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Clinical and functional impact of central sensitization on patients with familial Mediterranean fever: a cross-sectional study

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Abstract

This study aimed to investigate the frequency of CS and its clinical and functional effects on familial Mediterranean fever (FMF). A hundred FMF patients were included in this study. The presence of CS was investigated by the central sensitization inventory (CSI). In addition to the detailed clinical features of patients and genetic mutations, quality of life, disability, sleep disorders, depression, anxiety, and fibromyalgia frequency were examined to evaluate the negative effects of CS on the individual. Patients were divided into groups according to the presence and severity of CS, and their results were compared. Correlation and multivariate regression analysis were performed to investigate the association of CS with selected demographic and clinical parameters. The mean CSI was 37.72 (SD: 19.35), and thirty-eight (38%) patients had CS. Sacroiliitis occurred in 11 patients (11%), amyloidosis in 3 (3%), and erysipelas-like erythema in 11 (11%). The most prevalent genetic mutation was M694/any compound heterogeneous (35.7%), followed by M69V homogeneous (30%). Regarding comparing the patients with and without CS, the number of attacks, disease activity, daily colchicine dose, and all investigated comorbidities were significantly higher in the patients with CS ($p < 0.05$). In regression analysis, gender, colchicine dose and sleep disturbance were detected as related parameters with CS (OR (95% CI): 6.05 (1.39; 26.32), p: 0.017, OR (95% CI): 6.69 (1.65; 27.18), p: 0.008, OR (95% CI): 1.35 (1.35; 1.59), p: 0.001, respectively). Concomitant pain sensitization appears to be related to FMF patients' clinical and functional characteristics. These results suggest taking into consideration CS in the management of FMF patients.

Keywords Familial Mediterranean fever · İnflammation · Central sensitization · Central sensitization inventory

Introduction

Familial Mediterranean fever (FMF) is a self-limiting autoinflammatory disease with well-defined genetic and clinical features. Recurrent episodes of fever and serositis accompanied by increased acute phase reactants and an excellent response to colchicine are the core components of the disease [1]. In the pathogenesis of the disease, activation of proinflammatory pyrin inflammation triggers typical febrile attacks through the increase of interleukin-1β (IL-1β)

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[2]. Similarly, cytokines, especially IL-1β, IL-6, and TNF-α, play an essential role in the pathophysiology of pain, which is one of the main clinical features of rheumatic diseases [3]. Central sensitization (CS) is a popular physiological phenomenon characterized by dysfunction in central pain regulation. Although definitions in the literature vary, CS can be summarized as an increased response of nociceptive neurons in the central nervous system (CNS) to normal or sub-threshold stimuli [4]. A process that begins with the activation of nociceptors by inflammatory mediators results in sensitization of the peripheral and central pathways if the stimulus continues [5]. Although the effect of increased inflammation on the nociception and sensitization process is not fully known, it seems likely that they are involved in a complex, bidirectional interaction. In various studies, it has been shown that in diseases with peripheral inflammation such as rheumatoid arthritis (RA) and ankylosing spondylitis (AS), structural and functional changes occur in the CNS in proportion to the inflammatory load [6]. Experimental animal models have shown that inflammatory activation of NOD-like receptor protein 3 (NLRP3) causes hyperalgesia and sensitization with the release of IL-1β in microglia. Similarly, when an IL-1β antagonist was administered to rats with experimental inflammation, a remarkable decrease in pain sensitization was observed [7]. CS negatively affects the patient in various ways, especially pain. Concomitant pain sensitivity causes deterioration in patient-reported disease activity and health-related measures in parallel with the increase in pain scores. Since this point of attention in rheumatism, a significant increase in data on CS has been observed in many rheumatic diseases. Unlike other rheumatic diseases, chronic pain, which is the hallmark of CS, is not common in FMF. Instead, attack features, response to treatment, and other clinical findings are likely to be associated with the presence of CS in these patients. CS is an independent parameter that affects many CNS functions, and various symptoms and diseases such as depression, anxiety, and fatigue can also be seen in patients with CS. In addition, independent of all these components, CS is directly associated with disability and reduced quality of life. Therefore, a detailed assessment based on a multimodal person-centred approach is recommended, targeting the psychological, behavioral, and social components of CS [8]. The involvement of different CS-related symptoms and diseases in the already complex autoinflammatory process of FMF will further complicate the management of these patients. At first glance, FMF and CS seem to share many elements at the cellular level. However, it is not yet known how and to what extent this is reflected in the patient clinic. In this study, we aimed to investigate the frequency of CS and its relationship with clinical parameters in FMF patients. We hypothesized that CS is not uncommon in FMF and adversely affects the patient's clinic and functionality.

Material and methods

Design and study population

This is a cross-sectional, observational, and multi-centre study. One hundred FMF patients were included in the study during their routine follow-ups in the rheumatology outpatient clinics of three different training and research hospitals between June 2021 and March 2022. Patients aged 18–75 years who were willing to participate were included. Patients were excluded if they had other systemic inflammatory rheumatic diseases and were using centrally acting pain medications (e.g., pregabalin, duloxetine, opioids) or glucocorticoids (> 10 mg prednisone or its equivalent) [9]. Verbal and written consent was obtained from all participants with the approval of the local ethics committee for the study (protocol number: 09.2019.1053, approval date: 6.12.2019). The study protocol was registered with Clinical Trials.gov (ClinicalTrials.gov identifier: NCT05177120).

