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COVID-19 in patients with myasthenia gravis: Epidemiology and disease course

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Abstract

Introduction/Aims: Coronavirus disease 2019 (COVID-19), a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has become a global pandemic. Patients with myasthenia gravis (MG), often treated with immunosuppressants, might be at higher risk of developing COVID-19 and of demonstrating a severe disease course. We aimed to study prevalence and describe features of COVID-19 in MG patients.

Methods: In May 2020, we conducted telephonic interviews with MG patients followed at our referral center. We collected structured data regarding MG and COVID-19, which was diagnosed as probable or confirmed according to the European Centre for Disease Prevention and Control case definition. We compared confirmed-COVID-19 prevalence calculated from the beginning of the pandemic in MG patients with that of the overall Pavia district.

Results: We interviewed 162 MG patients (median age, 66 y; interquartile range 41-77; males 59.9%), 88 from the Pavia district. Three patients had SARS-CoV-2-confirmed by polymerase chain reaction and eight had probable-COVID-19. In the Pavia district, the prevalence of confirmed-COVID-19 among MG patients (1/88, 1.14%) and overall population (4777/546 515, 0.87%) did not differ (P = .538). Higher Myasthenia Gravis Foundation of America clinicalclass and the need for recent rescue treatment, but not ongoing immunosuppressive treatments, were associated with COVID-19 risk. Of 11 MG patients with probable/confirmed-COVID-19, 3 required ventilator support, and 2 elderly patients died of COVID-19 respiratory insufficiency. Only 1 of11 patients experienced worsening MG symptoms, which improved after increasing their steroid dose.

Discussion: The risk of COVID-19 in MG patients seems to be no higher than that of the general population, regardless of immunosuppressive therapies. In our cohort, COVID-19 barely affected MG course.

Abbreviations: MG, myasthenia gravis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; NMJ, neuromuscular junction; MGFA, Myasthenia Gravis Foundation of America Clinical Classification.

Pietro Businaro, Gloria Vaghi, Diego Franciotta, Matteo Gastaldi contributed equally.

KEYWORDS
comorbidities, corticosteroids, COVID-19, epidemiology, immunosuppressive treatments, myasthenia gravis

1 | INTRODUCTION

In the past year coronavirus disease 2019 (COVID-19), a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has rapidly spread to become a worldwide pandemic.[1] Therapeutic management is particularly challenging due to the lack of specific antiviral treatment and is mainly based on supportive care. Italy and in particular the Lombardy region, was one of the most affected areas in Europe during the first wave of COVID-19 in early 2020. It is uncertain whether patients with myasthenia gravis (MG), an autoimmune disorder affecting the neuromuscular junction (NMJ), might be at higher risk of developing COVID-19, for example, due to the immunosuppressive treatment often received.[2] Moreover, these patients might face a particularly severe COVID-19 course since infections can trigger MG exacerbations, and some treatments administered in COVID-19, such as hydroxychloroquine, might further worsen MG manifestations.[3-6] Management of MG patients during the SARS-CoV-2 pandemic has been guided by expert consensus, but data on COVID-19-MG patients are still lacking.[7] We aimed to study COVID-19 infection risk and disease course in MG patients followed at our Institution, located in an area severely affected by the pandemic (the Pavia district in Lombardy), during the first COVID-19 wave in Italy.

2 | METHODS

We screened our electronic records for patients with a diagnosis of suspected MG with at least one outpatient visit at our Institution in the past 3 years, identifying 264 patients (Figure 1). A total of 102 patients were excluded from the study (Figure 1). MG diagnosis was confirmed by the presence of acetylcholine receptor or muscle specific tyrosine kinase autoantibodies and/or compatible neurophysiological findings of decreased compound muscle action potential after repetitive nerve stimulation and/or increased jitter on single-fiber electromyography. In double seronegative patients, MG diagnosis required the combination of neurophysiological abnormalities, clinical improvement after cholinesterase inhibitor administration, and the exclusion of other NMJ diseases.[10]

After receiving informed consent, we administered a telephonic interview investigating current MG condition and treatments. All the patients were contacted between April 26 and May 15, 2020, which corresponded to the final weeks of lockdown and subsequent downward trend of the SARS-CoV-2 infection curve. If appropriate, information on COVID-19 occurrence was collected. If the patients were not able to respond to the interview themselves, information was collected from the caregiver. Additional information regarding the MG status at last visit was collected from our electronic records.

