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Original article

B-cell depleting therapies may affect susceptibility to acute respiratory illness among patients with multiple sclerosis during the early COVID-19 epidemic in Iran

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ABSTRACT

Objective: To determine whether the course of COVID-19 is more severe in patients with MS and if MS disease-modifying treatments (DMTs) affect the risk of contracting the disease.
Methods: In a cross-sectional survey, data were collected by sending a questionnaire to 2000 patients with a demyelinating disease through an online portal system. Collected data included the current MS DMT and patient-reported disability level, history of recent sick contact, recent fever, respiratory symptoms, diagnosis with COVID-19, and the disposition after the diagnosis. We defined a COVID-19-suspect group as patients having fever and cough or fever and shortness of breath, or a presumptive diagnosis based on suggestive chest computed tomography. We calculated the proportion of COVID-19-suspect patients and compared their demographics, clinical characteristics, and DMT categories with the rest of survey-responders, using univariable and multivariable models.
Results: Out of 712 patients, 34 (4.8%) fulfilled our criteria for being in the COVID-19-suspect group. Only two patients required hospitalization. No patient required intensive care. In a multivariable model, disease duration (p-value = 0.017), DMT category (p-value = 0.030), and history of sick contact (p-values < 0.001) were associated with the risk of being in the COVID-19-suspect group. Being on B-cell depleting antibodies (as compared to non-cell depleting, non-cell trafficking inhibitor DMTs) was associated with a 2.6-fold increase in the risk of being in the COVID-19-suspect group. (RR: 3.55, 95%CI: 1.45, 8.68, p-value = 0.005).
Conclusions: The course of infection in patients with MS suspected of having COVID-19 was mild to moderate, and all patients had a full recovery. B-cell depleting antibodies may increase the susceptibility to contracting COVID-19.

1. Introduction

The management of patients with chronic neurological diseases who receive immunomodulatory or immunosuppressive medications has become more challenging during the outbreak of the coronavirus disease 2019 (COVID-19). Most patients with multiple sclerosis are on long-term DMTs. They are concerned that their underlying illness or their medications may increase the risk of infection with the novel coronavirus or experiencing more severe or fatal disease. In fact, respiratory tract infections are generally more common in MS, and their incidence increases with age, level of disability, and male sex (Wijnands et al., 2017). Influenza-related hospitalizations and mortality are also significantly higher in patients with MS (Nelson et al., 2015). Additionally, DMTs, depending on their mechanisms of action, may increase the risk of infections (Luna et al., 2019; Williamson and Berger, 2015; Winkelmann et al., 2016).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly described member of the coronaviridae family with a zoonotic origin. Although, there is a 79% nucleotide similarity between SARS-CoV-2 and previously recognized SARS-Cov-1, the etiology of SARS outbreak in 2002–2003, SARS-CoV-2 has higher infectivity and transmissibility in human and can manifest as severe pneumonia or life-threatening acute respiratory distress syndrome (Huang et al., 2020; Zhang and Holmes, 2020). Several lines of investigation suggest that

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Table 1
Demographic, clinical characteristics and symptoms of survey respondent, and the COVID-19-suspect patients.

