Prevalence and clinical course of SARS-CoV-2 infection in patients with Behçet's syndrome

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ABSTRACT

Objective. *We aimed to assess the prevalence of SARS-CoV-2 infection among Behçet's syndrome (BS) patients, evaluating the possible association between demographic and clinical features and the risk of infection. Moreover, we aimed to evaluate the possible association between BS disease activity and treatment, and the risk of SARS-CoV-2 infection.*

Methods. *A survey was conducted on BS patients followed at the Behçet's Centre of the Careggi University Hospital, Florence, Italy. We further evaluated the possible association between BS disease activity and treatment, and the risk of SARS-CoV-2 infection.*

Results. *Out of 335 BS patients contacted, fourteen cases of SARS-CoV-2 were identified between April 1st, 2020 and February 9th, 2021, suggesting a prevalence of SARS-CoV-2 infection among BS patients of 4.2%, in line with the data of the general population in Italy (4.4%). When comparing clinical features between SARS-CoV-2 cases and matched SARS-CoV-2 negative BS patients, we found that the presence of different disease manifestations did not significantly differ between the two groups. SARS-CoV-2 cases and controls were also comparable in terms of immunosuppressive therapy, with the only exception of corticosteroids (71.4% vs. 35.7%, p=0.030), whose daily dose was significantly higher in cases than controls [5mg/day (IQR 0–10,) vs. 0 mg/day (IQR 0–5), p=0.005], suggesting that the right timing of usage and the more appropriate dosage of corticosteroid are a key question for the better management of these patients.*

Conclusion. *Based on our results, patients with BS do not seem to be at a greater risk of SARS-CoV-2 infection or severe complications compared with the general population.*

Introduction

Current studies on infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients with Behçet's syndrome (BS) are limited to two small case series from European centres (1, 2).

An international registry from the COVID-19 Global Rheumatology Alliance recently assessed the risk of infection in patients with different autoimmune diseases (AD), including vasculitis, but not specifically focusing on BS (3-5). Moreover, it is still debated if patients with AD receiving immunosuppressive therapy are more susceptible to SARS-CoV-2 infection or not. Recent studies reported that patients with systemic AD seem not to carry an increased risk of SARS- CoV-2 infection as compared to the general population (6-8). However, all these studies were conducted at the dawn of the first pandemic wave, and the impact of subsequent changes in medical practice has not been considered.

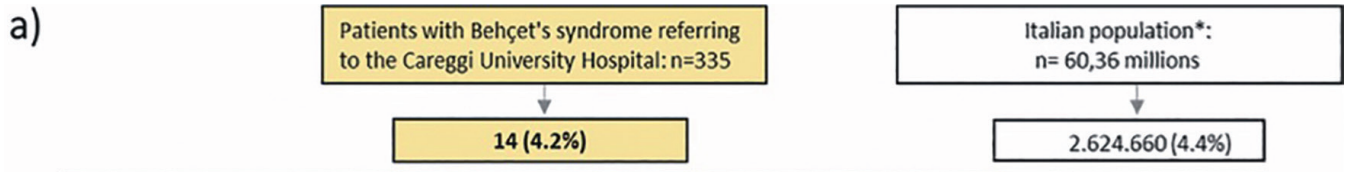
Therefore, we aimed to assess the prevalence of SARS-CoV-2 infection among BS patients, evaluating the possible association between demographic and clinical features and the risk of infection.

Materials and methods

On January 2021, a telephone survey was conducted on subjects diagnosed with BS and followed at the Behçet's Centre of the Careggi University Hospital, Florence, Italy. All contacted subjects accepted to respond to the interview. Confirmed cases of SARS-CoV-2 infection were defined by nasopharyngeal swab positivity and were described in terms of SARS-CoV-2 symptoms, clinical course, and pharmacological therapies (both immunomodulating and SARS-CoV-2 specific).

