

The course of COVID-19 in patients with Behçet's disease

Ayse Unal Enginar¹ , Mustafa Gundogdu² 

¹Department of Rheumatology, Konya City Hospital, Turkey

²Dermatology and Venereology Department, Ordu State Hospital, Turkey

Abstract

Objectives: To evaluate the frequency and clinical course of coronavirus disease 2019 (COVID-19) in patients with Behçet's disease (BD).

Material and methods: The study included patients diagnosed with BD according to the International Study Group for BD criteria who were being followed up in the Dermatology and Rheumatology clinics. Patients who applied to Rheumatology and Dermatology clinics and were not diagnosed with any rheumatological disease were taken as the control group. The medical records of the patients were examined retrospectively. A record was made of age, gender, additional systemic disease, for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), colchicine treatment dose, whether or not a polymerase chain reaction (PCR) test was performed, disease course in patients diagnosed with COVID-19, length of stay in hospital, and the need or not for intensive care unit (ICU) admission.

Results: Evaluation was made of 203 BD patients and a control group of 200 individuals. No difference was determined between the groups in respect of age and gender (respectively $p = 0.348$, $p = 0.828$). A polymerase chain reaction test for the SARS-CoV-2 was applied to 56 patients in the BD group, and 18 were reported positive, and to 80 subjects in the control group, of which 32 were determined positive. No difference was determined between the groups in terms of PCR test positivity ($p = 0.321$). No significant difference was determined between the groups in length of stay in hospital, lung involvement, ICU admissions, and mortality rates (respectively $p = 0.684$, $p = 1.000$, $p = 0.503$, $p = 1.000$). In the BD patient group, in all the parameters there was no significant difference between those who were positive or negative for COVID-19.

Conclusions: The results of this study showed no increased risk for BD patients compared to the normal population in respect of the frequency of SARS-CoV-2 infection, length of hospital stay, lung involvement, ICU admission and mortality.

Key words: colchicine, Behçet's disease, coronavirus disease (COVID-19), infection SARS-CoV-2.

Introduction

The virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) first emerged in China in December 2019, and within a few months with rapid spread around the world was declared a global pandemic by the World Health Organisation [1].

Unlike other coronaviruses, infection with SARS-CoV-2 causes severe pulmonary involvement and mortality. Risk factors for a poor outcome of COVID-19

include older age, obesity, hypertension, diabetes mellitus, chronic lung or kidney disease, and cardiovascular disease [2]. At the beginning of the pandemic, rheumatic diseases were not seen as a risk factor. When COVID-19-related deaths in those with rheumatic disease were later investigated, it was reported that there could be a greater risk for those with moderate-severe disease activity and those using ≥ 10 mg prednisolone, immunosuppressive drugs or rituximab, and those using sulfasalazine as monotherapy. No increased risk of mor-

Address for correspondence:

Ayse Unal Enginar, Department of Rheumatology, Konya City Hospital, Akabe District. No:135 42020 Karatay/KONYA, Turkey, e-mail: ftdrayseenginar@gmail.com

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tality was determined for other synthetic or biological disease-modifying anti-rheumatic drugs [3].

In the course of COVID-19, it has been observed that in addition to pneumonia, the infection can lead to thrombotic events. These thromboses can form in arteries or veins, and can form despite the use of thromboprophylaxis. This could be a condition similar to Behçet's disease (BD), as it is thought that inflammation in the vascular wall could lead to this. Therefore, there is an opinion that immunosuppressives could prevent thromboses, as in BD [4]. However, there is a need for evidence of this. Behçet's disease is a multisystem vasculitis which can cause oral ulcers, genital ulcers, ocular involvement, superficial or deep vein thrombosis, and neurological involvement [5]. There are very few studies in literature related to the frequency and effect of COVID-19 in patients with BD [6–9].

The aim of this study was to investigate the frequency and clinical course of COVID-19 in patients with BD.

