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COVID-19 in patients with myasthenia gravis

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Abstract

Introduction: Coronavirus disease 2019 (COVID-19) has rapidly become a global pandemic, but little is known about its potential impact on patients with myasthenia gravis (MG).

Methods: We studied the clinical course of COVID-19 in five hospitalized patients with autoimmune MG (four with acetylcholine receptor antibodies, one with muscle-specific tyrosine kinase antibodies) between April 1, 2020-April 30-2020.

Results: Two patients required intubation for hypoxemic respiratory failure, whereas one required significant supplemental oxygen. One patient with previously stable MG had myasthenic exacerbation. One patient treated with tocilizumab for COVID-19 was successfully extubated. Two patients were treated for MG with intravenous immunoglobulin without thromboembolic complications.

Discussion: Our findings suggest that the clinical course and outcomes in patients with MG and COVID-19 are highly variable. Further large studies are needed to define best practices and determinants of outcomes in this unique population.

KEYWORDS

COVID-19, immunosuppression, myasthenia gravis, neuroimmunology, neuromuscular disorders

1 | INTRODUCTION

Coronavirus disease 2019 (COVID-19) has rapidly evolved into a global pandemic.[1] COVID-19–associated respiratory failure and mortality are driven in part by a massive inflammatory response.[2] Neurological sequelae, including cerebrovascular events, impaired consciousness, skeletal muscle injury, and meningoencephalitis, may complicate the disease.[3–8] Interleukin inhibitors (anakinra and tocilizumab) and other therapies that target inflammation are currently in clinical trials for treatment of severe cases of COVID-19.[2] It is unknown whether COVID-19 causes more severe disease in patients with chronic neuromuscular disorders like myasthenia gravis (MG), which can cause respiratory muscle weakness, or for those who are immunosuppressed. Existing guidelines for management of COVID-19 in patients with MG are based on expert consensus.[9] Herein we describe the clinical course and outcomes of COVID-19 in five patients with pre-existing diagnoses of MG.

Abbreviations: AChR, acetylcholine receptor; COVID-19, coronavirus disease 2019; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MMF, mycophenolate mofetil; MuSK, muscle-specific tyrosine kinase; PCR, polymerase chain reaction.

2 | METHODS

This observational study was approved by the institutional review boards of Boston University Medical Center and Partners Healthcare. Diagnosis of COVID-19 was based on clinical history, chest imaging, and positive nasopharyngeal swab polymerase chain reaction (PCR) testing for severe acute respiratory syndrome coronavirus 2. Cases were identified through routine inpatient neurology consultations and outpatient neuromuscular

TABLE 1 Patients' characteristics

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	M	M	F	F	F
Age	57	64	90	42	64
Duration of diagnosis (years)	20	4	1	6	2
Comorbidities	Hypertension	Diabetes mellitus	Dementia, hypertension	Hepatitis B	Diabetes mellitus, hypertension
Prior maximum MGFA severity class[24]	Class V	Class V	Class III B	Class III B	Class I
MGFA severity class at the time of COVID-19	Class I	Pharmacological remission	Class I	Class II B	Class I
Antibody status	AChR$^+$	AChR$^+$	AChR$^+$	MuSK$^+$	AChR$^+$
History of thymoma?	N	N	N	N	N
History of thymectomy?	Y, 6 months before admission	Y, 18 months before admission	N	N	N
Home immunosuppressive regimen	AZA 50 mg every day	MMF 1000 mg twice daily, Pred 5 mg every other day	MMF 1000 mg twice daily, Pred 30 mg every day IVIg 0.8 g/kg IBW monthly	Pred 5 mg alternating with 2.5 mg every other day	MMF 750 mg twice daily, Pred 15 mg every day
Previous immunosuppressive therapies tried (including maximum corticosteroid dose)	IVIg 2 g/kg IBW, Pred 60 mg every day	IVIg 2 g/kg IBW, Pred 60 mg every day	AZA, Pred 60 mg every day	IVIg, Pred 40 mg every day	AZA, Pred 60 mg every day
Presenting symptoms	10 days of sore throat and cough	4 days of cough and chills	2 days of shortness of breath, cough, and fever	3 days of sore throat and myalgias, followed by worsening dysphagia, neck weakness, and diplopia	10 days of cough, night sweats, and chills
Treatments for MG administered during hospitalization	AZA 50 mg every day continued throughout hospitalization	MMF initially held, resumed on HD11 Pred continued (10 mg every day for 9 days then 5 mg every day)	MMF held Pred reduced to 25 mg every day × 6 days, then 20 mg every day IVIg continued	Pred increased to 20 mg every day IVIg 2 g/kg IBW added	Home regimen continued during admission, MMF held for 1 week after discharge
Treatment(s) administered for COVID-19	HCQ 400 mg twice daily × 1 day, 200 mg every day × 2 days; AZM 500 mg every day × 1 day, 250 mg every day × 2 days; TOZ 300 mg × 1 dose	HCQ 400 mg twice daily × 1 day, 400 mg every day × 4 days; AZM 500 mg every day × 1 day, 250 mg every day × 4 days; CTX 2 g every day × 2 days, 1 g every day × 3 days	HCQ 400 mg twice daily × 1 day, 200 mg twice daily × 4 days; AZM 500 mg every day × 5 days CTX 1 g every day × 5 days	None	None
Required respiratory support?	Y, intubated HD2, extubated HD7	Y, intubated HD1, required tracheostomy on HD21 and ongoing mechanical ventilation as of HD35	Y, high-flow oxygen with a non-rebreather mask from HD10 to HD17, weaned to nasal cannula	N	N

