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Disease Activity in Turkish Patients with Behçet's Disease: Association with Fatigue, Psychological Status and Quality of Life

Behçet Hastalarında Depresyon Düzeyi ve Hastalık Aktivitesi, Yorgunluk ve Yaşam Kalitesi İlişkisi

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ABSTRACT Objective: We aimed to determine disease activity in Behcet's patients and to assess its association with quality of life, pain, fatigue, and functional and psychological status. **Material and Methods:** Sixty seven Behcet's patients (39 males, 28 females) were included. Disease activity were determined by using Behcet Disease Current Activity Form (BDCAF). Quality of life was assessed by Short Form-36 (SF36), psychological status by Beck Depression Scale (BDS), and fatigue by Fatigue Severity Scale (FSS). **Results:** All BDCAF subscores were found to be positively correlated with BDS scores ($p<0.05$). All BDCAF subscores except oral ulcers were correlated with FSS scores ($p<0.05$). Disease activity subgroups of BDCAF were negatively correlated with both physical and mental domains of SF36 ($p<0.05$). Oral ulcer was found to be negatively correlated with only bodily pain subgroup of SF36 ($r=-0.26$) ($p<0.05$). Genital ulcer and skin lesions were negatively correlated with only physical function and physical role subgroups of SF36 ($p<0.05$). Eye and central nervous system involvement were found as negatively correlated with all SF36 subgroups except emotional role ($p<0.05$). **Conclusion:** Treatment approaches focusing on fatigue, eye and joint involvement in Behçet's patients may improve quality of life in terms of physical, social and emotional functioning.

Keywords: Quality of life; Behçet syndrome; depression; fatigue

ÖZET Amaç: Behçet hastaları'nda hastalık aktivitesi ile hastaların yaşam kalitesi, ağrı, halszlik, fonksiyonel ve psikolojik durumları arasındaki ilişkiyi belirlemeyi hedefledik. **Gereç ve Yöntemler:** Altmış yedi Behçet hastası (39 erkek, 28 kadın) çalışmaya dahil edildi. Hastalık aktivitesi Behçet Hastalığı Anlık Aktivite Formu (BHAAF) ile değerlendirildi. Kısa Form-36 (SF-36) yaşam kalitesi ölçeği ile, Beck Depresyon Ölçeği (BDÖ) ile psikolojik durum, Yorgunluk Şiddet Ölçeği (YŞÖ) ile yorgunluk durumu değerlendirildi. **Bulgular:** Bütün BHAAF alt grup skorları ile BDÖ arasında pozitif ilişki bulundu ($p<0.05$). Oral ülser haricindeki bütün BDCAF alt grup skorları ile YŞÖ'nün korele olduğu bulundu ($p<0.05$). BHAAF'nin hastalık aktivitesi alt grubu SF-36'nın hem fiziksel hem de mental değerlendirmeleriyle negatif korele saptandı. Oral ülser, SF-36'nın bedensel ağrı alt grubu ile negatif korele idi ($r=-0.26$) ($p<0.05$).Genital ülser ve deri lezyonları, SF-36'nın fiziksel fonksiyon ve fiziksel rol alt gruplarıyla negatif korele idi ($p<0.05$). Göz ve santral sinir sistemi tutulumu, SF-36'nın duygusal rol dışındaki tüm alt gruplarıyla negatif korele idi ($p<0.05$). **Sonuç:** Behçet hastalarında yorgunluk, göz ve eklem tutulumuna yönelik tedavi yaklaşımları, fiziksel, duygusal ve sosyal açıdan yaşam kalitesini artırabilir.