	All respondents	COVID-suspect patients	The rest of survey respondents	p-value*
	712	N = 34	N = 678	
Female, n (%)	559 (78.5%)	27 (79.4%)	532 (78.5%)	1.00
Age mean (SD), y	35.0 (8.0)	34.8 (8.0)	35.0 (8.1)	0.97
MS type, n (%)				0.80
Relapsing-Remitting	563 (79.1%)	27 (79.4%)	536 (79.1%)	
Progressive	115 (16.2%)	7 (20.0%)	108 (15.9%)	
CIS, RIS, others	12 (1.7%)	0	12 (1.8%)	
Unknown or Not Reported	22 (3.1%)	0	22 (3.2%)	
Disease duration mean (SD), y	7.7 (7.7)	6.6 (4.2)	7.8 (7.9)	0.68
DMT, n (%)				0.37
Rituximab	285 (40.0%)	21 (61.8%)	264 (38.9%)	
Interferons	111 (15.6%)	3 (8.8%)	108 (15.9%)	
Teriflunomide	16 (2.2%)	1 (2.9%)	15 (2.2%)	
DMF	96 (13.5%)	2 (5.9%)	94 (13.9%)	
Fingolimod	116 (16.3%)	5 (14.7%)	111 (16.4%)	
Natalizumab	18 (2.5%)	0	18 (2.7%)	
Glatiramer Acetate	26 (3.7%)	0	26 (3.8%)	
Ocrelizumab	12 (1.7%)	0	12 (1.8%)	
No DMT	32 (4.5%)	2 (5.9%)	30 (4.4%)	
DMT category, n (%)				**0.059**
B-cell depleting antibodies	297 (41.7%)	21 (61.8%)	276 (40.7%)	
Immune-cell trafficking inhibitors	134 (18.8%)	5 (14.7%)	129 (19.0%)	
All other DMTs	249 (35.0%)	6 (17.7%)	243 (35.8%)	
No DMT	32 (4.5%)	2 (5.9%)	30 (4.4%)	
Duration of current DMT, n (%)				0.83
Longer than 3 months	588 (82.6%)	30 (88.2%)	558 (82.3%)	
Shorter than 3 months	64 (9.0%)	2 (5.9%)	62 (9.1%)	
Not on DMT or not answered	60 (8.4%)	2 (5.9%)	58 (8.6%)	
PDDS category n (%)				0.37
PDDS less than 4	643 (90.3%)	29 (85.3%)	614 (90.6%)	
PDDS 4 or more	69 (9.7%)	5 (14.7%)	64 (9.4%)	
Observing "stay at home" recommendations, n (%)				0.45
100% stayed home	333 (46.8%)	19 (55.9%)	314 (46.3%)	
Mostly reduced my outdoor activities	297 (41.7%)	11 (32.4%)	286 (42.2%)	
Moderately reduced my outdoor activities	57 (8.0%)	2 (5.9%)	55 (8.1%)	
Mildly reduced my outdoor activities	25 (3.5%)	2 (5.9%)	23 (3.4%)	
Fever, n (%)	59 (8.3%)	32 (91.4%)	27 (4.0%)	**<0.001**
Cough, n (%)	138 (19.4%)	29 (85.3%)	109 (16.1%)	**<0.001**
Shortness of breath, n (%)	63 (8.8%)	16 (47.1%)	47 (6.9%)	**<0.001**
Sore throat, n (%)	164 (23.0%)	16 (47.1%)	148 (21.8%)	**0.001**
Sneezing or runny nose, n (%)	216 (30.3%)	18 (52.9%)	198 (29.2%)	**0.006**
Nausea/vomiting, n (%)	48 (6.7%)	11 (32.4%)	37 (5.5%)	**<0.001**
Diarrhea, n (%)	68 (9.6%)	6 (17.6%)	62 (9.1%)	0.13
Was in contact with a diagnosed COVID-19 case, n (%)	29 (4.1%)	3 (8.8%)	26 (3.8%)	0.16
Was in contact with a person with fever or cough or shortenss of breath, n (%)	81 (11.4%)	14 (41.2%)	67 (9.9%)	**<0.001**

MS: multiple sclerosis, CIS: clinically isolated syndrome, RIS: radiologically isolated syndrome, DMT: disease-modifying treatment, DMF: dimethyl fumarate, PDDS: Pateient Determined Disease Steps.

* Fisher's exact test or Kruskal-Wallis test.

intense innate immune response and lack of enough adaptive immunity may contribute to the pathogenesis of the disease, and the release of a large number of inflammatory cytokines may result in poor prognosis (Cao, 2020). For these reasons, a variety of immunomodulatory medications have been proposed as potential treatments for complications of COVID-19 and are currently being tested in clinical trials (Stebbing et al., 2020). So far, there have been a few case reports or case series reporting on the risk and course of COVID-19 in patients with MS (Borriello G, 2020; Quinti et al., 2020; Sormani, 2020). However, we still do not know the association of demographic features, disability level, or various DMTs with the risk of this infection.

