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Depression in Behçet's disease patients: Relationship with disease pattern, activity and quality of life

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ABSTRACT

Aim of the work: To determine the frequency of depression in Behçet's disease (BD) patients and to clarify its burden on patients' clinical manifestations, disease activity status and quality of life (QoL).
Patients and methods: 35 BD patients with 35 matched control were included in this study. Disease activity was assessed by Behçet Syndrome Activity Score (BSAS). All participants were requested to complete the Hamilton depression rating scale (HDRS), Multidimensional assessment of fatigue (MAF) questionnaire and the short form-36 (SF-36) QoL Scale.
Results: The mean age of the patients was 40.3 ± 13.5 years (17–72 years) and they were 27 males and 8 females. The frequency of depression in BD patients was 74.3% with increased male frequency ($p = 0.007$) and major organ involvement ($p = 0.04$) among depressed patients. Significant differences ($p < 0.001$, $p = 0.04$, $p = 0.001$ respectively) between depressed and non depressed BD patients with respect to BSAS, MAF and SF-36. Highly significant positive correlations between HDRS and number of major organ, BSAS, MAF, ($p < 0.001$) and significant correlation with number of non major organs ($r = 0.3$, $p = 0.04$). Significant negative associations were observed between HDRS and SF-36 ($r = -0.6$, $p < 0.001$). On regression number of major organ involvement ($p < 0.001$), BSAS ($p = 0.01$), MAF ($p = 0.002$), and SF-36 QoL ($p < 0.001$) significantly correlated with HDRS.
Conclusion: Depression is a significant comorbidity in patients with BD and is closely related to fatigue, number of major organ involvement and overall disease activity with a negative impact on QoL. Therefore, early interference and depression management in routine clinical practice is important to reduce patients' symptoms, and improve QoL.
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1. Introduction

Behçet's disease (BD) is a multisystem chronic inflammatory disease of unknown etiology most frequently observed along the ancient Silk Road [1]. Although vasculitis and perivascular inflammation are responsible for the pathology of BD, genetic predisposition, autoimmunity and infections are among the possible causes of the disease [2]. Recurrent oral and genital ulcers, severe ocular inflammation, cutaneous lesions, and other manifestations involving gastrointestinal (GI), circulatory and neurological systems characterize the disease [1]. In Egyptian BD patients, the central nervous system (CNS), deep venous thrombosis, and GI involvement were higher in males while joint affection and disease activity were increased in females [3].

The psychological aspects of BD have gained much attention as the disease may also affect the CNS, with associated psychiatric symptoms including personality changes [4]. The stress factor has been recognized in many BD patients prior the onset of the disease or the occurrence of relapses [5]. In addition to this, psychiatric disorders can be associated with chronic diseases with high morbidity and mortality as is the case in diseases such as BD [6].

The most commonly reported psychiatric manifestations include psychosomatic signs, anxiety and depression with reported incidence up to 86% of cases [2]. Moreover, major depressive symptoms were encountered in approximately 1/5 of BD patients [7]. Although functional disability, glucocorticoids use and CNS involvement are all relevant suggested factors, the exact pathogenesis of these types of symptoms in BD patients has not yet been confirmed [2]. Likewise, fatigue has been shown to be a common symptom in active BD patients, which may be exacerbated by con-

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tributing elements such as depressive symptoms, sleep disorders, and poor lifestyle [8]. Further, fatigue, depression, and disease activity were among the factors reported to affect the quality of life (QoL) of BD patients [9].

The relationship between disease activity, psychological symptoms, and QoL in BD patients was not sufficiently investigated. Therefore this study aimed to determine the frequency of depression among Behçet's disease (BD) patients and to clarify its burden on patients' clinical manifestations, disease activity status and QoL.

2. Patients and methods

This is a cross-sectional study of thirty five BD patients who satisfied the new set of diagnostic criteria published by the International Study Group for Behçet's Disease [ISG] [10], along with 35 asymptomatic healthy volunteers matched for age and sex as controls were enrolled into this study.All were recruited from the inpatient and outpatient clinics of the Rheumatology, Rehabilitation and Physical medicine Department of Benha University Hospitals. Participants were excluded if they suffer from other connective tissue diseases, diabetes mellitus (DM), chronic liver or kidney disease, malignancy, pregnancy or known to suffer from mental or other psychiatric disorders. Moreover, patients treated with corticosteroids greater than 10 mg/day were also excluded. The study protocol was explained to all subjects and an informed written consent was obtained prior to participation in this study and the study was approved by the ethical committee of Benha University and confirms to the declaration of Helsinki.