(Continues)

TABLE 1 (Continued)

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Evidence of myasthenic exacerbation?	Examination limited by intubation and sedation	Examination limited by intubation and sedation	N	Y	N
Disposition	Discharged home on HD9	Remains hospitalized, requires ongoing mechanical ventilation	Discharged to a skilled nursing facility on HD19	Discharged home on HD5	Discharged home on HD9

AZA, azathioprine; AZM, azithromycin; CTX, ceftriaxone; HCQ, hydroxychloroquine; HD, hospital day; IBW, ideal body weight; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MuSK, muscle-specific tyrosine kinase; N, no; Pred, prednisone; TOZ, tocilizumab; Y, yes.

care among authors at Boston University Medical Center and Massachusetts General Hospital between April 1, 2020-April 30-2020.

3 | RESULTS

Table 1 shows complete clinical information regarding each patient. Five patients with MG and COVID-19 were identified, including four with acetylcholine receptor (AChR) antibodies and one with muscle-specific tyrosine kinase (MuSK) antibodies. One patient with previously well-controlled MuSK-positive MG had a myasthenic exacerbation characterized by dysphagia, neck weakness, and diplopia, and was treated with intravenous immunoglobulin (IVIg) with an increased dose of steroids (patient 4). Three patients on mycophenolate mofetil (MMF) at home had this medication transiently held (patients 2, 3, and 5), whereas one patient on maintenance IVIg received this medication during her hospitalization (patient 3). Three patients had hypoxemic respiratory failure secondary to COVID-19 (patients 1, 2, and 3). Two of these patients were intubated and sedated, limiting the ability to detect worsening myasthenic weakness that may have contributed to respiratory failure (patients 1 and 2). However, none of these patients had definite new or worsening weakness to support a myasthenic exacerbation. One patient had no respiratory failure or worsening myasthenic weakness (patient 5).

4 | DISCUSSION

Infections are a common trigger for myasthenic exacerbations.[10] In the setting of COVID-19, hypoxemic respiratory failure secondary to the virus itself is common, but the course of the illness may also be complicated by myasthenic exacerbation and resultant neuromuscular respiratory failure. COVID-19 poses unique challenges to the evaluation and management of patients with MG. Respiratory mechanics, the gold standard of evaluation for neuromuscular respiratory failure, and non-invasive ventilation, often used for MG patients with mild or moderate respiratory distress, are avoided in patients with COVID-19 because of the risk of aerosolization of viral particles and viral transmission.[11] As seen for patients 1 and 2, patients with COVID-19 are at risk of developing acute respiratory distress syndrome, requiring high doses of sedating medications and paralytics for management of their respiratory failure, limiting access to a neurological examination and potentially adding to the risk of a myasthenic exacerbation.[12] In patients who are intubated, spontaneous tidal volumes can be used as a proxy, with a predicted normal value of 5 mL/kg and significantly lower values suggesting some contribution of neuromuscular respiratory failure.[13]

In addition to the risk of myasthenic exacerbation from COVID-19, experimental therapies for COVID-19 like azithromycin and hydroxychloroquine may also trigger a myasthenic exacerbation.[14,15] Unless azithromycin and hydroxychloroquine become standard of care for COVID-19, they should likely be avoided or used with caution in patients with MG given the potential to worsen MG.[16]