Clinical variables

Demographic variables include age, gender, body mass index (BMI) and clinical variables including duration of disease, diagnosis time, presence of MEFV mutation/genotyping, number of attacks in the last 3–6 months, attack features, presence of amyloidosis/positive family history, colchicine dose/resistance, other FMF medications, and acute-phase reactant levels between attacks were obtained [10]. Colchicine resistance was defined as one or more attacks per month for three months or acute phase elevation in between attacks [11]. Pras activity score was used to assess disease severity. This scoring system includes the age of year onset, number of attacks per month, colchicine dose, and presence of arthritis, erysipelas-like erythema, and amyloidosis. A score of 3–5 indicates mild disease, a score of 6–8 indicates moderate disease, and a score of 9 or higher indicates severe disease [2].

Outcome measures

To investigate the effects of accompanying pain sensitization on the patient, comorbidities associated with CS were evaluated using the following scales. The most well-known are psychiatric disorders, such as depression and anxiety, fatigue, sleep disturbances, poor quality of life, and increased disability. In addition, the prevalence of fibromyalgia, accepted as the neurobiological continuum of CS, was also examined [4]. In

this way, it is aimed to determine the detailed clinical profiles of patients with CS.

Central sensitization inventory (CSI)

CSI was used as the primary outcome measure in the investigation of pain sensitivity. This scale consists of two parts, A and B; part A contains 25 questions about CS-related symptoms, while part B investigates the presence of central sensitivity syndromes. Only part A is used for scoring, and 40 points or higher are interpreted in favour of CS [12]. In addition to the presence of CS, scoring-based CS severity levels were defined on this scale; 0–29: subclinical; 30–39: mild; 40–49: moderate; 50–59: severe; and 60–100: extreme. The validity and reliability of CSI have been demonstrated in the Turkish population (test–retest reliability: 0.92, Cronbach's alpha: 0.93) [13].

Short form-36 (SF-36)

SF-36 is a frequently used self-reported quality-of-life (QoL) measure. This scale consists of 36 questions in eight domains of health. The content of this scale can be grouped under two main headings: physical and mental well-being. The scoring algorithm or SF-36v2 scoring software is used to calculate the SF-36, and the score range is between 0 and 100. Higher scores are associated with better health status and increased QoL [14].

Familial Mediterranean Fever – Quality-of-Life Scale (FMF–QoL)

The FMF–QoL was developed to evaluate the QoL in FMF patients. This scale consists of 20 questions in the form of a Likert scale, and the total score is between 0 and 80. High scores indicate a decrease in QoL [15, 16].

Health Assessment Questionnaire (HAQ)

This questionnaire was developed to assess disability in patients with arthritis. On the scale, the difficulty in performing 20 specific tasks from 8 categories is questioned, and the scoring is between 0 and 60. High scores are associated with increased disability [17].

Hospital Anxiety And Depression Scale (HADS)

HADS is one of the most frequently used scales to determine the presence of anxiety and depression in patients with physical illness. This scale consists of 14 questions; anxiety symptoms are questioned in half of the questions and depression-related complaints in the other half. A subscore of 8 or higher for depression or anxiety is considered a clinical case [18]. The HADS is frequently used to detect accompanying anxiety and depression in various rheumatic diseases.

Pittsburgh Sleep Quality Index (PSQI)

PSQI is used to quantitatively measure sleep quality in research settings. The questionnaire includes 21 questions covering seven components that investigate the symptoms of sleep disturbances. Scores range from 0 to 21, and a score of more than 5 is considered a sleep disorder [19].

Fibromyalgia Rapid Screening Tool (FiRST)

This scale consists of 6 questions investigating fibromyalgia's most relevant clinical features. The questions are answered as yes/no, and five or more out of six points in total are in favour of fibromyalgia (FM) [20].

Statistical analysis

The sample size calculated based on the previous study was 32 per group to achieve an error alpha of 0.05 for a 95% confidence interval (CI) and power of 0.95 [21]. Normality tests were first applied for statistical model selection. The Shapiro–Wilk test, skewness–kurtosis, and histogram graphics were used to evaluate the data distribution. Parametric data were reported as mean and standard deviation (SD), while non-parametric data were reported as median and interquartile range (IQR). In comparing patients with central sensitization (CS), the Mann–Whitney *U* test and independent *t* test were used for continuous data. Fisher's exact test was used for categorical variables when more than 20% of cells had expected frequencies < 5, and Pearson's chi-square test was used for others [22]. Analysis of CS subgroups was applied using ANOVA and the Kruskal–Wallis test. Multiple comparisons were performed with post hoc tests for significant differences between groups; the Tukey test for parametric data and the Mann–Whitney *U* test with Bonferroni correction were used for non-parametric data in post-hoc analysis. Variables that differed between groups were reanalyzed according to the severity of CS. Patients were compared by dividing them into five levels: subclinical, mild, moderate, severe, and extreme CS. Kruskal Wallis and Mann–Whitney *U* test with Bonferroni correction was used for attack number and HAQ analysis, while ANOVA and post-hoc Tukey test were used for other variables.

