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Prevalence of coronavirus disease 2019 in patients with neuromyelitis optica in Isfahan, Iran, and a review on recent reports and literature

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Keywords
Neuromyelitis Optica; Autoimmune Disease; SARS-CoV-2; COVID-19

Abstract

Background: Despite many studies, it is still unclear how patients with neuromyelitis optica spectrum disorder (NMOSD) would respond to coronavirus disease 2019 (COVID-19). We conducted a research on prevalence of COVID-19 in patients with NMOSD in Isfahan, Iran. We have also reviewed the recent publications on this issue.

Methods: 149 patients with NMOSD who were under medications were monitored for confirmed cases of COVID-19. Prevalence of COVID-19 in addition to mean age, mean duration of disease, and mean age of onset of infected patients and uninfected patients were calculated via Microsoft Excel software.

Results: The prevalence of COVID-19 in studied patients with NMOSD was 5.37%. Mean age, mean duration of disease, and mean age of onset of eight patients (male to female ratio: 1:3) diagnosed with COVID-19 were 33.62 ± 5.20 years, 6.87 ± 6.05 years, and 26.75 ± 6.94 years, respectively, while they were 39.97 ± 11.37 years, 7.50 ± 3.91 years, and 32.46 ± 11.29 years for uninfected patients with NMOSD (n = 141). No significant association was observed between the type of medications and prevalence of COVID-19 (P > 0.05).

Conclusion: There is not a consensus in the literature on the prevalence of COVID-19 in patients with NMOSD and the effect of NMOSD medications on susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The prevalence of

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COVID-19 in our sample was 5.37%. The impact of the kind of NMOSD medication on the prevalence of COVID-19 in patients with NMOSD was found to be insignificant. Moreover, the infected patients were relatively younger, and their disease started earlier in comparison to uninfected patients.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or 2019 novel coronavirus (2019-nCoV), also known as coronavirus disease 2019 (COVID-19), emerged in China and spread to the rest of the world very quickly. Different studies have shown that patients with underlying diseases, including hypertension (HTN), cardiovascular diseases (CVDs), and autoimmune diseases (ADs), are at higher risk of hospitalization and death compared to the general population as a result of COVID-19 infection.[1,2]

Neuromyelitis optica spectrum disorder (NMOSD) is a rare, severe, and relapsing autoimmune disorder of the central nervous system (CNS) causing unilateral or bilateral acute optic neuritis (ON) and antibody-mediated demyelination of the cervical or thoracic spinal cord.[3-5] NMOSD was previously considered as a variant of multiple sclerosis (MS), but now it is defined as a separate disorder due to the different pathophysiology. MS and NMOSD are both ADs with shared inflammatory underlying causes; however, the discovery of anti-aquaporin 4 antibodies (anti-AQP4-Abs) led to differentiation of NMOSD from MS. It has been found that NMOSD is mediated by AQP4-Abs.[3,4,6] The prevalence of NMOSD is low, estimated at 0.86 per 100000 in Iranian population with a female to male ratio of 5:1.[7] No definite cure exists for NMOSD, but it is possible to prevent the attacks, decrease its severity, and restore neurological functions.[3]

Herein, we have investigated the prevalence of COVID-19 in 149 Iranian patients in Isfahan Province, Iran, diagnosed with NMOSD. Moreover, we have reviewed recent publications regarding the prevalence of COVID-19 in patients with NMOSD.

Materials and Methods

Study design and participants: We have conducted a descriptive and retrospective cohort study on 149 patients with NMOSD to evaluate the prevalence of COVID-19 and its determinants in these patients in Isfahan. This study was approved by the Ethical Committee of Isfahan University of Medical Sciences, and it was conformed to the ethical guidelines of the Deceleration of Helsinki. The participants were diagnosed with NMOSD by a specialist according to guidelines, and they were visited regularly at the MS clinic of Isfahan University of Medical Sciences. The medical information of patients with NMOSD was collected on a data depository and their demographic and clinical information, including age, duration of NMOSD, and age at onset, was obtained from data registries. On tele-follow-up sessions until November 1, 2020, the patients were asked about any symptoms related to COVID-19 and the duration of these symptoms. Moreover, they were asked about their SARS-CoV-2 ribonucleic acid (RNA) real-time reverse transcriptase–polymerase chain reaction (RT-PCR) test result if they got one. All COVID-19 cases among 149 patients with NMOSD until November 1, 2020 were included in this study. The patients with positive RT-PCR test results or evidence of COVID-19 in computed tomography (CT) scan were considered as confirmed cases of COVID-19.

