Association Between Behcet’s Disease and Depression

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ABSTRACT

**Background:** Behcet’s disease (BD) is a chronic vasculitic multi-systemic disease of unknown etiology. BD is characterized by recurrent attacks of oral aphthae, genital ulcers, and uveitis. BD is a multisystemic disorder and as such it may provoke various psychiatric manifestations, including depression.

**Objectives:** To evaluate the association between BD and depression, adjusting for established risk factors for depression.

**Methods:** We executed a cross-sectional study based on the Clalit Health Services database, the largest healthcare organization in Israel, serving over 4.4 million members. For this study 873 BD patients were detected and matched with 4369 controls by age and sex.

**Results:** The rate of depression was higher among the BD patients compared with the control group (9.39% vs 5.49%, respectively, odds ratio [OR] 1.79, 95% confidence interval [95%CI] 1.37-2.31, P < 0.001). An association between BD and depression was also observed on multivariable analysis (OR 1.83, 95%CI 1.39-2.39, P < 0.001). When stratifying the data, according to established risk factors, the association between BD and depression was prominent in the youngest age group (18–39 years of age), low and high socioeconomic status, and non-smokers.

**Conclusions:** Establishing the association between BD and depression should influence the attitude and the treatment of BD patients, as this relationship requires a more holistic approach and a multidisciplinary treatment regimen for all patient needs.

KEY WORDS: anxiety, Behcet’s disease, co-morbidity, depression, inflammation

Behcet’s disease (BD) is a chronic, multi-systemic inflammatory disorder characterized by acute exacerbations as well as long term remissions [1]. The main manifestations of BD, which were first described by the Turkish dermatologist Hulusi Behcet, are mucocutaneous lesions such as recurrent oral aphthae, genital ulcers, erythema nodosum, and papulopustular lesions. Central nervous system, cardiovascular, gastrointestinal, uveitis, and musculoskeletal manifestations may appear during the course of the disease and may cause a great deal of morbidity and mortality [2]. BD is common among individuals whose genetic backgrounds originate from the ancient Silk Road, including the Mediterranean area, central Asia, and the far east. The highest prevalence is found in Turkey: approximately 20 to 421 per 100,000 of the adult population present with BD. BD commonly occurs in the third and fourth decades of life, equally affecting both sexes; however, males tend to present with a more severe course of this ailment. The underlying mechanism is believed to be vasculitis, unique for its ability to involve blood vessels of all sizes and types, both arteries, and veins [3]. Although the etiology is still unknown, there is an assumption that BD is triggered by exogenous factors, such as infectious agents, in individuals with genetic susceptibility [1]. The genetic factor most strongly associated with BD is the HLA-B51 allele. Yet, according to recent studies, its contribution to the overall genetic BD susceptibility is only 20%, suggesting that other genes also play a role in the pathogenesis of the disease [3].

The chronicity, acute exacerbations, and progressive functional disability in BD can lead to the development of a variety of psychiatric features such as depression [4]. Other factors, which are an inherent element of the disease progression, such as corticosteroids and adverse effects of other anti-inflammatory drug therapy as well as direct central nervous system involvement are also believed to contribute to depressive behavior and ideation [5]. Previous studies have investigated the relationship between BD, quality of life, fatigue, anxiety, and depression. These studies used the Hospital Anxiety and Depression (HADS) scale or the Beck Depression Invento-

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*These authors contributed equally to this study*
ry (BDI) for the depression diagnosis. These instruments all found that patients with BD have higher rates of depression compared to controls [4-6]. The quality of life in BD had been well studied and is known to be impaired [5-8]. Numerous factors negatively affect it, such as disease activity and depression.

The aim of this study was to evaluate the association between BD and depression, adjusting for established risk factors for depression.

PATIENTS AND METHODS

DATA ACQUISITION

This study was designed as a cross-sectional study, utilizing data from the Clalit Health Services chronic disease registry. Clalit is the largest healthcare organization in Israel, providing service for approximately half of Israel’s population. The computerized Clalit database includes information about outpatients and inpatients throughout the country. This study is a part of a series of analytical studies based on Clalit’s chronic disease registry. Previous studies regarding BD have tested the associations with ischemic heart disease and familial Mediterranean fever [9].

