ORIGINAL ARTICLE

COVID-19 infection and vaccination against SARS-CoV-2 in myasthenia gravis

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Abstract

Introduction Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction which is typically presented with muscle weakness and excessive fatigability. Majority of MG patients require long-term immune suppression. Our aim was to analyze the frequency and severity of COVID-19 infection in MG patients, as well as the frequency of vaccinated MG patients against SARS-CoV-2.

Methods We included 125 MG patients from the central Belgrade municipalities—60% females, age at MG onset 50.1 ± 19.7 years, age at testing 61.7 ± 16.8 years, anti-acetylcholine receptor (anti-AChR) positive 78% and muscle specific tyrosine kinase (MuSK) positive 8.6%.

Results One-third of our MG patients had a COVID-19 infection and they were younger compared to those without verified COVID-19. Severe COVID-19 infection was registered in 28% of MG patients, mostly in elder subjects with comorbidities such as cardiac diseases and malignancies. MG worsening was noted in 21% of patients during/after COVID-19 and 42% had COVID-19 sequelae. Majority of MG patients were vaccinated against SARS-CoV-2 (almost 70%). Vaccination was more common among MG patients with diabetes and in those with a milder form of MG. The most common types of vaccines were Sinopharm (42%) and Pfizer-BioNTech (25.6%). Adverse events were observed in 36% of vaccinated patients, with flu-like symptoms (77%) and local reactions (13%) being the most common ones. MG worsening was noticed in 5 (5.8%) patients after vaccination.

Conclusion COVID-19 has placed a significant new burden for MG patients. Elder MG patients and patients with comorbidities are in higher risk of having adverse outcome following SARS-CoV-2 infection. Percentage of vaccinated MG patients was higher than in general Serbian population.

Keywords Myasthenia gravis · COVID-19 infection · SARS-CoV-2 · Vaccination

Introduction

Myasthenia gravis (MG) is a rare autoimmune disease of the neuromuscular junction, which is typically presented with muscle weakness and fatigability [1, 2]. It is of note that respiratory muscles can also be affected in MG, leading to

respiratory failure and, rarely, lethal outcome [3, 4]. The first case of pneumonia caused by an unknown virus was reported in Wuhan, China in December 2019. The virus was subsequently identified as SARS-CoV-2 (*severe acute respiratory syndrome coronavirus 2*), and several months later the World Health Organization declared the COVID-19 infection pandemic [5].

It is supposed that COVID-19 infection might affect MG patients in several ways. For instance, MG is considered as an immune-mediated disease which could have a bidirectional interaction with infections such as COVID-19. In particular, viruses (and other infectious pathogens) are one of the major environmental triggers of autoimmunity [6, 7]. Before the SARS-CoV-2 pandemic, viral and bacterial respiratory and urinary tract infections were the most frequent

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reasons for hospitalization of MG patients [7]. Further on, patients with MG are usually on long-term immunosuppressive treatment regimens, which make them more susceptible to infections. For instance, only 32% of our MG patients were treatment-free after a 10-year follow-up period [8]. On the other hand, it has been shown that several medications, including the ones used for COVID-19 treatment (hydroxychloroquine and several antibiotics), and vaccines, can trigger MG exacerbation and myasthenic crisis in these patients [9, 10].

The official recommendation of *Myasthenia Gravis Foundation of America* (MGFA) and *Centers for Disease Control and Prevention* (CDC) stated that patients with MG, as a vulnerable population, should get vaccinated against SARS-CoV-2 [11, 12]. Regardless of these recommendations, concerns not only about MG worsening after vaccination and their potential side effects, but also about its effectiveness in medically immunocompromised patients, are still present in both patients and doctors.

Therefore, our aim was to assess the frequency and other characteristics of COVID-19 infection in patients with MG, as well as to analyze the influence of this infection on the course of MG. We also analyzed vaccination rates against SARS-CoV-2 and their potential influence on the course of this autoimmune disease.