Patients' characteristics including demographic features, disease duration, clinical manifestations and current medications were obtained. Thorough clinical examination was performed and skin pathergy test was done as described by Altac et al. [11]. Patients were defined to have major organ involvement if one or more of the following systems were affected (ocular, central nervous system, major vessel and\or gastrointestinal). Laboratory investigations included erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Behçet Syndrome Activity Score (BSAS) was assessed [12].

Depression was assessed using the 17-item version of the Hamilton Depression Rating Scale (HDRS). Scores range from 0 to 54; a higher score indicates higher symptom severity with 0–7 being considered normal; 8–13 indicates mild depression; 14 to 18 indicates moderate depression; 19 to 22 indicates severe depression from; and 23 or more indicates very severe depression [13].The SF-36 is a generic health status instrument that measures QoL and a higher score indicates better quality [14]. The Multidimensional Assessment of Fatigue (MAF) assessed fatigue in study participants. It is a 16-item self-report with 4 domains including distress, severity, timing of onset of fatigue, and impact on activities of daily living. The composite scores from each domain include the Global Fatigue Index (GFI), with anchor points from 0 = no fatigue to 50 = extreme fatigue, and higher scores correspond to greater fatigue [15].

*Statistical analysis:*The results were analyzed by IBM-SPSS (version 25). Qualitative variables were expressed as number and percentage. Quantitative data were expressed as means, standard deviation. Chi square test, Student's t-test, Mann Whitney test, Kruskal Wallis test, and Fisher's exact test were used to examine the significance of differences according to type of data. Spearman's correlation was considered and linear regression analysis used to find the significance predictors of HDRS. P-value < 0.05 was considered significant.

3. Results

The 35 BD patients were 27 (77.2%) men and 8 (22.9%) women with a mean age 40.3 ± 13.5 years (17–72 years). 35 age (38.3 ± 11. 3 years; 20–60 years) and sex: 26 males (74.3%) and 9 females (25.7%) matched control were also studied (p = 0.5 and p = 0.7 respectively). Table 1 shows basic characteristics of the BD patients.The HDRS and MAF were significantly higher in patients (14.9 ± 7.5 and 29.6 ± 12.8) compared to the control (6.1 ± 3.8 and 6.3 ± 2.9; p < 0.001 respectively). In the patients, the HDRS was normal in 9 (25.7%), mild in 6 (17.1%), moderate in 12 (34.3%), severe in 5 (14.3%) and very severe in 3 (8.6%). In the control, 23 (65.7%) were normal, 10 (28.6%) mild and only 2 (5.7%) moderate. The SF-36 was significantly lower in the patients compared to the control (54.1 ± 23.5 vs 84.6 ± 7.9; p < 0.001). Comparisons between depressed and non depressed BD patients are presented in Table 2

Relation between HDRS and medications are expressed in (Fig. 1). Higher depression (HDRS) was significantly observed in those receiving biologics (26.5 ± 4.9), cyclosporine A (16.1 ± 1.9) and cyclophosphamide (15.7 ± 4.6) than those receiving chlorambucil (10.3 ± 4.7), steroids (7.4 ± 2.4), colchicine (6.2 ± 1.2) and azathioprine (5.2 ± 1.1) (p < 0.001).

The correlation between HDRS and different disease parameters are shown in Table 3.On linear regression; HDRS significantly cor-

Table 1
Characteristics of the Behcet's disease patients.