On February 19, 2020, the first confirmed cases of COVID-19 were announced in Iran. During the next few weeks, COVID-19 was reported in every major city, and the country turned into an epicenter of the disease in the region with a total reported case of more than 70,000 and around 5,000 deaths.

The aim of the current study was to determine the incidence of the clinical presentations suggestive for COVID-19 infection among patients with MS in Iran during the first few weeks of the epidemic and explore the association of demographics, clinical characteristics, and use of -DMTs with the risk of developing COVID-19.

2. Methods

This is a cross-sectional study of patients with central nervous system demyelinating diseases (mostly relapsing-remitting and progressive MS) who are managed by a neurologist in a tertiary care center in Tehran (AA). The study was approved by the ethics committee at the Tehran University of Medical Sciences, and the written consent requirement was waived.

We sent a questionnaire to 2000 patients through an online portal system. One thousand, two hundred forty-five patients confirmed receiving the survey, and 712 completed and returned the questionnaire from March 26 to April 3, 2020. The data elements included age, sex, type of MS, MS disease duration, current DMT and the length of being on the current DMT, disability level (patient-determined disease steps or PDDS: a PDDS of four and higher requires assistance with walking), the level of compliance with "stay at home recommendations," recent

contact with a person with respiratory symptoms or a patient with COVID-19 diagnosis, whether they have developed any of these symptoms after February 20, 2020: fever, cough, shortness of breath, sore throat, sneezing and runny nose, nausea and vomiting, and diarrhea, whether and how they have been diagnosed with COVID-19 by a healthcare professional and if so, their disposition (home, hospital ward or an ICU). None of the survey responders reported PCR-confirmed diagnosis so that we defined a COVID-19-suspect group as patients who had 1) fever and cough, or 2) fever, and shortness of breath, or 3) fever or cough or shortness of breath, plus a chest computed tomographic (CT) scan that was interpreted as compatible with COVID-19 by a healthcare professional.

Analyses were performed using Stata 14.1 (StataCorp, TX). Significant differences in the demographic, clinical characteristics and the acute disease symptom frequency between COVID-19-suspect cases and the rest of the respondents were tested using Fisher's exact test for categorical variables and Kruskal–Wallis tests for continuous variables. Because the prior reports of an association between B-cell depleting antibodies (Luna et al., 2019), fingolimod (Cohen et al., 2010) and natalizumab (Polman et al., 2006) with increased risk of infections, we categorized the DMTs into four groups: B-cell depleting antibodies (rituximab and ocrelizumab), immune-cell trafficking inhibitors (fingolimod and natalizumab), other DMTs (including glatiramer acetate, interferons, dimethyl fumarate, and teriflunomide) and no DMT group. There were no patients on other lymphocyte-depleting DMTs, such as alemtuzumab or cladribine. To determine if any variable was independently associated with the COVID-19-suspect status, we fit a multivariable Poisson regression model with robust error variance with the COVID-19-suspect status as the dependent variable and the following variables as predictors: age, sex, MS type, disease duration, PDDS category, the level of compliance with "stay at home recommendations," report of recent contact with a person with respiratory symptoms, report of a recent contact a patient with COVID-19 diagnosis, and DMT category (categorized as B-cell depleting antibodies, immune-cell trafficking inhibitors, other DMTs, and no DMT). As a sensitivity analysis, we fit a log-binomial regression model with the same variables. P-values smaller than 0.05 were considered statistically significant.