Methods

This cross-sectional study included patients who visited inpatient unit, day hospital and/or outpatient unit in a one-year period before the pandemic (from January 1, 2019. to December 31, 2019) at the Neurology Clinic, University Clinical Centre of Serbia. The diagnosis of MG was established according to clinical, pharmacological, electrophysiological and immunoserological MGFA criteria [13, 14]. In this way, we have initially identified 220 patients who fulfilled the criteria. Forty-seven patients were excluded after a minimum of two attempts of telephone-contact, 43 patients refused to participate, three patients died before the COVID-19 pandemic, one patient had the diagnosis of Lambert-Eaton myasthenic syndrome and one patient had his MG diagnosis revised. Thus, a total number of 125 patients was included in the final analysis. Informed consent was obtained from all investigated patients.

Different sociodemographic data (including information about gender, age, age at the onset of disease, serological status, and severity of clinical presentation according to MGFA classification at the beginning and at the peak of the disease) were acquired from the medical informational system of the Neurology Clinic—InfoMedis. We have also collected data about different therapy modalities and comorbid disorders.

During the period of two months (November and December of 2021), data were collected using telephone questionnaires. This specifically designed questionnaire comprised four main domains: MG status at the time of testing, data about COVID-19 infection, data about vaccination against SARS-CoV-2, while the fourth section was filled only in the case of death. All data were obtained from patients or from specific contact persons if the patient had previously died. Severity of the disease was evaluated using the MGFA classification, and further dichotomized into mild (I–IIIA) and a more severe form (IIIB-V) of the disease [14]. Applied treatment modalities were divided into main groups: cholinesterase inhibitors, corticosteroids, non-steroidal immunosuppressive agents (azathioprine, cyclosporin A), therapeutic plasma exchange (PLEx) or intravenous immunoglobulins (IVIg) and experimental study drugs (efgartigimod, mezagitamab, and rozanolixizumab). Patients who had a verified COVID-19 infection from March 6, 2020 (first identified COVID-19 case in The Republic of Serbia) to the moment of testing were guided to the second domain of the questionnaire. Clinical severity of COVID-19 infection was divided into six categories (from "asymptomatic" to "mechanical ventilation needed") according to the WHO clinical progression scale [15], and further dichotomized into mild ("no hospitalization") and severe COVID-19 form ("hospitalized patients"). All patients who were vaccinated against SARS-CoV-2 provided information about the type of vaccines they received. MG worsening was considered related to the infection/vaccination if happened during 6 weeks after first symptoms of COVID-19 or 6 weeks after any dose of the vaccine. Finally, heteroanamnestic data were provided for patients who had died, and it included the time of death, cause of death and its relation to COVID-19 infection.

In addition, using the MG-ADL scale (*Myasthenia Gravis—specific Activities of Daily Living scale*) we have evaluated data about MG status before and after COVID-19 infection/vaccination of all patients who had a verified COVID-19 infection and/or were vaccinated against SARS-CoV-2 [16]. Experienced neuromuscular experts filled out the MG-ADL scale form according to the patient's recollection via phone call.

Statistical analysis

Descriptive statistics methods were used to describe the population: proportion, mean and standard deviation. Chi-square test was used for comparison of non-continuous variables. Mann–Whitney U test was used to compare continuous nonparametric variables and Student's t-test was used for parametric variables. The level of statistical significance was set at $p < 0.05$.

Results

Main sociodemographic and clinical data of our examined MG patients are presented in Table 1. The mean age at testing was 61.7 ± 16.9 years, and there were 75 (60%) female patients. Anti-acetylcholine receptor (Anti-AChR) antibodies were detected in 91 (78.4%) patients, muscle specific tyrosine kinase (MuSK) antibodies in 10 (8.6%), while 15 (12.9%) patients were diagnosed with double-seronegative myasthenia gravis (dSNMG). According to the MGFA classification, 94.1% of patients had mild MG forms at time of diagnosis. On the other hand, severe MG forms were present in 23.3% of patients, of which three patients needed mechanical ventilation. At time of testing, mild disease form was present in 72.5% of patients, while 22.5% were in MG remission. Different therapeutic modalities, applied both at time of diagnosis and time of testing in our cohort of patients, are noted in Table 1.

