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Full Length Research Paper

Clinical characteristics, re-infection, seropositivity and the role of Disease Modifying Drugs (DMDs) in COVID-19 infected MS and NMOSD patients: A 12 months prospective observational study

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Abstract

Objectives: Multiple Sclerosis (MS) and Neuromyelitis Optica Spectrum Disorder (NMOSD) patients may have higher risk of contracting COVID-19 infection due to the medications, disability and other comorbidities leading to immune system dysfunction. COVID-19 may aggravate MS and NMOSD or lead to their progression. Methods: We investigated the clinical characteristics of COVID-19 infection and the relationship between using disease modifying drugs (DMDs) and other possible contributing factors with the rate and severity of COVID-19 infection in MS/NMOSD patients through a cohort as a longitudinal observational cross-sectional study. The sample was all MS and NMOSD patients those whom visited in a referral MS clinic in Tehran, Iran, and went through three-monthly follow-ups for 12 months. Patients were assessed for clinical symptoms, re-infection with COVID-19 and its seropositivity. Results: From the total 2878 patients, 2328 were under treatment with DMDs. In confirmed COVID-19 contracted patients (42), 12 patients used Rituximab, 6 Beta interferon, 3 Teriflunomide, 5 Natalizumab, 9 Fingolimod, 3 Dimethyl fumarate, one Azathioprine and 3 were no DMD using. Some patients treated with DMDs such as Rituximab, Fingolimod and Natalizumab were at a higher risk of COVID-19 infection or even re-infection compared to other DMDs. It is probable that some drugs could have relatively protective effects.We had limited report of exacerbation of MS and NMOSD among confirmed cases not close to the infection time, at least in our short-term follow-up. Conclusions: MS and NMOSD patients had no higher risk of contracting COVID-19 infection than general population. Some DMDs had a role in severity of infection or re-infection and also in the rate of seropositivity.

Key words: COVID-19, seropositivity, re-infection, multiple sclerosis, Neuromyelitis Optica Spectrum Disease.

INTRODUCTION

Following the detection of the first confirmed SARS-COV-2 case in Wuhan, China, the world has been affected by one of the most troubling pandemics in history.

An important aspect of COVID-19 is involvement of the immune system, including depletion of lymphocytes B, T and Natural Killer cells[1, 2]. Multiple Sclerosis (MS) is an autoimmune inflammatory demyelinating and neurodege-

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nerative disorder treated with immunomodulatory disease modifying therapies (DMDs). Neuromyelitis Optica Spectrum Disorder (NMOSD) is a relapsing neuro inflammatory disease of the central nervous system that typically presents with optic neuritis or myelitis and may cause severe disability; immunosuppressive agents have been demonstrated to prevent acute exacerbations[3]. Due to the neurological disabilities in patients with MS and NMOSD, the probable effects of SARS-CoV-2 on disease course, and the role of some DMDs on COVID-19 susceptibility and infection severity, MS and NMOSD patients might be at higher risk of mortality and morbidity from COVID-19 than the general population [4].

Moli Fan et al, conducted a study to evaluate the risk of COVID-19 in patients with MS and NMOSD. They detected no increased risk of COVID-19 infection in patients with MS or NMOSD, irrespective of whether these patients received DMDs [5].

In another study by Etemadifar M. et al, 45 COVID-19-infected patients with MS have been assessed and it was proved that out of the 45 MS patients infected with COVID-19, 5 had unfavorable outcomes. Two patients who died received rituximab as part of their MS treatment. They concluded that disease-modifying therapy use in MS patients should be cautiously applied as their effect on COVID-19 infection prognosis is not yet studied [6].

Also, BigautK et al reported lower humoral response after COVID-19 in patients with MS receiving fingolimod or anti-CD20 mAb[7]. On the other hand, a study conducted by Ghayeghran A. et al, shows that there was no significant relationship between the COVID-19 infection with MS medication, type of medication, and change in medication [8].

In another study, Wijnands JMA et al, showed that disclosure to a second generation DMT was concomitant with an increase in the risk of infection, particularly Natalizumab. First generation DMTs like IFN-β were not associated with an increased risk which the authors guess could be due to its anti-viral effect [9].

