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THE COURSE OF BEHÇET'S DISEASE FOLLOWING COVID-19 DIAGNOSIS: A LARGE RETROSPECTIVE COHORT STUDY

COVID-19 TANISINI TAKİBEN BEHÇET HASTALIĞININ SEYRİ: GENİŞ BİR RETROSPEKTİF KOHORT ÇALIŞMASI

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ABSTRACT

Objective: Behçet's disease (BD) is a chronic vasculitic disease with mucocutaneous and systemic involvements. This study aims to examine the effects of COVID-19 on the symptoms and course of BD.

Material and Method: The BD patients who were followed up in our department with a history of COVID-19 were evaluated regarding the course of infection and the course of BD post-COVID diagnosis, assessed by Behçet's Disease Activity Index (BDAI).

Result: Among 449 BD patients, 68 (15.1%) had contracted COVID-19. The mean age of the patients was 42.7±11.8 years of whom 63.2% (n=43) were female. While most (n=48, 70.6%) had only mucocutaneous symptoms, others also had systemic symptoms (n=20, 29.4%) during their BD course; 86.8% (n=59) had received colchicine only at the time of infection. Prior to infection, 85.3% (n=58) had been in remission (BDAI score of 0), while 14.7% (n=10) already had active BD (BDAI score between 1-3). Post-COVID-19 diagnosis, activation or exacerbation of activation was seen in 39.7% (n=27) of BD patients, as characterized by increased BDAI scores (BDAI score between 1-4). No change was recorded in 60.3% (n=41) of the patients. Disease activation in the BD patients was mostly mucocutaneous (n=21, 30.9%). Comparison of the BD patients' BDAI scores pre- and post-COVID-19 diagnosis revealed the scores to be significantly elevated ($p<0.001$; $z=-4.691$), demonstrating the possible effects of COVID-19 on BD severity.

ÖZET

Amaç: Behçet hastalığı mukokutanöz ve sistemik bulgularla seyredebilen kronik vaskülitik bir hastalıktır. Bu çalışmada COVID-19 enfeksiyonunun Behçet hastalığı semptomları ve seyri üzerine etkisini incelemeyi amaçladık.

Gereç ve Yöntem: Üçüncü basamak bir Dermatoloji merkezinde takip edilen Behçet hastaları COVID-19 enfeksiyonu açısından sorgulandı. Daha önce PCR ile kanıtlanmış COVID-19 geçiren hastalarda Behçet hastalığı seyri ve aktivasyonu Behçet Hastalığı Aktivite İndeksi (BHAİ) ile retrospektif olarak değerlendirildi.

Bulgular: Bu çalışma sürecinde poliklinik kontrolüne başvuran 449 Behçet hastasının 68'inin (%15,1) COVID-19 enfeksiyonu geçirme öyküsü mevcuttu. Hastaların yaş ortalaması 42,7±11,8 yıl olup, %63,2'si (n=43) kadındı. Behçet hastalarının çoğunda (n=48, %70,6) Behçet hastalığı sadece mukokutanöz tutulum ile seyrederken, bir kısmında (n=20, %29,4) çeşitli sistemik tutulumlar hastalık sürecinde gelişmişti. Bu hastaların büyük bir çoğunluğu (n=59, %86,8) enfeksiyon öncesinde sadece kolşisin tedavisi almaktaydı. COVID-19 enfeksiyonu öncesi BHAİ skorlama sistemine bakıldığında hastaların %85,3'ü (n=58) remisyondaydı (BHAİ-0), %14,7'si (n=10) ise halihazırda aktivasyondaydı (BHAİ-1-3). COVID-19 enfeksiyonunu takiben hastaların %39,7'sinde (n=27) aktivasyon veya hastalık şiddetinde artış görüldü (BHAİ-1-4). Behçet hastalarımızda enfeksiyonu takiben görülen hastalık aktivasyonu çoğunlukla mukokutanöz (n=21, %30,9) lezyonlar ile karakterizeydi. Hastaların %60,3'ünde (n=41) ise hastalık seyrinde herhangi bir değişiklik kaydedilmedi. Behçet hastalarında COVID-19 enfeksiyonu öncesi ve enfeksiyon sonrası BHAİ skor-

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Conclusion: COVID-19 infection may lead to activation of BD symptoms, with new organs being involved in some patients, which should be confirmed by prospective large series.

