How do central sensitisation features affect symptoms among patients with rheumatoid arthritis? Analysis of pain descriptors and the effect of central sensitivity syndrome on patient and evaluator global assessments

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Abstract

Objective

Central sensitivity syndrome (CSS) comprises various symptoms caused by central sensitisation (CS). Using the central sensitisation inventory (CSI), a screening questionnaire developed for detecting CSS, this syndrome was recently identified in patients with long-standing rheumatoid arthritis (RA). However, the descriptors of CS-related pain and the effects of CSS on symptoms in patients with rheumatoid arthritis (RA) remain unknown. We examined the characteristics of pain and influence of CSS on patient and evaluator global assessment among multiple clinical variables.

Methods

We used the central sensitisation inventory (CSI) and short-form McGill pain questionnaire to evaluate CSS and characteristics of pain in 240 outpatients with RA. Disease activity, fibromyalgia, neuropathic pain, anxiety, depression, pain catastrophising, and health-related quality of life were evaluated. We used multivariate analysis to analyse the characteristics of CS-related pain according to CSI and the effect of CSS on patient global assessment (PGA), evaluator global assessment (EGA), and PGA minus EGA among relevant clinical variables.

Results

In patients with RA, the main descriptors of pain according to severity of CSI scores were "sharp" and "stabbing", whereas those of pain according to disease activity were "tender" and "throbbing". CSS was associated with EGA ($p=0.000$, $\beta=-0.199$) and PGA minus EGA ($p=0.021$, $\beta=0.147$), but not with PGA.

Conclusion

In patients with RA, descriptors for CS-related pain differ from those for disease activity-related pain. CSS may have an important impact on EGA and PGA minus EGA. Additionally, CSI may be helpful in identifying why there is discordance between PGA and EGA.

Key words

rheumatoid arthritis, central sensitisation, nociplastic pain, patient-reported outcome

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Introduction

Rheumatoid arthritis (RA), a chronic inflammatory disorder, mainly affects synovial tissue. The primary symptoms are caused by inflammation and deformity and include joint tenderness, swelling, and impaired quality of life (1). Chronic joint inflammation often causes various accessory symptoms, including pain, general fatigue, depression, anxiety, insomnia, and loss of appetite (2). RA activity is evaluated by evaluator global assessment (EGA), which comprises assessing the primary symptoms/indicators of RA, including the swollen joint count (SJC) and markers of inflammation, and by patient global assessment (PGA), in which both the abovementioned accessory characteristics and primary symptoms are assessed (3). Inconsistencies between PGA and EGA have been the focus of assessment of RA activity. Previous studies have reported that these inconsistencies can be attributable to the tendency of patients to emphasise symptoms, which are by nature subjective; whereas evaluators tend to emphasise objective indicators, such as SJC or markers of inflammation (4). Therefore, evaluation of symptoms by patients with RA has becoming increasingly important (5).

Recent studies have reported the phenomenon of central sensitisation (CS), which may cause symptoms such as pain, depression, and anxiety in patients with RA; CS is assessed using functional magnetic resonance imaging or quantitative sensory testing (6, 7). In addition, use of the central sensitivity inventory (CSI) has reportedly resulted in identification of central sensitisation syndrome (CSS), a syndrome comprising various symptoms caused by CS, in patients with long-standing RA (8, 9, 10). However, it remains unclear when the CSI should be used in patients with RA in daily practice. In a previous study, we found a clear discordance between PGA and EGA in patients with RA and CSS (PGA 38.9 ± 28.1 mm, EGA 13.9 ± 13.8 mm) (10). We therefore hypothesised that PGA, EGA, or discordance between PGA and EGA are associated with development of CSS.

In 2016, the term "nociplastic pain", a third pain descriptor to be added to nociceptive and neuropathic pain, was proposed (11). This term was added to the taxonomy of the International Association for the Study of Pain in 2017 (12). Nociplastic pain is defined as "pain that arises from altered nociception despite no clear evidence of actual or threatened tissue damage causing the activation of peripheral nociceptors or evidence for disease or lesion of the somatosensory system causing the pain" (12). The major mechanism of nociplastic pain is thought to be peripheral and/or central sensitisation (13). In our previous study, we showed that, among patients with relatively inactive RA and long disease duration, CSS is not associated with evidence of inflammation, such as erythrocyte sedimentation rate (ESR) and SJC (10). We therefore concluded that peripheral sensitisation caused by inflammation was unlikely to be involved in the mechanism of nociplastic pain. The pain of RA patients sometimes includes all three of the abovementioned types of pain, resulting in mixed pain states (10, 14, 15). However, the characteristics of nociplastic pain among RA patients has been unclear. It is important that clinicians familiarise themselves with the pain descriptors for nociplastic pain (pain due to CS). Given that nociplastic pain is due to CS, we hypothesised that pain descriptors for CS-related pain according to the CSI differ from those associated with disease activity in RA patients.

