than chronic musculoskeletal pain disorders.[14,15] These results indicate that the CSI score of patients with back pain and/or multiple pain sites may be higher compared with that of patients with a single pain site in the limb.

CS-related symptoms are generally found in many chronic musculoskeletal pain disorders,[3,16–18] which indicate evidence of CS across miscellaneous chronic pain conditions.[19] However, higher CSI scores may be found even in patients with acute pain. Tanaka et al.[20] reported that the pain duration is not related to CSI severity levels. In addition, psychological factors, including depression and anxiety, are correlated with direct measures of CS,[7,21] and CS-related symptoms, including psychological factors, are found even in patients with acute pain.[22–24] These findings indicate that CS-related symptoms could be influenced not only by pain duration but also by interactions with other factors.

To date, although pain location and pain duration have been investigated separately, these 2 factors might be intricately related. Thus, these 2 factors were assessed simultaneously to examine the relationships between pain location and pain duration and CS-related symptoms. We hypothesized that evaluation of the combination of pain location and pain duration could be associated with a higher CSI score. Therefore, this study aimed to investigate the association between CS-related symptoms and pain location and/or pain duration in patients with musculoskeletal disorders.

METHODS

Ethical approval was obtained from the Institutional Ethics Committee of Konan Women's University (Approval no. 2018011). Written informed consent was obtained from all participants before the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Study Design

In this cross-sectional study, all data were collected from November 2015 to May 2019 from an orthopedic clinic in a primary care setting. Seven hundred two patients aged between 20 and 80 years were consecutively assessed for eligibility. Patients with musculoskeletal pain (eg, neck, shoulder, low back, hip, knee, and/or ankle pain) were included regardless of pain duration. Exclusion criteria were as follows: (1) diagnosis of cancer, multiple sclerosis, brain or spinal cord injury, history of stroke, and dementia; (2) poor Japanese comprehension; (3) patients who indicated "0" for pain intensity from the brief pain inventory (BPI) at initial assessment; and/or (4) patients with neuropathic pain diagnosed according to the algorithm of the IASP Special Interest Group on Neuropathic Pain.[25]

Measures

All participants who signed the informed consent form were assessed for demographic data (age, sex, height, and weight), pain duration, CS-related symptoms, health-related quality of life, pain intensity, and pain interference. In addition, participants were asked to indicate the place where they had pain by using a body chart in the BPI.

Brief Pain Inventory. Pain intensity and pain interference were assessed using the BPI. The BPI consists of 4 pain intensity and 7 pain interference items, which are rated using an 11-point scale (0 = no and 10 = worst [completely]).[26] The body chart in the BPI was used for

assessment of painful locations. Patients were asked to mark a painful site on the chart. Previous studies have demonstrated the validity and clinical utility of the BPI.[27,28] The Japanese version of the BPI was also validated.[29]

Central Sensitization Inventory. CS-related symptoms were assessed using the CSI. The CSI consists of 25 items about CS-related symptoms. The total score ranges from 0 to 100, with each item ranging from 0 to 4. The Japanese version of the CSI has been validated.[30]

EuroQol-5 Dimension. Health-related quality of life was assessed using the EuroQol 5-dimension (EQ5D).[31] It can generate a single index value for patients' health state, which is expressed in numbers ranging from 0 (dead) to 1 (full health). The Japanese value set was produced.[32]

Statistical Analyses

Categorization. For the analyses, the participants were categorized by 2 factors: pain location and pain duration. With regard to pain location, the participants were categorized into 3 groups based on their pain location on the body chart of the BPI: (1) spinal (including trunk), (2) limb, and (3) both spinal and limb. In the odds ratio (OR) analysis, the participants were divided into 2 groups: (1) spinal or limb, and (2) both spinal and limb. In addition, we categorized 2 groups (acute [< 3 months] or chronic [≥ 3 months]) based on pain duration.

Analyses. The differences in characteristics according to the groups of pain location (spinal, limb, and both spinal and limb) were assessed using the Kruskal-Wallis test with post hoc comparisons of Mann-Whitney *U* test for continuous variables and chi-square test for categorical variables. To assess the effects of pain location and pain duration on CSI score, we conducted a logistic regression analysis. The analysis was conducted using categorical CSI score (high: ≥ 40; and low: < 40) as dependent variable and pain location (both spinal and limb pain/spinal or limb pain) and pain duration (chronic pain/acute pain) as independent variables, with controlling for demographic data (age, sex, height, and weight). In addition, the associations between pain duration and pain location, and between higher CSI score (≥ 40) and combination of pain duration and pain location were assessed using the chi-square test. A significance level of $P < 0.05$ was used for the statistical analyses.

