Turk J Phys Med Rehab 2016;1(62):45-50
DOI: 10.5606/tftrd.2016.81226

Original Article / Özgün Araştırma

Impact of fibromyalgia syndrome on quality of life in patients with Behçet's disease

Behçet hastalarında fibromiyalji sendromunun yaşam kalitesi üzerine etkisi

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Received / *Geliş tarihi*: December 2014 Accepted / *Kabul tarihi*: May 2015

ABSTRACT

Objectives: In this study, we aimed to investigate the prevalence of fibromyalgia syndrome (FMS) among patients with Behçet's disease (BD) and to assess the impact of FMS on quality of life in this patient population.

Patients and methods: Between September 2014 and December 2014 60 BD patients and 60 age- and sex-matched healthy controls were included in the study. The presence of FMS was evaluated based on the American College of Rheumatology (ACR) diagnostic criteria. The tender point count (TPC) scores were recorded. The disease severity of FMS was measured with the Fibromyalgia Impact Questionnaire (FIQ), while the disease activity of BD was determined by the Behçet Disease Current Activity Form (BDCAF). A Short Form 36 (SF-36) was used to assess the quality of life.

Results: According to the ACR criteria, the prevalence of FMS was 16.7% in BD patients and 3.3% in the controls, indicating significantly higher rates in the FMS group with BD [odds ratio (OR)= 5.8; confidence interval (CI) 95% (1.21-27.72)] (p=0.015), compared to the controls. Behçet's disease patients with FMS scored significantly higher in headache, central nervous system involvement, patient's and physician's impression of disease activity subgroups of BDCAF, and significantly lower in all subgroups of SF-36 (p<0.05), compared to the those without FMS. The FIQ scores were positively correlated with the disease activity variables, except oral ulcers, while the FIQ scores were negatively correlated with the SF-36 subgroups (p<0.05). The TPC scores were positively correlated with the disease activity variables except oral and genital ulcers, skin lesions and pustules, while they were negatively correlated with the SF-36 subgroups (p<0.05).

Conclusion: Fibromyalgia syndrome is common among BD patients and is associated with higher disease activity and poorer quality of life. Diagnosis of concomitant FMS in BD patients may help us find more effective treatment strategies.

Keywords: Behçet disease; disease activity; fibromyalgia; quality of life.

ÖZ

Amaç: Bu çalışmada Behçet hastalarında fibromiyalji sendromunun (FMS) sıklığı araştırıldı ve FMS'nin bu hasta popülasyonunda yaşam kalitesi üzerindeki etkisi değerlendirildi.

Hastalar ve yöntemler: Eylül 2014 - Aralık 2014 tarihleri arasında 60 Behçet hastası ve 60 yaş ve cinsiyet eşleştirilmiş sağlıklı kontrol çalışmaya alındı. Fibromiyalji sendromu varlığı Amerikan Romatoloji Derneği (ACR) tanı kriterlerine göre değerlendirildi. Hassas nokta sayısı (TPC) skorları kaydedildi. Fibromiyalji sendromu hastalık şiddeti Fibromiyalji Etki Anketi (FIQ) ile ölçülürken, Behçet hastalık aktivitesi Behçet Hastalığı Anlık Aktivite Formu (BDCAF) ile belirlendi. Yaşam kalitesi, Kısa Form-36 (KF-36) ile değerlendirildi.

Bulgular: ACR kriterlerine göre, FMS sıklığı Behçet hastalarında %16.7 ve kontrollerde %3.3 idi; bu da, kontrollere kıyasla Behçet hastalıklı FMS grubunda anlamlı düzeyde daha yüksek oranları gösteriyordu [olasılık oranı (OR)= 5.8 güven aralığı (GA) %95 (1.21-27.72)] (p=0.015). Fibromiyalji sendromu olmayanlara kıyasla, FMS'li Behçet hastalarında BDCAF'nin baş ağrısı, merkezi sinir sistemi tutulumu, hasta ve hekim hastalık aktivitesi algısı alt gruplarında anlamlı düzeyde daha yüksek ve KF-36'nın tüm alt gruplarında anlamlı düzeyde daha düşük skorlama görüldü (p<0.05). Oral ülserler dışındaki hastalık aktivitesi değişkenleri ile FIQ skorları arasında pozitif bir ilişki varken, KF-36 alt grupları ile FIQ skorları arasında negatif bir ilişki vardı (p<0.05). TPC skorları, oral ve genital ülserler, cilt lezyonları ve püstüller dışındaki hastalık aktivitesi değişkenleri ile pozitif ilişkili iken, KF-36 alt grupları ile negatif ilişki gösterdi (p<0.05).