In this study, we examined descriptors for CS-related pain and the effects of CSS (CSI ≥40) on PGA, EGA, and PGA minus EGA among relevant clinical variables and calculated an optimal cut-off value for predicting CSS based on our previous data (10).

Materials and methods

Study cohort and design

The study design and characteristics of all patients have been described previously (10). We conducted a study with 240 outpatients with established RA (16) who were undergoing long-term follow-up (>6 months from RA onset) at The Jikei University Hospital from May 2017 to September 2018. The Japanese version of the CSI (17) was used to identify CSS. It examines 25

symptoms related to CSS. Each item is scored from 0 to 4, the overall score ranging from 0 to 100. An overall CSI score ≥40 is diagnostic of CSS. The quality of pain was assessed using the Short-Form McGill Pain Questionnaire (SF-MPQ) (18). The SF-MPQ includes 11 sensory terms (throbbing, shooting, stabbing, sharp, cramping, gnawing, hot/burning, aching, heavy, tender, and splitting) and four emotional terms (tiring/exhausting, sickening, fearful, and punishing/cruel). The respondents rate each of these terms from 0 (none) to 3 (severe). Clinical and patient-reported outcomes were also evaluated, as described previously (10). We selected the following variables: age, sex, body mass index (BMI) as patient characteristics; disease duration as clinical information; Steinbrocker stage as a measure of structural damage; EGA (0–100 mm), PGA (0–100 mm), pain visual analogue scale (Pain VAS) (0–100 mm), SJC, tender joint count (TJC), C-reactive protein, ESR (19), and modified health assessment questionnaire disability index (mHAQ-DI) (20) scores as measures of physical function; anticyclic citrullinated peptide antibody (ACPA) as an indicator of immunological abnormality; fibromyalgia symptom (FS) (21) scale score as a measure of fibromyalgia; painDETECT (PDQ) (22) questionnaire score as a measure of neuropathic pain-like symptoms; pain catastrophising scale (PCS) (23) score as a measure of pain catastrophising; scores on the hospital anxiety and depression scale (HADS) (24) and physical component (PC), mental component (MC), and role-social component (RC) summaries of the 36-item short (SF-36) (25) form health survey as indicators of health-related quality of life (HRQOL). This study was performed in accordance with the Helsinki Declaration of 1975, as revised in 1983. Approval for the study was obtained from the ethics committee of the Jikei University School of Medicine (approval no. 28-329[8572]). Written informed consent was obtained from all patients.

Statistics

To assess differences in characteristics of CS-related and disease activity-related pain in patients with RA, we performed multivariate linear regression analysis with a backward stepwise procedure using CSI score or Disease Activity Score-28 for Rheumatoid Arthritis with ESR (DAS28 [ESR]) as the objective variable together with each item on the SF-MPQ. To analyse the degree to which CSS affects PGA, EGA, or discordance between PGA and EGA among the various clinical variables, we defined discordance between PGA and EGA as PGA minus EGA (calculated as PGA minus EGA) and performed multivariate linear regression analysis with a backward stepwise procedure using PGA, EGA, and PGA minus EGA as objective variables. We selected the following variables: age; sex; BMI; disease duration; Steinbrocker stage; SJC; TJC; pain VAS, ESR; mHAQ-DI score; ACPA; FS score; PCS score; PDQ score; HADS score; PC, MC, and RC on SF-36; and CSS. We used standardised β to compare the strengths of the relationships. Area under the curve (AUC), cut-off value, sensitivity, and specificity of PGA minus EGA for detecting CSS were identified using receiver-operating characteristic (ROC) curves and Youden index analysis. These analyses were performed using Stata 13.0 (Stata Corp, College Station, TX, USA) and EZR (Easy R), which is a modified version of R commander designed to add statistical functions that are frequently used in biostatistics (26). Statistical significance was set at $p<0.05$.