RESULTS

Characteristics of the Participants

Of the 702 participants, 65 patients were excluded based on the exclusion criteria: (1) history of diagnosis (ie, cancer and history of stroke; $n = 17$), (2) poor Japanese comprehension ($n = 14$), (3) patients who indicated "0" for pain intensity ($n = 13$), and (4) patients who indicated neuropathic pain ($n = 21$). In addition, 2 patients were excluded because of missing values. The remaining 635 patients were included in the analyses. Among all patients, 210 patients (33.1%) had pain for more than 3 months, and the prevalence of pain location was as follows: spinal = 162 patients (25.5%), limb = 301 patients (47.4%), and both spinal and limb = 172 patients (27.1%). With regard to categorization by pain duration, significant differences were found in age, proportion of women, and pain duration (all $P < 0.05$). In the categorization of pain location, significant differences were observed in age, proportion of women, height, and pain duration (all $P < 0.01$; Table 1). The details of the diagnoses were as follows: nonspecific low back pain = 122 patients (19.2%), osteoarthritis = 114 patients (18.0%), periarthritis of the shoulder = 71 patients (11.2%), nonspecific neck pain = 67 patients (10.6%), fracture = 52 patients (8.2%); and others = 209 patients (32.9%).

Comparison of Clinical Symptoms Based on Pain Duration and Pain Location

With regard to categorization by pain duration, the median score (interquartile range) of CSI scores and pain intensity in patients with chronic pain were significantly higher than those in patients with acute pain (CSI: acute = 19.0 [16.0], chronic = 22.0 [19.0], $P < 0.01$; pain intensity: acute = 2.5 [2.3], chronic = 3.0 [2.3], $P < 0.05$), whereas no significant differences were found in the EQ5D and pain interference (both $P > 0.05$). On the other hand, the CSI score, pain intensity, and pain interference in the "both spinal and limb" group were significantly higher than those in the "spinal" and "limb" groups (all $P < 0.05$). The EQ5D in the both spinal and limb group was significantly lower than that in the spinal group ($P < 0.01$; Table 1).

Table 1. Characteristics of the Participants

Variables	Pain Duration			Pain Location			
	Acute $n = 425$	Chronic $n = 210$	*P* Value	Spinal[1] $n = 162$	Limb[2] $n = 301$	Both Spinal and Limb[3] $n = 172$	*P* Value
Age (year)	51.3 ± 15.4	55.8 ± 13.5	< 0.01	46.8 ± 15.2[2,3]	54.6 ± 14.6[1]	55.3 ± 13.7[1]	< 0.01
Female *n* (%)	263 (61.9)	148 (70.5)	< 0.05*	84 (20.4)	212 (51.6)	115 (28.0)	< 0.01*
Height (cm)	162.4 ± 8.6	161.2 ± 8.7	0.08	164.3 ± 8.5[2,3]	161.0 ± 8.5[1]	161.5 ± 8.8[1]	< 0.01
Weight (kg)	60.1 ± 12.8	59.6 ± 11.6	0.63	60.7 ± 13.5	59.2 ± 12.1	60.5 ± 11.8	0.32
body mass Index (kg/m^2)	22.7 ± 3.8	22.6 ± 3.3	0.13	22.4 ± 4.0	22.7 ± 3.7	23.1 ± 3.3	0.23
Pain duration (weeks)	3.6 ± 2.2	79.8 ± 146.2	< 0.01	29.7 ± 98.9[2,3]	18.0 ± 44.6[1,3]	46.9 ± 132.9[1,2]	< 0.01
CSI score	19.0 (16.0)	22.0 (19.0)	< 0.01	19.0 (16.0)[3]	17.0 (13.0)[3]	25.0 (18.8)[1,2]	< 0.01
EQ5D	0.724 (0.120)	0.724 (0.120)	0.43	0.768 (0.080)[2,3]	0.724 (0.120)[1]	0.705 (0.140)[1]	< 0.01
Pain intensity (BPI)	2.5 (2.3)	3.0 (2.3)	< 0.05	2.6 (2.0)[3]	2.5 (2.1)[3]	3.7 (2.5)[1,2]	< 0.01
Pain interference (BPI)	2.0 (2.9)	2.0 (3.0)	0.54	1.9 (2.9)[3]	1.9 (2.7)[3]	2.6 (3.9)[1,2]	< 0.01

BPI, brief pain inventory; CSI, central sensitization inventory; EQ5D, EuroQol-5 dimension.
Values are numbers (percent values) for categorical variables and mean ± SD or median (interquartile range) for continuous variables unless otherwise indicated. Superscript numbers indicate which groups significantly differed from each other in post hoc comparison.
*Assessed by chi-square test.