COVID-19 diagnosis was assessed according to the European Centre for Disease Prevention and Control case definition as: (a) probable: at least one suggestive clinical symptom (fever, cough, shortness of breath, anosmia/ageusia/dysgeusia) with an epidemiological link and/or radiological evidence of interstitial pneumonitis; (b) confirmed: any patient with SARS-CoV-2 polymerase chain reaction (PCR) -positive nasopharyngeal swab.[11]

Numerical variables are described as median and quartiles, categorical variables as percentage or row count. Categorical variables were analyzed using Fisher's exact test or Pearson's chi-squared test, while numerical data using Mann-Whitney test. COVID-19 prevalence in the overall population were obtained from the SARS-CoV-2-integrated-surveillance system of the "Istituto Superiore di Sanità"

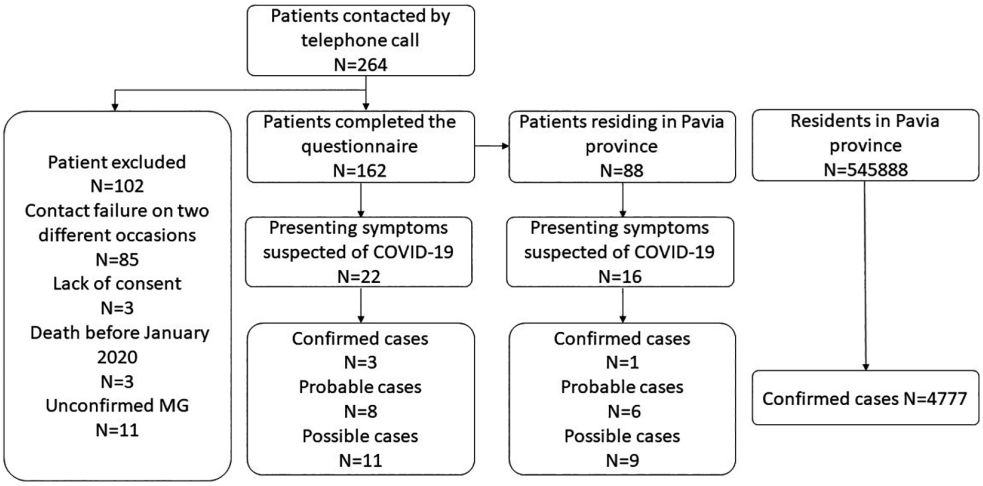

FIGURE 1 Algorithm of the study. Data regarding the Pavia province population were obtained from the national institute of statistics.[8] Data regarding the Pavia province COVID-19 prevalence were obtained from the SARS-CoV-2 surveillance system[9]

(Figure 1).[9,12] COVID-19 prevalence in MG patients was calculated from February 1 and was reported with 95% confidence intervals (CIs).[8] Our hospital is the main referral center for MG in the Pavia district; thus, we considered our cohort as representative of the MG population in this area. Prevalence estimated in MG patients was compared with that of the overall population using the exact binomial test. *P* values <.05 were considered significant. The study was approved by the local ethics committee.

3 | RESULTS

Overall, 162 patients completed the telephonic interview. Eleven had symptoms suggestive of COVID-19, and 6 underwent nasopharyngeal swab testing with SARS-CoV-2 real-time PCR. Three patients were positive and diagnosed with "confirmed-COVID-19." The remaining eight patients were classified as "probable-COVID-19" based on compatible symptoms and close contact with an infected subject in the weeks preceding symptoms