Finally, bivariate correlation analysis was performed to investigate the relationship between the presence of CS and other clinical variables. A forward stepwise multivariate regression model was constructed with covariates significantly associated with CS in univariate analysis. Regression assumptions were tested, including the linearity of the relationship and the absence of multicollinearity. $P < 0.05$ is considered statistically significant with a 95% CI using SPSS, version 23.0 (IBM Corporation, Armonk, NY, USA).

Results

Seventy-three of the 100 patients were female, and the mean age was 38.38 (SD: 13.60). The patients' mean diagnosis time and disease duration were 10.81 (SD: 9.16) and 17.55 (SD: 12.73) years, respectively. Ninety-seven percent of the patients were on regular colchicine treatment, and the mean colchicine dose was 1.34 (SD: 0.49) mg/day. Thirteen patients had colchicine resistance, and 10% of all patients were receiving biologic therapy. Half of these patients (5%) were under anakinra, and the other half (5%) were under canakinumab treatment. The mean number of attacks was calculated as 1.47 (SD: 2.14) for the last three months and 2.58 (SD: 3.74) for the last six months. Disease severity was mild in 57%, moderate in 32%, and severe in 11%, with a mean Pras score of 5.31 (SD: 2.43). Sacroiliitis occurred in 11 patients (11%), erysipelas-like erythema in 11 (11%), exercise-induced leg pain in 23 (23%), arthralgia in 35 (35%), polyneuropathy in 2 (2%), amyloidosis in 3 (3%) and proteinuria in 10 (10%). The mean ESR (mm/h) between attacks was 18 (SD: 15.21), and the median CRP level (mg/dl) was 3.2 (IQR: 11.2). Serum amyloid A (U/L) results were available in 34 patients, and the median value was 1.01 (IQR: 2.96). Table 1 represents the demographic and clinical characteristics of the patients according to CS.

Genetic tests were performed on 88 patients, and MEFV mutations were detected in 66 (75%) of them. The most prevalent genetic mutation was M694/any compound heterogeneous (35.7%), followed by M69V homogeneous (30%), and multiple genetic mutations were detected in nineteen patients. No significant difference was found in genetic mutations according to the presence of CS. Detailed genetic results are listed in Table 2.

The mean CSI was 37.72 (SD: 19.35), and 38 (38%) patients had CS according to the CSI. With respect to gender distribution, the mean CSI score was 41.76 (SD: 18.38) in women and 26.78 (SD: 17.88) in men, and the difference was statistically significant ($p < 0.001$; 95% CI: 6.83–23.15). The frequency of the CS-related diseases included in the CSI part B was found to be 7% for restless legs syndrome, 6% for chronic fatigue syndrome, 4% for FM, 2% for temporomandibular joint disease, 16% for tension headaches/migraines, 6% for irritable bowel syndrome, 2% for multiple chemical sensitivities, 1% for neck injury, 14% for anxiety or panic attacks, and 11% for depression. The comparison of patient characteristics according to the presence of CS is shown in Table 3.

According to CS, significant differences were found in all clinical scores in FMF patients ($p < 0.05$). All other scores, except SF-36, were significantly higher in patients with CS; all domains of SF-36 were low in patients with CS, indicating poor quality of life. The frequency of FM investigated with FiRST was calculated as 29% (in 29 out of 100 patients). According to the depression subscale of HADS, 33 patients (33%) had clinical depression, and this frequency was significantly higher in the CS group (p 0.03). Anxiety was detected in 47 patients (47%), and its incidence was significantly higher in patients with CS ($p < 0.001$). In the evaluation of sleep quality, sleep disturbance was found in 80.6% of the patients, and this rate did not differ significantly according to the presence of CS (p 0.09). However, the mean PSQI scores of patients with CS are significantly higher than those without. All the clinical scores of the patients are summarized in Table 3.

A Kruskal–Wallis test showed a statistically significant difference in the number of attacks and HAQ score between different CSI levels; H(4): 17.69, p 0.001 and H(4): 19.33, p 0.001 for the number of attacks in the last 3–6 months, respectively, and H(4): 25.55, $p < 0.001$ for HAQ. In a one-way analysis of variance, the effect of CSI severity on colchicine dose and all clinical scales was found to be significant, but the similar relationship was not observed in Pras score (F(4,92): 4.76, p: 0.002 for colchicine dose; F(4,95): 2.26, p: 0.068 for Pras score). Comparisons of the patients according to the CS levels (subclinical, mild, moderate, severe, and extreme CS) and the results of post hoc analysis are shown in Table 4.

The number of attacks, colchicine dose, Pras disease severity score, and correlations of all clinical scales with CSI, which differed between the groups, were investigated. Negative correlations are observed in all domains of SF-36 (correlation coefficient is ranged from − 383 to − 648, $p < 0.001$), while positive correlations are observed in all other variables. Correlation analysis results are shown in Table 5.

