identify ALS patients who would benefit from inpatient initiation and titration of NIV and avoid unwanted morbidity with prolonged outpatient titration, or more acute decompensation resulting in unwanted intubation or death. Further studies assessing the survival benefit of ambulatory TCO_2 monitoring and rapid initiation of NIV to tolerance with correction of CO_2 are also warranted.

CONFLICT OF INTEREST

Kellen Quigg: none. Matthew Wilson: none. Philip Choi: none.

ETHICAL PUBLICATION STATEMENT

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.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Kellen H. Quigg https://orcid.org/0000-0003-4365-2298
Philip J. Choi https://orcid.org/0000-0003-3609-5999

REFERENCES

1. Bruijn LI, Miller TM, Cleveland DW. Unraveling the mechanisms involved in motor neuron degeneration in ALS. *Annu Rev Neurosci*. 2004;27:723-749.
2. Lechtzin N, Rothstein J, Clawson L, Diette GB, Wiener CM. Amyotrophic lateral sclerosis: evaluation and treatment of respiratory impairment. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2002;3:5-13.
3. Cedarbaum JM, Stambler N, Malta E, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (Phase III). *J Neurol Sci*. 1999;169:13-21.
4. Niedermeyer S, Murn M, Choi PJ. Respiratory failure in amyotrophic lateral sclerosis. *Chest*. 2019;155:401-408.
5. Aarrestad S, Tollefsen E, Kleiven AL, et al. Validity of transcutaneous PCO_2 in monitoring chronic hypoventilation treated with non-invasive ventilation. *Respir Med*. 2016;112:112-118.
6. Rafiq MK, Bradburn M, Proctor AR, et al. Using transcutaneous carbon dioxide monitor (TOSCA 500) to detect respiratory failure in patients with amyotrophic lateral sclerosis: a validation study. *Amyotroph Lateral Scler*. 2012;13:528-532.
7. Morris JF, Koski A, Johnson LC. Spirometric standards for healthy nonsmoking adults. *Am Rev Respir Dis*. 1971;103:57-67.
8. Ackrivo J, Hsu JY, Hansen-Flaschen J, Elman L, Kawut SM. Noninvasive ventilation use is associated with better survival in amyotrophic lateral sclerosis. *Ann Am Thorac Soc*. 2021;18:486-494.
9. Bourke SC, Tomlinson M, Williams TL, et al. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomised controlled trial. *Lancet Neurol*. 2006;5:140-147.
10. O'Brien D, Stavroulakis T, Baxter S, et al. The optimisation of noninvasive ventilation in amyotrophic lateral sclerosis: a systematic review. *Eur Respir J*. 2019;54:1–14.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Quigg KH, Wilson MW, Choi PJ. Transcutaneous CO_2 monitoring as indication for inpatient non-invasive ventilation initiation in patients with amyotrophic lateral sclerosis. *Muscle & Nerve*. 2022;65(4):444-447. doi:10.1002/mus.27457

Clinical course and outcome of an outpatient clinic population with myasthenia gravis and COVID-19

Ozlem Gungor Tuncer MD | **Feza Deymeer MD, MS (Epid)**

Department of Neurology, Memorial Sisli Hospital, Istanbul, Turkey

Correspondence
Ozlem Gungor Tuncer, MD, Department of Neurology, Memorial Sisli Hospital, Istanbul, Turkey.
Email: ozlemgtuncer@hotmail.com

Abstract

Introduction/Aims: Coronavirus disease-2019 (COVID-19) may have a more severe course in patients with myasthenia gravis (MG). We aimed to assess severity of the infection and factors contributing to its severity in a group of MG patients, most of whom were not hospitalized.

Abbreviations: AChR, acetylcholine receptor; MuSK, muscle-specific kinase; COVID-19, coronavirus disease-2019; CS, corticosteroids; HCQ, hydroxychloroquine; IS, immunosuppressive; IVIg, intravenous immunoglobulin; MG, myasthenia gravis; MGFA, Myasthenia Gravis Foundation of America clinical classification; NM, neuromuscular; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome–coronavirus-2.

