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Clinical characteristics and outcomes of COVID-19 infection among myasthenia gravis patients in a national referral hospital in Indonesia

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ABSTRACT

Introduction. Due to their immunocompromised state from immunosuppressive therapy and respiratory efficiency, patients with Myasthenia Gravis (MG) are more likely to get infected with COVID-19. Currently, reports on MG patients exposed with COVID-19 in Indonesia are still limited. Therefore, this study was conducted to determine the clinical characteristics and outcomes of MG patients infected with COVID-19, especially in Jakarta, Indonesia.

Methods. It is a retrospective study of MG patients in a National Referral Hospital in Indonesia from September 2021 to December 2022. The data obtained includes demographics, medical history, clinical characteristics, and severity of MG assessed by MG composite scale (MGCS), Myasthenia Gravis Foundation of America (MGFA) classification, symptoms, and therapy.

Results. Of the 8 patients, 7 patients were female. The range of age at COVID-19 onset was 28-62 years old. On admission to the hospital, 2 patients were mild MG, 2 patients were moderate MG, 3 patients with severe MG, and one patient could not be identified because the patient came in an unconscious state. Five patients were classified as moderate COVID-19, two patients had severe COVID-19, and one patient was classified as critical COVID-19. Most patients experience MG exacerbation or require oxygen support during hospitalization. Only one patient deceased while receiving treatment at the emergency room, while the rest improved and were discharged home.

Conclusion. MG patients exposed with COVID-19 tend to experience moderate, severe, and critical COVID-19 symptoms. However, with proper management of the infection and other comorbidities, MG patients with COVID-19 may achieve favorable outcome.

Keywords: myasthenia gravis, COVID-19, Myasthenia Gravis Foundation of America, Myasthenia Gravis composite scale

INTRODUCTION

Myasthenia Gravis (MG) is a disease that attacks the neuromuscular junction, in which autoantibodies cause functional and morphological abnormalities in the postsynaptic membrane [1]. This results in disturbances in neuromuscular transmission and muscle weakness [1]. Weakness in the respiratory muscle causing life-threatening conditions, the need for ICU room, and breathing assistance which is called a myasthenic crisis [2]. The administration of the critical care unit and improvements in respiratory care have had a significant impact on mortality in the myasthenia crisis [3].

Infection and antibiotic use can trigger MG exacerbations and crises [4]. Due to their immunocompromised state from immunosuppressive therapy and decreased baseline respiratory efficiency, patients with MG are more likely to get COVID-19 infection. In MG patients with confirmed COVID-19, MG exacerbations accompanied by respiratory muscle failure can lead to secondary respiratory failure [5].

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From a pathogenic perspective, there is a hypothesis that an imbalance of regulatory T-cells (Treg) or T helper 17 cells (Th17) can trigger an exaggerated autoimmune response. Although there is no direct evidence that pro-inflammatory cytokines and chemokines are associated with pulmonary pathology, changes in laboratory parameters, including elevated serum cytokine and chemokine levels in infected patients, are associated with disease severity and outcome [5].

Prior research suggested that COVID-19 patients with MG had higher hospitalization and mortality risks than COVID-19 patients without MG [6-8]. Patients with MG who tested positive for COVID-19 experience a longer-than-average hospital stay. Seven of the 27 MG patients with COVID-19 positivity were hospitalized, with an estimated mean stay of 8.28 days, while the non-COVID-19 group's hospital stay lasted an average of 4.33 days [9].

MG is a progressive disease and can cause various complications. Currently, reports on the clinical characteristics and outcomes of MG patients infected with COVID-19 in Indonesia are still limited. Therefore, this study was conducted to determine the clinical characteristics and outcomes of MG patients infected with COVID-19, especially in Jakarta, Indonesia.

METHODS

This research was conducted using a retrospective descriptive method by collecting data from medical records of MG patients with a history of or currently being infected with COVID-19 and treated in a National Referral Hospital Jakarta, Indonesia from September 2021 to December 2022. The inclusion criteria for this study included subjects aged ≥18 years and had MG and were currently infected with COVID-19 which is shown by positive results of PCR swabs or antigen swabs. While the COVID-19-infected MG patients who could not be monitored because they were transferred to another hospital were excluded.

The severity of MG was assessed based on the Myasthenia Gravis Foundation of America (MGFA) classification which was as ocular MG (class 1), mild (class II A and IIB), moderate (class IIIA and IIIB), and severe (class IVA, IVB, and V). The MG Composite Scale (MGCS) was also used to assess the symptoms severity of MG patients.

