Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Multiple Sclerosis and Related Disorders 46 (2020) 102472

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Original article

Evaluation of the rate of COVID-19 infection, hospitalization and death among Iranian patients with multiple sclerosis

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ARTICLE INFO

Keywords:
Multiple sclerosis
COVID-19
Hospitalization
Death

ABSTRACT

Background: COVID-19 is increasingly expanding all over the world. People who have an underlying disease or taking immunosuppressive drugs are generally more likely to be infected than the others. Multiple sclerosis (MS) patients may also be at risk of the disease and its complications depending on the medication they are taking. In this study, we evaluated a large population of patients with MS with different disease modifying drugs to show if any of them increases the risk. In addition, this study evaluates the incidence of COVID-19 in patients with MS, the rate of hospitalization or death in these patients.

Method: This study was performed at the MS Clinic of Sina Hospital. All patients were contacted and their demographic characteristics were recorded. They were then asked about their COVID-19 symptoms. Patients with these symptoms were further evaluated. The documents were reviewed by treating neurologist and MS nurses to be sure about diagnosis of COVID19. The positive polymerase chain reaction (PCR) result or compatible lung computed tomography (CT) scan was acceptable for COVID-19 diagnosis.

Results: 4647 patients answered the phone contact. Of these, 68 were infected with the COVID-19. The rate of hospitalization was 25% which is far more than general population. Two patients died from COVID-19. Rituximab was associated with increase rate of COVID-19 infection but not with hospitalization rate. There was no significant correlation between use of other drugs and rate of infection.

Conclusion: This study revealed that the incidence of COVID-19 in MS patients is not more than general population, but the risk of hospitalization in these patients is higher than estimated for the disease. This highlights the importance of communicating to patients the severity of COVID-19 and the importance of risk reduction behaviors like social distancing and mask use.

1. Introduction

Multiple sclerosis (MS) is an autoimmune disease that can cause a variety of symptoms by affecting the central nervous system (CNS). In this disease, two phenomena of inflammation and neurodegeneration occur simultaneously, which complicate the manifestation of the disease (Friese et al., 2014). Most drugs affect the inflammatory phase of the disease and can only indirectly reduce neurodegeneration (Ontaneda et al., 2017). Due to the progressive nature of the disease, several drugs have been introduced to treat it. Since the introduction of the first MS drug in 1993 (Betaseron, 1998), all efforts have been made to develop more potent drugs. Although the primary used drugs were immunomodulatory, immunosuppressive drugs were gradually preferred due to their high efficacy and very positive results (Le Page and Edan, 2018). Despite their high effectiveness, these drugs can expose patients to various infections due to their immunosuppressive effect. Studies have shown that drugs such as rituximab,alemtuzumab, and fingolimod increase the risk of infectious diseases (Wijnands et al., 2018). Therefore, paying attention to these complications and preventing them is very important in the treatment of MS patients, and care should always be taken to avoid possible infections due to the use of these medications.

One of the infectious diseases that is highly regarded these days and affects the treatment of MS patients is COVID-19 (Gavin Giovannoni et al, 2020). The disease is caused by the SARS-CoV-2, which was first reported in December 2019 in Wuhan, China (LS Wang et al., 2020). It has increasingly involved individuals and has caused mortality. In general, people who have an underlying disease or are taking immunosuppressive drugs are more likely to be infected. The same concern applies to COVID-19 and its impact on a wide range of diseases. A

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https://doi.org/10.1016/j.msard.2020.102472
Received 30 June 2020; Received in revised form 21 August 2020; Accepted 28 August 2020
Available online 29 August 2020

large number of diseases require the use of immunosuppressive drugs for better control. MS also needs high-potency drugs due to its pathophysiology and progressive nature, which also weaken the immune system.

Therefore, the question then arises of how much MS patients are at risk of COVID-19 and its complications due to their underlying disease and the use of a wide range of drugs. To date, some reports of MS patients infected with the disease have been published (Safavi et al., 2020; Fan et al., 2020; Montero-Escribano et al., 2020; Sormani, 2020; Louapre et al., 2020). The preliminary studies suggested that CD20-depeleting monoclonal antibodies may expose people to increased risk of developing COVID-19 (Safavi et al., 2020). Here, we have studied a larger population of patients with MS with different disease modifying therapies to determine whether this risk was still evident.