Anahtar Kelimeler: Yaşam kalitesi; Behçet sendromu; depresyon; yorgunluk

Behcet's disease (BD) is a chronic systemic inflammatory disease which is characterized by oral and genital ulcers, uveitis and skin lesions.[1] Musculoskeletal involvement such as arthritis, arthralgia, enthesitis and sacroiliitis can be seen in the course of BD.[2] The prevalence of BD is

highest in the eastern Mediterranean, the Middle East and the eastern Asian countries.[3] Causes and pathogenesis of BD are still unclear; however several reports have suggested that autoinflammatory mechanisms, infectious factors and genetic and immune system abnormalities may play a crucial role in its development.[4]

Disease activity is an outcome measure, which is used to evaluate health outcome in the patients with rheumatic diseases.[5] It is difficult to define disease activity of BD because of its fluctuating course, absence of laboratory tests reflecting all clinical findings, and lack of standardized form representing the severity of BD manifestations.[6] Various scales have been used for measuring disease activity in BD. The first BD disease activity scale "Turkish Behcet Disease Activity Index" was developed by Yazici et al. in 1984. It has five dimensions including eye involvement, skin lesions, vascular involvement, arthritis and neurological involvement.[7] The most widely used BD disease activity index is "Behcet Disease Current Activity Form" (BDCAF) developed by Bhakta et al. in 1999. This scale is not a patient-based self-assessment measure, it needs clinical evaluation.[8] It is based on the clinical features including fatigue, 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 doctor's global assessment of disease activity.[6] Its adaptation to Turkish language and validation were proven by Hamuryudan et al.[9]

The aim of our study is two-fold: (i) to determine disease activity in Turkish patients with BD; (ii) to evaluate the possible associations of disease activity with quality of life (QoL), pain, fatigue, and functional and psychological status.

MATERIAL AND METHODS

A total of 67 BD patients (39 males and 28 females) who were admitted to physical medicine and rehabilitation, rheumatology and dermatology outpatients clinics fulfilling the International Study Group Criteria for BD included in the study. Patients with coexisting inflammatory rheumatic diseases, infections, severe chronic psychological diseases excluded from the study.[10] Patient data including age, gender, ESR (erythrocyte sedimentation rate), disease duration, and history of joint involvement was recorded. Joint involvement was defined as pain, swelling or limitations of peripheral joints. X-ray of involved joints and sacroiliac joints were obtained when required. Disease activity was measured by using Turkish version of BDCAF.[9] Clinical parameters including fatigue, 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. Duration of clinical features was scored between 0 and 4. Eye activity was assessed by the same ophthalmologist and scored between 0 and 3. Oral aphthae, genital ulcers and skin lesions were evaluated by the same dermatologist. QoL was evaluated by Short Form-36 (SF36).[11] Psychological status was assessed by using Beck Depression Scale (BDS), and fatigue by Fatigue Severity Scale (FSS).[12,13] The severity of pain was measured by 100 mm Visual Analog Scale-Pain (VAS-pain).[14]

Written informed consent was obtained from all of the patients. Study protocol was approved by medical research ethics committee of medical faculty. The study conforms to the provisions of the World Medical Association's Declaration of Helsinki.

STATISTICAL ANALYSIS

In these 67 BD patients, scores of the above-mentioned scales were obtained for statistical analyses. Depending on these values, the level of the linear relation between these scales was evaluated by correlation analysis. The presence of correlation between these scales was evaluated by Spearman's correlation coefficient. A value of $P<0.05$ was considered statistically significant. All analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) for Windows, Version 21.0 (Armonk, New York, USA).

RESULTS

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF THE PATIENTS

Sixty-seven patients with BD (39 men and 28 women) participated in this study. The male female ratio was 1.39. We evaluated the demographic and clinic patient data (Table 1) and scores of BDCAF subgroups (Table 2).

JOINT INVOLVEMENT

During the disease course, the rate of sacroiliitis was 13.43%. Peripheral joint involvement was seen in 31 patients (46.27%). The most common form was asymmetric oligoarthritis (18 patients, 58.06 %). Monoarthritis (11 patients, 35.48%) and polyarthritis (2 patients, 6.45%) followed this, respectively. In 58.06% (18 patients) of these cases the ankles, in 38.71% (12 patients) the knees, in 9.68% (3 patients) the wrists, in 9.68% (3 patients) the elbows, in 9.68% (3 patients) small joints of the hand, in 6.45% (2 patients) the hips, in 3.23% (1 patient) the shoulders, in 3.23% (1 patient) small joints of the foot were affected.