Methods: One hundred forty outpatients with MG followed between March 2020 and April 2021 were included in our study. Patients were asked to respond to a brief questionnaire in person, by telemedicine, or through electronic messages.

Results: Nineteen patients tested positive for COVID-19 by polymerase chain reaction. Two were asymptomatic. Of the 17 symptomatic patients, 11 had mild symptoms. They either had no treatment or received antivirals, antibiotics, and anticoagulants. Their myasthenia was well-controlled before infection and was unaffected by COVID-19. Three patients with moderate COVID-19 required hospitalization, but not intensive care, and had full recovery. Three other patients, the oldest in the cohort, had severe disease: One patient with a post-surgery myasthenic exacerbation before the infection needed intensive care without intubation, but recovered completely; two morbidly obese patients with comorbidities required intubation and died. Corticosteroids were increased in four of the six moderate/severely affected patients. Immunosuppressive (IS) agents were generally continued. Hydroxychloroquine (HCQ) for COVID-19 was used in one patient.

Discussion: Most patients had mild COVID-19 and all but two patients recovered. The design of the study made it possible to capture mild cases. Having well-controlled MG before infection and absence of comorbidities likely affected the course of the infection favorably. IS did not influence the progression.

KEYWORDS
COVID-19, infection, mild, myasthenia gravis, treatment

1 INTRODUCTION

Coronavirus disease-2019 (COVID-19), in parallel with other infections, has the potential to have a severe course and worse outcome in patients with neuromuscular (NM) disorders.[1,2] Myasthenia gravis (MG), an autoimmune NM disease, is particularly important because of the possible development of weakness in respiratory muscles in generalized MG and requirement for continuous use of immunosuppressive (IS) drugs. Also, some antibiotics may worsen or trigger MG.

Information obtained during the pandemic indicates that COVID-19 infection may have a more severe course in MG patients, and that these patients may need more intensive care support.[3-5] Among 179 patients previously reported, 56% to 100% were hospitalized, and many were intubated.[3-20] It is noteworthy that most of the reported studies were in hospitalized inpatients. Only one study identified patients with COVID-19 by self-report.[4] It is likely that mild cases not hospitalized were missed.

Herein we present a questionnaire-based study assessing the severity of the COVID-19 infection and factors contributing to its severity in a defined group of MG patients who were being followed up at our outpatient clinic during the pandemic.

2 METHODS

All MG patients seen in the outpatient clinic of Memorial Sisli Hospital in person or through telemedicine between March 1, 2020 and April 30, 2021 were considered for the study. In these patients who had fatigable muscle weakness, the diagnosis of MG was made by the presence of one or more of the following: positive anti–acetylcholine receptor antibody (anti-AChR) or anti–muscle-specific kinase antibody (anti-MuSK) test, an unequivocally positive response to anticholinesterases, decrement of over 10% on repetitive nerve stimulation, or abnormal jitter/blocking on single-fiber electromyography.

Patients were contacted by electronic message in March to April 2021. The messages were not anonymous, but addressed to the patient. Those seen in person/by telemedicine in the outpatient clinic in February, March, and April of 2021 were not recontacted because they had already been questioned.

The first questionnaire aimed to find out which patients had COVID-19 (Table S1, part A). If the patient had COVID-19, they were recontacted and further questions were asked (Table S1, part B). The Myasthenia Gravis Foundation of America (MGFA)[21] clinical classification was determined on the basis of an overall assessment of the severity of symptoms and signs. MGFA 0 was used for asymptomatic patients.[22] Medical records were reviewed to check the consistency of their responses regarding their clinical status before infection and the medications they received.

