Myasthenia Gravis Exacerbation and Myasthenic Crisis Associated With COVID19: Case Series and Literature Review.

Cleonisio Leite Rodrigues

Hospital Geral de Fortaleza

Hermany Capistrano Freitas

Hospital Geral de Fortaleza

Paulo Reges Oliveira Lima

Universidade Federal do Ceara

Pedro Helder de Oliveira Junior

Universidade Federal do Ceara

José Marcelino Aragão Fernandes

Universidade Federal do Ceara

José Artur Costa D'Almeida

Hospital Geral de Fortaleza

Paulo Ribeiro Nóbrega (✉ paulo_r_med@yahoo.com.br)

Universidade Federal do Ceara <https://orcid.org/0000-0002-0021-9358>

Research Article

Keywords: Myasthenia gravis, neuromuscular junction diseases, myasthenic crisis, neurological symptoms, coronavirus, COVID-19

Posted Date: August 10th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-790941/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Myasthenia Gravis (MG) is an autoimmune disorder of the neuromuscular junction that can be exacerbated by many viral infections, including COVID19. Management of MG exacerbations is challenging in this scenario. We report 8 cases of MG exacerbation or myasthenic crisis associated with COVID19 and discuss prognosis and treatment based on a literature review. Most patients were female (7/8), with an average age of 47.1 years. Treatment was immunoglobulin (IVIG) in 3 patients, plasma exchange (PLEX) in 2 patients, and adjustment of baseline drugs in 3. In-hospital mortality was 25% and 37.5% in 2-month follow-up. This is the largest case series of MG exacerbation or myasthenic crisis due to COVID19 to this date. Mortality was considerably higher than in myasthenic crisis of other etiologies. Previous treatment for MG or acute exacerbation treatment did not seem to interfere with prognosis, although sample size was too small to draw definitive conclusions. Further studies are needed to understand the safety and effectiveness of interventions in this setting, particularly of PLEX, IVIG, rituximab and tocilizumab.

Introduction

In mid-November 2019, an outbreak of pneumonia of unknown cause in the city of Wuhan, Hubei province, China, began to attract the attention of Chinese health authorities [1]. The virus was identified as a new type of coronavirus (CoV), named SARS-CoV-2 and its associated disease received the name of COVID-19, which was declared a pandemic by the World Health Organization Health on March 11, 2020, with high levels of contamination and mortality in China, Italy and Spain, and later in the United States and Brazil [1].

Myasthenia gravis (MG) is an autoimmune disorder that affects the neuromuscular junction and may lead to respiratory muscle weakness with respiratory insufficiency (myasthenic crisis) [2]. It can often be exacerbated by common viral or bacterial infections, including COVID19 infection [3].

Exacerbation of MG during COVID19 infection appears to be uncommon, ranging from 10-15% [4,5]. The scenario of myasthenia exacerbation due to COVID19 can be challenging, both due to diagnostic concerns (is respiratory insufficiency related to hypoventilation secondary to muscle weakness or hypoxia secondary to pulmonary involvement?) and treatment (are plasma exchange [PLEX] and intravenous immunoglobulin [IVIG] safe and effective for the treatment of myasthenic crisis in this setting?).

Previous studies have reported outcomes of myasthenic patients with COVID infection, but few of them have focused especially on those who had exacerbations. We report 8 cases of myasthenia exacerbation or myasthenic crisis associated with acute COVID19 infection and discuss prognosis and treatment based on a literature review.

Materials And Methods

This was an observational retrospective study including all consecutive adult patients diagnosed with MG (based on antibodies or on electrophysiology) and admitted with acute COVID-19 infection and myasthenia exacerbation at two reference hospitals in Fortaleza, state of Ceará in the northeast of Brazil, from May 2020 to April 2021. Diagnosis of Covid-19 was confirmed with real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay (LightMx Modular SARS-CoV (COVID19) Egene and LightMx Modular SARS-CoV (COVID19) RdRP, Roche Diagnostics S.L.) from oropharyngeal-nasopharyngeal swab, sputum or lower respiratory tract in all cases. Informed consent was waived because of the retrospective observational nature of the study and the analysis used anonymous clinical data.

All patients underwent detailed clinical and neurological examination, and neuromuscular specialists in each hospital reviewed medical charts. The diagnosis of MG based on clinical aspects, serology (positive Acetylcholine receptor-AChR autoantibodies or Muscle specific tyrosine kinase -MuSK antibodies) and electrophysiological findings (abnormal decrement in repetitive nerve stimulation-RNS). Myasthenia Gravis Foundation of America (MGFA) scores [6] were defined based on the clinical descriptions one month prior to hospitalizations when available. MG exacerbation was defined as a MGFA score worsening from baseline or respiratory insufficiency needing mechanical ventilation (MV).

