


CLINICAL COMMENTARY

Myasthenia gravis and COVID-19: A case series and comparison with literature

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Objective: To describe presenting symptoms, clinical outcomes, and therapeutic management of concurrent Coronavirus disease 2019 (COVID-19) infections in patients with a pre-existing myasthenia gravis (MG).

Methods: We conducted a retrospective study in patients with preexisting MG presenting with concurrent COVID-19 between September 21st and November 4th, 2020 when attending the emergency department or routine neurology consultation at the National Institute *Mongi Ben Hamida* of Neurology of Tunis, Tunisia.

Results: Five patients were identified. The Myasthenia Gravis Foundation of America scores (MGFA) prior to COVID-19 infection were class I in one patient, class II (IIa, IIb) in two patients, and class IIIb in one patient.

Four patients had mild to moderate courses of COVID-19 infection. One patient presented a critical infection with acute respiratory disease syndrome (ARDS) requiring mechanical ventilation. Two of them also demonstrated signs of MG exacerbation requiring the use of intravenous immunoglobulin in one case.

We maintained immunosuppressant therapy to MG in all our patients. All our patients received Azithromycin (AZM) as a part of specific drug treatment of COVID-19 infection. Outcome was favorable in 4 patients and rapidly fatal evolution was observed in the patient with ARDS.

Discussions and conclusion: The results from our study suggest that prior MG activity could partially influence the subsequent clinical outcomes. It emerged also that ongoing long-term immunosuppressive immunotherapy to MG should be maintained during the COVID-19 pandemic and that AZM can be used safely in MG patients and concurrent COVID-19 infection.

KEYWORDS

COVID-19, myasthenia gravis, myasthenic crisis, SARS

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). It is a novel coronavirus that first emerged in Wuhan, China, in December 2019¹ and then quickly escalating to a global pandemic and then it spread around the world to become a global pandemic.

The risk for poor outcomes after SARS-CoV-2 infection in patients with autoimmune (AI) neurological diseases, including myasthenia gravis (MG) is still a subject of debate, and data with regard to this issue are still lacking.² Moreover, when infected by SARS-CoV-2, this category of patients, usually taking immunosuppressive therapy, is associated with higher mortality.¹ The underlying mechanism of the relationship between MG and COVID-19 is not yet established.

Currently, the available literature concerning management of patients with neuromuscular disorders in the setting of this pandemic³ is limited. Disease-modifying therapies, used in this category of patients, may increase the risk of COVID-19 infections or result in a more severe outcome.³

Soon after the beginning of the pandemic, the International MG/COVID-19 Working Group⁴ published guidelines for the management of MG. Given the relative immunosuppressed state under therapy for the majority of MG patients, a theoretical concern arose. Those patients might be at higher risk of severe manifestations due to COVID-19, especially respiratory failure.⁴ The dilemma faced by the neurologist is whether to stop or to maintain ongoing immunosuppressive therapy⁴ given the combined risk of increased MG activity and the risk of being infected by SARS-CoV-2.

At the time of publishing these guidelines, clinical data about the association between the two diseases were not available.⁵ Later, a small number of case reports and small case series of COVID-19 infection in patients with pre-existing MG have been published.⁵⁻⁸

Some authors suggested, from their experience, that active COVID-19 infection has a little effect on the control of MG activity.^{5,6} However, the triggering effect of COVID-19 infection on myasthenia gravis crisis is not yet known.⁹

The therapeutic management of MG patients during this pandemic is problematic. Chloroquine and Azithromycin (AZM), two specific drugs for COVID-19 infection, significantly impair the neuromuscular function³ Moreover, it is already known that they may trigger MG exacerbation or worsen the clinical course of the disease.¹⁰

Here, we describe the presenting symptoms, clinical outcomes, and therapeutic management of concurrent COVID-19 infection in patients with pre-existing MG disease. Patients were recruited from Mongi Ben Hamida National Institute of Neurology.

2 | METHODS

An observational retrospective study was performed. Patients presenting to the emergency department or those attending routine neurology consultation at Mongi Ben Hamida National Institute

of Neurology from September 21st to November 4th, 2020, were recruited. The severity of MG was evaluated by the Myasthenia Gravis Foundation of America (MGFA) scores.¹¹ The MGFA scores prior to the infection and at the time of consulting with COVID-19 symptoms were evaluated.

The symptoms of MG exacerbation were defined (impending MG crisis or manifest MG crisis) according to the international consensus guidance for management of MG.¹²

Diagnosis of COVID-19 was based on the clinical history, results of chest X-Ray, chest Computed-Tomography (CT), and nasopharyngeal swab Real Time-Polymerase Chain Reaction (RT-PCR) testing.

