Case series of COVID-19 in patients with myasthenia gravis: a single institution experience

Sven Županić1 · Martina Perić Šitum1 · Maja Majdak1 · Mirna Karakaš1 · Silvio Bašić2 · Davor Sporiš1

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Abstract
Coronavirus disease 2019 (COVID-19), caused by the late 2019 outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes a respiratory disease which could put myasthenia gravis patients at a greater risk of developing severe disease course. This paper presents a single-institution case series of hospitalized myasthenia gravis patients with COVID-19. We identified eight patients previously diagnosed with myasthenia gravis, four of whom presented with clear signs of myasthenia gravis symptom worsening on admission. No form of respiratory support was needed during the complete duration of stay for three patients, oxygen therapy was administered to two patients, while the remaining three patients required mechanical ventilation. Treatment was successful for seven patients, six of whom were discharged without any myasthenia gravis symptoms. One patient died after eleven days of intensive care unit treatment. Although treatment of patients with myasthenia gravis and COVID-19 patients is challenging, case series of myasthenia gravis patients with COVID-19 treated in our institution demonstrates relatively favorable treatment outcome. Our data seem to support the notion that immunosuppressive medication does not seem to result in worse outcomes. Our data also support the notion that intravenous immunoglobulin treatment is safe and should be administered to patients with myasthenia gravis and COVID-19 in case of myasthenia gravis worsening since benefits seem to greatly outweigh the risks.

Keywords COVID-19 · Immunosuppression · Myasthenia gravis · Neuromuscular disorders · SARS-CoV-2

Introduction
Coronavirus disease 2019 (COVID-19), caused by the late 2019 outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causes a respiratory disease with a wide spectrum of disease severity that ranges from mild or almost no upper respiratory symptoms to severe acute respiratory distress syndrome, pneumonia, multiorgan failure, and death [1]. Higher morbidity and mortality rates are seen among the elderly and those with underlying comorbidities and immunologic deficiencies [2]. Myasthenia gravis (MG) is an autoimmune disease characterized by fluctuating muscle weakness with potentially life-threatening symptoms due to insufficiency of respiratory muscles [3]. Therapeutic options for patients with MG include, but are not limited to cholinesterase inhibitors, corticosteroids, and other immunosuppressive treatment. It is therefore postulated that COVID-19 could pose a significant risk for MG patients [4].

Although guidelines for the management of COVID-19 in patients with MG treatment exist, they are based on expert consensus instead of real-world clinical data [5]. At the time
of writing this paper only a handful of case reports and small case series were published on the topic of clinical data of COVID-19 in MG patients [3, 4, 6–12]. Hereby we present a case series of eight hospitalized MG patients with COVID-19.

Methods

Clinical Hospital Dubrava has been serving as a regional Croatian COVID-19 center for wider Zagreb area comprising approximately a quarter of Croatia’s population ever since the beginning of the COVID-19 outbreak in the Republic of Croatia. Included in the study were patients who met the following criteria: 1. had the diagnosis of MG established by the expert neurologists 2. were diagnosed with active COVID-19 infection 3. required hospital stay in our institution. It should be mentioned that since the outbreak of COVID-19 in Croatia the spread of the disease remained relatively stable up until October 2020, all patient cases date after the said date. Diagnosis of COVID-19 was based on clinical history, chest imaging, and positive nasopharyngeal swab polymerase chain reaction (PCR) testing for SARS-CoV2. All patients were treated during the stay in accordance with the best medical practice.

Results

To date, eight patients who met the inclusion criteria have been hospitalized and treated in our COVID-19 center, two female and six male, mean age of 62 years, and average time since MG diagnosis of 5.5 years. The average hospital stay for all patients was 12.8 days. Table 1. shows complete time since MG diagnosis of 5.5 years. The average hospital stay for all patients was 12.8 days. Table 1. shows complete clinical information regarding each patient.

