Caspian Journal of Neurological Sciences
"Caspian J Neurol Sci"
Journal Homepage: http://cjns.gums.ac.ir

Research Paper: The Impact of COVID-19 Pandemic on Neuromyelitis Optica Disorder Patients, After one Year

Fereshteh Ashtari[1], **Roshanak Mehdipour**[2*]

1. Department of Neurology, Isfahan Neuroscience Research Center, Isfahan University of Medical Science, Isfahan, Iran.
2. Isfahan Neuroscience Research Center, Isfahan University of Medical Science, Isfahan, Iran.

Use your device to scan and read the article online

Citation Ashtari F, Mehdipour R. The Impact of COVID-19 Pandemic on Neuromyelitis Optica Disorder Patients, After one Year. Caspian J Neurol Sci. 2022; 8(2):117-123. https://doi.org/10.32598/CJNS.8.29.8

Running Title Pandemic and NMOSD

https://doi.org/10.32598/CJNS.8.29.8

Article info:
Received: 11 Dec 2021
First Revision: 25 Dec 2021
Accepted: 26 Feb 2022
Published: 01 April 2022

ABSTRACT

Background: Coronavirus Disease 2019 (COVID-19) recently created a pandemic with high mortality. People with underlying diseases are prone to severe infection. The nature of NMOSD disease and its treatment by immunosuppressants predisposes patients to infection.

Objectives: This study aimed to evaluate the effect of the COVID-19 pandemic on the clinical course of NMOSD and the characteristics of COVID-19 infection in NMOSD patients.

Materials & Methods: This descriptive study was performed in Isfahan City, Iran, Iran, from March 2020 to March 2021. We considered relapses during the epidemic and the year before and the presentation of COVID-19 infection in the patients of NMOSD Clinic of Isfahan Kashani hospital.

Results: The study included 120 patients. Their Mean±SD age was 36.37±9.69 years, and the mean duration of disease was 8.49±5.35 years. Overall, they experienced 36 relapses during the year before the epidemic (ARR:0.3) and 29 during the COVID-19 epidemic (ARR:0.24). The maintenance therapy of NMOSD was rituximab in 96 cases, azathioprine in 22, and methotrexate in 2 ones. 35 patients infected by COVID-19 (based on RT-PCR test). 6 were admitted to the hospital, and two patients received ICU care. There was one death due to respiratory failure.

Conclusion: Despite the suppression of the immune system, neither incidence nor the number of severe complications of COVID-19 infection was high. Therefore, regarding the disabling nature of NMOSD and the prolonged epidemic period, it may be reasonable to continue the routine treatment of these patients and train them to stick to health protection instructions.

Keywords: SARS-CoV-2, Pandemics, Neuromyelitis Optica, Demyelinating autoimmune diseases, CNS

*** Corresponding Author:**
Roshanak Mehdipour
Address: *Isfahan Neuroscience Research Center, Isfahan University of Medical Science, Isfahan, Iran.*
Tel: *+98 (913) 3176637,* ***Fax:*** *+98 (31) 37755041*
E-mail: *roshym13@gmail.com*

Caspian Journal of Neurological Sciences

Highlights

- The autoimmune nature of the NMOSD disease leads to the use of immunosuppressive therapy, like anti-CD20 drugs, in its treatment. Using immunosuppressive drugs potentially makes patients more susceptible to infections.

- This survey showed that despite immunosuppressive therapy in NMOSD patients, the cases infected by COVID-19 experienced no severe complications or atypical presentation.

- The NMOSD annual relapse rate did not increase during the COVID-19 pandemic.

- We suggested that immunosuppressant therapy be continued routinely in NMOSD patients during the COVID-19 epidemic. Still, any expansion of dosing interval should be according to the clinical and paraclinical findings of patients under the neurologist's recommendation.

Introduction

A new coronavirus was introduced to the world in December 2019, causing severe pneumonia. It was initially called SARS-CoV-2 [1]. The outbreak began in China and spread to many other countries within a few weeks. On March 11, 2020, the World Health Organization (WHO) announced that Coronavirus Disease 2019 (COVID-19) could be identified as a pandemic [2].

In Iran, the first death due to COVID-19 was announced in late February 2020 [3]. Iran is a western Asian region with a high prevalence of COVID-19. The incidence of this disease is estimated at about 4.6 per 1000000 individuals [4, 5].

In Isfahan, the largest city in the central region of Iran, both the prevalence and incidence rate of COVID-19 disease are high. Isfahan almost ranks as the 2nd or 3rd city of high prevalence COVID-19 patients [5, 6].

