Central sensitisation features are associated with neuropathic pain-like symptoms in patients with longstanding rheumatoid arthritis: a cross-sectional study using the central sensitisation inventory

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Abstract

Objective

Several studies have indicated that arthralgia may be driven by central sensitisation. Central sensitivity syndrome (CSS) is a concept that unifies various symptoms due to central sensitisation. Recently, the central sensitisation inventory (CSI) was developed as a screening questionnaire to detect CSS. Using the CSI, we examined the prevalence, the clinical characteristics of CSS, and the association between CSS and neuropathic pain (NP)-like symptoms among rheumatoid arthritis (RA) patients.

Methods

The CSI was administered to 240 RA outpatients. We evaluated their disease activity and several potentially relevant patient-reported outcomes. We compared the clinical parameters depending on the severity of CSS and examined the effect of the CSI score on NP-like symptoms among the relevant clinical parameters using multivariate analyses.

Results

The mean disease duration was 9.58 ± 7.76 years. Eighteen (7.5 %) patients had CSS, which was associated with evaluator global assessment (EGA) (odds ratio (OR) 0.860); fibromyalgia symptom scale (OR 1.46); painDETECT questionnaire score (OR 1.24); hospital anxiety and depression scale-anxiety (OR 1.35); and physical (OR 0.898), mental (OR 0.828), and role-social (OR 0.946) component summary scores on the Short-Form 36-Item Health Survey. CSI score was the factor that contributed most to NP-like symptoms ($p=0.000$, $\beta=0.266$).

Conclusion

NP-like symptoms might be one of the symptoms of CSS in longstanding RA patients. In longstanding RA patients who have disproportionately greater NP-like symptoms and/or widespread pain compared with degree of inflammation, detecting CSS using CSI might help to understand the pathogenesis of patients.

Key words
rheumatoid arthritis, central sensitisation, neuropathic pain, fibromyalgia

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that affects mainly the synovial tissue due to immune abnormalities. Synovial proliferation and inflammation cause the destruction of cartilage and bone, which ultimately lead to deformity (1). The typical symptoms caused by inflammation and deformity include joint tenderness, swelling, and impaired quality of life. Chronic inflammation in the joints can often cause various subjective symptoms, including pain, general fatigue, depression, anxiety, insomnia, and appetite loss (2).

Recent progress in the treatment of RA, such as methotrexate and biologics, has enabled most RA patients to achieve low disease activity or remission (3, 4). However, a proportion of patients continue to experience persistent subjective symptoms, such as pain, despite improvements in objective inflammation markers, such as swollen joint count (SJC), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) (5). Moreover, it is often difficult for clinicians to determine the pathogenesis and offer the correct treatment (6).

Central sensitisation is defined by the International Association for the Study of Pain as "increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input" (7). It has been reported that in OA patients, one of the reasons for intractable pain is central sensitisation (8-10). Several reports have shown that central sensitisation occurs in RA patients (11-13). However, the sample size is relatively small in these reports because the evaluation of central sensitisation was mainly performed using either functional magnetic resonance imaging or quantitative sensory testing (QST) (14), which are not routinely performed by clinicians. Therefore, we cannot fully recognise the clinical characteristics, prevalence, and severity of RA patients who have central sensitisation, even though central sensitisation might be one of the causes of intractable pain in RA patients. Additionally, we have recently reported that neuropathic pain (NP)-like symptoms were found in longstanding RA patients, and we speculated that the symptoms might be due to central sensitisation (15). However, the association between central sensitisation and NP-like symptoms has not yet been elucidated.

The concept of central sensitivity syndrome (CSS) was established by Yunus in 2007 (16). CSS is the unification of various syndromes that are caused by central sensitisation, which comprise fibromyalgia syndrome, chronic fatigue syndrome, irritable bowel syndrome, tension-type headache, migraine, temporomandibular disorder, myofascial pain syndrome, restless legs syndrome, periodic limb movements in sleep, multiple chemical sensitivity, primary dysmenorrhea, female urethral syndrome, interstitial cystitis, posttraumatic stress disorder, and depression. To detect patients who have CSS, the central sensitisation inventory (CSI) was recently developed by Mayer (17) and clinically relevant severity levels were established by Neblett (18). The CSI is now validated in English, Japanese, Italian, and Dutch (19-21).

Taking these factors into consideration, we hypothesised that CSS using the CSI will be associated with NP-like symptoms. We therefore examined the characteristics of CSS and the association between CSS and NP-like symptoms using the CSI in RA patients.

Patients and methods

Study population and design

We conducted a study of 240 outpatients with established RA (according to the American College of Rheumatology/European League Against Rheumatism criteria) (22) who were being followed-up long term (more than 6 months from the onset of RA) at Jikei University Hospital from May 2017 to September 2018. Patients who had objective findings of sensory damage in neuroanatomically innervated regions were excluded from the study. CSS was evaluated using the CSI. Clinical and patient-reported outcomes were also evaluated. We classified RA patients into three groups according to the CSI results: those with CSS, with mild CSS, and without CSS. We then compared clinical and patient-reported outcomes

between the groups. We performed this study according to the Helsinki Declaration of 1975, as revised in 1983. Approval for the study was obtained from the Ethics Committee of Jikei University School of Medicine (approval no. 28-329 [8572]). All patients provided written informed consent.