Sonuç: Fibromiyalji sendromu Behçet hastaları arasında yaygın olup, daha yüksek hastalık aktivitesi ve daha kötü yaşam kalitesi ile ilişkilidir. Behçet hastalarında eş zamanlı FSM tanısı, daha etkili tedavi stratejilerinin belirlenmesinde bizlere yardımcı olabilir.

Anahtar sözcükler: Behçet hastalığı; hastalık aktivitesi; fibromiyalji; yaşam kalitesi.

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Cite this article as:
Garip Y, Güler T, Çifçi N, Dörtbaş F, Karcı AA. Impact of fibromyalgia syndrome on quality of life in patients with Behçet's disease. Turk J Phys Med Rehab 2016;62:45-50.

Behçet's disease (BD) was first described by the Turkish physician, Hulusi Behçet in 1937, as a triad of recurrent aphthous stomatitis, genital aphthae, and relapsing uveitis.[1] It is a chronic progressive disorder which also affects cardiovascular, pulmonary, neurological, and gastrointestinal systems.[2] Musculoskeletal involvement such as arthritis, arthralgia, enthesitis and sacroiliitis can be seen in the course of BD.[3]

Fibromyalgia syndrome (FMS) is a chronic disorder of unknown etiology, characterized by chronic widespread musculoskeletal pain accompanied by fatigue, sleep disturbance, and mood disorders such as anxiety and depression.[4] Epidemiological surveys have suggested that the prevalence of FMS ranges between 2 and 7% in the overall population.[5,6] Fibromyalgia syndrome can coexist with other rheumatic diseases; in earlier studies, the frequency of coexisting FMS was reported to be 15% in rheumatoid arthritis,[7] 16.9% in ankylosing spondylitis,[8] 35.7% in systemic lupus erythematosus,[9] 12% in systemic sclerosis, and 7.1% in familial Mediterranean fever.[6] Although fatigue, pain, depression, anxiety, and sleep disorders are prominent characteristics of FMS, they are also significant aspects of other rheumatic diseases.[10] Since FMS and other rheumatic diseases require different treatment strategies, differential diagnosis is of utmost importance.

In this study, we aimed to investigate the prevalence of FMS among the patients with BD and to assess the impact of FMS on the quality of life (QoL) in terms of severity of pain, vitality, and social and emotional functioning.

PATIENTS AND METHODS

Between September 2014 and December 2014, a total of 60 patients with BD who were admitted to outpatient physical medicine and rehabilitation and rheumatology clinics were consecutively enrolled. Inclusion criteria were as follows: age between 18 and 65 years and meeting the International Study Group Criteria for Behçet's disease.[11] Exclusion criteria were coexisting inflammatory rheumatic diseases, endocrine diseases including diabetes mellitus, thyroid dysfunction, and severe chronic psychological diseases.

We assessed the presence of FMS according to 1990 American College of Rheumatology (ACR) diagnostic criteria:[12] *(i)* chronic generalized pain in both sides of the body, both axial and peripheral, below and above the waist; *(ii)* the presence of at least 11 of 18 tender points on digital palpation with a pressure of approximately 4 kg/cm^2. The tender point count (TPC) was measured by the same physician. The patients were divided into two groups: group 1 consisted of 10 patients with FMS and group 2 consisted of 50 patients without FMS. A control group was constituted including 60 age- and sex-matched healthy individuals. Fibromyalgia Impact Questionnaire (FIQ) was used to determine fibromyalgia disease severity.[13] Patient data including age, sex, disease duration, and history of joint involvement were recorded. Joint involvement was defined as pain, swelling or restriction of the peripheral joints. Behçet's disease activity was assessed with the Turkish version of Behçet Disease Current Activity Form (BDCAF).[14] Clinical features of the patients including headache, oral and genital ulcers, skin lesions, joint involvement, gastrointestinal system involvement, eye involvement, central nervous system involvement, major vessel involvement and patient's and physician's impression of disease activity were evaluated. Eye activity was determined by a single ophthalmologist and scored between 0 and 3. Oral aphthae, genital ulcers, and skin lesions were assessed by a single dermatologist. Severity of pain was measured by using 100 mm visual analog scale-pain (VAS-pain).[15] Quality of life was evaluated by using Short Form 36 (SF-36).[16]

A written informed consent was obtained from each patient. Medical Research Ethics Committee approved the study protocol. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Statistical analysis

The statistical analysis was performed using IBM SPSS for Windows, version 21.0 software (IBM Corporation, Armonk, NY, USA). Descriptive data were presented in mean ± standard deviation (SD) and median scores. The Mann-Whitney U test was used to analyze abnormally distributed data. Categorical variables were evaluated by the chi-square and Fisher's exact tests. The Spearman's correlation analysis was used to analyze the level of the correlation between the variables. A p value of <0.05 was considered statistically significant.