Furthermore, COVID-19 infection can be severe and fatal in healthy people of any age. Critical infection mainly affects adults with advanced age or underlying medical comorbidities (such as hypertension, diabetes, coronary artery disease, and cancers and patients under immunosuppressive treatment), and deaths occur predominantly in this group [7].

Neuromyelitis Optica Spectrum Disorder (NMOSD) is an autoimmune astrocytopathy of the Central Nervous System (CNS), mainly involving the spinal cord and optic nerves [8]. Since disability in NMOSD patients is relapse-dependent, Immunosuppressive long-term therapy is widely used for maintenance therapy, even after the first attack [9, 10].

Because severe disabling relapse may occur after long-time remission; thus, continuous and regular use of immunosuppressive drugs such as rituximab, azathioprine, and methotrexate are critical [10].

Rituximab, a chimerical Monoclonal Antibody (mAb) that targets CD20 protein on B-lymphocyte, is among the most frequent interventions in NMOSD [11, 12].

The Immune response to the COVID-19 probably consists of two parts; initially, the secretion of inflammatory cytokines, such as TNF α, increases, followed by a decrease in the number of lymphocyte subset B cells, T and natural killer cells [13]. Therefore, using anti-CD20 drugs, such as rituximab, potentially has a significant risk [14].

Although there is inadequate evidence regarding the nature of NMOSD and the need for long-term use of immunosuppressive drugs, these patients are more prone to develop a severe infection [15].

Therefore, continuing treatment during the outbreak of COVID-19 remains a challenge, and it can be a conflict area for neurologists to decide whether to continue routine immunosuppressive therapy.

This study investigated the prevalence of COVID-19 infection in patients registered in the NMOSD Clinic as the main referral center in Isfahan. We reported cases of NMOSD who were infected with COVID-19, considering the severity of the infection. The relapses of NMOSD and immunosuppressive treatment status were also noticed during the COVID-19 epidemic. We have considered all of the above during one year since the epidemic's beginning in our country, which has rarely been done in other studies in our geographical area.

Materials and Methods

An observational and descriptive study was performed on 120 patients at the NMOSD clinic of Kashani hospital, Isfahan City, Iran. The inclusion criteria were all the patients with definite NMOSD diagnosis according to the Wingerchuk diagnostic criteria (2015 revision) [16]. who had the electronic record in our database. Moreover, 4, 8, and 12 months after the outbreak declaration in Iran, we telephoned all patients (about the COVID-19 epidemic conditions and social distance laws). The study was explained to the patients. Data collection and filling questionnaires were done if they agreed to participate. All examined patients declared informed consent. They knew it was a voluntary task and would not impact their treatment plan. They were assured that all the information would be kept completely confidential. Any patient who did not answer the phone or did not answer the questions was excluded.

Primary data of participants were collected from resources such as electronic medical records, our clinic's comprehensive NMOSD database, and hospital admission records. Based on the information needed for this study, every patient was interviewed by a phone call with the same neurologist three times. Repeating the calls was just for keeping in touch with patients and updating the information rather than comparing the results.

Demographic characteristics such as age, age at disease onset, gender, last relapse, annual relapse rate, current Disease-Modifying Treatment (DMT), and any changes in treatment protocol during the COVID-19 epidemic period were recorded for each patient.

Furthermore, identifying the patients who suffered from COVID-19 was the second goal. We asked about the type and severity of symptoms and hospitalization in the patients infected with COVID-19.

The sampling method included all available populations who met the inclusion criteria (all documented NMOSD patients in our clinic database).

A professional statistical analyzer performed all the statistical tests (i.e., mean, proportion, percentage, and t-test) using SPSS.

Results

We initially called 130 NMOSD patients; however, 10 cases withdrew from the survey during follow-up. Thus, 96 (80%) females and 24 males (20%) were included finally. The Mean±SD age of participants was 36.37±9.69 years. Besides, the Mean±SD disease duration was 8.49±5.35years (ranging from 1 to 25). Among all the patients, 41 cases were seropositive for anti-aquaporin 4 antibody (34.16 % of all) (Table 1). Overall, 36 relapses were reported from 34 patients during one year before the epidemic, and the Annual Relapse Rate (ARR) was 0.30.

Since the beginning of the COVID-19 epidemic in our country, Iran (in late February 2020), a total of 29 relapses have occurred during one year (attacks from 1st of March 2020 concluded). These 29 relapses consist of 8 optic neuritis, 5 brain stem-related symptoms, and 16 myelitis. All relapses were treated routinely by Intravenous corticosteroid, with good response. Three patients needed plasmapheresis. If we estimate ARR regarding this period, it will be about 0.24 (Table 2).