Variable Mean ±SD or n (%)	BD patients (n=35)
Age:	40.3 ± 13.5
Sex (female/male)	8/27
Disease duration (years)	10.1 ± 8.7
HDRS	14.9 ± 7.5
MAF	29.6 ± 12.8
SF-36	54.1 ± 23.5
BSAS	49 ± 26.6
Clinical manifestation	
Joint	28 (80)
Eye	35 (100)
Genital ulcer	33 (94.3)
Oral ulcer	35 (100)
Acne	16 (45.7)
CNS	3 (8.6)
GIT	3 (8.6)
DVT	2 (5.7)
STP	5 (14.3)
Positive pathergy	12 (34.3)
Major organs involved	
1	23 (65.7)
2	8 (22.9)
3	4 (11.4)
Non major organ	
2	2 (5.7)
3	20 (57.1)
4	7 (20)
5	6 (17.1)
ESR (mm/1sthr)	21.1 ± 43
CRP (mg/l)	5.7 ± 3.12
Medications	
Corticosteroids	20 (57.1)
Colchicine	17 (48.6)
Azathioprine	5 (14.3)
Biologics	6 (17.1)
Cyclophosphamide	6 (17.1)
Cyclosporine A	10 (28.6)
Chlorambucil	8 (22.9)

BD: Behcet's disease, HDRS: Hamilton depression rating scale, MAF: multidimensional assessment of fatigue, SF-36: short form-36, BSAS: Behcet's Syndrome Activity Score, CNS: central nervous system, GIT: gastrointestinal tract, DVT: deep venous thrombosis, STP: superficial thrombophlebitis, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

Table 2
Comparison between depressed and non depressed Behcet's disease patients.

Variablen(%)	BD patients (n=35)		p
	Depressed (n=26)	non-depressed (n=9)	
Age (years)	39.9 ± 11.9	41.4 ± 18.2	0.6
Sex (female/male)	3/23	5/4	**0.007**
Disease duration (years)	11.6 ± 9.3	5.8 ± 4	0.07
MAF	39.1 ± 14	25.2 ± 7.4	**0.04**
SF-36	45.1 ± 19.6	79.9 ± 11	**<0.001**
BSAS	57.3 ± 25.7	25.0 ± 8.3	**0.001**
Joint	19 (73.1)	9 (100)	0.1
Genital ulcer	24 (92.3)	9 (100)	0.4
Acne	10 (38.4)	6 (66.6)	0.7
CNS	3 (11.5)	0 (0)	0.3
Vascular	7 (26.9)	0 (0)	0.2
GIT	3 (11.5)	0 (0)	0.3
Positive pathergy	10 (38.5)	2 (22.2)	0.4
Major organs involved			
1	14 (53.8)	9 (100)	**0.04**
2	8 (30.8)	0 (0)	
3	4 (15.4)	0 (0)	
Non-major organs			
2	1(3.8)	1 (11.1)	0.2
3	13(50)	7 (77.8)	
4	6 (23.1)	1 (11.1)	
5	6 (23.1)	0 (0)	
ESR (mm/1sthr)	20.1 ± 1.8	18.1 ± 2.3	0.2
CRP (mg/l)	3.9 ± 2.6	4.1 ± 1.2	0.1
Medications			
Corticosteroids	14 (53.3)	6 (66.7)	**<0.001**
Colchicine	12 (46.2)	5 (55.5)	
Azathioprine	0 (0)	5 (55.6)	
Biologics	6 (23.1)	0 (0)	
Cyclophosphamide	5 (19.2)	1 (11.1)	
Cyclosporine A	9 (34.6)	1 (11.1)	
Chlorambucil	3 (33.3)	5 (19.23)	

BD: Behcet's disease, MAF: multidimensional assessment of fatigue, SF-36: short form-36, BSAS: Behcet's Syndrome Activity Score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.CNS: central nervous system, GIT: gastrointestinal tract. Bold values are significant at p < 0.05.

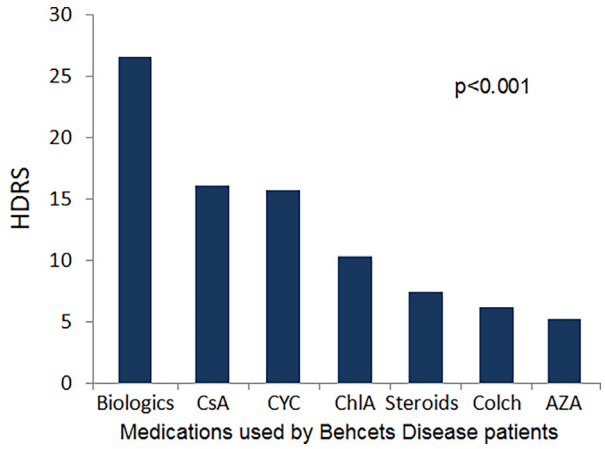

Fig. 1. Relation between Hamilton depression rating scale and medications used by Behcet's disease patients. CsA: cyclosporine A, CYC: cyclophosphamide, ChlA: chlorambucil, Colch: colchicines, AZA: azathioprine.