Variables

Demographic data (age, sex, and body mass index [BMI]) and clinical information, including disease duration, Steinbrocker stage, positivity of anti-cyclic citrullinated peptide antibody (ACPA), were collected from the patients' medical records. In addition, we evaluated clinical and patient-reported outcomes, as described in the following sections.

Clinical assessment of disease activity

We evaluated the tender joint count (TJC) and SJC for 28 joints, evaluator global assessment (EGA), patient global assessment (PGA), pain visual analogue scale (VAS), CRP, and ESR at the time of the patient's visit to the outpatient clinic. We calculated the disease activity score for 28 joints with the erythrocyte sedimentation rate (DAS28 ESR), with CRP (DAS28 CRP), the clinical disease activity index (CDAI), and the simplified disease activity index (SDAI) (23). Physical function was evaluated using the Modified Health Assessment Questionnaire Disability Index (mHAQ-DI) (24).

Central sensitisation inventory

CSS was assessed with the Japanese version of the CSI (19). The CSI consists of parts A and B. Part A examines 25 symptoms related to CSS. Each item is scored from 0 to 4, with the overall score ranging from 0 to 100. An overall score ≥40 indicates the presence of CSS. The CSI is divided into five categories of severity: subclinical (0 to 29); mild (30 to 39); moderate (40 to 49); severe (50 to 59); and extreme (60 to 100) (18). Patients with CSI scores indicating moderate, severe, or extreme were classified as having CSS. Those with scores indicating mild were classified as having mild CSS. Those with scores indicating subclinical was classified as not having CSS. Part B examines seven specific CSS diagnoses, which include fibromyalgia, chronic fatigue syndrome, temporomandibular joint disorder, migraine or tension headaches, multiple chemical sensitivities, and restless leg syndrome; three CSS-related disorders, which include depression, anxiety, and panic attacks; and previously diagnosed neck injury.

Clinical assessment of fibromyalgia

We evaluated fibromyalgia (FM) according to the 1990 American College of Rheumatology classification criteria (25). The severity of FM was assessed with the Japanese version of the fibromyalgia symptom scale (FS) (26), which was recently developed by the 2010 American College of Rheumatology as preliminary diagnostic criteria for FM (27). The scores consist of the widespread pain index (0 to 19) and the modified symptom severity scale (0–12). The overall score ranges from 0 to 31.

PainDETECT questionnaire

Neuropathic pain (NP)-like symptoms were assessed with the Japanese version of the painDETECT questionnaire (PDQ), as described previously (15, 28, 29).

Pain Catastrophising Scale and Hospital Anxiety and Depression Scale

The pain catastrophising scale (PCS) (30) and the hospital anxiety and depression scale (HADS) (31) were used to assess pain catastrophising and the levels of anxiety and depression, respectively.

Medical Outcome Study 36-item Health Survey (version 2)

The Medical Outcome Study 36-item Health Survey (SF-36) comprehensively assesses health-related quality of life (HRQOL) (32) and generates three component scores: physical component summary (PC), mental component summary (MC), and role-social component summary (RC).

Statistical analysis

A one way analysis of variance (ANOVA) followed by Dunn's method was used to analyse differences in age, BMI, disease duration, Steinbrocker stage, EGA, PGA, pain VAS, SJC, TJC, CRP, ESR, DAS28 (CRP), DAS28 (ESR), CDAI, SDAI, mHAQ-DI, FS, PDQ score, PCS, HADS-Anxiety (HADS-A), HADS Depression (HADS-D), PC, MC, RC on the SF-36, CSI score, and the number of CSS-related diseases between the three CSS patient groupings. Fisher's exact test followed by the Holm method was used to analyse differences in sex ratio, positivity of ACPA, and prevalence of definite FM among the groups. Data were analysed using SigmaPlot v. 13 (Systat Software, Erkrath, Germany) and EZR (Easy R) (33), which is a modified version of R commander designed to add statistical functions that are frequently used in biostatistics. To analyse the relationships between CSS and mild CSS and relevant variables, we performed multivariate regression analysis using a backwards stepwise procedure. We selected age, sex, and BMI as demographic variables; disease duration as clinical information; Steinbrocker stage as a measure of structural damage; EGA, PGA, pain VAS, SJC, TJC, CRP, ESR, and mHAQ-DI as measures of disease activity; ACPA as an immunological abnormality; FS as a measure of FM; PDQ score as a measure of NP-like symptoms; PCS as a measure of pain catastrophising; HADS as indicators of mental status; and PC, MC, and RC of the SF-36 as indicators of HRQOL. To analyse the degree to which CSS affects the PDQ score among the various clinical parameters that may influence NP-like symptoms, we performed multivariate linear regression analysis with a backwards stepwise procedure using the PDQ score as the objective variable. We selected age, sex, BMI, disease duration, Steinbrocker stage, SJC, TJC, CRP, ESR, ACPA, FS, PCS, HADS, and CSI score as the variables that may influence NP-like symptoms. We used standardised ß to compare the strength of the relationships.

Results

Patient characteristics

Table I shows the patient characteristics of our study. A total of 240 patients (63 men, 177 women; mean age = 59.7±14.3

Table I. Patient characteristics of the study (n=240).