This study examines the rate of diagnosis of COVID-19 as well as the rate of hospitalization and prognosis in MS patients. In addition, our study assesses these ratios using a larger sample size and different patients from previous report from Iran (Safavi et al., 2020).

2. Method

2.1. Participants

The study was performed at the MS Clinic of Sina Hospital from 5 - 25 May 2020. MS patients of this clinic are registered in its registry system. Therefore, the demographic characteristics of all patients, including age, gender, disease duration, medication, and type of MS were extracted from the registry system. All of these patients were contacted and asked about COVID-19 disease. Most contacts were made by phone and not in person. In some patients, multiple attempts to contact them were made. Those who came to the clinic for a routine visit during this time were interviewed in person. The calls were made by 10 people. All of them asked patients the same specific questions about the COVID-19 disease. In addition, more detailed information regarding patients infected by COVID-19 was obtained from their medical reports. The information of patients who were hospitalized and could not respond to the call or had died prior to contact was obtained from their relatives.

Additional data were obtained from all patients who responded positively, such as the symptoms of the COVID-19 disease, the characteristics of the computed tomography (CT) scan of the lungs, the polymerase chain reaction (PCR) test, and the medications used for COVID-19. Also, hospitalization, duration of hospitalization, and its final result were recorded. To be more precise, patients were asked to submit all documents related to the infection, including tests, PCR results, and CT scans of the lungs. These documents were reviewed by treating neurologist and MS nurses to be sure about diagnosis of COVID19. The positive PCR result or compatible lung CT scan was acceptable for COVID-19 diagnosis.

Data are expressed as mean ± SD for quantitative variables and counts (%) for categorical variables. We used SPSS 21 (SPSS, Chicago, IL, USA) for the statistical analysis of data. Between-group differences were analyzed by Student's *t*-test for quantitative variables. The association of categorical variables were tested by Chi-Square or Fisher's Exact tests, where indicated. Logistic regression was performed for estimation of odds ratio.

3. Results

From all the calls and interviews (5012 registered patients), 4647 patients (77.94% female) answered the questions (Table 1). The mean age of patients was 36.84 ± 9.21. 68 patients (1.46%) had been diagnosed as COVID-19 and the mean age of COVID-19 patients was 37.27 ± 9.10. Overall, 25% of them had been hospitalized. Two patients (2.94%), who both were receiving rituximab, died during COVID-19 pandemic. They had underlying diseases; the first patient suffered from Sjögren's syndrome and hypothyroidism simultaneously, and the second patient suffered from morbid obesity.Table 2 shows the medications history of study population during the COVID-19 pandemic. Approximately 40% of patients were receiving rituximab.

There was no significant difference between COVID-19 MS patients and other MS patients regarding age ($p = 0.74$). We observed an insignificant relationship between male/female gender and COVID in MS patients (fisher exact test;0.46, Odds Ratio = 1.32; 95% CI = 1.12–1.52).

We detected a significant relationship between rituximab and COVID-19 in MS patients (p-value = 0.011; fisher exact test; 0.012, OR = 1.85; 95% CI = 1.37–2.33). From 400 patients who were not receiving any disease modifying drugs (DMDs), 2 of them were afflicted by COVID-19 (p-value; 0.005, fisher exact test; 0.12, OR = 0.31; 95% CI = 1.09–1.72). Interferons, Glatiramer acetate and also oral therapies have not increased the risk.

We found out that 17 patients out of 68 COVID-19 MS patients had been hospitalized (25%). The mean age of hospitalized patients was 40.26 ± 12.20. Among COVID-19 patients, 82.35% were female. As Table 3 shows none of DMDs were correlated with hospitalization.

Mean disease duration was 6.79 ± 5.42 and 6.868 ± 6.2 in non-COVID MS patients and COVID-19 MS patients, respectively. No significant difference was observed between COVID-19 and non-COVID MS patients in terms of disease duration ($p = 0.92$).