Keywords: Behcet's disease, COVID-19, disease activity

ları karşılaştırıldığında anlamlı düzeyde (p<0,001 ve z=-4,691) Behçet hastalık şiddetinde artış tespit edildi.

Sonuç: COVID-19 enfeksiyonu bazı hastalarda Behçet hastalığı semptomlarının aktivasyonuna, alevlenmesine ve hatta yeni organ tutulumuna yol açabilmektedir. Bu durum prospektif geniş serilerle doğrulanmalıdır.

Anahtar Kelimeler: Behçet hastalığı, COVID-19, hastalık aktivitesi

INTRODUCTION

Hulusi Behçet first described Behçet's disease (BD) in 1937 as a triple-symptom disorder characterized by oral aphthae, genital ulceration, and uveitis. Although particularly prevalent in countries on the Silk Road, BD can be seen worldwide. Türkiye is one of the countries where the disease is most commonly encountered, with a prevalence between 20:100,000 and 420:100,000. Immunological and environmental factors such as bacterial and viral infections are thought to play an important role in the pathogenesis of the disease. BD is a chronic, inflammatory, and systemic vasculitic disease with various mucocutaneous and multiorgan involvements. The ocular and vascular involvements of the disease that adversely affect prognosis are more commonly seen in males (1).

The coronavirus disease 2019 (COVID-19) caused by the SARS-CoV-2 virus hit the world in December 2019 and was declared a pandemic by the World Health Organization (WHO) in March 2020. While affecting all age groups, individuals with chronic diseases have been implicated as being at greater risk (2). BD patients under immunosuppressive and immunomodulatory treatments have been previously suggested to be in the high-risk spectrum for COVID-19. However, only a few studies have evaluated the course of BD post-COVID-19 diagnosis in large groups of BD patients (3–16). This study aims to delineate the effects of COVID-19 on BD and to describe the course of COVID-19 infection in a large BD patient group in an experienced tertiary center in Türkiye.

MATERIALS and METHODS

The study retrospectively evaluates the data from consecutive patients who'd been diagnosed with BD, focusing on the routine follow-up visits between February-August 2021 with a history of COVID-19 diagnosis. Patients without a polymerase chain reaction (PCR) confirmation were not included in the study group, regardless of whether their symptoms or radiological findings were compatible with COVID-19. Moreover, the study group consists of unvaccinated patients due to lack of community COVID-19 vaccination program in Türkiye during this period. Data regarding patients' symptoms, including the need for hospitalization and oxygen support, were also collected.

The study records individual data regarding clinical status and ongoing treatments and gives the BD patients' Behçet's Disease Activity Index (BDAI; Table 1) scores based on their symptoms three months prior to and one month after their COVID-19 diagnosis. According to this scoring system, patients with a score of 0 were accepted as being in remission, while any score above 0 was treated as an active BD case. When assessing the status of the disease following COVID-19, any increase in the BDAI score was considered an activation or exacerbation of activation of BD.

Statistical analysis

The study expresses the data as averages, means, medians, and percentages and uses the program SPSS (Version 22; IBM, SPSS Corp., Armonk, NY, USA) for all statistical analyses, with $p<0.05$ being considered significant. The study uses the Wilcoxon Sign Rank Test to evaluate the patients pre- and post-COVID-19 BDAI scores.

The patients gave written informed consent to publishing their case details. This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the İstanbul University, İstanbul Faculty of Medicine local ethical committee (Date: 10.09.2021; No: 16).

RESULTS

Among the 449 BD patients (42.3% males; 57.7% female; mean age = 42.9 years) who underwent follow-up

Table 1: Behçet's disease activity index (BDAI) score

BDAI-0	Less than two oral aphthae per month
BDAI-1	More than two oral aphthae, pseudofolliculitis, and/or erythema nodosum per month
BDAI-2	The same findings as BDAI-1, as well as genital ulcer, joint involvement, and/or superficial thrombophlebitis
BDAI-3	The same findings as BDAI-2, as well as eye involvement, vascular involvement, neurological involvement, and/or other system involvements
BDAI-4	New organ involvement

