

Suicidal ideation among patients with Behçet's syndrome

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ABSTRACT

Objective. To evaluate the frequency of suicidal ideation among Behçet's syndrome (BS) patients compared to healthy and diseased controls and to delineate possible factors predicting an increase in suicidal ideation.

Methods. We included consecutive BS patients attending our outpatient clinic, patients with ankylosing spondylitis (AS) and healthy hospital staff as controls. Suicidal ideation was assessed by a standard questionnaire. Linear regression was used to identify the factors associated with suicidal ideation, such as demographic and clinical features, drugs, disease activity assessed using the Behçet's disease current activity form (BDCAF) for BS patients and BASDAI for AS patients, Behçet's disease quality of life (BDQoL) and Beck Depression Inventory (BDI) score.

Results. We surveyed 303 BS patients, 52 AS patients and 106 healthy controls. Suicidal thoughts, as reflected by a positive response to the first three items of the questionnaire, were higher among BS patients with major organ involvement (42%) than those with mucocutaneous involvement (35%) and the control groups. There were significantly more BS patients with active major organ involvement who had thought to terminate their lives without plans within the last year (25.5%) compared to those with active mucocutaneous involvement (8.7%) and active AS patients (10%) ($p=0.012$). Patient-reported joint pain ($\beta=-0.155$, $p=0.046$), BDQoL ($\beta=0.176$, $p=0.032$), and BDI ($\beta=0.017$, $p<0.0001$) scores, suicidal thoughts before the onset of BS ($\beta=-0.124$, $p=0.043$), neurologic involvement ($\beta=0.119$, $p=0.047$) and past prednisone use ($\beta=0.212$, $p=0.005$) were independent predictors of suicidal thoughts.

Conclusion. BS patients with major organ involvement have increased thoughts of suicide during the active stages of their disease. A number of risk factors could help physicians to identify patients with increased suicidal thoughts.

Introduction

Behçet's syndrome (BS) is a systemic vasculitis of unknown aetiology characterised by a heterogeneous nature of organ involvement and a chronic, undulating disease course. For many patients BS is an annoying disease impairing their quality of life with frequently relapsing mucocutaneous or joint manifestations. However, there are also others who develop significant disability or are at risk of increased mortality due to vital organ involvement. Being a male and developing the disease at a younger age are the 2 widely acknowledged factors associated with a more severe disease course. However, predicting the outcome in the long term is not so straightforward (1).

Having a chronic disease can disrupt lives and is an important risk factor for anxiety and depression. Previous studies have shown that patients with chronic rheumatologic conditions have higher rates of depressive symptoms (2-6). The most devastating consequence of depression is suicide or suicidal thoughts. The prevalence of suicidal ideation has been reported to be associated with the intensity of physical disability and depressive mood (3). The incidence of suicidal ideation in the preceding month was reported to be 12% in patients with systemic lupus erythematosus (SLE) (7), and 11% of outpatients with rheumatoid arthritis (RA) were reported to experience suicidal thoughts (8).

Higher rates of unemployment and dependence, lower socioeconomic status, significant physical and mental impairment, inability to achieve certain life goals due to disability, and uncertainties about disease course cause significant psychosocial stress in BS patients (9). BS patients have higher rates of mood and anxiety disorders and this was especially the case in patients with chronic pain, joint involvement, and longer disease duration (10-12). Moreover, major depression is an important factor influencing QoL (13). Additionally, drugs used in the management

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of BS, such as corticosteroids and interferon alpha, can also lead to mood disorders and even increased incidence of suicidal thoughts (14-16). However, whether patients with BS have increased suicidal thoughts is not known. Thus, we formally evaluated the frequency of suicidal thoughts among BS patients with suitable controls and also aimed to delineate factors denoting to increased suicidal ideation.