Four patients (patients 1,2,4 and 7) presented with worsening of MG symptoms on admission, three showed no signs of worsening (patients 3,5 and 6), while for the remaining patient (patient 8) we weren’t able to reach a conclusion whether worsening symptoms were in part or at all caused by MG symptom worsening. During hospital stay four patients (patients 1,2,3 and 5) have not shown any signs of MG symptom worsening, two (patients 4 and 7) showed clear signs of MG symptom worsening. For the remaining two patients we weren’t able to reach a conclusion whether worsening symptoms were in part or at all caused by MG symptom worsening. To further clarify, patient 6 had no signs of ocular, bulbar or limb weakness at presentation, but did however show signs of dyspnea and supine respiratory intolerance. He also had clear signs of bilateral pneumonia on chest radiograms. Patient 8 was admitted to our institution after rapid respiratory failure preceded by febrile state, cough, and dyspnea. We are inclined to think that patient 6 had a respiratory failure due to COVID-19 infection intensified by the MG symptoms worsening, while patient 8 most probably had not had any MG symptom worsening, with COVID-19 being the sole cause of respiratory symptoms. All patients with clear or suspected signs of MG symptom worsening (patients 1,2,4,6,7 and 8) received intravenous immunoglobulin (IVIg) therapy in appropriate dose, one of whom (patient 7) had his treatment stopped due to side effects in form of flu-like symptoms. No form of respiratory support was needed during the complete duration of stay for three patients (patients 1,2 and 5), oxygen therapy was administered to two patients (patients 3 and 7, although we do need to point out that patient 3 required oxygen therapy for just 8 h of his 10-day hospital stay), while the remaining three patients required mechanical ventilation (patients 4, 6 and 8). Treatment was successful for 7 patients, 6 of whom were discharged without any MG symptoms with the remaining patient discharged with only minimal symptoms. One patient died after eleven days of intensive care unit treatment.

Discussion

This paper presents one of the largest series of MG patients with COVID-19. Management of COVID-19 infection in MG patients can be challenging for multiple reasons: infections are known to trigger MG exacerbations/crises, MG patients may be at increased risk of such infections due to immunosuppressive medications, and respiratory distress can be seen in both conditions which can complicate identification and management [11].

In contrast to the largest existing case series on the subject which reported 30% death rate of hospitalized MG patients with COVID-19 [4], survival rate in our series of patients remains much lower at 12.5%. The discrepancy can be the result of many factors; the aforementioned paper was published much earlier in 2020 when the treatment protocol of COVID-19 was not at the level of effectiveness it is at the time of the publishing of this paper. Additionally, both studies analyzed only hospitalized patients, no matter the reason for their hospital stay, which could result in Brazilian group treating more difficult cases then we did. Other case series reported no fatal outcomes, although all of the mentioned papers had smaller sample sizes then our own [3, 7, 9, 10].

Using immunosuppressant drugs during the COVID-19 pandemic remains a challenge [13]. Per recommendation by a panel of MG experts, therapy decisions should be tailored to each patient; immunosuppressive medication should be continued unless specifically discussed and approved by healthcare providers [5]. Our data seem to support the notion that immunosuppressive medication does not seem to result in worse outcomes. The only
### Table 1  Patient characteristics