Results

We identified 8 patients with myasthenia exacerbation or myasthenic crisis during acute COVID19 infection. Most patients were female (7/8), with an average age of 47.1 years. The majority (6/8) required mechanical ventilation. Treatment of exacerbation was IVIG in 3 patients, PLEX in 2 patients, and adjustment of baseline myasthenia drugs in 3. Average hospital stay was 42.62 days. Mortality during hospital stay was 2/8 and 3/8 in short-term follow-up (2 months). Of those with myasthenic crisis, mortality in follow-up was 50% (3/6). Here we present the details, clinical course and treatment of these 8 patients (Table 1) in chronological order of symptom onset.

Case 1

A 49-year-old female patient had been diagnosed with generalized MG since 2013 (clinical findings, abnormal RNS and positive AChR autoantibodies), MGFA class IIa, having been treated with azathioprine, prednisone and pyridostigmine. In 2015 she was diagnosed with thymoma and underwent thymectomy and radiotherapy. Two days before admission in May 2020, the patient reported fever, shivering, odynophagia, headache and dyspnea. One day before admission she also reported cough. RT-PCR was positive for SARS-Cov-2 infection. After admission, dyspnea got worse; ptosis and muscle weakness in four limbs were noted. Chest high resolution CT scan revealed a pattern suggestive of COVID pneumonia.

She was transferred to an intensive care unit. Azathioprine was suspended due to suspected associated bacterial infection; prednisone dosage was increased to 60mg/day. Five days after admission, patient had respiratory failure and required orotracheal intubation, remaining for 30 days under sedation and neuromuscular block. During this period, she performed 2 cycles (5 days each) of IVIG at a dose of 1 g/kg at an interval of 21 days. After extensive treatment with antibiotics for bacterial pneumonia and sepsis she achieved clinical improvement, but still needed prolonged mechanical ventilation through a tracheostomy. She was discharged two months after admission still using a tracheostome, but without the need for mechanical ventilation. She is currently decannulated, independent for activities of daily living, and returned to her previous treatment with Azathioprine 150mg/day, pyridostigmine and prednisone 20mg/day.

Case 2

A 90-year-old female patient reported cough and adynamia seven days before admission in June 2020. On admission she had worsening of cough and dyspnea. Chest high resolution CT scan revealed a pattern suggestive of COVID pneumonia. RT-PCR was negative for SARS-Cov-2 infection in two occasions, but serology was positive. Two days after hospitalization her breathing pattern worsened, and orotracheal intubation was performed. Her family reported diplopia, ptosis and transient cervical weakness for the preceding year. Imaging and laboratory tests were performed and AChR antibodies were identified, establishing the diagnosis of MG - MGFA class III. RNS was not carried out. For religious reasons, she was not treated with IVIG or PLEX. The patient had severe respiratory muscle weakness and multiple infections in a hospital stay of 4 months. After discussion with family members, immunoglobulin was administered and the patient was successfully weaned from mechanical ventilation. She left the hospital tracheostomized, using prednisone 40mg/day and pyridostigmine. Azathioprine was started after hospital discharge. The patient was in good control of the disease. However, she died at home two months later.

Case 3

A 34-year-old female patient had a diagnosis of generalized MG since the age of 15 (clinical findings, abnormal RNS and positive AChR autoantibodies), MGFA class III, having been treated with azathioprine, prednisone and pyridostigmine. She also had hypothyroidism in use of levothyroxine. The patient had a history of multiple hospitalizations due to myasthenia exacerbations having required orotracheal intubation and PLEX in the past. Five days before admission in March 2021 she reported fever, cough and diarrhea. On admission she had worsening dyspnea. RT-PCR was positive for SARS-Cov-2 infection. Chest high resolution CT scan revealed a pattern suggestive of COVID pneumonia. Two days after admission, the patient progressed to acute respiratory failure and needed orotracheal intubation. Azathioprine was suspended due to suspected associated bacterial infection and prednisone was switched to dexamethasone in the context of COVID pneumonia. Plasma exchange was indicated for the treatment of myasthenic crisis on the unavailability of immunoglobulin at that moment. The patient underwent two sessions without complications. On the fifth day of hospitalization, however, she developed refractory septic shock and cardiorespiratory arrest.

