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

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Abstract

Objective

The aim of this study is to investigate the cumulative incidence and the severity of COVID-19 infections in patients with Behçet's disease.

Methods

A retrospective cohort study of patients with Behçet's disease was conducted. We obtained the data systematically from electronic patient files and through telephone interviews between February 2020 and May 1, 2021. The main outcomes were COVID-19 infection, disease duration, hospitalisation, intensive care admission and mortality. The secondary outcome was adherence to quarantine measures as recommended by the government.

Results

185 Behçet's disease patients were included (mean age 42.2 years, 54% female); 58% of the patients were receiving colchicine, 30% anti-TNFα, 16% azathioprine and 8% systemic steroids. 30 patients (16.2%) were positive for COVID-19. Within our cohort, the cumulative incidence of COVID-19 was therefore 16.2% (95% CI 11.2–22.3%), which is significantly increased when compared to the general Dutch population (8.7% (95% CI 8.72–8.73%)) ($p<0.001$). Four out of 30 (13%) patients were admitted to the hospital. There was no COVID-19 related mortality observed. Patients adhered to government measures; except in the period between the 1st of June and the 28th of September, this cohort received more visitors than in period 1 and 3.

Conclusion

In this cohort, Behçet's disease patients have a higher risk for COVID-19 infection, without an increase of virus-related mortality. The course of COVID-19 disease in this cohort is relatively mild, with a lower admission rate than expected of patients using immunosuppressive medication.

Key words

Behçet's disease, COVID-19, immunosuppressants, systemic autoimmune diseases

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Introduction

Behçet's disease (BD) is a chronic, auto-inflammatory disease characterised by recurrent painful orogenital ulcerations, uveitis and skin lesions such as erythema nodosum or pustular lesions (1).

The aetiopathogenesis of BD remains unknown, both genetic and environmental factors are considered to determine the inflammatory background (2). Increased neutrophil function and T-lymphocyte abnormalities are thought to play a role in the pathogenesis of BD (3). Treatment is directed against the inflammatory reaction and should be indicated according to severity, organ involvement, patient characteristics and patient's preferences. Treatment options consist of anti-inflammatory treatment or immunosuppressive treatment such as biologicals or corticosteroids (4), which are associated with an increased risk of infections (5, 6). Coronavirus disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global health crisis with over 5.5 million deaths and 330 million confirmed cases worldwide (7). The clinical spectrum of a COVID-19 infection ranges from asymptomatic infection to severe illness. The infection can cause several systemic, especially respiratory symptoms. The most common are fever and cough, which can progress to pneumonia and acute respiratory distress syndrome (ARDS) or even to multi-organ failure. Risk factors for complications of a COVID-19 infection are older age and the presence of comorbidities (8). Emerging evidence reveals that patients with rheumatic diseases have similar rates of hospitalisation as patients without rheumatic diseases (9). Strikingly, an increased risk in patients with rheumatic disease for intensive care admission and/or mechanical ventilation compared to patients without rheumatic disease (48% *vs*. 18%) is observed (9). Higher morbidity is seen in patients with auto-immune diseases using prednisone >10 mg, methotrexate, cyclosporine and cyclophosphamide (10). A previous international study showed that the Dutch cumulative incidences of COVID-19 in BD patients are significantly higher than the general population up to December 2020 (11). So far, it remains unclear whether patients with BD are at higher risk of COVID-19 and its complications. Therefore, the aim of this study is to investigate the cumulative incidence and clinical presentation of COVID-19 in patients with updated data of infected BD patients.

Methods

Participants and study design

This retrospective cohort study was performed at the Erasmus Medical Centre, Rotterdam, The Netherlands. The study protocol was approved by the Medical Ethical Committee of Erasmus MC (MEC-2020-0645). All patients provided informed consent, according to the Declaration of Helsinki. This study included patients (≥18 years old) attending the outpatient clinic of the Clinical Immunology department of the Erasmus Medical Centre in Rotterdam, all diagnosed with BD according to the International Study Group of BD Criteria(12).

