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ORIGINAL ARTICLE

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

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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

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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 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	1	2	3	4
Age (years)	55	67	80	63
Sex	Female	Male	Male	Male
Time since MG diagnosis (years)	5	4	2	5
Prior maximum MGFA severity class	3b	4b	1	4a
MGFA severity class at the time of COVID-19	2b	3b	MG asymptomatic	2b
Antibody status	AChR	AChR	Unknown	AChR
History of thymectomy	No	No	No	No
Home pyridostigmine therapy (dose)	240 mg/day	300 mg/day	90 mg/day	360 mg/day
Home immunosuppressive regimen	AZA 100 mg, prednisolone 20 mg/day	Prednisolone 20 mg/day	None	Prednisolone 60 mg/day, AZA 100 mg/day
History of IVIG or PE	No	Yes, last IVIg 1 year prior to admission	No	Yes, last PE 3 year prior to admission
Reason for hospital admission	Worsening of MG symptoms (oropharyngeal and bulbar weakness)	Worsening of MG symptoms (oropharyngeal and bulbar weakness)	COVID-19 symptoms (febrile state, disorientation, flu-like symptoms)	Worsening of MG symptoms (oropharyngeal and bulbar weakness)
Maximum MGFA severity class during hospital stay	2b	3b	MG asymptomatic	5
Requiring respiratory support	No	No	Yes, non-invasive oxygen therapy	Yes, mechanical ventilation
Pneumonia on RTG	No	No	Yes	Yes
Treatments for MG administered during hospitalization	IVIG 0,4 g/kg/day for 5 days, prior therapy continued	IVIG 0,4 g/kg/day for 5 days, intensified prednisolone (60 mg/day), prior therapy continued	Prior therapy continued	IVIG 0,4 g/kg/day for 5 days, prior therapy continued
Treatment(s) administered for COVID-19	None	None	Remdesivir/5 days, dexamethasone 8 mg/10 days	None
Received anticoagulant therapy (yes/no) and dose	Yes, prophylactic doses	Yes, prophylactic doses	Yes, therapeutic doses	Yes, therapeutic doses
Hospital stay complications	No	No	No	No complications
Duration of stay and outcome	7 days, asymptomatic at discharge	12 days, asymptomatic at discharge	10 days, asymptomatic at discharge	16 days, asymptomatic at discharge
Patient number	5	6	7	8
Age (years)	59	58	51	66
Sex	Female	Male	Male	Male
Time since MG diagnosis (years)	17	4	0,2	7

Table 1 (continued)

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	None	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 witheld 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 IVIg, 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.

References

1. Zhang L, Liu Y (2020) Potential interventions for novel coronavirus in China: a systematic review. J Med Virol 92:479–490. https://doi.org/10.1002/jmv.25707
2. Singhal T (2020) A review of coronavirus disease-2019 (COVID-19). Indian J Pediatr 87:281–286. https://doi.org/10.1007/s12098-020-03263-6
3. Hübers A, Lascano AM, Lalive PH (2020) Management of patients with generalised myasthenia gravis and COVID-19: four case reports. J Neurol Neurosurg Psychiatry 91:1124–1125. https://doi.org/10.1136/jnnp-2020-323565
4. Camelo-Filho AE, Silva AMS, Estephan EP, Zambon AA, Mendonça RH, Souza PVS, Pinto WBVR, Oliveira ASB, Dangoni-Filho I, Pouza AFP, Valerio BCO, Zanoteli E (2020) Myasthenia

