

Myasthenia gravis and coronavirus disease 2019: A report from Iran

Received: 12 Mar. 2020
Accepted: 10 May 2021

Masoud Etemadifar¹, Mahsa Akafzadeh-Savari², Mehri Salari³, Amirhossein Akhavan Sigari², Sara Ebrahimi-Pelarti², Nahad Sedaghat², Koorosh Etemad⁴

¹ Department of Neurosurgery, Al-Zahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran

² Al-Zahra Research Institute, Al-Zahra University Hospital, Isfahan University of Medical Sciences, Isfahan, Iran

³ Department of Neurology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

⁴ Department of Epidemiology, School of Public Health and Safety, Shahid Beheshti University of Medical sciences, Tehran, Iran

Keywords

Myasthenia Gravis; COVID-19; Thymectomy; Neurology

Abstract

Background: Coronavirus disease 2019 (COVID-19) is spreading rapidly and has affected millions of people worldwide. Comorbid diseases have complicated the course of infection and increased mortality. Myasthenia gravis (MG) affects the neuromuscular junctions (NMJs) and can compromise respiratory muscle action, leading to worse clinical outcomes in individuals infected with the COVID-19 theoretically. In this study, the aim is to assess the pattern of COVID-19 infection in patients with MG based on several factors.

Methods: This was a prospective cohort study following 150 patients with MG over a six-month period. The patients were monitored for the development of signs and symptoms of the COVID-19 infection.

Results: Comparison of the patients infected with COVID-19 with MG and those not infected was performed independently based on age, duration since MG diagnosis, status of thymectomy, and current clinical status of MG disease. Data analysis did not reveal increased susceptibility or increased severity of

COVID-19 illness based the criteria assessed.

Conclusion: COVID-19 related deaths and susceptibility were not related to age, thymectomy status, and disease duration in patients with MG.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes considerable mortality worldwide. The Covid-19 pandemic has infected millions of people, along with a high mortality rate and a grave concern regarding the health of people.¹ The disease contributes to systemic inflammation and multi-organ dysfunction, and is linked to severe respiratory demise in susceptible populations. Immunosuppressive agents, respiratory muscle weakness, and dysregulated immune response are among the possible reasons for worse critical outcomes.

How to cite this article: Etemadifar M, Akafzadeh-Savari M, Salari M, Akhavan Sigari A, Ebrahimi-Pelarti S, Sedaghat N, et al. Myasthenia gravis and coronavirus disease 2019: A report from Iran. *Curr J Neurol* 2021; 20(3): 162-5.

Myasthenia gravis (MG) is an autoimmune disease presenting with fluctuating fatigue and muscle weakness, caused by circulating antibodies against postsynaptic proteins of the neuromuscular junction (NMJ).² Clinical presentations of MG and COVID-19 are vastly variable.³

There is a theoretical concern that patients with MG maybe at higher risk of being infected with COVID-19 or experiencing a more severe course of illness.⁴ The close relationship between COVID-19 and neurological disorders, mainly neuro-immune diseases, made us eager to identify the pattern of infection in patients with MG. This study has been designed to assess the pattern and incidence of COVID-19 infection in patients with MG.

Materials and Methods

This is a prospective cohort study involving 150 previously diagnosed patients with MG from the beginning of April 2020 until the end of September 2020 from Al-Zahra University Hospital, Isfahan, Iran, and neurology clinics in Isfahan. Demographic data (age and gender), disease duration, initial symptoms of MG, history of thymectomy, period from thymectomy, drug history (azathioprine, rituximab, etc.), and comorbidities [hypertension, diabetes mellitus (DM), cardiovascular diseases (CVDs), etc.] were obtained from the patients. None of the patients had a history of COVID-19 infection at the start of the study. All patients were followed during the six-month period for the development of possible COVID-19 infection. Diagnosis of COVID-19 was based on typical clinical manifestations and either positive nasopharyngeal swab [polymerase chain reaction (PCR)] or positive computed tomography (CT) scan of the lung. Information about their COVID-19 infection status, duration, and severity were collected during office visits or by telephone call. Patients who did not consent to cooperate were excluded from the study. The data collected were recorded in SPSS software (version 23, IBM Corporation, Armonk, NY, USA). Independent t-test was used for analyzing quantitative variables and chi-square tests for analyzing qualitative variables. The study was approved by the Isfahan University of Medical Sciences ethical committee.

Results

A total of 53 males and 97 females (35.3 and 64.6%, respectively) with MG with a mean age of 46.4 years were included in the study. There was not a significant relationship between the mean age

of the patients infected with COVID-19 and uninfected patients (48.28 and 46.21 years, respectively). A total of 14 patients with MG were infected with COVID-19 (10.3% of females and 7.5% of males). Further analysis revealed no relationship between gender and infection with COVID-19. The mean duration of MG in patients who suffered from COVID-19 was 9.28 ± 9.10 years, which showed no relationship with uninfected patients with a mean MG duration of 8.83 ± 9.03 years.