The patients were classified using the severity classification (mild, moderate, severe, or critical) according to the World Health Organization classification of COVID-19 infection.¹

This study was approved by our local ethics committee.

3 | RESULTS

Five patients (one male and four females) with pre-existing MG and concurrent COVID-19 infection were identified (Table 1). The patients' median age was 54 years (age range: 37–60 years). The median duration of MG disease was 9 years (range: 3–15 years). Only one patient had obesity as comorbidity associated with MG. No discontinuation of baseline treatment was noted before the onset of COVID-19 symptoms. All our patients presented with suggestive symptoms of SARS-CoV-2 infection. Fever, headache, and myalgia were the most frequent complaints. They were observed in three patients. (Table 1). The median duration of symptoms prior to the consultation was 4 days (range: 3–5 days).

Patients 1, 2, 3, and 5 presented with mild to moderate COVID-19 infection. Patient 4 had a critical infection with acute respiratory disease syndrome (ARDS), requiring mechanical ventilation in an intensive care unit and he ultimately died. His prior MGFA severity class was IIIb (Table 1). Chest X-ray did not show pulmonary infiltration for patients 1, 2, and 3. Chest CT scan of patient 4 showed large bilateral pulmonary opacities (supplementary data). Patient 5 had parenchymal pulmonary involvement estimated at 35% (supplementary Figure S1).

Mycophenolate Mofetil (Patient 1), azathioprine (Patients 2, 4, and 5), and prednisone (Patient 4) were the immunosuppressant drugs used prior to COVID-19 infection (Table 1).

Patient 2 (MGFA IIIb on admission) and patient 5 (MGFA IIb) presented symptoms of MG exacerbation in addition to COVID-19 symptoms (Table 1).

Patient 2 had a rapid improvement in symptoms under COVID-19 specific treatment and did not require immunomodulatory treatment, whereas patient 5 underwent an intravenous immunoglobulin (IVIg) treatment with a favorable response.

Our national consensus treatment guidelines for COVID-19 infection were applied to all our patients (Table 1). All our patients continued to take pyridostigmine and immunosuppressive therapy after COVID-19 confirmation.

TABLE 1 Clinical characteristics, immunomodulatory and COVID-19 treatments, and outcomes in five patients with myasthenia gravis and COVID-19

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	F	F	F	M	F
Age	40	60	37	57	54
Duration of MG (years)	9	15	11	3	3
Antibody status	Negative (AChR and MuSK)	Negative (AChR and MuSK)	AChR positive/MuSK negative	AChR positive/MuSK negative	AChR positive/MuSK negative
Comorbidities	N	Obesity	N	N	N
History of thymoma	N	N	N	Y	Y
History of thymectomy	N	N	N	N Delayed (in order to control MG)	Y 24 months before admission
Myasthenia muscle score	85	60	100	65	70
MGFA severity class before COVID-19 infection	Ila	Ila	I	IIIb	Ila
MGFA severity class during COVID-19 infection	Ila	IIIb	I	NA	Ilb
MG baseline treatment prior to COVID-19 infection	MMF 500 mg ×2 per day, Pyridostigmine 60 mg ×8	AZA 150 mg Pyridostigmine 60 mg ×8	Pyridostigmine 60 mg ×8	AZA 150 mg Prednisone 40 mg Pyridostigmine 60 mg ×8	AZA 150 mg Pyridostigmine 60 mg ×8
Presenting symptoms and duration	Ansomnia, agueusia myalgia during preceding 5 days	Fever, headache, diarrhea, and shortness of breath during preceding 3 days	Fever, anosmia headache myalgia during preceding 5 days	Fever, delirium, asthenia shortness of breath, cough during preceding 3 days	muscle weakness, swallowing troubles 2 weeks earlier; myalgia rhinorrhea and headache during preceding 5 days
WHO classification (1)	Mild disease	Pneumonia	Mild disease	ARDS	Pneumonia
Treatment for MG during hospitalization	-	AZA 150 mg Pyridostigmine 60 mg ×8	-	Pyridostigmine 60 mg ×8 Prednisone 40 mg, AZA 150 mg	AZA 150 mg Pyridostigmine 60 mg ×8 IVIg 0,4 g/kg/day ×5 days
Specific treatment for COVID-19	AZM 500 MG/day ×5 days, Vit C 1000 mg/day ×10 days, Vit D 20,000 IU, LMWH ×10 days	AZM 500 mg ×5 days, Vit C 1000 mg/day ×10 days, Vit D 20,000 IU ×10 days	AZM 500 MG/day ×5 days, Vit C 1000 mg/day ×10 days Vit D 20,000 IU,	Mechanical ventilation, Levofloxacin 500 mg/day	AZM 500 mg/day ×5 days, Vit C 1000 mg/day ×10 days, Vit D 20,000 IU, LMWH ×10 days
Clinical outcome (short term)	Sent home for self-quarantine quarantine Symptoms resolved within 10 days except anosmia which is slowly improving	Dry cough discharged day 10	Sent home for self-quarantine Symptoms resolved within 7 days except anosmia which is slowly improving	Death on day 20	Improvement of all symptoms before discharge
Specific intervention after COVID-19	Full recovery	Prescription for a physiotherapy follow up	Full recovery	NA	Prescription for a physiotherapy follow up