Characteristic of COVID-19 infection in MG patients

COVID-19 infection was verified in 43 (34.4%) patients with MG. Milder COVID-19 forms were recorded in 72.1% of our patients, while 27.9% of patients had a more severe form of the disease (Table 2). Antibiotics which are considered as unsafe for use in patients with MG, such as macrolides and quinolones, were used in 11 (25.6%) patients with COVID-19. Sociodemographic factors of our MG patients, which were associated with a more severe form of COVID-19 infection, were patients' age at the moment of infection (51.5 ± 13.3 years in patients with mild COVID-19 vs. 67.5 ± 16.7 years in patients with severe COVID-19, $p < 0.01$) and the presence of comorbid disorders (42.3% of patients with comorbidities vs. 6.7% of patients without comorbidities, $p < 0.05$). After further analysis of individual comorbid disorders, it was noted that 80% of patients with a cardiovascular disease had severe COVID-19 form compared to one-fifth of patients without the presence of cardiovascular diseases ($p < 0.01$). Similar findings were observed in patients with a history of malignancy (100% vs. 24.4%, $p < 0.05$).

Course of myasthenia gravis during and after COVID-19 infection

Myasthenia gravis exacerbation during and after COVID-19 infection has occurred in nine (21.4%) patients. Mean time of MG exacerbation after the first symptom of COVID-19 was 23 days. Among these nine patients, four patients were not vaccinated, one patient got only the first dose of the vaccine, and four patients were completely vaccinated against SARS-CoV-2 (two patients got the Sinopharm vaccines while two got the Pfizer-BioNTech vaccines). In addition to COVID-19, two patients had other reasons for MG exacerbation, such as malignancy and a prolonged stressful situation. The average MG-ADL score before COVID-19 infection in patients who experienced MG exacerbation was 2.5 ± 2.6 and 7.1 ± 4.1 after infection, with an average difference of 4.8 ± 4.8 and with a span from 2 up to 17 points. One of two patients who have died as a result of MG worsening was not vaccinated, while the other one was not completely vaccinated against SARS-CoV-2 (this patient got only one dose of Sputnik V vaccine). None of the investigated sociodemographic and clinical features of our cohort correlated with MG exacerbation during and after COVID-19 infection.

Post-COVID-19 sequelae in MG patients

Post-COVID-19 sequelae were observed in 41.8% of MG patients, with cardiac arrhythmias, chest pain, dyspnea and hair loss being the most common. Novel autoimmune diseases after COVID-19 were not detected in our cohort of MG patients.

The relationship between vaccination against SARS-CoV-2 and MG

Up to 70% of our MG patients were vaccinated against SARS-CoV-2 (Table 3). The main reason against vaccination in our group of patients was the fact that the patients did not want to get vaccinated. Most of the vaccinated patients received three doses of the vaccine (62.8%). Most frequently applied vaccines were Sinopharm (48.8%), followed by Pfizer-BioNTech, Sputnik V and AstraZeneca. Adverse effects after vaccination were recorded in 36% of patients, mostly presented as flu-like symptoms (including fever, headaches, chills, and muscle aches) and local reactions. Novel autoimmune diseases after vaccination were not observed in our cohort of MG patients.

Course of myasthenia gravis after vaccination against SARS-CoV-2

Myasthenia gravis exacerbation after vaccination against SARS-CoV-2 was documented in five (5.8%) patients, which appeared 6.3 ± 3.9 days after vaccination. MG worsening was observed in three (7.1%) of 42 patients after Sinopharm vaccine and two (9.1%) of 22 patients after Pfizer-BioNTech vaccine. The average MG-ADL score before vaccination of patients who had exacerbation was 2.0 ± 2.3 vs. 7.4 ± 5.6 after vaccination (average difference of 5.4 ± 6.5, in the range from 2 to 17 points). Factors that have been shown to be statistically significant for MG worsening after vaccination were usage of non-steroidal