Effects of Pain Location and Pain Duration on Higher CSI Score

Table 2 shows ORs and 95% confidence intervals (CI) from logistic regressions of CSI high score that adjust for the patients' demographic data (age, sex, height, and weight). No significant interaction between pain location and pain duration was found on CSI score ($P > 0.05$). Compared with patients with spinal or limb pain, patients with both spinal and limb pain were significantly associated with higher CSI score (OR = 2.64, 95% CI = 0.11 to 0.86, $P = 0.01$). However, the OR for higher CSI score in pain duration (≥ 3 m/< 3 m) was not significant (OR = 1.31, 95% CI = 0.57 to 3.01, $P = 0.52$).

Associations Between Pain Duration and Pain Location, and Between CSI Score and the Combination of These Factors

A significant relationship was found between pain duration and pain location (chi-square [2] = 18.94, $P < 0.01$, Cramer's $V = 0.17$). More patients with chronic pain were in the both spinal and limb group (adjusted residual = 4.01; Table 3). In addition, a significant relationship existed between whether the CSI score was higher than 40 and the combination of the 2 factors (chi-square [5] = 25.04, $P < 0.01$, Cramer's $V = 0.20$). The prevalence of higher CSI score (≥ 40) in the combination of chronic and "both spinal and limb" pain was high ($n = 18$, 23.1%, adjusted residual = 4.48; Table 4).

Table 2. Effects of Pain Location and Pain Duration on Higher CSI Score

	Adjusted OR (95% CI)	*P* Value
Duration		
Acute (< 3 m)	Ref.	
Chronic (≥ 3 m)	1.31 (0.57 to 3.01)	0.52
Location		
Spinal or limb	Ref.	
Both spinal and limb	2.64 (0.11 to 0.86)	0.01

95% CI, 95% confidence interval; CSI, central sensitization inventory; OR, odds ratio. Adjusted for age, sex, height, and weight. *P* value for interaction = 0.44.

DISCUSSION

This study explored the association between CS-related symptoms and pain location and/or pain duration in patients with musculoskeletal disorders. No interaction was found between pain location and pain duration on CSI score. However, the OR for CSI high score (≥ 40) in pain location (2.64) was higher than that in pain duration (1.31). In addition, the combination of both

Table 3. The Association Between Pain Duration and Pain Location

Pain Location	Pain Duration		Chi-square	Cramer's *V*
	Acute (< 3 m) $n = 425$	Chronic (≥ 3 m) $n = 210$		
Spinal	124 (76.5) *3.0*	38 (23.5) *−3.0*	18.94*	0.17
Limb	207 (68.8) *0.9*	94 (31.2) *−0.9*		
Both spinal and limb	94 (54.7) *−4.0*	78 (45.3) *4.0*		

Values indicate number of patients (percent values). Adjusted standardized residuals are indicated in italics below group frequencies.
*$P < 0.01$.

Table 4. The Association Between Higher CSI Score and Combination of Pain Duration and Pain Location

	CSI Score			
	CSI < 40	CSI ≥ 40	Chi-square	Cramer's *V*
Acute/spinal pain	118 (94.4)	7 (5.6)	25.04*	0.20
	1.6	*−1.6*		
Chronic/spinal pain	33 (89.2)	4 (10.8)		
	−0.3	*0.3*		
Acute/limb pain	194 (93.7)	13 (6.3)		
	1.8	*−1.8*		
Chronic/limb pain	89 (94.7)	5 (5.3)		
	1.4	*−1.4*		
Acute/both spinal and limb pain	82 (87.2)	12 (12.8)		
	−1.3	*1.3*		
Chronic/both spinal and limb pain	60 (76.9)	18 (23.1)		
	−4.5	*4.5*		

CSI, central sensitization inventory.
Values indicate number of patients (percent values). Adjusted standardized residuals are indicated in italics below group frequencies.
*$P < 0.01$.

spinal and limb pain and chronic pain indicated a higher prevalence of 40-point CSI score or more than the other combinations. Therefore, the combination of these 2 factors is an important clue that points to CS-related symptoms.