Results

Multivariate linear regression analysis of pain descriptors contributing to CSI score and DAS28 (ESR)

We enrolled 240 Japanese patients (63 men and 177 women; mean age 59.7±14.3 years). The mean disease duration and activity scores according to DAS28 (ESR) were 9.58±7.76 years and 2.39±1.7, respectively. Eighteen of 240 patients (7.5%) had CSI scores ≥40 and were accordingly classified as having CSS (10). Tables I and II show the results of multivariate linear logistic regression analysis. "Heavy", "sharp", "stabbing", "shooting", and "splitting" were identified as the most important pain descriptors associated with CSI scores. "Heavy" (p=0.000, β=0.246), "sharp" (p=0.003, β=0.227), "stabbing" (p=0.026, β=0.193), and "splitting" (p=0.026, β=-0.174) were significantly associated with CSI scores (Table I), whereas "heavy" (p=0.001, β= 0.257), "tender" (p=0.004, β= 0.204), "throbbing" (p=0.015, β=0.172), and "splitting" (p=0.024, β=-0.173) were significantly associated with DAS28 (ESR) (Table II).

Table I. Multivariate linear regression analysis of pain descriptors contributing to CSI score.

	Adjusted standardised β	*p*-value
Heavy	0.246	0.000
Sharp	0.227	0.003
Stabbing	0.193	0.026
Shooting	0.124	0.074
Splitting	–0.174	0.026

CSI: central sensitisation inventory.

Table II. Multivariate linear regression analysis of pain descriptors contributing to DAS28 (ESR).

	Adjusted standardised β	*p*-value
Heavy	0.257	0.001
Tender	0.204	0.004
Throbbing	0.172	0.015
Splitting	-0.173	0.024

DAS: disease activity score; ESR: erythrocyte sedimentation rate.

Results of multivariate linear regression analysis of various clinical variables affecting PGA, EGA, and PGA minus EGA

Tables III, IV, and V show the results of the multivariate linear logistic regression analysis. Pain VAS (p=0.000, β=0.537), BMI (p=0.001, β=0.157), mHAQ-DI (p=0.014, β=0.121), ESR (p=0.008, β=0.120), MC of SF-36 (p=0.000, β=-0.213), and RC of SF-36 (p=0.010, β=-0.118) were significantly associated with PGA (Table III). SJC, PDQ score, Pain VAS, TJC, BMI, ESR, CSS, PC of SF-36, and MC of SF-36 were identified as the most important variables associated with EGA. SJC (p=0.000, β=0.377), PDQ score (p=0.000, β=0.206), Pain VAS (p=0.003, β=0.186), TJC (p=0.003, β=0.150), BMI (p=0.024, β=0.105),

Table III. Multivariate linear regression analysis of clinical variables contributing to PGA.

	Adjusted standardised β	*p*-value
Pain VAS	0.537	0.000
BMI	0.157	0.001
mHAQ-DI	0.121	0.014
ESR	0.120	0.008
MC (SF-36)	-0.213	0.000
RC (SF-36)	-0.118	0.010

BMI: Body Mass Index; ESR: erythrocyte sedimentation rate; MC: mental component summary; mHAQ-DI: modified Health Assessment Questionnaire Disability Index; Pain VAS score: pain visual analogue scale score; PGA: patient global assessment; RC: role-social component summary; SF-36: 36-item short-form health survey.

Table IV. Multivariate linear regression analysis of clinical variables contributing to EGA.

	Adjusted standardised β	*p*-value
SJC	0.377	0.000
PDQ score	0.206	0.000
Pain VAS	0.186	0.003
TJC	0.150	0.003
BMI	0.105	0.024
ESR	0.0839	0.075
CSS (CSI score >40)	-0.199	0.000
PC (SF-36)	-0.139	0.014
MC (SF-36)	-0.119	0.020

BMI: Body Mass Index; CSI: central sensitisation inventory score; CSS: central sensitivity syndrome; EGA: evaluator global assessment; ESR: erythrocyte sedimentation rate; MC: mental component summary; Pain VAS score: pain visual analogue scale score; PC: physical component summary; PDQ: painDETECT questionnaire; SF-36: 36-item short-form health survey; SJC: swollen joint count; TJC: tender joint count.

Table V. Multivariate linear regression analysis of clinical variables contributing to PGA minus EGA.

	Adjusted standardised β	*p*-value
Pain VAS	0.439	0.000
CSS (CSI score >40)	0.147	0.021
SJC	-0.217	0.000
PDQ score	-0.185	0.009
MC (SF-36)	-0.149	0.018
RC (SF-36)	-0.115	0.055

CSI: central sensitisation inventory; CSS: central sensitivity syndrome; EGA: evaluator global assessment; HADS-D: hospital anxiety and depression scale-depression; MC: mental component summary; PGA: patient global assessment; Pain VAS score: pain visual analogue scale score; PDQ: painDETECT questionnaire; RC: role-social component summary; SF-36: 36-item short-form health survey; SJC: swollen joint count.