Materials and methods

BS Research Centre at the Cerrahpasa Medical Faculty is a tertiary referral centre that meets regularly every Monday with the participation of related specialists (rheumatology, dermatology, ophthalmology, neurology, gastroenterology and cardiovascular surgery) since its inception in 1977. This study enrolled consecutive BS patients who had been seen in our centre between December 2012 and November 2013. Consecutive AS patients who were being followed-up in our rheumatology outpatient clinic and healthy hospital staff and their relatives who did not have any known diseases served as the control groups. All participants were aged between 16 and 68 years, and BS and AS patients were fulfilling the International Study Group (17) and the Assessment of SpondyloArthritis International Society criteria (18), respectively. BS patients were divided into two groups according to the presence or absence of major organ involvement during their entire follow-up period: the first group had only mucocutaneous involvement either with or without joint involvement; the second group had at least one major organ involvement such as the eye, large vessel, gastrointestinal system, and neurological involvement. The study was approved by the Cerrahpasa Medical School Ethics Committee and a written informed consent was obtained from all participants.

A standard questionnaire was applied to all participants by one of two physicians (CS and DU) in order to survey the frequency of suicidal ideation and suicidal plans during the preceding 1 year (7). During this structured interview, questions were asked in the native language of the patients, which was Turkish for

all patients. The questions were: (i) In the preceding one year, have you ever thought that life was meaningless and was not worth living?; (ii) In the preceding one year, have you ever thought of terminating your life, but without plans?; (iii) In the preceding one year, have you ever thought of terminating your life with solid plans?; (iv) If yes, was it your disease which had led to these thoughts or plans? (v) Had you ever thought of terminating your life before the diagnosis? A positive response to any one of the first three questions indicated the presence of suicidal thoughts while question five asked for suicidal thoughts or attempts that were present before the onset of BS. Participants were also asked about their education, employment status, financial difficulties, disabilities preventing them from working, their marital status, any divorce after diagnosis, the impact of disease on marriage plans, number of children, miscarriages and terminations after diagnosis, and the impact of disease on the idea of having a child.

Behçet's Disease Current Activity Form (BDCAF) (19) and Behçet's Disease Quality of Life questionnaire (BDQoL) (20) (ranging from 0 to 30) were applied to all BS patients. BDCAF scores the clinical features present in the preceding four weeks (ranging from 0 to 10) and with this form, currently active mucocutaneous and joint disease, eye involvement, major vascular involvement, gastrointestinal involvement and central nervous system involvement, patient's impression of current disease activity (ranging from 0 to 7) and doctor's impression of current disease activity (ranging from 0 to 7) were evaluated. Disease activity in AS patients was assessed with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) (ranging from 0 to 10) (21) and function was assessed using Bath Ankylosing Spondylitis Functional Index (BASFI) (ranging from 0 to 10) (22). AS patients who had BASDAI scores equal to 4 or higher were accepted to have active disease. Beck Depression Inventory (BDI) (23) was used to evaluate depression in all participants. Sites of disease involvement and the drugs (*i.e.* prednisone, interferon, anti-

TNF drugs) that the patients have used during their entire follow-up were retrieved from the medical records.

Statistical analysis

Parametric variables were compared with analysis of variance (ANOVA), and categorical variables were compared with chi-square test. A linear regression model was used to investigate factors associated with suicidal ideation. The following factors were considered as covariates in the regression model: age, sex, age at diagnosis, disease duration, sites of involvement during entire follow-up, previous and current prednisone use, interferon and anti-TNF use, disease sequela, BDCAF, patient-reported disease activity score, patient-reported joint pain score, marital status, unemployment, education, financial difficulties, BDQoL, previous suicidal ideation, and BDI.

Results

The questionnaire was applied to 303 BS patients (having major organ involvement = 160; having mucocutaneous disease with or without joint involvement = 143). The control group consisted of 52 AS patients and 106 healthy individuals. Table I shows the demographic findings of the study group. The percentage of men was significantly higher among BS patients with major organ involvement and among AS patients ($p < 0.0001$), whereas age at disease onset was significantly lower among BS patients with major organ involvement ($p = 0.002$).

The number of married participants was significantly higher in BS patient groups ($p < 0.0001$). Among 60 single patients with BS, 9 (15%) saw their disease as the main reason precluding them from marriage and 58 out of 234 (24.8%) married patients reported that their disease considerably decreased their wish to parent a child, of whom 21 patients (36.2%) still tried to parent a child.