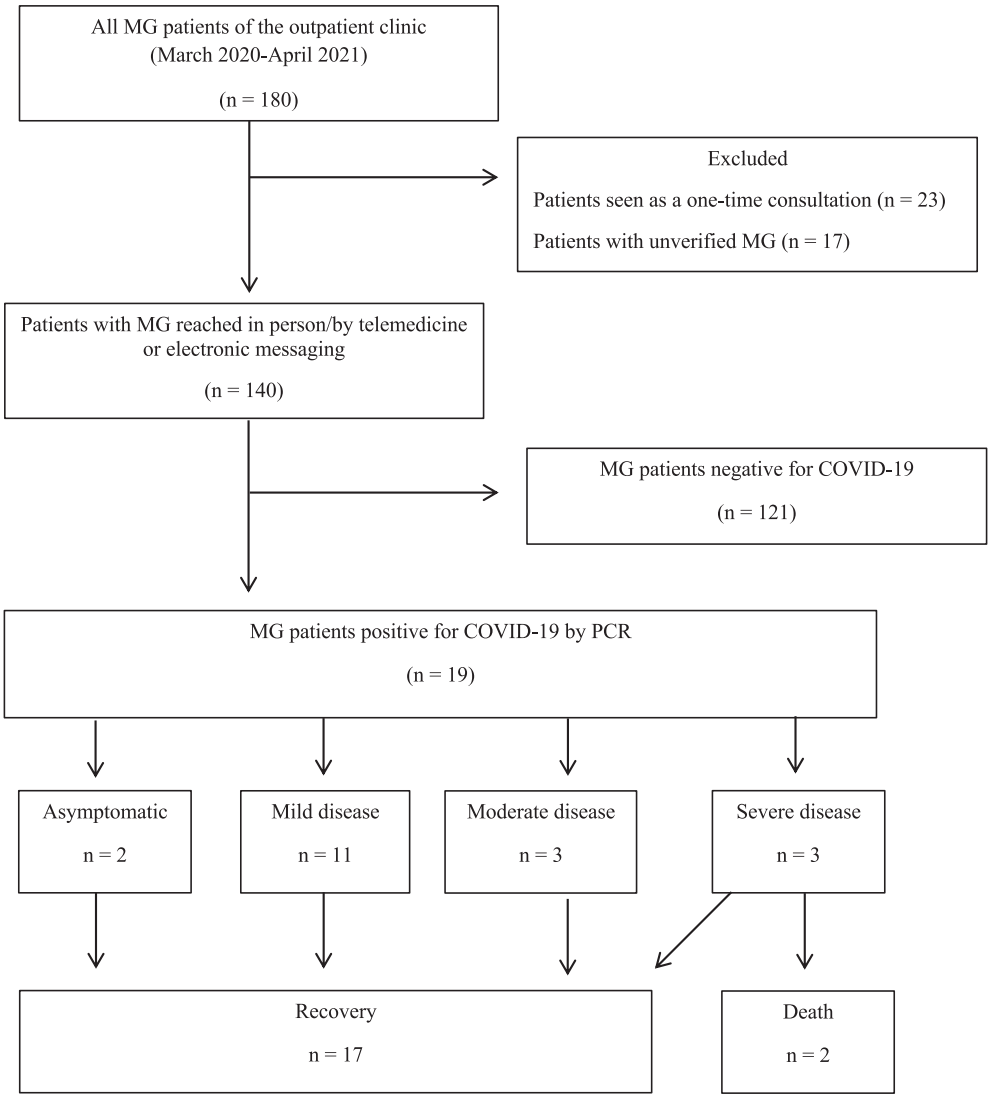

FIGURE 1 Study flowchart. MG, myasthenia gravis; COVID-19, coronavirus disease-2019; PCR, polymerase chain reaction

Mild disease was defined as presence of fever, muscle pain, fatigue, and loss of smell; moderate disease was defined as illness that required hospitalization but not intensive care; and severe disease was defined as illness that required intensive care with or without intubation. Informed consent was obtained from the patients. The study was approved by the institutional review board.

