Original Article

The effect of central sensitization on disease activity measures, quality of life and clinical parameters in axial spondyloarthritis: a cross-sectional study

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Objective: Despite biological drug therapy, pain remains a persistent complaint in patients with axial spondyloarthritis (axSpA). We aimed to investigate the effect of central sensitization (CS) on disease activity measures, quality of life, and clinical parameters in axSpA patients.
Methods: We consecutively recruited axSpA patients who were followed up at our rheumatology outpatient clinic, and age- and sex-matched controls in this cross-sectional study. The central sensitization inventory, douleur neuropathique 4 (DN4) questions, and 2010 American College of Rheumatology fibromyalgia (FM) diagnostic criteria were applied to all individuals. The patients' clinical parameters were recorded. The data of the patient and control groups were compared.
Results: Of the 116 axSpA patients (57 female) and 95 controls (46 female) who participated in this study, CS was determined in 46.6% of axSpA patients and 13.7% of controls (p<0.001). Patients with CS exhibited high disease activity, and poor quality of life and functionality than without it (all p<0.001). The median CS, frequency of FM and frequency of neuropathic pain were higher in patients than in the controls (all p<0.001). CS-related conditions, including anxiety and depression, were higher in axSpA patients than in controls (both p<0.05).
Conclusion: The results showed that CS was common in axSpA patients, and patients with CS had higher disease activity, worse quality of life, and worse functional status than those without CS.

Keywords: Central sensitization, Pain, Axial spondyloarthritis, Quality of life

INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic immune-mediated inflammatory disease associated with inflammation in the spine and sacroiliac joints, accompanied by chronic back pain, morning stiffness and fatigue, and deterioration of quality of life [1]. Since 2009, axSpA has been divided into two important subgroups: radiographic axSpA, namely, ankylosing spondylitis (AS), and non-radiographic axSpA (nr-axSpA); this division provides better and early diagnosis of the disease [2]. Treatments include non-steroidal anti-inflammatory drugs, sulfasalazine in the presence of peripheral joint involvement, and tumor necrosis factor alpha inhibitors (anti-TNFs) and interleukin (IL)-17 blockers, both of which are biological agents [3]. Pain is a leading symptoms of axSpA, and it has a complex or multifactorial nature that can be caused by inflammation (e.g., enthesitis, osteitis, and discitis), structural damage, degenerative changes [4], chronic widespread pain, fibromyalgia (FM), central sensitization (CS), or nociplastic pain—a recent definition [5].

CS is an increased neural response in the central pain path-

ways following a painful stimulus. It occurs because of neuro-inflammation in the peripheral and central nervous systems. With the release of chemokines and cytokines from the brain as a result of neuroinflammation, widespread pain and CS develop throughout the body [6]. In the current literature, CS is defined as a type of nociplastic pain featuring increased nociceptive sensitivity with normal or sub-threshold afferent input from neurons in the central nervous system [7]. Pain amplification in CS likely facilitates hyperexcitability due to a reduced synaptic inhibition, as the increased excitability of the membrane of neurons elicits pain hypersensitivity. These mechanisms are seen in chronic pain disorders as well as in different musculoskeletal diseases, joint diseases accompanied by degeneration and preceded by inflammation, and FM [6,7].

Recently, it has been reported that 15% to 40% of inflammatory rheumatic diseases are accompanied by CS [8]. Although CS is considered common in FM patients [9], there are few reports state that CS negatively affects disease activity and quality of life in axSpA patients [10-12]. In addition, pain, older age, worse health status, and female sex have been found to contribute to persistent widespread pain in spondyloarthritis (SpA) [13].

Despite standard treatment in axSpA patients, some experience persists pain, and the underlying cause may be the presence of CS. For this reason, we aimed to investigate the CS in axSpA patients and assess its effects on measures of disease activity, indices of quality of life, and clinical parameters.

