ORIGINAL ARTICLE

The Frequency of Fibromyalgia and its Relationship With Disease Activity in Female Patients With Behçet's Disease: A Cross Sectional Study

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ABSTRACT

Objectives: This study aims to determine the incidence of fibromyalgia (FM) in female patients with Behçet's disease (BD) and to investigate whether disease activity changes in the presence of FM in female patients with BD.

Patients and methods: This cross-sectional study included 72 female patients with BD (mean age 39.7±10.5 years; range, 22 to 74 years) between June 2018 and February 2019. The frequency of FM was evaluated according to the American College of Rheumatology alternative criteria. Active clinical features and BD activity were evaluated with the Behçet's disease activity form (BDCAF).

Results: The prevalence of FM was 29.2% in the BD patients. BD clinical activity index, patients' perceptions of disease activity and clinicians' overall perceptions of disease activity scores were significantly higher in BD patients with FM (p=0.003, p<0.001 and p=0.025, respectively). The active clinical features of BD were not different between the groups except for genital ulcer. The prevalence of active genital ulcers was higher in BD patients with FM than in BD patients without FM (38.1% vs. 13.7%, respectively).

Conclusion: Disease activity is higher in female BD patients with FM than those without FM. High disease activity in female BD patients with FM may be associated with the presence of genital ulcers.

Keywords: Behçet's disease, fibromyalgia, genital ulcer.

Fibromyalgia (FM) is a common cause of chronic widespread musculoskeletal pain, often accompanied by fatigue, cognitive disturbance, psychiatric symptoms and multiple somatic symptoms. The prevalence of FM varies between 1.7% and 6.4% in the community and the frequency is increased among patients with chronic inflammatory arthritis and systemic autoimmune rheumatic disease.[1-7] In recent years, extensive research has been conducted on the immunological background of FM. In general, the findings do not support the belief that FM is a non-inflammatory rheumatic disease.[8-12] In addition, disease activity was found to be higher in rheumatic diseases such as rheumatoid arthritis (RA), axial spondyloarthropathy and Sjögren's syndrome (SS) accompanied by FM.[13-15] Behçet's disease (BD) is characterized by recurrent oral aphthae and any of the several systemic manifestations including genital aphthae, ocular disease, skin lesions, gastrointestinal involvement, neurologic disease, vascular disease or arthritis. The incidence of FM in BD is higher than in the

normal population and its frequency ranges from 5.7% to 37.1% according to data from a limited number of studies.[16] The results of studies investigating the relationship between FM and BD activity are contradictory.[17-20] BD is known to be more severe in males and FM is more common in females.[3,21] Therefore, it is not appropriate to evaluate the relationship between disease activity and FM in patients with BD without grouping by sex. In 2013, alternative criteria for classifying FM were developed by the American College of Rheumatology (ACR) and these criteria were easier to use and found to be high in specificity compared to the 2010 ACR preliminary diagnostic criteria for FM.[22] In this study, we aimed to determine the incidence of FM in female patients with BD and to investigate whether disease activity changes in the presence of FM in female patients with BD.

PATIENTS AND METHODS

This cross-sectional study was conducted at Bursa Yüksek İhtisas Training and Research Hospital between June 2018 and February 2019. Among 155 female patients diagnosed with BD in the rheumatology outpatient clinic records, 97 patients who volunteered to participate in the study were included in the first evaluation (ClinicalTrials.gov ID: NCT03543709). Finally, 72 female BD patients (mean age 39.7±10.5 years; range, 22 to 74 years) were included according to the inclusion criteria which were being between the ages of 18 and 75 years and meeting the International Study Group classification criteria.[23] The exclusion criteria were not cooperating sufficiently to complete the surveys or having thyroid disease, pregnancy, diabetes, chronic renal failure, cancer or systemic rheumatic disease. The participants who were not included in the study as a result of the initial evaluation are summarized in Figure 1 together with the reasons for exclusion. The study protocol was approved by the Uludağ University School of Medicine Clinical Research Ethics Committee (2018-02/14). A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patients' clinical features, demographic characteristics and medications were recorded. Human leukocyte antigen (HLA)-B51 genetic test results were obtained from patient charts. Behçet's disease activity form (BDCAF) was used by the clinician to assess disease activity.[24] In BDCAF, the presence of 12 clinical features of BD within the last four weeks were questioned. These features consisted of arthralgia, arthritis, diarrhea, erythema nodosum, eye inflammation, genital ulcers, headaches, mouth ulcers, nausea/vomiting, new central nervous system involvement, new major vessel inflammation and pustules. The presence of each clinical feature was scored as 1 point. Behçet's disease clinical activity index (BDCAI) values of the patients were calculated as a result of the evaluation of these 12 clinical features. In addition, since the symptom of arthralgia would be common in patients with FM and could lead to misinterpretation of the results, the BDCAI values were also calculated on 11 clinical findings without considering the arthralgia symptom and compared between the groups. The patients' and clinicians' perceptions of disease activity were evaluated separately with two questions. A Likert scale represented by a 'smiley face' was used in these questions. In this scale, clinicians' and patients' perceptions of disease activity in the last four weeks were graded with seven different facial expressions ranging from very good to bad. According to these perceptions, patients' perception of disease activity (PPDA) and clinician's overall perception of disease activity (CPDA) were scored between 1-7 points.