RESULTS

Sixty patients with BD (33 males, 27 females; mean age 37.0±11.7 years; range 18 to 64 years) and 60 healthy controls (33 males, 27 females; mean age

Table 1. Clinical characteristics of Behçet's disease patients with/without fibromyalgia syndrome

	Group 1 (BD patients with FMS) (n=10)				Group 2 (BD patients without FMS) (n=50)				
	n	%	Mean±SD	Median	n	%	Mean±SD	Median	*p*
Age (years)			38.8±8.7	37			36.7±12.2	36	0.473
Sex ratio									0.09
Male	3				30				
Female	7				20				
Visual analog scale-pain			66±30.3	75			33.2±29.8	30	0.005*
Tender point count			13.4±2.1	13			2.8±2.9	2	<0.001*
Disease duration (year)			8.9±5.7	7.5			8.5±8.3	5.5	0.365
Joint involvement	4	40			24	48			0.741

BD: Behçet's disease; FMS: Fibromyalgia syndrome; SD: Standard deviation; * p<0.05 (significant).

34.5±10.2 years; range 18 to 60 years) participated in this study. The male-female ratio was 1.22. Age did not significantly differ among the groups (p>0.05).

According to the ACR criteria, the rate of FMS was found to be 16.7% in BD patients and 3.33% in the controls, indicating significantly higher rates in the FMS group with BD [odds ratio (OR)=5.8 confidence interval (CI) 95% (1.21-27.72)] (p<0.05), compared to the controls.

The patients with BD were divided into two groups according to the presence of FMS. Group 1 consisted of 10 patients (3 males, 7 females; mean age 38.8±8.7 years; range 27 to 58 years) with FMS and group 2 consisted of 50 patients (30 males, 20 females; mean age 36.7±12.2 years; range 18 to 64 years) without FMS. Age and sex did not significantly differ among the groups (p>0.05). Demographic and clinical data were shown in Table 1.

The patients in group 1 scored significantly higher in headache, central nervous system involvement, patient's impression of disease activity today and last 28 days and physician's impression of disease activity today subgroups of BDCAF, while the scores were significantly lower in all subgroups of SF-36, compared

Table 2. Comparison of the groups in terms of disease activity and quality of life

	Group 1 (BD patients with FMS) (n=10)		Group 2 (BD patients without FMS) (n=50)		
	Mean±SD	Median	Mean±SD	Median	*p*
Headache (0-4)	2.1±1.6	2.5	0.8±1.2	0	0.020*
Oral ulcers (0-4)	1.7±1.8	1.5	1.0±1.3	0	0.200
Genital ulcers (0-4)	0.3±1.0	0	0.3±0.9	0	0.758
Erythema nodosum/superficial thrombophlebitis (0-4)	0.4±0.8	0	0.4±0.9	0	1.000
Pustules (0-4)	0.8±1.1	0	0.6±1.0	0	0.452
Arthralgia (0-4)	2.1±1.5	2	1.2±1.4	0.5	0.069
Arthritis (0-4)	0.8±1.5	0	0.5±1.1	0	0.381
Gastrointestinal system involvement (0-4)	0.3±0.7	0	0.1±0.3	0	0.139
Eye involvement (0-3)	1.1±1.3	0.5	0.5±1.1	0	0.091
Central nervous system involvement (0-5)	1.4±1.6	1	0.4±0.9	0	0.010*
Major vessel involvement (0-4)	0.5±0.9	0	0.2±0.7	0	0.080
Patient's impression of disease activity-today (0-6)	2.8±1.8	4	1.8±1.5	2	0.040*
Patient's impression of disease activity-last 28 days (0-6)	3.1±1.5	4	1.8±1.4	2	0.020*
Physician's impression of disease activity-today (0-6)	3.2±1.2	3.5	1.7±1.3	2	0.001*
SF-36-physical function	47.5±29.4	42.5	78.9±25.7	90	0.004*
SF-36-physical role	22.5±34.3	0	66.5±41.5	100	0.004*
SF-36-bodily pain	25.4±17.7	0	66.8±22.6	62	<0.001*
SF-36-general health	22.4±18.4	20	56.7±3.0	61	0.001*
SF-36-vitality	22.0±14.9	25	60.2±24.0	65	<0.001*
SF-36-social functioning	47.5±22.7	37.5	83.8±23.5	100	<0.001*
SF-36-emotional role	36.7±45.7	16.65	8.0±37.5	100	0.003*
SF-36-mental	39.6±16.6	40	60.2±14.3	60	0.001*