Abbreviations: AChR, acetylcholine receptors; ARDS, acute respiratory distress syndrome; AZA, azathioprine; AZM, azithromycin; F, female; g, gram; IU, international unit; IVIg, intravenous immunoglobulin; LMWH, low molecular weight heparin; M, male; mg, milligram; MG, myasthenia gravis; MGFA, myasthenia gravis foundation of America; MMF, mycophenolate mofetil; MuSK, muscle-specific tyrosine kinase; N, no; NA, not applicable; NG, nasogastric; Vit, vitamin; WHO, world health organization; Y, yes.

4 | DISCUSSION

Five patients with pre-existing MG and concurrent COVID-19 infection were involved in this work. A favorable outcome was observed in four patients despite the continuation of immunomodulatory therapy for MG. One patient presented with ARDS due to SARS-CoV-2 pneumonia with fatal evolution.

From the reported series, clinical outcomes after SARS-CoV-2 infection are highly variable.⁷ Most patients in the series of Camelo-Filho et al.² had a severe course, and 4 out of 15 patients died. Moreover, three out of five patients reported by Anand et al.⁷ needed respiratory support. However, Hüber et al.⁵ observed favorable outcomes in all their patients. We agree with their point of view that prior MG activity partly influences the clinical outcomes of COVID-19 infection, as shown by the variable MGFA scores prior to COVID-19 observed in our patients (Table 1).

In the setting of COVID-19 pandemic, respiratory symptoms can be secondary to COVID-19 itself or to neuromuscular respiratory failure due to MG.⁷ Linking symptoms to each etiology may be difficult in this context. However, the signs of COVID-19 infection have already been associated with the signs of MG exacerbation.^{5,7}

In our series, concomitant signs of COVID-19 and MG exacerbation were observed in two patients (Table 1).

The favorable outcomes in our two patients support the hypothesis that COVID-19 infection has little impact on MG disease course as previously reported.⁵ The median age in our series was 54 years which was comparable to the one reported in other MG series^{2,7} (Table 2). In addition, it was observed that COVID-19 involved patients with a prolonged MG-disease course (Table 2).^{2,7}

In an attempt to explain these findings, a possible pathophysiologic mechanism is the immunosenescence, an age-related alteration of the immune system, which is accompanied by an upregulation of T-cells function concerning their vital role of viral clearance through cytotoxic effect.^{13,14} In relation to COVID-19 infection, their tissue accumulation contributes to ARDS and multisystem failure.¹³

In MG patients, the relationship between antibody status and COVID-19 remains unclear. Our series, along with others^{2,5,7} included a majority of patients with AchR antibodies or double-seronegative MG. Only a few patients had MuSK antibodies.^{2,7} These findings allow us to suppose a probable pathophysiological role of antibody status in the occurrence of COVID-19 and its evolution. This role is yet to be established.

Concerning comorbidities, only one patient in our study had obesity associated with MG. This patient improved and was discharged on Day 10. It is important to note that case series of hospitalized MG patients with COVID-19 (Table 2)^{2,5,6} as well as patients with other AI conditions¹⁵⁻¹⁷ presented cardiovascular diseases as comorbidities. This is in accordance with the meta-analysis finding of Yang et al.¹⁴ that assessed the prevalence of comorbidities in the COVID-19 patients and found that underlying disease, including cardiovascular disease, may be risk factors for severe patients compared with non-severe patients.

The use of short-term immunomodulatory therapy is an important consideration in the management of MG exacerbation signs when associated with COVID-19 infection. In our series, treatment with IVIg was effective in one patient. A similar favorable outcome was also reported in prior series.^{5,6} Currently, there is no evidence that IVIg or plasma exchange increases the risk of SARS-CoV-2 infection or its clinical phenotype.³

On the other hand, the management of long-term immunomodulatory therapy of MG is also challenging.⁷ Therapeutic approach varied, Huber et al.⁵ stopped AZA in one patient and maintained baseline treatment for the three other patients of their series.