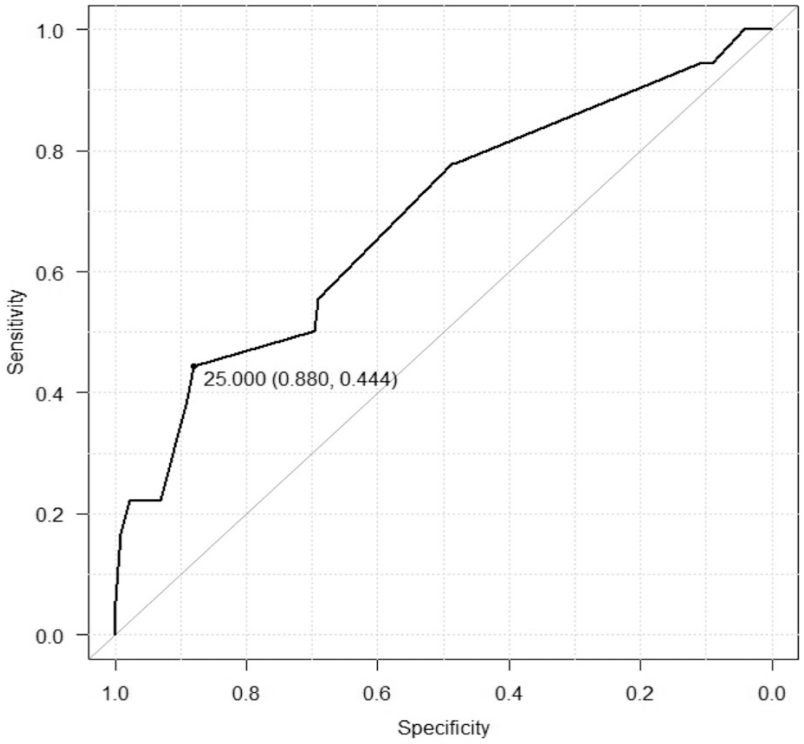

Fig. 1. Results of ROC analysis of PGA minus EGA for predicting CSS.
ROC analysis revealed the AUC and optimal cut-off value (black dot) of ≥25 for PGA minus EGA regarding screening for CSS, with 44.4% sensitivity and 88.0% specificity.
AUC: area under the curve; CSS: central sensitivity syndrome; EGA: evaluator global assessment; PGA: patient global assessment; ROC: receiver-operating characteristic curve.

CSS (p=0.000, β=-0.199), PC of SF-36 (p=0.014, β=-0.139), and MC of SF-36 (p=0.020, β=-0.119) were significantly associated with EGA (Table IV). Pain VAS, CSS, SJC, PDQ score, MC of SF-36, and RC of SF-36 were identified as the most important variables associated with PGA minus EGA. Pain VAS (p=0.000, β=0.419), CSS (p=0.021, β=0.147), SJC (p=0.000, β=-0.217), PDQ score (p=0.009, β=-0.185), and MC of SF-36 (p=0.018, β=-0.149) were significantly associated with PGA minus EGA (Table V).

Cut-off value for PGA minus EGA for CSS screening

Figure 1 shows the AUC (68.8%, CI: 55.0–82.7%) and optimal cut-off value (black dot) for PGA minus EGA regarding screening for CSS. PGA minus EGA ≥25 was determined as the optimal cut-off value, with 44.4% sensitivity and 88.0% specificity.

Discussion

To the best of our knowledge, this study is the first to identify associations between CSS and PGA, EGA, and PGA minus EGA in Japanese patients with long-standing RA. The symptoms of CSS include accessory symptoms of RA, such as depression, anxiety, and pain. Therefore, we expected that CSS would be associated with PGA, which reflects symptoms, rather than EGA, which reflects objective findings. In contrast, we found that CSS does not affect PGA, but negatively affects EGA. We have previously shown that CSS is negatively associated with EGA (p=0.008, odds ratio 0.860, 95% confidence interval: 0.770–0.962) (10), indicating that EGA and CSS influence each other negatively.