The ACR alternative criteria were used to classify FM.[22] Alternative criteria were derived from Symptom Impact Questionnaire (SIQR) symptoms and the 28-area pain location inventory (PLI). In SIQR symptoms, each of the intensities of the common 10 symptoms of FM over the last seven days was graded over 10 points by the patients. The SIQR symptoms score was obtained as half of the total score obtained from the SIQR. In PLI, the patients were asked about 28 specific locations in the body in which they defined persistent pain in the last seven days. The total number of painful locations is the pain location score of the patient. A patient fulfilling the following was defined as having FM: SIQR symptom score ≥21, pain location score ≥17

Table 1. Age, disease duration, human leukocyte antigen-B51 genetic test results and clinical features of female patients with Behçet's disease

	Female patients with BD (n=72)				
	n	%	Mean±SD	Median	Min-Max
Age (year)			39.7±10.5		
Disease duration (month)				24.0	0-480
HLA-B51					
+	48				
-	18				
Oral ulcerations	72	100			
Genital ulcerations	43	59.7			
Erythema nodosum	46	63.9			
Acneiform lesions	56	77.8			
Eye lesions	14	19.4			
Venous disease	6	8.3			
Neurologic disease (parenchymal)	2	2.8			
Pathergy	48	66.7			

BD: Behçet's disease; SD: Standard deviation; HLA-B51: Human leukocyte antigen.

and symptoms and pain locations persistent for at least three months. Patients were grouped according to the presence of FM, and the activity of BD was compared between the groups.

Statistical analysis

The SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to statistically analyze all data. Kolmogorov-Smirnov test was used to determine whether the data were in normal distribution. To compare quantitative variables, Student's t-test was used for normally distributed variables, and Mann-Whitney U test was used for variables that were not normally distributed. For the comparison of qualitative data, χ^2 test or Fischer's exact χ^2 test was used. All tests were two-tailed, and p values

<0.05 were considered to indicate statistical significance.

RESULTS

Mean age, median disease duration, HLA-B51 genetic test results and clinical features of the patients are given in Table 1. Frequency of FM and PLI and SIQR scores of the patients are given in Table 2. The median disease duration of patients with or without FM was 14.0 months (range, 0-360 months) and 36.0 months (range, 0-480 months), respectively. The median disease duration was not different between groups (p=0.081). Active clinical features and BDCAI, BDCAI (without arthralgia), PPDA

Table 2. Frequency of fibromyalgia and 28-area pain location inventory and Symptom Impact Questionnaire scores in female patients with Behçet's disease

	Female patients with BD (n=72)		
	n	%	Mean±SD
28-area pain location inventory score			11.7±7.7
SIQR symptoms score			22.5±10.3
28-area pain location inventory score ≥17	23	31.9	
Symptom Impact Questionnaire score ≥21	41	56.9	
Frequency of fibromyalgia	21	29.2	

BD: Behçet's disease; SD: Standard deviation.

Table 3. Active clinical features and Behçet's disease clinical activity index, patient's perception of disease activity and clinician's overall perception of disease activity scores of patients according to data obtained from Behçet's disease activity form, and medications of patients with or without fibromyalgia

