Fibromyalgia in Behçet's disease is associated with anxiety and depression, and not with disease activity

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ABSTRACT

Objective. *To determine the prevalence of fibromyalgia (FM) in Korean patients with Behçet's disease (BD) and to evaluate the association between FM and clinical and psychological variables.*

Methods. *Seventy patients with BD were examined for FM tender points and asked to complete a Korean version of the Fibromyalgia Impact Questionnaire (FIQ). Disease activity was measured using the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and a clinical activity score, which was calculated by summing the clinical manifestations. The State-Trait Anxiety Inventory (STAI) and Beck Depression Inventory (BDI) were used for psychometric scoring.*

Results. *Twenty-six BD patients (37.1%) met the American College of Rheumatology criteria for FM. The patients who met the criteria for FM were more frequently female, less frequently employed, and less well educated. Age, disease duration, clinical manifestations, medication, and measures of disease activity did not differ between BD patients with and without FM. Nevertheless, BD patients with FM had higher STAI and BDI scores than did patients without FM (all $p < 0.05$). FM tender points were significantly correlated with the STAI and BDI, and not with disease activity variables. The FIQ scores were also strongly correlated with the STAI and BDI scores, and not with disease activity.*

Conclusion. *FM was very common among BD patients and was associated with the presence of anxiety and depression, and not with disease activity.*

Introduction

Chronic widespread pain (CWP) is a common major health problem; approximately 10-11% of the general population have this symptom at any given time (1,2). The American College of Rheumatology (ACR) has adopted classification criteria for fibromyalgia (FM) that require both a history of CWPand the finding of 11 of 18 tender points on examination (3). Using the ACR criteria, the reported prevalence of FM in industrialized countries ranges from 0.5% to 4% in the population (4,5). Like many rheumatologic diseases, FM may occur when a person who is genetically predisposed is exposed to a certain environment, such as physical trauma, infection, emotional distress, endocrine disorders, and various autoimmune disorders (6). As many as 25% of the patients with rheumatologic disorders, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and ankylosing spondylitis, meet the ACR criteria for FM (7). In clinical practice, the co-expression of both diseases deserves special attention. First, the development of FM may go unrecognized, especially when it develops after a rheumatologic disease. More commonly, FM is misdiagnosed as an autoimmune disorder. In the clinical setting, it is important to differentiate FM and FM-related symptoms from pre-existing rheumatologic disorders.

Behçet's disease (BD) is a chronic disease with multisystem involvement that is characterized by oral and genital ulcers, cutaneous lesions, and ophthalmologic, neurologic, and gastrointestinal manifestations (8). It is generally regarded as more frequent in the Far East, Middle East, and Mediterranean region, while it is relatively uncommon in northern Europe and the United States. Patients with ocular or intestinal involvement have a poor quality of life (9, 10) and are more susceptible to anxiety and depression (11). The relationship of FM with SLE and RAhas been well studied, but study on the relationship between FM and BD is limited. Therefore, we analyzed the prevalence

Table I. Demographic and laboratory data for Behçet's disease with and without fibromyalgia.

	Behçet's disease with FM (n = 26)	Behçet's disease without FM (n = 44)	p value
Age at diagnosis (yr)	35.7 ± 2.0	34.9 ± 1.4	0.285
Age at study visit (yr)	40.2 ± 2.0	38.4 ± 1.3	0.169
Disease duration (yr)	3.76 ± 0.72	3.53 ± 0.52	0.523
Sex (M/F)	4/22	26/18	< 0.001
Marital status (married)	22/26	35/44	0.754
Employment	10/26	28/44	0.05
Education (yr)	10.1 ± 0.6	12.7 ± 0.5	0.002
ESR (mm/hr)	9.60 ± 3.08	12.57 ± 2.09	0.413
CRP(mg/dl)	0.41 ± 0.01	0.66 ± 0.14	0.114
Disease activity at time of study visit	1.27 ± 0.18	1.30 ± 0.17	0.922
Disease activity during past month	1.92 ± 0.28	1.61 ± 0.18	0.338

Data are shown as the mean ± SEM.

of FM in 70 Korean patients with Behçet's disease in order to evaluate whether the occurrence of FM is associated with disease activity.