BS patients were less educated compared to AS patients and healthy controls. The unemployment frequency was also higher among both BS groups than the controls. The number of unemployed BS patients who considered their disease as the cause of unemployment

Table I. Demographic features of study groups.

	BS (major organ)	BS (mucocutaneous)	AS	Healthy	p-value
Total, n	160	143	52	106	
Men, n (%)	82 (51.2)	37 (25.9)	36 (69.2)	29 (27.4)	0.000
Age, mean (S.D.), years	36.7 (10.9)	39.0 (11.1)	37.5 (10.3)	35.9 (10)	0.130
Age at onset, mean (S.D.), years	26.8 (7.9)	30.4 (9.1)	29.3 (10.2)	–	0.002
Disease duration, mean (S.D.), years	10.3 (9.3)	8.5 (8.7)	8.4 (7.8)	–	0.153
Marital status					
Married, n (%)	113 (70.6)	121 (84.6)	35 (67.3)	59 (55.7)	0.000
Single, n (%)	42 (26.3)	18 (12.6)	15 (28.8)	45 (42.6)	
Divorced, n (%)	4 (2.5)	2 (1.3)	2 (1.3)	2 (1.3)	
Widowed, n (%)	1 (0.6)	2 (1.3)	0	0	
Education (%)					
Elementary school	67.9	59.6	35.4	21.7	
High school	19.5	21.3	27.1	30.2	
University	9.4	12	37.5	48.1	
None	3.1	7	0	0	
Unemployment (%)	47.5	62.9	34.6	19.8	0.000
Financial difficulties (%)	35.2	37.7	41.1	50	0.100
Disease activity* mean (S.D.)	3.41 (2.3)	3.89 (1.9)	4.32 (2.3)	–	0.015
BDI, mean (S.D.)	12.40 (10.5)	11.81 (9)	10.78 (10.1)	8.96 (7.7)	0.027
Drugs (%)					
Prednisone, current	25.3	10.6			
Prednisone, past	48.3	20.6			
Interferon, current	6.3	0.8			
Interferon, past	22.8	2.7			
Anti-TNF drugs	3.6	0			

*Disease activity was measured with Behçet's Disease Current Activity Form (BDCAF) in BS patients and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) in AS patients.

BS: Behçet's syndrome; AS: ankylosing spondylitis; BDI: Beck Depression Inventory.

ment was significantly higher in patients with major organ involvement (37 out of 84, 44%) compared to patients with mucocutaneous disease (22 out of 92, 23.9%) ($p=0.004$, χ^2 : 7.988, df:1).

Suicidal ideation

Suicidal thoughts, as reflected by the responses of the participants to the first 3 questions of the questionnaire, were somewhat more frequent among BS patients with major organ involvement compared to BS patients with mucocutaneous involvement and the control groups, but the difference was not statistically significant (Table II). On the other hand, when only patients with active disease were considered, ideation for terminating life within the last year with or without plans was significantly more frequent among BS patients with major organ involvement compared to BS patients with mucocutaneous involvement and the control groups. The percentage of patients holding

their disease responsible for having suicidal thoughts was significantly less among BS patients with mucocutaneous involvement compared to BS patients with major organ disease and AS patients ($p=0.05$). None of the AS patients had suicidal ideation before disease onset but this was the case in 13% of BS patients with mucocutaneous disease and 5.6% of BS patients with major organ involvement ($p=0.003$).

Among 303 BS patients included in this study, 238 had at least one site of active involvement at the time of interview and the disease was under remission in 65 patients. When 238 BS patients were stratified according to sites of active involvement, patients with eye involvement were found to have increased incidence of thoughts of terminating their lives without plans in the preceding one year compared to patients with active disease at other sites ($p=0.042$, χ^2 : 9.881, df:4) (Table III). Moreover, patients with eye involve-

ment and CNS involvement had higher frequency of solid plans for suicide in the preceding one year ($p=0.032$, χ^2 : 10.531, df:4).