3 RESULTS

Among 180 patients considered for the study, 23 were excluded because they had been seen as a one-time consultation, as they were under the care of another center, and 17 others were excluded because MG was suspected, yet definite diagnosis was not established. The study design is given in the flowchart (Figure 1). Of the remaining 140 patients, 38 were seen in the outpatient clinic or by telemedicine between February and April, and 102 were reached by electronic messages. All patients responded to the questionnaire.

There were 19 patients with COVID-19 (13.5%). Seventeen had symptomatic COVID-19 disease. For the 11 nonhospitalized patients with mild COVID-19, polymerase chain reaction (PCR) positivity was self-reported; for five of them, we were contacted during the infection. In four of the six hospitalized patients, the treating physician contacted us. The family of one patient who died was contacted. The other patients were contacted by telephone, in addition to the questionnaire. Fifteen patients were anti–AChR-positive, one patient was anti–MuSK-positive, and three patients were anti–AChR-negative/anti–MuSK-negative. Table 1 describes the demographics and clinical features of the patients with COVID-19.

Two patients were positive for severe acute respiratory syndrome–coronavirus-2 (SARS-CoV-2) infection but were asymptomatic (patients 1 and 2). One had a positive COVID-19 PCR test without any family member having a positive test, and the other had a spouse with symptomatic COVID-19. Vaccination was not yet available during the study period.

Of the 17 patients who had symptomatic COVID-19, 11 (9 women, 2 men) had mild COVID-19 symptoms (patients 3-13). All but one of these patients had well-controlled MG with MGFA classes, varying between 0 (asymptomatic) and 2 (mild) before the infection. The patient with a moderate MGFA class of 3a (patient 13) had extremity weakness, but no bulbar/respiratory symptoms, before contracting COVID-19. They did not need hospitalization except one woman (patient 13) with Sjögren

TABLE 1 Demographic and clinical characteristics of MG patients with COVID-19

Patient no.	Age (years), gender	Maximum MGFA[a]	Thymectomy	Comorbidity	MGFA before COVID	IS treatment before COVID	Hospitalization	Severity of COVID	Pulmonary involvement[b]	Treatment during COVID
1	42, F	2a	Yes	None	0	None	No	Asymptomatic	NT	None
2	29, F	3b	Yes	None	1	PRED, IVIg	No	Asymptomatic	NT	None
3	60, F	2a	Yes	None	0	AZA	No	Mild	NT	Increased pyridostigmine dose
4	54, F	3b	No	None	2a	PRED, AZA	No	Mild	NT	Standard
5	63, M	2b	No	None	0	PRED, AZA	No	Mild	No	Standard
6	44, F	2a	Yes	None	1	PRED, RTX	No	Mild	No	Standard
7	44, F	4b	Yes	None	2b	PRED, AZA	No	Mild	NT	None
8	41, F	3b	No	None	0	PRED	No	Mild	NT	Standard
9	21, F	3b	Yes	None	0	PRED, AZA	No	Mild	NT	None
10	46, M	3a	Yes	OSA	2a	None	No	Mild	NT	Standard
11	68, F	2a	No	None	1	PRED	No	Mild	No	Standard
12	42, F	2a	Yes	None	0	None	No	Mild	NT	None
13	51, F	3b	No	Sjögren syndrome	3a	PRED, MM	Yes[c]	Mild	No	Standard, HCQ[d]
14	62, F	2a	No	None	0	PRED	Yes	Moderate	Yes	Standard, increased PRED dose
15	37, F	5	Yes	None	2b	PRED, AZA	Yes	Moderate	Yes	Standard treatment, increased PRED dose, oxygen
16	47, M	2a	Yes	None	1	PRED	Yes	Moderate	Yes	Standard treatment, oxygen
17	72, M	3a	No	Following 2 consecutive surgeries and recovery from MG exacerbation	3b	PRED, AZA	Yes	Severe (high-flow oxygen)	Yes	Standard, increased PRED and pyridostigmine dose, IVIg
18	85, F	2b	No	Obesity, congestive heart disease	2a	None	Yes	Severe (MV)	Yes	Standard, PRED and increased pyridostigmine dose
19	75, F	4b	No	Morbid obesity, diabetes	0	PRED, AZA	Yes	Severe (MV)	Yes	Not known

