Fatigue is correlated with disease activity but not with the type of organ involvement in Behçet's syndrome: a comparative clinical survey

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ABSTRACT

Objective. *Fatigue is an important problem in inflammatory diseases and affects the quality of life (QoL). We aimed to evaluate the severity and impact of fatigue in Behçet's syndrome (BS) and to determine its association with type of organ involvement and gender.*

Methods. *One hundred and fifty-two BS, 51 rheumatoid arthritis (RA), 51 systemic lupus erythematosus (SLE), 51 ankylosing spondylitis (AS) patients and 65 healthy controls were evaluated by the fatigue severity scale, fatigue impact scale, fibromyalgia impact questionnaire (FIQ), RAPID3, SF-36 and Behçet's syndrome activity scale (the latter only in BS patients). We also analysed subgroups of BS patients with predominantly eye, vascular, joint and mucocutaneous involvement and did an additional gender analysis.*

Results. *Fatigue severity and fatigue impact scores were similar among BS, RA, SLE and AS patients and significantly higher than that in healthy controls (F_{4df} =8.51; p<0.001 and F_{4df} = 8.67; p<0.001, respectively). The fatigue severity and fatigue impact scores were similarly high in BS subgroups with different types of organ involvement, and in both genders.*

Conclusion. *Fatigue is an important problem in BS, as it is in other inflammatory conditions. It is similarly severe in subgroups of patients with eye, vascular, joint and mucocutaneous involvement and in either gender. Fatigue is a candidate outcome measure for clinical trials, to assess the life impact of Behçet's syndrome.*

Introduction

Behçet's syndrome (BS) is a systemic vasculitis of unknown aetiology, affecting the skin, mucosa, joints, eyes, arteries, veins, the nervous system and the gastrointestinal system. It usually starts in early adulthood and can be disabling and fatal when it involves the major organ systems. It runs a more severe course in men, especially when the disease onset is at a younger age (1-4).

Fatigue is an important problem in several inflammatory conditions, affecting the quality of life (QoL). It has become one of the patient reported outcomes used in disease assessment and it is one of the domains that are considered important to assess alongside the rheumatoid arthritis (RA) core set of outcome measures (5-7). Moreover, it is frequently assessed in drug trials (8, 9). BS is most active during young adulthood, affecting social life and work productivity. Although BS patients frequently complain from fatigue, this has not been well studied. In one study which evaluated sleep disorder in BS, it was observed that BS patients had higher fatigue severity scores compared to healthy controls (10). Another study showed that BS patients had higher fatigue scores on a visual analogue scale compared to rheumatoid arthritis patients (11). Two other studies reported increased fatigue as assessed by the older version of the Behçet's Disease Current Activity Form (BDCAF) which included one question on fatigue (12, 13). In one, Bodur *et al*. reported higher levels of fatigue in BS patients compared to healthy controls and showed that fatigue was closely correlated with pain and physical activity and impaired QoL (12). The other study did not include diseased or healthy controls, but reported a significant correlation between fatigue and fibromyalgia (FM) impact score in Behçet's patients (13).

However, there were no formal studies evaluating the severity and impact of

fatigue in BS patients and their relation to various types of organ involvement.
The aim of this study was to evaluate fatigue in patients with Behçet's syndrome compared to diseased and healthy controls, to determine whether it is related to the type of organ involvement and to gender, and to assess the association of fatigue with disease activity, QoL and the presence of FM.

Methods

Study subjects

We included consecutive BS, RA, systemic lupus erythematosus (SLE), and ankylosing spondylitis (AS) patients who were attending our outpatient clinic for regular follow up visits, along with healthy controls (HC). HC were relatives and friends of the patients and hospital staff. All patients and controls provided an informed consent and the study was approved by the Ethics Committee of the Cerrahpasa Medical Faculty.