Procedures: The patients were classified into different subgroups with respect to their COVID-19 history and their medications (i.e., rituximab and azathioprine). Male to female ratio, mean age, mean duration of NMOSD, and mean age at onset have been analyzed for COVID-19 and non-COVID-19 subgroups. The prevalence of COVID-19 in patients with NMOSD in total and in different medication subgroups has been evaluated. The prevalence of COVID-19 in different medication subgroups, including rituximab and azathioprine, was compared with each other. The percentage/ratio of first NMOSD presentation and the medications of patients with NMOSD infected with SARS-CoV-2 were calculated. The ratio of hospitalization of patients with NMOSD infected with SARS-CoV-2 was calculated. The whole population and patients with COVID-19 were evaluated for mortality.

Outcome: The primary outcome of this study is composed of the prevalence of COVID-19 in patients with NMOSD in total and the association between the type of medications and COVID-19 prevalence. Moreover, COVID-19 prevalence, mean age, mean duration of NMOSD, and mean age at onset for COVID-19 and non-COVID-19 subgroups have been calculated. First, NMOSD presentation of the patients with COVID-19 was also stated. The data that support the findings of this study are

available from the corresponding author upon reasonable request.

The prevalence of COVID-19 in patients with NMOSD has been calculated. The association of medications and COVID-19 prevalence has been evaluated via Fisher's exact test. All statistical analyses and calculations of mean age, mean duration of NMOSD, and mean age at onset were carried out via Microsoft Excel software. The significance for all statistical analyses was defined as $P < 0.050$.

Results

We identified 149 patients with NMOSD. 8 (5.37%) patients were reported to be confirmed cases of COVID-19 (2 men, 6 women, mean age: 33.62 ± 5.20 years, mean duration of the disease: 6.87 ± 6.05 years, and mean age of onset: 26.75 ± 6.94 years), with positive SARS-CoV-2 RNA RT-PCR test results. The mean age, mean duration of disease, and mean age of onset for the other 141 uninfected patients with NMOSD were 39.97 ± 11.37 years, 7.50 ± 3.91 years, and 32.46 ± 11.29 years, respectively (Table 1). Moreover, the male/female ratio in these 141 patients was 1:3.7 (men: 21.28%, women: 78.72%). Half of the infected patients with SARS-CoV-2 were taking rituximab and the other half were on azathioprine, while only one of the patients was using prednisolone in addition to azathioprine. 7 out of the 8 confirmed cases of COVID-19 presented lower extremities' weakness and/or paresthesia as their first NMOSD presentation, while one of them also presented blurred vision additionally. One patient only suffered from blurred vision as his first NMOSD presentation. Patients 6 and 7 (Table 2) were hospitalized due to their severe symptoms, while other patients were managed on an outpatient basis. No deaths have occurred among patients with COVID-19. We were not able to detect any significant association between the kind of medications and prevalence of COVID-19 in patients with NMOSD ($P > 0.05$).

Discussion

It is thought that production of autoantibodies against water channel protein (WCP) AQP4 in patients with NMOSD begins a sequential cascade of events, such as immunoglobulins G and M (IgG/IgM) deposition, complement-dependent astrocyte cytotoxicity, leucocyte infiltration, cytokine release, and blood-brain barrier (BBB) disruption, which ultimately leads to oligodendrocyte death, demyelination, and neuronal death. It is found that peripheral plasmablasts activated by interleukin 6 (IL-6) are the main source of AQP4 autoantibodies. These cells enter the CNS, following the disruptions (e.g., by infections or normal fenestrated endothelium in specific brain area) in the BBB. The periphery source of autoantibodies and the key role of IL-6 would make various treatment options possible.[4] Interfering with lymphocytes' proliferation (e.g., azathioprine) and their surface glycoproteins (e.g., rituximab), suppressing their function (e.g., mitoxantrone), and interfering with the effects of cytokines (e.g., tocilizumab), along with cytotoxic (e.g., cyclophosphamide) and anti-metabolic (e.g., methotrexate) drugs are among NMOSD treatment strategies.[3]

Due to the nature of ADs, these drugs would suppress the immune system in a specific or non-specific manner. Therefore, it is thought that these drugs can hinder the immune system's capabilities to encounter pathogens; hence, the rate of infectious diseases would probably be higher in these patients.[8] In this sense, some studies have shown a strong association between NMOSD and the existence of some pathogens [e.g., John Cunningham virus (JC virus),[9] Epstein-Barr virus (EBV),[10] mumps virus[11]].