Table 1 Main sociodemographic and clinical features of examined patients with MG

Demographic dana	Number (%) or mean ± SD		
Sex—female	75 (60%)		
Age at the time of testing	61.7 ± 16.9		
Comorbidities			
Any comorbidity	99 (79.2%)		
Arterial hypertension	60 (63.8%)		
Diabetes mellitus	25 (20%)		
Cardiovascular diseases	17 (13.6%)		
Pulmonary diseases	9 (7.2%)		
Neuropsychiatric disorders	9 (7.2%)		
Personal history of malignancies	12 (9.6%)		
Other	59 (47.2%)		
Autoimmune diseases			
Any autoimmune disease	11 (9%)		
Hashimoto's thyroiditis	5 (4.1%)		
Sjögren's syndrome	3 (2.5%)		
Polymyositis	1 (0.8%)		
Systemic lupus	1 (0.8%)		
Multiple autoimmune syndrome	1 (0.8%)		
Thymus			
Normal/atrophic	78 (74.3%)		
Hyperplasia/persistent	14 (13.3%)		
Thymoma	13 (12.4%)		
Thymectomy	44 (36.4%)		
Antibodies			
Anti-AChR Ab	91 (78.5%)		
Anti-MuSK Ab	10 (8.6%)		
Double seronegative	15 (12.9%)		
MGFA classification[a]	At the time of diagnosis N (%)	At the disease nadir N (%)	At the time of testing N (%)
Remission	/	/	27 (22.5%)
I	44 (37.3%)	23 (19.3%)	29 (24.2%)
IIA	19 (16.1%)	15 (12.6%)	30 (25.0%)
IIB	43 (36.5%)	39 (32.8%)	18 (15.0%)
IIIA	5 (4.2%)	15 (12.6%)	10 (8.3%)
IIIB	7 (5.9%)	21 (17.7%)	5 (4.2%)
IVA	/	2 (1.7%)	1 (0.8%)
IVB	/	1 (0.8%)	/
V	/	3 (2.5%)	/
Therapy	During the course of the disease N (%)	At the nadir N (%)	At the time of testing N (%)
Anticholinesterase therapy	122 (100.0%)	116 (98.3%)	107 (89.2%)
Corticosteroids	108 (88.5%)	103 (87.3%)	64 (53.3%)
Non-steroidal immunosuppressants (azathioprine, cyclosporin A)	67 (54.9%)	76 (64.4%)	47 (39.2%)
PLEx or IVIg	20 (16.4%)	25 (21.2%)	1 (0.8%)
Experimental study drugs (efgartigimod, mezagitamab, rozanolixizumab)	9 (7.4%)	3 (2.6%)	5 (4.2%)
No treatment	/	/	9 (7.5%)

SD standard deviation, *MG* myasthenia gravis, *AchR* acetylcholine receptor, *MuSK* muscle specific tyrosine kinase, *MGFA* Myasthenia Gravis Foundation of America, *PLEx* plasma exchange, *IVIg* intravenous immunoglobulins;