We further evaluated the possible association between BS disease activity and

a)



b)

	SARS-CoV-2 POSITIVE PATIENTS (N=14)	SARS-CoV-2 NEGATIVE PATIENTS (N=42)	p-value§
Female sex	9 (64.3%)	27 (64.3%)	Matching variable
Median age	39.5 (IQR 32-42)	40 (IQR 32-43)	Matching variable#
Median disease duration	6 (IQR 5-9)	6 (IQR 3-7)	Matching variable#
Active disease (BDCAF>0)	6 (42.9%)	28 (66.7%)	0.129
Immunomodulating therapy			
Corticosteroids –	10 (71.4%)	15 (35.7%)	**0.030**
Median dosage (IQR)	5 (IQR 0-10)	0 (IQR 0-5)	**0.005**
Colchicine	2 (14.3%)	13 (31.0 %)	0.307
HCQ	1 (7.1%)	1 (2.4%)	0.441
Traditional DMARDs	5 (35.7%)	9 (21.4%)	0.304
Azathioprine	4 (28.6)	7 (16.7%)	
Methotrexate	1 (7.1%)	0	
Biologic DMARDs	11 (78.6%)	32 (76.2%)	1.000
Adalimumab	7 (50%)	16 (38.1%)	
Infliximab	2 (14.3%)	7 (16.7%)	
Secukinumab	1 (7.1%)	3 (7.1%)	
Canakinumab	1 (7.1%)	0	
Active disease involvement			
Mucocutaneous	6 (42.9%)	15 (35.7%)	0.752
Articular	6 (42.9%)	20 (47.6%)	1.000
Ocular	0	2 (4.8%)	n.a.
Vascular	0	0	n.a.
Neurological	2 (14.3%)	8 (19.1%)	1.000
Gastrointestinal	2 (14.3%)	7 (16.7%)	1.000

*https://www.epicentro.iss.it/coronavirus/sars-cov-2-dashboard, last updated on February 9th 2021
§p-value from Fisher exact test for categorical variables or from Mann-Whitney test for continuous variables; tests are for unpaired data between the first and the third columns

Fig. 1. a) Prevalence of SARS-CoV-2 infection among: i) patients with Behçet's syndrome referring to the Italian Behçet Association (SIMBA); ii) patients with Behçet's syndrome referring to the Behçet's Centre of the Careggi University Hospital; iii) the Italian general population. **b)** Demographic and clinical features of SARS-CoV-2 positive and negative patients with Behçet's syndrome referring to the Careggi University Hospital, Florence, Italy.

treatment, and the risk of SARS-CoV-2 infection. SARS-CoV-2 negative BS patients, matched 1: 3 by sex, age, and disease duration (matching variable ± 5 years) to SARS-CoV-2 positive patients, were randomly selected. For both SARS-CoV-2 cases and controls, we collected data on demographic and clinical parameters, disease activity (by the Behçet's Disease Current Activity Form, BDCAF) (9) and ongoing immunomodulating/immunosuppressive treatments. Data were related to the period before SARS-CoV-2 infection for cases and to the last available follow-up for SARS-CoV-2 negative controls. Continuous variables were compared between the two groups by the Mann-Whitney test whereas categorical variables by the Fisher exact test for unpaired data. Statistical significance was considered for p-value <0.05.

Results

Out of 335 BS patients referring to our centre, fourteen cases of SARS-CoV-2 were identified between April 1st, 2020 and February 9th, 2021, suggesting a prevalence of SARS-CoV-2 infection among BS patients of 4.2% (Fig. 1a).

Among our 14 SARS-CoV-2 cases, nine were females (64.3%), with a median age of 39.5 years (range: 32–42), and a median duration of BS disease of 6 years (range: 5–9).

Before SARS-CoV-2 infection, 6 patients with BS had active disease (42.9%), and all had mucocutaneous and articular involvement, 2 neurological, and 2 gastrointestinal manifestations (Fig. 1b).

Common SARS-CoV-2 symptoms reported by these patients were fever (n=10), arthromyalgia (n=8), gastrointestinal manifestations (including vomiting and diarrhoea, n=5), anosmia/ageusia (n=7), cough (n=6), headache (n=5), tiredness (n=4), breathlessness (n=3). Panic attacks and dizziness were reported each in one patient (n=1).