TABLE 1 Clinical features in MG patients with and without COVID-19

MG patients, n (%)	All patients 162 (100)	No COVID-19 151 (100)	Probable/confirmed COVID-19 11 (100)	*P* Value
Age at the time of the interview (y), median (IQR)	66 (54-77)	66 (53-77)	65 (55-86)	1.0[a]
Age at MG onset (y), median (IQR)	57 (43-69)	57 (43-69)	53 (50-73)	1.0[a]
Males, n (%)	84 (51.9)	78 (51.7)	5 (45.5)	1.0
Antibody status				
AChR	102 (63.0)	94 (62.3)	8 (72.7)	.70
MuSK	6 (3.7)	6 (4.0)	0 (0.0)	
Seronegative	54 (33.3)	51 (33.8)	3 (27.3)	
MG duration (y), median (IQR)	5 (2-10)	5 (2-10)	6 (2-12)	.73[a]
Leaving the house once/week	96 (59.3)	88 (58.3)	8 (72.7)	.53
Comorbidities, n (%)				
Cerebrovascular	13 (8.0)	12 (7.9)	1 (9.1)	1.0
Hematologic disease	10 (6.2)	9 (6.0)	1 (9.1)	.51
Autoimmune	23 (14.2)	18 (11.9)	5 (45.5)	.01
Cardiovascular	66 (40.7)	58 (38.4)	8 (72.7)	.05
Malignancies	35 (21.6)	29 (19.2)	6 (54.5)	.01
Diabetes	37 (22.8)	33 (21.9)	4 (36.4)	.28
Smoking, n (%)				
Active	17 (10.5)	17 (11.3)	0 (0.0)	.26
Previous	45 (27.8)	40 (26.5)	5 (45.5)	
Thymectomy, n (%)	32 (19.8)	29 (19.2)	3 (27.3)	.75
MG symptoms, n (%)				
Ocular	53 (32.7)	52 (34.4)	1 (9.1)	
Generalized	109 (67.3)	99 (65.6)	10 (90.9)	.08
Bulbar involvement	91 (56.2)	82 (54.3)	9 (81.8)	.08
Active treatments, n (%)				
Prednisone <10 mg/d	31 (19.1)	28 (18.5)	3 (27.3)	.48
Prednisone >10 mg/d	39 (24.1)	37 (24.5)	2 (18.2)	.64
AZA	47 (29.0)	42 (27.8)	5 (45.5)	.21
Other immunosuppressants	7 (4.3)	7 (4.6)	0 (0)	.47
No immunosuppressants	63 (38.9)	59 (39.1)	4 (36.4)	.86
Treatment with IvIg/PlEx in the previous year, n (%)	26 (16.0)	21 (13.9)	5 (45.5)	.02
MGFA >/= 3 at last visit	22 (13.69	17 (11.3)	5 (45.5)	.01
MG-ADL at last visit, median (IQR)	1 (0-4)	1 (0-4)	4.0 (0-10)	.43[a]

Abbreviations: AChR, acetylcholine receptor; AZA, azathioprine; IQR, interquartile range; IvIg, intravenous immunoglobulin; MG, myasthenia gravis; MG-ADL, myasthenia gravis activity of daily living scale; MGFA, Myasthenia Gravis Foundation of America clinical classification; MuSK, muscle specific tyrosine kinase; PlEx, plasma exchange.

[a]Mann-Whitney test.