Abbreviations: AZA, azathioprine; F, female; IS, immunosuppressive; IVIg, intravenous immunoglobulin; MGFA, Myasthenia Gravis Foundation of America; M, male, MM, mycophenolate mofetil; MV, mechanical ventilation; NT, not tested; None, no treatment for COVID, no change in MG treatment; OSA, obstructive sleep apnea; PRED, prednisolone; RTX, rituximab; Standard, favipiravir, azithromycin, anticoagulant, acetaminophen.

[a]The worst MGFA score during the entire course of the disease.

[b]By chest computed tomography.

[c]For isolation.

[d]For Sjögren syndrome.

syndrome, who was hospitalized at the beginning of the pandemic for isolation purposes. Their myasthenic symptoms were not affected and the medications for MG were not changed. All these patients had either no treatment for COVID-19 or received, at home, the standard treatment used at the time in Turkey, consisting of favipiravir, azithromycin, enoxaparin, and acetaminophen. None of them received intravenous immunoglobulin (IVIg) or underwent plasma exchange. Corticosteroids (CS) were not increased in any of the patients. Only one patient received hydroxychloroquine (HCQ) for COVID-19. The patient with Sjögren syndrome was already on HCQ for her disease. All patients had full recovery.

COVID-19 was moderate in three patients (patients 14-16) requiring hospitalization, and all recovered. Of the three patients with severe COVID-19 (patients 17-19), two (patients 18 and 19), who had underlying comorbidities were intubated, died due to COVID-19. The third patient (patient 17) had two consecutive prostate surgeries 1 month before COVID-19, after which he had a myasthenic exacerbation. These three were the oldest in the cohort. It was not possible to separate the contribution of myasthenic weakness from that of respiratory involvement due to COVID-19 in these patients, who were not under our care during COVID-19. The death rate was 10% (2 of 19) among myasthenic patients with COVID-19.

4 DISCUSSION

It is noteworthy that COVID-19 was mild/asymptomatic in 13 of 19 (68%) affected patients, and full recovery was attained in the majority, including 4 patients with moderate-severe infection. The outpatient-based design of our study likely made it possible to capture milder cases, compared with previous studies[3-5] that evaluated patients admitted to the hospital for COVID-19 infection.

In some of the reported patients, there were comorbidities such as obesity, advanced age, and others that could adversely influence progression of the disease.[7] Three patients who had severe disease had major comobidities. Two of them died and one eventually recovered completely.

Those with more severe MG, particularly at the onset of infection, were reported to be more likely to have severe COVID-19.[4] Recent data on patients with milder MG supported this observation in that COVID-19 was noted to be more benign in these patients.[6] In line with these observations, a possible reason for the benign course in most of our patients is that myasthenia was well-controlled at the time of COVID-19 in almost all of them, and none had bulbar symptoms. This outcome is not surprising because infections and antibiotics are better tolerated in patients whose myasthenia is in remission or mild.[6]

A considerable number of the patients reported were given HCQ, a drug used in the first few months of the pandemic.[23] Initiation and exacerbation of MG with HCQ have been reported, although HCQ may not always have a negative influence on MG.[24] Most of our patients had not received HCQ. Azithromycin, used in most of our patients, had no adverse effect noted, as reported in another study in this patient group.[6]

In some studies, the use/increase of CS was reported to have a positive effect on moderate and severe COVID-19 disease.[25,26] Increasing evidence suggests that immune suppression can play a protective role by reducing the immune response that leads to cytokine storm and clinical impairment.[27] It is possible that increasing CS played a role in the recovery of three of our patients with moderate-severe COVID-19.