MATERIALS AND METHODS

Study design and patients

The study comprised 116 axSpA patients (59 male and 57 female) meeting the classification criteria of the Assessment of Spondyloarthritis International Society [2] and 95 controls (49 male, 46 female) aged 18 and 65 years. The study was managed cross sectionally between July 2021 and November 2021 in our rheumatology outpatient clinic. Exclusion criteria were hepatic, renal, cardiac, or pulmonary insufficiency, infection, malignancy, and neurological or psychiatric diseases; taking antidepressants (i.e., duloxetine) and/or anticonvulsants (gabapentin and pregabalin) and previously diagnosis of FM syndrome and/or neuropathic pain (NP). The control group was selected from subjects who visited our outpatient department of rheumatology for any reason, but who did not have rheumatoid disease, FM, or NP, and who satisfied the exclusion criteria. Written informed

consent was obtained from all individuals included in the study. The study was carried out in accordance with the Declaration of Helsinki. Ethics committee approval was obtained from Erciyes University Clinical Research Ethics Committee (Approval no: 2021-343/date: 05.05.21).

Main outcome variables

Age, sex, duration of illness, duration of first symptoms, medications used, and the morning stiffness of the patients participating in the study were noted. The drugs used were classified as biological drugs or non-biological (non-steroidal anti-inflammatory drugs, sulfasalazine in appropriate patients) therapies. Pain, patient global assessment (PtGA), and Physician Global Assessment (PGA) were assessed between 0 and 10 by a visual analogue scale (VAS). The patients' results were also recorded according to Maastricht Ankylosing Spondylitis Enthesitis score (MASES) [14], quality of life through the 18-item Ankylosing spondylitis quality of life (ASQoL) questionnaire marked yes and no, functional level via Bath Ankylosing Spondylitis Functional Index (BASFI) [15], Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [16], Bath Ankylosing Spondylitis Metrology Index (BASMI) [17], erythrocyte sedimentation rate and C-reactive protein (CRP) value, and Ankylosing Spondylitis Disease Activity Score with CRP (ASDAS-CRP) [18]. FM was assessed via the 2010 American College of Rheumatology (ACR) FM diagnostic criteria [19], and NP was evaluated by douleur neuropathique 4 (DN4) questions [20]. The DN4 scale consists of ten questions, responses to seven relate to symptoms and responses to three are determined by clinical examination. The maximum total score is 10. Patients with a score of ≥4 are considered to have NP. The part of the DN4 questionnaire determined by examination was administered to all individuals by the same doctor.

Central sensitization

The patient and control groups were evaluated using the CS inventory (CSI), which comprises two parts, A and B. CSI-A consists of 25 questions relating to emotional and somatic disorders. Each question is scored between 0 and 4, with total scores thus between 0 and 100. High scores indicate more serious symptoms. A score ≥40 was considered significant. CSI-B comprises patients' details of previously diagnosed CS-related syndromes, including FM, restless legs syndrome, chronic fatigue syndrome, migraine, temporomandibular joint dysfunc-

Table 1. Comparisons of demographic and clinical variables in axSpA patients without central sensitization vs. with central sensitization