	Variables
Age (years)	59.7 ± 14.3
Sex (Female/Male)	177 / 63
BMI (kg/m^2)	21.9 ± 3.53
Duration (years)	9.58 ± 7.76
Stage	1.97 ± 1.15
EGA (mm)	14.9 ± 13.6
PGA (mm)	24.7 ± 20.2
Pain VAS (mm)	19.7 ± 20.1
SJC	0.571 ± 1.57
TJC	0.888 ± 2.37
CRP (mg/dl)	0.325 ± 0.608
ESR (mm/hr)	17.0 ± 14.6
DAS28 (CRP)	1.91 ± 0.801
DAS28 (ESR)	2.39 ± 1.07
CDAI	5.40 ± 5.22
SDAI	5.70 ± 5.41
mHAQ-DI	0.127 ± 0.280
ACPA	194 (80.8)
FS	5.00 ± 3.22
Definite FM	4 (1.67)
PDQ score	7.48 ± 5.21
PCS	15.8 ± 12.8
HADS-A	4.59 ± 3.36
HADS-D	5.44 ± 3.21
PC (SF-36)	42.0 ± 12.3
MC (SF-36)	49.8 ± 10.1
RC (SF-36)	50.5 ± 11.9

Values shown are number of patients (%) or mean ± standard deviation.
BMI body mass index, EGA evaluator global assessment, PGA patient global assessment, Pain VAS pain visual analogue scale, SJC swollen joint count, TJC tender joint count, CRP C-reactive protein, ESR erythrocyte sedimentation rate, ACPA anti-cyclic citrullinated peptide antibody, DAS-28 28-joint disease activity score, CDAI clinical disease activity index, SDAI simplified disease activity scale, mHAQ-DI health assessment questionnaire disability index, FS fibromyalgia symptom scale, FM fibromyalgia, PDQ painDETECT questionnaire, PCS pain catastrophising scale, HADS-A hospital anxiety and depression scale-anxiety, HADS-D hospital anxiety and depression scale-depression, SF-36 36-item short form health survey, PC physical component summary, MC mental component summary, RC role-social component summary.

years) were included in this study. The mean BMI was 21.9±3.53 kg/m^2. The mean disease duration was 9.58±7.76 years, which indicated relatively long-standing RA in our sample. The mean Steinbrocker stage was 1.97±1.15, which indicated early-to-moderate joint destruction. The means of the EGA, PGA, and pain VAS were 14.9±13.6 mm, 24.7±20.2 mm, and 19.7±20.1 mm, respectively. The means of the SJC and TJC were 0.571±1.57 and 0.888±2.37, respectively. The means of CRP and ESR were 0.325±0.608 mg/ml and 17.0±14.6 mm/hr, respectively. The means of the DAS28 (CRP), DAS28 (ESR), CDAI, and SDAI were 1.91±0.801, 2.39±1.07, 5.40±5.22, and 5.70±5.41, respectively. These results indicated that the average disease activity was in "remission" according to the DAS28 (CRP) and DAS28 (ESR) and "low" according to the CDAI and SDAI. The mean mHAQ-DI for patients in the sample was 0.127±0.280, which indicated a relatively low level of physical disability. One hundred ninety-four patients (80.8 %) had ACPA. The mean FS was 5.00±3.22, with four patients (1.67%) having definite FM, which indicated that the prevalence of RA complicated by FM in the sample was low. The mean PDQ score was 7.48±5.21. The means of PCS, HADS-A, and HADS-D were 15.8±12.8, 4.59±3.36, and 5.44±3.21, respectively. These results indicated that the sample had a low level of pain catastrophising, anxiety, or depression. The PC, MC, and RC of the SF-36 were 42.0±12.3, 49.8±10.1, and 50.5±11.9, respectively. The PC was lower than that found in the general Japanese population (32).

Central sensitisation inventory

Table II shows the results of the CSI. The mean CSI score was 18.3±11.8. One patient (0.417 %) had a CSI score ≥60, indicating "extreme"; 3 patients (1.25 %) had CSI scores ranging from 50 to 59, indicating "severe"; 14 patients (5.83%) had CSI scores ranging from 40 to 49, indicating "moderate"; 21 patients (8.75%) had CSI scores ranging from 30 to 39, indicating "mild"; and 201 patients (83.8%) had CSI scores ≤29, indicating "subclinical". Of the seven specific CSS diagnoses that had been previously diagnosed, the most common were temporomandibular joint disorder (12.9%) and migraine or tension headaches (6.67%), while other specific CSS diagnoses were rare. Of the three CSS-related disorders that had been previously diagnosed, the most common were neck injury (5.83%) and depression (5.42%).