Variables collected in this study were age, sex, type of MG, duration of suffering from MG, chronic MG treatment, MGFA classification before exposure to COVID-19, MGFA classification and MGCS during admission, MGFA classification and MGCS when discharged from the hospital, MG symptoms when infected with COVID-19, myasthenic crisis medication, COVID-19 symptoms and therapy used, comorbidity, and outcomes of MG patients (e.g. discharged home or deceased).

RESULTS

During the evaluation period, there were 11 MG patients with a history of or currently being infected with COVID-19, who came for treatment and were treated at a National Referral Hospital in Indonesia from September 2021 to December 2022. Three patients had been reported previously during the early COVID-19 pandemic.10 Therefore, we reported 8 patients in this study. Of the 8 patients, 7 patients were female. The range duration of MG was 3-10 years. The range of age at COVID-19 onset was 28-62 years old.

Seven patients had generalized MG and 1 patient had ocular MG. The evaluation before admission to the hospital showed six patients with mild MG (1 patient with ocular MG, 3 patients with MGFA class IIa, 2 patients with grade IIb), and 1 patient with a normal condition. The MG severity of one patient before hospital admission was unknown since she was admitted to the emergency unit in an unconscious condition and not a patient who had routine medication from our hospital. On admission to the hospital, 2 patients with mild MG (MGFA class IIa and IIb), 2 patients were classified as moderate MG (MGFA class IIIa and IIb), 3 patients with severe MG (MGFA class IVb), while one patient could not be identified because the patient came in an unconscious state (see the details in Table 1). At the time of discharge from the hospital, six patients had improved conditions and improved MGFA classification. One patient could not be evaluated and deceased during treatment in the emergency unit. While the others found no change in MGFA (Table 1).

An improvement in the MGCS of more than three points after the end of therapy indicates a successful outcome. Six of the 8 patients had an increase in their MGCS. At either hospital admission or discharge, the MGCS of one patient did not change. While a patient's severe condition makes it challenging to determine the MGCS (Table 1).

Four patients had SBCT values <15 at the time of admission. Of these four patients, a patient required respiratory support with a ventilator, a patient used a high-flow nasal cannula (HFNC), and two patients improved with oxygen support from a nasal cannula. All patients had SBCT improvement after hospitalization.

Fever was the most common COVID-19-presenting symptom. Cough, dyspnea, ptosis, and extremity weakness were common symptoms. All patients were suffering from comorbid conditions. One patient had cancer, three had elevated blood pressure, two had type 2 diabetes, two had other autoimmune

TABLE 1. Characteristics of MG patients with COVID-19

Case number	Age (sex)	MG subtype (generalized, ocular, bulbar)	History of MG (y)	Chronic MG treatment	MGCS at admission	MGCS at discharge	MGFA classification before COVID-19	MGFA classification at admission	MGFA classification at discharge	SBCT at admission	SBCT at discharge
1	43 (F)	Generalized	9	Pyridostigmine, AZA	24	2	IIb	IVb	IIb	7	17
2	44 (F)	Ocular	4	Pyridostigmine, AZA	N/A	Death	N/A	N/A	Death	N/A	N/A
3	62 (M)	Generalized	8	Pyridostigmine bromide, AZA	2	0	II	IIb	I	16	17
4	53 (F)	Generalized	3	Pyridostigmine, MP, MM	19	8	IIa	IIIa	IIa	8	12
5	28 (F)	Generalized	6	Pyridostigmine, MP, MM	18	10	IIb	IVb	IIb	14	15
6	50 (F)	Generalized	5	Pyridostigmine bromide, MP, MM	4	4	IIa	IIa	IIa	20	30
7	43 (F)	Generalized	10	Pyridostigmine bromide, MP	20	4	IIa	IIIb	IIa	21	35
8	61 (F)	Generalized	6	Pyridostigmine bromide, MM	24	4	I	V	I	7	22

Note: AZA= Azathioprine; MM= Mycophenolate Mofetil; MP= Methylprednisolone; N/A= Not Available

conditions, 3 patients with cardiovascular problems, and 2 patients with overweight. Five patients were classified as moderate COVID-19, two patients had severe COVID-19, and one patient was classified as critical COVID-19 (Table 2). Two patients required hospitalization in an Intensive Care Unit (ICU). A patient deceased while undergoing treatment in the emergency unit. Most patients experience MG exacerbation or require oxygen support during hospitalization. Three patients needed an oxygen nasal cannula, two patients used high-flow nasal cannula (HFNC) oxygen therapy, and one patient required intubation.