MEDICATIONS

All of the patients were under colchicine therapy. The ratio of the patients receiving colchicine monotherapy was 62.69% (42 patients). Of all the patients, 31.34% (21 patients) were under azathioprine therapy, 26.87% (18 patients) were under corticosteroid therapy and 2.99% (2 patients) were under sulphasalazine therapy. 1 patient (1.49%) was receiving methotrexate, 1 patient (1.49%) cyclophosphamide and 1 patient (1.49%) adalimumab (Table 3).

THE RELATION BETWEEN BDACF AND OTHER SCALES

The relation of BDCAF subscores with SF36, FSS and BDS scores was evaluated. All BDCAF subscores were found to be positively correlated with BDS scores ($p<0.05$). Additionally, except oral ulcers, all BDCAF subscores were correlated with FSS scores ($p<0.05$). Fatigue, headache, major vessel involvement, patient's and physician's impression of disease activity subgroups of BDCAF were negatively correlated with both physical and mental domains of SF36 ($p<0.05$). Oral ulcer was negatively correlated with only bodily pain subgroup of SF36 ($r=-0.26$) ($p<0.05$).Genital ulcers and skin lesions were found as correlated with only physical function and physical role subgroups of SF36 ($p<0.05$). Eye involvement and central nervous system involvement were negatively correlated with all SF36 subgroups except emotional role ($p<0.05$). We evaluated the correlation coefficients between the

TABLE 1: Demographic and clinical characteristics of the patients

	Minimum	Maximum	Mean	Standard Deviation
Age (year)	18	64	38.18	11.99
Disease duration (year)	1	47	10.6	10.09
ESR (mm/hr)	2	47	10.25	5.72
VAS-pain	0	100	39.85	31.59
FSS	7	63	34.75	18.03
BDS	0	53	14.1	14.45
SF36-physical function	0.0	100.0	73.43	29.21
SF36-physical role	0.0	100.0	58.58	42.54
SF36-bodily pain	0.0	100.0	60.4	27.81
SF36-general health	0.0	100.0	52.34	29.93
SF36-vitality	0.0	100.0	54.55	28.55
SF36-social functioning	0.0	100.0	76.67	27.51
SF36-emotional role	0.0	100.0	71.63	41.54
SF36-mental	0.0	100.0	57.85	19.13

VAS: Visual analog scale, ESR:erythrocyte sedimentation rate, CRP: C-reactive protein, FSS: Fatigue Severity Scale, BDS: Beck Depression Scale, SF36: Short Form36

TABLE 2: Distribution of BDCAF scores.

	0(n)	1(n)	2(n)	3(n)	4(n)	5(n)	6(n)
Fatigue (0-4)	9	10	10	25	13		
Headache (0-4)	34	14	6	5	8		
Oral ulcers (0-4)	35	10	8	8	6		
Genital ulcers (0-4)	56	4	1	5	1		
EN/ST (0-4)	52	5	6	4	0		
Pustules (0-4)	46	9	7	4	1		
Arthralgia (0-4)	30	9	12	8	8		
Arthritis (0-4)	53	1	6	3	4		
GIS involvement (0-4)	61	4	2	0	0		
Eye involvement (0-3)	47	6	5	8	1		
Central nervous system involvement (0-5)	56	6	2	2	1		
Major vessel involvement (0-4)	58	5	3	0	1		
Patient's impression of disease activity- today (0-6)	17	13	11	8	6	6	6
Patient's impression of disease activity- last 28 days (0-6)	14	14	13	9	6	6	5
Physician's impression of disease activity- today (0-6)	16	10	19	9	5	3	5

BDCAF: Behcet Disease Current Activity Form, EN/ST: erythema nodosum/superficial thrombophlebitis.

TABLE 3: Drug use in 67 BD patients.

	Number	Percentage
Colchicine	67	100
Azathioprine	21	31.34
Corticosteroids	18	26.87
Sulphasalazine	2	2.99
Methotrexate	1	1.49
Cyclophosphamide	1	1.49
Adalimumab	1	1.49

scores of BDCAF and scores of SF36, FSS and BDS were shown in (Table 4).