	Female patients with BD without FM (n=51)					Female patients with BD with FM (n=21)					p
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	
Age (year)			40.0±10.4					39.0±10.8			0.692
BDCAF sections											
Headache	36	70.6				18	85.7				0.178
Mouth ulceration	35	68.6				17	81.0				0.289
Genital ulceration	7	13.7				8	38.1				0.021
Erythema	14	27.5				10	47.6				0.099
Skin pustules	18	35.3				11	52.4				0.179
Joints-arthralgia	39	76.5				20	95.2				0.060
Joints-arthritis	6	11.8				2	9.5				0.783
Nausea/vomiting/abdominal pain	7	13.7				6	28.6				0.137
Diarrhea + altered/frank blood per rectum	-	-				-	-				-
Eye involvement	3	5.9				0	0				0.256
Nervous system involvement	1	2.0				1	4.8				0.511
Major vessel involvement	1	2.0				1	4.8				0.511
Scores of disease activity											
BDCAI				3.0	0-8				5.0	1-6	0.003
BDCAI (without arthralgia)				2.0	0-7				4.0	0-6	0.004
PPDA				3.0	1-5				5.0	1-7	<0.001
CPDA				2.0	1-4				3.0	1-5	0.025
Drugs											
Colchicine	33	64.7				11	52.4				0.330
Azathioprine	4	7.8				0	0				0.187
Infliximab	1	2.0				0	0				0.518
Corticosteroid	6	11.8				5	23.8				0.197
Duloxetine	2	3.9				2	9.5				0.575

BD: Behçet's disease; FM: Fibromyalgia; SD: Standard deviation; Min: Minimum; Max: Maximum; BDCAF: Behçet's disease activity form; BDCAI: Behçet's disease clinical activity index; CPDA: Clinician's overall perception of disease activity; PPDA: Patient's perception of disease activity.
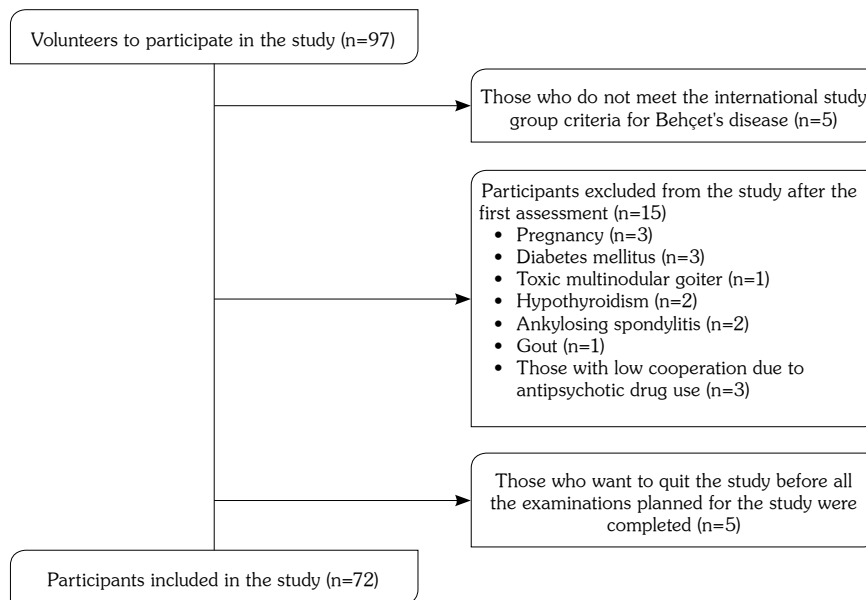
Figure 1. Flowchart summarizing the patient selection process to the study.

and CPDA scores according to data obtained from BDCAF, and medications of patients with or without FM are shown in Table 3. Active genital ulceration was significantly more frequent in the FM group (p=0.021). All other active clinical features were not significantly different between the groups. The use of corticosteroids, colchicine, azathioprine, infliximab and duloxetine was not different between the groups. Four patients had been using duloxetine treatment for the diagnosis of FM, but two of them did not meet the 2013 ACR classification criteria. The BDCAI, BDCAI (without arthralgia), PPDA and CPDA scores were significantly higher in the FM group (p=0.003, p=0.004, p<0.001 and p=0.025, respectively).