3. Results

A total of 712 patients participate in the study (responded to the questionnaire) (Table 1). 78.5% of patients were female with a mean (SD) age of 35 (8) years. 79.1 % had relapsing-remitting, and 16.2% had progressive MS (primary or secondary). MS disease duration was 7.7 +/- 7.7 years. 95.5% of the respondents received one of the DMTs for MS as follow: rituximab 40%, fingolimod 16.3%, interferons 15.6%, dimethyl fumarate (DMF) 13.5%, teriflunomide 2.2%, natalizumab 2.5%, glatiramer acetate3.7% and ocrelizumab 1.7%. Most patients (82.6%) were treated with the current DMT for more than three months. The baseline PDSS score was less than 4 in 90.3%.

Out of 712 patients, 34 (4.8%) fulfilled our criteria for the COVID-19-suspect group, as described in the methods. Thirty patients were qualified by their reported symptoms only (fever and cough or fever and shortness of breath); two patients were diagnosed based on the presence of fever or cough or shortness of breath, plus a compatible chest CT. Two patients had a compatible CT and defining symptoms (either fever and cough or fever and shortness of breath). Twenty out of 34 patients did not seek medical attention and improved by staying home. Fourteen patients presented to their physician due to their symptoms. Twelve were recommended to stay home and monitor the symptoms. They all improved. Two out of 14 patients got admitted to a hospital due to the severity of pulmonary symptoms and shortness of breath; however, they did not require ICU care or intubation and were eventually discharged from the hospital.

The demographic and clinical characteristics of COVID-19-suspect and non-suspect patients are summarized in Table 1. There was no statistically significant difference in age, sex, disease type, disease duration, and adherence to the recommended social distancing measures between groups. The difference in the proportion of patients on different DMT categories between the two groups did not reach statistical significance (Fisher's exact test p-value = 0.059): 62% of patients in the COVID-19-suspect group were on a B-cell depleting antibody while only 41% patient in the rest of participants (the none-COVID-19-suspect group) were on B-cell depleting medications. Patients treated with interferons or DMF had a lower chance of being in the COVID-19-suspect group: the proportion of interferon-treated and DMF-treated patients were 8.8% and 5.9% in the COVID-19-suspect group and 15.9% and 13.9%, in the non-COVID-19-suspect group, respectively. 41.2% of patients in the COVID-19-suspect group reported a recent contact with a person with a fever or cough or shortness of breath. The proportion of patients in the non-COVID-19-suspect group who reported a recent sick contact was only 9.9% (p-value < 0.001).

In the multivariable Poisson regression model, MS disease duration, the DMT category, and the report of contact with a person with respiratory symptoms were all independently associated with the risk of being in the COVID-19-suspect group (Table 2). A one-year increase in the MS disease duration was associated with an 8% decrease in the risk of being in the COVID-19-suspect group (95%CI: 0.86, 0.99, p-value = 0.017). Being on B-cell depleting antibodies (as compared to non-cell depleting, non-cell trafficking inhibitor DMTs) was associated with a 2.6-fold increase in the risk of being in the COVID-19-suspect group. (RR: 3.55, 95%CI: 1.45, 8.68, p-value = 0.005). There was no statistically significant difference between patients who were on cell trafficking inhibitors or on no DMT and those who were in the "other DMTs" group. Recent contact with a person with fever, cough or shortness of breath, was associated with a 6.2-fold increase in the risk of being in the COVID-19-suspect group (RR: 7.23, 95%CI: 3.48, 15.02, p-value < 0.001). The results of the sensitivity analysis model were in line

Table 2
Results of the multivariable Poisson regression model.