| Patient number | Age (years) | Sex  | Time since MG diagnosis (years) | Prior maximum MGFA severity class | MGFA severity class at the time of COVID-19 | Antibody status | History of thymectomy | Home pyridostigmine therapy (dose) | Home immunosuppressive regimen | History of IVIG or PE | Reason for hospital admission | Maximum MGFA severity class during hospital stay | Requiring respiratory support | Pneumonia on RTG | Treatments for MG administered during hospitalization | Treatment(s) administered for COVID-19 | Received anticoagulant therapy (yes/no) and dose | Hospital stay complications | Duration of stay and outcome | Patient number | Age (years) | Sex | Time since MG diagnosis (years) |
|----------------|-------------|------|---------------------------------|----------------------------------|--------------------------------------|--------------|------------------------|---------------------------------|----------------------------------|-----------------|--------------------------------|---------------------------------|-----------------------------|----------------|--------------------------------|----------------------------------|-------------------------------|------------------|--------------------------------|----------------|----------------|----------------------|--------------------------|
| 1              | 55          | Female | 5                               | 3b                               | 2b                                   | AChR         | No                    | 240 mg/day                      | AZA 100 mg, prednisolone 20 mg/day | No               | Worsening of MG symptoms (oro-pharyngeal and bulbar weakness) | 2b                        | No                         | No              | IVIG 0,4 g/kg/day for 5 days, prior therapy continued | None                                | Yes, prophylactic doses | No               | 7 days, asymptomatic at discharge | 5              | 59              | Female               | 17                        |
| 2              | 67          | Male   | 4                               | 4b                               | 3b                                   | AChR         | No                    | 300 mg/day                      | Prednisolone 20 mg/day                    | Yes              | Worsening of MG symptoms (oro-pharyngeal and bulbar weakness) | 3b                        | No                         | No              | IVIG 0,4 g/kg/day for 5 days, intensified prednisolone (60 mg/day), prior therapy continued | None                                | Yes, prophylactic doses | No               | 12 days, asymptomatic at discharge | 6              | 58              | Male                | 4                        |
| 3              | 80          | Male   | 2                               | 1                                | MG asymptomatic                       | Unknown      | No                    | 90 mg/day                       | None                             | No               | COVID-19 symptoms (febrile state, disorientation, flu-like symptoms) | 4a                       | No                         | No              | None                       | None                                      | Yes, therapeutic doses | No               | No complications   | 10 days, asymptomatic at discharge | 7             | 51              | Male                | 0,2                       |
| 4              | 63          | Male   | 5                               | 4a                               | MG asymptomatic                       | AChR         | No                    | 360 mg/day                      | Prednisolone 60 mg/day, AZA 100 mg/day | Yes              | Worsening of MG symptoms (oro-pharyngeal and bulbar weakness) | 5                        | Yes                        | Yes             | Prior therapy continued | IVIG 0,4 g/kg/day for 5 days, prior therapy continued | Yes, therapeutic doses | No               | No complications   | 16 days, asymptomatic at discharge | 8             | 66              | Male                | 7                        |
| 5              | 59          | Female | 17                              | 5                                | MG asymptomatic                       | AZA 100 mg, prednisolone 20 mg/day | No          | No                    | 240 mg/day                      | None                             | No               | Yes, non-invasive oxygen therapy | 5                        | No                         | No              | None                       | None                                      | Yes, therapeutic doses | No               | No complications   | 7 days, asymptomatic at discharge | 5             | 59              | Female               | 17                        |
| 6              | 58          | Male   | 4                               | 4a                               | MG asymptomatic                       | AChR         | No                    | 300 mg/day                      | None                             | Yes              | Yes, mechanical ventilation | 5                        | No                         | Yes             | Yes, mechanical ventilation | IVIG 0,4 g/kg/day for 5 days, prior therapy continued | Yes, therapeutic doses | No               | No complications   | 12 days, asymptomatic at discharge | 6             | 66              | Male                | 4a                       |
| 7              | 63          | Male   | 0,2                             | 7                                | Male                                 | AChR         | No                    | 360 mg/day                      | Prednisolone 60 mg/day, AZA 100 mg/day | Yes              | Worsening of MG symptoms (oro-pharyngeal and bulbar weakness) | 7                        | Yes                        | Yes             | Yes, non-invasive oxygen therapy | IVIG 0,4 g/kg/day for 5 days, prior therapy continued | Yes, therapeutic doses | No               | No complications   | 12 days, asymptomatic at discharge | 8             | 66              | Male                | 7                        |
| 8              | 66          | Male   | 7                               | 7                                | Male                                 | AChR         | No                    | 360 mg/day                      | Prednisolone 60 mg/day, AZA 100 mg/day | Yes              | Worsening of MG symptoms (oro-pharyngeal and bulbar weakness) | 7                        | Yes                        | Yes             | Yes, non-invasive oxygen therapy | IVIG 0,4 g/kg/day for 5 days, prior therapy continued | Yes, therapeutic doses | No               | No complications   | 12 days, asymptomatic at discharge | 8             | 66              | Male                | 7                        |
| Table 1 (continued) | 3a | 3b | 1 | Unknown |
|---------------------|----|----|---|---------|
| **Prior maximum MGFA severity class** | 3a | 3b | 1 | Unknown |
| **MGFA severity class at the time of COVID-19** | MG asymptomatic | MG asymptomatic | 1 | Inconclusive |
| **Antibody status** | Antibody negative | Antibody negative | AChR | Unknown |
| **History of thymectomy** | No | Yes | No | Unknown |
| **Home pyridostigmine therapy** | 300 mg/day | 420 mg/day | 180 mg/day | 300 mg/day |
| **Home immunosuppressive regimen** | Prednisolone 10 mg/every other day | Prednisolone 30 mg/day | No | Prednisolone 20 mg/day |
| **History of IVIg or PE** | No | Yes, last IVIG 4 months prior to admission | No | Unknown |
| **Reason for hospital admission** | Dyspnea, febrile state, cough | Dyspnea | Received COVID-19 positive test during hospital assessment for MG in another institution | Dyspnea, cough, occipital headache |
| **Maximum MGFA severity class during hospital stay** | MG asymptomatic | Inconclusive | 2b | Inconclusive |
| **Requiring Respiratory support** | No | Yes, mechanical ventilation | Yes, non-invasive oxygen therapy | Yes, mechanical ventilation |
| **Pneumonia on RTG (yes/no)** | Yes | Yes | Yes | Yes |
| **Treatments for MG administered during hospitalization** | Prior therapy continued | IVIg 0.4 g/kg/day for 5 days, prior therapy continued | IVIg 0.4 g/kg/day for 1 day (discontinued due to side effects), prednisolone 40 mg/day, pyridostigmine therapy intensified (300 mg/day) | IVIg 0.4 g/kg/day for 5 days, pyridostigmine therapy withheld during mechanical ventilation |
| **Treatment(s) administered for COVID-19** | Dexamethasone 8 mg/10 days | Remdesivir/5 days, | Remdesivir/5 days | Remdesivir 5/days |
| **Received anticoagulant therapy (yes/no) and dose** | Yes, prophylactic doses | Yes, therapeutic doses | Yes, prophylactic doses | Yes, therapeutic doses |
| **Hospital stay complications** | No complications | DVT | No complications | Sepsis |
| **Duration of stay and outcome** | 8 days, asymptomatic at discharge | 15 days, MGFA score 1 at discharge | 24 days, asymptomatic at discharge | 11 days, deceased |