related with number of major organs involved (p < 0.001), BSAS (p = 0.01), MAF (p = 0.002) and SF-36 (p < 0.001) (Table 4)

4. Discussion

Behçet's disease is a chronic, relapsing vasculitis of unknown etiology and involvement of parenchymal CNS (neuro-BD) is a serious complication and leading cause of mortality [16]. 70% of patients with BD reported a stress factor before the occurrence of disease, while 79.4% declared such stress in the relapse period [5]. Interleukin-6 and IL-15 are involved in neuro-BD and a role of IL-23 and its gene polymorphism in Egyptian neuro-BD has also been presented [17]. It has been reported that depressive symptoms can be the leading clinical manifestations of BD [18]. In the current study, a high frequency of depression (74.3%) was found in BD patients, while it was lower in a Korean (46%) [19] and in a Turkish (40.6%)[20] study. The difference may be related to the use of different tools for assessment of depression, different sample size, and the variable individual's lifestyle. Moreover, depression has been reported as a significant comorbidity in Egyptian patients with rheumatoid arthritis (RA) [21,22], systemic lupus erythematosus [23] and juvenile idiopathic arthritis [24].

Consistent with previous results [25], there was a significant increase in depression in BD patients compared to controls. In addition, depression correlated with disease activity in BD patients which is in line with *Koca et al.* [2] and *Ilhan et al.* [8]. Conversely, *Sandikci et al.* [20] reported similar depression scores in BD patients with active and inactive disease using the Hospital Anxiety and Depression Scale- depression (HADS). *Melikoglu and Melikoglu* [26] reported a non-significant relationship between disease activity and depression except for joint pain and patients' impression of disease activity, however, they used different tools to assess BD activity (Behçet's Disease Current Activity Form) and depression (Beck Depression Inventory).

A trend for a higher frequency of depression among BD male patients was found in the current study, which may be explained by the fact that BD prefers the male gender. In this work there

Table 3
Correlation between Hamilton depression rating scale and different parameters in Behcet's disease patients.

Variable r (p)	HDRS in BD patients (n = 35)
Age	−0.07 (0.7)
Disease duration	0.3(0.1)
Major organs involved	0.6(<0.001)
Non major organs	0.3 **(0.04)**
MAF	0.6 **(<0.001)**
SF-36	−0.6 **(<0.001)**
BSAS	0.7 **(<0.001)**
ESR	0.1 (0.3)
CRP	0.2 (0.4)

HDRS: Hamilton depression rating scale, BD: Behcet's disease, MAF: multidimensional assessment of fatigue, SF-36: short form-36, BSAS: Behcet's Syndrome Activity Score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein. Bold values are significant at p < 0.05.

Table 4
Regression analysis of Hamilton depression rating scale predictors in Behcet's disease patients.

Variable	β	Sig.	(CI 95%)	
Age	0.32	0.09	0.16	0.19
Disease duration	0.38	0.1	0.29	0.36
Major organ involved	0.09	**<0.001**	0.76	1.31
Non major organs	0.22	0.07	1.51	2.25
MAF	0.29	**0.002**	0.14	0.21
SF-36	1.78	**<0.001**	0.54	0.73
BSAS	−0.22	**0.01**	−0.08	−0.04
ESR	0.29	0.06	0.14	0.21
CRP	0.31	0.08	0.24	0.34

HDRS: Hamilton depression rating scale, BD: Behcet's disease, MAF: multidimensional assessment of fatigue, SF-36: short form-36, BSAS: Behcet's Syndrome Activity Score, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein. Bold values are significant at p < 0.05.

was no association between depression and patients' age or disease duration which was similar to a previous study [27]. In contrast, Koca et al. [2] noted a significant relationship between depression and age of the patients. However, although disease duration may be considered as a triggering factor of depression in patients with chronic illnesses, no significant relation was found in patients with RA [28].