Case 4

A 28-year-old woman had been diagnosed with MG in December 2020 (clinical manifestations, abnormal RNS and positive AChR autoantibodies), MGFA class IIb, initially treated with pyridostigmine 300 mg/day. A chest CT scan showed a thymoma. In January 2021 she had clinical worsening with dysphagia and dyspnea and was admitted to a hospital for stabilization and evaluation for possible thymectomy. After therapy with two monthly cycles (5 days) of immunoglobulin (2 g/kg) and prednisone (1 mg/kg/day) her condition stabilized, as dyspnea and dysphagia resolved. However, before the evaluation of the thoracic surgery team the patient started with fever, cough, and dyspnea. After 48 hours she had respiratory failure, requiring mechanical ventilation. RT-PCR was positive for SARS-Cov-2 infection and chest CT scan showed a COVID pneumonia pattern involving 25-50% of her lungs. She was tracheostomized and prednisone was switched to dexamethasone. Antibiotic therapy for secondary bacterial pneumonia was also started. The patient remained on mechanical ventilation for 10 days. Two days after removal of invasive ventilation, the patient was out of oxygen support and able to feed orally. She was discharged taking prednisone (0.75 mg/kg/day) and, in the follow up (30 days later), her condition had a significant improvement (MGFA class IIa). Azathioprine (100 mg/day) was started, and she was referred to thoracic surgery for scheduling thymectomy.

Case 5

A 37-year-old female patient started with dysphagia, dysphonia and post-prandial cough, followed by bilateral ptosis, diplopia and mild dyspnea on exertion 3 months before admission. There was no previous illness and no family history of neurologic diseases. Three months later she had sudden worsening of dyspnea, needing supplementary oxygen, and was intubated the following day. RT-PCR was positive for SARS-Cov-2 infection. Chest high resolution CT scan revealed a pattern suggestive of COVID pneumonia. Five days later, after waning of sedation, bilateral ptosis, facial weakness and ophthalmoparesis were perceived, and a clinical diagnosis of MG was suggested (characterized as MGFA class IIIB based on previous symptoms). She received dexamethasone treatment for COVID19 pneumonia and was submitted to PLEX. Anti-AChR and MuSK antibodies were negative, but a decremental response on RNS was present. She underwent tracheostomy and was successfully weaned from mechanical ventilation. After one month of admission she had another exacerbation with worsening of ptosis, diplopia and dysphagia, and underwent another five sessions of PLEX. Considering her MG to be refractory, Rituximab 750 mg/m² in two divided doses was administered. After one week of initial Rituximab infusion she had significant improvement, was decannulated, and discharged home on prednisone 60mg/day and pyridostigmine.

Case 6

A 37-year-old female patient had anti-AchR generalized MG (MGFA class IIA) since childhood, having been previously treated with azathioprine and had a diagnosis of myelodysplastic syndrome for 12 years. She was currently treated with methotrexate, pyridostigmine and prednisone. Two days before admission the patient reported fever, shivering, odynophagia and rhinorrhea, as well as hyperemia in her left gluteal region. RT-PCR was positive for SARS-Cov-2 infection. After admission, tachypnea and worsening of ptosis and muscle strength in four limbs were noted. Chest CT scan revealed a pattern of COVID pneumonia. The lesion in her gluteal region was suggestive of cellulitis and ceftriaxone and oxacillin were started. Methotrexate was suspended due to possible pulmonary side effects and prednisone was switched to dexamethasone in the context of COVID pneumonia. There was no need for supplementary oxygen or noninvasive ventilation. Immunoglobulin was considered, but after 4 days of antibiotics there was resolution of skin lesions and gradual improvement in strength, diplopia and ptosis. After seven days she was discharged home with resolution of all neurologic symptoms.

Case 7

A 51-year-old male patient had been diagnosed with generalized MG in 2010 (clinical findings, abnormal RNS and positive AchR autoantibodies), MGFA class II, having been treated with azathioprine, prednisone and pyridostigmine. He also had type I Chiari malformation. Seven days before admission in April 2021 he reported fever, odynophagia and headache. Worsening dyspnea led to hospital admission, and he required oxygen via nasal cannula. RT-PCR was positive for SARS-Cov-2 infection. Chest X-ray revealed bilateral infiltrates at pulmonary bases. Prednisone was switched to dexamethasone in the context of COVID pneumonia, azathioprine and pyridostigmine were maintained. Antibiotics were not used. After four days oxygen support was removed, and the patient was discharged the next day. He continued his treatment with Azathioprine 100 mg/day and pyridostigmine 240 mg/day.