The causes of discordance between PGA and EGA reported thus far include pain, SJC, fatigue, depression, decreased HRQOL, and functional impairment (27, 28, 29). Consistent with this, we found associations between pain, SJC, and decreased MC on SF-36 and PGA minus EGA. CSS was also positively associated with PGA minus EGA, but not as strongly as Pain VAS, SJC, and MC on SF-36. In addition, we

found that evaluators tend to emphasise SJC, whereas patients tend to emphasise Pain VAS and MC on SF-36, as previously reported (4). Additionally, we found that the gap between evaluators and patients in recognising activity of RA, namely, SJC, Pain VAS, and MC on SF-36, corresponds with discordance between PGA and EGA. We believe that evaluators do not generally regard CSS as denoting activity of RA and that the negative effects of CSS on EGA may explain the discordance between PGA and EGA. It has recently been reported that evaluators perceive patients with fibromyalgia caused by CS as more difficult than patients with RA (30). This difference in evaluators' perception of RA versus fibromyalgia may contribute to the negative association between CSS and EGA.

We attempted to use PGA minus EGA to predict CSS. In our previous study, we identified associations between CSS and widespread pain, anxiety, and decreased HRQOL (10). In the light of these findings, we hypothesised that using PGA minus EGA would assist clinical prediction of CSS. We identified PGA minus EGA ≥25 as the optimal cut-off value for detecting CSS; this value has low sensitivity and high specificity. Patients with PGA minus EGA ≥25 may be at considerable risk of having CSS.

Next, we discuss the pain descriptors of RA. We showed that, among RA patients, the descriptors of CS-related pain (nociplastic pain) in part differ from the descriptors of disease activity. The pain descriptors "throbbing" and "tender" were characteristically used for disease activity. Pain descriptors for arthritis reportedly include "throbbing", "hot/burn", "sore", "tender", "puffy", "stretched to pieces", and "inside of knee is growing" (31, 32). "Throbbing" is typically used for inflammation-associated pain, whereas "tender" indicates peripheral sensitisation caused by local inflammation. Therefore, these terms are used as descriptors of nociceptive pain, as reported previously. Because patients with CS are sometimes anxious and depressed, both of which can result in affective symptoms, we expected that the descriptors of CS-related pain would include terms used for affective pain. However, the descriptors of CS-related pain in patients with RA were not those used for affective pain; rather, they were "sharp" and "stabbing". Descriptors of CS-related pain among RA patients have not yet been reported. Reported descriptors of CS-related pain include "heavy", "tingling", "throbbing", "dull", "deep" and "aching" (33, 34); these descriptors differ from those used by RA patients for CS-related pain. "Sharp" is reportedly one of the terms used for arthralgia regardless of presence or degree of inflammation, whereas "stabbing" is used for arthralgia with less inflammation (32). CS could exacerbate pre-existing RA-related pain because CS is defined as "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" (35). Hence, the phenotypes of CS with and without RA may differ. Our RA patients commonly used "heavy" and "non splitting" to describe both CS- and disease activity-related pain. It has recently been reported that, among RA patients with fibromyalgia, functional MRI has shown strong associations between ESR and functional connectivity between the left inferior parietal lobe and pain matrix, including insula, dorsal anterior cingulate, medial prefrontal cortex, the latter being related to fibromyalgia (35, 36). These findings indicate that peripheral inflammation caused by RA leads to fibromyalgia, which is typically caused by CS, by mediating pronociceptive patterns of brain connectivity. Thus, these findings may explain the similar phenotypes of CS- and disease activity-related pain among RA patients. Further studies are needed to identify the factors associated with CS in RA patients. Considering the common pathogenesis of RA activity and CS, rheumatologists may need to more strongly recognise the role of CS in development of symptoms of RA.

Our study had several limitations. First, there were too few patients with CSS (n=18) to calculate a precise cut-off value. Moreover, the ROC curve was close to the case line. These findings therefore need to be validated in studies with larger cohorts. Second, our study patients with RA were all Japanese individuals with relatively low disease activity and long disease duration. Because the prevalence of CSS may vary with race and disease duration, our findings may not be applicable to non-Japanese patients with RA or to those in an early, highly active phase of RA. Multicenter studies to resolve this issue should be conducted worldwide. Third, CS is not included in the definition of nociplastic pain. However, we believe that the pain phenotype of CSS is similar to that of nociplastic pain because of the underlying mechanism (namely CS) of nociplastic pain.

In conclusion, the characteristics of CS-related pain differ from those of disease activity-related pain among RA patients. CSS may be an important contributor to EGA and PGA minus EGA. Additionally, the CSI may be helpful in identifying the cause of discordance between PGA and EGA.

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