Factors predicting suicidal ideation in BS patients

Table IV shows linear regression analyses of the demographic, clinical, and psychosocial factors associated with higher incidence of suicidal ideation in BS patients. Univariate analysis revealed that female sex, BDCAF score, patient-reported disease activity and joint scores, having financial difficulties, previous suicidal ideation, BDQoL and BDI scores were significantly associated with suicidal ideation. In a multivariate model, the patient-reported joint pain ($\beta=-0.155$, $p=0.046$) BDQoL ($\beta=0.176$, $p=0.032$), and BDI ($\beta=0.017$, $p<0.0001$) scores, neurologic involvement ($\beta=0.119$, $p=0.047$) and past prednisone use ($\beta=0.212$, $p=0.005$) were independent predictors of suicidal thoughts.

Discussion

Our results suggest that major organ involvement arises a tendency for suicidal thoughts among BS patients that becomes significant during active disease. Eye, neurologic and joint involvement appear to be important predictors of suicidal thoughts along with poor quality of life, higher depression scores, previous suicidal ideations, and steroid therapy. Disease duration, use of interferon and anti-TNF drugs, marital status, unemployment and education did not have a significant contribution to suicidal ideation in our patients. BS patients along with the AS group had higher depression scores compared to healthy controls. High depression scores and poor quality of life are important predictors of suicidal ideation. It was reported that quality of life in BS patients without major depression was similar to that of healthy controls (13). However, the incidence and intensity of depression in BS patients were shown to be higher than patients with RA (11), psoriasis (12), and healthy controls (24). The finding of increased incidence of current suicidal ideation in BS patients who also reported to

Table II. Suicidal ideation in study groups.

	BS (major organ)	BS (mucocutaneous) n=160	AS n=143	Healthy n=52	p-value n=106
Thought that life was meaningless in the last one year (%)	58 (36.3)	45 (31.5)	17 (32.7)	29 (27.4)	0.499
Currently active	20/47 (42.5%)	37/115 (32.2%)	11/29 (37.9%)	–	0.281
Currently stable	38/113 (33.6%)	8/28 (28.6%)	6/23 (26.1%)	–	0.844
Thought of terminating his/her life in the last year, without plans (%)	25 (15.6)	12 (8.4)	5 (9.6)	7 (6.6)	0.078
Currently active	12/47 (25.5%)*	8/115 (7%)	4/29 (13.8%)	–	0.001
Currently stable	13/113 (11.5%)	4/28 (14.3%)	1/23 (4.4%)	–	0.661
Thought of terminating his/her life in the last year, with solid plans (%)	25 (15.6)	13 (9.1)	4 (7.7)	9 (8.5)	0.154
Currently active	12/47 (25.5%)*	10/115 (8.7%)	3/29 (10.3%)	–	0.012
Currently stable	13/113 (11.5%)	3/28 (10.7%)	1/23 (4.4%)	–	0.898
Suicidal ideation in the last year (%) (positive response to any of the first three questions)	67 (41.9)	50 (34.9)	17 (32.7)	33 (31.1)	0.286
Currently active	22/47 (46.8%)	41/115 (35.6%)	11/29 (37.9%)	–	0.419
Currently stable	45/113 (39.8%)	9/28 (32.1%)	6/23 (26.1%)	–	0.574
Held their disease responsible for their suicidal ideations (%)	42/67 (62.7)	21/50 (42)	10/16 (62.5)	–	0.051
Previous suicidal ideation (%)	9/160 (5.6)	19/143** (13.3)	0/52 (0)	–	0.003

*BS patients with currently active major organ involvement had higher rates of suicidal thoughts with or without solid plans when compared to other diseased and healthy controls.

**The frequency of previous suicidal ideation (*i.e.* before the diagnosis) is significantly higher in mucocutaneous BS patients. BS: Behçet's syndrome; AS: ankylosing spondylitis.

Table III. Suicidal ideation and active disease involvement in Behçet's syndrome (n=303).