Case 8

A 51-year-old female patient had a diagnosis of generalized MG since 2004 (clinical findings, abnormal RNS and positive Musk autoantibodies), MGFA class II, having been treated with rituximab, prednisone and pyridostigmine. She also had hypertension. The patient had a history of multiple hospitalizations due to myasthenia exacerbations having required orotracheal intubation, PLEX and IVIG in the past. Fourteen days before admission in April 2021 the patient reported fever, cough, diarrhea, headache and thoracic pain. On admission she reported dyspnea and worsening cough. RT-PCR was positive for SARS-Cov-2 infection. Chest high resolution CT scan revealed a pattern suggestive of COVID pneumonia. Four days after admission, the patient progressed to hypoxemia and needed orotracheal intubation on the seventh day of hospitalization. Pyridostigmine was suspended and prednisone was switched to dexamethasone in the context of COVID pneumonia. Neither PLEX nor immunoglobulin was prescribed. The patient progressed to multiple organ dysfunction syndrome. On the eleventh day of hospitalization, hemodialysis was started and she needed increasing doses of vasoactive drugs. She developed refractory septic shock and cardiorespiratory arrest after one month of admission.

Discussion

This is one of the first case series to include only patients with myasthenia exacerbation or myasthenic crisis triggered by acute COVID19 infection. We discuss clinical characteristics, pulmonary and systemic involvement, previous MG treatment and acute exacerbation treatment and prognosis in our patients and compare to a literature review.

Viral and bacterial respiratory infections are common triggers for exacerbation in MG. COVID19 has also been described as a trigger for exacerbation [3, 7-9], although MG worsening appears to be uncommon in COVID, affecting only 10-15% of patients [4,5]. Comparing this number to seasonal influenza, a recent study performed before the coronavirus pandemic has shown that an influenza-like illness (defined as fever of $\geq 38^{\circ}\text{C}$ accompanied by cough and/or sore throat) resulted in exacerbation in 40% of myasthenic patients [10]. In the same study, a common cold (defined as signs of upper respiratory infection without fever) resulted in exacerbation in 15.6%. It is still unclear if this discrepancy is a result of underreporting of MG worsening due to severity of pulmonary symptoms in COVID or if it represents a lower potential for exacerbating MG symptoms in COVID infection.

Some studies have established MG as an independent risk factor for worse prognosis in COVID [4], and found that unsatisfactory control of MG symptoms, long term corticosteroid treatment, older age, cancer and rituximab use were risk factors for death in these patients. However, very few of these patients had MG exacerbations and death was related to pulmonary involvement by viral or secondary pneumonia in most cases. In the present study we systematically focus on patients with exacerbations.

Exacerbations of MG and myasthenic crisis associated with COVID19 pose unique challenges, as immunosuppressive therapies may influence the course of viral infection.

The impact of plasma exchange in COVID19 has been under study recently. One of the main causes of tissue damage in COVID 19 is a widespread immune dysregulation referred to as cytokine storm syndrome (CSS). Inflammatory manifestations in COVID-19 are attributed to CSS with elevated interleukin-1 (IL-1), interleukin-6 (IL-6), granulocyte-colony stimulating factor (GCSF), tumor necrosis factor (TNF), ferritin, and other immune-inflammatory mediators [11]. Some of these factors could be removed by plasma exchange, possibly aborting the cytokine cascade activation. In a case series of 31 patients with acute respiratory distress syndrome (ARDS) due to SARS-CoV-2, PLEX has been shown to reduce 28-day mortality (0 vs 35%, $p=0.033$) and improve extubation rates (73% vs 20%, $p=0.018$) [12]. PLEX has also reduced mortality in secondary thrombotic

microangiopathy (TMA) and diffuse intravascular coagulation (DIC), complications that have been extensively reported in critically ill COVID patients [13,14]. Major concerns involving PLEX in COVID are hypotension, which can be partially overcome with administration of intravenous fluids [15], and risk of bleeding due to procoagulant depletion. Plasma exchange also leads to immunosuppression, possibly increasing the risk of secondary bacterial infections. Immediately after PLEX the levels of IgA, IgG, IgM, C3, C4 and CH50 are reduced by 50-70% [16]. Some authors have found high infection rates in patients undergoing PLEX [17], but we found no robust evidence based on controlled trials to quantify that risk. In our series two patients were treated with PLEX. One of them died but the other had a very significant improvement and was discharged in a better MGFA class than before COVID infection.