Variable	All axSpA (n=116)	axSpA without CS (n=62)	axSpA with CS (n=54)	p-value
Age (yr)	42.0±10.2	42.5±11.2	41.4±8.9	0.572
BMI (kg/m^2)	28.1±4.9	27.8±4.8	28.5±5.1	0.461
Sex				0.042*
Male	59 (50.9)	37 (59.7)	22 (40.7)	
Female	57 (49.1)	25 (40.3)	32 (59.3)	
Education				0.822
Middle school and below	55 (47.4)	30 (48.4)	25 (46.3)	
High school and above	61 (52.6)	32 (51.6)	29 (53.7)	
Morning stiffness				0.001*
Yes	94 (81.0)	43 (69.4)	51(94.4)	
No	22 (19.0)	19 (30.6)	3 (5.6)	
Medication				0.001*
Biologic drugs	41 (35.3)	31 (50.0)	10 (18.5)	
Non-biologic drugs	75 (64.7)	31 (50.0)	44 (81.5)	
NP (DN4)				0.001*
Yes	27 (23.3)	5 (8.1)	22 (40.7)	
No	89 (76.7)	57 (91.9)	32 (59.3)	
FM				0.001*
Yes	28 (24.1)	3 (4.8)	25 (46.3)	
No	88 (75.9)	59 (95.2)	29 (53.7)	
axSpA				0.625
AS	67 (57.8)	37 (59.7)	30 (55.6)	
nr-axSpA	49 (42.2)	25 (40.3)	24 (44.4)	
First symptom duration (yr)	11.5 (6~18)	12 (6~18.5)	10 (5.8~18.5)	0.606
Disease duration (yr)	6.5 (2~10)	7.5 (2.8~11)	6 (2~10)	0.337
Age of IBP onset (yr)	27.6±8.5	27.7±8.6	27.4±8.5	0.842
VAS-pain	5 (3~7)	4 (2~6)	7 (5~8)	0.001*
PtGA	5 (3~7)	4 (2~5.3)	7 (5~8)	0.001*
PGA	5 (3~7)	4 (2~5)	6 (5~8)	0.001*
BASDAI	4.5 (2.4~6.4)	2.7 (1.5~4.4)	6.4 (5~7.3)	0.001*
BASMI	1 (0~3)	1 (0~3.3)	1 (0~2.3)	0.785
BASFI	2.9 (1~5.2)	1.3 (0.5~2.9)	4.9 (3~6.6)	0.001*
ASQoL	6 (2~11)	3 (0~5.3)	11 (7~15)	0.001*
ESR (mm/h)	6 (3.3~17)	5 (3~15.3)	7.5 (3.8~19.3)	0.500
CRP (mg/L)	3.3 (1.6~7.1)	2.8 (1.8~6.8)	3.75 (1.3~9.2)	0.823
ASDAS-CRP (mg/L)	2.7±1.1	2.2±1.1	3.2±0.9	0.001*
MASES	2 (0~4)	0.5 (0~2)	3.5 (0~6)	0.001*
CSI-A	38 (19.3~54.8)	20.5 (13~31)	55 (46.8~64)	0.001*

Values are presented as mean±standard deviation, number (%), or median (interquartile range). axSpA: axial spondyloarthritis, CS: central sensitization, BMI: body mass index, NP: neuropathic pain, DN4: douleur neuropathique en 4 questions, FM: fibromyalgia, AS: ankylosing spondylitis, nr-axSpA: non-radiographic axial spondyloarthritis, IBP: inflammatory back pain, VAS: visual analogue scale, PtGA: Patient Global Assessment, PGA: Physician Global Assessment, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASMI: Bath Ankylosing Spondylitis Metrology Index, BASFI: Bath Ankylosing Spondylitis Functional Index, ASQoL: ankylosing spondylitis quality of life, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ASDAS-CRP: ankylosing spondylitis disease activity score C-reactive protein, MASES: Maastricht Ankylosing Spondylitis Enthesitis Score, CSI-A: central sensitization inventory part A. *Statistically significant (p<0.05).

Table 2. Comparisons of demographic variables, NP, FM, CSI-A, and CSI-B values between patients with axSpA and healthy controls

Variable	axSpA (n=116)	Control (n=95)	All (n=211)	p-value
Age (yr)	42.0±10.2	41.6±11.3	41.8±10.7	0.769
Sex				0.917
Male	59 (50.9)	49 (51.6)	108 (51.2)	
Female	57 (49.1)	46 (48.4)	103 (48.8)	
NP (DN4)				<0.001*
Yes	27 (23.3)	5 (5.3)	32 (15.2)	
No	89 (76.7)	90 (94.7)	179 (84.8)	
FM				<0.001*
Yes	28 (24.1)	6 (6.3)	34 (16.1)	
No	88 (75.9)	89 (93.7)	177 (83.9)	
CSI-A	38 (19.3~54.8)	23 (10~33)	28 (14~46)	<0.001*
Presence of CS				<0.001*
Yes ≥40	54 (46.6)	13 (13.7)	67 (31.8)	
No <40	62 (53.4)	82 (86.3)	144 (68.2)	
CSI-B, syndromes				
FM syndrome				0.066
Yes	11 (9.5)	3 (3.2)	14 (6.6)	
No	105 (90.5)	92 (96.8)	197 (93.4)	
RL syndrome				0.151
Yes	9 (7.8)	3 (3.2)	12 (5.7)	
No	107 (92.2)	92 (96.8)	199 (94.3)	
CF syndrome				0.517
Yes	109 (94.0)	92 (96.8)	201 (95.3)	
No	7 (6.0)	3 (3.2)	10 (4.7)	
TMJ disorders				0.629
Yes	3 (2.6)	1 (1.1)	4 (1.9)	
No	113 (97.4)	94 (98.9)	207 (98.1)	
Migraine/TTH				0.587
Yes	19 (16.4)	13 (13.7)	32 (15.2)	
No	97 (83.6)	82 (86.3)	179 (84.8)	
IBS				0.703
Yes	3 (2.6)	4 (4.2)	7 (3.3)	
No	113 (97.4)	91 (95.8)	204 (96.7)	
MSC				0.589
Yes	1 (0.9)	2 (2.1)	3 (1.4)	
No	115 (99.1)	93 (97.9)	208 (98.6)	
Whiplash injury				-
Yes	-		-	
No	116 (100)	95 (100)	211 (100)	
Anxiety/panic attack				0.042*
Yes	10 (8.6)	2 (2.1)	12 (5.7)	
No	106 (91.4)	93 (97.9)	199 (94.3)	
Depression				0.043*
Yes	12 (10.3)	3 (3.2)	15 (7.1)	
No	104 (89.7)	92 (96.8)	196 (92.9)	