Comparison of clinical parameters according to CSS severity

Of the 240 patients, 18 (7.5%) were classified as having CSS with CSI scores ≥40; 21 patients (8.75%) with mild CSS ranging from 30 to 39; and 201 patients (83.8%) without CSS. The comparison of clinical parameters between these three groupings (Table III) found no significant differences in age, sex, disease duration, Steinbrocker stage, SJC, positivity rate of ACPA, or DAS28 (ESR). The means of PGA, pain VAS, FS, PDQ score, PCS, HADS-A, HADS-D, MC of the SF-36, and CSI score were significantly different between patients with CSS and mild CSS *versus* those without CSS. The means of BMI, mHAQ-DI, and HADS-A were significantly different between patients with CSS *versus* those with mild CSS and without CSS. The means of BMI and RC of the SF-36, and the number of CSS-related diseases were significantly different between patients with and without CSS. Mean EGA was significantly higher among patients with mild CSS *versus* those with and without CSS. The means of TJC, DAS28 (CRP), CDAI, and SDAI were significantly higher among patients with mild CSS *versus* without CSS. To summarise, these results indicated that patients with CSS and mild CSS showed high PGA, pain VAS, FS, PDQ score, PCS, and low PC on the SF-36; those with CSS showed higher HADS

Table II. Prevalence rates of CS severity levels and prevalence of diagnoses.

	n=240
Mean CSI score (range : 0-100)	18.3 ± 11.8
Subclinical (0-29)	201 (83.8)
Mild (30-39)	21 (8.75)
Moderate (40-49)	14 (5.83)
Severe (50-59)	3 (1.25)
Extreme (≥60)	1 (0.417)
CSS related diagnoses	
Restless leg syndrome	2 (0.833)
Chronic fatigue syndrome	1 (0.417)
Fibromyalgia	2 (0.833)
Temporomandibular joint disorder	31 (12.9)
Migraine or tension headaches	16 (6.67)
Irritable bowel syndrome	3 (1.25)
Multiple chemical sensitivities	0 (0)
Neck injury (including whiplash)	14 (5.83)
Anxiety or panic attacks	9 (3.75)
Depression	13 (5.42)

Values shown are number of patients (%).
CS: central sensitisation; CSI: central sensitisation inventory; CSS: central sensitivity syndrome.

and lower MC and RC scores than those with mild CSS; and those with mild CSS showed higher RA activity, which was attributed to high EGA and TJC than the other groups.

Multivariate regression analysis of clinical parameters associated with patients with CSS and mild CSS

Figure 1a shows the results of multivariate regression analysis of the patients with CSS. EGA, FS, PDQ score, HADS-A, PC, MC, and RC of the SF-36 were identified as important variables associated with CSS: EGA (p=0.008, odds ratio (OR)=0.860, 95% confidence interval (CI): 0.770–0.962), FS (p=0.005, OR=1.46, 95% CI: 1.12–1.91), PDQ score (p=0.034, OR=1.24, 95% CI: 1.016–1.51), HADS-A (p=1.35, OR=1.35, 95% CI: 1.035–1.75), PC (SF-36) (p=0.019, OR=0.898, 95% CI: 0.820–0.982), MC (SF-36) (p=0.002, OR=0.828, 95% CI: 0.733–0.935), and RC (SF-36) (p=0.048, OR=0.946, 95% CI: 0.896–0.999). Figure 1b shows the results of multivariate regression analysis of the patients with mild CSS. BMI, EGA, ESR, and FS were identified as important variables associated with mild CSS: BMI (p=0.017, OR=1.16, 95% CI: 1.0022–1.35), EGA (p=0.017, OR=1.049, 95% CI: 1.0087–1.0902), ESR (p=0.010, OR=0.935, 95% CI: 0.889–0.984), and FS (p=0.010, OR=1.47, 95% CI: 1.23–1.76).

Multivariate linear regression analysis of the clinical parameters that contribute to the PDQ score

Table IV shows the results of the multivariate linear regression analysis. TJC, FS, PCS, and CSI scores were identified as important variables associated with the PDQ score: TJC (p=0.027, ß=0.121), FS (p=0.003, ß=0.003), PCS (p=0.000, ß=0.261), and CSI (p=0.000, ß=0.266).

Table III. Comparison of clinical parameters according to CSS severity.