Tocilizumab, a humanized interleukin-6 receptor monoclonal antibody, is also used experimentally in severe cases of COVID-19.[2]

Patient 1, who had a history of myasthenic crisis, received tocilizumab for COVID-19 and was extubated and discharged without clear evidence of a myasthenic exacerbation. Interleukin-6 stimulates the production of autoantibodies from plasma cells, and tocilizumab has shown efficacy in the treatment of some autoantibody-mediated disorders.[17] In the absence of COVID-19, tocilizumab use has shown safety and efficacy in treatment of refractory MG in a series of two cases.[18]

Management of immunosuppression in patients with MG and COVID-19 is challenging. Limited literature exists on the clinical course and recovery of COVID-19 in immunocompromised patients.[19,20] In our case series, three patients developed severe respiratory distress secondary to COVID-19 requiring intubation or high-flow oxygen, whereas two experienced a milder course of COVID-19 without respiratory complications. Of the patients with severe disease, one was successfully extubated and one was able to be weaned off of high-flow oxygen, whereas the third patient required tracheostomy and ongoing ventilation. Four of five immunosuppressed patients presented here had favorable outcomes.

Patients 2 and 3 had MMF held during the course of their illness; the impact of this short-term discontinuation of MMF is unclear, as studies suggest that the drug may remain active for up to 6 weeks after cessation.[21] As suggested by existing expert consensus guidelines,[9] decisions regarding continuation of immunosuppression and initiation of acute interventions, such as high-dose corticosteroids and IVIg, should be made on a case-by-case basis based on the relative severities of COVID-19 and MG. Of note, although an increased risk of thromboembolic events has been described in both patients receiving IVIg and those with COVID-19,[22] patients 3 and 4 in our series received IVIg without complications.

These 5 patients with COVID and MG demonstrate the unique evaluation and management considerations in this patient population. Our series is limited by the small number of patients and short duration of follow-up, which did not include the postinfectious period, a time of risk for myasthenic exacerbation. Larger and longer studies are needed to more fully understand: 1) whether patients with MG face special risks from COVID-19 or treatments; 2) whether baseline therapies impact risk; and 3) best practices for management of COVID-19 in patients with MG. To this end, the International Myasthenia Gravis/COVID-19 Working Group and the Myasthenia Gravis Rare Disease Network have developed an open registry called COVID-19 Associated Risks and Effects in Myasthenia Gravis to track outcomes of COVID-19 of any severity in patients with myasthenia gravis.[23] A large registry is needed because, as illustrated by the patients described in this series, outcomes in smaller groups can be highly variable.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

ETHICAL PUBLICATION STATEMENT

We confirm that we have reviewed the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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A telephonic single breath count test for screening of exacerbations of myasthenia gravis: A pilot study

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Abstract

Background: Patients with myasthenia gravis (MG) may experience worsening symptoms outside of a clinical setting. A method of diagnosing and triaging such individuals would be valuable. This study gauged the viability of a nurse-administered single breath count test (SBCT) over the telephone for assessing MG exacerbations.

Methods: This was a retrospective, single-center review of a pilot study of 45 telephone calls from patients with MG who had worsening baseline symptoms. SBCTs were administered over the telephone to patients by trained nurses. Patients with a breath count of 25 or less were sent to the emergency department.

Results: Using a cutoff count of 25, the nurse-administered telephonic SBCT had a positive predictive value of 71%, sensitivity of 80%, and specificity of 60% in diagnosing an MG exacerbation.

Conclusions: SBCT administered by trained nurses by means of telephone may be a useful screening tool for assessing decreased respiratory function in patients with MG.

KEYWORDS
breath count, exacerbation, myasthenia gravis, myasthenic crisis, SBCT, telemedicine

1 | INTRODUCTION

Patients with myasthenia gravis (MG) are susceptible to episodes of exacerbation, which can lead to serious respiratory complications. In 20% of patients with generalized MG, exacerbation leads to a

Abbreviations: Anti-AChR, anti-acetylcholine receptor; Anti-MuSK, anti-muscle specific receptor tyrosine kinase; CME, continuing medical education; ED, emergency department; IRB, Institutional Review Board; MC, myasthenic crisis; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America; NF, neck flexor strength test; ROC, receiver operating characteristic; SBCT, single breath count test.

Klaudia Kukulka and Rohit Reddy Gummi contributed equally to this work.