DISCUSSION

BD was first described in 1937 by Hulusi Behcet, a Turkish physician, as a triad of recurrent aphthous stomatitis, genital aphthae, and relapsing uveitis.[15] Firstly in 1969, Mason and Barnes defined arthritis as a clinical manifestation of BD.[16] In 1974, O'Duffy placed arthritis among the diagnostic criteria of BD.[17] Arthritis and arthralgia are the most frequent musculoskeletal findings of BD with a prevalence which varies between 40 and 70%.[2] In our study, the frequency of arthritis was 46.27% and the most common type was asymmetric oligoarthritis (58%). The most commonly involved joints were ankles, followed by knees, wrists and elbows, respectively. Similarly, Kim et al. reported oligoarticular involvement as the most common type of arthritis in BD (75%) and most commonly involved sites were knees and ankles.[18] In the study of Gur et al. the frequency of articular involvement was 41.3%, confirming our study.[19] They reported the most commonly affected joints as larger joints such as the wrist, knee and ankle. On the other hand, Mason and Barnes suggested that BD arthritis was poliarticular affecting most frequently the knees and ankles.[16] In the study of Yurdakul et al. which was conducted in 47 BD patients with arthritis, monoarthritis was reported as the most common form of arthritis with a rate of 68%.[20] Knees, ankles and wrists were the most commonly involved joints. Findings of Gurler et al. were similar to ones of Yurdakul et al. They performed a study in a large cohort with 2147 BD patients and declared that 67% of their patients had arthritis, most commonly monoarticular and affecting knees, ankles and wrists.[20,21]

The high rate of depression among the patients with BD has been mentioned in the previous studies.[22,23] There are several mechanisms that can explain depressive symptoms in BD. First, functional

TABLE 4: Correlation coefficients between scores of BDACF and scores of SF36, FSS and BDS.

	SF36-physical function	SF36-physical role	SF36-bodily pain	SF36-general health	SF36-vitality	SF36-social functioning	SF36-emotional role	SF36-mental	FSS	BDS
Fatigue	-0.59**	-0.7**	-0.62**	-0.65**	-0.64**	-0.59**	-0.48**	-0.45**	0.9**	0.7**
Headache	-0.39**	-0.42**	-0.39**	-0.37**	-0.47**	-0.43**	-0.27*	-0.35**	0.34**	0.36**
Oral ulcers	-0.22	-0.15	-0.26*	-0.22	-0.08	-0.13	-0.03	-0.06	0.18	0.24*
Genital ulcers	-0.28*	-0.31*	-0.13	-0.18	-0.22	-0.09	-0.19	-0.21	0.29*	0.39**
EN/ST	-0.33**	-0.37**	-0.21	-0.17	-0.22	-0.05	-0.05	-0.09	0.33**	0.31*
Pustules	-0.3*	-0.34**	-0.32**	-0.19	-0.16	-0.17	-0.1	-0.12	0.25*	0.3*
Arthralgia	-0.49**	-0.53**	-0.56**	-0.49**	-0.5**	-0.46**	-0.21	-0.31*	0.44**	0.42**
Arthritis	-0.35**	-0.36**	-0.47**	-0.33**	-0.35**	-0.4**	-0.08	-0.3*	0.27*	0.29*
GIS involvement	-0.13	-0.21	-0.2	-0.33**	-0.31*	-0.34**	-0.32**	-0.25*	0.24*	0.31*
Eye involvement	-0.27*	-0.3**	-0.44**	-0.41**	-0.43**	-0.46**	-0.01	-0.32**	0.34**	0.5**
CNS involvement	-0.38**	-0.33**	-0.49**	-0.38**	-0.44**	-0.39**	-0.21	-0.29*	0.48**	0.49**
Major vessel involvement	-0.36**	-0.33**	-0.44**	-0.34**	-0.36**	-0.49**	-0.4**	-0.34**	0.37**	0.39**
PIDA- today	-0.41**	-0.5**	-0.57**	-0.5**	-0.43**	-0.49**	-0.25*	-0.39**	0.39**	0.39**
PIDA last 28 days	-0.46**	-0.51**	-0.61**	-0.55**	-0.47**	-0.52**	-0.32**	-0.44**	0.41**	0.43**
PhIDA	-0.52**	-0.58**	-0.63**	-0.62**	-0.57**	-0.61**	-0.33**	-0.46**	0.54**	0.53**