Morales R P, et al. reported that the incidence of COVID-19 was slightly higher in their sample than in the general population. Unfavorable prognosis was associated with older age and higher EDSS scores. DMT and lymphocytopenia did not influence the clinical course of COVID-19. Seroprevalence of antibodies against the virus in their patients was similar to that reported for the general population with positive PCR [10].

It seems that a thorough investigation on clinical characteristics, re-infection, seropositivity and the role of DMDs in COVID-19 infected MS and NMOSD patients is necessary in order to have a concise overview in these conditions.

MATERIALS AND METHODS

In this cohort follow-up study, we observed 2878 patients in "Arya referral neurology and MS clinic" in Tehran, Iran who were visited between April 20 to October 22, 2020.These patients were from the data pool of 4145 MS and NMOSD patients those whom registered in the clinic. The patients then went through three-monthly follow-ups for 12 months and were assessed for clinical symptoms, re-infection with COVID-19 and its seropositivity.

This study was designed in the spirit of ethical principles with origin in the Declaration of Helsinki or equivalent, and consistent with Good Clinical Practices. Since the data was confidential and only used for research purpose without the patients' name and only by dedicated code, there was no need for ethical approval, but all subjects gave informed consent to participate in the study.

All the patients who provided evidence of infection were considered as confirmed COVID-19 infected. These evidences were included: 1- polymerase chain reaction (PCR) with nasopharyngeal swab, 2- thoracic computed tomography (CT), and 3- neutralizing antibodies against COVID-19 virus.

We also encountered 139 NMOSD patients (from the data pool of 439 registered NMOSD patients)those whom were visited in the clinic during this period. All these patients were being treated with Azathioprine and Rituximab.

Confirmed COVID-19 positive patients were categorized in four groups in terms of severity[11]; 1) Asymptomatic: patients with no symptom but positive evidence according to close contact with infected persons, 2) mild: patients with mild symptoms whom were suggested to stay at home and continue their DMDs, 3) moderate: patients who were admitted to hospital while cutting down their DMD therapy, 4) severe: patients who admitted in Intensive Care Unit or died of COVID-19.

Among 2878 patients, 2739 had MS (95.17%) and 139 had NMOSD. Also, from the total 2878 patients, 2328 were under treatment with DMDs (80.88%).

103 patients were suspected to have COVID-19 (3.57%); 42 patients (1.45% of total patients and 40.77% of suspected COVID-19 patients) were confirmed by diagnostic tests (**Table 1**).

In our study, confirmed patients had an Expanded Disability Score Scale (EDSS) range of 0 to 4.

Statistical analysis

In this study we used descriptive statistics including: average, standard deviation, frequency for demographics and clinical characteristics. Univariate logistic regression model was used to determine the relationship between type of DMDs and risk of COVID-19 infection. Significance level was considered as P value less than 0.5 (*P*- value<0.05). Data analysis of this study was performed using SPSS version 18.

RESULTS

From 42 patients, 38 were MS-patients and four NMOSD (**Table 2**). Of 42 confirmed cases, 6 (14.28%) were detected in the first peak of COVID-19 before April 2019 (the first cases of COVID-19 were detected in Iran in March

Table 1. Evidence measures for COVID-19 in confirmed cases.

Number of positive cases	Diagnostic tests
28*	PCR
14*	AntiCOVID-19 Ab
8*	Diagnostic chest CT

*Some patients had more than one evidence.

Table 2. Baseline characteristics of confirmed COVID-19 infected patients.

Sex	male	female								
	9	33								
Age	Range	Mean								
	57-24	37.30								
EDSS	Range	Mean								
	4-0	2								
Type of MS	RRMS	PPMS	SPMS	NMOSD						
	34	0	4	4						
DMD using	Yes	No								
	39	3								
Risk factors	HTN	DM	Age>55y	35<BMI	Smoking	[1]PD	[2]RD	[3]CVD	4≤EDSS	Lymph 200≥count
	2	2	4	1	0	0	0	0	2	0

[1]Pulmonary disease, 2. Renal disease, 3. Cardiovascular disease.