[a]I–IIIA represent milder MG forms, IIIB-V represent more severe MG forms

Table 2 Main characteristics of COVID-19 infection in patients with MG

Feature		N (%) or mean ± SD
Total (N)		43 (34.4%)
Positive antigen test		13 (30.2%)
Positive PCR test		5 (11.6%)
Positive both tests		23 (53.5%)
No test		2 (4.7%)
Severity of clinical presentation[a]		
1	Asymptomatic infection	4 (9.3%)
2	Mild clinical symptoms without hospitalization	27 (62.8%)
3	Hospitalization without O_2 use	3 (7.0%)
4	Hospitalization with O_2 use via mask or nasal cannula	3 (7.0%)
5	Non-invasive ventilation or *high-flow* O_2	5 (11.6%)
6	Intubation and mechanical ventilation	1 (2.3%)
Antibiotics used during the infection[b]		
β-Lactames		12 (27.9%)
Macrolides[b]		8 (18.6%)
Quinolones		3 (7.0%)
Sulphonamides		1 (2.3%)
Metronidazole		3 (7.0%)
None		9 (20.9%)
No dana		7 (16.3%)
Features of patients with MG worsening after COVID-19		
Total (N)		9 (20.9%)
MG-ADL before COVID-19		2.3 ± 2.6
MG-ADL after COVID-19		7.1 ± 4.1
MG-ADL difference		4.8 ± 4.8
Time from the first symptom of COVID-19 until worsening in days		23.1 ± 25.8
Post-COVID sequelae		
Total (N)		18 (41.8%)
General weakness and fatigue		9 (50.0%)
Cardiological disorders		5 (27.8%)
Pulmonological disorders		1 (5.5%)
Other		5 (27.8%)
Lethal outcome		
Total (N)		5 (4.0%)
Years of age		80.2 ± 6.4
Cause of death		
COVID-19		2 (40.0%)
Ileus		1 (20.0%)
Myocardial infarction		1 (20.0%)
Aortic aneurysm rupture		1 (20.0%)
Novel autoimmune diseases after COVID-19		
Total (N)		0 (0.0%)

MG myasthenia gravis, *MG-ADL* myasthenia gravis activities of daily living

[a]Categories 1 and 2 are considered milder form, categories 3–6 are more severe form;

[b] macrolides and quinolones are considered antibiotics that are not safe for use in MG patients according to MGFA recommendations;

immunosuppressive agents (11.9% of patients on non-steroidal immunosuppressive regimen vs. 0% of patients who were not on this regimen, $p < 0.05$) and the utilization of experimental study drugs (33.3% on experimental study drugs vs. 5.2% of patients who were not on this regimen, $p < 0.05$).

Table 3 Vaccination against SARS-CoV-2 in patients with MG

Unvaccinated MG patients	N (%) or mean ± SD
Total (N)	39 (31.2%)
Reasons not to get vaccinated	
Does not want to	12 (30.8%)
Is afraid of MG worsening	10 (25.6%)
Neurologist's advice	8 (20.5%)
General practitioner's advice	6 (15.4%)
Death before vaccination	3 (7.7%)
Vaccinated MG patients	Number (%)
Total (N)	86 (68.8%)
Number of doses	
One	3 (3.5%)
Two	29 (33.7%)
Three	54 (62.8%)
Vaccine type (manufacturer)	
Sinopharm	42 (48.8%)
Pfizer-BioNTech	22 (25.6%)
Sputnik V	5 (5.8%)
Astra Zeneca	2 (2.2%)
Combination	15 (17.6%)
Adverse effects	
Total (N)	31 (36.0%)
Flu-like symptoms	24 (77.4%)
Local reaction	4 (12.9%)
Other	3 (9.7%)
Dose after which adverse effects occurred	
First	9 (29.0%)
Second	11 (35.5%)
Third	5 (16.1%)
First and the second	2 (6.5%)
First and the third	1 (3.2%)
Second and the third	2 (6.5%)
First, second and the third	1 (3.2%)
Features of patients with MG worsening after vaccination	N (%) or mean ± SD, span
Total (N)	4 (4.6%)
After (days)	6.3 ± 3.9
MG-ADL before vaccination	2.0 ± 2.3
MG-ADL after vaccination	7.4 ± 5.6
MG-ADL difference	5.4 ± 6.5
Novel autoimmune diseases after vaccination	
Total (N)	0 (0.0%)

MG Myasthenia gravis, *MG-ADL* myasthenia gravis activities of daily living

Discussion

The results of our study have shown that one-third of our MG patients had a COVID-19 infection. According to available WHO data, this percentage is insignificantly lower among the general population of the Republic of Serbia (around 27% on the day of February 25th, 2022) [17]. Moreover, these data are in accordance with a Polish study where 33.3% of MG patients had COVID-19 [18]. On the other hand, previous studies from Turkey and France reported significantly lower prevalence of COVID-19 infection (0.96% and 13.5%, respectively) among patients with MG [19, 20]. The basic cause of these differences might be the disparity between the study conducting time and the course of the pandemic, as well as different prevalence among general population in these countries. For instance, the French cohort study included a shorter period (3 months) at the beginning of the pandemic when strict anti-epidemic and self-isolation measures were applied [20].