Epstein et al. suggested that there are both primary and secondary relationships between the physical clinical manifestations of BD and the emotional problems [29]. Furthermore, it has been suggested that some proinflammatory cytokines, such as IL-1 ß, IL-8, and tumor necrosis factor-α, affect the neuroendocrine activity and lead to changes in the central neurotransmitter systems and, thus, may cause predisposition to the development of mental signs [30].

Psychological factors have been identified to be associated with clinical features in patients with several chronic diseases [2]. The current study showed an increased frequency of major organs involvement among depressed BD compared to others. Furthermore, a significant correlation was reported between depression score and the number of major organs involved and a significant correlation was also observed with respect to the number of non major organs involved. Whereas, joint and ocular involvement has been reported to be associated with depression in patients with BD by *Tanriverdi et al.* [31], *Sandikci et al.* [20] did not show any relationship between depression and major organ involvement.

Although the exact cause of fatigue is not clearly understood, it is an important symptom and consequence of many rheumatic diseases with many potential contributing factors such as disease activity, pain, impaired function and poor sleep quality [32]. BD can affect patients in a negative way, cause fatigue and reduce quality of life. Increased inflammation may contribute to increased fatigue in BD patients [20]. Fatigue, which is a common symptom in BD was evaluated in the current study using MAF and was significantly higher than in control and also in BD patients with depression compared to those without which was in agreement with *Sandikci et al.* [20]. Inflammatory mediators have been shown to play a role in the pathogenesis of fatigue in RA [33]. .However, in light of the current data, when the relationship between the worsening of the clinical or emotional status in BD patients is considered, it is difficult to say which one is the cause and which one is the result. In the current study, SF-36 QoL was higher in BD patients compared to control. Also a significant difference was reported between depressed and non depressed BD patients and a significant negative relation was reported between depression score and SF-36 QoL**.** *Uguz et al.* [34] reported that major depression had a negative impact on QoL of BD patients and negatively correlated with the severity of depressive symptoms. In another study, [35] life satisfaction and quality were impaired in BD patients.

Medications of the BD seem to correlate with depression as well in the current study. Depressed BD patients were more likely to be receiving biologic, cyclosporine A and cyclophosphamide medications compared to non-depressed patients. Moreover, a significant link between depression severity and the use of these medications was observed. This observation supports findings obtained from this study which indicate that depression is associated with a more active disease. Corticosteroids are regularly prescribed to patients with active autoimmune diseases including BD with risk of adverse psychiatric effects. Some researchers have suggested that psychiatric manifestations in patients with BD are a consequence of corticosteroid therapy rather than an organic disease [36]. The psychiatric sequelae of corticosteroids, including depression, usually occur during the first two weeks of treatment and appear to be dosing related [37]. While *Nishimura et al.*[33] showed psychiatric symptoms in 20 SLE patients with a daily dose of at least 40 mg prednisolone, 97 patients did not exhibit any psychiatric symptoms at the same doses. Another study also indicated a strong dose-related association and described mood disturbances in 18 patients after receiving 30–60 mg/ day of prednisone equivalent [38]. Inthe present study, it wasimportant that none of BD patients received corticosteroids at a daily dose greater than 10 mg to avoid any possibility of steroid-induced depression. Colchicine is the most commonly prescribed drug to treat the mucocutaneous manifestations of BD. In experimental studies, colchicine has been applied intracranial, being an effective microtubule depolymerization agent; it has caused memory deficitand thus has been used as a selective neurotoxin for Alzheimer's disease and epilepsy in animal models [39]. In humans, its absorption is rapid when taken orally and appears in high concentrations in kidney, spleen and liver while not absorbed by the skeletal muscle, heart and brain [40]. No association of either corticosteroids or colchicine has been demonstrated with depression in BD patients involved in this study.

The main limitations of the current study arethe observational cross-sectional design and the limited number of patients. However, it was strengthened by the use of standard tools for the assessment of disease activity, depression, fatigue and QoL. In addition, this study is the first one to investigate the association between depression and number of major and non-major organ involved in BD patients as well as the relationship with different medications.

In conclusion, depression is a significant comorbidity in patients with BD and is closely related to fatigue, number of major organ involvement and overall disease activity with a negative impact on QoL. Therefore, early interference and depression management in routine clinical practice is important to reduce patients' symptoms, and improve QoL**.**

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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