Values are presented as mean±standard deviation, number (%), or median (interquartile range). axSpA: axial spondyloarthritis, NP: neuropathic pain, DN4: douleur neuropathique en 4 questions, FM: fibromyalgia, CSI-A: central sensitization A, CS: central sensitization, CSI-B: central sensitization B, RL: restless leg, CF: chronic fatigue, TMJ: temporomandibular joint, TTH: tension-type headache, IBS: irritable bowel syndrome, MCS: multiple chemicals sensitization. *Statistically significant (p<0.05).

tion, irritable bowel syndrome, multiple chemical sensitivity, neck whiplash syndrome, anxiety/panic attacks, and depression. The CSI-B should be administered by a physician [21].

Statistical analysis

Data analysis was performed using IBM SPSS v26 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used for conformity of normal distribution. Categorical variables were compared via χ^2 and Fisher's exact tests. Continuous variables were compared using the Mann–Whitney U test or t-test. The correlation coefficients, which were used to analyze the relationship among continuous variables, were calculated via Pearson, or Spearman's rho correlation tests according to normality. As a correlation coefficient, a rho >0.60 was considered strong, between 0.40 and 0.60 was considered moderate, and <0.40 was considered weak. Risk parameters for CS were calculated by binary logistic regression analysis. Quantitative data were given as mean and standard deviation, or median interquartile range, and categorical data were given as frequency and percentages. A p-value below 0.05 was regarded as significant.

RESULTS

Patients' characteristics

In total, 211 individuals (116 axSpA patients, 95 controls) were added in this study. The baseline characteristics of the patients with axSpA are shown in Table 1. The mean age of patients was 42.0±10.2 years and mean body mass index was 28.1±4.9 kg/m^2. Of these, 81.0% had morning stiffness, and 35.3% of patients were receiving biological drugs therapy. The median BASDAI score, mean ASDAS-CRP score, median diagnosis durations were 4.5 (2.4~6.4), 2.7±1.1, and 6.5 (2~10) years, respectively. In addition to demographic variables (i.e., age, sex, and education), commonly described clinical variables (i.e., first symptom duration and age of inflammatory back pain onset), disease-related symptoms (i.e., VAS-pain and morning stiffness), medications, and specific tools to assess the disease status of axSpA patients (i.e., BASDAI, BASFI, ASDAS-CRP, PGA, PtGA, MASES, and ASQoL) are shown in Table 1.

Comparisons between patients with and without central sensitization

Among all the axSpA patients, CS was detected in 54 (46.6%) patients. The group with CS had the high ratios of female sex

and morning stiffness and less biological drugs therapy than the group without CS. In addition, higher median VAS-pain, PtGA, PGA, BASDAI, BASFI, ASQoL ASDAS-CRP, MASES, and CSI-A scores and higher frequencies of FM and NP were observed in the axSpA group with CS compared group without CS (Table 1).