Based on this idea, many neurologists would make this assumption that certain medications of NMOSD would increase the risk of COVID-19 infection due to their immunosuppressive nature. In a study by Rezaei et al., 60% of the American and Canadian neurologists were unsure about the safety of the NMOSD treatments during the pandemic.

Table 1. Information of infected and uninfected patients with neuromyelitis optica spectrum disorder (NMOSD)

	Infected patients with NMOSD	Uninfected patients with NMOSD
Age (year) (mean ± SD)	33.62 ± 5.20	39.97 ± 11.37
Duration (year) (mean ± SD)	6.87 ± 6.05	7.50 ± 3.91
Age of onset (year) (mean ± SD)	26.75 ± 6.94	32.46 ± 11.29
Male/female ratio	1:3	1:3.7

NMOSD: Neuromyelitis optica spectrum disorder; SD: Standard deviation

Table 2. Coronavirus disease 2019 (COVID-19) cases

#	Age (year)	Sex	Duration (year)	First NMOSD symptoms	Medications	COVID-19 symptoms
1	27	Male	6	Blurred vision	Azathioprine	Cough, sweating
2	34	Female	3	Lower extremities' weakness and paresthesia	Azathioprine, prednisolone	Myalgia, fever, chill, anosmia
3	43	Male	2	Lower extremities' weakness and paresthesia	Rituximab	Myalgia, fever, weakness, vomiting
4	31	Female	4	Lower extremities' weakness and paresthesia	Azathioprine	Myalgia, fever, headache
5	37	Female	17	Lower extremities' paresthesia	Azathioprine	Myalgia, fever, chill
6	31	Female	3	Lower extremities' weakness	Rituximab	Dyspnea, fever, headache
7	29	Female	4	Blurred vision, lower extremities' weakness	Rituximab	Dyspnea, fever, myalgia
8	37	Female	16	Lower extremities' weakness and paresthesia	Rituximab	Vertigo, fever, anosmia

NMOSD: Neuromyelitis optica spectrum disorder; COVID-19: Coronavirus disease 2019

Intravenous Ig (IVIg) and tocilizumab were thought to be safer drugs than other NMOSD treatments in most neurologists' opinion (who believed in the safety of certain NMOSD treatments). On the other hand, steroids, inebilizumab, methotrexate, and rituximab are thought be to safe by less than 15% of neurologists.[12] In another study on the management protocols of NMOSD during the COVID-19 pandemic in Latin America, half of the physicians considered azathioprine as a safe treatment, while mycophenolate mofetil (MMF), and rituximab were considered to be not safe for initiation of NMOSD treatment during the pandemic for uninfected patients. Most physicians decided to suspend oral steroids, MMF, and azathioprine in patients with grade 3 lymphopenia. About 32% of physicians would continue rituximab with regular infusions in patients with highly active NMOSD with an appropriate CD19/CD20 count, while about 24% of them would continue the treatment regardless of CD19/CD20 count. In the case of eculizumab and tocilizumab, about 14% of physicians stated that they would stay with this treatment. In the scenario of infected patients, half of the physicians believe that MMF, rituximab, eculizumab, and tocilizumab should be discontinued. It is generally believed that the treatment should be stopped in patients with lymphopenia, who are under azathioprine, MMF, oral steroids, and rituximab. In the failure of the treatment, rituximab, eculizumab, and tocilizumab are considered to be the alternatives to these drugs, respectively.[13] Abboud et al. have discussed that more selective immunomodulating medications are safer options during the pandemic. Rituximab and inebilizumab cause selective depletion of B-cells and therefore, they are considered to be safer than non-selective immunosuppressive medications such as azathioprine and MMF. Moreover, it has been stated that eculizumab and satralizumab which inhibit complement system and IL-6 are thought to be even safer.[14] Further suggestions on the drug choices for NMOSD - considering the mechanism of actions of the drugs - during the pandemic are discussed in the reference.[15] In conclusion, there is not a consensus on how to manage patients with NMOSD during the COVID-19 pandemic. Apart from the drug choices, mechanism of action, route of administration, the effect on the immune system in terms of responsiveness to the future COVID-19 vaccine, and medication options for relapses are some factors that are needed to be considered in the management of NMOSD during the pandemic.[14]