Logistic regression was performed to evaluate the effect of selected variables on the presence of CS at the last stage of the analysis. In the univariate logistic regression analysis, gender (odds ratio (OR) 5.01; 95% CI: 1.58–15.94), number of attacks in the last 6 months (OR 1.16, 95% CI: 1.02–1.31), colchicine dose (OR 7.68; 95% CI: 2.50–23.56), colchicine resistance (OR 0.23; 95% CI: 0.07–0.83), Pras score (OR 1.27; 95% CI: 1.06–1.52), HADS total (OR 1.12; 95% CI: 1.06–1.19) and PSQI (OR 1.32; 95% CI: 1.14–1.53) were significantly associated

Table 1 Baseline characteristics of the study population

	FMF patients (*n*:100)		
	CS positive (*n* = 38)	CS negative (*n* = 62)	*P* value
Gender, *n* (%)			0.004*
Female	34 (89.50)	39 (62.90)	
Male	4 (10.50)	23 (37.10)	
Age (year), mean (SD)	36.79 (12.62)	39.35 (15.11)	0.362
BMI (kg/m^2), mean (SD)	28.44 (8.31)	26.10 (5.81)	0.100
Age at onset (year), mean (SD)	16.59 (14.51)	18.14 (11.61)	0.565
Age at diagnosis (year), mean (SD)	9.27 (6.98)	11.74 (10.21)	0.159
Family history of FMF, *n* (%)	19 (50.00)	35 (56.50)	0.530
Family history of amyloidosis, *n* (%)	3 (7.90)	5 (8.10)	0.976
Number of attacks in the last 3 months, median (IQR)[a]	2.00 (2.00)	0 (1.00)	< 0.001*
Number of attacks in the last 6 months, median (IQR)[a]	3.50 (4.25)	0 (2.00)	< 0.001*
Attack features, *n* (%)			
Fever (≥ 38°)	23 (60.50)	36 (58.10)	0.808
Abdominal pain	30 (78.90)	53 (85.50)	0.398
Chest pain	17 (44.70)	24 (38.70)	0.552
Arthritis	10 (26.30)	15 (24.20)	0.812
Erythema	4 (10.50)	7 (11.30)	> 0.99
Myalgia	10 (26.30)	18 (29.00)	0.769
Exercise induced leg pain, *n* (%)	11 (28.90)	12 (19.40)	0.269
Arthralgia, *n* (%)	13 (34.20)	22 (35.50)	0.897
Sacroiliitis, *n* (%)	4 (10.50)	7 (11.30)	> 0.99
Polyneuropathy, *n* (%)	1 (2.60)	1 (1.60)	> 0.99
Proteinuria, *n* (%)	4 (10.50)	6 (10.00)	> 0.99
Amyloidosis, *n* (%)	0 (0)	3 (4.80)	0.286
APRs levels between attacks,			
ESR (mm/h), mean (SD)	15.53 (14.98)	19.48 (14.03)	0.337
CRP (mg/L), median (IQR)[a]	3 (9.16)	3.4 (7.83)	0.809
Serum amyloid A (U/L), median (IQR)[a] (*n*)	0.98 (1.02) (15)	1.18 (3.28) (19)	0.891
Colchicine dose (mg/day), mean (SD)	1.58 (0.50)	1.19 (0.41)	< 0.001*
Colchicine resistance, (%)	9 (23.70)	4 (6.80)	0.017*
Biologics use, *n* (%)	2 (5.30)	8 (12.90)	0.216
Pras FMF severity score, mean (SD)	6.13 (2.40)	4.81 (2.29)	0.008*
Pras-mild, *n* (%)	16 (42.10)	41 (66.1)	0.06
Pras-moderate, *n* (%)	16 (42.10)	16 (25.8)	
Pras-severe, *n* (%)	6 (15.80)	5 (8.1)	

CS Central sensitization, *SD* Standard deviation, *BMI* Body mass index, *IQR* Inter-quartile range, *APR* Acute phase reactant

*Statistically significance

[a]Mann–Whitney *U* test was performed

with the presence of CS ($p < 0.05$). Subsequently, multiple regression models were created according to the significance levels of these variables. The first model including PSQI (chi-square: 17.885, df: 1, Nagelkerke's R2: 0.251), the second model including PSQI and Col dose (chi-square: 27.076, df: 2, Nagelkerke's R2: 0.361), and the full model including PSQI, Col dose, and gender variables (chi-square: 34.186, df: 3, Nagelkerke's R2: 0.439) were statistically significant ($p < 0.001$). The logistic regression results indicate that gender, PSQI, and Col dose are significant predictors of CS and that all three covariates explain 43.9% of the variability of CS. Col dose is the most significant predictor, with an OR of 6.69 (95% CI: 1.65–27.18). When the gender changes from male to female, the odds of CS are 6.05 times higher if all other variables stay the same (95% CI: 1.39–26.32). Univariate and multivariate regression analysis results are shown in Table 6.