Intravenous immunoglobulin (IVIG) has anti-inflammatory and immunomodulating effects. Previous studies have shown efficacy of IVIG in the treatment of patients with severe inflammatory response associated with influenza [18] and SARS-CoV [19] infection, but there are not sufficient evidence to ascertain its safety and effectiveness in COVID19. There are some reports of myasthenic exacerbations due to COVID treated with IVIG without major side effects [20]. Two major side effects are thrombotic events that have an estimated incidence of 1–16.9% [21], and may be even higher in a COVID setting, and transfusion-related acute lung injury (TRALI), an immune-mediated process that can lead to ARDS [21] or worsen an already established pulmonary inflammation. Two patients in our series received IVIG. None of them died. One was discharged in a better MGFA than at admission and the other in a worse functional status.

As previously stated, medications used for chronic immunosuppressive treatment in MG might also influence COVID19 disease course. Evidence from small series suggested that corticosteroids in higher doses and rituximab might increase mortality. Azathioprine, mycophenolate mofetil and cyclosporine did not influence outcomes [4]. Of the 3 patients in our series who died during follow-up, two were taking corticosteroids, one of them associated with azathioprine and the other with rituximab. The third patient was not using any medication as she did not have a previous diagnosis of MG before myasthenic crisis. Among survivors, most patients also used corticosteroids chronically (3/5). Only two out of 8 patients did not need mechanical ventilation, and both were taking oral prednisone >40mg/kg. Both these patients had a very short hospital state and were discharged in a similar MGFA to the one they were in before admission.

Some antibiotics and other classes of drugs which might be used for general supportive care in COVID19 might also exacerbate myasthenic symptoms. Three of our patients took azithromycin, a macrolide antibiotic that may be able to suppress inflammation in ARDS [22], but has failed to demonstrate clinical efficacy in COVID [23]. Two of these patients died (66%). Azithromycin is known to worsen myasthenic symptoms and may precipitate myasthenic crisis [24,25]. All patients taking azithromycin required mechanical ventilation. Only one patient received hydroxychloroquine, another drug that has shown in vitro antiviral activity but has failed to demonstrate clinical benefit [26]. Chloroquine and hydroxychloroquine also have the potential to exacerbate MG symptoms [24,25].

Antibiotics are usually prescribed in critically ill COVID19 patients to treat known or suspected secondary bacterial infection. Many antibiotics may also exacerbate MG. In our series some patients received aminoglycosides (gentamicin and amikacin), clindamycin and polymyxin, which are all on the list of medications to be avoided in myasthenic patients. The small sample and absence of a control group prevent us from assessing possible effects of these drugs on clinical course. Care should be taken when treating any myasthenic patient with antibiotics.

Our case series showed a very high mortality rate of 37.5% (3/8) on short-term follow up. Two of these patients died during hospitalization and another died 2 months after discharge. Cause of death was septic shock in two patients and unknown in the one who died at home. A study with COVID-19 patients requiring hospitalization in Brazil revealed ICU admission rates of 39% and in-hospital mortality rate of 38% [27]. Mortality in myasthenic crisis of varied etiologies was 12% in a large case series, and main cause of death was multiorgan failure, mostly due to sepsis [28]. Of the patients who had myasthenic crisis (defined as the need for intubation or noninvasive ventilation) in our series mortality was even higher (3/6 – 50%). Despite the small sample in our series, it is possible that mortality of myasthenic crisis due to COVID19 is considerably higher than that of MG crisis due to other etiologies.

Considering current evidence, we believe that the decision to treat MG exacerbations in COVID with PLEX or Immunoglobulin should be taken based on particularities of individual patients, such as risk of thrombotic complications, secondary bacterial or fungal infections and hemodynamic parameters. Immunoglobulin probably results in less hemodynamic compromise, less interference with cytokines, chemokines, and innate immunity factors (which might have a positive or negative effect on outcomes). On the other hand, immunoglobulin might increase the risk of thrombosis, which is also high in COVID infections. PLEX has been studied for the treatment of cytokine storm syndrome in COVID, although evidence is limited to small studies and potential risks such as bleeding, hypotension and possible predisposition to secondary infections raise concerns about its widespread use.

Tocilizumab, a monoclonal anti-IL6 receptor antibody, was shown to have some beneficial effects in MG exacerbations [29] and COVID-19 hospitalized patients [30]. It could be an effective drug for myasthenic exacerbations due to COVID, although it is not widely used in our country and was not used in any patients in our series.

The main limitation of our study is that it was an observational retrospective study with a small number of patients, which limited comparative statistical analysis. Nevertheless, this is the largest case series to date to include only patients with MG exacerbation and myasthenic crisis due to COVID19.

Conclusion

Myasthenia exacerbations and myasthenic crisis seem to be uncommon complications of COVID19 infections. Prognosis in these patients, however, might be very poor. Further studies are needed to understand the safety and effectiveness of interventions in this setting, particularly of PLEX, IVIG, rituximab and tocilizumab.