Our analysis encompassed socio-demographic data (e.g., age, sex, socioeconomic status [SES], ethnicity, marital status), lifestyle factors (e.g., smoking history and alcohol use), and chronic disease diagnoses (e.g., BD and depression). The large number of Clalit members (approximately 4,400,000 individuals), in addition to the extensive information regarding each one of them, enabled us to perform a wide-scale epidemiological study on a heterogeneous population with high-quality medical information effectively.

BD patients were defined as such if there was at least one diagnosis of BD in their medical records, made by either a community physician or by a physician during a hospital stay. Depression was defined in the same manner. Controls were randomly selected from the Clalit database, excluding those who presented with BD. For each BD patient five controls were frequency matched by age and sex [Figure 1]. SES was defined according to the poverty index of each member as specified during the 2008 National Census, which considers several parameters, including household income, education, crowding, material conditions, and car ownership. The poverty index ranges from 1 to 20, based on cluster analysis, with 1 being the lowest SES and 20 the highest. We divided our study population into three categories according to their SES. Body mass index (BMI) was also divided into four categories to reflect a nonlinear relation between BMI and dependent variables.

The study was approved by the Clalit Health Services Ethics Committee located in Tel Aviv, Israel.

Figure 1. Study design

STATISTICAL ANALYSES

We compared categorical variables such as SES and sex between BD patients and controls using the chi-square test, while Student's t-test was used for continuous variables, such as age.

The proportion of depression was compared between BD patients and controls in the study sample group. We examined the interaction between depression and BD separately across the different strata of categorical variables. For the estimation of the association between depression and BD, adjusted for confounders, we used a multivariable logistic regression model. Statistical analysis was performed using R Statistical Software (version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

In this study, we included 873 BD patients and 4369 controls matched by age and sex. The mean age was 48.9 years in the BD group and 49.7 years in the control group. The percentage of females was the same in both groups: 47.3%. Characteristics of the study population are presented in Table 1. Depression was diagnosed in 9.39% of BD patients in contrast to 5.49% in the control group, with unadjusted odds ratio (OR) 1.79, 95% confidence interval [95%CI] 1.37–2.31, P < 0.001. The smoking rate
Table 1. Behçet’s disease patients and controls basic characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Controls (n=4369)</th>
<th>Behçet’s disease (n=873)</th>
<th>Odds ratio (95% confidence interval)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>49.7 ± 15.5</td>
<td>48.9 ± 15.5</td>
<td>1.00 (0.99–1.00)</td>
<td>0.209</td>
</tr>
<tr>
<td>Sex (female, %)</td>
<td>2046 (47.3%)</td>
<td>413 (47.3%)</td>
<td>1.00 (0.87–1.16)</td>
<td>0.991</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>27.1 ± 5.40</td>
<td>27.3 ± 5.62</td>
<td>1.01 (0.99–1.02)</td>
<td>0.305</td>
</tr>
</tbody>
</table>

Socioeconomic status (n, %)

<table>
<thead>
<tr>
<th>Low</th>
<th>1779 (41.7%)</th>
<th>461 (53.2%)</th>
<th>Ref.</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium</td>
<td>1582 (36.7%)</td>
<td>275 (31.8%)</td>
<td>0.68 (0.57–0.80)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>High</td>
<td>931 (21.6%)</td>
<td>130 (15.0%)</td>
<td>0.54 (0.44–0.67)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smoking history (n, %)</td>
<td>1663 (38.1%)</td>
<td>369 (42.3%)</td>
<td>1.19 (1.03–1.38)</td>
<td>0.020</td>
</tr>
<tr>
<td>Depression (n, %)</td>
<td>240 (5.4%)</td>
<td>82 (9.3%)</td>
<td>1.79 (1.37–2.31)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

SD = standard deviation

was also significantly higher among BD patients than the one noted among the control group (42.3% vs. 38.1%, respectively, OR 1.19, 95%CI 1.03–1.38, p = 0.020). The SES seems to have an inverse association with BD. It seems that fewer people belong to the medium and high SES in the BD group in contrast to their numbers in the control group. This finding may be explained by the fact that many BD patients in the West are of Arab descent, belonging more often to the lower SES group, as we demonstrated in a previous publication regarding BD [2].