At the time this study was conducted, negativisation of the nasopharyngeal swab had occurred in 11/14 patients (78.6%), after a median time from the first positive swab of 16 days (range: 7–46), whereas 3 were still positive (for 12–18 days).

When comparing clinical features between SARS-CoV-2 cases and matched SARS-CoV-2 negative controls, we found that in both groups, the most frequent disease manifestations were mucocutaneous (42.9% cases *vs*. 35.7% controls), articular (42.9% *vs*. 47.6%), neurological (14.3% *vs*. 19.1%), and gastrointestinal (14.3% *vs*. 19.1%). The presence of different disease manifestations did not significantly differ between the two groups, even though disease activity, tended to be higher in controls compared to cases [median BDCAF of 0 (IQR 0–5; range: 0–9) for cases and 3 (IQR 0–5; range: 0–9) for controls, p=0.384].

Before SARS-CoV-2 infection, 10/14 patients were on corticosteroid therapy, at a median dosage of 5 mg/day (IQR 0–10; range: 4–25), two on colchicine, and one on hydroxychloroquine. Five patients were on traditional disease-modifying anti-rheumatic drugs (DMARDs), namely azathioprine (n=4) and methotrexate (n =1), and 11/14 on biologics DMARDs, including adalimumab (n=7), infliximab (n=2), secukinumab (n=1), and canakinumab (n=1).

Nine of these patients (64.3%) discontinued/reduced part of the immunomodulatory therapy: eight patients interrupted biologic therapy, one methotrexate, and one reduced azathioprine dosage (Fig. 1b). Therapy was suspended for a median time of 33 days (12-47) and resumed after a median time of 5 days from negativisation (range: 1–11).

Regarding specific therapy for SARS-CoV-2 infection, seven patients (50%) started or increased corticosteroids (dosage range: 2.5–15 mg/day), whereas heparin and antipyretic drugs were used in four (28.6%). Notably, none of these patients required hospitalisation or died.

SARS-CoV-2 cases and negative controls were also comparable in terms of immunomodulating/immunosuppressive therapy, with the only exception of corticosteroids (71.4% *vs*. 35.7%, p=0.030), whose daily dose was significantly higher in cases than controls [5mg/day (IQR 0-10) *vs*. 0 mg/day (IQR 0-5), p=0.005].

Discussion

In conclusion, the prevalence of SARS-CoV-2 infection among our BS patients was 4.2%, in line with the data of the general population in Italy (4.4%) (10). (Fig. 1a) However, differently from what observed in the general population, all cases of SARS-CoV-2 infection reported among our BS patients were mild, as no patient developed severe pneumonia, required hospitalisation, or died.

According to the COVID-19 Global Rheumatology Alliance, low disease activity is associated with a lower risk of death among SARS-CoV-2 positive patients with autoimmune/immune-mediated diseases (3).

Coherently, most patients in our study were in remission or had low disease activity at the time of infection. Based on our findings, disease activity did not appear to be associated with an increased risk of infection, in agreement with Espinosa *et al*. (1). Only one patient had an exacerbation of the disease after infection, presenting gastrointestinal symptoms related to BS (mucorrhea, bloody diarrhoea and increase in calprotectin levels), while other five patients presented non-specific manifestations (arthromyalgia).

Most patients interrupted biologics DMARDs. However, the use of DMARDs, either traditional or biologic, seemed not to be associated with an increased risk of SARS-CoV-2 infection. Conversely, the use of corticosteroids resulted to be more common and at higher dosage among patients with SARS-CoV-2 infection as compared to BS SARS-CoV-2 negative patients (11). According to a recent meta-analysis, the use of traditional DMARDs and corticosteroids is associated with a higher risk of SARS-CoV-2-related severe complications (12), suggesting that the right timing of usage and the more appropriate dosage of corticosteroid are a key question for the better management of these patients.

Waiting for further data from the Global Rheumatology Association (13) and from the International Society for Behçet's Disease (14), our study suggests that BS patients do not appear to be at a greater risk of SARS-CoV-2 infection or severe complications than the general population.

However, further investigation is advocated in order to clarify the role of immunosuppressive and corticosteroid therapy on the risk of SARS-CoV-2 infection.

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