Moreover, relapse-remitting MS (RRMS) was found as the most frequent MS type in all patients (75.42%), and was significantly associated with COVID-19 ($p = 0.0009$; OR = 2.46; 95% CI = 1.72–3.20).

4. Discussion

The current study was conducted on 4647 patients with MS and showed 1.46% infection rate with COVID-19 in these patients. This rate was not different from the prevalence of COVID-19 in the general population (Signorelli et al., 2020; L Wang et al., 2020).Another study also did not show an increase in the risk of COVID-19 in MS patients compared to the general population;of 1804 patients with MS, none had COVID-19 (Fan et al., 2020).The reason why the rate of infection with COVID-19 in these patients is not more than general population, despite initial predictions (i.e., higher probability of involvement due to the use of immunosuppressive drugs), is probably because these patients pay more attention to health tips. According to a study conducted in Iran on 100 patients, these patients had a good knowledge of COVID-19 and factors related to its prevalence, and were aware of the importance of following medical advice (Sahraian et al., 2020).

In addition, young age of MS patients, their female gender, and the low incidence of comorbidities in these patients can justify the low risk of developing COVID-19 (Vishnevetsky and Levy, 2020). Moreover, it should be noted that MS drugs are not particularly targeting the biology important to viral elimination (innate immune system) and do not influence the vascular pathology that is central to COVID-19 pathophysiology (Baker et al., 2020). Furthermore, some medications especially interferons have anti-viral effect and can attenuate the symptoms of COVID-19 in these patients (Irvani et al., 2020).

The present study indicated that the use of rituximab increases the risk of developing COVID-19. This was not documented in the study of Fan et al. (2020). However, in another study in Iran, 712 patients with MS filled out a questionnaire about COVID-19 symptoms, of which 34 patients (4.8%) had COVID-19 symptoms. It was indicated that the use of B-cell depletion drugs can increase the risk of COVID-19 (Safavi et al., 2020), which is consistent with our findings. Increase in the risk of COVID-19 through B-cell depleting therapies was expected. Previous studies have all confirmed an increased risk of infection in inpatients consuming these drugs (Luna et al., 2020).

Increase in the risk of other infections following the use of these drugs correlates with the increase in the risk of developing COVID-19 through using these drugs (Willis and Robertson, 2020). However, we find that this risk did not increase with interferons, glatiramer acetate

Table 1
The characteristics of MS patients.

	COVID-19 (n = 68)	Hospitalized COVID-19 patients (n = 17)	Other MS patients (n = 4579)	Total (n = 4647)
Male	12 (17.65%)	5 (29.41%)	1013 (22.12%)	1025 (22.05%)
Female	56 (82.35%)	12 (70.58%)	3566 (77.88%)	3622 (77.94%)
Age	37.27 ± 9.10	40.26 ± 12.20	36.84 ± 9.2	36.84 ± 9.21
RRMS	60 (88.23%)	14 (82.35%)	3445 (75.23%)	3505 (75.42%)
PPMS	0 (0%)	0 (0%)	232 (5.06%)	232 (4.99%)
SPMS	3 (4.41%)	2 (2.94%)	687 (15%)	690 (14.84%)
OTHERS	0	0	125 (2.72%)	125 (2.68%)
Disease Duration (year)	6.86 ± 6.21	10.40 ± 8.10	6.79 ± 5.42	6.79 ± 5.43

RRMS: relapsing-remitting multiple sclerosis; MS: multiple sclerosis; PPMS: primary progressive multiple sclerosis; SPMS: secondary progressive multiple sclerosis.

Table 2
The medications history of study population during the COVID-19 pandemic.