Materials and methods

Subjects

This study examined 70 consecutive patients with BD (25 males and 45 females) who satisfied the International Study Group criteria (12) in two tertiary referral centers located in South Korea. The mean (SD) age of the patients was 39.0 (9.4) years. The control group was 100 healthy individuals selected from among hospital nurses and 90 patients with systemic lupus erythematosus (SLE). The mean (SD) ages of the healthy controls and SLE patients were 26.9 (4.0) and 32.8 (10.9) years, respectively. All of the subjects were ethnically homogeneous Koreans who were unrelated to each other. The study was approved by the Hospital Ethics Committee and informed consent was obtained from all of the subjects.

Interview and clinical examination

The patients were interviewed to determine their demographic and clinical characteristics, including age, disease duration, marital status, education level, and employment status. The clinical activity score of the BD was calculated by summing the clinical manifestations present at the time of the study and during the previous month, as described in an earlier study (13). The cumulative history of severe manifestations in BD patients was investigated. The presence of one or more of the following clinical features during the course of the disease was regarded as a severe manifestation, as described in our previous study (14): posterior uveitis or retinal vasculitis, gastrointestinal ulcerations with bleeding or perforation, major organ involvement, and major vessel involvement. The Westergren erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were also measured.

Tender point examination involved applying a uniform manual finger pressure (ca. 4 kg), until the fingernail bed blanched, at each of 9 paired anatomical locations. Definite tenderness at any point was considered to be present if some involuntary verbal or facial expression of pain was noted or if a wince or withdrawal was observed. The tender point count was calculated by summing the number of tender points. The tender point score was calculated as the sum of the score for each tender point, i.e., no pain: 0, tender when asked: 1, spontaneous verbal response: 2, withdrawal: 3.

Questionnaires

The patients were asked to complete the Korean version of the Fibromyalgia Impact Questionnaire (FIQ), which we have validated (15). The State-Trait Anxiety Inventory (STAI) (16) and Beck Depression Inventory (BDI) (17, 18) were used for psychometric scoring.

Statistics

The data were analyzed using the SPSS software package (SPSS Inc., Chicago, IL, USA). Quantitative variables such as age, disease duration, tender point counts and scores, and FIQ scores in patients with and without FM, were compared using non-parametric methods such as the Mann-Whitney test. Qualitative variables, such as sex, education level, and clinical manifestations, were compared using Fisher's exact test. Continuous variables were

Table II. Clinical manifestations for Behçet's disease with and without fibromyalgia.

Variables	Behçet's disease with fibromyalgia (n = 26)	Behçet's disease without fibromyalgia (n = 44)	p value
General manifestations			
Oral ulcer	26/26	44/44	1.000
Genital ulcer	24/26	34/44	0.107
EN-like lesion	11/26	22/44	0.533
Pseudofolliculitis	21/26	37/44	0.722
Ocular lesion	5/26	12/44	0.448
Pathergy test	11/26	12/44	0.196
Arthritis	9/26	9/44	0.190
GI ulcerations	4/26	13/44	0.182
Vascular lesions	0/26	4/44	0.113
Severe manifestations			
Post-uveitis or retinal vasculitis	4/26	6/44	0.840
GI bleeding or perforation	3/26	4/44	0.742
Major organ involvement	1/26	4/44	0.410
Major vessel involvement	0/26	4/44	0.113
Presence of any one or more of severe manifestation	7/26	15/44	0.602

Table III. Mean score of the Korean FIQ items and total Korean FIQ score in Behçet's disease with and without fibromyalgia.

FIQ item	Behçet's disease with FM (n = 26)	Behçet's disease without FM (n = 44)	p value
Physical functioning	3.41 ± 0.45	2.92 ± 0.39	0.435
Number of days felt well	4.10 ± 0.45	6.22 ± 0.59	0.004
Number of workdays missed	0.39 ± 0.29	0.01 ± 0.01	0.401
Ability to do job	4.55 ± 1.17	2.59 ± 0.57	0.170
Pain	4.80 ± 0.57	2.65 ± 0.44	0.004
Fatigue	6.31 ± 0.65	4.27 ± 0.43	0.008
Morning tiredness	6.02 ± 0.54	4.41 ± 0.43	0.045
Stiffness	4.92 ± 0.64	2.74 ± 0.44	0.010
Anxiety	5.82 ± 0.62	4.18 ± 0.46	0.037
Depression	5.07 ± 0.71	3.73 ± 0.46	0.158
Total FIQ	43.43 ± 4.00	30.67 ± 2.45	0.005

Data are shown as the mean ± SEM.