BD: Behçet's disease; FMS: Fibromyalgia syndrome; SD: Standard deviation; SF-36: Short Form 36; * p<0.05 (significant).

to the group 2 ($p<0.05$) (Table 2). There was no difference in the scores of oral-genital ulcers, erythema nodosum/superficial thrombophlebitis, pustules, arthralgia, arthritis, eye, gastrointestinal system, and major vessel involvement among the groups ($p>0.05$).

The Spearman's rank correlation test revealed that the FIQ scores were linearly correlated with headache, genital ulcers, erythema nodosum/superficial thrombophlebitis, pustules, arthralgia, arthritis, gastrointestinal system involvement, eye involvement, central nervous system involvement, major vessel involvement, patient's impression of disease activity today and last 28 days and physician's impression of disease activity today subgroups of BDCAF (r=0.41, 0.26, 0.25, 0.3, 0.49, 0.3, 0.37, 0.45, 0.6, 0.44, 0.39, 0.43 and 0.53, respectively) ($p<0.05$), while they were negatively correlated with physical function, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental subgroups of SF-36 (r= -0.6, -0.69, -0.77, -0.68, -0.78, -0.71, -0.5, and -0.64, respectively) ($p<0.05$). No correlation was found between the FIQ scores and oral ulcers ($p>0.05$).

According to Spearman's rank correlation test, the TPC was found to be linearly correlated with headache, arthralgia, arthritis, gastrointestinal system involvement, eye involvement, central nervous system involvement, major vessel involvement, patient's impression of disease activity today and last 28 days and physician's impression of disease activity today subgroups of BDCAF (r=0.32, 0.45, 0.28, 0.31, 0.39, 0.43, 0.33, 0.28, 0.28, and 0.44, respectively) ($p<0.05$), while it was negatively correlated with physical function, physical role, bodily pain, general health, vitality, social functioning, emotional role and mental subgroups of SF-36 (r= -0.46, -0.57, -0.63, -0.49, -0.64, -0.66, -0.37, and -0.48, respectively) ($p<0.05$). There was no correlation between TPC and BDCAF scores including oral and genital ulcers, erythema nodosum/superficial thrombophlebitis and pustules ($p>0.05$).

DISCUSSION

Fibromyalgia syndrome is a chronic rheumatic disorder characterized by chronic widespread pain as well as a combination of symptoms including fatigue, cognitive dysfunction, anxiety and depression, sleep disturbance, stiffness, headache, muscle spasm, and swelling of joints.[17] It has been suggested that neuroendocrine, neurotransmitter and sleep physiology disturbances, and psychological factors may play a role in the development of FMS.[18] Giacomelli et al.[19] explained the etiopathogenesis of FMS with central sensitization and impaired descending pain modulation, which are two main mechanisms prompting pain hypersensitivity.

In addition, FMS may present with other rheumatic diseases. It is important to identify the association of FMS with other rheumatic diseases which share a number of common features such as chronic pain, fatigue, and mood disorders.[10]

There are possible mechanisms which can explain FMS in rheumatic diseases. First, immune dysregulation may precipitate the development of FMS.[20] Caro et al.[21] reported immunoglobulin deposition at the dermal-epidermal junction of the patients with FMS. Second, it may be due to the effects of cytokines. It has been suggested that proinflammatory cytokines such as interleukin (IL)-1β, IL-6, IL-8 and tumor necrosis factor alpha (TNF-α) cause "cytokine-induced sickness behavior".[22] There are similarities between fibromyalgia symptoms and these behavior changes including general malaise, fatigue, reduced activity, impairment in social interaction, sleep disorders.[22]