A more severe form of COVID-19 (hospitalization required) was recorded in approximately one third of our SARS-CoV-2 infected MG patients. These results coincide with data obtained in the Turkish study [19], but not with the results from the French cohort study where this percentage was nearly twice as high [20]. The explanation for this dissimilarity may be the fact that 60% of patients in the French study had a severe form of MG at the time of COVID-19 infection, while most of our patients had a mild form of MG.

The main risk factors for the appearance of the severe form of COVID-19 in our MG population were patients' age at the moment of testing and the presence of comorbid disorders (especially cardiovascular diseases and malignancies). Accordingly, the risk for developing a severe form of COVID-19 in the general population was associated with older age and different comorbidities such as cardiovascular disorders, diabetes mellitus and several malignancies [21]. Lupica et al. reported that MG patients who died due to COVID-19 were older and had more comorbid diseases [22]. Thus, it seems that to-date literature data has identified same risk factors for the appearance of severe COVID-19 forms in both patients with MG and general population [23].

In one fifth of our MG patients who had COVID-19, MG exacerbation was confirmed during or after the infection. On the other hand, previous studies with smaller groups of patients showed a more significant prevalence of MG exacerbation (in a range from 50 to 87% of infected MG patients) [24–26]. However, observed contrast in reported disease deterioration could, at least partially, be explained by sociodemographic and clinical inter- and intra-cohort differences of comprised patients. For instance, our study included all MG patients from one territory, regardless of disease severity and remission status.

Post-COVID sequelae were present in 42% of our patients with MG. These data are in accordance with a general population study of Hirschtick et al., where post-COVID sequelae occurred in almost one half of the patients that had COVID-19 [27].

In our MG cohort, 69% of patients were vaccinated against SARS-CoV-2, which is higher compared to the general population of the Republic of Serbia (47% on February 23rd, 2022) and the WHO world data (55%) [28]. The main reason for this higher percentage of vaccination in our MG population could be the well-established advisory role of doctors, as well as patients' fear of getting a more severe COVID-19 form due to both their primary autoimmune disease and medical immunosuppression. However, a significant part of MG population was not vaccinated due to different reasons. It means that vaccine-related skepticism is still present among MG population, and even doctors, mostly due to the revolutionary rapid development of the SARS-CoV-2 vaccines [29]. It is of note that MG worsening after vaccination, analyzed by patient self-evaluation, was present in only 6% of vaccinated patients, primarily in patients on non-steroidal immunosuppressants and experimental study drug regimens. These findings were similar to the Italian cohort data where MG-ADL scores did not worsen in most of the patients after vaccination [22]. The main reason for primary disease worsening after vaccination in our patients could be the fact that this group of patients was generally presented with a more severe form of MG. Interestingly, compared to disease worsening after vaccination, MG exacerbation after COVID-19 infection was noted only in a slightly higher number of patients (nine (10.5%) of 89 vaccinated patients vs. five (11.6%) of 43 patients who had COVID-19 infection). Indeed, according to previous data MG worsening appears to be uncommon in COVID-19, appearing in only 10–15% of infected patients [25], which is similar to our findings.

The main limitation of our study is the telephone-based approach of obtaining patients' data since this may cause a recall bias. Further prospective longitudinal studies are needed to evaluate MG course and prognosis during and after the COVID-19 pandemic era. Despite these limitations, the study comprises a relatively large cohort of MG patients and provides useful data about the COVID-19 infection and vaccination against SARS-CoV-2 in a rare immune-mediated disease such as MG, offering valuable data for treatment and care of these patients.

Conclusions

COVID-19 has placed a significant new burden for MG patients. Elder MG patients and patients with comorbidities (especially with cardiovascular and malignant diseases) are in higher risk of having adverse outcome following SARS-CoV-2 infection. Percentage of vaccinated MG patients was higher compared to general Serbian population, and MG worsening after vaccination was mostly seen among vaccinated patients with more severe MG forms.

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