9 patients reported fever as the most common complaint. Dyspnea and myalgia were the next most common complaints in the infected individuals (6 patients reported each symptom).

MG in 104 patients was under control and they were experiencing no symptoms, 20 patients had partially controlled disease with only transient symptoms, and 24 experienced constant symptoms and their disease was poorly controlled. COVID-19 infection was assessed separately in each class of clinical status (under control, partially controlled, and poorly controlled), nonetheless, none of the set of patients were found to be more susceptible to the infection.

Among all patients with MG, 98 people had undergone thymectomy, of whom 9 patients reported infection with COVID-19. The mean time duration after thymectomy was 7.88 years in patients who were infected by COVID-19 compared to 6.55 years in uninfected patients. Data analysis revealed no significant relationship between susceptibility of COVID-19 and thymectomy or the duration since the procedure.

6 (42.9%) patients from those infected with COVID-19 had at least one underlying disorder beside MG. Hypertension, DM, thyroid disease, multiple sclerosis (MS), ischemic heart disease, and fatty liver were among the comorbidities. The hospitalization rate in COVID-19 infected individuals with MG was 28.6%.

Most of the patients were being treated for MG, and pyridostigmine was among the most common drugs used. However, drug combinations with azathioprine, rituximab, and prednisolone was also common. A summary of drug regimens taken by patients is provided in table 1.

Unfortunately, 2 (14.3%) patients eventually died during their hospitalization course due to the complicated COVID-19 infection. Both patients were under treatment with prednisolone and pyridostigmine, only one of whom had undergone thymectomy. Data of these two patients is summarized in table 2.

Table 1. Drug regimens taken by patients during the study

Drug regimen	Number of patients	Covid-19 infection status-Number of infected patients (where applicable)
Pyridostigmine only	39	Yes-3 patients
Pyridostigmine + Azathioprine	13	Yes-1 patient
Pyridostigmine + Rituximab	12	Yes-2 patient
Pyridostigmine + Prednisolone	42	Yes-3 patients
Pyridostigmine + Azathioprine + Prednisolone	30	Yes-1 patient
Pyridostigmine + Prednisolone + Mycophenolate mofetil	4	Yes-1 patients
Pyridostigmine + Prednisolone + Methotrexate	2	Yes-1 patient
No treatments	8	Yes-2 patients

COVID-19: Coronavirus disease 2019

Discussion

MG is an autoimmune disorder, with antibodies targeting postsynaptic proteins at the NMJ. Immunoglobulins against acetylcholine receptors (AChR), lipoprotein receptor-related protein 4 (LRP4), and muscle-specific kinase (MuSK) are among the main antibodies detected in patients with MG. Clinically, the disease is characterized by fluctuating muscle weakness, most commonly, the ocular and bulbar muscles. Infections can act as a trigger for MG exacerbations. Although evidence is scarce, COVID-19 can also complicate the disease course and management in patients with MG. Respiratory failure seen in patients with severe COVID-19 infection demands full function of respiratory muscles, which may be compromised in patients with MG.³

The COVID-19 infection may by itself predispose patients to MG. In an interesting report by Restivo et al., three patients with a mean age of 67 years with no history of autoimmune or neurologic disease, developed MG symptoms in less than 10 days after the onset of the COVID-19 symptoms. All patients were AChR positive, and the diagnosis of MG was confirmed. Theories suggest either a cross reaction of COVID-19 antibodies against the NMJ or self-tolerated immunological compromise.⁵

Increased amounts of interferon (IFN)-gamma and interleukin (IL)-4 suggest both a Th1 and Th2 response in the pathogenesis of MG. In patients with MG with thymoma, increased amounts of Th17 have been also observed. The proliferation of

B cells and the production of antibodies is a main feature of MG, however, this proliferation mainly occurs in the thymus, demonstrating the fact that AChR antibodies are extremely decreased, but not eliminated after thymectomy in selected patients.⁶ Theoretically, as B cells have a minor role in the pathogenesis of COVID-19, thymectomy would not affect susceptibility to the disease or increase disease severity. This is consistent with our finding that increased susceptibility to COVID-19 was not observed in thymectomy patients.