Material and methods

The study included patients diagnosed with BD according to the International Study Group for BD criteria who were being followed up in the Dermatology and Rheumatology Clinics of our hospital between March 2020 and May 2021. Patients who applied to Rheumatology and Dermatology clinics and were not diagnosed with any rheumatic disease were taken as the control group. The medical records of the patients were examined retrospectively. A record was made of age, gender, additional systemic disease, colchicine treatment dose, whether or not a polymerase chain reaction (PCR) test was performed for SARS-CoV-2, disease course in patients diagnosed with COVID-19, length of stay in hospital, and the need or not for intensive care unit (ICU) admission. It was also recorded whether or not BD activation developed during COVID-19 infection.

Patients were not included in the study if they were aged < 18 years, pregnant or breastfeeding, or had a history of malignancy.

The study protocol was approved by the Turkish Ministry of Health General Directorate of Health Services and by the Ordu University Ethics Committee (Approval date/no: 12.07.2021/2021-174).

Statistical analysis

Data analysis was performed using IBM SPSS vn. 23 software. Descriptive statistics were reported as mean \pm standard deviation (SD) values for continuous variables with normal distribution, as median, minimum and maximum values for those not showing normal distribution, and as number (*n*) and percentage (%) for categorical variables.

The significance of the difference of mean values between groups was investigated with the t-test and for median values with the Mann-Whitney U Test. Categorical variables were evaluated with the Pearson χ^2 test or the Fisher Exact test. A value of $p < 0.05$ was accepted as statistically significant.

Results

A retrospective evaluation was made of the data of 203 BD patients and of 200 control group patients who presented at the Rheumatology and Dermatology Clinics between March 2020 and May 2021. None of the subjects in either group had been vaccinated against COVID-19. The mean age was 41.32 ± 12.77 years (range 18–74 years) in the BD group and 40.44 ± 13.15 years (range 18–71 years). No statistically significant difference was determined between the groups in respect of age ($p = 0.348$). The Behçet's disease group comprised 130 females and 73 males, and the control group, 126 females and 74 males, with no significant difference determined in respect of gender ($p = 0.828$). Comorbidities were determined at a statistically significantly higher rate in the BD group as well as arterial hypertension (Table I).

A polymerase chain reaction test for SARS-CoV-2 infection was applied to 56 (27.6%) of the 203 BD patients, and 18 (32.1%) were reported positive, and to 80 (40%) of the 200 control group subjects, of which 32 (40%) were determined positive. The polymerase chain reaction test was applied at a significantly higher rate to the control group compared to the BD group ($p = 0.008$). No difference was determined between the groups in respect of PCR test positivity ($p = 0.321$). Hospital in-patient treatment was required by 2 patients in the BD group and by 3 patients in the control group, and 1 patient from each group was admitted to ICU. Pulmonary involvement was determined in 6 patients in the BD group and in 3 patients in the control group. Mortality developed in 1 patient in the BD group and in none of the control group.

No statistically significant differences were found between the groups in respect of hospitalization, ICU admission, lung involvement and mortality (Table II).

The patient who was admitted to ICU and was later died was a 22-year-old female with a BD diagnosis for approximately 6 years. This patient had involvement with almost complete loss of sight in both eyes. There was a history of using cyclophosphamide prescribed from another centre because of neuro-BD and for the last 2 years the patient had been taking azathioprine 150 mg/day and colchicine 1 mg/day. The patient had presented with complaints of dyspnea and cough and the COVID-19 PCR test was reported as positive. COVID-19 pneumonia was determined on thorax computed tomography (CT). The patient was admitted to ICU with the

Table I. Demographics and comorbidities patients in groups

Parameters	Group		p-value
	Behçet disease (n = 203)	Control (n = 200)	
Age	41.32 ±12.77 41 (18–74)	40.44 ±13.15 39 (18–71)	0.348
Gender	Female	130 (64%)	0.828
	Male	73 (36%)	
Comorbidity	40 (19.7%)	21 (10.5%)	0.010
Hypertension	27 (13.3%)	13 (6.5%)	0.022
Diabetes mellitus	14 (6.9%)	8 (4%)	0.201
Asthma	1 (0.5%)	1 (0.5%)	1.000
Heart disease	0	1 (0.5%)	0.496
Hyperthyroidism	0	3 (1.5%)	0.121
Rheumatoid arthritis	1 (0.5%)	0	1.000
Hypothyroidism	4 (2%)	0	0.123
Hepatit B	1 (0.5%)	0	1.000