Comparisons between axial spondyloarthritis patients and controls

There was no difference between the axSpA patients and controls in terms of age and sex (p>0.05). According to the ≥40 CSI-A cut-off score, CS was detected in 54 (46.6%) axSpA patients and 13 (13.7%) controls, and there was a statistically significant difference between the groups in terms of CS proportion (p<0.001). The frequencies of FM and NP were higher in axSpA patients compared to controls (both p<0.001). In addition, when the syndromes related to CSI-B were calculated, the

Table 3. Evaluation of the relationship between clinical parameters and CSI-A score in axSpA patients

Variable	CSI-A	
	r	p-value
Age (yr)[†]	0.083	0.374
Disease duration (yr)	0.021	0.820
First symptom duration (yr)	0.050	0.592
Age of Inflammatory back pain onset[†]	–0.014	0.885
VAS-pain score	0.582	<0.001*
Patient Global Assessment score	0.608	<0.001*
Physician Global Assessment score	0.596	<0.001*
BASDAI score	0.720	<0.001*
BASFI score	0.593	<0.001*
BASMI score	0.072	0.440
ASQoL score	0.728	<0.001*
ESR (mm/h)	0.074	0.432
CRP (mg/L)	0.026	0.781
ASDAS-CRP score[†]	0.519	<0.001*
MASES score	0.434	<0.001*

axSpA: axial spondyloarthritis, CSI-A: Central Sensitization Inventory A, VAS: visual analogue scale, BASDAI: Bath Ankylosing Spondylitis Disease activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, BASMI: Bath Ankylosing Spondylitis Metrology Index, ASQoL: Ankylosing Spondylitis Quality of Life, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score-C-reactive protein, MASES: Maastricht Ankylosing Spondylitis Enthesitis Score. *Statistically significant (p<0.05). [†]Pearson's correlation analysis, and unmarked indicates Spearman's correlation analysis.

rates of anxiety and depression were higher in axSpA patients than in controls (both p<0.05) (Table 2).

Correlations

There was a positive and strong correlation between CSI-A score and PtGA, BASDAI, and ASQoL (r=0.608, r=0.720, and r=0.728, respectively, all p<0.001), as well as a moderate correlation between CSI-A and PGA, VAS-pain, BASFI, ASDAS-CRP, and MASES (r=0.582, r=0.582, r=0.593, r=0.519, and r=0.434, respectively, all p<0.001). The results are shown in Table 3.

Predictors of central sensitization

The variables thought to affect CS were included in a binary logistic regression analysis (Table 4). The significant results for the univariate model were as follows: female sex odds ratio (OR) 2.153, 95% confidence interval (CI) 1.024, 4.526; VAS-pain OR 1.678, 95% CI 1.361, 2.068; BASDAI OR 2.399, 95% CI 1.779, 3.237; ASDAS-CRP OR 2.889, 95% CI 1.821, 4.582; MASES OR 1.423, 95% CI 1.187, 1.106; ASQoL OR 1.393, 95% CI 1.243,

1.562; NP OR 7.837, 95% CI 2.707, 22.694; and FM OR 16.954, 95% CI 4.726, 60.818. Predictors that could affect the presence of CS or had a significant p-value in the univariate model were included in the multiple model. In the multivariate model, using the enter method, only the ASQoL score (OR 1.209, 95% CI 1.019, 1.433) and biological drugs (OR 0.125, 95% CI 0.020, 0.780) were found to be statistically significant. In addition, FM (OR 6.322, 95% CI 0.957, 41.748) and DN4 (OR 5.514, 95% CI 0.875, 34.744) had borderline p values (p=0.056 and p=0.069, respectively).

DISCUSSION

To the best of our knowledge, this study is the first to compare CS, NP, and FM in axSpA patients with healthy controls. Our study results showed that CSI scores and the frequency of NP, FM, and CSI-related syndromes, including anxiety/panic attacks and depression, were significantly higher in axSpA patients than in healthy controls. CS prevalence was found to be 46.6% in

Table 4. Assessment of risk factors affecting central sensitization positivity by binary logistic regression analysis