The proportion of depression among BD patients compared to the control group stratified by sex, age, SES, BMI, and smoking status is represented by the relevant OR in Table 2. The association was prominent for the younger age groups (18–39, 40–69 years) that were included in our study; however, the strongest association appeared to be in the youngest group: 18–39 years of age.

In terms of the SES, it seems that being part of the higher or lower SES group increases the strength of the association between BD and depression relative to the medium SES.

The association between BD and depression was also significant regardless of the subcategories according to smoking, sex, or BMI [Table 2]. Female and male BD patients exhibited a similar OR with depression OR 1.80 (1.28–2.50) and OR 1.78 (1.14–2.7), respectively.

After controlling the confounders, age, sex, SES, BMI, and smoking status, BD demonstrated a significant independent association with depression on a multivariate logistic regression model (OR 1.83, P < 0.001, 95%CI 1.39–2.39). Female sex, age

Table 2. Interaction of Behçet’s disease and depression across strata of study covariates

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.80</td>
<td>1.28–2.50</td>
</tr>
<tr>
<td>Male</td>
<td>1.78</td>
<td>1.14–2.70</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18–39 years</td>
<td>3.11</td>
<td>1.44–6.45</td>
</tr>
<tr>
<td>40–69 years</td>
<td>2.25</td>
<td>1.54–3.23</td>
</tr>
<tr>
<td>&gt; 70 years</td>
<td>1.19</td>
<td>0.74–1.86</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1.96</td>
<td>1.33–2.83</td>
</tr>
<tr>
<td>Medium</td>
<td>1.56</td>
<td>0.95–2.45</td>
</tr>
<tr>
<td>High</td>
<td>1.94</td>
<td>1.06–3.51</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 20</td>
<td>2.40</td>
<td>0.60–8.15</td>
</tr>
<tr>
<td>20–25</td>
<td>1.88</td>
<td>1.12–3.04</td>
</tr>
<tr>
<td>25–30</td>
<td>1.66</td>
<td>1.05–2.56</td>
</tr>
<tr>
<td>&gt; 30</td>
<td>1.71</td>
<td>1.04–2.74</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No smoking</td>
<td>2.07</td>
<td>1.45–2.91</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.45</td>
<td>0.94–2.15</td>
</tr>
</tbody>
</table>

95%CI = 95% confidence interval
DISCUSSION

The mental health aspect of BD has attracted interest in recent years; however, compared to other chronic inflammatory disorders, the knowledge about this linkage is scarce since most of the studies were conducted in small cohorts.

The large number of enrollees in the Clalit database enabled us to examine the association between BD and depression, reaching a significantly higher number of patients compared to previous studies. We also described the anthropometric and demographic characteristics of our study population and explored possible trends with depression. Our findings corroborated the general belief that the proportion of depression is more prominent among patients with BD opposed to subjects without BD. In our study 9.39% of BD patients were diagnosed with depression, a rate that is lower than reported in earlier studies, although most studies used a higher Beck Depression Inventory score as an indication of depression rather than pursing the proportion itself [4-8]. Multivariate analysis indicated that BD was a significant and independent factor associated with depression. When we further examined the impact of other significant factors such as age, sex, SES, BMI, and smoking status on the association between BD and depression, we found a stronger association in the youngest age group (18-39 years of age). The association between BD and depression is of major importance since this co-morbidity may have a deleterious effect on prognosis.

One of the earliest studies addressing psychiatric aspects of BD was published by Epstein and colleagues [5]. In their small study of 10 BD patients, they observed that all their patients presented with concomitant psychiatric disorders. At least half of them had a substantial depressive mood, which was attributed to their physical illness while other BD patients were diagnosed with central nervous system involvement, suggesting a direct relationship between BD and psychiatric disorders as well [5]. Currently, most studies underline the association between BD and depression and conclude that the psychiatric symptoms are secondary to the physical illness and not the primary outcome of the disease itself [5,7,10].