	Risk ratio	95% CI	p-value
Female (compared to male)	1.05	0.44, 2.53	0.91
Age (one year increase)	1.00	0.96,1.04	0.87
MS type (compared to relapsing-remitting)			0.79
Progressive	0.86	0.29, 2.59	0.79
RIS, CIS, other demyelinating diseases	0	0	0
Unknown or unreported	0	0	0
Disease duration (one year increase)	0.92	0.86, 0.99	**0.017**
DMT category (compared to Other DMTs group)			**0.030**
B-cell depleting antibodies	3.55	1.45, 8.68	**0.005**
Cell trafficking inhibitors	1.53	0.46, 5.11	0.49
No DMT	3.00	0.61, 14.77	0.18
PDDS category (4 or more compared to less than 4)	1.65	0.50, 5.49	0.41
Observing quarantine recommendations (compared to stayed home)			0.38
Mostly reduced outdoor activities	0.61	0.29, 1.28	0.19
Moderately reduced outdoor activities	0.63	0.15, 2.64	0.53
Mildly reduced outdoor activities	1.89	0.38, 9.50	0.44
Report of a recent contact with a patient with COVID-19 diagnosis	0.67	0.20, 2.23	0.51
Report of a recent contact with a person with respiratory symptoms	7.23	3.48, 15.02	**<0.001**

MS: multiple sclerosis, CIS: clinically isolated syndrome, RIS: radiologically isolated syndrome, DMT: disease-modifying treatment, PDDS: Pateient Determined Disease Steps, B-cell depleting antibodies included rituximab and ocrelizumab, Cell trafficking inhibitors included fingolimod and natalizumab, Other DMTs group included glatiramer acetate, interferon, dimethyl fumarate and teriflunomide.

with the main model (data not shown).

4. Discussion

In this cross-sectional study, we showed that a proportion of patients with MS developed symptoms suggestive for COVID-19 in the early days of the epidemic in Iran. Most of the symptomatic patients had a mild course, and only two required hospitalization, with eventual recovery.

About 5% of our respondents could be categorized as COVID-19 suspects. This study was not designed to estimate the incidence of COVID-19 among patients with MS. Population-based studies are needed to achieve that goal. However, based on these results and prior reports of increased incidence of respiratory infections among patients with MS (Wijnands et al., 2017; Wijnands et al., 2018), it is probable that the incidence of COVID-19 could be higher in this patient population. On the other hand, it is possible that patients with MS and other chronic diseases may follow quarantine and social distancing guidelines more stringently and, in the long term, experience a lower incidence of COVID-19 compared to the general population.

Despite the observation of a relatively high proportion of COVID-19-suspect patients in the survey respondents, the course of the disease did not seem to be more severe as compared to the general population. The good outcome in MS patients contracted with COVID-19 is also supported by a report of the Italian study group on COVID-19 in MS patients (Sormani, 2020). The patients with MS in our study were relatively young, and the observed favorable outcomes are consistent with the reported good outcomes in young, otherwise healthy COVID-19 patients. These findings might be reassuring, but the selection bias inherent in survey studies may underly this observation. Patients with more severe disease (for example, those who were still in a hospital or an ICU) were less likely to respond to the survey. This may lead to an incorrect conclusion of a more benign course of the disease in MS. On the other hand, symptomatic people were more motivated to participate in the survey (or asymptomatic patients were less likely to participate). This selection bias could lead to finding a higher proportion of the disease-suspects when compared to the general population.

The most important independent risk factor for being categorized in the COVID-19 suspected group, aside from having close contact with people with upper respiratory symptoms, was the DMT category. Patients who were on a B-cell depleting antibody, as compared to patients on other none-lymphocyte-depleting, non-cell-trafficking inhibitor DMTs, had a higher risk of being in the COVID-19-suspect group. The only two patients who needed hospitalizations were on a B-cell depleting antibody. However, all patients with MS on B cell depleting agents suspected for COVID-19 were eventually recovered. This finding is also supported by other groups who studied the course of COVID-19 in patients with MS (Quinti et al., 2020; Sormani, 2020).

