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Research Paper: COVID-19 and its Outcomes in Multiple Sclerosis Patients

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ABSTRACT

Background: Coronavirus Disease 2019 (COVID-19) is a highly contagious disease that resulted in 4533645 deaths until September first, 2021. Multiple Sclerosis (MS) patients receive immunosuppressive drugs. Thus, there is a concern that these drugs will reduce the patient's immune system resistance against COVID19.

Objectives: This study aimed to evaluate the epidemiology of COVID19 and its impact on MS patients in our university hospital in Tehran City, Iran.

Materials & Methods: A cross-sectional study was conducted based on hospital-based registry data from May 2020 to March 2021. Among more than 500 registered MS patients in Imam Khomeini Hospital in Tehran City, Iran, referring within our study period, 84 patients reported SARS-COV2 infection. The diagnosis of MS was confirmed by the McDonald criteria. Moreover, the diagnosis of COVID-19 in MS patients was established by the real-time-PCR technique and chest computed tomography.

Results: Out of 84 MS patients with SARS-COV2 infection, 55(65.5%) were women, and their mean age was 37.48 years. The most commonly used medications by MS patients were Rituximab 20 (26.3%) and Dimethyl Fumarate 14(18.4%). Totally, 9(10.8%) of the patients needed to be hospitalized due to COVID-19, with a mean hospitalization duration of 5.88 days. A total of 1 (1.2%) death was reported.

Conclusion: Compared to the healthy population, COVID-19 is not more serious in MS patients. Most MS patients with COVID-19 infection were not hospitalized and continued their medication during the infection.

Keywords: Multiple Sclerosis (MS), Coronavirus Disease 2019 (COVID-19), Epidemiology

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Highlights

- The most commonly used disease-modifying therapy among MS patients is Rituximab.
- Disease-modifying therapies did not have adverse outcomes during Coronavirus Disease 2019 (COVID-19) pandemic.
- The mortality rate of MS patients is not higher than the general population.

Introduction

Coronaviruses are a group of enveloped single-stranded positive-sense Ribonucleic Acid (RNA) viruses [1] that cause respiratory tract infection and lead to lethal outcomes [2]. In December 2019, a new coronavirus was identified (SARS-COV2). It caused COVID-19 disease and spread from Wuhan city in China [3]. The COVID-19 virus infected more than 218,541,560 people, resulting in approximately 4533645 deaths by September 1, 2021 [4].

Multiple Sclerosis (MS) is a chronic autoimmune neurodegenerative condition that requires long-term treatment by immunosuppressive drugs. Studies suggested that these drugs may increase the risk of infection in patients [5]. Most of our information on the relationship between the characteristics of MS and immunosuppressive medications used by patients with COVID-19 infection was obtained from case reports or case series studies [6, 7]. MS is an autoimmune disabling neurological disease of young adults. The prevalence of MS in females is two to three times more than in males. Besides, the mean onset age of the disease is about 30 years. The primary age range and individuals affected by the disease is 20-40 years [8]. Studies on COVID-19 patients indicated that men are more prone to be infected with the virus than women [9]. COVID-19 disease mainly infects adults, and the elderly population is the second group at the highest risk of infection with COVID-19 [10, 11].

It is a matter of considerable concern that cell-depleting Disease-Modifying Treatments (DMT) might increase the risk of COVID-19 infection in MS patients [12]. There is also a hypothesis that DMTs alleviate the cytokine-storm response in COVID-19 infection, although it remains speculative. Considering this point, few epidemiological studies have been performed on MS patients with COVID-19. Most of these studies have been conducted in case reports and case series, and because we have little knowledge about the effects of COVID-19 on MS patients, we performed the study.

This study aimed to identify the epidemiological characteristics of Covid-19 in patients with MS and their outcomes to improve quality of care and achieve better prevention and treatment.

Material and Methods

We conducted a cross-sectional study and obtained data from MS patients with COVID-19 diagnosis who were referred within the time of our study to Imam Khomeini Hospital Complex (IKHC) in Tehran City, Iran, a tertiary referral center of MS cases [13].

MS-COVID-19 registry is a prospective and ongoing clinical and hospital-based system based on inpatients and outpatients visits who were diagnosed with COVID-19 infection.

The present data were obtained from our hospital-based registry among more than 500 registered MS patients in Imam Khomeini Hospital. They were referred within the time of our study. From May 2020 to March 2021, 88 patients were infected by the SARS-CoV-2 virus. Eighty-Four of them were MS patients, and 4 were NMOSD patients. NMOSD patients were excluded from the analysis.