Declarations

Funding

The research was funded by the researchers.

Competing interests

The authors report that they have no competing interests.

Authors' Contributions

The authors confirm contribution to the paper as follows: study conception and design: Paulo Ribeiro Nóbrega, Cleonísio Leite Rodrigues; data collection: Hermany Capistrano Freitas, Paulo Reges Oliveira Lima, Pedro Helder de Oliveira Junior, Paulo Ribeiro Nóbrega, José Marcelino Aragão Fernandes; analysis and interpretation of results: Paulo Ribeiro Nóbrega, Cleonísio Leite Rodrigues, José Artur Costa D`Almeida; manuscript draft preparation: Paulo Ribeiro Nóbrega, Cleonísio Leite Rodrigues, Hermany Capistrano Freitas. All authors reviewed the results and approved the final version of the manuscript.

Ethics Approval

The study was approved by the local ethics committee under the number 4881736.

Consent to participate

Informed consent was waived because of the retrospective observational nature of the study and the analysis used anonymous clinical data as approved by the research ethics committee.

Consent for publication

The manuscript contains no individual person's data in any form.

Availability of data and material

All materials used in this study will be made available subject to a material transfer agreement.

Code availability

Not applicable

ACKNOWLEDGMENTS:

We would like to acknowledge the staff in both participating centers for their hard work and support.

References

1. World Health Organization. Coronavirus disease (COVID-19) pandemic. Published online 2021. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>
2. Bedlack RS, Sanders DB (2002) On the concept of myasthenic crisis. *J Clin Neuromuscul Dis* 4(1):40–42. doi:10.1097/00131402-200209000-00009
3. Camelo-Filho AE, Silva AMS, Estephan EP et al. Myasthenia Gravis and COVID-19: Clinical Characteristics and Outcomes. *Front Neurol*. 2020;11(September). doi:10.3389/fneur.2020.01053
4. Jakubíková M, Týblová M, Tesař A et al. Predictive factors for a severe course of COVID-19 infection in myasthenia gravis patients with an overall impact on myasthenic outcome status and survival. *Eur J Neurol*. 2021;(870177):1–8. doi:10.1111/ene.14951
5. Businaro P, Vaghi G, Marchioni E et al. COVID-19 in patients with myasthenia gravis: Epidemiology and disease course. *Muscle Nerve*. 2021; (May):1–6. doi:10.1002/mus.27324