B-Cell depleting therapies like rituximab and ocrelizumab have striking therapeutic effects in MS. However, they remove a large portion (or all) of circulating B-cells and impair the humoral arm of the immune system and increase the risk of Infections (Luna et al., 2019). Recent studies on immune response against SARS-C0V-2 infection reiterate the fact that intact adaptive immune response and generation of neutralizing antibodies against the virus play protective roles in the host during the symptomatic period and less severe phase of the disease (Shi et al., 2020). Therefore, patients with MS treated with B-cell depleting agents might be more prone to COVID-19. However, patients with X-linked agammaglobulinemia (XLA) who suffer from lack of B-cells showed full recovery following COVID-19 infection, implying that neutralizing antibodies might be less crucial in the later phase of infection and its recovery (Quinti et al., 2020; Soresina et al., 2020). XLA patients receive therapeutic IVIG intermittently that may also contribute to their recovery from COVID-19.

It is possible that patients who were on the DMTs other than B-cell depleting antibodies were protected from the infection. In that case, the differences were driven by the patients receiving interferons and DMF: Among patients on interferons or DMF, the proportion of patients in the COVID-19 group was smaller than the non-COVID-19 group. Antiviral properties of type I interferons that may subside SARS-COV-2 infection (Barrat et al., 2019) could be relevant to this finding. Patients on DMF have less inflammatory T-cell responses (Najjar et al., 2020). It has been shown that a strong virus-specific T-cell response could lead to more severe disease in another coronavirus respiratory disease (SARS-Cov-1 infection) (Prompetchara et al., 2020).The Italian preliminary data also demonstrate that patients who were on DMF recover well from COVID-19 (Sormani, 2020). We did not observe any differences in the proportion of fingolimod- and natalizumab-treated patients between the COVID-suspect group and the rest of the participants. None of the patients who participated in the survey received other lymphocyte-depleting medications, such as alemtuzumab and cladribine. These findings are preliminary, the number of participants with the outcome (being in the COVID-19-suspect group) was small, and these results should be interpreted with caution.

We did not find an association between the age, type of MS, level of disability, the degree of observing "stay at home" recommendations, and the risk of being in the COVID-19 group. There is probably a lag between the effectiveness of quarantine measures and a reduction in the risk of an epidemic infection (Pan et al., 2020). That might explain our observation that in the early days of the epidemic, there was no association between the degree of observing quarantine recommendations and the risk of being in the COVID-19-suspect group.

In the multivariable analysis, longer disease duration seemed to be an independent protective factor. Patients with longer disease duration might be more disabled (lower chance to go out and be exposed) and are less likely to be on DMTs. Although we adjusted our models for the disability levels and the DMTs, the residual confounding may explain this observation.

This study provides an early overview of the severity and the risk factors for developing COIVD-19 in patients with MS in the early days of the epidemic in Iran. We had a relatively large sample size and used a multivariable model for finding independent risk factors. The study has many limitations. We alluded to biases that could have led to the observations of a higher proportion of disease-suspect patients and a more benign course in our study. None of our patients were tested with the gold standard testing for the diagnosis of COVID-19 (the PCR of the nasopharyngeal swab). We were also not aware of the spectrum of symptoms associated with COVID-19 at the time of study design. For example, anosmia has been reported to be a common symptom of COVID-19 (Lechien et al., 2020), but it was not part of our questionnaire, and we may have underestimated the number of patients with less severe symptoms.

5. Conclusion

In conclusion, we found that a relatively high proportion of patients with MS developed symptoms suggestive for COVID-19 during the early days of the epidemic in Iran, but no patient required intensive care or intubation. Different DMTs may increase or decrease the susceptibility to the COVID-19 infection. Several reporting databases (registries) (https://msdataalliance.com/covid-19/for-healthcare-professionals/) are currently collecting data to understand the risk of CIVD-19 infection and its course in patients with MS.

CRediT authorship contribution statement

Farinaz Safavi: Conceptualization, Methodology, Visualization, Writing - original draft. **Bardia Nourbakhsh:** Conceptualization, Formal analysis, Visualization, Writing - review & editing. **Amir Reza Azimi:** Investigation, Supervision, Writing - review & editing.

Declaration of Competing Interest

Farinaz Safavi declares no financial conflict of interest.
Bardia Nourbakhsh declares no financial conflict of interest.
Amir Reza Azimi declares no financial conflict of interest.

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