visits throughout the study, 68 (15.1%) had COVID-19 infection that was verified with PCR. These patients' mean age was 42.7±11.8 years, of whom 63.2% (n=43) were female. The median treatment duration for BD was 11.7±6.8 years before COVID-19 diagnosis. These BD patients either had only mucocutaneous symptoms (n=48, %70.6) or developed systemic symptoms (n=20, 29.4%) during their course of BD (Table 2). In managing BD during at the time of COVID-19 diagnosis, 59 (86.8%) patients only received colchicine, 5.9% (n=4) received azathioprine and colchicine, and one patient received adalimumab. One patient received no treatment due to pregnancy. Three patients (4.4%) were followed up without any medication due to BD being in remission (Table 2). When evaluating the patients based on their pre-COVID-19 BDAI scores, 85.3% (n=58) had been in remission with a BDAI score of 0, while 14.7% (n=10) had already had an active BD status. Of these latter patients, seven (10.3%) had a score of 1, two (2.9%) had a score of 2, and one had a score of 3 (Table 3). The following pre-COVID-19 BDAI scores were found for BD patients who'd undergone any systemic involvement in the course of BD (n=20) that had been managed with various immunosuppressives including systemic corticosteroids (n=15), azathioprine (n=10), and/or adalimumab (n=2): BDAI-0 (n=14), BDAI-1 (n=4), BDAI-2 (n=1), and BDAI-3 (n=1).

Of note, only one female patient (57 years old) with a BDAI-0 was hospitalized due to COVID-19 symptoms. All other BD patients had COVID-19 with mild or moderate symptoms. Arthralgia (n=30) was the most common COVID-19 clinical finding recorded in the BD patients, followed by myalgia (n=28), headache (n=24), cough (n=17), shortness of breath (n=14), fatigue (n=13), loss of smell (n=9), and loss of taste (n=5). Furthermore, 15 patients had asymptomatic COVID-19. Of these patients, 29 were treated with favipiravir, two with favipiravir and enoxaparin, three with hydroxychloroquine, and two with enoxaparin. Five patients received no treatment, while information regarding the COVID-19 treatments

Table 2: The clinical features and treatments of patients with Behçet's disease before COVID-19 infection

Variables	n (%)	Male/Female
BD course		
- Only mucocutaneous involvement	48 (70.6)	13/35
- Mucocutaneous and systemic involvement	20 (29.4)	12/8
Mucocutaneous involvements		
Recurrent aphthous stomatitis	68 (100)	25/43
Genital ulcer	35 (51.5)	9/26
Erythema nodosum	51 (75)	17/34
Pseudofolliculitis	30 (44.1)	7/23
Extragenital ulcer	1 (1.5)	0/1
Systemic involvements		
Joint involvement	17 (25)	5/12
Vascular involvement	14 (20.6)	9/5
- Deep venous thrombosis	12 (17.6)	7/5
- Superficial thrombophlebitis	4 (5.9)	4/0
Uveitis	7 (10.3)	4/3
- Uveitis and vascular involvement	1 (1.5)	1/0
Neurological and vascular involvement	1 (1.5)	0/1
Treatment		
Colchicine only	59 (86.8)	19/40
Immunosuppressive	5 (7.4)	4/1
- Azathioprine and colchicine	4 (5.9)	4/0
- Adalimumab	1 (1.5)	0/1
No treatment	4 (5.9)	2/2
- Pregnancy	1 (1.5)	0/1
- Remission	3 (4.4)	2/1

BD: Behcet's disease

Table 3: Comparison of clinical features of Behçet's disease in patients before and after COVID-19 infection

Pre-COVID-19 clinical status (BDAI)	Post-COVID-19 clinical status	n (%)	Male/Female
Remission (n=58, 85.3%), BDAI-0 (n=58)	**Activation** BDAI-1 (n=17), BDAI-2 (n=5), BDAI-3 (n=2), BDAI-4 (n=1)	**25 (36.8)**	**8/17**
	Systemic involvement	4 (5.9)	3/1
	-Deep venous thrombosis	1 (1.5)	1/0
	-Superficial thrombophlebitis	1 (1.5)	1/0
	-Uveitis	1 (1.5)	0/1
	-Joint involvement	2 (2.9)	2/0
	Mucocutaneous involvement	21 (30.9)	5/16
	-Recurrent aphthous stomatitis	17 (25.0)	4/13
	-Genital ulcer	5 (7.4)	1/4
	-Erythema nodosum	5 (7.4)	1/4
	-Pseudofolliculitis	3 (4.4)	0/3
	No change BDAI-0 (n=33)	**33 (48.5)**	**13/20**
Activation (n=10, 14.7%), BDAI-1 (n=7), BDAI-2 (n=2), BDAI-3 (n=1)	**Exacerbation of activation** BDAI-3 (n=1); BDAI-4 (n=1)	**2 (2.9)**	**1/1**
	Systemic involvement		
	- Deep venous thrombosis	1 (1.5)	0/1
	- Deep venous thrombosis and epididymo-orchitis	1 (1.5)	1/0
	No change BDAI-1 (n=6), BDAI-2 (n=1), BDAI-3 (n=1)	**8 (11.8)**	**3/5**