Procedure of data collection

In the period between 15th of October until 18th of December 2020, BD patients attending the Clinical Immunology outpatient clinic in the past three years were contacted by telephone. Besides demographic characteristics, the use of immunosuppression and relevant comorbidities, questionnaires regarding COVID-related symptoms, COVID testing, COVID-19 severity (defined as hospital/ICU admission or mortality) and social distancing measures were obtained. In line with the number of COVID-19 infections in the Netherlands, three different periods were distinguished concerning the questions regarding the quarantine measures. The periods noticed are: COVID-19 wave one (March till 1st of June, 2020), the summer period (1st of June till the 28th of September, 2020) and COVID-19 wave two (the 28th of September till date of interview). The questionnaire was made by L.E. van der Aa (Supplementary Appendix). Comorbidities and gender information were retrieved from electronic pa-

tient files. Comorbidities with known increased risk of developing severe illness from COVID-19 were registered such as cardiovascular disease, diabetes, overweight, obesity, malignancies, chronic lung disease, kidney disease and solid organ transplantation (13-17). Overweight was defined as a body mass index (BMI) >25 kg/m^3. Obesity was defined as a BMI >30 kg/m^3. Colchicine and dapsone are defined as immunomodulatory treatment. Azathioprine, prednisone, dexamethasone, apremilast, methotrexate, adalimumab and infliximab are defined as immunosuppressive treatment.

A COVID-19 infection in patients with BD was diagnosed by a polymerase chain reaction (PCR) test. Disease activity during the COVID-19 infection was retrospectively measured using the BD Current Activity Form (BDCAF) (18). In the period after 18th of December all physicians asked their patients if they had COVID-19. To update the cumulative incidence electronic patient files were re-checked from the 18th of December 2020 until the 1st of May, 2021.

Data analysis

In the baseline table (Table I) categorical variables were presented as number (percentage), and continuous variables are reported as mean ±SD. Cumulative incidence of COVID-19 in patients with BD in comparison to the general Dutch population above 18 years old was analysed by using the one sample t-test for proportions. Through the site of CBS and RIVM the data from the Dutch population was retrieved on the 1st of May 2021 (19, 20) The level of significance was set at p-value <0.05. SPSS version 25 was used for all analyses.

Table I. Demographic and clinical characteristics of the patients.

Characteristic	Total (n=185)	Covid negative (n=155)	Covid positive (n=30)
Age (mean, SD, years)	42.2 ± 12.1	42.2 ± 12.2	42.6 ± 12.8
Female	100 (54)	88 (57)	12 (40)
Active disease (BDCAF <0)	75 (41)	65 (42)	10 (33)
Comorbidity	106 (57)	88 (57)	18 (60)
BMI>25kg/m2	75 (41)	63 (41)	12 (40)
BMI>30kg/m2	33 (18)	27 (17)	6 (20)
Cardiovascular disease	14 (8)	13 (8)	1 (3)
Diabetes	6 (3)	5 (3)	1 (3)
Chronic lung disease	3 (2)	3 (2)	0 (0)
Active malignancy	1 (1)	0 (0)	1 (7)
Immunomodulatory medication	108 (58)	87 (56)	21 (70)
Colchicine	107 (58)	86 (55)	21 (70)
Dapson	15 (8)	13 (8)	2 (7)
Immunosuppressive medication	111 (60)	93 (60)	18 (60)
Anti-TNF	55 (30)	47 (30)	8 (27)
Azathioprine	31 (16)	28 (18)	3 (10)
Systemic steroids	15 (8)	12 (8)	3 (10)
Methotrexate	10 (5)	9 (6)	1 (3)
Local steroids	9 (5)	7 (5)	2 (7)
Apremilast	6 (3)	5 (3)	1 (3)
Immunsuppressive & immunomodulatory treatment	48 (26)	41 (26)	7 (47)
Anti- coagulants	11 (6)	9 (6)	2 (7)

Data are represented by mean ± SD or number (percentage). No significant differences between COVID-19 positive or COVID-19 negative BD patients are observed (p-values not shown)
Cardiovascular disease included hypertension, coronary artery disease, arrhythmia and congenital heart defect.
Chronic lung disease included interstitial lung disease, asthma and chronic obstructive pulmonary disease.
Active malignancy means currently being treated with chemotherapeutics for their malignancy.
Anti-TNF included infliximab and adalimumab.
Systemic steroids included prednisone (dose 5-10 mg/day) and dexamethasone (dose 1.5 mg/day). Local steroids included glucocorticoid eyedrops.
Anti-coagulants included vitamin K antagonists and direct oral coagulants (DOACs).