The study has several limitations. Although we were able to obtain objective documentation through the treating physicians in most of the hospitalized patients, we had to rely on the patients' reports for COVID-19 positivity in nonhospitalized patients. Reporting bias was present regarding symptoms and severity of COVID-19 in those patients giving information retrospectively. However, reviewing the medical records in all patients diminished the reporting bias on MG status before the disease. The study population may not be representative of all MG patients. More severe cases, possibly attending university/state hospitals, were missed because the study was done on outpatients of a private hospital. Moreover, all asymptomatic/mild cases may not have been captured as the patients were not involved in a prospective screening protocol.

In conclusion, our study has shown that COVID-19 does not necessarily have a severe course or poor outcome in MG patients. Absence of comorbidities and having well-controlled MG before infection likely affected the course of the infection favorably. As has been reported, IS medications did not seem to influence clinical severity or outcome of COVID-19 in our patients.

ACKNOWLEDGMENTS

We thank our patients for their prompt replies and their kind cooperation.

CONFLICT OF INTEREST

None of the authors has any conflict of interest to disclose.

ETHICAL PUBLICATION STATEMENT

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.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable. No new data were generated.

ORCID

Ozlem Gungor Tuncer https://orcid.org/0000-0001-7186-2175

REFERENCES

1. Guidon AC, Amato AA. COVID-19 and neuromuscular disorders. *Neurology*. 2020;94:959-969.
2. Gilhus NE, Romi F, Hong Y, Skeie GO. Myasthenia gravis and infectious disease. *J Neurol*. 2018;265:1251-1258.
3. Muppidi S, Guptill JT, Jacob S. COVID-19-associated risks and effects in myasthenia gravis (CARE-MG). *Lancet Neurol*. 2020;19:970-971.
4. Solé G, Salort-Campana E, Pereon Y, et al. Guidance for the care of neuromuscular patients during the COVID-19 pandemic outbreak from the French Rare Health Care for Neuromuscular Diseases Network. *Rev Neurol (Paris)*. 2020;176:507-515.
5. Camelo-Filho AE, Silva AMS, Estephan EP, et al. Myasthenia gravis and COVID-19: clinical characteristics and outcomes. *Front Neurol*. 2020;11:1053.