6. Jaretzki A, Barohn RJ, Ernstoff RM et al (2000) Myasthenia gravis: Recommendations for clinical research standards. *Neurology* 55(1):16–23. doi:10.1212/WNL.55.1.16
7. Rein N, Haham N, Orenbuch-Harroch E et al (2020) Description of 3 patients with myasthenia gravis and COVID-19. *J Neurol Sci* 417(July):117053. doi:10.1016/j.jns.2020.117053
8. Anand P, Slama MCC, Kaku M et al (2020) COVID-19 in patients with myasthenia gravis. *Muscle Nerve* 62(2):254–258. doi:10.1002/mus.26918
9. Županić S, Perić Šitum M, Majdak M, Karakaš M, Bašić S, Sporiš D (2021) Case series of COVID-19 in patients with myasthenia gravis: a single institution experience. *Acta Neurol Belg* Published online. doi:10.1007/s13760-021-01662-w
10. Hung Youl Seoka B*, Ha Young Shinc*, Jong Kuk Kimd Byoung Joon Kime, Jeeyoung Ohf Bum Chun Suhg S-YKS-YK, Ahnj S-W, Baek JS, Kima B-J, A. The Impacts of Influenza Infection and Vaccination. *J Clin Neuro*. 2017;13(4):325–330
11. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. *Clin Immunol*. 2020;215(April). doi:10.1016/j.clim.2020.108427
12. Khamis F, Al-Zakwani I, Al Hashmi S, Al Dowaiqi S, Al Bahrani M, Pandak N, Al Khalili H, Memish Z. Therapeutic plasma exchange in adults with severe COVID-19 infection. *Int J Infect Dis*. 2020 Oct;99:214–218. doi: 10.1016/j.ijid.2020.06.064. Epub 2020 Jun 23. PMID: 32585284; PMCID: PMC7308750
13. Pene F, Vigneau C, Auburtin M et al (2005) Outcome of severe adult thrombotic microangiopathies in the intensive care unit. *Intensive Care Med* 31(1):71–78. doi:10.1007/s00134-004-2505-0
14. Chang JC. Acute Respiratory Distress Syndrome as an Organ Phenotype of Vascular Microthrombotic Disease: Based on Hemostatic Theory and Endothelial Molecular Pathogenesis. *Clin Appl Thromb*. 2019;25. doi:10.1177/1076029619887437
15. Sarabjot Singh M (2020) Therapeutic Plasma Exchange And COVID-19: A Rapid Review. *Clin Immunol Immunother* 6(4):1–5. doi:10.24966/ciit-8844/1000041
16. Keller AJ, Urbaniak SJ (1978) Intensive Plasma Exchange on the Cell Separator: Effects on Serum Immunoglobulins and Complement Components. *Br J Haematol* 38(4):531–540. doi:10.1111/j.1365-2141.1978.tb01078.x
17. Wing EJ, Bruns FJ, Fraley DS, Segel DP, Adler S (1980) Infectious Complications With Plasmapheresis in Rapidly Progressive Glomerulonephritis. *JAMA J Am Med Assoc* 244(21):2423–2426. doi:10.1001/jama.1980.03310210025020
18. Liu Q, Zhou YH, Yang ZQ (2016 Jan) The cytokine storm of severe influenza and development of immunomodulatory therapy. *Cell Mol Immunol* 13(1):3–10. doi:10.1038/cmi.2015.74. Epub 2015 Jul 20. PMID: 26189369; PMCID: PMC4711683
19. Hung IFN, To KKW, Lee CK et al (2013) Hyperimmune IV immunoglobulin treatment: A multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. *Chest* 144(2):464–473. doi:10.1378/chest.12-2907
20. Costamagna G, Abati E, Bresolin N, Comi GP, Corti S (2021 May) Management of patients with neuromuscular disorders at the time of the SARS-CoV-2 pandemic. *J Neurol* 268(5):1580–1591. doi:10.1007/s00415-020-10149-2. Epub 2020 Aug 17. PMID: 32804279; PMCID: PMC7429942
21. Woodruff RK, Grigg AP, Firkin FC, Smith IL (1986) Fatal thrombotic events during treatment of autoimmune thrombocytopenia with intravenous immunoglobulin in elderly patients. *Lancet* 328(8500):217–218. doi:10.1016/s0140-6736(86)92511-0
22. Haydar D, Cory TJ, Birket SE et al (2019) Azithromycin Polarizes Macrophages to an M2 Phenotype via Inhibition of the STAT1 and NF-κB Signaling Pathways. *J Immunol* 203(4):1021–1030. doi:10.4049/jimmunol.1801228
23. Rosenberg ES, Dufort EM, Udo T, Wilberschied LA, Kumar J, Tesoriero J, Weinberg P, Kirkwood J, Muse A, DeHovitz J, Blog DS, Hutton B, Holtgrave DR, Zucker HA. Association of Treatment With Hydroxychloroquine or Azithromycin With In-Hospital Mortality in Patients With COVID-19 in New York State. *JAMA*. 2020 Jun 23;323(24):2493–2502. doi: 10.1001/jama.2020.8630. PMID: 32392282; PMCID: PMC7215635
24. Van Berkel MA, Twilla JD, England BS (2016 Feb) Emergency Department Management of a Myasthenia Gravis Patient with Community-Acquired Pneumonia: Does Initial Antibiotic Choice Lead to Cure or Crisis? *J Emerg Med* 50(2):281–285. doi:10.1016/j.jemermed.2015.04.019. Epub 2015 Oct 16. PMID: 26472607
25. Sheikh S, Alvi U, Soliven B, Rezania K (2021) Drugs That Induce or Cause Deterioration of Myasthenia Gravis: An Update. *J Clin Med*. Apr 6;10(7):1537. doi: 10.3390/jcm10071537. PMID: 33917535; PMCID: PMC8038781
26. Cavalcanti AB, Zampieri FG, Rosa RG, Azevedo LCP, Veiga VC, Avezum A, Damiani LP, Marcadenti A, Kawano-Dourado L, Lisboa T, Junqueira DLM, de Barros E, Silva PGM, Tramuja L, Abreu-Silva EO, Laranjeira LN, Soares AT, Echenique LS, Pereira AJ, Freitas FGR, Gebara OCE, Dantas VCS, Furtado RHM, Milan EP, Golin NA, Cardoso FF, Maia IS, Hoffmann Filho CR, Kormann APM, Amazonas RB, Bocchi de Oliveira MF, Serpa-Neto A, Falavigna M, Lopes RD, Machado FR, Berwanger O; Coalition Covid-19 Brazil I Investigators. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. *N Engl J Med* (2020) Nov 19;383(21):2041–2052. doi: 10.1056/NEJMoa2019014. Epub 2020 Jul 23. Erratum in: *N Engl J Med*. 2020 Nov 19;383(21):e119. PMID: 32706953; PMCID: PMC7397242
27. Ranzani OT, Bastos LSL, Gelli JGM, Marchesi JF, Baião F, Hamacher S, Bozza FA (2021 Apr) Characterisation of the first 250,000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. *Lancet Respir Med* 9(4):407–418. doi:10.1016/S2213-2600(20)30560-9. Epub 2021 Jan 15. PMID: 33460571; PMCID: PMC7834889
28. Neumann B, Angstwurm K, Mergenthaler P, Kohler S, Schönenberger S, Bösel J, Neumann U, Vidal A, Huttner HB, Gerner ST, Thieme A, Steinbrecher A, Dunkel J, Roth C, Schneider H, Schimmel E, Fuhrer H, Fahrendorf C, Alberty A, Zinke J, Meisel A, Dohmen C, Stetefeld HR; German Myasthenic Crisis Study Group. Myasthenic crisis demanding mechanical ventilation: A multicenter analysis of 250 cases. *Neurology*. 2020 Jan