BDCAF: Behcet Disease Current Activity Form, EN/ST: erythema nodosum/superficial thrombophlebitis, FSS: Fatigue Severity Scale, BDS: Beck Depression Scale, SF36: Short Form36: P < 0.05 (significant), **: P<0.01 (highly significant),CNS: Central nervous system, PIDA: Patient's impression of disease activity, PhIDA: Physician's impression of disease activity*

disability and stressful events resulting from the disease process may cause depression.[24] Second, the proinflammatory cytokines that cause acute flares may have a direct neural effect in promoting sickness behavior and corresponding depressive symptoms.[25] Previous studies have demonstrated higher serum levels of interleukin (IL)-1β, IL-2, IL-6 and tumor necrosis factor-α (TNF-α) in BD patients than in healthy controls.[26-29] We found that all BD disease activity parameters were correlated with depression levels of the patients. Association between disease activity and depression in the patients with BD was previously investigated in only one study. Melikoglu et al. found positive correlations between BDS and arthralgia and patient's impression of disease activity subgroups of BDCAF.[30] To our knowledge, this is the first study to demonstrate a significant association between depression and all components of BDCAF.

Fatigue is defined as 'a sense of persistent tiredness or exhaustion that is often distressing to the individual'.[31] It is a hallmark of many rheumatologic conditions.[32] Alder et al. demonstrated that BD patients had high levels of fatigue as measured by using Multi-dimensional Health Assessment Questionnaire (MDHAQ).[33] Moreover, it is a part of routine clinical assessment in BD and included in the disease activity core set measures as an outcome measure.[9] We evaluated fatigue severity of our patients by using FSS and found that all components of BDCAF, except oral ulcers, were correlated with FSS scores. Additionally, fatigue sub group of BDCAF was negatively correlated with both physical and mental domains of SF36.Bodur et al. reported that only physical domains of QoL such as pain and physical activity were correlated with fatigue subgroup of BD disease activity, which was evaluated with BDCAF.[15]

In our study, we found that disease activity parameters -except oral ulcers, genital ulcers and skin lesions- had a negative impact on QoL in terms of pain, vitality, physical, social, emotional and mental functioning in the patients with BD. Oral ulcers were associated with bodily pain, whereas genital ulcers and skin lesions were associated with physical impairment. We concluded that deterioration in QoL of BD patients mostly resulted from clinical manifestations including fatigue, headache, joint, eye, central nervous system and vascular involvement. Association between BD disease activity and QoL was previously reported in the study of Bodur et al. where QoL was evaluated by using Nottingham Health Profile (NHP).[15] They reported that fatigue, joint involvement and genital ulcers were significantly associated with impaired QoL in the patients with BD. On the other hand, Mumcu et al. reported significantly worse QoL scores in role-physical, role-emotional and vitality subscales of

SF36 in active BD patients.[34] They assessed BD disease activity by Krause score.[35] Similarly, in the study of Ertam et al. conducted in 195 Turkish BD patients, it was found that general health, vitality physical health domains of SF36 were impaired in the patients with active BD, where disease activity was measured by using Krause score.[36] They suggested that arthritis, eye involvement and vascular involvement mostly contributed to this impairment.

In conclusion, this study is the first to demonstrate that disease activity in BD is strongly correlated with three important items: QoL, depression and fatigue. We concluded that high disease activity had a negative impact on QoL, psychological functions and vitality. Treatment strategies focusing on fatigue, eye and joint involvement will improve QoL in terms of physical, social and emotional functioning.

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Writing and Discussion: *Tuba Güler, Yeşim Garip;* ***Literature Review:*** *Nurşad Çifci Aslan, Ayşe Aslıhan Karcı, Fulya Dörtbaş;* ***Idea, Design, Analysis:*** *Tuba Güler, Yeşim Garip, Fulya Dörtbaş;* ***Critical Review:*** *Tuba Güler, Nurşad Aslan, Ayşe Aslıhan Karcı.*

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