In the series of Anand et al.⁷ MMF was initially withheld in three patients. It is worth mentioning that despite this discontinuation, two out of these three patients needed respiratory support.

In our own experience, long-term immunosuppressive therapy was maintained for all our patients with favorable outcomes in four patients. This may apply to corticosteroids. Indeed, it is recommended that corticotherapy should not be discontinued in symptomatic SARS-CoV-2 infected patients, given its proven role in reducing mortality.¹⁰ This was substantiated by the results observed by Camelo-Filho et al.² who continued prednisone in 14 out of 15 patients. The majority of these patients did not require mechanical ventilation. Rein et al.⁶ maintained steroids regimen in two patients and increased prednisone in the third patient with favorable clinical outcome.

In our series, fatal evolution was observed in patient 4, for whom we maintained steroids. This death was probably caused by the severity of SARS-CoV-2 pneumonia as attested by the clinical and radiological findings (Table 1, supplementary data). Our patients' demographic and clinical data are in accordance with those in patients with fatal SARS-CoV-2 infection previously reported by Camelo-Filho et al.² (male patients, aged more than 50 years, no use of specific MG during hospitalization). The mortality rate reported in our work (20%) was comparable to the COVID-19-associated risks and effects in myasthenia gravis (CARE-MG) registry interim analysis published in December 2020¹⁸ including 91 MG patients with COVID-19 (mortality rate of 24%) and to the results of the study of Camelo-Filho et al.² (26.66%). It was also comparable to the mortality rate observed in multiple sclerosis patients with COVID-19 (29.4%).¹⁴ However, it was much higher than the mortality rate reported in the COVID-19-Global Rheumatology Alliance physician registry¹⁷ including 600 patients with rheumatoid arthritis, systemic lupus erythematosus (SLE), and psoriasis arthritis with a mortality rate of 9%. Thus, a clinical and demographic profile of a subgroup of MG patients with concurrent COVID-19 infection that may be linked to higher mortality may be assumed. Further data would be necessary to substantiate this observation.

The autoimmune (AI) rheumatic diseases are associated with a chronic inflammatory status and multiple organ damage.¹⁶ In addition, patients are usually taking long-term IS therapy. Together, these elements, confer this category increased susceptibility to severe forms of COVID-19 infections.

TABLE 2 Comparison of our series to early reported series of Myasthenia Gravis patients with COVID-19

	N Rein et al. ⁶	Camelo-Filho et al. ²	Huber et al. ⁵	Anand et al. ⁷	Our study
Number of patients	3	15	4	5	5
Gender (F/M)	2/1	9/6	2/2	3/2	4/1
Age in years, median (ranges)	42 (38–66)	61,3	36 (25–55)	64 (42–90)	54 (37–60)
Antibody status (number)	NS	AchR (10), Musk (1), SN (4)	AchR (3), SN (1)	AchR (4), Musk (1)	AchR (3), SN (2)
Thymectomy number (percentage)	2 (66,66%)	6 (40%)	3 (75%)	2 (40%)	1 (20%)
Mean duration of MG in years (ranges),	10 (1–4)	9 (1–22)	3.5 (2–6)	4 (1–20)	9 (3–15)
Comorbidities (number of patients)	Diabetes and hypertension (1), hypothyroidism (1).	Diabetes (4), hypertension and LES (1), asthma (1).	Basedow disease (1), Behçet disease, migraine, endocrinopathy and obesity (1), hypertension (1), obesity, and sleep apnea (1).	Dementia (1), Hepatitis B (1).	Obesity (1).
MGFA severity classification before COVID-19 infection (number of patients)	Complete remission (1), IIa (2)	I(5), IIa or IIb (9), III(1)	IIa (2), IIIb (1), V(1)	I(3), IIb (1), pharmacological remission(1)	I(1), IIa (3), IIIb(1).
Number of MG Exacerbation during COVID-19 infection (percentage)	1 (33,33%)	13 (86,66%), 11 needing M.V	2 (50%), 1 needing M.V.	1 (25%)	2 (40%).
Treatment change of MG during hospitalization for COVID-19 infection (number of patients)	Initiation and/or maintenance of IV Ig (2), increased prednisone dose (1).	Initiation of IV Ig (1), Plasmapheresis (4), IS therapy withheld (5).	Increased dose of pyridostigmine (1), Prior IS therapy withheld (1).	IS therapy withheld (3), Prednisone dose maintained or increased (2), prednisone dose reduced (1).	Maintenance of prior IS therapy (4), Iv Ig (1).
Specific therapy of COVID-19 infection (number of patients)	HCQ, lopinavir and ritonavir (1).	Macrolides (11), Oseltamivir (2).	AZM (3), TZB/PIP (1).	HCQ (3), AZM (3), CTX (1).	AZM (4), LEV (1).
Clinical outcomes (number of patients)	Discharged or recovered at home with improvement (3).	13/15 admissions in an ICU (11 needing M.V).	Discharged at home with full recovery (1), with residual mild to moderate signs (2), Prolonged M.V. period, weakness of pharyngeal muscles (1)	Discharged at home with improvement (4), requires of ongoing VM (1).	Discharged or recovered at home with improvement (4), death (1).
Mortality, number of patients (percentage)	0	4 (26,66%)	0	0	1 (20%)