(AChR acetylcholine receptor, AZA azathioprine, COVID-19 coronavirus disease 2019, DVT deep vein thrombosis, IVIg intravenous immunoglobulin, MG myasthenia gravis, MGFA myasthenia gravis foundation of America, PCR polymerase chain reaction, PE plasma exchange, SARS-COV 2 severe acute respiratory syndrome coronavirus 2)
patient that had a fatal outcome was on only low doses of corticosteroids. This is in line with current COVID-19 pathophysiology understandings and treatment recommendations since findings from both observational studies and randomized control trials confirm a beneficial effect of corticosteroids on short-term mortality and a reduction in need for mechanical ventilation in COVID-19 patients [14]. Interestingly, in accordance with published case series, immunosuppression with AZA or other similar immunosuppressive agents is not linked to worse outcome [4]. We treated two patients with AZA during the study, both of which were successfully treated and eventually discharged without MG symptoms.

Regarding treatment for MG exacerbation, concerns existed about IVIg treatment not only because of immunosuppressive effects of IVlg, but also because IVIg, like COVID-19, has thromboembolic properties [15, 16]. Studies have reported thromboembolic complications in patients treated with IVIg in 13% [17] and hospitalized patients with COVID-19 in 15% to 86% of cases [18]. Real-world data have however shown that administration of IVIg in patients with MG and COVID 19 is safe [3, 4, 6, 7, 9, 10], and is recommended in published guidelines [5]. Moreover, although the mechanism of action is still largely unknown, Xie et al. reported a statistically significant reduction in 28-day mortality between patients receiving IVIG for COVID-19 pneumonia within 48 h of admission compared to those who received IVIG after 48 h of admission [19]. Several randomized controlled trials evaluating the efficacy of IVIG therapy in severe COVID-19 are underway [20]. During treatment of patients presented in this study, we decided to administer IVIg upon first signs of MG symptom worsening. Of six patients that received full doses of IVIg, only one patient did develop deep vein thrombosis (DVT). To our knowledge, this could be the first example in the published literature of DVT in patients with MG and COVID-19. One patient treated with IVIg had fatal outcome, albeit we did not verify any thromboembolic complications in the reported patient. In summary, we feel like IVIG treatment is safe and should be administered to patients with MG and COVID-19 in case of MG worsening since benefits seem to greatly outweigh the risks.

The survival rate of patients with MG and COVID-19 on ventilatory support seems to be higher in contrast to the general COVID-19 population [21]. Of three patients in our series treated with mechanical ventilatory support, two had favorable outcome, which is also in line with previously published research [4, 10]. When respiratory weakness is encountered, however, in patients with MG and COVID-19, it can be very challenging, sometimes impossible even, to determine to what extent COVID-19, MG or some other condition contributed to the respiratory weakness.

Our study has some limitations. First, this observational study included only hospitalized patients. We did not address the impact of MG and COVID-19 in outpatient settings. Additionally, the favorable course of COVID 19 in our patient series may be associated with other variables. The small number of patients and the absence of a control group limits the results of the study. Studies with a larger group of patients are needed to confirm results observed in this and other studies.

Conclusions

Although treatment of patients with MG and COVID-19 is challenging, case series of MG patients with COVID-19 treated in our institution demonstrates relatively favorable treatment outcome. IVIg are in general safe and effective treatment option for MG exacerbations even in the time of COVID-19 pandemic. Studies with larger sample sizes are needed to determine best practice guidelines of management of MG patients with COVID 19.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

Ethics approval We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication All participants have consented to the submission of the case reports to the journal.

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