All patients were using pyridostigmine, 4 patients were taking a corticosteroid, and 7 patients were receiving oral immunosuppressant (Table 2). Five patients received antibiotics, 6 patients received antiviral, and 1 patient was treated with plasma convalescent as COVID-19 treatment. Seven patients recovered from COVID-19 and had satisfactory outcomes after hospitalization (Table 2). Only one patient deceased; 44 years old female, was unconscious when she arrived at the emergency room. She received favipiravir, azithromycin, and cefepime as COVID-19 treatment. She did not receive either intravenous immunoglobulin (IVIg) or plasma exchange during hospitalization.

DISCUSSION

Patients with MG are at risk for a myasthenia crisis due to COVID-19 [2,10]. Additionally, MG patients are more likely to have a negative outcome (when infected with COVID-19 compared to populations without this autoimmune condition). This happens as a result of the immunocompromised state of MG patients brought on by immunosuppressive medication, immune system dysregulation, weak respiratory muscle, and respiratory failure (because of pneumonia and pulmonary thromboembolism) [11].

Furthermore, due to cytokine storm in MG patients, COVID-19 infection can increase the likelihood of new-onset MG, myasthenic crises, respiratory failure, and mortality rate [11]. In a study, high MGFA classification was strongly associated with severe COVID-19 [12]. Similarly, our study also showed that patients with moderate and severe MGFA tend to experience moderate, severe, and critical COVID-19 symptoms. While mild COVID-19 symptoms are experienced by MG patients with normal and ocular MGFA classification [13].

According to a study, concomitant conditions such as hypertension, diabetes mellitus, SLE, asthma, hepatitis C, generalized anxiety disorder, and epilepsy were present in 7 out of 15 MG patients with COVID-19.8 Our study found that all MG patients had comorbidities, 2 patients had other autoimmune diseases, 1 patient was diagnosed with cancer, 3 patients

TABLE 2. Symptoms, therapy, and outcome of MG patients during COVID-19 infection

Case number	MG symptoms during COVID-19	COVID-19 severity	Oxygenation support	Myasthenic crisis medication	COVID-19 medication	Comorbidity	Outcome
1	Dyspnea, ptosis, upper and lower extremities muscle weakness	Severe	high-flow nasal cannula (HFNC)	PLEx	Plasma convalescent, remdesivir, N-acetylcysteine	1. Hypercoagulable state 2. Hypertension	Discharged home
2	Unconscious	Severe	HFNC + Non rebreathing oxygen face mask (NRM)	None	Favipiravir, azithromycin, cefepime, acetylcysteine, vitamin C, vitamin D	1. Hypertension 2. Hyponatremia 3. Septic shock 4. Hospital Acquired Pneumonia (HAP) 5. Acute Respiratory Distress Syndrome (ARDS)	Deceased
3	Right upper and lower extremities muscle weakness	Moderate	Nasal cannula	None	Remdesivir, heparin, Ceftriaxone, acetylcysteine,	1. Coronary artery disease 2. Type 2 Diabetes Mellitus on insulin 3. Hypercoagulable state 4. Chronic Kidney Disease 5. Overweight	Discharged home
4	Ptosis, nasal speech, shoulder, and proximal limb weakness	Moderate	Nasal cannula	PLEx	Vitamin C, acetylcysteine, ceftriaxone, azithromycin	1. Crohn's Disease 2. Other specific types of Diabetes Mellitus 3. Hypertension 4. Non-toxic goiter	Discharged home
5	Ptosis, nasal speech, dysphagia, shoulder, and proximal limb weakness	Moderate	Nasal cannula	PLEx	Vitamin C, azithromycin	Overweight	Discharged home
6	Upper and lower extremities weakness	Moderate	Room air	PLEx	Heparin, clopidogrel, Remdesivir, vitamin C, Vitamin D, zinc,	1. Carcinoma mammae on therapy (dextra) 2. Cerebral small vessel disease 3. Ischemic stroke	Discharged home
7	Dyspnea, ptosis, generalized muscle weakness, dysphagia	Moderate	Room air	MP	Favipiravir, Zinc, Vit D, Codein, omeprazole	1. Systemic Lupus Erythematosus (SLE) 2. Secondary Sjogren's Syndrome 3. Severe depression with psychosis symptoms	Discharged home
8	Dyspnea, ptosis, generalized muscle weakness, diplopia	Critical	On ventilator	PLEx	Remdesivir, heparin, Meropenem, acetylcysteine, codein, omeprazole, Zinc, Vit B, Vit C, Vit D	Hypertension	Discharged home