The chronic nature of BD is a well-established predictor for depression [1,4]. There are few studies that compared the prevalence of depression among BD and other chronic disorders. One of them compared BD patients with patients presenting with chronic plaque-type psoriasis and another used rheumatoid arthritis (RA) patients as a control group. Both studies concluded that the proportion of depression in patients with BD was more significant than in psoriasis or RA, implying that there is more than chronicity of BD that leads to depression [5,7]. One of the goals of the study of Melikoglu et al. [11] was to compare BD patients with RA patients and to assess the relationship between disease activity and depression. The only parameters that showed an association with depression were arthropalgia and the patient’s impression of disease activity [11]. Karlidag et al. [12] showed that inadequate coping mechanisms also contributed to the emergence of depression. One of these failed coping mechanisms is alexithymia, difficulty identifying and expressing emotions. Alexithymia can either be a personality trait or a state, secondary to a traumatic event, and was shown to have a positive relationship with depression [12,13]. Another study that focused mainly on arthritis affecting BD patients found that the way individuals cope with the disease, the beliefs they hold regarding the illness and themselves, and the ability to deal with pain all impact the overall psychological perception of well-being [10]. The association between quality of life (QoL) and depression in BD is the focus of many studies. Impaired QoL can lead to depression or be affected by it. Many other factors associated with BD can influence QoL, the symptoms, the pain, the relapses, the progressive, and the debilitating nature of the disease. Nevertheless, the impact of depression on the QoL might be more significant than that of BD itself, turning it into a valuable treatment goal [14-16].

The association between inflammatory disorders and depression is complex since both components can either be the etiology or the result of one another.

The fact that there is a linkage between stress and autoimmune and autoinflammatory responses is well known by now, as seen in the meta-analysis conducted by Segerstrom et al. [17] and in our previous reports [18,19]. Stressful events can lead to the development of inflammatory disorders through activation of the
sympathetic nervous system and release of catecholamines, which have a direct effect on the innate and adaptive arms of the immune system. Another axis that plays a major role in the stress response is the hypothalamic-pituitary-adrenal axis via the adrenal gland secretion of glucocorticoids, which inhibit cellular immunity by depressing the production of numerous pro-inflammatory cytokines; however, these same glucocorticoids can also increase the levels of other cytokines such as IL-4, playing an essential immunoregulatory role [18,20]. Another study that dealt with children showed that high levels of interleukin 6 (IL-6) carried an increased risk of developing major depression by the age of 18 years in contrast to the general population [21]. Such observations have led the medical community to explore the possible roles of anti-inflammatory drugs in the treatment of mood disorders [22]. For example, a recent Israeli study showed the beneficial anti-depressant and anxiolytic effects of therapy with tocolizumab (a monoclonal anti-IL6 receptor) in patients with rheumatoid arthritis [23].

Another plausible explanation for the linkage between inflammatory disorders and depression is that patients who suffer from depression have elevated circulating pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-a), IL-1beta (IL-1b) and IL-6 prior to their somatic illness, subjecting them to develop inflammatory diseases [24].

The strengths of this study are mainly related to the Ciltali database. Its extent and validated information were retrieved from both primary care and tertiary care facilities. However, the diagnoses of BD patients were determined according to their medical records. We did not have tools to validate whether the formal BD criteria were met as in clinical studies. This misclassification applied to the diagnosis of depression as well and could have led to over or under diagnosis. However, specialists are required to affirm the diagnosis and several previous studies that used this database have indicated the data’s reliability [9,25]. The cross-sectional design has drawbacks. It lacks an accurate timeline of the diagnosis, and therefore limited our ability to determine causality.

CONCLUSIONS
This study reinforces the association between BD and depression. A validation of such a connection, and the effect it has on the QoL and prognosis of the patients, has clinical implications and should be better established in further studies.

References