Variables	Patients with CSS (CSI ≥40: n=18)	Patients with mild CSS (30 ≤CSI ≤39: n=21)	Patients without CSS (CSI ≤29: n=201)	p-value
Age (years)	55.1 ± 13.0	56.3 ± 14.9	60.5 ± 14.3	0.063
Sex (Female/Male)	16 / 2	18 / 3	143 / 58	0.129
BMI (kg/m2)	19.9 ± 2.89	23.1 ± 3.71	22.0 ± 3.51	0.007 a*c$^{\#}$
Duration (years)	9.58 ± 6.35	11.8 ± 9.58	9.33 ± 7.66	0.548
Steinbrocker stage	1.61 ± 0.850	1.86 ± 1.06	2.02 ± 1.18	0.497
EGA (mm)	13.9 ± 13.8	25.7 ± 14.0	13.8 ± 13.1	<0.001 a$^{\#}$b*
PGA (mm)	38.9 ± 28.1	37.4 ± 20.3	22.1 ± 18.4	<0.001 b*c$^{\#}$
Pain VAS (mm)	36.7 ± 27.8	35 ± 22.2	16.6 ± 17.5	<0.001 b*c*
SJC	1 ± 3.22	1.24 ± 2.12	0.463 ± 1.24	0.216
TJC	1.39 ± 2.57	2.48 ± 4.11	0.677 ± 2.03	<0.001 b*
CRP (mg/dl)	0.197 ± 0.570	0.420 ± 0.703	0.326 ± 0.602	0.092
ESR (mm/hr)	10.8 ± 11.4	12.0 ± 12.1	18.0 ± 14.9	0.007 c$^{\#}$
DAS28 (CRP)	2.20 ± 0.994	2.49 ± 0.968	1.82 ± 0.734	0.004 b*
DAS28 (ESR)	2.43 ± 1.31	2.65 ± 1.23	2.35 ± 1.03	0.637
CDAI	7.67 ± 6.98	10.0 ± 6.72	4.72 ± 4.55	<0.001 b*
SDAI	7.89 ± 7.20	10.4 ± 7.12	5.01 ± 4.71	<0.001 b*
mHAQ-DI	0.430 ± 0.569	0.214 ± 0.345	0.0902 ± 0.209	<0.001 c$^{\#}$
ACPA	16 (88.9)	18 (85.7)	160 (79.6)	0.672
FS	9.06 ± 2.62	9.05 ± 3.89	4.22 ± 2.54	<0.001 b*c*
Definite FM	2 (11.1)	2 (9.52)	1 (0.498)	0.00269
PDQ score	13.4 ± 4.57	11.9 ± 4.65	6.49 ± 4.73	<0.001 b*c*
PCS	27.4 ± 12.4	23.2 ± 11.3	14.1 ± 12.2	<0.001 b*c*
HADS-A	9.83 ± 3.26	5.95 ± 3.34	3.98 ± 2.91	<0.001 a$^{\#}$b$^{\#}$c*
HADS-D	8.94 ± 2.98	6.76 ± 3.10	4.99 ± 3.02	<0.001 b$^{\#}$c*
PC (SF-36)	36.9 ± 15.9	33.1 ± 15.4	43.4 ± 11.1	<0.001 b*
MC (SF-36)	38.5 ± 8.22	45.4 ± 6.54	51.3 ± 9.86	<0.001 b$^{\#}$c*
RC (SF-36)	39.8 ± 18.2	47.2 ± 13.1	51.8 ± 10.6	0.001 c*
CSI score	45.6 ± 5.84	34.5 ± 2.73	14.2 ± 7.25	<0.001 b*c*
The number of CSS related diseases	1.44 ± 1.58	0.333 ± 0.730	0.289 ± 0.580	<0.001 a$^{\#}$c*

Values shown are number of patients (%) or mean ± standard deviation.
a comparison between patients with CSS and mild CSS; b comparison between patients with mild CSS and without CSS; c comparison between patients with CSS and without CSS;
$^{\#}p$<0.05, $^{*}p$<0.01
BMI: body mass index; EGA: evaluator global assessment; PGA: patient global assessment; Pain VAS: pain visual analogue scale; SJC: swollen joint count; TJC: tender joint count; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ACPA: anti-cyclic citrullinated peptide antibody; DAS-28: 28-joint disease activity score; CDAI: clinical disease activity index; SDAI: simplified disease activity scale; mHAQ-DI: health assessment questionnaire disability index; FS: fibromyalgia symptom scale; FM: fibromyalgia; PDQ: painDETECT questionnaire; PCS: pain catastrophising scale; HADS-A: hospital anxiety and depression scale-anxiety; HADS-D: hospital anxiety and depression scale-depression; SF-36: 36-item short form health survey; PC: physical component summary; MC: mental component summary; RC: role-social component summary; CSI: central sensitisation inventory; CSS: central sensitivity syndrome.

Discussion

Our study demonstrated the prevalence and severity of CSS, the clinical factors that contribute to CSS, and the association between CSS and NP-like symptoms among patients with RA in Japan, who have low disease activity and long duration.

The prevalence and severity of RA patients with CSS have not been fully studied previously. Our results showed that the prevalence of CSS was 8.75% and the severity was "moderate" in most patients who have CSS. Tanaka *et al*. reported that the prevalence of CSS was 11.03% and the mean CSS score was 21.91±13.31 among patients who have musculoskeletal pain disorders in Japan (19), which is similar to our results. In Japan, the prevalence of CSS in RA patients with long disease duration and low disease activity appears to be remarkably similar to that of musculoskeletal disorders. The most common CSS specific diagnosis in RA patients was temporomandibular joint disorder (12.9%), which is higher than that of musculoskeletal disorders (7.24%). This may be attributed to the inflammation of the temporomandibular joint due to RA. The rates of other CSS specific diagnoses and related disorders were similar between patients with RA and musculoskeletal disorders. To date, there have been two reports that employed CSI in patients with RA (20,