IKHC is the largest hospital of Tehran University of Medical Sciences in Tehran, with a comprehensive medical center to provide care for patients whose diagnosis of COVID19 was confirmed since the beginning of the epidemic in Tehran [13-15]. The diagnosis of All MS patients was confirmed by neurologists based on the latest McDonald criteria [16]. All subjects were included with a confirmed diagnosis of COVID-19 along with attached documents, including definite diagnosis of COVID-19 with Real-Time Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and definite diagnosis by

Table 1. The baseline characteristics of the study participants

Variables		Mean±SD/ No. (%)
Age (y)		37.48±10.05
Gender	Female	55(65.5)
	Male	29(34.5)
Treatment for Multiple Sclerosis	Interferon B.1a (IM)	5(6.6)
	Interferon B.1a (SQ)	5(6.6)
	Interferon B.1b	3(3.9)
	Glatiramer acetate	8(10.5)
	Fingolimod	10(13.2)
	Teriflunomide	2(2.6)
	Dimethyl Fumarate	14(18.4)
	Rituximab	20(26.3)
	Natalizumab	1(1.3)
	None	6(7.9)
Interval of the last rituximab injection		3.83±3.83

chest Computed Tomography (CT) scan findings compatible with COVID-19 [7, 17].

A trained physician recorded patients' treatment history. In cases of non-referral by the patient for more than three months since their last visit for follow-up, the follow-up was performed by phone and recorded. If the patient was not available, as in the case of death, questions were asked from a first-degree relative of the patient by telephone.

Data entry was conducted by a trained registrant of MS Comprehensive Center and a questionnaire. A written informed consent form was provided by all patients to use their medical records in research projects at admission.

We used descriptive analysis to study the distribution of patients' baseline and clinical data and treatment and mortality through different strata of variables, including age, gender, MS medications, the discontinuation or continuation of the drug during treatment of COVID-19, hospitalization and its length, and COVID-19 outcome.

SPSS was used to analyze the obtained data. Frequency, mean, and Standard Deviations (SD) values were calculated. Chi-square was used to compare proportions and t-test to compare mean scores. $P<0.05$ was considered significant.

Results

Of 84 patients with MS who were SARS-COV2 infected, 55 (65.5%) were female. The Mean±SD age was 37.48(10.05%) years. The three most MS medications received by participants were Rituximab, Dimethyl Fumarate and Fingolimod which were received by 20(26.3%), 14(18.4%), and 10(13.2%) of patients respectively following by Glatiramer acetate: 8(10.5%), Interferon B.1a (SQ): 5(6.6%), Interferon B.1a (IM): 5(6.6%), Interferon B.1b: 3(3.9%), Teriflunomide: 2(2.6%), and Natalizumab: 1(1.3%). Moreover, 6(7.9%) subjects received no pharmacotherapy for MS. In patients who received Rituximab, the Mean±SD interval from the last injection was 3.83±3.83 months (Table 1).

The diagnosis of COVID-19 infection in 4(4.8%) of the patients was according to the positive result of the Polymerase Chain Reaction (PCR) test. Furthermore,

Table 2. COVID-19-related clinical data in the study participants

Variables		No.(%)/Mean±SD
Positive PCR test	Positive	4(4.8)
Status of receiving MS treatment after COVID-19 infection	Continue	37(66.1)
	Discontinue	11(19.6)
	No MS treatment	6(10.7)
	MS diagnosis after COVID-19	2(3.6)
Hospitalization	Yes	9(10.8)
	No	74(89.2)
Hospitalization duration*		5.88±3.23
Death	Yes	1(1.2)
	No	83(98.8)
Age (Y)	Hospitalized patients	38.00±8.77
	Non hospitalized patients	37.3 ±10.31
	P	0.86

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PCR: Polymerase chain reaction; MS: Multiple Sclerosis; SD: Standard deviation; P-value was calculated using Independent Samples t-test.

37(66.1%) of patients continued receiving MS treatment after COVID-19 infection; however, 11(19.6%) of them stopped taking MS medications. Moreover, 2(2.3%) of the study participants were diagnosed with MS after COVID-19. Totally 9(10.8%) subjects were hospitalized by the Mean±SD 5.88±3.23 days; however, 74(89.2%) of the patients were not hospitalized. The Mean±SD age of hospitalized patients was 38.00±8.77years vs. 37.37±10.31 years in non-hospitalized patients which the difference was not significant (P=0.86). Just 1(1.2%) death was reported (Table 2).

Discussion

Our study assessed the effects of COVID-19 on MS patients. The mean age of the explored MS patients was 37.48 years, i.e., higher than the mean age of MS patients. It could be due to more COVID- 19 disease incidence in older patients. Furthermore, 65.5% of MS patients infected by COVID-19 were women. This may be due to the higher prevalence of MS in women than men.

The prevalence of MS in women in Iran is 44.8/100000 (95%CI: 36.3-61.6), i.e., 3 times higher than men (16.5/100000; 95%CI: 13.7-23.4) [1].