A total of 96 patients out of 120 patients received rituximab as maintenance therapy (80%). Since the onset of the COVID-19 epidemic in Iran, 32 patients have received treatment with a Mean±SD delay of 1.95±1.16 months. They postponed their treatment because they were afraid of complications in the pandemic, but their physician confirmed the CD19 and CD20 levels and rechecked it monthly. The most delay and irregularities occurred during the first 6 months from the epidemic's beginning and then returned to a routine schedule. Despite the delay in receiving immunosuppressants, the relapse rate did not increase during the epidemic.

Furthermore, 22 patients used azathioprine as maintenance therapy. Two patients declared they continued treatment, receiving just half the routine dose from the epidemic's beginning for about three to four months, and then returned to the total dose.

The last 2 patients received methotrexate as their routine treatment, and none of them reported any change of drug use in the period of the COVID-19 epidemic.

COVID-19 evaluation

In total, 42 patients reported close contact with COVID-19 cases among their close relatives, but 20 of them developed symptomatic COVID-19 infection. Four other persons had only a rising positive RT-PCR test for COVID-19 without experiencing any typical sign of infection.

Moreover, 35 patients were infected with COVID-19 (definite cases with positive RT-PCR test and symp-

Table 1. The demographics and disease information of studied NMOSD patients (N: 120)

Variables	Mean±SD
Age, y	36.37±9.69
Sex: F/M	96/24
Disease duration (1-25 year)	8.49±5.35
NMO ab	Positive: 41 Negative: 79
Presenting sign	Optic Neuritis: 50 (41.66) Myelitis: 51(42.5) Brainstem syndrome: 19(15.83)
Maintenance therapy	Rituximab:96 Azathioprine:22 Methotrexate:2
Number of COVID-19 infections in relatives	42
Number of COVID-19 infection	35

CJNS

tomatic infection). So the prevalence of symptomatic COVID-19 infection within NMOSD patients is about 29.16%. Six were admitted to the hospital, and two patients received ICU care. Their Mean±SD age was 36.02±10.11 years, and the Mean±SD disease duration was 6.82±4.62 years. 29 patients received rituximab as maintenance therapy (Table 3). The prevalence of COVID-19 was 30.20 % in patients taking rituximab.

One death was due to respiratory failure in a woman with severe cervical LETM and permanent paraplegia. She was 42 years old and suffered NMOSD from 5 years ago. She had a history of about 4 relapses, a total of which 3 were transverse myelitis and led to permanent weakness and paraplegia. She received the last dose of rituximab one month before getting infected by COVID-19.

Five patients experienced gastrointestinal symptoms as the presentations of COVID-19, and 4 others reported GI problems during the infection period. 16 cases lost their sense of smell and taste during the infection period (in 3 persons, it was the presenting symptom). Fever occurred in 28 patients, and it continued at least for about 24 hours; however, just 4 cases reported high fever more than 39 degrees centigrade. The presenting signs were respiratory symptoms in 13 patients, flu-like symptoms (malaise, myalgia, fatigue) in 6, common cold in 2, and finally fever and chill in 4 cases. One patient reported that she encountered a headache prior to any other signs and experienced vertigo and nausea.

Discussion

The primary purpose of this study was to report the effect of the COVID-19 pandemic on disease course and treatment of NMOSD patients in one year. The second aim was to report COVID-19 infection characteristics and prognosis among NMOSD patients.

The main confounder variable was the odds of some asymptomatic or mild cases that might have been missed because the RT-PCR test was not done.

Despite immunosuppressive therapy, COVID-19 infection was usually mild to moderate in our patients. This is similar to an uncomplicated case of COVID-19 infection with underlying NMOSD receiving rituximab, reported by Marina Creed. However, considerable concern

Table 2. Relapse characteristics

Number of Patients	Relapses in the Past Year	Relapses During COVID-19 Epidemic	ARR in the Preceding Year	Estimated ARR in COVID-19 Epidemic Period
120	36	29	0.30	0.24

CJNS

Table 3. The COVID-19 patients' characteristics (N: 35)

Variables	Mean±SD/ No.(%)
Age, y	36.02±10.11 years
Gender: F/M	96 / 24
Disease duration	6.82±4.62
Hospital Admission	6
ICU Care	2
Maintenance therapy	Rituximab:29 Azathioprine:6
Number of COVID-19 infection in relatives	20
Total Death	1
Presenting Sign	Respiratory Symptoms: 13(37.14) Flu-like: 6(17.14) Gastrointestinal: 5(14.28) Fever and Chills: 4(11.42) Loss of Smell and Taste : 3(8.57) Common Cold : 2(5.71) Headache: 1(2.85) Vertigo: 1(2.85)

CJNS

remains about the potential effect of B- cell depletion therapy on the worsening of COVID-19 infection [17]. The fatality rate in our study was 0.02%. In comparison, in the normal Iranian population, it is reported about 4.3 to 5%, it is because our study population was younger than the mean age of the normal population. Younger patients experienced milder symptoms, which could be the reason for nonsevere infection in our sample. The common signs and symptoms of COVID-19 infection in NMOSD patients are almost similar to that of the normal population [18].