Assessment

In order to assess fatigue, patients and controls were asked to fill the validated Turkish translations of the fatigue severity scale and the fatigue impact scale (14, 15). To assess the association of fatigue with FM, disease activity and QoL, we used the Turkish versions of the FIQ, routine assessment of patient index data 3 (RAPID3) form, and the short form 36 (SF-36) (16-18). BS patients also filled the Behçet's syndrome activity scale (BSAS) questionnaire (19).
The fatigue severity scale is a validated tool to assess the effects of fatigue on motivation, exercise, physical functioning, carrying out duties, work and on the familial and social life of individuals. The total score for this scale ranges between 0 and 63. The fatigue impact scale was developed to evaluate the effect of fatigue on the QoL. It contains 40 questions, 10 of which relate to cognitive, 10 to physical, and 20 to psychosocial subscales. The total score for this scale ranges between 0 and 160. Both of these scales have been utilised in a wide variety of inflammatory or non-inflammatory chronic diseases with varying results (20-21).
The presence of FM was defined as chronic widespread pain lasting more than 3 months along with 11/18 tender points. The manual examination of FM tender points was performed by one of the authors (DB) blinded to the diagnoses. The FIQ was used to assess the effect of FM on individuals. The total score ranges between 0–180 (22).
SF-36 was used to measure the QoL in patients and control groups. It is a self-administered questionnaire containing 36 items with mental and physical components and is a generic tool which has been used in different disciplines. The total score ranges between 0-100 scored separately for the mental and physical components (18).
Considering the possible effect of disease activity on fatigue, we aimed to use a tool for disease assessment that would be informative on all of the conditions we used as controls in addition to BD patients. We used RAPID3, a patient reported outcome measure, for this purpose. RAPID3 is a composite of physical function, pain and global status, where physical function is evaluated using 10 questions and pain and global function are evaluated on a visual analogue scale. The maximum score is 30 (17).
The disease activity among BS patients was additionally evaluated using a disease specific measure, the Behçet's syndrome activity scale (19). This questionnaire includes items concerning the number of oral ulcers, genital ulcers, skin lesions and the degree of discomfort they cause, in addition to gastrointestinal, ocular symptoms and deep vein thrombosis that occurred during the last 4 weeks. We modified this scale by adding a question about the presence of arthritis episodes during the previous 4 weeks. The total score of this modified version ranges between 0 and 110.
In all of the measures, higher scores show worse disease except for SF-36 where lower scores show worse QoL.

Statistical analysis

The groups were compared with stepwise ANOVA for parametric variables and Pearson chi-square test for non-parametric variables. Women with BS, RA and SLE and healthy women were separately analysed due to the known higher frequency of FM among women. Among the BS patients, those with predominantly eye, vascular, joint and mucocutaneous involvement were also separately analysed. The associations between fatigue severity score and fatigue impact score with the FIQ, RAPID3, BSAS and SF-36 scores were assessed using correlation analysis. Behçet subgroups with different types of involvement and men and women with BS were analysed separately since disease expression differs in BS between men and women as mentioned in the introduction.

Results

We consecutively studied 152 BS, 51 RA, 51 SLE, 51 AS patients who were visiting the outpatient clinic for their regular controls together with 65 healthy controls. Among the BS patients 42 had predominantly eye, 30 had vascular, and 40 had joint involvement while the other 40 had only mucocutaneous involvement. RA patients were significantly older than the other groups (F_{4df}=9.87, p<0.001). Women were significantly more frequent among SLE (F_{4f} χ^2=67.8, p<0.001) and RA (F_{3df} χ^2=38.5, p<0.001) patients. RAPID3 score was significantly higher among RA than all other groups (F_{4df}=20.88; p<0.001). The score was similar among BS, SLE and AS patients and significantly higher than healthy controls (F_{3df} =21.32; p<0.001) (Table I).

Fatigue assessment

Mean fatigue severity and mean fatigue impact scores were similar among BS, RA, SLE and AS patients and significantly higher than healthy controls (F_{4df}=8.51; p<0.001) (F_{4df}=8.67; p<0.001), respectively (Table II). When we separately analysed women with BS, RA, and SLE and healthy women, we observed that BS, RA, and SLE patients had significantly higher fatigue severity and fatigue impact scores compared to healthy controls (F_{3df}=6.575; p<0.001 and F_{3df}=8.668; p<0.001 respectively) (Table III). Comparison of patients without FM in each group gave similar results (data not shown).