Table 2 Genetic features of the FMF patients

	FMF patients (*n*:100)		
	CS positive (*n* = 38)	CS negative (*n* = 62)	*P* value
Unknown	12 (15.80)	14 (12.90)	0.448
No mutation detected	3 (7.90)	3 (4.80)	
Positive	23 (72.60)	45 (60.50)	
M694V (homozygous)	4 (19.00)	11 (37.90)	0.150
M694V (heterozygous)	4 (18.20)	8 (25)	0.742
M694V (heterozygous-any)	7 (31.80)	13 (38.20)	0.625
M680I (heterozygous)	1 (4.80)	3 (10.30)	0.630
M680I (heterozygous-any)	3 (14.30)	5 (16.70)	> 0.99
V726A (heterozygous)	1 (4.80)	1 (3.60)	> 0.99
V726A (heterozygous-any)	2 (9.50)	4 (13.80)	> 0.99
R202Q (homozygous)	2 (9.50)	2 (6.90)	> 0.99
R202Q (heterozygous)	3 (14.30)	2 (6.70)	0.637
R202Q (heterozygous-any)	1 (4.80)	4 (12.90)	0.367
Another	1 (4.80)	0 (0)	> 0.99

CS Central sensitization, data are presented as *n* (%)

Discussion

It is now well-known that musculoskeletal inflammation is not the only driver of rheumatic diseases. The peripheral and central nervous systems play an active role in this neuro-immune interaction [23]. Central sensitization (CS) is the main mechanism that comes to the fore in this context, and it has brought a new perspective to various clinical parameters, especially pain in rheumatism. Inflammatory mediators play a role in the sensitization process's fundamental stages, making CS important in rheumatic diseases. One of these is pyrin activity in FMF, which causes severe inflammatory burden through persistent subclinical inflammation and recurrent systemic attacks, which seems likely to affect sensitization mechanisms. Therefore, this study aimed to investigate the relationship between CS and FMF and the clinical consequences of this possible association. CS was detected according to CSI in 38 of one hundred (38%) FMF patients. Sixty-three percent of the participants in the study were female. In the analysis of the effect of gender on the distribution of CS, it was observed that the ratio of female gender was significantly higher in patients with CS (89.5%). In addition, the mean CSI scores of female patients were also higher. It has been reported that CS is more common in females in different patient groups, and the female gender was identified as a risk factor for developing CS in axial SpA patients [21]. The identical association with regression analysis was confirmed in FMF patients. The effect of gender on the initiation and maintenance of neuroinflammation appears to be directly related to the increased frequency of CS in women [24]. Behaviours of immune cells in women differs compared to men, and this is explained by the effects of sex hormones at the molecular level [25]. While the course of the disease and adherence to treatment did not differ according to gender in FMF, findings, such as anxiety, depression, and migraine were reported to be higher in female patients [26]. Similar results were observed in FMF patients with CS, suggesting that female gender influences the patient with FMF through pain sensitivity rather than the disease itself. When the clinical characteristics of the patients are analyzed in terms of CS presence, an increase in the frequency of attacks and disease activity draws attention to patients with CS. Detailed examination of the pathophysiology of FMF and CS at the cellular and molecular level may make the difference between these groups understandable. As a result of the pyrin–microtubule interaction disrupted by the MEFV mutation in FMF, pyrin inflammasome formation is triggered, and the release of proinflammatory cytokines, especially IL-1β, increases [27]. The NLRP3 inflammasome is the main source of IL-1β and has been implicated as one of the potential treatment targets for chronic pain. IL-1β plays an active role at almost all levels in the nociception and pain sensitization process: while it causes pain and peripheral sensitization with direct stimulation at the nociceptor level, it triggers glial activation at the spinal and supraspinal levels. The role of NLRP3 inflammasome and IL-1β in nociception has been demonstrated in large patient groups, including central neuropathic and visceral pain [28]. Abdominal pain is the predominant symptom of FMF, but unlike other rheumatological diseases, it is acute, severe, self-limiting, and not chronic. Although the type and character of pain are different in FMF, the fundamental principles of CS are the same in these patients. Visceral hyperalgesia (VH) is the non-musculoskeletal

Table 3 Comparison of patients with and without central sensitization in terms of function, quality of life, sleep and fibromyalgia

	FMF patients (*n*:100)		
	CS positive (*n*:38)	CS negative (*n*:62)	*P* value
CSI-B, *n* (%)			
Restless leg syndrome	1 (2.60)	6 (9.70)	0.247
Chronic fatigue syndrome	4 (10.50)	2 (3.20)	0.197
FM	3 (7.90)	1 (1.60)	0.152
Temporomandibular joint disorder	2 (5.30)	0 (0)	0.142
Tension headaches/migraines	11 (28.90)	5 (8.10)	0.006*
Irritable bowel syndrome	3 (7.90)	3 (4.80)	0.671
Multiple chemical sensitivities	1 (2.60)	1 (1.60)	> 0.99
Neck injury	1 (2.60)	0 (0)	0.380
Anxiety or panic attacks	9 (23.70)	5 (8.10)	0.029*
Depression	7 (18.40)	4 (6.50)	0.063
FMFQoL, mean (SD)	39.30 (13.35)	20.92 (17.51)	< 0.001*
HAQ, median (IQR)[a]	0.30 (0.57)	0 (0.13)	< 0.001*
HAD-anxiety, mean (SD)	10.13 (4.83)	5.87 (4.55)	< 0.001*
HAD-depression, mean (SD)	7.61 (4.41)	4.79 (3.48)	0.001
PSQI, mean (SD)	9.68 (3.95)	6.58 (2.98)	< 0.001*
FiRST, mean (SD)	4.05 (1.87)	2.21 (1.92)	< 0.001*
FM, *n* (%)	18 (47.40)	11 (17.70)	0.002*
SF-36, physical functioning, mean (SD)	58.33 (22.74)	81.53 (18.43)	< 0.001*
SF-36, role physical, mean (SD)	32.64 (36.75)	74.60 (36.63)	< 0.001*
SF-36, role emotional, mean (SD)	38.89 (41.02)	68.82 (41.32)	0.001*
SF-36, Energy/fatigue, mean (SD)	32.78 (19.17)	57.90 (23.34)	< 0.001*
SF-36, emotional well-being, mean (SD)	46.47 (20.32)	65.56 (20.81)	< 0.001*
SF-36, social functioning, mean (SD)	50.69 (27.05)	75.20 (23.79)	< 0.001*
SF-36, bodily pain, mean (SD)	34.23 (26.52)	65.44 (25.10)	< 0.001*
SF-36, general health, mean (SD)	30.14 (21.40)	50.08 (21.38)	< 0.001*
SF-36, health change, mean (SD)	40.97 (28.13)	56.05 (22.94)	0.005*