To the best of our knowledge, there are few studies in the literature investigating the prevalence of FMS in the patients with BD. In our study, 10 patients (3 males and 7 females) with BD fulfilled the 1990 ACR criteria for classification of FMS. We found the prevalence of FMS in Turkish patients to be 16.7% (25.9% among women and 9.1% among men). The prevalence of FMS in Turkish patients was previously reported to be 9.2% by Yavuz et al.,[23] 5.7% by Haliloglu et al.,[6] and 18% by Melikoglu and Melikoglu.[24] In the study of Al-Izzi and Jabber[25] conducted in 90 Iraqi patients with BD, the rate of concomitant FMS was reported to be 8.9%. Lee et al.[26] reported the FMS frequency in 70 Korean patients with BD (25 males and 45 females) to be 37.1%. However, they concluded that high FMS prevalence might be due to female predominance in their study cohort.[26] Female predominance is an important characteristic of FMS, due to the hormone-associated mechanisms and sex-related response to the tender points.[24]

Our study investigated the relationship between FMS and disease activity in the patients with BD. We found higher activity scores in headache, central nervous system involvement, patient's and clinician's impression of disease activity subgroups of BDCAF in the patients with FMS than in the patients without FMS. Given the fact that these parameters are not objective disease parameters of BD, we initially considered that BD activity might not be associated with the presence of FMS. However,

when the correlation of TPC and FIQ with BDCAF scores was analyzed, we detected a strong association between the disease severity of FMS and almost all disease activity variables of BD. Among disease activity parameters, arthralgia, headache, and central nervous system involvement showed the highest associations with fibromyalgia disease severity. There may two reasons for this relation. First, headache and central nervous system involvement parameters of BD might be linked with a predisposition to develop FMS, as central nervous system dysfunction is the primary pathophysiologic mechanism underlying FMS. Second, arthralgia and headache are parameters of BDCAF which refer pain. Pain may be the possible pathogenic link among these diseases. Vierck[27] reported that central pain associated with FMS might result from abnormal peripheral pain input. Our results also support this mechanism whereby chronic nociceptive input induces central sensitization and activates the sympathetic nervous system.

Based on these findings, we concluded that disease activity in BD was associated with disease severity of FMS. Headache, arthralgia, and central nervous system involvement were the most important variables which induced FMS symptoms in the patients with BD. However, oral and genital ulcers, skin lesions and pustules were less associated with exacerbation of FMS. Similarly, in the study of Haliloglu et al.[6] conducted in 53 Turkish BD patients, a significant correlation between FIQ and BDCAF scores was found. The authors reported that concomitant FMS in BD might cause increased pain, fatigue, and functional impairment, leading to perception of increased disease activity. On the other hand, Melikoglu and Melikoglu[24] found differences only in fatigue, headache, arthralgia, and patient's impression of disease activity between the patients with/without FMS. Oral and genital ulcers, erythema nodosum, thrombophlebitis and pustular lesion parameters did not differ among the groups. Additionally, FIQ scores were correlated with only headache and arthralgia items of BDCAF. Therefore, the authors suggested that higher prevalence of FMS in BD was affected by BD itself, rather than its severity. On the other hand, in the study of Lee et al.,[26] neither FIQ scores nor TPC were correlated with the disease activity levels determined by summing the clinical manifestations of BD. The presence of FMS did not differ significantly between BD patients with/without severe manifestations. Additionally, the authors assessed anxiety and depression levels of the patients and found a correlation between FMS disease severity and State-Trate Anxiety Inventory and Beck Depression Inventory scores. They concluded that the severity of BD did not influence the development of FMS.

There were two limitations in the study. The first one was relatively small number of patients. The second one was cross-sectional design which limited the interpretation of the link between BD and FM.

To the best of our knowledge, this is the first study to examine the effect of FMS on QoL domains in the patients with BD. We found deterioration in QoL in BD patients with FMS, compared to the patients without FMS. Moreover, we determined strong associations between the disease severity of FMS and QoL domains. Our study showed that FMS had a negative impact on QoL in terms of pain, functional status, energy, general and mental health, and social and emotional functioning in the patients with BD.

In conclusion, FMS is common in the patients with Behçet's disease and is associated with higher disease activity and poorer quality of life. Among the disease activity variables, headache, arthralgia, and central nervous system involvement are more strongly associated with FMS severity rather than oral and genital ulcers, skin lesions and pustules. Fibromyalgia syndrome may mimic increased activity of other rheumatic diseases due to its common symptoms such as pain, functional limitation and fatigue. Since FMS and other rheumatic diseases require different treatment strategies, differential diagnosis is of utmost importance.

Declaration of conflicting interests

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

Funding

The authors received no financial support for the research and/or authorship of this article.

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