Table I. Demographic features and disease activity in each group.

	BS	RA	SLE	AS	HC
n=	152	51	51	51	65
Female:male*	79:73	41:10	48:3	12:39	44:21
Age (mean±SD)**	37.5 ± 11.7	46.2 ± 13.3	39.1 ± 13	39.3 ± 8.7	33 ± 9.5
RAPID3***	10.7 ± 6.3	14 ± 7.1	11.2 ± 8.3	10.8 ± 6.4	3.8 ± 4.1

*There were significantly more women among SLE ($F_{4f}\chi^2$=67.8, p<0.001) and RA ($F_{3f}\chi^2$=38.5, p<0.001) patients. **RA patients were significantly older than the other groups (F_{5df}=9.87, p<0.001). ***RAPID3 score was significantly higher among RA than all other groups (F_{4df}=20.88; p<0.001). The score was similar among BS, SLE, and AS patients and significantly higher than healthy controls (F_{3df}=21.32; p<0.001).

Table II. Fatigue severity and impact scores, number of patients with fibromyalgia, fibromyalgia impact scores, and SF-36 mental and physical component summary scores in groups (mean ± SD).

	BS (n=152)	RA (n=51)	SLE (n=51)	AS (n=51)	HC (n=65)	p
Fatigue severity score*	32.9±13.5	36.7±13.5	34.6±13	34.2±12.8	24.1±12.5	< 0.001
Fatigue impact score**	42.9±32.1	52.2±31.8	49.5±39.3	34.9±32.5	22.2±23.2	< 0.001
Patients with fibromyalgia (n=)***	12/152 (8%)	15/51 (30%)	10/51 (20%)	3/51 (6%)	3/65 (5%)	0.023
Fibromyalgia impact score†	38.8±21.7	47.1±21.3	44.3±24.9	35.7±22.8	20.0±15.5	< 0.001
SF-36 physical component‡	40.6±10.4	32.1±11.9	38.8±11.6	40.4±10.6	53.1±6.6	<0.001
SF-36 mental component	43.6±10.7	43.9±11.8	43.6±11.3	47.0±11.3	45.8±9.8	0.276

*Mean fatigue severity score was similar among BS, RA, SLE and AS patients and significantly higher than healthy controls (F_{4df}=8.51; p<0.001). **Mean fatigue impact score was similar among BS, RA, SLE and AS patients and significantly higher than healthy controls (F_{4df}=8.67; p<0.001).
***The number of patients with fibromyalgia was highest among the RA group ($F_{4f}\chi^2$=25.7, p<0.001), followed by the SLE group ($F_{3f}\chi^2$=9.6, p=0.023). †Fibromyalgia impact score was similar among BS, SLE and AS patients, and significantly lower than RA patients (F_{3df}=3.026, p=0.03). ‡Physical component summary scale score of SF-36 was similar among BS, SLE and AS patients and was significantly lower among RA patients compared to all other groups (F_{4df}=32.37; p<0.001).

Table III. Fatigue severity scores, fatigue impact scores, fibromyalgia impact scores (mean ± SD) and number of patients with fibromyalgia among women.

WOMEN	BS (n=79)	RA (n=41)	SLE (n=49)	HC (n=44)	p
Fatigue severity score*	34.9 ± 13.2	36.6 ± 14.2	34.4 ± 13.1	25.2 ± 11.4	<0.001
Fatigue impact score**	47.5 ± 32.4	53.8 ± 33.6	49.4 ± 39	22.5 ± 22.3	<0.001
Number of patients with fibromyalgia***	9/79 (11%)	15/41 (37%)	10/48(20%)	3/44 (7%)	0.001
Fibromyalgia impact score†	43.3 ±19.4	50.0 ± 21.3	43.8 ± 24.8	23.5 ± 14.5	<0.001
SF-36 mental component	41.4 ± 10.2	43.1 ± 12.4	43.6 ± 11.3	44.8 ± 9.6	0.406
SF-36 physical component‡	39.8 ± 9.8	31.9 ± 12.3	38.8 ± 11.6	51.7 ± 7.2	<0.001