Table IV. Tender point count and score in Behçet's disease with and without fibromyalgia.

	Behçet's disease with FM (n = 26)	Behçet's disease without FM (n = 44)	p value
Tender point count	14.92 ± 0.45	2.34 ± 0.38	< 0.001
Tender point score	29.23 ± 1.99	2.95 ± 0.51	< 0.001

Data are shown as the mean ± SEM.

Table V. State-Trait Anxiety Inventories and Beck Depression Inventory in Behçet's disease with and without fibromyalgia.

Inventory	Behçet's disease with FM (n = 26)	Behçet's disease without FM (n = 44)	p value
State Anxiety Inventory	51.75 ± 2.39	44.56 ± 1.54	0.017
Trait Anxiety Inventory	49.83 ± 2.13	45.14 ± 1.38	0.035
Beck Depression Inventory	15.65 ± 1.77	10.55 ± 1.31	0.016

Data are shown as the mean ± SEM.

Table VI. Correlation between tender point and disease activity variables.

	ESR	CRP	Activity at the study visit	Activity during the past month
Tender point count	–0.073	–0.190	0.043	0.125
Tender point score	–0.182	–0.201	0.130	0.185

Table VII. Correlation between tender point and psychometric variables.

Inventory	Tender point count	Tender point score
State-Anxiety	0.286*	0.329**
Trait-Anxiety	0.282*	0.310*
Beck Depression	0.401**	0.430***

* p < 0.05, ** p < 0.01, *** p < 0.001

compared using Spearman's correlation coefficient. A p value of less than 0.05 was considered statistically significant.

Results

Twenty-six of the 70 BD patients (37.1%) were diagnosed with FM according to the American College of Rheumatology (ACR) criteria. Two of the 100 healthy controls met the ACR criteria for FM, and fourteen SLE patients (15.6%) had secondary FM. The FM prevalence of 37.1% among our BD patients was significantly higher than that among the healthy controls or SLE patients (p < 0.001, p = 0.003 respectively).

The patients with FM were more frequently female (p < 0.001), less frequently employed (p = 0.05), and were less well educated (p = 0.002). Age, disease duration, marital status, and measures of disease activity did not differ between BD patients with and without FM (Table I). There were no differences in the clinical manifestations of BD between the two groups. The presence of FM did not differ significantly between BD patients with and without severe manifestations (Table II).

The BD patients with FM had significantly higher total FIQ scores and FIQ items that addressed pain, fatigue, morning tiredness, stiffness, and anxiety than did the patients without FM (Table III). Patients with FM felt well on significantly fewer days than did patients without FM. Compared with the patients without FM, those with FM had significantly higher tender point counts and scores (all p < 0.001, Table IV). The scores on the STAI and BDI scale were elevated in patients with FM compared with the patients without FM (all p < 0.05, Table V).

The tender point counts or scores were not correlated with the ESR, CRP, disease activity on the study visit, nor with disease activity during the previous month (Table VI). There was a significant correlation between the tender point counts or scores and the STAI or BDI scores (Table VII). The total FIQ scores or FIQ items were not correlated with the ESR, CRP, disease activity on the study visit, or disease activity during the previous month (data not shown). There was a significant correlation between the total FIQ scores or FIQ items and the STAI or BDI scores (Table VIII).

Discussion

In this study, we found a high frequency of FM among our 70 BD patients. As the prevalence of FM in the general

Table VIII. Correlation between the FIQ item and psychometric variables.

FIQ item	State Anxiety	Trait Anxiety	Beck Depression
Physical functioning	0.228	0.256*	0.311**
Number of days felt well	0.375**	0.295*	0.466***
Number of work days missed	0.128	0.068	0.027
Ability to do job	0.265	0.291	0.243
Pain	0.308*	0.307*	0.331**
Fatigue	0.376**	0.307*	0.406**
Morning tiredness	0.432***	0.339**	0.218
Stiffness	0.447***	0.422***	0.443***
Anxiety	0.452***	0.495***	0.407**
Depression	0.388**	0.429***	0.403**
Total FIQ	0.529***	0.513***	0.529***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