Table II. Comparison of COVID-19 positivity and other parameters between groups

	Group		p-value
	Behçet disease (n = 203)	Control (n = 200)	
COVID-19 testing	56 (27.6%)	80 (40%)	0.008
COVID-19 positive	18 (32.1%)	32 (40.5%)	0.321
Hospitalization	2 (1%)	3 (1.5%)	0.684
Intensive care unit	1 (0.5%)	1 (0.5%)	1.000
Lung involvement	6 (3%)	3 (1.5%)	0.503
Death	1 (0.5%)	0	1.000

development of respiratory problems. The patient was applied with mechanical ventilation and treated in ICU for approximately 3 weeks to death.

The another hospitalized BD patient had mucocutaneous and joint involvement and was treated with colchicine 1.5 mg/day. The patient had lung involvement and was discharged after 5 days with no additional complications. Throughout this time the patient continued taking the colchicine treatment.

Other drugs than colchicine and low-dose corticosteroids taken by the BD patients with COVID-19 positivity, were terminated or given at lower doses throughout the period of infection.

In the BD group, COVID-19 was not found to be associated with drugs or clinical picture of the disease (Table III).

Discussion

The results of this study showed that SARS-CoV-2 positivity and COVID-19 (symptomatic infection) were

confirmed in 8.8% in the BD studied group of patients, 33.3% of these patients presented lung involvement, 11.1% were hospitalized, 5.6% were admitted to ICU and 5.6% died. No statistically significant differences were determined between the BD and control group. In the BD group, one young female patient died. There was no increase in BD activity and no thrombotic events developed related to COVID-19 in the BD group.

In another study of 54 BD patients by Dursun et al. [6], none developed COVID-19 infection and 11% of the patients had a history of thrombophlebitis. Yurttas et al. [7] determined pneumonia in 6 of 10 patients with BD, 8 patients were treated in hospital, 2 were admitted to ICU, and 1 patient died was a 38-year old female with grand mal epilepsy, not being followed up for BD and not receiving any treatment. In addition, deep vein thrombosis developed in a 37-year-old male patient, who was taking colchicine, azathioprine, glucocorticosteroids (GCs), and adalimumab for a diagnosis of neuro-BD [7].

Table III. Comparison of clinical features of COVID-19 positive and negative patients in the Behçet group

		Behçet disease		
		COVID-19		p-value
		Positive (n = 18)	Negative (n = 38)	
Age		39.50 ±12.77 39 (20–63)	42.84 ±12.97 44 (20–68)	0.304
Gender	Female	13 (72.2%)	25 (65.8%)	0.630
	Male	5 (27.8%)	13 (34.2%)	
Behçet's disease involvement	Mucocutaneous	15 (83.3%)	29 (76.3%)	0.735
	Ocular	1 (5.6%)	5 (13.2%)	
	Mucocutaneous and arthritis	0	1 (2.6%)	
	Mucocutaneous and ocular	0	1 (2.6%)	
	Mucocutaneous, ocular and arthritis	1 (5.6%)	2 (5.3%)	
	Mucocutaneous, ocular, neurological	1 (5.6%)	0	
Drug	Colchicine	16 (88.9%)	30 (78.9%)	0.429
	Colchicine, azathioprine	1 (5.6%)	4 (10.5%)	
	Colchicine, sulfasalazine	0	1 (2.6%)	
	Colchicine, azathioprine, methylprednisolone	0	3 (7.9%)	
	Colchicine, methylprednisolone, infliximab	1 (5.6%)	0	
Comorbidity		4 (22.2%)	7 (18.4%)	0.732
Hospitalization		2 (11.1%)	0	0.099
Intensive care unit		1 (5.6%)	0	0.321
Lung involvement		6 (33.3%)	0	0.001
Death		1 (5.6%)	0	0.321

In the current patient series, no thromboembolic events developed, and the patient who died was a young female with a history of neuro-BD. Information on this subject is limited as there are very few studies in literature of BD patients with neuro-BD or vascular involvement.