*The fatigue severity score was similar among women with BS, RA, and SLE, and significantly higher than healthy controls (F_{3df}=6.575; p<0.001). **The fatigue impact score was similar among women with BS, RA, and SLE, and significantly higher than healthy controls (F_{3df}=8.668; p<0.001).
***The number of patients with fibromyalgia was highest among the RA group (χ^2=16.266, p=0.001) compared to the rest of the groups. †The Fibromyalgia impact score was similar among women with BS, RA, and SLE, and significantly higher than healthy controls (F_{3df}=14.296; p<0.001). ‡The SF-36 physical component summary scale score was significantly higher among the healthy controls compared to all diseased groups (F_{3df}=27.545; p<0.001).

Fibromyalgia assessment

The number of patients with FM was highest among the RA group (F_{4f} χ^2=25.7, p<0.001), followed by the SLE group (F_{3f} χ^2=9.6, p=0.023). When we analysed women with BS, RA, and SLE and healthy women, again the number of women with FM was highest among the RA group (F_{3f} χ^2=16.266, p=0.001). FM impact score was also highest among RA patients (F_{3df}=3.026, p=0.03), similar among BS, SLE and AS patients, and significantly lower among healthy controls. However when women were analysed separately, the FM impact score was similar among women with BS, RA, and SLE, and significantly higher than healthy controls (F_{3df}=14.296; p<0.001) (Table II, III).

Quality of life

Physical component summary score of SF-36 was highest among healthy controls, similar among BS, SLE and AS patients and was significantly lower among RA patients compared to all other groups (F_{4df}=32.37; p<0.001). The mental component summary scale score of SF36 was similar among the groups (F_{4df}=1.28; p=0.276) (Table II).

Assessment of BS subgroups

The fatigue severity and fatigue impact scores, and SF-36 mental and physical component summary scale scores were similar among BS subgroups with eye, vascular, mucocutaneous and joint involvement. Disease activity assessed by the BSAS was also similar among BS patients with mucocutaneous, eye, vascular and joint involvement (p=0.85). However, RAPID3 and the FIQ scores tended to be higher among BS patients with joint involvement (p=0.048 and p=0.049, respectively) (Table IV).

Assessment of men and women with BS

The fatigue severity and fatigue impact scores were similar among men and women with BS. The FIQ score was higher in women (p=0.012) while the mental component of SF-36 was higher in men (p=0.012) with BS (Table V). A comparison between men and women in each subgroup of BS showed that among BS patients with mucocutaneous involvement, the fatigue severity and fatigue impact scores, and FIQ score were significantly higher in women (p=0.011, p=0.002, and p=0.008 respectively) while both physical and mental component summary scale scores of SF-36 were significantly higher in men (p=0.013 and

Table IV. Disease activity, fatigue, fibromyalgia and quality of life in Behçet's subgroups.

	Eye involvement (n=42)	Vascular involvement (n=30)	Joint involvement (n=40)	Mucocutaneus involvement (n=40)	*p*
BS activity scale score	28.7 ± 18.3	28.2 ± 16.8	28.6 ± 19.9	31.5 ± 14.4	0.846
RAPID3	10.4 ± 6.4	9.5 ± 5.8	13.0 ± 6.9	9.5 ± 6.2	0.048
Fatigue severity score	33.5 ± 12.8	31.7 ± 12.8	34.7 ± 12	31.6 ± 16.1	0.692
Fatigue impact score	44.7 ± 32.4	36 ± 29.6	44.7 ± 30.7	44.3 ± 35.3	0.632
Fibromyalgia impact questionnaire score	36.8 ± 23.4	32.4 ± 19.6	46.6 ± 19.9	38.1 ± 21.5	0.049
SF-36 mental component	41.1 ± 11.1	47.7 ± 8.4	43.5 ± 9.5	42.9 ± 11.8	0.08
SF-36 physical component	41.9 ± 9.8	39.8 ± 11,2	37.4 ± 9.2	43.3 ± 11.0	0.07

Table V. Fatigue severity core, fatigue impact score, fibromyalgia impact questionnaire, SF-36 mental component and physical component summary scores among women and men with Behçet's syndrome.