	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (yr)	0.990 (0.954~1.026)	0.568		
Sex (reference: male)	2.153 (1.024~4.526)	0.043*	1.881 (0.494~7.159)	0.354
Morning stiffness (reference: no)	7.512 (2.081~27.111)	0.002*	0.086 (0.007~1.082)	0.058
Medication (reference: non-biologic)	0.227 (0.097~0.531)	0.001*	0.125 (0.020~0.780)	0.026*
BMI (kg/m^2)	1.029 (0.955~1.109)	0.457		
VAS-pain score	1.678 (1.361~2.068)	<0.001*	1.615 (0.552~4.729)	0.382
BASDAI score	2.399 (1.779~3.237)	<0.001*	1.687 (0.939~3.032)	0.080
BASFI score	1.713 (0.875~1.146)	0.001*	1.553 (0.957~2.520)	0.075
BASMI score	1.000 (0.854~1.184)	0.995		
ASDAS-CRP score	2.889 (1.821~4.582)	<0.001*	1.394 (0.459~4.139)	0.550
MASES score	1.423 (1.187~1.106)	<0.001*	0.802 (0.542~1.186)	0.269
ASQoL	1.393 (1.243~1.562)	<0.001*	1.209 (1.019~1.433)	0.029*
ESH (mm/h)	1.009 (0.974~1.046)	0.604		
CRP (mg/L)	1.026 (0.980~1.075)	0.275		
DN4 (reference: no)	7.837 (2.707~22.694)	<0.001*	5.514 (0.875~34.744)	0.069
FM (reference: no)	16.954 (4.726~60.818)	<0.001*	6.322 (0.957~41.748)	0.056
PGA score	1.781 (1.406~2.206)	<0.001*	0.459 (0.092~2.290	0.342
PtGA score	1.780 (1.416~2.238)	<0.001*	1.084 (0.226~5.200)	0.920

OR: odds ratio, CI: confidence interval, BMI: body mass index, VAS: visual analogue scale, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, BASMI: Bath Ankylosing Spondylitis Metrology Index, ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score C-reactive protein, MASES: Maastricht Ankylosing Spondylitis Enthesitis Score, ASQoL: Ankylosing Spondylitis Quality of Life, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, DN4: douleur neuropathique en 4 questions, FM: fibromyalgia, PGA: Physician Global Assessment, PtGA: Patient Global Assessment. *Statistically significant (p<0.05).

individuals with axSpA and 13.7% in controls. Regarding comparisons between axSpA patients with CS and those without CS, higher scores of disease activity measures, including BASDAI, ASDAS-CRP, and MASES, and morning stiffness were found in patients with CS compared those without CS. In addition, VAS-pain, PtGA, PGA, and ASQoL scores were higher for axSpA patients with CS than for those without it. According to the correlation coefficients, BASDAI, ASQoL, and PtGA scores were strongly associated with CSI scores. Although BASDAI, BASFI, VAS-pain, ASDAS-CRP, MASES, PtGA, PGA, ASQoL, NP, and FM were substantial predictors of the presence of CS in the univariate analysis, only ASQoL and biologic drugs were contributing factors in the multivariate analysis.

CS, a hyperalgic state with increased pain sensitivity to stimuli, is common in rheumatic diseases and is included in the definition of chronic nociplastic pain in rheumatoid arthritis (RA), inflammatory bowel disease, SpA, and osteoarthritis [7,10,22]. In a study of RA and psoriatic arthritis, the rate of CS was reported as 35% according to the CSI ≥40 score [8]. The occurrence of CS in rheumatic diseases is often responsible for their pathogenesis. The immune cells involved in the production of proinflammatory cytokines and vasoactive substances contribute to the development of CS by affecting the spinal cord dorsal horn via nociceptive neurons. In animal models, TNF-α, IL-1β, IL-6, and IL-17 receptors have been shown to cause CS and pain by increasing C-fiber action potentials by affecting nociceptive and sensory neurons [23]. These findings can be regarded as reflecting the results of research into the interactions between disease activity and CS in clinical practice.

Some recent studies have focused on possible presence of CS in individual with axSpA. It has been reported that approximately 45% of patients have CS according to cut-off score of CSI ≥40 [10-12]. Kieskamp et al. [10] have also reported that CS is not only common in axSpA patients but is associated with poor quality of life. In addition, they reported that disease perception and obesity also affect disease activity apart from CS [11]. In the results of our study, when the data of axSpA for those with CS and those without CS are compared, the BASFI, BASMI, PtGA, PGA, BASDAI, ASDAS-CRP, MASES, and VAS-pain scores were higher in patients with CS than in those without it. In terms of comparisons between patients and controls, CS was present in 46.6% patients and 13.7% of controls. In our study, CS prevalence was higher than in previously reported studies. This result was similar to the findings of a relationship between emotional state, CS, and pain intensity by Serrano-Ibáñez et al. [24], who evaluated the results of COVID-19 in patients with chronic pain.