Finally, despite irregularities and delays in receiving immunosuppressive drugs, the relapse rate did not increase significantly due to short-term delays or a short study period. However, as the duration of the epidemic becomes longer, further delays in treatment can increase the risk of recurrence and permanent disability. As Zrzavy et al. concluded, we propose to continue routine treatment with immunomodulatory drugs without many changes [19]. But as Langer-Gould suggested for MS patients, to avoid severe COVID-19 infection, it is recommended to expand the interval between doses of rituximab or use the lowest effective dose in some NMOSD cases CD19/CD20 level and clinical situation if they are under closed observation [20].

Sahraian et al. reported some cases of COVID-19 among NMOSD patients from the same country in June 2020. They concluded that rituximab did not increase the incidence rate but may worsen the severity of COVID-19 infection. In our study, 29 out of 35 patients with COVID-19 received rituximab, one of which expired. Along with their results, none of the COVID-19 patients had worsening neurological symptoms [21].

Therefore, more prospective and multicenteric studies with extended follow-up periods are needed to decide how to continue treatment with immunomodulatory drugs during the COVID-19 epidemic. It is assumed that there will be fewer challenges with whole population vaccination against COVID-19. Still, unfortunately,

in many developing countries such as Iran, the best vaccination coverage would not be achieved until the end of 2021. We tried to show what NMOSD patients experienced during one year of the COVID-19 epidemic. The follow-up period is more extended than other similar studies. A significant limitation is the small sample size, which was due to the rarity of this disease and short duration of the COVID-19 epidemic, but regarding the disabling nature of this disease and the need to continue treatment, collecting these results helps make better decisions about the treatment process during the pandemic.

Conclusion

Our results showed that neither relapse rate nor the risk of COVID-19 infection increased in our patients within a year of pandemic.

Although the risk of severe COVID-19 infection is thought to be high in patients treated with B-cell-lowering drugs, most patients in our study presented no severe COVID-19 complications. It is suggested to continue maintenance therapy for NMOSD patients routinely during the epidemic period. It can be postponed for a short while regarding CD19 and CD20 levels and the clinical course of patients. They should be encouraged to stick to protective measures and health protocols more and more and keep in touch with their neurologist.

Ethical Considerations

Compliance with ethical guidelines

All the aspects of human research had been considered by the research team, and study procedures complied with the ethical guidelines of the Declaration of Helsinki 2013. This study has been approved by the Ethics Committee of Isfahan Medical University (Code: 1399379).

Funding

This study was supported by the Isfahan University of Medical Sciences and Isfahan Neuroscience Research Center.

Authors contributions

Conceptualization, writing – review & editing, funding acquisition, resources, & supervision : Fereshteh Ashtari; Methodology, investigation, data curation, writing – original draft: Roshanak Mehdipour.

Conflict of interest

The authors declared no conflicts of interest.

References

[1] Wang L, Wang Y, Ye D, Liu Q. A review of the 2019 Novel Coronavirus (COVID-19) based on current evidence. Int J Antimicrob Agents. 2020; 55(6):105948. [DOI:10.1016/j.ijantimicag.2020.105948] [PMID] [PMCID] .

[2] Johns Hopkins CSSE Wc-ngcO, https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/d, 2020. bfbeeAJ.

[3] Takian A, Raoofi A, Kazempour-Ardebili S. COVID-19 battle during the toughest sanctions against Iran. Lancet. 2020; 395(10229):1035-6. [DOI:10.1016/S0140-6736(20)30668-1]

[4] Sahraiana MA, Gheinib MR, Rezaeimanesha N, Ghajarzadeh M, Naser Moghadasi A. Knowledge regarding COVID-19 pandemic in patients with multiple sclerosis (MS): A report from Iran. Mult Scler Relat Disord. 2020; 42:102193. [PMID] [PMCID]

[5] Sami R, Soltaninejad F, Amra B, Naderi Z, Haghjooy Javanmard S, Iraj B, et al. A one-year hospital-based prospective COVID-19 open-cohort in the Eastern Mediterranean region: The Khorshid COVID Cohort (KCC) study. PLoS One. 2020; 15(11):e0241537. [DOI:10.1371/journal.pone.024153]