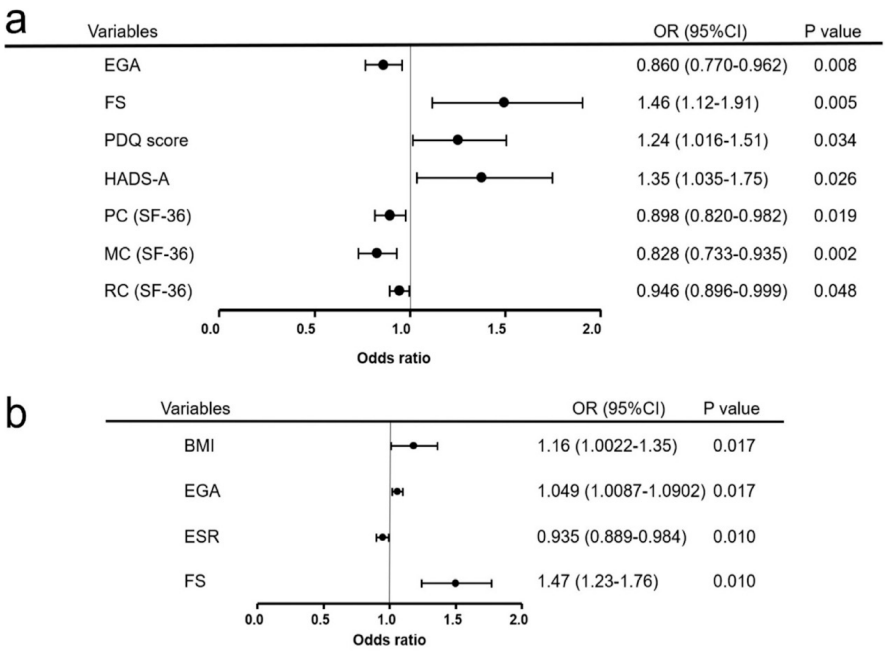

Fig. 1. Multivariate analysis of the clinical parameters that contribute to CSS in patients with RA.
a: Multivariate analysis of the clinical parameters that contribute to CSS (CSI ≥40)
b: Multivariate analysis of the clinical parameters that contribute to mild CSS (39 ≥ CSI ≥30)
Error bars indicate 95% confidence intervals.
BMI: body mass index; CSS: central sensitivity syndrome; CSI: central sensitisation inventory; EGA: evaluator global assessment; ESR: erythrocyte sedimentation rate; FS: fibromyalgia symptom scale; HADS-A: hospital anxiety and depression scale-anxiety; PDQ: painDETECT questionnaire; PC: physical component summary; MC: mental component summary; RC: role-social component summary; OR: odds ratio; CI: confidence internal.

Table IV. Multivariate linear regression analysis of the clinical parameters that contribute to the PDQ score in patients with rheumatoid arthritis.

	Adjusted standardised β	*p*-value
TJC	0.121	0.027
FS	0.209	0.003
PCS	0.261	0.000
CSI score	0.266	0.000

TJC: tender joint count; FS: fibromyalgia symptom scale; PDQ: painDETECT questionnaire; PCS: pain catastrophising scale; CSI: central sensitisation inventory.

Table V. Characteristics of long duration low activity RA patients complicated by CSS (summary of Fig. 1).

Severity of CSS	Mild	Moderate-severe
Subjective symptoms	Wide spread pain↑	Wide spread pain ↑ Anxiety ↑ Neuropathic-like symptoms ↑
EGA	↑	↓
HRQOL		Physical ↓ Mental ↓ Role-Social ↓
others	BMI ↑ ESR ↓	

CSS: central sensitivity syndrome; RA: rheumatoid arthritis; BMI: body mass index; EGA: evaluator global assessment; ESR: erythrocyte sedimentation rate; HRQOL: health-related quality of life.

34). Guler *et al*. described that in Turkey, 41.1% of RA patients (n=56) with long duration and low disease activity, had CSS with a mean CSS score of 38.43±16.2. Their patient backgrounds were similar to our patients, except for BMI (BMI = 32.55±4.54). Similarly, Chiarotto *et al*. reported a mean CSS score of 34.55±17.29 in 44 RA patients. In contrast, our results revealed lower prevalence and severity of CSS, which may result from variations related to race, BMI, and social background. Further prospective studies are required to confirm the factors that are associated with the development of CSS.

Second, we discuss the clinical factors that are associated with CSS and mild CSS. We showed that CSS was associated with FM, anxiety, NP-like symptoms, and decreases in EGA and HRQOL. FM is included as a component of CSS and anxiety is included as a CSS-related diagnosis; therefore, these associations were not surprising. However, few patients in the sample met the 1990 American College of Rheumatology classification criteria for a diagnosis of FM, which indicates that the CSS patients had not yet developed FM but experienced widespread pain. When evaluating RA patients with CSS, we need to be aware of this point. A decrease in EGA indicated that evaluators did not regard CSS symptoms as RA symptoms because the patients who had CSS showed various symptoms that are not typical of RA, including FM and psychological symptoms, such as anxiety. We suspect that evaluators may have recognised the symptoms of CSS but not had the knowledge of CSS as a condition. In this study, the patients defined as having mild CSS were analysed in detail because the prevalence of the patients who had mild CSS was higher than that of the patients who had CSS. Interestingly, patients who had mild CSS showed striking characteristics (Table V). The multivariate analysis showed that mild CSS was associated with an increase in EGA. Furthermore, univariate analysis showed that TJC and disease activities, including DAS28 (CRP), CDAI, and SDAI, were higher in RA patients with mild CSS compared with patients without CSS,

even though objective inflammatory markers, such as CRP and SJC, were similar across both groups. The patients with CSS and mild CSS showed a tendency for FM; however, patients with mild CSS showed fewer psychological symptoms and higher MC and RC of the SF-36 than those with CSS. FM affects the evaluation of tenderness. We suspect that it is difficult for evaluators to differentiate symptoms of FM from "real tenderness" due to RA because mild CSS patients do not show symptoms that specifically indicate CSS. As such, evaluators might overestimate tenderness because of the tendency for FM. Taken together, evaluators need to consider that RA patients with mild CSS may have FM tendencies that may affect disease activity.