During the past several months, some reports have been released concerning the prevalence and quality of COVID-19 infection in patients with NMOSD, yet there is no strong consensus on this matter. Moreover, these studies may illuminate the darkness of how medications impact the susceptibility to coronavirus infection. In an evaluation of 28 patients (NMOSD: 17 and control: 11), 3 of them (NMOSD: 2 and control: 1) presented with flu-like symptoms without documented confirmation of COVID-19. It has been revealed that there was no significant difference between the prevalence of flu-like symptoms between NMOSD and the control groups ($P > 0.05$). It worth to note that all patients with NMOSD were under

preventive immune therapy (rituximab: 88%, azathioprine: 6%, and tocilizumab: 6%), while 64% of the control group were taking such treatments (ocrelizumab: 36%, alemtuzumab: 9%, glatiramer acetate: 9%, and natalizumab: 9%).[16] Fan et al. have conducted a survey on 3060 Chinese patients diagnosed with NMOSD from whom 2129 were receiving disease-modifying drugs (DMDs). Interestingly, only two patients were diagnosed with COVID-19, and an increased risk of COVID-19 was not observed in patients with NMOSD. These researchers further declared that through non-official communications with centers in Korea, Japan, and Singapore, they notified that similarly, no increased risk of coronavirus infection in patients with NMOSD was observed. The low prevalence of COVID-19 in the patients with NMOSD might be due to minimized exposure of these patients to viral sources in the following of tight preventive protocols. Moreover, some patients, especially those with mild and minimal symptoms, may have been missed due to the methods of data collecting (i.e., self-reporting and questionnaire).[17] In a report from Iran by Sahraian et al., 3.8% of patients (among 130 NMOSD cases) were infected with the SARS-CoV-2. 72.3% of these patients were under rituximab, and the prevalence of COVID-19 among them was 5.1%, while the prevalence of COVID-19 was 0% in patients using other drugs. The age of patients was noted to be unimportant in the prevalence of COVID-19. They have indicated that no significant difference was observed in the prevalence of COVID-19 in patients with NMOSD taking rituximab in comparison with the normal population. They have hypothesized that rituximab may increase the severity of the COVID-19 rather than the prevalence of the disease.[18] In another study conducted in Iran, six patients were detected with COVID-19 in a group of 157 patients with NMOSD. About half of the patients were treated with rituximab, and less than 50% of them were under azathioprine treatment. Two patients with COVID-19 who were using rituximab were admitted to the hospital.[19] A French study showed a prevalence of 6.7% (highly suspected and confirmed COVID-19 cases) among 75 patients with NMOSD. Among the COVID-19 cases, two patients were treated with azathioprine, two patients were under anti-CD20 therapy, and one patient was taking MMF.[20] The same results were reported about the patients with MS, treating with similar medications,[21] while some other reports have noted the opposite.[22] Besides, in another study conducted by Etemadifar et al. on 25436 patients with MS, it turned out that the risk of COVID-19 was higher in rituximab-treated patients.[23] Although previous reports have indicated not statistically significant higher prevalence of COVID-19 in patients with NMOSD, other reports have stated the opposite. In a study on 409 patients in 9 centers in Chile, which about 1% of patients (5 patients) had NMOSD, 98% of them were diagnosed with MS, and 88% of all patients were receiving immunomodulatory drugs; cumulatively, 18 patients were detected with COVID-19. 4 out of the 18 patients had a history of NMOSD, which leads to the conclusion that 80% of the patients with NMOSD in the population were infected with COVID-19, while this rate was about 3.5% in the population of patients with MS.[24] However, the high prevalence of COVID-19 in patients with NMOSD in comparison with patients with MS may be due to the composition of the population and lower number of patients with NMOSD in comparison with patients with MS. It can be said that most studies have consensus on the insignificance of a relation between the history of NMOSD and high COVID-19 prevalence in comparison with the normal/control population. It can also be concluded that although rituximab (as an anti-CD20 agent) is a suspect for increasing the risk or severity of the COVID-19, more trials are needed for a decisive conclusion.