	Women (n=79)	Men (n=73)	*p*
Fatigue severity score	34.8 ± 13.2	31 ± 13.6	0.07
Fatigue impact score	47.1 ± 32.3	38.2 ± 31.4	0.087
Fibromyalgia impact questionaire	43.1 ± 19.4	34.2 ± 23.2	0.012
Number of patients with fibromyalgia	9/79 (11%)	3/73 (4.1%)	0.134
SF-36 physical component summary scale score	39.8 ± 9.8	41.5 ± 11.1	0.318
SF-36 mental component summary scale score	41.4 ± 10.3	45.8 ± 10.8	0.012

p=0.007, respectively). There were no significant differences between genders among the other BS subgroups (data not shown).

Correlation of fatigue with disease activity, QoL *and fibromyalgia*

Fatigue severity and fatigue impact scores correlated with disease activity measured by RAPID3 and BSAS, with SF-36 items and with FM in BS, RA, SLE, and AS patients (Table VI).

Discussion

Our study showed that fatigue is an important problem in BS, as it is in other inflammatory conditions. It is correlated with disease activity and is independent from both the type of organ involvement and from gender. We also observed that fatigue is correlated with QoL in BS patients and this makes it a potential candidate for formal disease assessment and an outcome for clinical trials.

Our study is unique for evaluating the severity and impact of fatigue in BS patients, in relation to disease activity and QoL, and to gender, in comparison with other rheumatological disorders such as RA, SLE, AS and also with healthy controls. The severity and impact of fatigue was more pronounced in our BS patients and diseased controls compared to the healthy controls.

Fatigue, which is the enduring, subjective sensation of generalised tiredness or exhaustion, is influenced by biological, psychological, social and personal factors. It has been documented as an important problem in several inflammatory conditions and is considered an independent domain in patient assessment. RA is one of the diseases where fatigue has been extensively studied. Measures of fatigue in RA are considered to be reliable and sensitive to change and fatigue is considered to be an important domain to be assessed along with the core set of outcome measures for RA in clinical trials (7). It is also a common manifestation in SLE patients. A systematic review of fatigue in SLE has shown that fatigue is correlated with Systemic Lupus Activity Measure, pain, poor quality of sleep, depression, and with each subscale of the SF-36 (20). In AS patients, fatigue is associated with functional disability, pain and disease activity and is used as an outcome measure in drug trials (23). Among patients with vasculitis, it was observed that fatigue is a major domain of disease assessment which has an impact on the QoL (24, 25). However it is not always associated with disease activity (24).

When evaluating fatigue across different patient groups it is important to assess disease activity, since the level of disease activity may be correlated with the severity of fatigue. We decided to use RAPID3 for evaluating activity in our groups, because although it was originally developed for RA, it was previously shown to work well also in SLE, AS, BS, and other rheumatologic conditions (17, 26). We have observed that both the fatigue severity scores and the fatigue impact scores are correlated with RAPID3 scores in all of the groups.

The RAPID3 scores were higher in our RA patients compared to the other groups. The lower QoL and higher FM scores in RA patients may be related to this. However it is difficult to tell whether the higher RAPID3 score indicates a higher activity in our RA patients compared to the other groups, since RAPID3 was not developed or validated to compare disease activity in different diseases. It is possible that this tool is more sensitive to capture activity in RA patients, the disease that it was originally developed for.

In our study there was no difference in BSAS scores among our BS patients with eye, vascular, joint or only mucocutaneous involvement and fatigue was highly correlated with it in all BS subgroups. However the RAPID3 score tended to be higher among BS patients with joint involvement. This may be related to the high weight of questions related to musculoskeletal function in the RAPID3 questionnaire.