	Active orogenital ulcerations n=206	Active joint involvement n=83	Active eye involvement n=29	Active vessel involvement n=21	Active CNS involvement n=4	p value
Thought that life was meaningless in the last year	74 (35.9%)	33 (39.8%)	14 (48.3%)	8 (38.1%)	2 (50%)	0.731
Thought of terminating his/her life in the last year, without plans	26 (12.6%)	16 (19.3%)	10* (34.5%)	3 (14.3%)	1 (25%)	0.042
Thought of terminating his/her life in the last year, with solid plans	31 (15%)	16 (19.3%)	10** (34.5%)	2 (9.5%)	2** (50%)	0.032
Suicidal ideation in the last year (positive response to any of the first three questions)	84 (40.8%)	39 (47%)	16 (55.2%)	8 (38.1%)	2 (50%)	0.564

*BS patients with active eye involvement at the time of interview had increased frequency of positive response to question 2. **BS patients with eye or CNS involvement at the time of interview were found to have an increased frequency of suicidal thoughts with solid plans. BS, Behçet's syndrome; CNS, central nervous system.

have had suicidal thoughts before their diagnosis might be due to their premorbid personality and poor psychological resources to cope with stressors. Patients with active disease had higher rates of suicidal ideas, especially with solid plans, when compared to healthy controls. Active eye and CNS involvements were more strongly associated with suicidal thoughts and the latter

was also an independent predictor of suicidal ideation in the multivariate analysis. Of interest, correlation between the patient-reported joint pain score and suicidal thoughts was demonstrated in univariate and multivariate analyses, but clinically diagnosed active joint disease did not put these patients at a higher risk when compared to other sites of active involvement. In

a nationwide survey of patients with rheumatism, Thompson *et al.* showed that adults with arthritis had two times increased risk of committing suicide in the last year (3). It was also demonstrated that presence of joint involvement and disease activity in BS patients were related to depression scores (11). Reciprocally, BS patients with high levels of pain were found to be at

Table IV. Linear regression analysis of factors predicting suicidal ideation in Behçet's syndrome patients

	Univariate			Multivariate		
	Slope (SE)	β	<i>p</i> -value	Slope (SE)	β	<i>p</i> -value
<i>Demographic factors</i>						
Age	0.001 (0.003)	0.024	0.679	–		
Sex	-0.165 (0.057)	-0.166	0.004	-0.050 (0.073)	-0.049	0.496
Age at diagnosis	0.001 (0.003)	0.025	0.668	0.000 (0.004)	-0.005	0.935
Disease duration	-6.000 (0.003)	0.000	0.998	0.000 (0.004)	-0.005	0.939
<i>Clinical features</i>						
Mucocutaneous disease	-0.069 (0.056)	-0.071	0.219	-0.091 (0.152)	-0.092	0.553
Eye involvement	0.059 (0.057)	0.059	0.304	-0.038 (0.133)	-0.038	0.776
Vessel involvement	-0.034 (0.074)	-0.026	0.650	0.016 (0.116)	0.012	0.889
Gastrointestinal involvement	0.336 (0.186)	0.104	0.072	0.365 (0.206)	0.118	0.078
Neurologic involvement	0.336 (0.186)	0.104	0.072	0.368 (0.185)	0.119	0.047
Previous prednisone use	0.051 (0.060)	0.050	0.393	0.217 (0.077)	0.212	0.005
Current prednisone use	0.035 (0.073)	0.027	0.637	-0.157 (0.094)	-0.120	0.096
Interferon	0.072 (0.091)	0.050	0.433	0.097 (0.094)	0.069	0.306
Anti-TNF drugs	0.194 (0.223)	0.055	0.384	0.303 (0.265)	0.070	0.253
BDCAI	0.059 (0.013)	0.255	<0.0001	0.031 (0.019)	0.135	0.103
Patient-reported disease activity score	0.033 (0.009)	0.217	<0.0001	-0.013 (0.013)	0.083	0.327
Patient-reported joint pain score	0.020 (0.007)	0.159	0.006	-0.020 (0.010)	-0.155	0.046
<i>Psychosocial factors</i>						
Marital status (single/divorced vs. married)	0.050 (0.067)	0.043	0.459	0.135 (0.074)	0.115	0.069
Unemployment	-0.105 (0.056)	-0.107	0.063	-0.052 (0.070)	-0.052	0.459
Education	-0.040 (0.038)	-0.061	0.289	0.026 (0.042)	0.040	0.536
Financial difficulties	0.134 (0.058)	0.133	0.021	-0.074 (0.062)	-0.072	0.239
BDQoL	0.023 (0.003)	0.414	<0.0001	0.010 (0.005)	0.176	0.032
Beck Depression Inventory	0.025 (0.002)	0.510	<0.0001	0.017 (0.004)	0.329	<0.0001