BDAI: Behçet's Disease Activity Index

for other patients was unobtainable due to the study's retrospective nature. According to current recommendations and the authors' clinical experience, when the patients had positive PCR result, the immunosuppressive treatments of this patient group were stopped, whereas the colchicine treatment was continued (17).

Post-COVID-19 diagnosis, activation (n=25) or exacerbation of activation (n=2) was noted in 27 (39.7%) patients as a result of increased BDAI scores, while no change in BDAI scores was recorded in 41 (60.3%) patients (Table 3). Disease activation in the BD patients was mostly mucocutaneous (n=21, 30.9%), of whom 16 were female. Systemic activation was recorded in only six (8.8%) patients, which manifested as deep venous thrombosis (n=3), superficial thrombophlebitis (n=1), joint involvement (n=2), uveitis (n=1), or epididymo-orchitis (n=1). One patient with BD who was in remission (BDAI-0) had their first genital ulcer attack post-COVID-19 diagnosis. Another patient with active BD (BDAI-2) had their first epididymo-orchitis episode and a recurrence of deep venous thrombosis post-COVID-19 diagnosis. Finally, the BDAI scores of all post-COVID-19 BD patients in the cohort were as follows: BDAI-0 (n=33), BDAI-1 (n=23), BDAI-2 (n=6), BDAI-3 (n=4), and BDAI-4 (n=2; Table 3). The patients who had no change in symptoms (n=41) had the following BDAI scores: BDAI-0 (n=33), BDAI-1 (n=6), BDAI-2 (n=1), and finally BDAI-3 (n=1; Table 3).

Of the 27 BD patients showing disease activation or exacerbation in activation post-COVID-19 diagnosis, 25 had been in remission (BDAI-0) pre-COVID-19 diagnosis, one had had a score of BDAI-1, and one a score of BDAI-2. Post-COVID-19 diagnosis, most of the patients had mild BD activation, with a BDAI score of BDAI-1 (n=17) or BDAI-2 (n=5), as well as severe disease activation observed in five patients, with BDAI-3 (n=2) or BDAI-4 (n=1, first genital ulcer attack). Moreover, BDAI scores increased from 1 to 3 in one patient and from 2 to 4 in another (the patient with their first epididymo-orchitis episode), accompanied by aggravated BD activation (Table 3).

Furthermore, when comparing the patients pre- and post-COVID-19 BDAI scores using the Wilcoxon signed rank test, the results are found to be highly significant ($p<0.001$; $z=-4.691$), proving COVID-19 to likely have an impact on the course of BD.

DISCUSSION

Limited data is found in the literature on the complications of COVID-19 in patients with BD and COVID-19's effects on the course of BD (3-16). The present study has