Third, we discuss the association between NP-like symptoms and central sensitisation. Several studies have reported that NP-like symptoms shown by high PDQ scores occur in patients with RA and this has shown to lower HRQOL (15, 35). However, the cause is unknown, though it has been speculated that NP-like symptoms are primarily due to central sensitisation as described in the introduction. In our study, we showed that the PDQ score of RA patients was strongly associated with CSS and various clinical variables. Moreover, CSS was the factor that had the strongest effect on the PDQ score. Generally, NP is caused by organic and functional changes in neurotransmission due to changes in the plasticity of the sensory nerve. Peripheral sensitisation is a change in plasticity that occurs in the peripheral nerves, whereas central sensitisation is a change in plasticity that occurs above the spinal cord (36). Therefore, NP-like symptoms in RA patients, such as allodynia and hyperalgesia reflect peripheral and/or central sensitisation. Peripheral sensitisation in RA may be caused by local inflammation and mechanical pain due to deformity. In our study, there was no significant association between PDQ score and Steinbrocker stage, which is an indicator of deformity, and there were no significant associations between PDQ score and objective inflammation markers, such as CRP and ESR. TJC, which is a peripheral stimulation marker, was associated with PDQ score; however, the effect on the PDQ score was not as large as that of FM, pain catastrophising, or CSI scores, which are components related to the central nervous system. Collectively, the results indicate that peripheral sensitisation caused by inflammation and mechanical pain is not involved in NP-like symptoms. We therefore believe that NP-like symptoms might be an indicator of CSS in RA patients with low disease activity and long disease duration in cases where the patient does not have a neurological abnormality.

Our study has several limitations. First, our sample was entirely Japanese. The characteristics of the patients who have CSS may vary depending on race. In fact, as mentioned previously, in Turkey, the prevalence of CSS in patients with RA was higher than in Japan. Second, we enrolled long-term follow-up outpatients, and our sample did not include patients in the early stages. Therefore, we cannot determine the effect of inflammation on CSS in these patients. Third, we did not use an objective indicator to assess central sensitisation of the patients, such as QST or functional magnetic resonance imaging, therefore, CSS may not correspond to central sensitisation in some cases. Forth, our study was a cross-sectional design, hence we could not examine whether CSS in RA patients was associated with the status of arthritis at onset. Prospective studies are needed to identify the factors that lead to the development of CSS in RA patients. Further investigation to address these issues is warranted. In conclusion, we demonstrated the prevalence and severity of CSS in longstanding RA patients and the differing phenotypes of mild CSS and CSS. NP-like symptoms might be one of the symptoms of CSS in longstanding RA patients. When seeing longstanding RA patients who overproportionately have NP-like symptoms and/or widespread pain compared to the degree of inflammation, to detect CSS using CSI might help to understand the pathogenesis of the patients and the intervention to CSS may lead to improve their subjective symptoms.

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References

1. CATRINA AI, SVENSSON CI, MALMSTRÖM V, SCHETT G, KLARESKOG L: Mechanisms leading from systemic autoimmunity to joint-specific disease in rheumatoid arthritis. *Nat Rev Rheumatol* 2017; 13: 79-86.
2. STURGEON JA, FINAN PH, ZAUTRA AJ: Affective disturbance in rheumatoid arthritis: psychological and disease-related pathways. *Nat Rev Rheumatol* 2016; 12: 532-42.
3. SINGH JA, SAAG KG, BRIDGES SL JR *et al*.: 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol* 2016; 68: 1-26.
4. SILVAGNI E, GIOLLO A, SAKELLARIOU G *et al*.: One year in review 2020: novelties in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2020; 38: 181-94.
5. ISHIDA M, KUROIWA Y, YOSHIDA E *et al*.: Residual symptoms and disease burden among patients with rheumatoid arthritis in remission or low disease activity: a systematic literature review. *Mod Rheumatol* 2018; 28: 789-99.
6. ALOUSH V, NIV D, ABLIN JN, YAISH I, EL-KAYAM O, ELKANA O: Good pain, bad pain: illness perception and physician attitudes towards rheumatoid arthritis and fibromyalgia patients. *Clin Exp Rheumatol* 2020 Dec 15 PMID 33338002 [Online ahead of print].
7. IASP. Available at: https://www.iasp-pain.org/terminology?navItemNumber=576#Pain. Accessed 30 July, 2020.
8. GWILYM SE, KELTNER JR, WARNABY CE *et al*.: Psychophysical and functional imaging evidence supporting the presence of central sensitization in a cohort of osteoarthritis patients. *Arthritis Rheum* 2009; 61: 1226-34.
9. MEASE PJ, HANNA S, FRAKES EP, ALTMAN RD: Pain mechanisms in osteoarthritis: understanding the role of central pain and current approaches to its treatment. *J Rheumatol* 2011; 38: 1546-51.
10. O'LEARY H, SMART KM, MOLONEY NA, BLAKE C, DOODY CM: Pain sensitization associated with nonresponse after physiotherapy in people with knee osteoarthritis. *Pain* 2018; 159: 1877-86.
11. MEEUS M, VERVISCH S, DE CLERCK LS, MOORKENS G, HANS G, NIJS J: Central sensitization in patients with rheumatoid arthritis: a systematic literature review. *Semin Arthritis Rheum* 2012; 41: 556-67.
12. LEE YC, BINGHAM CO 3RD, EDWARDS RR *et al*.: association between pain sensitization and disease activity in patients with rheumatoid arthritis: a cross-sectional study. *Arthritis Care Res* (Hoboken) 2018; 70: 197-204.
13. ZHANG A, LEE YC: Mechanisms for joint pain in rheumatoid arthritis (RA): from cytokines to central sensitization. *Curr Osteoporos Rep* 2018; 16: 603-10.
14. GRAVEN-NIELSEN T, ARENDT-NIELSEN L: Assessment of mechanisms in localized and