SE: standard error; BDCAI: Behçet's Disease Current Activity Index; BDQoL: Behçet's Disease Quality of Life form.

higher risk of depression and anxiety (10). It is likely that depression itself contributes to the patients' pain experience and when painful conditions coexist with depression, the odds of suicidal thoughts and attempts increase dramatically (25).

Active disease periods are times of heightened vulnerability in terms of depression and suicide. In their case control study of 80 participants, Maca *et al.* reported a higher frequency of depressive mood in acute anterior uveitis patients during an acute attack with a reduction in mental and physical scores, and occupational satisfaction (26). In another report, Cavaco *et al.* demonstrated no increased depression and anxiety scores in neuro-BS patients when compared to other BS patients (27). However, the relationship between neurological involvement and mood disorders as well as the suicide risk in patients with active neuro-BS is still unclear. Despite the low number of BS patients with active CNS disease at interview, we consider neurological involvement as an independent risk factor for suicidal ideation.

In patients with rheumatological conditions, younger age, unmarried status, financial difficulties, and having at least a high school or higher degree education were associated with an increased risk of suicidal ideation in the preceding one year (3). Moreover, unemployment and work disability may lead to social isolation and loss of self-esteem which increases the risk of depression. Although we could not demonstrate a relationship between these psychosocial factors and suicidal ideation in our BS patients, we have seen that they had significantly higher rates of being married, lower education degrees and unemployment. There were significantly more BS patients with major organ involvement who indicated their disease as the cause of their unemployment (44.04%) when compared to patients with mucocutaneous disease (23.4%) ($p=0.004$). Of interest, 78.2% of unemployed male patients with major organ involvement (18 out of 23) had quit their job due to disease-related issues. Uncertain prognosis and recurrent disease flares may also affect patients' marriage plans and family planning.

We investigated the relationship between drugs and suicidal risk in our BS patients and only the past prednisone use longer than 6 months predicted suicidal ideation in multivariate analysis. However, this contrasts with the current knowledge on corticosteroid-induced psychiatric disorders (CISD) which usually appear during the first 6 weeks of treatment, attributed to the higher initial dose (14). Almost 90% of CISD cases have complete recovery after dose tapering or discontinuation of steroids, suggesting that our findings are subject to further investigation. Interferon treatment causes dose-dependent neuro-psychiatric side effects which includes depression in 8–14% of patients (15). However, it did not correlate with suicidal thoughts in our BS patients. On the other hand this may be due to our careful consideration of depression and suicidal ideation in our patients using interferon-alpha, and stopping the drug if there is such suspicion, based on our previous experience with a patient who committed suicide while using interferon-alpha. Infliximab therapy was shown to decrease depression

and anxiety scores in patients with AS after second and third infusions (28). Although we could not demonstrate a relationship between suicidal ideation and infliximab therapy, this might be due to the low number of our BS patients who used anti-TNF drugs (n=5). The main limitation of this study is its cross-sectional nature which might underestimate the frequency of suicidal ideation due to the natural exclusion of patients who died because of suicide before this survey. Second, questioning suicidal thoughts in the preceding year or even before the disease started may arise recall bias, also contributing to the underestimation of frequency. In conclusion, the incidence of suicidal ideation with or without solid plans was significantly increased in our BS patients with active major organ involvement. Physicians need to be alert in order to identify patients with suicidal ideation.

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