6. Saied Z, Rachdi A, Thamlaoui S, et al. Myasthenia gravis and COVID-19: a case series and comparison with literature. *Acta Neurol Scand*. 2021; 144(3):334–340. doi:10.1111/ane.13440
7. Županić S, Perić Šitum M, Majdak M, Karakaš M, Bašić S, Sporiš D. Case series of COVID-19 in patients with myasthenia gravis: a single institution experience. *Acta Neurol Belg*. 2021;1:1-6.
8. Anand P, Slama MCC, Kaku M, et al. COVID-19 in patients with myasthenia gravis. *Muscle Nerve*. 2020;62:254-258.
9. Hübers A, Lascano AM, Lalive PH. Management of patients with generalised myasthenia gravis and COVID-19: four case reports. *J Neurol Neurosurg Psychiatry*. 2020;91:1124-1125.
10. Rein N, Haham N, Orenbuch-Harroch E, et al. Description of 3 patients with myasthenia gravis and COVID-19. *J Neurol Sci*. 2020; 417:117053.
11. Octaviana F, Yugo HP, Safri AY, et al. Case series: COVID-19 in patients with mild to moderate myasthenia gravis in a national referral hospital in Indonesia. *eNeurol Sci*. 2021;23:100332.
12. Peters BJ, Rabinstein AA, DuBrock HM. Use of remdesivir in myasthenia gravis and COVID-19. *Pharmacotherapy*. 2021;41:546-550.
13. Hofstadt-van Oy U, Stankovic S, Kelbel C, et al. Complement inhibition initiated recovery of a severe myasthenic crisis with COVID-19. *J Neurol*. 2021;268:3125-3128.
14. Singh S, Govindarajan R. COVID-19 and generalized myasthenia gravis exacerbation: a case report. *Clin Neurol Neurosurg*. 2021;196:106045.
15. Kushlaf H. COVID-19 in muscle-specific kinase myasthenia gravis: a case report. *Muscle Nerve*. 2020;62:E65-E66.
16. Ramaswamy SB, Govindarajan R. COVID-19 in refractory myasthenia gravis---a case report of successful outcome. *J Neuromuscul Dis*. 2020;7:361-364.
17. Salik I, Rodhouse HB, Barst S. Myasthenic crisis in the setting of coronavirus disease 2019 (COVID-19). *J Clin Anesth*. 2020;67:110001.
18. Delly F, Syed MJ, Lisak RP, Zutshi D. Myasthenic crisis in COVID-19. *J Neurol Sci*. 2020;15(414):116888.
19. Aksoy E, Oztutgan T. COVID-19 presentation in association with myasthenia gravis: a case report and review of the literature. *Case Rep Infect Dis*. 2020;2020:8845844.
20. Moschella P, Roth P. Isolated COVID-19 infection precipitates myasthenia gravis crisis: a case report. *Clin Pract Cases Emerg Med*. 2020;4: 524-526.
21. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, et al. Myasthenia gravis: recommendations for clinical research standards. Task force of the medical scientific advisory board of the Myasthenia Gravis Foundation of America. *Neurology*. 2000;12(55):16-23.
22. Pasnoor M, Wolfe GI, Nations S, et al. Clinical findings in MuSK-antibody positive myasthenia gravis: a U.S. experience. *Muscle Nerve*. 2010;41:370-374.
23. Singh B, Ryan H, Kredo T, Chaplin M, Fletcher T. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. *Cochrane Database Syst Rev*. 2021;2:CD013587.
24. Jallouli M, Saadoun D, Eymard B, et al. The association of systemic lupus erythematosus and myasthenia gravis: a series of 17 cases, with a special focus on hydroxychloroquine use and a review of the literature. *J Neurol*. 2012;259:1290-1297.
25. Angus DC, Derde L, Al-Beidh F, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-19 corticosteroid domain randomized clinical trial. *JAMA*. 2020;324:1317-1329.
26. Fadel R, Morrison AR, Vahia A, et al. Henry Ford COVID-19 management task force. Early short-course corticosteroids in hospitalized patients with COVID-19. *Clin Infect Dis*. 2020;71:2114-2120.
27. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. HLH across speciality collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395:1033-1034.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Gungor Tuncer O, Deymeer F. Clinical course and outcome of an outpatient clinic population with myasthenia gravis and COVID-19. *Muscle & Nerve*. 2022;65(4): 447-452. doi:10.1002/mus.27497

Review of needle electromyography complications in thrombocytopenic cancer patients

Mazen Zein DO[1] | Sudhakar Tummala MD, MBA, FACNS[2] | Laura Prince MD[1] | Jack B. Fu MD[1]

[1]Department of Palliative, Rehabilitation & Integrative Medicine, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

[2]Department of Neuro-Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas

Abstract

Introduction/Aims: Needle electromyography (EMG) is understood to be a relatively safe procedure based on clinical experience. There are no evidence-based guidelines for EMG procedures in thrombocytopenic patients. The purpose of this study was to

Abbreviations: AANEM, American Association of Neuromuscular and Electrodiagnostic Medicine; EDX, Electrodiagnosis; EMG, Electromyography; ICD, *International Classification of Diseases*; IRB, institutional review board; NCI, National Cancer Institute; NCS, nerve conduction study; Plt, Platelet.