The immune system, both innate and adaptive, is disrupted in patients infected with COVID-19, leading to severe inflammatory responses in critically ill patients. This immune dysregulation is evident by the corruption of normal immune cell counts, especially in the severely ill patients. Lymphopenia is a unique feature of COVID-19 infected patients indicating reduced numbers of T cells and natural killer cells. Notable reductions are also seen in CD8+ T cells, which may indicate disease severity. Paradoxically, the increased T cell activation is demonstrated by the expression of CD38, CD44, and CD69 on CD4+ and CD8+ T cells. Sars-CoV-2 can directly infect T lymphocytes through the interaction of the spike protein (S protein) on the surface of the virus and angiotensin-converting enzyme 2 (ACE2) receptors on T cells. This interaction is also what mediates cell entry into lung parenchymal cells.⁷ Direct injury to lymphatic organs and indirect injury to lymphocytes by the generation of lactic acidosis are also proposed as causes of lymphocyte depletion.⁸

Table 2. Data of the two deceased patients due to the coronavirus disease 2019 (COVID-19) infection

	Drug regimen	Hospitalization duration (days)	Thymectomy	Age (year)	Gender	Initial MG symptoms
Patient #1	Pyridostigmine + Rituximab	7	No	83	Male	Diplopia
Patient #2	Pyridostigmine + Azathioprine	14	Yes (22 years ago)	72	Female	Dysphagia

MG: Myasthenia gravis

Activation of CD4+ T lymphocytes produces T helper (Th) 1 cells which generate certain inflammatory cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), INF-gamma, interleukin-6 (IL-6), etc. This cytokine milieu induces a burst in the number of CD14+ and CD16+ monocytes which then causes a more extensive release of cytokines such as IL-6, further exacerbating the inflammation. Increased levels of monocytes and macrophages are also proven by increased amounts of CD14 and CD163 levels in the serum, with the markers, indicating monocyte and macrophage activation.⁹

These activated cells can directly damage the pulmonary tissue by entering the pulmonary circulation, causing extensive lung damages seen especially in intensive care unit (ICU) hospitalized patients with COVID-19. Monoclonal antibodies targeted against cytokines that play an essential role in immune-mediated inflammatory damage are being investigated for possible treatment potential.¹⁰

B cells are usually in the normal range, pinpointing the fact that these subsets of lymphocytes may be less affected by the virus.

However, the increased Immunoglobulin G (IgG) production stemming from the increased B cell activation and proliferation has been linked to poorer disease outcomes.⁷ In a study, however, B cells were shown to be reduced in numbers, along with other lymphocytes and natural killer (NK) cells.¹¹

Conclusion

In the current study, 150 patients with MG were followed for six months, 14 of whom were infected with COVID-19 in the screening period. The severity and incidence of COVID-19 was not associated with thymectomy, age, sex, or the medications taken by the patients with MG. However, large scale studies and more extensive follow-ups are needed for more concrete results.

Conflict of Interests

The authors declare no conflict of interest in this study.

Acknowledgments

None.

References

- Lazzari C, Shoka A, Nusair A, Rabottini M. Psychiatry in time of COVID-19 pandemic. *Psychiatr Danub* 2020; 32(2): 229-35.
- Weninger S, Schoser B. Myasthenia gravis: Current status of antibody diagnostics and aspects on refractory myasthenia gravis. *Fortschr Neurol Psychiatr* 2018; 86(9): 551-8. [In German].
- Anand P, Slama MCC, Kaku M, Ong C, Cervantes-Arslanian AM, Zhou L, et al. COVID-19 in patients with myasthenia gravis. *Muscle Nerve* 2020; 62(2): 254-8.
- Jacob S, Muppidi S, Guidon A, Guptill J, Hehir M, Howard JF, et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. *J Neurol Sci* 2020; 412: 116803.
- Restivo DA, Centonze D, Alesina A, Marchese-Ragona R. Myasthenia gravis associated with SARS-CoV-2 infection. *Ann Intern Med* 2020; 173(12): 1027-8.
- Wang Z, Yan Y. Immunopathogenesis in myasthenia gravis and neuromyelitis optica. *Front Immunol* 2017; 8: 1785.
- Yang L, Liu S, Liu J, Zhang Z, Wan X, Huang B, et al. COVID-19: Immunopathogenesis and Immunotherapeutics. *Signal Transduct Target Ther* 2020; 5(1): 128.
- Tan L, Wang Q, Zhang D, Ding J, Huang Q, Tang YQ, et al. Lymphopenia predicts disease severity of COVID-19: A descriptive and predictive study. *Signal Transduct Target Ther* 2020; 5(1): 33.
- Gomez-Rial J, Curras-Tuala MJ, Rivero-Calle I, Gomez-Carballa A, Cebej-Lopez M, Rodriguez-Tenreiro C, et al. Increased serum levels of sCD14 and sCD163 indicate a preponderant role for monocytes in COVID-19 immunopathology. *Front Immunol* 2020; 11: 560381.
- Zhou Y, Fu B, Zheng X, Wang D, Zhao C, Qi Y, et al. Pathogenic T-cells and inflammatory monocytes incite inflammatory storms in severe COVID-19 patients. *Natl Sci Rev* 2020; 7(6): 998-1002.
- Tan M, Liu Y, Zhou R, Deng X, Li F, Liang K, et al. Immunopathological characteristics of coronavirus disease 2019 cases in Guangzhou, China. *Immunology* 2020; 160(3): 261-8.