There are conflicting reports regarding the association of FM with disease activity in BS. In a previous survey of FM among BS patients by our group, 9.2% of BS patients had FM and the presence of FM was not associated with disease activity, but musculoskeletal complaints were more common in BS patients with FM (27). Similarly, Lee *et al*. did not observe an association between FM and disease activity (28). However, Melikoglu *et al*. reported that FM was correlated with fatigue and pain, but not with other items of Behçet's disease current activity index

Table VI. Correlation of fatigue severity score and fatigue impact score with other outcome measures.

	FSS											
	Total		BS		RA		AS		SLE		HC	
	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
FIQ	0.545	<0.001	0.505	<0.001	0.522	<0.001	0.434	0.003	0.695	<0.001	0.300	0.015
RAPID3	0.571	<0.001	0.517	<0.001	0.494	<0.001	0.489	<0.001	0.623	<0.001	0.487	<0.001
BSAS *	NA	NA	0.357	<0.001	NA	NA	NA	NA	NA	NA	NA	NA
SFMCS	0.615	<0.001	0.564	<0.001	0.527	<0.001	0.616	<0.001	0.754	<0.001	0.400	<0.001
SFPCS	0.484	<0.001	0.431	<0.001	0.467	<0.001	0.580	<0.001	0.550	<0.001	0.576	<0.001
	FIS											
	Total		BS		RA		AS		SLE		HC	
	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*	r	*p*
FIQ	0.682	<0.001	0.628	<0.001	0.620	<0.001	0.681	<0.001	0.772	<0.001	0.582	<0.001
RAPID3	0.679	<0.001	0.672	<0.001	0.564	<0.001	0.659	<0.001	0.737	<0.001	0.474	<0.001
BSAS *	NA	NA	0.488	<0.001	NA	NA	NA	NA	NA	NA	NA	NA
SFMCS	0.642	<0.001	0.606	<0.001	0.553	<0.001	0.624	<0.001	0.721	<0.001	0.481	<0.001
SFPCS	0.625	<0.001	0.600	<0.001	0.677	<0.001	0.636	<0.001	0.641	<0.001	0.712	<0.001

FSS: Fatigue severity score; FIS: Fatigue impact score; FIQ: Fibromyalgia impact score; BSAS: Behçet's syndrome activity scale; SFMCS: Short form 36 mental component summary scale scor; SFPCS: Short form 36 physical component summary scale score; BS: Behçet's syndrome; RA: rheumatoid arthritis; AS: ankylosing spondylitis; SLE: systemic lupus erythematosus; HC: healthy controls. *BSAS was evaluated among BS patients only.

(13). In this study we observed that FM was associated with disease activity assessed with BSAS in all BS subgroups. The FIQ score tended to be higher among BS patients with joint involvement.

One of our limitations was the expected imbalance in the number of men and women among RA, SLE and AS patients. As one would expect, there were more women among RA and SLE and more men among AS groups. This may have impacted the analyses for FM, since this condition is known to be more frequent among women. Thus the increased FM impact score and FM frequency among RA patients compared to the other groups may be influenced by the fact that 80% of the subjects in this group were women. In this line, when we analysed the results of FM assessments separately among women with BS, RA, SLE and healthy controls, FM impact scores were similar in the diseased groups and significantly higher than healthy controls. The other limitation is the lack of an activity measure developed for comparing disease activity across different rheumatologic conditions. We used RAPID3 which was validated to measure disease activity in several inflammatory conditions. However several questions in the first part of the questionnaire assess physical function, mostly depending on musculoskeletal involvement.

In conclusion, fatigue is an important problem in BS similar to that observed in other rheumatological disorders. It merits special emphasis in the evaluation of patients with BS and its incorporation into disease assessment during routine follow-up and clinical trials would improve patient care.

Key messages

- Fatigue is an important problem in BS, as it is in other rheumatological disorders.
- Fatigue is highly correlated with disease activity and similarly severe in all BS subgroups.
- Fatigue is a candidate outcome for clinical trials, to assess the life impact of BS.

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