Results

In total, 193 BD patients were contacted by telephone between October 15, 2020 and December 18, 2020, of whom 30 were COVID-19 positive. 118 patients were included in the study by telephone interviews, 67 patients were included by screening the patient files. We were unable to reach 64 patients, despite multiple attempts. 7 patients declined to participate. Reasons not to participate were: no interest, no time or migration. In total 4 patients were not able to participate due to a language barrier. Cumulative incidence of COVID-19 at May 1, 2021 in the BD cohort and the general population were 16.2% (95% CI 11.2–22.3%) and 8.7% (95% CI 8.72–8.73%), respectively. There was a significant difference in the proportion of patients with confirmed COVID-19 infection between our cohort and the general Dutch population (p<0.001). The cumulative incidence at the end of the first wave in the general population was 2.7% (95% CI 2.6–2.7%). In the BD cohort the cumulative incidence at the end of the first wave was 2.5% (95% CI 0.5–7.3%). There was no significant difference in the proportion at the end the first wave (p=0.05). Figure 1 shows the cumulative incidence of COVID-19 in the past year.

Table I depicts the demographic and clinical characteristics of included patients. The mean age of all included patients was 42.2 years old (SD 12.1). Slightly more than half (54%) of all patients were female, as compared to 40% of the COVID-19 positive BD patients. About 57% of all patients had comorbidities, of the COVID-19 positive patients 60% had comorbidities that were related with severe course of disease. In the COVID-19 positive group 70% used immunomodulatory medication and in the COVID-19 negative group 56%. Colchicine was most frequently used (58% of the total cohort and 73% in the COVID-19 positive cohort). Anti-TNF treatment was similar in the COVID-19 and all patient group (27% *vs*. 30%). 11 patients (6%) used anti-coagulants, of the COVID-19 positive patients 2 (7%) used anti-coagulants (Table I).

Outcomes of patients infected with COVID-19 are shown in Table II. Disease duration ranged from 3 to 30 days. None of the patients reported a thrombotic event. Four patients were admitted to the hospital. Three of them were

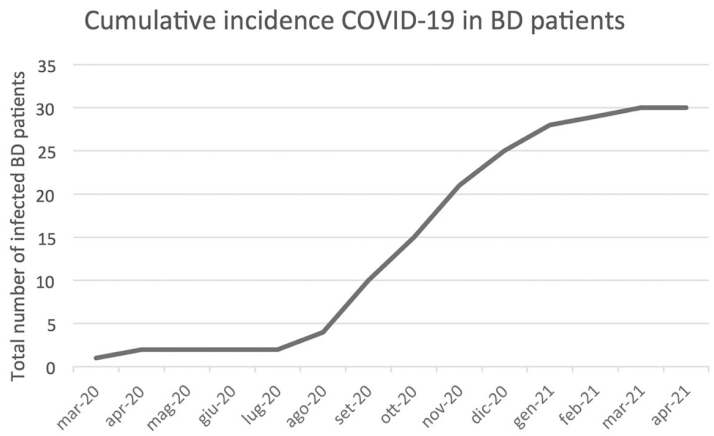

Fig. 1. Cumulative incidence of COVID-19 in BD patients.

female and one of them was male. All four had a BMI >25 kg/m^2, including two with a BMI >30 kg/m^2. Duration of hospital admission ranged from 8 to 25 days. One patient was admitted to the ICU for one day for observation because of impending respiratory failure. Moreover, this 55-year-old patient had neutropenic fever after chemotherapeutic treatment for a nasopharyngeal carcinoma. The second patient was admitted for 18 days for oxygen support. This 58-year-old patient had a BMI of 35 kg/m^2 and was treated with colchicine on demand since BD was in remission. During the admission colchicine was not used. The third 22-year-old patient was hospitalised for 8 days and recovered fully after antibiotics (azithromycin and ceftriaxone) and oxygen supply by nasal cannula. The fourth 42-year-old patient was admitted to the hospital for 12 days. This patient had a BMI of 37 kg/m2 and was treated with amoxicillin and oxygen through a nasal cannula during the admission. No mortality due to COVID-19 was reported. The BDCAF during the COVID-19 infection ranged from 0 to 6 with an average score of 3. Most patients experienced transient headache and arthralgia. Oral and genital ulcers were only seen in one patient who stopped adalimumab treatment because of the COVID-19 infection. The other 7 patients who discontinued treatment (apremilast or adalimumab) during COVID-19 infection did not develop orogenital ulcers, or progressive disease (Table II).