2019), and other 36 confirmed patients were infected after that time.

The range of confirmed patients' age in this study was 24 to 57 years-old with a mean age of 37.30years-old.

We rechecked the EDSS of confirmed patients and only two of them had score of 4 (with moderate and severe disabilities) and more. Among these patients, 11 had risk factors for COVID-19 infection severity (Table **2**).

In reviewing the diseases modifying drugs(DMDs) that confirmed COVID-19 patients received; 12 patients used Rituximab, 6 Beta interferon, 3 Teriflunomide, 5 Natalizumab, 9 Fingolimod, 3 Dimethyl fumarate, and 1 Azathioprine. However, 3 patients were being followed up and had not yet started medication for MS or ever used while having COVID-19 (**Table 4**). The relation between using DMDs and COVID-19 infection is also shown in **table 3**.

A closer look at the patients revealed that 6 patients who took Rituximab (50% of confirmed), 1 under Beta interferon (16.6% of confirmed), and 1 patient with no DMD drug (33.3% of confirmed) experienced severe COVID-19 and were admitted in hospital. Unfortunately, one of the patients under Rituximab therapy passed away due to complications of severe COVID-19 infection.

Table 3. DMD using in confirmed COVID-19 cases.

DMDs	**Number of COVID-19 confirmed patients**	**Number of total patients**	OR	***P*-value**
Rituximab	12	402	2.51	0.012*
Interferons	6	795	0.43	0.056
Teriflunomide	3	111	1.94	0.219
Natalizumab	5	72	5.58	0.004*
Fingolimod	9	309	2.31	0.039*
Dimethyl fumarate	3	287	0.69	0.794
Azathioprine	1	75	0.91	>0.999
Glatiramer acetate	0	238	0.00	>0.999
Ocrelizumab	0	15	0.00	>0.999
No DMD	3	550	0.32	0.048*
Others (cellcept, mitox)	0	24	0.00	>0.999
Total	42	2878	-	-

*P-value <0.05

Table 4. Severity of SARS-COV-2 infection in MS-NMOSD patients

DMD/Symptoms	**asymptomatic**	**mild**	**moderate**	**severe**	**death**
Rituximab	1	1	3	6	1
Interferons	1	2	2	1	0
Teriflunomide	1	2	0	0	0
Natalizumab	0	3	2	0	0
Fingolimod	0	5	2	2	1
Dimethyl fumarate	0	2	1	0	0
Azathioprine	0	1	0	0	0
No DMD	0	1	1	1	0
Glatiramer Acetate	0	0	0	0	0
Ocrelizumab	0	0	0	0	0
Others: mycophenolate…	0	0	0	0	0

Another expired case was under Fingolimod therapy. Also, we had 3 asymptomatic patients who took Beta interferon, Teriflunomide and Rituximab (**Table 4**).

6 out of 42(14.2%) confirmed patients were admitted to the ICU; 4 of these 6 underwent intubation and ventilation, which two were released and two unfortunately passed away. In total, two patients (4.76%) expired due to COVID-19 till 22 October2020, that one of them used Rituximab and another one used Fingolimod.

The mortality rate of confirmed patients attained 4.76% (2 of 42). Finally, with follow-ups, we found that 40 patients (95.23%) were completely cured and later continued their daily life and their previous MS therapy.

Only 9 patients were decided to discontinue their DMDs while in acute COVID-19 infection maximum for two weeks (8 users of Fingolimod and 1ofAzathioprine) and others continued their DMDs in spite of COVID -19 infection.

Table 5. Number of re-infections and seropositivities.