[6] Janani M, Beheshti-Nia F, Ahmadi H, Khazeni A, Yadegarafar G. Epidemiological features and hotspot of COVID-19 in Isfahan Province of Iran: Results of a cohort study [Internet]. 2021 [Updated 2021 July 14]. Availble from: https://assets.researchsquare.com/files/rs-39464/v1/f62fcfd9-aa47-45c3-9912-456104e58bbb.pdf?c=1631845676

[7] Zhang L, Hou J, Ma FZ, Li J, Xue S, Xu ZG. The common risk factors for progression and mortality in COVID-19 patients: A meta-analysis. Arch Virol. 2021; 166(8):2071-87. [DOI:10.1007/s00705-021-05012-2] [PMID] [PMCID]

[8] Lana-Peixoto MA, Talim N. Neuromyelitis optica spectrum disorder and Anti-MOG syndromes. Biomedicines. 2019; 7(2):42. [DOI:10.3390/biomedicines7020042] [PMID] [PMCID]

[9] Papadopoulos MC, Bennett JL, Verkman AS. Treatment of neuromyelitis optica: State-of-the-art and emerging therapies. Nat Rev Neurol. 2014; 10(9):493-506. [DOI:10.1038/nrneurol.2014.141] [PMID] [PMCID]

[10] Kleiter I, Gold R. Present and future therapies in neuromyelitis optica spectrum disorders. Neurotherapeutics. 2016; 13(1):70-83. [DOI:10.1007/s13311-015-0400-8] [PMID] [PMCID]

[11] Collongues N, de Seze J. An update on the evidence for the efficacy and safety of rituximab in the management of neuromyelitis optica. Ther Adv Neurol Disord. 2016; 9(3):180-8. [DOI:10.1177/1756285616632653] [PMID] [PMCID]

[12] Memon AB, Javed A, Caon C, Srivastawa S, Bao F, Bernitsas E, et al. Long-term safety of rituximab induced peripheral B-cell depletion in autoimmune neurological diseases. PLoS One. 2018; 13(1):e0190425. [PMID] [PMCID]

[13] Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan , China. Clin Infect Dis. 2020; 71(15):762-8. [PMID]

[14] Mansoor S, Kelly S, Murphy K, Waters A, Siddiqui NS. COVID-19 pandemic and the risk of infection in multiple sclerosis patients on disease modifying therapies: "What the bleep do we know?". Egypt J Neurol Psychiatr Neurosurg. 2020; 56(1):44. [PMID] [PMCID]

[15] Fan M, Qiu W, Bu B, Xu Y, Yang H, Huang D, et al. Risk of COVID-19 infection in MS and neuromyelitis optica spectrum disorders. Neurol Neuroimmunol Neuroinflamm. 2020; 7(5):e787. [DOI:10.1212/NXI.0000000000000787] [PMID] [PMCID]

[16] Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015; 85(2):177-89. [DOI:10.1212/WNL.0000000000001729] [PMID] [PMCID]

[17] Creed MA, Ballesteros E, Jr LJG, Imitola J. Mild COVID-19 infection despite chronic B cell depletion in a patient with aquaporin-4-positive neuromyelitis optica spectrum disorder. Mult Scler Relat Disord. 2020; 44:102199. [PMID] [PMCID]

[18] Zaferani Arani H, Dehghan Manshadi G, Atashi HA, Rezaei Nejad A, Ghorani SM, Abolghasemi S, et al. Understanding the clinical and demographic characteristics of second coronavirus spike in 192 patients in Tehran, Iran: A retrospective study. PLoS One. 2021; 16(3):e0246314. [DOI:10.1371/journal.pone.0246314] [PMID]

[19] Zrzavy T, Wimmer I, Rommer PS, Berger T. Immunology of COVID-19 and disease-modifying therapies: The good, the bad and the unknown. Eur J Neurol. 2021; 28(10):3503-16. [DOI:10.1111/ene.14578] [PMID] [PMCID]

[20] Langer-Gould A, Smith JB, Li BH; KPSC MS Specialist Group. Multiple sclerosis, rituximab, and COVID-19. Ann Clin Transl Neurol. 2021; 8(4):938-43. [DOI:10.1002/acn3.51342] [PMID] [PMCID]

[21] Sahraian MA, Azimi A, Navardi S, Rezaeimanesh N, Naser Moghadasi A. Evaluation of COVID-19 infection in patients with Neuromyelitis optica spectrum disorder (NMOSD): A report from Iran. Mult Scler Relat Disord. 2020; 44:102245. [PMID]