population in Korea has not been reported, it is impossible to compare it with our FM prevalence in BD. We evaluated the prevalence of FM in 100 healthy controls selected from among hospital nurses and in 90 patients with systemic lupus erythematosus. Two of the 100 healthy women met the ACR criteria for FM, and 14 SLE patients (15.6%) had secondary FM. The FM prevalence among our BD patients was significantly higher than that among the healthy controls or SLE patients. The reported prevalence of secondary FM in Turkish patients with BD was 9.2% (19), significantly lower than in our patients ($p < 0.001$). The high FM prevalence among our BD patients might be because the tender point requirement in the ACR criteria causes FM to become an almost entirely female disorder and our patient population had more female BD patients than did the Turkish study population. Moreover, variation in the clinical features of BD, such as ileocecal ulceration, the prevalence of HLA B51, and positive pathergy reactions, in different geographic areas might cause this difference in the prevalence of FM.

Our BD patients with FM were more frequently female, less frequently employed, and less well educated than the patients without FM. Population studies of FM conducted in Western countries using the ACR criteria have shown that females contract FM significantly more often than males, with estimates ranging from 1.0–4.9% in females as compared to 0.0–1.6% in males (1). The finding of an increased risk in females compared with males in our BD patients is consistent with other population studies and FM studies in several inflammatory rheumatic diseases. Although a recent review (20) concluded that there was little general evidence that the reporting of pain varies by social class, a number of studies have detected important sociocultural differences between patients and controls. A strong inverse gradient between level of education and the development of FM has been observed in several studies (21-25). Similarly, a low income appears to be associated with the development of FM (21,24) and being an assistant, non-manual, lower-level employee or a manual worker is associated with CWP (26). In addition to female sex, we identified other risk factors for FM, such as low employment status and less than a high school education. However, it is not clear whether these factors are secondary effects of long-standing, chronic BD or primary events in the etiopathogenesis of FM, and further epidemiological studies, particularly a prospective follow-up study, are needed.

In our patients, tender points and FIQs were not correlated with the ESR, CRP, disease activity during the study, or disease activity over the previous 4 weeks, but were correlated with the STAI and BDI scores. There was no generally accepted scoring system or tool for measuring the disease activity of BD when we started our study; therefore, we used the clinical activity score and laboratory variables such as the ESR and CRP. Although FM did not correlate with disease activity in our cross-sectional study, a long-term follow-up study is needed to provide a definitive answer to this question.

Our study investigated the cumulative history of severe manifestations in BD, because it is necessary to determine whether the presence of FM is affected by the severity of BD. The presence of BD did not differ significantly between BD patients with and without severe manifestations. These results suggest that the severity of BD does not influence the development of FM.

It is well known that depression and anxiety disorders are co-morbid psychiatric illnesses in patients with FM. The type of depression most commonly seen in FM is not the hallmark melancholic form of depression, but rather an atypical variant in which sleep onset is delayed, but total sleep time is increased, appetite is increased, and moods are reactive rather than flat (27,28). It is believed that FM and depression are distinct, but frequently co-occurring entities (29, 30). Furthermore, a review showed that depression was most frequently the consequence of pain rather than its initial cause (31).

In addition, psychological factors are closely associated with BD (32-34). Calikoglu *et al.* (11) reported that BD patients had a higher level of depression and anxiety as measured by the BDI and Beck Anxiety Inventory, compared with controls. Tanriverdi *et al.* (10) found that BD patients with ocular involvement were susceptible to anxiety and depression when compared to age- and sex-matched controls. Epstein *et al*. (32) evaluated depression in BD patients, in whom symptoms developed secondarily to a chronic, long-term, serious illness. In our study, BD patients with FM had higher STAI and BDI scores than did BD patients without FM. As both BD and FM can cause psychological symptoms such as depression and anxiety, the association with depression and anxiety found in our study is quite plausible. The cross-sectional design of our study limits the interpretation of the link between BD, FM, and psychological illnesses.

It is well known that FM patients attending tertiary hospitals and specialist clinics have more severe symptoms and a poorer prognosis than do those patients attending general practices (35). Although no study has compared Behçet's disease patients attending a tertiary hospital with patients attending general practices, patients with more severe manifestations are more likely to be seen in a tertiary hospital than in other clinical settings. As this study was conducted in a tertiary hospital, this selection process may have caused some biases in our study.

In conclusion, FM is a common, important clinical problem among patients with BD. The presence of FM does not seem to correlate with disease activity, and psychological factors are correlated with FM. Further investigation of the longitudinal variation in FM symptoms in relation to disease activity and treatment is needed.

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