Re-infection		Seropositivity	
6 patients	Rituximab 4 Fingolimod 2	2 patients	Rituximab 1 Fingolimod 1

Table 6. Seropositivity of Anti SARS-COV2 (Neutralizing antibody) according to type of DMD

	Number of positive patients	Number of infections	*Antibody titer
Rituximab	1	2	1.8
Fingolimod	1	2	2.34
Beta Interferon	6	1	18.3-7.5
Teriflunomide	3	1	9.8-3
DMF	3	1	7-1.3
Natalizumab	2	1	3.5-0.72

In 12 months follow-up of 40 infected patients, 6 were re-infected with COVID-19 between 3 - 9 months after the first COVID-19 infection, four of which were treated with Rituximab, and two with Fingolimod. All re-infections were with mild symptoms (**Table 5**).

Only two relapses occurred in the patients with history of COVID -19 during the 12 months period. No MS progression was observed.

Only one patient out of 12 infected those who were treated with rituximab was SARS-COV-2 IgG antibody positive (using antiCOVID-19 RBD detection). Antibodies were assessed in 22 out of 40 infected patients. The rate of detected antibodies in infected patients treated with different DMDs in order of frequency included: Interferons, GA, Teriflunomid, Natalizumab, Fingolimod, and Rituximab (**Table 6**).

Immunoglubolin IgG in all 12 patients treated with Rituximab who infected with COVID-19 were lower than normal limits.

DISCUSSION

In our study, MS/NMOSD-patients were affected by COVID-19 during the first six months of pandemic (1.35% among 2878 patients came to clinic and 4.76% death among confirmed cases) almost like general population in Iran in that time period. This may be due to their good observance of hygienic issues, limiting social interactions due to concern of getting infected, and/or lack of widespread access to diagnostic facilities at that time in Iran [12].

Also, in similar study of another cohort of 4647 MS patients in Iran, the rate of COVID-19 infection reported 1.46%[13].

According to our observation, number of COVID-19 patients increased over time of the pandemic in Iran (6 patients in first peak in comparison with 36 confirmed ones after April), due to breaking of lock-downs and increasing patient's transportation to working, shopping and social interactions. In our 12 months study we found no evidence of disease recurrence and progression in 42 COVID-19 infected patients. This may be due to our short-term follow-up, so we should recheck the matter after a while and regularly in a long-term pattern.

We advised patients with MS not to stop their DMDs during the COVID-19 pandemic without consultation with their treating physicians as Discontinuation carries the risk of deterioration or relapse of MS that could lead to an increase in disability and hospital admission [14].

Like Dutch and Italian cohort's[15, 16],our results revealed that there is statically significant higher number of infected patients among the consumers of Rituximab, Natalizumab, and Fingolimod; which were respectively 2.5, 5.6, and 2.3 times more than other DMD users. However, we could not say these medications lead the higher risk of COVID-19, because we could not evaluate all of the risk factors.

We assumed that Interferons even as borderline level and

having no DMDs can play a protective role against COVID-19 severity, as Barzegar and colleagues mentioned in their study [17]. Also, in some other studies, the protective effect of Interferons has been observed [18, 19].As our study proposed, like the French cohort [18], the risk of COVID-19 is significantly lower (68%) in patients who have not taken any DMDs.

As mentioned in previous articles, there are conflicting information about the role of DMDs in exacerbation or suppressing symptoms of COVID-19.

About anti-CD20 DMDs, some studies proposed a protective role against COVID-19 severity [20, 21], however, some suggested increasing the susceptibility of infection [22]as we have got some hints regarding that in our study.

According to our study, Natalizumab users were higher in COVID-19 cases, which is supported by another study performed in Italy [23], but recommended broad exploration about extending interval dosing to protect MS patients during the pandemic[19]. Perhaps lack of extended interval dosing or prior immune suppression in our patients might lead to this result.

No one of patients who received Ocrelizumab, contracted COVID-19. This finding might be due to the fact that the patients only received one dosage of 300 to 600 milligrams of the drug because of the availability in that time.

NMOSD patients infected by COVID-19 in our study were 4 patients among 139; three of them used Rituximab whom experienced severe infection, and one Azathioprine whom got mild infection. Similar results have been obtained in Sahraian and colleges` evaluation; the infection rate in their survey was 3.8% (5/130), almost the same as our results [24].