SD Standard deviation, *CS* Central sensitization, *CSI* Central sensitization inventory, *FMFQoL* Familial Mediterranean fever quality of life, *HAQ* Health assessment questionnaire, *HADS* Hospital anxiety depression Scale, *PSQI* Pittsburg sleep quality index, *FiRST* Fibromyalgia rapid screening tool, *FM* Fibromyalgia, *SF*-36 Short form-36

*Statistically significance

[a]Mann–Whitney *U*

counterpart of the increase in pain sensitivity, which is the main feature of CS. The most well-known example of VH is irritable bowel syndrome (IBS), one of the central sensitivity syndromes [29]. Although the pathophysiology of VH is not known completely, it is thought to occur due to a decrease in the visceral nociceptor threshold and maladaptive changes in the central pain processing [30]. In FMF, stimulation of nociceptors by inflammatory mediators, especially IL-1β, during subclinical inflammation and recurrent attacks is likely to initiate and maintain the VH process. According to this hypothesis, an increase in the frequency of attacks (and thus in disease activity scores) is observed with the increased sensitivity of nociceptors in the serosal membranes. On the other hand, it can be suggested as an alternative mechanism that the increased burden of inflammation facilitates the sensitization process in patients with more severe diseases. It has been reported that thalamocortical sensitization following persistent colonic inflammation in rat models of inflammatory bowel disease may be one of the central mechanisms of VH [31]. Colchicine (Col) resistance, early disease onset, high activity score, and long attack duration have been reported as predictors of persistent inflammation in pediatric patients with FMF [32]. Of these, the Col resistance and higher disease activity found in FMF patients with CS are likely to be associated with the persistence of inflammation and development of VH. Persistent inflammation is often recognized by elevated CRP and serum amyloid A (SAA) levels between attacks [33, 34]. In this study, no statistically significant increase was observed in ESR,

Table 4 Clinical features and post-hoc results of patients according to CSI levels