A study from Turkey found that axSpA patients with CS had worse disease activity scores, more sleep disturbance, and poorer quality of life than those without CS [12]. They reported higher rates of CS-related syndromes, such as migraine headache, irritable bowel syndrome, and chronic fatigue, in axSpA patients than in healthy controls, as assessed using CSI-B. Regarding disease activity measures and quality of life, our results were similar to results of this study. Although our patients with axSpA reported high rates of various CS-related syndromes, including depression and anxiety/panic attack, this may have been because we excluded patients previously diagnosed with FM and NP from our study. According to 2010 ACR FM diagnostic criteria, these syndromes are listed under the heading of somatic syndromes [25]. Another study conducted among AS patients revealed that the group with CS exhibited high disease activity, age, duration of disease, and NP rate than the group without CS. That study reported the prevalence of CS to be 45.7% and of NP to be 34.3% in AS patients [26]. Our results are comparable.

One study has suggested that patients with FM rarely meet the criteria for axSpA, while few axSpA patients meet the criteria for FM due to central pain sensitization. They reported FM at a rate of 24% in axSpA patients according to the 2010 ACR diagnostic criteria, but the rate varied in axSpA subgroups [27]. In our study, the presence of FM was found in 24.1% of the patients, while it was 6.3% in the controls. Our results thus support the findings of Baraliakos et al. [27]. In patients with FM and axSpA association, enthesitis, pain, and disease activity are more frequently reported, and functional status is reported as poor [28]. However, in a study in which patients with axSpA were evaluated by magnetic resonance imaging, the frequency of SpA in patients with FM was found to be 10.2% [29].

It has been reported that NP is seen at a rate of 7%~8% in society [30]. The presence of NP was reported at a rate of 31.6% in axSpA patients and 34.3% in AS patients [26]. In our study, NP was found at 23.3% in the axSpA group and 5.3% in controls. The low NP rate in our study can be explained by the sample size and the exclusion of patients with a previous NP diagnosis.

Central pain syndrome occurs despite the absence of painful stimuli in the individual's central nervous system. Chronic pain in rheumatic diseases can cover a diverse spectrum in terms of severity and stressors. This may result in an increased burden of

disease in axSpA patients [13]. In a study in which 644 patients with SpA were followed for 2.5 years, it was found that for the development of chronic widespread pain, advanced age, female sex, and anxiety were predictive factors [13].

The results of the current study showed that ASQoL scores and biologic drugs were independent risk factors for CS in the multivariate model. Our findings were consistent with the studies of Aykurt Karlıbel and Kasapoğlu Aksoy [12] and Kieskamp et al. [10], which revealed that ASQoL is associated with CS in axSpA. Since treatment with biologic drugs is effective in improving both disease activity and other disease-related outcomes [11], the inverse link between CS and biologic drug use found in this study may be explained by this mechanism.

The strengths of this study are as follows: this is the first study to evaluate the coexistence of CS, FM, and NP in axSpA patients and controls. It included a healthy control group, and the domains of disease-related outcome measures were adequately evaluated in axSpA patients. The study also has some limitations: it was conducted in a relatively small group during the COVID-19 pandemic, and given its cross-sectional nature, changes in CS and other parameters could not be evaluated in terms of long-term follow-up and treatment.

CONCLUSION

In this study, less than half of the axSpA patients exhibited CS. Patients with CS revealed higher disease activity, worse quality of life, and higher rates of FM and NP than did those without CS. More axSpA patients had FM and NP than control group members. Overall, CS, FM, and NP need to be considered in the treatment plans of axSpA patients.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

S.Ş, G.C., H.K. contributed equally to the collection, design, analysis, and interpretation of the data. S.Ş, G.C., H.K. contributed to the writing of the article and have read and approved the final version.

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