In our study the patients treated with Fingolimod were more affected with COVID-19. However, a review by Laroni et al suggested that Fingolimod does not increase the risk of severe COVID-19 infection [19].

In our study, the range of symptoms for COVID-19 in each DMD varied from asymptomatic to severe or death; for example, in COVID-19 patients under Rituximab although most of them experienced severe disease but, there was asymptomatic one too.We had both mild-moderate and severe symptoms with Fingolimod. We even had one case of severe COVID-19 in a patient without DMD using. So, it seems that a number of other risk factors such as genetics, immune condition at the time of contracting COVID-19 and some in apparent factors could lead to these diverse results.

In this cohort, we have succeeded in visiting and examining a significant number of patients in a certain period of time and getting confirmed information by using of reliable para clinics data.

One of our limitations in this study was not having exact time of infection in each patient and duration of disease, so we couldn't check the relation between laboratory profiles (leukopenia, lymphopenia) during the infection. Second, is lacking of facilities for testing all referral patients for COVID-19 and detecting asymptomatic/carrier individuals. Also, we could not have facility to detect antiCOVID-19 antibodies in different times and with different methods. Unfortunately, because of the time limitation and lack of exact information data in some patients, the multivariable analysis had not been performed.

It is suggested to have global data sharing to detect and follow-up MS and NMOSD patients in relation to DMDs and any change in disease trajectories during the pandemic and also COVID-19 vaccination effects. The hypothesis raised here, is the relationship between severity of COVID-19 and the interplay between genetics, immune system, unknown pharmacogenomics and also cellular factors of individuals.

CONCLUSION

According to this study, we guess that MS and NMOSD patients were not more susceptible to contract COVID-19 infection than general population. Among the DMD users, some are at higher risk for COVID-19 infection. It seems that DMDs play role in contracting COVID-19. However; some DMDs have protective role like Interferons, some DMDs such as: Rituximab, Fingolimod, and Natalizumab, might make patients more susceptible to COVID-19 infection which should be confirmed in repeated studies. No evidences of disease reactivation or progression were recorded in our visited MS and NMOSD patients who were infected by COVID-19 in a short-term follow-up after the infection. Some re-infections have been observed in DMD treated patients. The rate of seropositivity after COVID-19 were diverse in different DMD users.

Since the vaccination process against COVID-19 routinely and globally started from June 2021 in Iran, we did not mention the vaccination and its effects on the patients in this observational study.

Conflict of interest

There is no conflict of interest declared by all of the authors.

Ethical considerations

This study was designed in the spirit of ethical principles with origin in the Declaration of Helsinki or equivalent, and consistent with Good Clinical Practices. All subjects gave informed consent to participate in the study.

Data Availability

All data generated or analyzed during this study are included in this published article.

All of the data were recorded in the document archive of Arya MS and Neurology clinic in Tehran, Iran. The data was

confidential and only used for research purpose without the patients' name and only by dedicated code.

REFERENCES

.1 Yan, R., et al., *Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2.* Science, 2020. **367**(6485): p. 1444-1448.

.2 Qin, C., et al., *Dysregulation of immune response in patients with COVID-19 in Wuhan.* China (February 17, 2020), 2.013.

.3 Sahraian, M.A., et al., *Diagnosis and management of Neuromyelitis Optica Spectrum Disorder (NMOSD) in Iran: A consensus guideline and recommendations.* Multiple sclerosis and related disorders, 2017. **18**: p. 144-151.

.4 Moss, B.P., et al., *Multiplesclerosis management during the COVID-19 pandemic.* Multiple Sclerosis Journal, 2020. **26**(10): p. 1163-1171.

.5 Fan, M., et al., *Risk of COVID-19 infection in MS and neuromyelitis optica spectrum disorders.* Neurology-Neuroimmunology Neuroinflammation, 2020.(5)7 .

.6 Etemadifar, M., et al., *Outcome of COVID-19 infection in multiple sclerosis patients receiving disease-modifying therapies.* Journal of Research in Medical Sciences: The Official Journal of Isfahan University of Medical Sciences, 2021. **26**.