21;94(3):e299-e313. doi: 10.1212/WNL.0000000000008688. Epub 2019 Dec 4. Erratum in: Neurology. 2020 Apr 21;94(16):724. Schneider, Hauke [corrected to Schneider, Hauke]. PMID: 31801833

29. Jonsson DI, Pirskanen R, Piehl F (2017) Beneficial effect of tocilizumab in myasthenia gravis refractory to rituximab. Neuromuscul Disord 27(6):565–568. doi:10.1016/j.nmd.2017.03.007

30. Salama C, Han J, Yau L et al (2021) Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med 384(1):20–30. doi:10.1056/nejmoa2030340

Tables

Table 1 - Clinical characteristics and outcomes in eight patients with Myasthenia Gravis exacerbations due to COVID19.

Age group	MGFA pre-adm	Antibody	Baseline MG Treatment	Comorbidities	Respiratory support	Chest CT >50% Involvement	cNMB	Exacerbation treatment	Other drugs used	MGFA discharge
40-59	II	AchR +	Pred 40mg + AZA + Pyridost	Obesity	MV	Yes	Yes	IVIG	HCQ, OTV, CTX, AZM, TZP, MEM, PMB, AMK, FLUC, LEVOF, GENT, VAN	V
>60	IIIB	AchR +	None	HTN, Afib	MV	Yes	Yes	IVIG	CTX, AZM, TZP, MEM, PMB, AMK, GENT, VAN	V
20-39	IIB	AchR +	Pred 30mg, AZA, Pyridost	Hypothyroidism	MV	Yes	Yes	PLEX	AZM, DEX, TZP, VAN	Deceased
20-39	IIB	AchR +	Pyridost	None	MV	No	No	IVIG	DEX, MEM, TZP	IIA
20-39	IIIB	None	None	None	MV	No	Yes	PLEX RTX	DEX, MEM, CFM, CDM, VAN	IIB
20-39	IIA	AchR+	Pred 60mg, MTX, Pyridost	Myelodysplastic Syndrome	None	No	No	None	DEX, CTX, OXA	IIA
40-59	II	AchR +	Pred 40mg, AZA, Pyridost	Chiari	NC	No	No	None	DEX, IVMC	IIA
40-59	II	Musk +	Pred 40mg, Pyridost, RTX	HTN	MV	No	Yes	None	DEX, TZP, PMB, ANF, TCP, LEVOF	Deceased

AFib, Atrial fibrillation; AMK, Amikacin; ANF, Anidulafungin; AZA, Azathioprine; AZM, Azithromycin; CFM, Cefepime; CTX, Ceftriaxone; CDM, Clindamycin; cNMB, continuous neuromuscular blocking; DEX, dexametasone; GENT, gentamicina; HTN, Hypertension; IVMC, Ivermectin; IVIg, Intravenous immunoglobulin; LEVOF, Levofloxacin; MEM, Meropenem; MTX, Methotrexate; MGFA pre-adm, Myasthenia Gravis Foundation of America score at the month before admission; MV, mechanical ventilation; OTV, Oseltamivir; OXA, Oxacilin; PLEX, Plasma exchange; PMB, Polymyxin B; Pred, Prednisone; Pyridost, Pyridostigmine; RTX, Rituximab; TCP, Teicoplanin; TZP, Piperacillin-tazobactam; VAN, Vancomycin. *Written consent for

gender and age information could not be obtained due to pandemic. Age presented in the following groups: 20–39 years, 40–59 years, and 60 years and over.