TABLE 2 Characteristics of MG patients with COVID-19

	Probable COVID-19								Confirmed COVID-19		
Patient *N*	1	2	3	4	5	6	7	8	9	10	11
Sex	M	F	M	F	F	F	F	M	M	M	F
Age	66	86	55	65	65	78	42	93	54	61	86
MGFA at last visit	I	IIa	IIIa	IIIb	IIIb	IIa	IIIb	I	IIb	I	IIIb
MG duration (y)	1	35	2	12	1	5	9	10	3	19	7
MG signs and symptoms at last visit	Ptosis	Mild proximal weakness in UL and LL	Moderate proximal weakness in UL and LL; mild distal weakness in UL	Ptosis; diplopia; tongue weakness; neck flexors/ extensors weakness	Bilateral ptosis, dysphagia; neck flexors weakness; mild proximal weakness in LL	Mild neck flexors weakness	Diplopia; facial muscles weakness; tongue weakness; moderate proximal weakness in UL and LL.	None	Ptosis; mild facial muscles weakness	None	Dysphagia, facial weakness; neck flexors weakness; weakness in UL and LL
Thymectomy	No	No	No	No	No	No	Yes, thymoma	No	Yes, thymic hypertrophy	Yes, thymic hypertrophy	No
MG antibodies	AChR	AChR	Seronegative	Seronegative	AChR	AChR	AChR	AChR	AChR	AChR	AChR
Nasopahryngeal swab	Not performed	Neg	Neg	Not performed	Not performed	Not performed	Not performed	Neg	Pos	Pos	Pos
COVID-19 symptoms	Fever	Fever, cough	Fever, dyspnoea, myalgias	Fever, dyspnoea, cough, anosmia/ ageusia, myalgias	Cough, myalgias	Fever, dyspnoea, cough, anosmia/ ageusia, myalgias	Fever	Fever, cough	Dyspnoea, cough, myalgias	Fever, cough, anosmia/ ageusia	Fever, dyspnoea, cough, myalgias, chest x-ray: Interstitial pneumonia
Hospital admission/ O2 therapy	No	No	No	No	No	No	No	Yes, unspecified O2 therapy	Yes high flow O2 therapy	No	Yes, high flow O2 therapy
COVID-19 treatment	None	Piperacillin/ Tazobactam	None	None	Amoxicillin/ clavulanic acid	Ceftriaxone	Azithromycine, Trimetoprim/ Sulfametoxazole	Ceftriaxone	Ceftriaxone, hydroxicloroquine, heparin, lopinavir/ ritonavir	Azithromycine, ceftriaxone	Unspecified antibiotics
MG baseline treatment	Pr (12,5 mg every other day), PYR	Pr (25 mg), AZA (100 mg), PYR	PYR	Pr (25 mg), AZA (100 mg), PYR	PYR	PYR, AZA (150 mg)	PYR	PYR	Pr (5 mg), PYR	AZA (100 mg), PYR	Pr (10/5 mg every other day), AZA (50 mg), PYR
MG treatment modifications during COVID-19	None	None	None	None	None	None	Increased Pr	None	None	None	Increased Pr
Comorbidities	None	Autoimmune thyroiditis, metastatic colon cancer, atrial fibrillation	Coronary artery disease, type 2 diabetes	Neuromyelitis optica spectrum disorder, autoimmune thyroiditis	Breast cancer, hypertension	Abdominal aortic aneurism, dilated cardiomyopathy, type 2 diabetes	Polyglandular autoimmune syndrome, previous lung and, uterine cancer, psoriasis, diabetes	Immune trombocytopenia, atrial fibrillation, epilepsy	Hyperparath yroidism	Type 2 diabetes, hypertension	Breast cancer, COPD, polymyalgia

(Continues)

TABLE 2 (Continued)

	Probable COVID-19								Confirmed COVID-19			
MG ADL pre-COVID-19	0	4	7	6	8	7	8	0	3	0	9	
MG during COVID-19	Stable	Stable	Stable	Stable	Stable	Stable	Worsened (dysphagia and diplopia)	NA (death due to COVID-19)	Stable	Stable	NA (death due to COVID-19)	
Outcome (MG ADL post-COVID-19)	0	3	11	5	10	8	10	NA (death due to COVID-19)	4	0	NA (death due to COVID-19)	

Abbreviations: AChR, acetylcholine receptor; AZA, azathioprine; F, female; LL, lower limbs; M, male; MG, myasthenia gravis; MG-ADL, myasthenia gravis activity of daily living scale; MGFA, Myasthenia Gravis Foundation of America clinical classification; Pr, prednisone; PYR, pyridostigmine; UL, upper limbs.

onset. In the Pavia district, the estimate prevalence of "confirmed-COVID-19" was 1.14% (95% CI: 0.02%-6.17%) in our MG patients, and 0.87% (95% CI: 0.85%-0.90%) in the overall population, according to surveillance systems of the Italian Ministry of Health (Figure 1)[8,12] without difference in disease prevalence between the two cohorts ($P = .538$).