In this report, the prevalence of COVID-19 in 149 patients with NMOSD was 5.37%. The mean age, mean duration of the disease, and mean age of onset of NMOSD in patients infected with SARS-CoV-2 were slightly lesser than that of uninfected patients with NMOSD (33.62 ± 5.20 years, 6.87 ± 6.05 years, and 26.75 ± 6.94 years, respectively, for infected patients and 39.63 ± 11.21, 7.47 ± 4.02, and 32.15 ± 11.16, respectively, for uninfected patients). Moreover, the effect of medications on the prevalence of COVID-19 was found to be insignificant. However, our results may have been affected by the small size of our sample, and more investigations are needed.

Although suppression of the immune system following the NMOSD medications and subsequent COVID-19 infection is concerning, some researchers have hypothesized that some NMOSD medications may alter the immune system in a way that certain destructive reaction including cytokine storm in a coronavirus infection

will not occur severely. In this sense, Creed et al. have reported a mild course of COVID-19 in a patient with a history of NMOSD who was taking azathioprine and rituximab and was presenting B-cell depletion.[8] The same observation has been stated in the patients with long-term use of corticosteroids.[8] Similarly, Mantero et al. have reported a 44-year-old woman - diagnosed with NMOSD and treated with tocilizumab - presenting mild COVID-19 symptoms. This patient was treated with an anti-CD20 monoclonal antibody, and B-cell depletion was observed seven months before the infection. IL-6 is considered an important factor in cytokine storm, and a meta-analysis has shown that the elevated levels of IL-6 are related to a more severe course of COVID-19. The authors have hypothesized that the use of anti-IL-6 antibodies in this patient may hinder the immune system from developing a cytokine storm via blocking the function of IL-6, which ultimately would lead to a lower risk of severe complications in the course of COVID-19.[25,26] Currently, tocilizumab is under phase 2 clinical trials for this purpose.[27]

In addition, it is known that AQPs are involved in the pathophysiological process of coronavirus infection. As the result of cytokine storm, a set of cytokines including interferon gamma (IFN-γ), IL-12, IL-1ß, IL-6, and tumor necrosis factor alpha (TNF-α) affect AQPs leading to alveolar edema. It has been hypothesized that modulation of AQPs may affect the course of COVID-19.[28] Since AQPs are damaged in NMOSD via auto-antibodies, we further suggest that the condition of AQPs in patients with NMOSD may lead to a reduction in the complications of coronavirus infections.

It is also worth noting that despite the common perspective among physicians, patients treated with ocrelizumab and rituximab possess depletion in $CD20^+$ cells, while B-cells are preserved in secondary lymphoid organs which probably make the patients capable of developing initial immune responses against infections. Moreover, B-cells and Igs are not necessarily needed to encounter viral infections, and T-cell-mediated immune response (which is affected minimally by anti-CD20 medications) may be sufficient for this purpose.[20,21,29]

Some other researchers are concerned about the impact of NMOSD treatments on future COVID-19 vaccine. It has been reported that anti-CD20 medications prevented the development of antibodies against coronavirus.[20] Moreover, various studies have demonstrated that usage of anti-CD20 medications, including ocrelizumab and rituximab, would reduce the titer of antibodies and seroconversion rate following the vaccination for different pathogens in comparison with the normal population.[29] The impairment of humoral immune system as a result of anti-CD20 therapy may weaken the patient immune systems to develop a proper immune response to coronaviruses following the vaccination.[30] As a possible solution, it has been suggested that through adjusting and extending the dosing intervals of these drugs, specific B-cell subsets can repopulate to facilitate vaccination and generate immune response properly; at the same time, the level of the pathogenic B-cells is maintained low enough to prevent relapses.[29]

Conclusion

The relation between NMOSD pathophysiology and medications with the morbidity and mortality subsequent to SARS-CoV-2 is still unclear, and there is no consensus between the data collected from different studies on the prevalence of COVID-19 in patients with NMOSD, as we have reviewed the recent publications. We found that the prevalence of COVID-19 in 149 patients with NMOSD was 5.37%, in Isfahan Province in Iran, which is similar to some other reports. Moreover, it is found that the mean age, mean duration of the disease, and mean age of onset of patients with NMOSD infected with SARS-CoV-2 were slightly lesser than that of uninfected patients with NMOSD.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

This study is approved by the ethical committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1399.159).

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