DISCUSSION

In this study, we have found that the frequency of FM was 29.2% in female patients with BD and the activity of BD was higher in patients with FM. To the best of our knowledge, this study is the first to show that FM is associated with disease activity in female patients with BD. In rheumatic diseases such as SS, systemic lupus erythematosus, RA and ankylosing spondylitis, FM can be seen more frequently.[15,20,25,26] Although the frequency of FM has been adequately investigated in other rheumatic diseases, there are a limited number of studies evaluating the prevalence of FM in BD and the data obtained from these studies showed that the prevalence of FM is increased in patients with BD.[16] The first study in which the prevalence of FM was evaluated in BD was conducted by Yavuz et al.,[27] and the prevalence of FM was found to be 9.2% among all patients with BD and 90% of the patients with FM were females. In a study conducted by Al-Izzi and Jabber,[28] the prevalence of FM was found to be 8.2% in patients with BD and a high rate of female dominance (female/male: 7/1) was observed in BD patients with FM. There is little information about the prevalence of FM in females with BD in the literature. FM was found in 22 (55.0%) of 40 female patients with BD and 12 (21.4%) of 56 female patients with BD, respectively, in the studies of Melikoglu and Melikoglu[17] and Lee et al.[18] In this study, the frequency of FM was found to be 29.2% among 72 females with BD and the frequency of FM in this study was close to the frequency of FM in BD conducted in Turkey by Melikoglu and Melikoglu.[17] To the best of our knowledge, this study includes data from the largest population of female patients with BD in which FM has been investigated.

In many rheumatic diseases, FM is associated with disease activation.[13,14] However, the results

of studies evaluating the relationship between FM and disease activity in Behçet's patients are conflicting.[17-20] Melikoglu and Melikoglu[17] and Lee et al.[18] have found no association between FM and disease activity in Behçet's patients. However, in the study of Haliloglu et al.,[19] the frequency of FM in other rheumatic diseases and its relationship with disease activity were evaluated and disease activity was found to be higher in Behçet's patients with FM than in non-FM patients. In addition, in the study of El-Rabbat et al.,[20] BDCAF score was correlated with the widespread pain index. It may not be accurate to evaluate the relationship between disease activity and FM in patients with BD without sex discrimination since FM is common in females while BD is more active in males.[3,21] In this study, we found that BD activity was significantly higher in patients with FM than patients without FM. Since FM patients will suffer from arthralgia, we also calculated BDCAI and compared it between the groups ignoring the arthralgia, which is one of the parameters used to evaluate the activity of BD. The disease activity of BD was significantly higher in the FM group, even if the symptoms of arthralgia were not considered. In addition, both the clinicians' and the patients' perceptions of disease activity were significantly higher in BD patients who also had FM. As a result of studies conducted in the last 10 years, the opinion that FM is not an inflammatory disease has changed to the opinion that FM may have some relationship with inflammation.[8-12] In some studies, interleukin (IL)-6 and IL-8 levels were found to be high in FM compared to healthy controls and there are many studies showing that these cytokines are also increased in BD.[29-31] In addition, a study with a small sample size has demonstrated that patients with FM showed a reduction in T-helper-2 (Th2) cytokines, such as IL-4, IL-5 and IL-13.[32] In the literature, there are also data showing the increase of Th2 cytokines in BD.[33,34] We know from the data to date that FM is common in BD and according to the data obtained from this study, disease activation is higher in the presence of FM in female patients with BD. Perhaps the presence of FM contributes to inflammation, leading to increased disease activity in BD. Further data on this subject are needed to clarify whether FM contributes to inflammation in BD.

When we evaluated the active clinical features of female BD patients with or without FM, active clinical features were not different between the groups except for genital ulcer. The frequency of active genital ulcers was 38.1% in patients with FM and 13.7% in patients without FM, and the difference between the groups was significant (p=0.021). To our knowledge, no information has been reported on this subject in the literature. Genital ulcer may cause sleep disorder in patients with BD.[35,36] Sleep disorder is one of the well-known clinical features of FM.[37] Therefore, one of the factors contributing to the high prevalence of FM in patients with BD may be the presence of genital ulcer through sleep disturbance. Further studies are needed to clarify this issue.

This study has some limitations. Firstly, it was performed with a limited number of patients and the results should to be confirmed by further studies with larger sample size. Moreover, considering that sex affects the activity of BD and the frequency of FM in Behçet's patients differently, and that there may be different pathogenetic processes according to sex, we conducted our study only on female patients. Thus, we do not know if the same results would be obtained in male patients with BD, which was a limitation. Furthermore, in this study, the activity of BD was measured using BDCAF and the fact that we did not measure other markers of inflammation to assess disease activity was another limitation. Also, the lack of assessment of body mass index and smoking, which may affect inflammation, when comparing disease activation in Behçet's patients with or without FM was another limitation.

In conclusion, in this study, we have found that BD activity and perceptions of BD activity of both patients and clinicians were higher in female BD patients with FM than those without FM. The presence of FM in patients with BD may be associated with the presence of active genital ulcers. Further studies are required to clarify this situation in which the presence of active genital ulcer is evaluated together with other clinical conditions, such as sleep disorder, which may contribute to FM.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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