	FMF patients (*n*:100)					*P* value	Post-hoc
	CS levels						
	Subclinic (I) (*n*: 46)	Mild (II) (*n*: 16)	Moderate (III) (*n*: 17)	Severe (IV) (*n*: 7)	Extreme (V) (*n*: 14)		
Number of attacks in the last 3 months, median (IQR)[a]	0 (1.00)	0 (1.00)	1.00 (1.50)	2.00 (1.00)	1.50 (3.50)	0.001*	I vs III, IV, V II vs III, IV, V
Number of attacks in the last 6 months, median (IQR)[a]	0 (2.00)	0 (3.25)	3.00 (4.00)	4.00 (2.00)	2.00 (6.00)	< 0.001*	I vs III, IV, V II vs III, IV
Colchicine dose (mg/day), mean (SD)	1.16 (0.44)	1.29 (0.32)	1.56 (0.39)	1.71 (0.57)	1.53 (0.60)	0.002*	I vs III, IV, V II vs V
Pras FMF severity score, mean (SD)	4.91 (2.47)	4.50 (1.71)	6.58 (2.57)	5.71 (2.06)	5.79 (2.39)	0.068	–
FMFQoL, mean (SD)	19.07 (15.77)	26.33 (21.56)	33.65 (10.08)	41.14 (15.08)	28.11 (18.31)	< 0.001*	I vs III, IV, V II vs V
HAQ, median (IQR)[a]	0 (0.13)	0 (0.09)	0.12 (0.31)	0.62 (0.83)	0.53 (0.93)	< 0.001*	I vs III, IV, V II vs IV, V III vs V
HAD-anxiety, mean (SD)	5.35 (4.46)	7.38 (4.60)	7.88 (3.74)	11.14 (4.78)	12.36 (5.12)	< 0.001*	I vs IV, V II vs V
HAD-depression, mean (SD)	4.17 (2.88)	6.56 (4.49)	5.29(3.77)	8.86 (4.38)	9.79 (4.00)	< 0.001*	I vs IV, V III vs V
PSQI, mean (SD)	6.37 (3.15)	7.13 (2.47)	8.25 (3.94)	11.57 (4.37)	10.50 (3.29)	< 0.001*	I vs IV, V II vs IV III vs V
FiRST, mean (SD)	2.13 (2.04)	2.44 (1.59)	2.82 (1.51)	4.29 (1.11)	5.42 (1.60)	< 0.001*	I vs IV, V II vs V III vs V
SF-36, physical functioning, mean (SD)	85.00 (14.79)	71.56 (24.13)	73.24 (14.02)	55.83 (23.54)	40.00 (18.26)	< 0.001*	I vs IV, V II vs V III vs V
SF-36, role physical, mean (SD)	76.09 (37.25)	70.31 (35.61)	44.12 (40.05)	33.33 (40.82)	17.31 (25.79)	< 0.001*	I vs V II vs V
SF-36, role emotional, mean (SD)	69.57 (40.87)	66.67 (43.89)	52.94 (42.59)	44.45 (50.19)	17.94 (25.88)	0.001*	I vs V II vs V
SF-36, energy/fatigue, mean (SD)	61.30 (22.72)	48.13 (23.01)	43.53 (19.43)	20.00 (14.14)	24.62 (12.98)	< 0.001*	I vs III, IV, V II vs IV, V
SF-36, emotional well-being, mean (SD)	67.33 (21.61)	60.50 (18.00)	51.35 (22.10)	46.00 (23.01)	40.31 (16.03)	< 0.001*	I vs V
SF-36, social functioning, mean (SD)	76.09 (23.25)	72.66 (25.91)	58.09 (20.22)	45.83 (34.16)	43.27 (30.89)	< 0.001*	I vs IV, V II vs V
SF-36, bodily pain, mean (SD)	68.32 (24.68)	57.19 (25.25)	51.76 (22.62)	16.25 (18.42)	19.62 (19.97)	< 0.001*	I vs IV, V II vs IV, V III vs IV, V
SF-36, general health, mean (SD)	54.35 (22.50)	37.81 (11.10)	41.18 (22.47)	25.83 (15.63)	17.69 (14.52)	< 0.001*	I vs II, IV, V III vs V
SF-36, health change, mean (SD)	55.43 (23.52)	57.81 (21.83)	52.94 (26.34)	25.00 (22.36)	32.69 (27.74)	0.005*	I vs IV, V II vs IV

SD Standard deviation, *CS* Central sensitization, *CSI* Central sensitization inventory, *FMFQoL* Familial Mediterranean fever quality of life, *HAQ* Health assessment questionnaire, *HADS* Hospital anxiety depression scale, *PSQI* Pittsburg sleep quality index, *FiRST* Fibromyalgia rapid screening tool, *SF*-36 Short form-36

*Statistically significance

[a]Kruskal–Wallis and Bonferroni adjusted posthoc analysis

Table 5 Correlation of clinical variables with CSI

	CSI score	
	Correlation coefficent	*P* value
Number of attacks in the last 3 months[a]	0.348	<0.001*
Number of attacks in the last 6 months[a]	0.354	<0.001*
Colchicine dose (mg/day)	0.420	<0.001*
Pras FMF severity score	0.242	0.015*
FMFQoL	0.571	<0.001*
HAQ[a]	0.525	<0.001*
HADS-anxiety	0.575	<0.001*
HADS-depression	0.471	<0.001*
PSQI	0.447	<0.001*
FiRST	0.666	<0.001*
SF-36, physical functioning	−0.630	<0.001*
SF-36, role physical	−0.632	<0.001*
SF-36, role emotional	−0.481	<0.001*
SF-36, energy/fatigue	−0.648	<0.001*
SF-36, emotional well-being	−0.457	<0.001*
SF-36, social functioning	−0.476	<0.001*
SF-36, bodily pain	−0.645	<0.001*
SF-36, general health	−0.589	<0.001*
SF-36, health change	−0.383	<0.001*

CS Central sensitization, *CSI* Central sensitization inventory, *FMFQoL* Familial Mediterranean Fever Quality of Life, *HAQ* Health assessment questionnaire, *HADS* Hospital anxiety depression scale, *PSQI* Pittsburg sleep quality index, *FiRST* Fibromyalgia rapid screening tool, *SF*-36 Short form-36

*Statistically significance

[a]Spearman correlation was performed

CRP, or SAA values between attacks in patients with CS. Although significantly higher Pras scores were detected in patients with CS, this significance was not maintained in the CS subgroup comparison and regression analysis. CS and FMF disease activity parameters are not independent, and more comprehensive studies are needed to reach definitive conclusions.