The most commonly used drugs among MS patients are Rituximab, Dimethyl Fumarate, Interferons, Fingolimod, Glatiramer acetate, and Triflunomide, respectively. Interferons and Glatiramer acetate as first-line agents do not increase the risk of infection because they rarely develop leukopenia [2, 3]. Fumarate may increase the incidence of COVID-19 in patients with moderate to severe lymphopenia. Still, it seems safe in patients with normal lymphocyte count or mild lymphopenia or without lymphopenia [4]. By reducing the number of peripheral lymphocytes, Fingolimod can increase the risk of COVID-19 infection in MS patients [18]. Natalizumab does not reduce lymphocytes in circulation; thus, it is unlikely to make patients more susceptible to COVID-19 [5].

In patients with MS who take Rituximab, an anti-CD-20 medication, the COVID-19 infection, and mortality rate are considered more than patients who take other DMTs [6].

We investigated the epidemiological characteristics of COVID-19 in patients with MS to improve the quality of care and achieve better diagnosis and treatment. We found that most MS patients with COVID-19 infection were not hospitalized and continued their medica-

tion during infection. No significant age difference was found according to the length of hospitalization. Most MS patients survived, and there was just one death during our study. We have 2 newly diagnosed MS patients after the COVID-19. Recent studies revealed that having MS alone does not put the patient at higher risk of severe COVID-19 infection [7]. Like the general population, COVID-19 infection in most MS patients was mild [19] with no need for hospitalization. Still, we should consider other extra risk factors for severe COVID, like disability and comorbidities.

In this study, most of the MS patients did not experience hospitalization. The majority of MS DMTs target CD4 and Th17 T cells, memory (CD19+ CD27+), and naive (CD19+ CD27) B cells, behave as immunomodulators and may not have a remarkable effect on fighting COVID-19 infection. Still, some DMTs have immunosuppression consequences [9].

According to recent data, most DMTs have not had adverse outcomes despite continued use during COVID-19 [10]. Most MS patients continued their medication (66.1%) without any poor results in this study. DMTs discontinuation occurred in about 20% of the patients. Unfortunately, we accessed no data about the reason for discontinuation. Moreover, there is no data about the type of DMTs in discontinuation. Ongoing studies suggest that the mortality rate in MS patients with COVID-19 is the same as in the general population [19]. In another study from Iran, no death occurred in MS patients infected by COVID-19 [12], which is almost similar to our finding of one death (1.2%) among MS patients.

Most studies revealed that over 65 years of age is a significant risk factor for COVID-19 severity and mortality [13, 14]. Our study includes patients aged below 60 years; thus, the low rate of more severe cases for hospitalization and mortality may be induced by this demographic factor.

Evidence indicated that some viral infections might lead to demyelinating disease [15, 16]. Since the COVID-19 pandemic, a few cases report demyelinating events, including MS following infection [17]. In this study, we reported 2 new MS cases after COVID-19 infection without any related past medical history, like clinically isolated syndrome. Regardless of whether COVID-19 can cause MS or not, the diagnosis of MS in these two patients was made after COVID-19.

Considering the continuing COVID-19 epidemic and new mutations in the virus, we need to know more about the demographic characteristics and risk factors for infections that lead to hospitalization and mortality to prevent better and treat patients with MS.

Conclusion

This study demonstrated a higher number of COVID-19 among females and young cases. Accordingly, it can be reasonable considering the higher prevalence rate of MS in women and the younger age group. However, further studies with a larger sample size are essential to achieve more comprehensive findings.

We are in the fifth peak of coronavirus in Iran; thus, prevention is the best way to prevent COVID-19 in MS patients, such as fostering hygiene practices and social distancing.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (Code: IR.TUMS.NI.REC.1399.028).

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Authors contributions

The first and second authors have an equal contribution. Conceptualization: Sharareh Eskandarieh and Mohammad Hossein Harirchian; Methodology, software: Sharareh Eskandarieh; Validation: Sharareh Eskandarieh, Mohammad Hossein Harirchian, Nasim Rezaeemanesh, Marzieh Moosavi; Formal analysis: Sharareh Eskandarieh, Nasim Rezaeemanesh; Investigation: Sharareh Eskandarieh, Mohammad Hossein Harirchian, Marzieh Moosavi, Masood Najafi, Hora Heydari; Resources: Sharareh Eskandarieh, Mohammad Hossein Harirchian, Marzieh Moosavi; Data curation: Sharareh Eskandarieh, Mohammad Hossein Harirchian; Writing – original draft preparation: Masood Najafi, Hora Heydari; Writing – review & editing: All authors; Supervision: Mohammad Hossein Harirchian; Project administration: Sharareh Eskandarieh, Mohammad Hossein Harirchian; Funding acquisition: Sharareh Eskandarieh.

Conflict of interest

The authors declared no conflicts of interest.

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