widespread musculoskeletal pain. *Nat Rev Rheumatol* 2010; 6: 599-606.
15. NODA K, TAJIMA M, OTO Y *et al*.: How do neuropathic pain-like symptoms affect health-related quality of life among patients with rheumatoid arthritis?: A comparison of multiple pain-related parameters. *Mod Rheumatol* 2020; 30: 828-34.
16. YUNUS MB: Fibromyalgia and overlapping disorders: the unifying concept of central sensitivity syndromes. *Semin Arthritis Rheum* 2007; 36: 339-56.
17. MAYER TG, NEBLETT R, COHEN H *et al*.: The development and psychometric validation of the central sensitization inventory. *Pain Pract* 2012; 12: 276-85.
18. NEBLETT R, HARTZELL MM, MAYER TG, COHEN H, GATCHEL RJ: Establishing clinically relevant severity levels for the central sensitization inventory. *Pain Pract* 2017; 17: 166-75.
19. TANAKA K, NISHIGAMI T, MIBU A *et al*.: Validation of the Japanese version of the Central Sensitization Inventory in patients with musculoskeletal disorders. *PLoS One* 2017; 12: e0188719.
20. CHIAROTTO A, VITI C, SULLI A, CUTOLO M, TESTA M, PISCITELLI D: Cross-cultural adaptation and validity of the Italian version of the Central Sensitization Inventory. *Musculoskelet Sci Pract* 2018; 37: 20-8.
21. KREGEL J, VUIJK PJ, DESCHEEMAEKER F *et al*.: The Dutch Central Sensitization Inventory (CSI): factor analysis, discriminative power, and test-retest reliability. *Clin J Pain* 2016; 32: 624-30.
22. ALETAHA D, NEOGI T, SILMAN AJ *et al*.: 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; 62: 2569-81.
23. ALETAHA D, MARTINEZ-AVILA J, KVIEN TK, SMOLEN JS: Definition of treatment response in rheumatoid arthritis based on the simplified and the clinical disease activity index. *Ann Rheum Dis* 2012; 71: 1190-6.
24. PINCUS T, SUMMEY JA, SORACI SA JR, WALLSTON KA, HUMMON NP: Assessment of patient satisfaction in activities of daily living using a modified Stanford Health Assessment Questionnaire. *Arthritis Rheum* 1983; 26: 1346-53.
25. WOLFE F, SMYTHE HA, YUNUS MB *et al*.: The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990; 33: 160-72.
26. USUI C, HATTA K, ARATANI S *et al*.: The Japanese version of the modified ACR preliminary diagnostic criteria for fibromyalgia and the fibromyalgia symptom scale: reliability and validity. *Mod Rheumatol* 2013; 23: 846-50.
27. WOLFE F, CLAUW DJ, FITZCHARLES MA *et al*.: The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res* (Hoboken) 2010; 62: 600-10.
28. MATSUBAYASHI Y, TAKESHITA K, SUMITANI M *et al*.: Validity and reliability of the Japanese version of the painDETECT questionnaire: a multicenter observational study. *PLoS One* 2013; 8: e68013.
29. FREYNHAGEN R, BARON R, GOCKEL U, TÖLLE TR: painDETECT: a new screening questionnaire to identify neuropathic components in patients with back pain. *Curr Med Res Opin* 2006; 22: 1911-20.
30. SULLIVAN ML, BISHOP S, PIVIK J: The Pain Catastrophizing Scale: development and validation. Psychol Assess 1995; 7: 524-53.
31. ZIGMOND AS, SNAITH RP: The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983; 67: 361-70.
32. FUKUHARA S, BITO S, GREEN J, HSIAO A, KUROKAWA K: Translation, adaptation, and validation of the SF-36 Health Survey for use in Japan. *J Clin Epidemiol* 1998; 51: 1037-44.
33. KANDA Y: Investigation of the freely available easy-to-use software 'EZR' for medical statistics. *Bone Marrow Transplant* 2013; 48: 452-8.
34. GULER MA, CELIK OF, AYHAN FF: The important role of central sensitization in chronic musculoskeletal pain seen in different rheumatic diseases. *Clin Rheumatol* 2020; 39: 269-74.
35. KOOP SM, TEN KLOOSTER PM, VONKEMAN HE, STEUNEBRINK LM, VAN DE LAAR MA: Neuropathic-like pain features and cross-sectional associations in rheumatoid arthritis. *Arthritis Res Ther* 2015; 17: 237.
36. COLLOCA L, LUDMAN T, BOUHASSIRA D *et al*.: Neuropathic pain. *Nat Rev Dis Primers* 2017; 3: 17002.