	COVID-19 (n = 68)	Other MS patients (n = 4579)	P-Value	Odds Ratio	lower	upper
Rituximab	38 (55.88%)	1858 (40.57%)	0.01	1.85	1.37	2.33
Fingolimod	4 (5.88%)	494 (10.78%)	0.08	0.51	0	1.53
Ocrelizumab	1 (1.47%)	24 (0.52%)	0.51	2.83	0.81	4.84
Natalizumab	2 (2.94%)	68 (1.48%)	0.47	2.01	0.58	3.43
Glatiramate Acetate	5 (7.35%)	438 (9.56%)	0.48	0.75	0	1.66
DMF	2 (2.94%)	300 (6.55%)	0.08	0.43	0	1.84
Azathioprine	1 (1.47%)	35 (0.76%)	0.62	1.93	0	3.94
IFN-β 1α SC	5 (7.35%)	292 (6.37%)	0.75	1.16	0.24	2.08
Teriflunomide	2 (2.94%)	74 (1.61%)	0.51	1.84	0.41	3.27
IFN-β 1α IM	5 (7.35%)	522 (11.39%)	0.20	0.61	0	1.53
No medication	2 (2.94%)	398 (8.69%)	0.005 Fisher exact; 0.12	0.31	0	1.72
Others	1 (1.47%)	76 (1.65%)	0.89	0.88	0	2.87

DMF: dimethylformamide; IFN-β 1α IM: interferon-β 1α intramuscular; interferon-β 1α subcutaneous; MS: multiple sclerosis.

Table 3
The correlation between DMDs and the risk of hospitalization.

	Hospitalized (n)	Not hospitalized (n)	P-Value
Rituximab	12	26	0.15
Natalizumab	0	2	0.40
Ocrelizumab	1	0	0.08
Fingolimod	1	3	1
DMF	0	2	0.40
Glatiramer Acetate	0	5	0.17
IFN Beta 1A SC	0	5	0.17
IFN Beta 1A IM	0	5	0.17
Azathioprin	1	0	0.08
No medication	2	0	0.012 fisher exact; 0.059
OTHER MEDICATIONS	0	3	FISHER ECAT; 0.56

DMF: dimethylformamide; IFN-β 1α IM: interferon-β 1α intramuscular; interferon-β 1α subcutaneous.

and oral therapies. Another noticeable finding of our study was the high proportion of patients receiving natalizumab infected by COVID-19. 2.8% (2/70) of patients receiving natalizumab were infected by COVID-19 which was equal to patients received rituximab (38/1896). The small sample size of patients receiving natalizumab may result in a statistically insignificant correlation between receiving this drug and the risk of COVID-19.

The rate of hospitalization in our patients is 25%, which is much higher than the global statistics in the general population. Although the rate of hospitalization varies with age and underlying disease, the rate has been reported to be 3.4% - 4.3% for the age group associated with MS patients (Verity et al., 2020). This finding is in agreement with previous studies. Parrotta et el. have reported a high frequency of hospitalization (9/34 (26.4%)) following CD20 treatment (Parrotta et al., 2020). This has been seen in some cohorts treated with rituximab in Sweden (9/41 (22%)) (Hillert J. iWiMS MS Covid-19. 20 May 2020 (https://youtu.be/z4sRBQEv0yE)); France (9/17 (52.9%)) (Louapre et al., 2020), and with ocrelizumab in France (10/38 (26.3%)) (Louapre et al., 2020), the USA (Chaudhry et al., 2019) and in a ocrelizumab pharmacovigilance study (26/100 (26.0%)) (Hughes et al., 2020).

Although hospitalization of most MS patients can be attributed to the influences of their underlying drugs (Celius, 2017), which in many cases suppress the immune system, the current study found no relationship between medication and hospitalization in MS patients. Several factors can be assumed regarding the higher hospitalization rate of MS patients compared with general population. This hospitalization rate may indicate that physicians are more sensitive to these patients due to their underlying disease and the medication they are taking. Secondly, it is not yet clear whether MS itself can play a role in increasing hospitalization. We did not examine the disability rate of MS patients. We know that an increase in disability in MS patients is associated with an increase in the risk of developing infections (Luna et al., 2020) and thus developing COVID-19 which subsequently may increase the hospitalization rate; an issue that requires further research. However, patients with MS need to be more careful about healthcare issues. Although their overall risk of developing COVID-19 is not higher than the normal population, their course can be more severe in case they get infected.