Abbreviations: AchR, acetylcholine receptors; COVID-19, coronavirus disease 19; CTX, Ceftriaxone; F, female; HCQ, hydroxychloroquine; ICU, intensive care unit; IS, immunosuppressive; IV Ig, intravenous immunoglobulin; LEV, levofloxacin; M, male; MG, myasthenia gravis; MGFA, myasthenia gravis foundation of America; Musk, muscle specific kinase; MV, mechanical ventilation.

In this context, more specific features of the effect of infections on MG are to consider. Indeed, a reciprocal accentuation may occur between MG exacerbation (leading to secret stagnation and infection in the lower respiratory tract) and respiratory infections (making MG exacerbation worse).¹⁹

The immunopathology of MG involves the release of several cytokines by upregulated Th 17 cells resulting in a chronic inflammation of the neuromuscular junction.¹⁹ Also, it was demonstrated elevated production of INF 8 by memory T cell from a cohort of MG patients and Th 22 cells, secreting TNF α are increased in MG.^{19,20} This is

important to know since INF γ and TNF α are two components of the cytokine storm observed in ARDS related to SARS-CoV-2 infection,^{20,21} in addition to immunosenescence, that may contribute to ARDS.^{13,14}

Also, it was demonstrated a cellular dysfunction in the regulatory T cell extracted from MG patients thymus²² or from peripheral blood of MG patients.^{19,23} This may explain an increased susceptibility of MG patients to SARS-CoV-2 infection since regulatory T cell, in normal conditions, are chelated to infected pulmonary tissue by COVID-19 virus, in order to inhibit inflammation and repair tissue damage.^{22,24}

Finally, from a pathophysiological point of view, it is worth noting that the dysregulated immune state in MG patients is associated with an increased level of pro-inflammatory cytokines (Interleukine-6, Interleukine-17, and interferon-gamma). SARS-CoV-2 induces a similar immune profile by inducing B-cells and T-cells depletion.²⁵ This could help us understand the greater risk of COVID-19 in MG patients.

Ongoing immunosuppressive therapy for MG should be maintained during COVID-19 infection if it is considered to have a stabilizing effect on MG patients as previously shown by Camelo-Filho et al.² and Huber et al.⁵ This should be integrated in an individualized approach according to the infection severity and the intensity of the immunosuppressive therapy.³

The specific treatment of SARS-CoV-2 infection in MG patients is also challenging. Indeed, hydroxychloroquine may worsen the clinical manifestations of MG or induce MG itself.¹⁰ This drug was not used in our patients as it is not included in our national consensus treatment guidelines for SARS-CoV-2 infection. Our experience with the use of AZM argues in favor of its efficacy and safety in the treatment of SARS-CoV-2 infection in MG patients. This is a significant point, which in line with the experience of Camelo-Filho et al.² who safely used AZM in ten patients of their series. These reassuring results encourage its use in the context of COVID-19 pandemic.

5 | CONCLUSION

Concurrent COVID-19 infection in patients with preexisting MG is a complex and challenging issue. More insight into the pathophysiology associated with infection in this particular population is needed. Further studies are needed to determine if MG patients are at higher risks of COVID-19 infection and mortality. MG activity prior to COVID-19 infection could partially influence the subsequent clinical outcomes. Signs of MG exacerbation or crisis may be concurrent or following SARS-CoV-2 infection. In this situation, short-term immunomodulatory therapy (IVIg, plasma exchange) is a safe therapeutic option that would not negatively affect the course of COVID-19 infection. An increasing number of arguments in favor of maintaining ongoing long-term immunosuppressive immunotherapy, including corticosteroids, during COVID-19

pandemic have been advanced. The use of AZM, as a specific therapy for COVID-19 infection, was reassuring as shown in our study.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

DISCLOSURE

All authors have approved the final article.

DATA AVAILABILITY STATEMENT

N/A.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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