.7 Bigaut, K., et al., *Impact of disease-modifying treatments of multiple sclerosis on anti–SARS-CoV-2 antibodies: an observational study.* Neurology-Neuroimmunology Neuroinflammation, 2021. **8**.(5).

.8 Ghayeghran, A., et al., *COVID-19 Infection and Seropositivityin Multiple Sclerosis Patients in Guilan in 2021.* Caspian Journal of Neurological Sciences, 2023. **9**(1): p. 39-49.

.9 Wijnands, J.M.A., et al., *Disease-modifying drugs for multiple sclerosis and infection risk: a cohort study.* Journal of Neurology, Neurosurgery & Psychiatry, 2018. **89**(10): p. 1050-1056.

.10 Morales, R.P., M.R. Rivas, and F.B.J.N. HernJndez, *SARS-CoV-2 infection and seroprevalence in patients with multiple sclerosis.* 2021. **36**(9): p. 698-703.

.11 Goshayeshi, L., et al., *Demographic and clinical characteristics of severe Covid-19 infections: a cross-sectional study from Mashhad University of Medical Sciences, Iran.* BMC infectious diseases, 2021. **21**(1): p. 1-8.

.12 Signorelli, C., T. Scognamiglio, and A. Odone, *COVID-19 in Italy: impact of containment measures and prevalence estimates of infection in the general population.* Acta Bio Medica: Atenei Parmensis, 2020. **91**(Suppl 3): p. 175.

.13 Sahraian, M.A., et al., *Evaluation of the rate of COVID-19 infection, hospitalization and death among Iranian patients with multiple sclerosis.* Multiple sclerosis and related disorders, 2020. **46**: p. 102472.

.14 Korsukewitz, C., et al., *Neurological immunotherapy in the era of COVID-19—looking for consensus in the literature.* Nature reviews Neurology, 2020. **16** :(9)p. 493-505.

.15 Loonstra, F.C., et al., *COVID-19 in multiple sclerosis: the Dutch experience.* Multiple Sclerosis Journal, 2020. **26**(10): p. 1256-1260.

.16 Sormani, M.P., *An Italian programme for COVID-19 infection in multiple sclerosis.* The Lancet Neurology, 2020. **19**(6): p. 481-482.

.17 Barzegar, M., et al., *Characteristics of COVID-19 disease in multiple sclerosis patients.* Multiple Sclerosis and Related Disorders, 2020. **45**: p. 102276.

.18 Louapre, C., et al., *Clinical characteristics and outcomes inpatients with coronavirus disease 2019 and multiple sclerosis.* JAMA neurology, 2020. **77**(9): p. 1079-1088.

.19 Laroni, A., et al., *COVID-19 in patients with multiple sclerosis undergoing disease-modifying treatments.* Multiple Sclerosis Journal, 2021. **27**(14 :(p. 2126-2136.

.20 Montero-Escribano, P., et al., *Anti-CD20 and COVID-19 in multiple sclerosis and related disorders: a case series of 60 patients from Madrid, Spain.* Multiple sclerosis and related disorders, 2020. **42**: p. 102185.

.21 Novi, G., et al., *COVID-19 in a MS patient treated with ocrelizumab: does immunosuppression have a protective role?* Multiple sclerosis and related disorders, 2020. **42**: p. 102120.

.22 Safavi, F., B. Nourbakhsh, and A.R. Azimi, *B-cell depleting therapies may affect susceptibility to acute respiratory illness among patients with multiple sclerosis during the early COVID-19 epidemic in Iran.* Multiple sclerosis and related disorders, 2020. **43**: p. 102195.

.23 Iaffaldano, P., et al., *Risk of Getting COVID-19 in People With Multiple Sclerosis: A Case-Control Study.* Neurology-Neuroimmunology Neuroinflammation, 2022. **9**.(2)

.24 Sahraian, M.A., et al., *Evaluation of COVID-19 infection in patients with Neuromyelitis optica spectrum disorder (NMOSD): A report from Iran.* Multiple Sclerosis and Related Disorders, 2020. **44**: p. 102245.