gravis and COVID-19: clinical characteristics and outcomes. Front Neurol 11:1053. https://doi.org/10.3389/fneur.2020.01053
5. Jacob S, Muppidi S, Guidon A, Guptill J, Hehir M, Howard JF, Illa I, Mantegazza R, Murai H, Utsugisawa K, Vissing J, Wiendl H, Nowak RJ (2020) Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. J Neurol Sci 412:116803. https://doi.org/10.1016/j.jns.2020.116803
6. Kushlaf H (2020) COVID -19 in muscle-specific kinase myasthenia gravis: a case report. Muscle Nerve 62:E65–E66. https://doi.org/10.1002/mus.27020
7. Restivo DA, Centonze D, Alesina A, Marchese-Ragona R (2020) Myasthenia gravis associated with SARS-CoV-2 infection. Ann Intern Med 173:1027–1028. https://doi.org/10.7326/L20-0845
8. Aksoy E, Oztutgan T (2020) COVID-19 presentation in association with myasthenia gravis: a case report and review of the literature. Case Rep Infect Dis 2020:8845844. https://doi.org/10.1155/2020/8845844
9. Rein N, Haham N, Orenbuch-Harroch E, Romain M, Argov Z, Vaknin-Dembinsky A, Gotkine M (2020) Description of 3 patients with myasthenia gravis and COVID-19. J Neurol Sci 417:117053. https://doi.org/10.1016/j.jns.2020.117053
10. Anand P, Slama MCC, Kaku M, Ong C, Cervantes-Arslanian AM, Zhou L, David WS, Guidon AC (2020) COVID -19 in patients with myasthenia gravis. Muscle Nerve 62:254–258. https://doi.org/10.1002/mus.26918
11. Singh S, Govindarajan R (2020) COVID-19 and generalized myasthenia gravis exacerbation: a case report. Clin Neurol Neurosurg 196:106045. https://doi.org/10.1016/j.clineuro.2020.106045
12. Moschella P, Roth P (2020) Isolated COVID-19 Infection precipitates myasthenia gravis crisis: a case report. Clin Pract Cases Emerg Med 4:524–526. https://doi.org/10.5811/cpcem.2020.9.49049
13. Valencia-Sanchez C, Wingerchuk DM (2020) A fine balance: immunosuppression and immunotherapy in a patient with multiple sclerosis and COVID-19. Mult Scler Relat Disord 42:102182. https://doi.org/10.1016/j.msard.2020.102182
14. van Paassen J, Vos JS, Hoekstra EM, Neumann KMI, Boot PC, Arbous SM (2020) Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Crit Care 24:696. https://doi.org/10.1186/s13054-020-03400-9
15. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L (2020) The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. Thromb Res 194:101–115. https://doi.org/10.1016/j.thromres.2020.06.029
16. Paran D, Herishanu Y, Elkayam O, Shopin L, Ben-Ami R (2005) Venous and arterial thrombosis following administration of intravenous immunoglobulins. Blood Coagul Fibrinolysis 16:313–318. https://doi.org/10.1097/01.mbc.0000172694.85233.a8
17. Marie I, Maurey G, Hervé F, Hellot M-F, Levesque H (2006) Intravenous immunoglobulin-associated arterial and venous thrombosis; report of a series and review of the literature. Br J Dermatol 155:714–721. https://doi.org/10.1111/j.1365-2133.2006.07390.x
18. Ribes A, Vardon-Bounes F, Mémier V, Poette M, Au-Duong J, Garcia C, Minville V, Sié P, Bura-Rivière A, Voisin S, Payrastre B (2020) Thromboembolic events and COVID-19. Adv Biol Regul 77:100735. https://doi.org/10.1016/j.jbior.2020.100735
19. Xie Y, Cao S, Dong H, Li Q, Chen E, Zhang W, Yang L, Fu S, Wang R (2020) Effect of regular intravenous immunoglobulin therapy on prognosis of severe pneumonia in patients with COVID-19. J Infect 81:318–356. https://doi.org/10.1016/j.jinf.2020.03.044
20. Rizk JG, Kalantar-Zadeh K, Mehra MR, Lavie CJ, Rizk Y, Forthal DN (2020) Pharmaco-Immunomodulatory Therapy in COVID-19. Drugs 80:1267–1292. https://doi.org/10.1007/s40265-020-01367-z
21. King CS, Sahjwani D, Brown AW, Feroz S, Cameron P, Osborn E, Desai M, Djurkovic S, Kasarabada A, Hinerman R, Lantry J, Shlobin OA, Ahmad K, Khangoora V, Aryal S, Collins AC, Speir A, Nathan S (2020) Outcomes of mechanically ventilated patients with COVID-19 associated respiratory failure. PLoS ONE 15:e0242651. https://doi.org/10.1371/journal.pone.0242651