Albeit rituximab increased the rate of infection, it did not affect the rate of hospitalization in these patients. Several studies have indicated that B-cell depleting therapies do not increase the severity of COVID-19 disease (Montero-Escribano et al., 2020; Ghajarzadeh et al., 2020). However, recently a preprint of Italian registry data supports an increased occurrence of COVID-19 in people treated with CD20-depleting antibodies using ocrelizumab (Sormani and De Rossi Nicola, 2020).

There are other reports about the severity of COVID-19 in patients taking B-cell depleting therapies. For example, Safavi et al. reported that two hospitalized patients were taking rituximab (Safavi et al., 2020). Also, in a report from Isfahan on 543 patients with MS, 66 patients were suspected of having COVID-19, and one rituximab-consuming patient had developed a severe course of COVID-19 disease.

However, the authors did not mention anything about the patient's comorbidities (Barzegar et al., 2020). In the current study, although the rate of hospitalization was not related to the type of medication, the two patients who died both were rituximab users. They also had underlying diseases; the first patient suffered from Sjögren's syndrome and hypothyroidism simultaneously, and the second patient suffered from morbid obesity. Nevertheless, the mortality rate in the present study was 2.9%, which is line with global statistics in normal population (Baud et al., 2020; Spychalski et al., 2020). However, the extent to which rituximab was involved in the deaths of these two patients requires further research. It seems that rituximab does not play a role in exacerbating the symptoms of COVID-19. This dual behavior of rituximab (i.e., it affects the rate of developing COVID-19 while it does not affect the hospitalization rate) can be explained by the pathophysiology of COVID-19. According to this pathophysiology, COVID-19 is a complex disease, the severity and symptoms of which depend on the interaction between coronavirus and the patient's body. In general, there are two stages in this disease. The first stage is characterized by the invasion of the coronavirus and the infection of human cells. The virus attaches to the cell surface receptors, enters the cell, and releases after proliferation. The second stage of the disease, also known as cytokine storm, is related to the body's response to the virus. At this stage, the immune system may overreact to the virus, destroying the lung tissue and intensifying the symptoms (Yuki et al., 2020).

Immunosuppressive drugs, such as rituximab, may facilitate the first stage of COVID-19 and increase the risk. However, by suppressing the immune system, these drugs are at least theoretically capable of preventing the second phase of injury and thus prevent the development of severe stages of COVID-19 disease (Suwanwongse and Shabarek, 2020). But several other issues should be considered on the effect of rituximab on infection by coronavirus and its exacerbation in patients with MS:

1- CD20 depletion can inhibit antigen-presenting cell function to limit T cell activation which appears to be important in SARS-CoV-2 elimination (Sekine et al; Gallais et al). This would increase the risk of infection or may enhance the conversion of an asymptomatic individual into a symptomatic individual.
2- Rituximab depletes B cells and so inhibits the capacity to produce immunoglobulins to new antigens. IgM and IgA have been suggested to be part of the defense mechanism and so this will be inhibited (Baker et al., 2020).
3- Rituximab induces IgA, IgG and marked IgM hypogammaglobulinemia, which are known risk factors for serious infections (Baker et al., 2020). As immunity to COVID-19 is in part supported by cross-reactive immunity to cold-causing coronavirus (Baker et al., 2020; Sekine et al; Grifoni et al., 2020), CD20-depletion may have limited the production of protective antibody formation during past coronavirus infections
4- Alternatively hypogammaglobulinemia could limit protective antibody responses that have formed and so reduce protection from infection. It should be noticed that all of the mentioned explanation must be studied in further investigation.

The type of MS was also found to be associated with the risk of developing COVID-19, and its development was significantly more common among RRMS patients. This can be due to the better physical condition of these patients and the possibility of their greater presence in the community, as they do their personal affairs and job that may expose them to the disease.

5. Conclusion

The present study demonstrated that MS patients are not more likely to develop COVID-19 than general population. However, it was shown that they are more likely to be hospitalized than general population. This highlights the importance of communicating to patients the severity of COVID-19 and the importance of risk reduction behaviors like social distancing and mask use.

Declaration of Competing Interest

The authors declare there is no conflict of interest.

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