aimed to use a larger patient series to identify the changes in the progression of BD post-COVID-19 diagnosis. The article retrospectively analyzed 449 BD patients, of whom 68 had a PCR-confirmed COVID-19 diagnosis that resulted in a statistically significant activation and exacerbation of the disease as graded by BDAI. Therefore, the study's results imply COVID-19 likely leads to BD activation and/or exacerbation in some BD patients. The current study group had a 15.1% prevalence of COVID-19. Unlike the current study that only included BD patients whose COVID-19 diagnosis was confirmed through PCR, some previous studies had also included BD patients who were highly suspected of COVID-19 in addition to confirmed diagnoses (11, 14). Previous studies have also controversially discussed the prevalence of COVID-19 among BD patients. One study reported a higher prevalence of COVID-19 in BD patients, while another study described the opposite (11, 15). Yet another study found the prevalence of COVID-19 in BD patients to be 4.2% and concluded no increased risk of COVID-19 infection or complication to exist in BD patients compared to the general population, similar to other studies (4, 6). One study that included 10 BD patients reported BD patients to be much younger and appear to have an increased risk of severe outcome due to COVID-19 (8), a finding not supported by the current study. In addition, another study in Türkiye with a small number of patients reported the relative risk of COVID-19 infection and complications in BD patients to be higher than the other inflammatory diseases (3). However, another study in France evaluated 117 patients with autoinflammatory diseases, 21 of whom had been diagnosed with BD, and found no significant difference in the severity of COVID-19 between patients with systemic autoinflammatory disease and those without. Furthermore, the study in France suggested patients with systemic autoinflammatory disease under corticosteroid treatment should be considered at high risk for severe COVID-19 (14). Yet another study also found receiving glucocorticoids and cytotoxic drugs to be associated with an increased hospitalization rate (11). In contrast, a recent systemic review and meta-analysis concluded administering glucocorticoids have no significant correlation with hospitalization risk in patients with rheumatic diseases, as well as the risk of severe COVID-19 in this population was similar to that observed in the reference population (18). The current study found only one BD patient to have been hospitalized due to COVID-19. All other BD patients' COVID-19 infections had mild or moderate symptoms.

While this study found deep venous thrombosis to be the most common form of systemic activation, recurrent aphthous stomatitis was the most common form of mucocutaneous activation. Remarkably, one patient post-COVID-19 experienced their first epididymo-orchitis attack, with another experiencing their first genital ulcer attack; these attacks also significantly raised their BDAI scores. This study found systemic activation to be more common in males whereas mucocutaneous activation to be more common in females.

The higher rates of deep venous thrombosis in BD patients post-COVID-19 may be due to high levels of IL-1a in BD patients' serum. IL-1a is a cytokine responsible for susceptibility to vascular inflammation and clot formation. Similarly, IL-1a release and inflammasome formation have also been observed in COVID-19 infection. IL-1a released into the blood causes endothelial damage and inflammatory thrombosis formation, which might explain the exacerbation of activation observed in some BD patients (19-21). Contrary to previous results, a recent study in Türkiye reported COVID-19 not appearing to exacerbate thrombotic events during or after infection in a large series (10). Colchicine is widely used in BD worldwide to prevent inflammasome formation and suppress IL-1 levels, which may have a protective role against COVID-19. However, another study in Türkiye reported evaluating the frequency and severity of COVID-19 in patients with various rheumatic diseases (including BD) who'd been treated regularly with colchicine or hydroxychloroquine; these treatments did not result in preventing COVID-19 or ameliorating its manifestations (12). Another study showed BD patients to have asymptomatic COVID-19 and also suggested anti-tumor necrosis factor agents to be able to protect BD patients from severe COVID-19 (9). Biological agents were delayed following COVID-19 cases in many countries that were used to manage many diseases. During this period of treatment cessation, uveitis attacks were reported in BD patients using infliximab and adalimumab. Of the current work's study group, only one patient under adalimumab treatment had experienced an uveitis attack post-COVID-19. In addition, other systemic involvements have been reported, such as a Neuro-Behçet's disease being exacerbated by COVID-19 (22). Although the present study has only one patient with Neuro-Behçet's disease, no aggravation or change in her condition was observed. Furthermore, the fact that most of the current study's patients suffered exacerbations regarding BD, with mostly mucocutaneous symptoms in addition to mild COVID-19 symptoms, may be related to the protective role of colchicine.

This study's main limitations are its retrospective nature and the fact that it has been conducted in a single tertiary center. Furthermore, a direct comparison of activation ratios could not be performed due to the need for a control group of BD patients who'd not had COVID-19.

CONCLUSION

This study represents a large case series of BD patients who'd also contracted COVID-19 and shows BD acti-

vation or exacerbation of activation occurred mostly with mucocutaneous symptoms, in addition to the systemic involvements recorded in a few patients post-COVID-19 diagnosis. The findings suggest a complex relationship between COVID-19 and BD, however the underlying pathogenic mechanisms needs to be further studied.

Ethics Committee Approval: The study was approved by the İstanbul University, İstanbul Faculty of Medicine local ethical committee (Date: 10.09.2021; No: 16).

Informed Consent: All patients signed the informed consent form.

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