This study is the first to examine the influence of pain location and pain duration simultaneously on CS-related symptoms. We hypothesized that pain location and pain duration mutually affect the CSI scores. However, the interaction between pain location and pain duration on higher CSI score was not significant. In addition, the CSI score was significantly affected by pain location, whereas not significantly affected by pain duration. We considered that pain location independently influenced CS-related symptoms. Our findings supported some previous studies, which investigated the influence of pain location and pain duration on CSI, respectively. With regard to pain location, these showed that pain area was correlated with higher CSI score,[33] and CSI score of the patients with pain in 2 or more localization was higher than that of the patients with one localized pain.[34] The study by van Wilgen et al.[35] showed that widespread pain contributed to the variance in CSI score. In the present study, pain area may include the effect of peripheral sensitization, whereas pain distribution in the both spinal and limb may reflect generalized hypersensitivity, which is based on CS rather than peripheral sensitization. With regard to pain duration, our findings supported some previous studies that showed the possibility that CS-related symptoms are described in the acute phase.[22,24] In addition, CSI scores were not related to pain duration in patients with chronic and subacute pain.[35,36] Furthermore, signs of CS were found during the acute phase, which is the harbinger of chronicity when combined with psychological factors.[37] Actually, approximately 8% of the patients with acute pain indicated a 40-point CSI score or more, despite 13% in patients with chronic pain in the present study. Therefore, CSI score was not significantly affected by pain duration and the OR for high CSI score in pain duration was lower than that in pain location. Our findings suggested that the CSI score reflected pain location more than the pain duration even if the association with these 2 factors in CSI score investigated simultaneously.

The chi-square test on the associations between pain duration and pain location revealed that more patients with chronic pain were in the both spinal and limb group. Boudreau et al.[38] also reported that expanded pain distribution is associated with longer pain duration. In addition, the proportion of patients who indicated high CSI score (≥ 40) was higher in the combination of chronic and both spinal and limb pain than other combinations, which indicated the usefulness of evaluating the combination of those 2 factors. These findings supported a previous study that showed that CS is associated with a transition from acute localized pain to chronic widespread pain.[39] Our findings suggest that pain in both spinal and limb is likely to have CS-related symptoms, particularly in patients with chronic pain.

With regard to the relationship between clinical symptoms and pain location and pain duration, patients with expanded pain distribution and chronic pain indicated worse clinical symptoms. However, the effect of these 2 factors on clinical symptoms was slightly different. The patients who had both spinal and limb pain indicated lower EQ5D score and higher BPI score (both pain intensity and pain interference) than the patients who had pain in the spine or limb. On the other hand, patients with chronic pain had higher scores only in pain intensity than those with acute pain. However, the difference in the median score was merely 0.5 points. These findings were consistent with those of a previous study that showed expanded pain areas are related to more severe symptoms,[40,41] and clinical symptoms (EQ5D, pain intensity, and pain interference) in patients with acute pain vary in a manner similar to that in patients with chronic pain.[20]

To the best of our knowledge, this study is the first to examine the effect of both pain location and pain duration on CS-related symptoms. Our findings provide the benefit of evaluating the combination of these 2 factors on CS-related symptoms, which indicates that brief assessments

might prevent symptom complicatedness. However, categorization by pain location into 3 groups (ie, "spinal," "limb," and "both spinal and limb") was performed in the present study, and pain location in the arm and leg was placed in the same group. Further study is warranted to examine the difference in effect on CS-related symptoms by more detailed pain location.

The present study has several limitations. First, this was a cross-sectional study. Hence, a causal relationship between CS-related symptoms and pain location and/or pain duration was unknown. Further research is necessary to reveal causality in clinical practice. Second, the participants were not limited by particular diseases, such as fibromyalgia and osteoarthritis, and our study included patients with various symptoms. However, examination, including several diseases, may increase clinical utility because clinicians should treat patients with several diseases in clinical practice. Third, we excluded the patients who indicated overt neuropathic pain because neuropathic pain itself could be the reason for the higher CSI score. However, the patients with neuropathic pain could be included in the clinical setting, so further study targeting patients with neuropathic pain is needed. Fourth, the way of grouping by pain location (spinal, limb, and both spinal and limb pain) in the present study was original, which might have implications for the generalizability of findings. Finally, pain location was assessed using only a self-reported questionnaire in this study.

CONCLUSION

Pain location independently influenced CSI scores, and the combination of both spinal and limb pain and chronic pain indicated high CSI scores. Our findings revealed the usefulness of evaluating both pain location and pain duration. It is important for clinicians to be able to easily assess the possibility of having CS-related symptoms.

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CONFLICT OF INTEREST

The authors report and confirm that there is no conflict of interest.

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