In Table III is displayed to what extent BD patients adhered to the quarantine measures as recommend by the Dutch government during three different periods in line with the amount of COVID-19 infections in the Netherlands. This data includes the interviewed patients only. In the first period 28% of the population had no visitors at all. In the second and third period 5% and 16% received no visitors at all. The Dutch government recommends all individuals with COVID-19 suggestive symptoms should be tested for COVID-19. During the summer period the measures as recommended by the Dutch government were less strict due to decreasing COVID-19 incidence. Patients were also able to receive their guests outside in their garden. Therefore, in the period between the 1st of June and the 28th of September this cohort had more visitors than in period 1 and 3. Reasons to go outside were work, groceries, a walk, to pick up the children from school, walking the dog and visiting the doctor or physiotherapist. The adherence to the visitor measures in the third period (start of the second wave in the Netherlands) compared to the first period was decreased.

Table II. Clinical characteristics and outcomes of patients infected with COVID-19.

Characteristics COVID+ patients	Number (=30) (percentage)
Symptoms	
Fatigue	30 (100)
Rhinits	24 (80)
Muscle and/or joint pain	22 (73)
Anosmia	21 (70)
Headache	19 (63)
Cough	18 (60)
Sore throat	14 (47)
Fever	14 (47)
Dyspnoea	12 (40)
Diarrhoea	4 (13)
Chest pain	2 (7)
Skin abnormalities	0 (0)
Disease duration (days)	11.3 ± 7.7
Treatment of COVID	
None	17 (57)
Antibiotics	7 (23)
Dexamethasone	2 (7)
Remdesivir	1 (3)
Interruption immunosuppressant	8 (27)
Admission to hospital	4 (13)
Duration of hospital stay (days)	15.8 ± 7.4
Admission to ICU	1 (3)
Duration of ICU stay (days)	1
BDCAF	3 (range 0-6)

Discussion

In this retrospective cohort study, we observe an increased cumulative incidence of COVID-19 infections in BD patients compared to the general Dutch population above 18 years old. However, these patients appear not to have a higher risk for COVID-19 related mortality.

Our results show a significant higher cumulative incidence of COVID-19 in BD patients compared to the general Dutch population. These results should be interpreted with caution as it could be influenced by underreporting of infections in the Dutch population during the first wave, as a result of insufficient ability to test for COVID-19. However, there was no significant difference (2.7% *vs*. 2.6%) between the general Dutch population and the BD cohort at the end of the first wave. The increased cumulative incidence after the first wave could be explained by either an increased exposure to the coronavirus or because of an increased susceptibility to COVID due to BD itself or due to immunosuppressive medication used to treat BD. Increased exposure could be the result of insufficient adherence to social distancing measures. In our cohort, most BD patients encountered their COVID-19 infection in the second wave. Interestingly, in the second wave the BD patients adhered less to the visitor measures as advised by the Dutch Government. In period 1, 28% had no visitors and in period 3 (the start of the second wave) 16% had no visitors.

Another factor could be the lower socio-economic status of patients with BD. In Turkey, BD patients are ob-

Table III. Adherence to quarantine measures.

Quarantine measures* (n=118)	Period 1: March - 1 June	Period 2: 1 June - 28 September	Period 3: 28 September - present
Adherence	114 (97)	112 (95)	114 (97)
Number of visitors received			
>6 people	1 (1)	6 (5)	1 (1)
3-6 people	10 (8)	32 (27)	10 (8)
1-3 people	74 (63)	74 (63)	88 (75)
no visitors	33 (28)	6 (5)	19 (16)
Number of days outside per week			
never	4 (3)	3 (2)	2 (2)
1-2 days	14 (12)	8 (7)	13 (11)
3-6 days	16 (14)	14 (12)	14 (12)
Daily	84 (71)	93 (79)	89 (75)

served to have a lower monthly family income, lower education, lower wealth score and higher unemployment when compared to inflammatory bowel disease and ankylosing spondylitis patients (21). A lower socio-economic status is associated with higher rates of COVID-19 infections (22).

In Table IV we present an overview of the current literature on BD and COVID-19. We have added 4 studies which also used a sample survey (23-26). In total 2014 BD patients were discussed in these studies, 313 patients were tested positive.

In line with our findings, a Turkish prospective cohort study in patients with BD found an increased infection rate compared to the general Turkish population (26). Ozcifci *et al*. showed a cumulative incidence of COVID-19 in the BD patient group of 20.5%, in the Turkish general population the cumulative incidence of COVID-19 was 5.77% (26).