The clinical features of the 162 MG patients are summarized in Table 1. Median age was 66 y with a slight predominance of males. More than half of the patients were receiving immunosuppressive treatments at the time of the interview, most commonly oral steroids and azathioprine. Seven patients received other immunosuppressants including cyclosporine (n = 3), mycophenolate mofetil (n = 2), and rituximab (n = 2). The treatment regimen received did not correlate with the development of COVID-19.

COVID-19 was more frequent in MG patients with higher Myasthenia Gravis Foundation of America clinical class (MGFA), with need for rescue treatment for acute exacerbations in the previous year and with autoimmune or neoplastic comorbidities (Table 1).

Data regarding the 11 MG patients with COVID-19 are reported in Table 2. Only 3 of 11 patients were hospitalized and required ventilatory support. Two elderly patients (93 and 86 y old) died of COVID-19 related respiratory insufficiency, but given the rapid course of the disease, it was impossible to ascertain an MG worsening contribution to the poor outcome. In one of them oral prednisone dosage was increased, without modifying the disease course. Among the remaining patients, only one patient reported a worsening of MG symptoms during the COVID-19 (development of double vision and swallow impairment) that promptly improved after increasing the prednisone dosage. Treatments for COVID-19 included antibiotics (eight patients), antiviral (one patient treated with lopinavir/ritonavir), and hydroxychloroquine (one patient).

4 | DISCUSSION

Currently, no epidemiological studies on COVID-19 in MG patients are available, and data regarding SARS-CoV-2 infection risk in this population are scarce. Studies on patients with other autoimmune diseases suggest that immunosuppressive therapy does not represent a risk factor for SARS-CoV-2 infection and that some drugs might even be protective.[13,14] Indeed steroids, the most common medication for MG patients in our cohort, are effective in reducing the mortality in COVID-19.[15] In our study, we found that COVID-19 prevalence did not differ between MG patients and the general population in the Pavia district. Interestingly, among the whole cohort of MG patients, the type of treatment received did not influence the occurrence of COVID-19, supporting the safety of MG treatments in the current pandemic.

We found that MG patients with oncologic/autoimmune comorbidity were more likely to develop COVID-19, suggesting that SARS-CoV-2 infection might be more likely to manifest as a symptomatic disease in this fragile subgroup of patients. Patients with higher MGFA class/severe MG were more susceptible to COVID-19. However, the severity of MG did not correlate with the severity of COVID-19 infection. This might point to a higher susceptibility to COVID-19 in patients with an active autoimmune response, as it has

been suggested for other conditions, such as systemic autoimmune diseases.[13] However, it should also be considered that this particular subset of fragile patients might have been monitored and tested more carefully than the other MG patients.

In most patients, MG remains stable throughout the SARS-CoV-2 infection, but some of them experience worsening of MG symptoms.[2,5] In such cases, additional treatment, such as intravenous immunoglobulins or steroids, might be effective and should be considered early on to prevent severe complications.[7] In our study, the treatments received were not clearly related to the final outcome, that was overall favorable. Only two elderly patients died, possibly reflecting the high mortality rate found in COVID-19 in this age range.[16]

Our study has limitations. First of all, it is possible that some MG patients residing in the Pavia district could not be followed at our Institution. Second, the MG population we examined does not include children, who are more likely to develop an asymptomatic SARS-CoV-2 infection.[1] Third, no independent control for the province prevalence data was performed. Fourth, it is possible that MG patients, considering themselves as a fragile population, might have exhibited more cautious behavior and had less contact with others compared to the general population, or were more likely to undergo COVID-19 testing. All these factors might have contributed to an imprecise prevalence estimate. Finally, the low number of MG patients with COVID-19 does not permit us to define the full spectrum of COVID-19 manifestations or the effect of specific medications in this population. In severely ill patients, such as those who died of respiratory failure, it was impossible to discriminate between the effects of the infection and the MG worsening.

In conclusion, in accordance with consensus guidelines, our data suggest that patients with MG should continue their immunosuppressive therapy in the current pandemic, even in cases of clinically overt COVID-19. In most patients in our cohort, the infection did not dramatically influence the MG course, but larger studies are needed to clarify the course of COVID-19 in MG patients.

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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

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.

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