Espinosa et al. [8] reported 4 patients with BD determined with COVID-19 infection. All of these patients had mucocutaneous involvement, 2 had ocular involvement, 1 had vascular involvement, and 1 had neurological involvement. In the study of 335 BD patients by Mattioli et al. [9] COVID-19 was determined in 14 (4.2%). When compared with the general population, no difference was determined, no patients were treated in hospital, and no mortality developed. The authors compared COVID-19 BD patients with matched patients SARS-CoV negative in terms of immunosuppressive medications and there were no significant differences between the groups, except for GCs which doses was higher in the SARS-CoV positive-BD patients [9].

In the current study, few patients were using GCs and the mean dose was lower than prednisolone 5 mg/day, which could explain why no increase in COVID-19 was seen in those taking corticosteroids. In the study by Mattioli et al. [9], no difference was found between COVID-19 positive and negative cases according to the type of BD involvement. In both groups, a total of 10 pa-

tients had neurological involvement and 9 had gastrointestinal involvement.

In the current study, no difference was determined between subtypes in respect of COVID-19. Moreover, there was 1 patient in the presented study with neurological involvement and there were no patients with gastrointestinal involvement.

D'Silva [10] found symptoms, hospitalization, and mortality rates to be similar in COVID-19 patients with and without rheumatic disease. However, the rates of ICU admission and mechanical ventilation were determined to be 3-fold higher in these patients. Pablos et al. [11] reported older age and systemic autoimmune status as risk factors related to hospitalization in patients with rheumatic disease. Gianfrancesco et al. [12] reported that 10 mg prednisolone and comorbidities to be risk factors for hospitalization. A meta-analysis determined rates of 33% high oxygen support and 7% mortality in patients with rheumatic disease and COVID-19 infection [13]. Another study found the prevalence of COVID-19 to be 0.9% in patients with rheumatic disease, and the rates of hospitalization, ICU, and mortality to be 70.7%, 11.6%, and 10.2%, respectively. Rheumatic diseases can affect the severity and outcomes of COVID-19 [14].

When all these studies are examined, rheumatic diseases have been named in general and there are very

few or no BD patients among them. Therefore, there is no wider evaluation or discussion specific to BD.

Colchicine is a safe and inexpensive drug that has been used for many years in the treatment of BD. The effect of colchicine is seen through inhibition of microtubule polymerisation, phagocytosis, chemotaxis and the release of proinflammatory cytokines. It also inhibits the activation of NOD-LRR- and pyrin domain-containing protein 3 inflammasome. It is thought that with these mechanisms, it could be used in the treatment or prevention of the cytokine storm seen in COVID-19 [15]. A meta-analysis has reported that it could be effective in reducing mortality rates and protecting against severe COVID-19 [16]. In a previous randomized, controlled study, colchicine was found to improve the time to clinical deterioration in hospitalized COVID-19 patients [17]. Another study reported that colchicine shortened the period of oxygen support and length of stay in hospital [18].

Although there are studies showing positive results related to colchicine, there is a need for further research. In the current study, with the exception of 1 patient, all the others were using colchicine and continued to do so during SARS-CoV-2 infection.

Study limitations

The presented work was retrospective, conducted in a single centre and the number of patients included into final analysis was low. Also BD activity scale could not be determined due to the retrospective nature of the study. It could also be a limitation that the patients mostly had mucocutaneous involvement in the course of BD. Polymerase chain reaction tests were not applied to all the patients because in Turkey, the test is applied only to symptomatic individuals.

Conclusions

The results of this study demonstrated that the risk of COVID-19 was no greater in BD patients than in the normal population. There was not seen to be any greater risk of hospitalization, lung involvement, ICU admission or death in studied BD patients. No thrombosis was observed in any of the patients with COVID-19 from either group. The increase of BD-related disease activity was not observed. There were very few BD patients in this study with nervous system or vascular involvement and it is too small group to wider analysis.

Therefore, there is a need for further multicentre studies of larger patient populations to be able to evaluate this group from all BD patients.

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