Note: PLEx= Plasma Exchange; MP= Methylprednisolone

had hypertension, 2 patients experienced diabetes mellitus, 3 patients with cardiovascular problems, and 2 patients with overweight. Dysphagia, peripheral vascular disease, and cardiovascular disease were all substantially linked to a higher chance of death in a univariate analysis study, but after the multivariate analysis, only dysphagia remained so [10]. Therefore, comorbidities are not causally related to how effectively patients respond to treatment as long as they are properly managed.

In our study, septic shock was one of various comorbidities that the deceased patient suffered. Septic shock and multi-organ failure were the most prevalent immediate causes of mortality in individuals with severe COVID-19, frequently as a result of suppurative lung infection [14]. As a result, it is potential that MG is not always directly responsible for these patients' symptoms getting worse.

Patients with autoimmune conditions such as MG are thought to be more prone to severe infection, including viral upper respiratory infection [11]. In our study, a patient hospitalized for COVID-19 with previous MG had a severe course of the disease, with 6 patients requiring oxygenation support. Meanwhile, other studies also strengthened the need for oxygen support during hospitalization for MG patients, by mentioning that two elderly patients died from COVID-19 respiratory insufficiency and 3 of the 11 MG patients with probable or confirmed COVID-19 needed ventilator support [15]. Patients with MG may have an increased burden on their respiratory muscles since COVID-19 is typically linked to a high stimulation of the respiratory drive that leads to a vigorous inspiratory effort [5]. Therefore, the majority of MG patients with COVID-19 infection indicate a need for oxygenation support.

Azithromycin and hydroxychloroquine may contribute to MG exacerbations [4,16]. A retrospective study of 127 patients with autoimmune MG demonstrated disease progression after treatment with azithromycin, fluoroquinolones, and beta blockers [4]. In contrast, another study revealed that azithromycin can be used safely in MG patients with concomitant COVID-19 infection [17]. In our previous case series with three patients, two cases did not demonstrate any worsening of MG symptoms while being treated in the hospital despite receiving azithromycin and hydroxychloroquine [13]. In this study, 3 patients received azithromycin. One of the three patients was deceased during arrival at the emergency room and the other patients did not experience disease progression.

The use of plasmapheresis and intravenous immunoglobulin (IVIG) therapy for myasthenia crises is demonstrated in the literature, with consideration for the hemodynamic compromise and the thromboembolic character [18]. In our study, five individuals received plasma exchange (PLEx) therapy and one patient had methylprednisolone as part of the treatment for MG exacerbation. They all had favorable outcomes. None of the patients who received these therapies died or experienced complications and all of them were discharged from the hospital with better MGFA class than they had at admission. A study revealed that treatment for exacerbation in 8 patients with myasthenia gravis with COVID-19 included IVIG in 3 patients, PLEX in 2 patients, and adjusting baseline myasthenia medications in 3 individuals. One of the two patients who received PLEX died, but all of the patients who received IVIG survived [19]. In MG patients with COVID, the use of immunosuppressive therapies may not have a negative impact on patient outcomes. Favorable outcomes will be shown if MG symptoms that are aggravated by COVID-19 infection are treated adequately.

However, our study has some limitations. First, our study is an observational study using data on MG patients with COVID-19 who were admitted to the hospital and we did not use data on outpatient MG patients with COVID-19. Third, due to the small number of patients included in our study, we did not perform statistical analysis to better understand risk factors for COVID-19 severity in MG patients.

CONCLUSION

Patients with MG who are exposed to COVID-19 will likely develop moderate, severe, and critical COVID-19 symptoms in addition to an aggravation of their MG symptoms. However, with proper management of the infection and other comorbidities, MG patients with COVID-19 may achieve favorable outcome.

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Author contribution

Conception of the work, FO and AYS; methodology, FO, AYS, WW, LAI, NF, FM and MH; investigation, acquisition, analysis, and interpretation of data of the work, FO, AYS, WW, LAI, NF, FM and MH; writing—original draft preparation, FO, AYS, WW, LAI, NF, FM, and MH; writing—review and editing, FO, AYS, WW, LAI, NF, FM and MH; supervision, MH. All authors have read and agreed to the published version of the manuscript.

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