Col is a depolymerizing microtubule agent, and it has been reported to affect axonal transport in peripheral and central neurons and its effect on immune cells. Based on this mechanism, it has been suggested that Col prevents stress-induced FMF attacks by reducing neuro-immune interaction with neurosecretory inhibition [35]. In this study, patients with CS had higher daily Col doses and Col resistance than patients without CS, and there was a positive correlation between Col dose and CSI. In addition, colchicine dose was found to be associated with the presence of CS in the regression analysis. It is known that pain sensitization negatively affects the response to treatment for many diseases. A close relationship was found between dysregulated central pain processing and decreased response to treatment in RA, and it was reported that central inhibitory mechanisms may be a potential treatment target in these patients [36]. Similarly, CS was associated with the persistence of pain and inadequate response to treatment for chronic pelvic pain and interstitial cystitis [37]. A higher daily Col dose and resistance rate observed in patients with CS may be associated with decreased treatment response due to sensitization, or it can be interpreted in favour of an increase in the development of CS in patients with a high inflammatory burden. In patients with FMF unresponsive to Col, a significant decrease in attack frequency and acute phase reactants were demonstrated with SSRI treatment, supporting the effect of central mechanisms on disease activation and treatment response in FMF [38]. These results suggest that the need for higher doses of Col may be a clue to clinicians for the development of CS in FMF patients. The frequency of fibromyalgia (FM), the prototype of central sensitivity syndromes, was investigated with FiRST and was found to be higher in the group with CS (47.4% vs 17.7%). These results are reasonable, since CS is considered the neurobiological continuum of FM [4]. In addition, a study investigating genes related with

Table 6 Univariate and multivariate regression analysis results examining the relationship between CS and selected demographic and clinical parameters

Covariate	Univariate				Multivariate			
	OR	*P* value	95% CI		OR	*P* value	95% CI	
			Lower	Upper			Lower	Upper
Gender (Female/ Male)	5.01	0.006*	1.58	15.94	6.05	0.017*	1.39	26.32
Number of attacks in the last 6 months	1.16	0.022*	1.02	1.31				
Colchicine dose (mg/day)	7.68	<0.001*	2.50	23.56	6.69	0.008*	1.65	27.18
Colchicine resistance (yes/no)	0.23	0.024*	0.07	0.83				
Pras FMF severity score	1.27	0.011*	1.06	1.52				
HADS total	1.12	<0.001*	1.06	1.19				
PSQI	1.32	<0.001*	1.14	1.53	1.35	0.001*	1.35	1.59

HADS Hospital Anxiety Depression Scale, *PSQI* Pittsburg Sleep Quality Index, *OR* Odds ratio, *CI* confidence interval

*Statistically significance

inflammatory pathways showed that MEFV gene missense mutations were associated with FM and increased plasma IL-1β levels. The authors have suggested that rare missense variants in the MEFV gene may trigger FM [39]. As mentioned above, this increase in IL-1β is noteworthy, because it is the intersection point of FMF and CS mechanisms. In another study, the frequency of the R202Q polymorphism of the MEFV gene was significantly higher in FM patients compared to controls. Morning fatigue and irritable bowel syndrome (IBS) have been associated with the R202Q polymorphism [40]. In our study, no significant difference was found between the groups in FMF-related MEFV mutations, and the effect of the missense mutations on the clinical course of FMF patients is unknown. These missense mutations related with the MEFV gene predispose to pain sensitivity and CS-related diseases, such as FM and IBS.

In addition to the aforementioned clinical effects of CS in FMF, its negative impacts on the functionality of patients can be observed in this study. CS affects the pain pathways of the nervous system and leads to various comorbidities, poor quality of life, and disability. Therefore, the diagnosis of diseases, such as chronic fatigue syndrome and depression, which are known to be associated with CS, is questioned in the CSI part-B. Although only tension-type headaches and migraines, anxiety, and panic attacks among those diagnosed in part B differed between groups, all comorbidities investigated in FMF increased in parallel with the severity of CS. While the general perception is that these comorbidities are a consequence of the underlying chronic disease, the strong correlation of all scores with CSI indicates the role of pain sensitization. Among these, the fact that the PSQI score was associated with CS in the regression analysis necessitates more attention to sleep disturbances in FMF patients. It has been shown that anxiety and hyperalgesia develop after a one-night total sleep deprivation period in healthy individuals. These results were interpreted by the authors as meaning that sleep distubances may trigger pain sensitization by causing hyperexcitability in the central nervous system [41]. Similarly, Nijs et al. suggest that sleep disturbances increase glial stress, leading to neuroinflammation and thus CS [42]. This relationship seems to be reasonable in FMF patients as well. Considering the clinical implications of CS, early diagnosis and treatment of sleep disorders in rheumatologic patients, including FMF, may yield greater benefits than thought. CS was identified as an independent risk factor for the poor quality of life in SpA patients and disability in patients with RA and PsA [43, 44]. The increase in disability and decrease in QoL parallel with the severity of CS detected in FMF patients are consistent with these findings. As a result, in the long term, CS dominates the clinical picture and adversely affects the functionality of most patients in different ways.

One of the strengths of this study is that the FMF–CS relationship was examined for the first time. In addition to analyzing FMF patients' detailed clinical and genetic characteristics, possible comorbidities associated with CS have also been extensively investigated. In this way, it aims to determine the detailed clinical and functional profiles of FMF patients with CS and increase awareness. The cross-sectional design and the absence of a control group are limitations of this study.

Conclusions

CS was detected in 38% of FMF patients, and in parallel with the severity of CS, an increase in disease activity, treatment resistance, and comorbidities were observed. This association in the absence of a chronic pain background indicates the need for a different perspective both in managing FMF patients and in the role of CS in rheumatic diseases.

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