Four patients, one male and three female, in our cohort were admitted because of severe symptomatic COVID-19 infection. The patients submitted to the hospital were all overweight, with a BMI >25 kg/m^2. Recent studies showed that patients having a higher BMI, older age and male gender are at increased risk of COVID-19 hospitalisation (8, 13, 27). We observed a hospital admission rate of 13%. Table IV shows that hospital admission rates in other cohorts were low and in line with our patients. Out of all the BD patients 313 had COVID-19, of which 32 were admitted to the hospital. Only one patient died because of COVID-19, she was known with neuro-BD.

One patient was admitted to the ICU because of pending respiratory failure. The severity of the COVID-19 infection in this patient was probably affected by the treatment with chemotherapeutics, gemcitabine and cisplatin, because of nasopharyngeal carcinoma. D'Silva *et al*. reported that patients with rheumatic disease and COVID-19 infection were more likely to require mechanical ventilation compared to those without rheumatic diseases (9). However, none of our patients required mechanical ventilation.

The COVID-19 Global Rheumatology alliance showed that low disease activity in rheumatic diseases is associated with a lower risk of a severe COVID-19 infection in COVID-19 positive patients with autoimmune disease (10). Most BD patients in our study had a low disease activity or were in remission at the time of their COVID-19 infection. Based on our findings, disease activity is not associated with the severity of the COVID-19 infection, in agreement with Espinosa *et al*. and Mattioli *et al*. (25, 28).

Disease activity as measured by BD-CAF appeared not influenced by COVID-19 infection. Most patients scored on headache and arthralgia. Both are also seen as symptoms of COVID-19 (29, 30). Five of the COVID-19 positive patients stopped their immunosuppressive treatment. The impact on outcomes of continuing or temporarily discontinuing immunosuppression in context of COVID-19 is unknown. In this context, current recommendations by the EULAR and the Dutch association for Allergy and Clinical Immunology suggest patients to contact their physician when tested positive for COVID-19, and physicians to approach patients case-by-case (31, 32). Current recommendations by the Dutch association for Allergy and Clinical Immunology suggest continuing medication in case of a mild infection. In case of fever, it is advised to discontinue biologicals temporary, with potential exception of interleukin-1 receptor inhibitors (32). In our cohort stopping immunosuppressive therapy did not lead to a disease flare with major organ involvement, but 1 patient developed orogenital ulcerations. No BD-activation after COVID-19 was seen.

Our systematic and active approach of BD patients is the main strength of this study. However, there are some important limitations to this study. First, we considered patients COVID-19 positive when the infection was confirmed by PCR test. Therefore, asymptomatic patients or patients experiencing symp-

Table IV. Overview of all the sample surveys regarding BD and COVID-19 studies.

Study	Correa-Rodríguez *et al*.	Enginar *et al*.	Mattioli *et al*.	Ozfici *et al*.	Den Otter *et al*.
Country	Spain	Turkey	Italy	Turkey	Netherlands
Cumulative incidence total population	Unknown	Unknown	4.4%	5.77%	8.7%
Cumulative incidence BD population	36 (14.8%)	18 (8.8%)	14 (4.2%)	215 (20.5%)	30 (16.2%)
Study population	244	203	335	1047	185
Mortality	0	1	0	0	0
Submitted to the hospital	1 (2.8%)	2 (11.1%)	0 (0%)	25 (11.6%)	4 (13.3%)

toms during the first period when PCR testing for COVID-19 was restricted available are not recognised as COVID-19 positive. It might be possible that BD treating physicians and BD patients were more vigilant towards infections and COVID-19, thus accounting for the relative high numbers. Also, we were unable to contact 64 patients. The still ongoing pandemic with new cases possibly occurring after our evaluation is another limitation of this study. The option of an asymptomatic thrombo-embolic event cannot be excluded since patient with mild disease were not examined for thrombo-embolic events. During our study the vaccination campaign had not started in the Netherlands for the BD population, therefore no data regarding the vaccination coverage in our BD population was obtained. It is favourable to investigate the vaccination coverage in BD patients in future studies.

In conclusion, in our cohort of BD patients no increased risk of mortality or exaggerated course of COVID-19 infection occurred. However, a significantly increased cumulative incidence of COVID-19 compared to the general population is observed. COVID-19 infections appear to be relatively mild in our cohort of BD patients. Since the pandemic is currently ongoing, these results should be extended and confirmed in other BD patient cohorts worldwide.

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