NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

RESEARCH ARTICLE

Arch Neuropsychiatry 2024;61:213–220
https://doi.org/10.29399/npa.28418

Evaluation of Clinical Effects of COVID-19 Infection and Vaccines on Myasthenia Gravis

Levent ÖCEK[1, 2], Tuğba DEMİR ÖZEN[1], Özge ÖCEK[3], Alp SARITEKE[1], Ufuk ŞENER[1, 2]

[1]University of Healthy Sciences, Tepecik Education and Research Hospital, Department of Neurology, İzmir, Turkey
[2]University of Healthy Sciences, İzmir Faculty of Medicine, Department of Neurology, İzmir, Turkey
[3]University of Healthy Sciences,İzmir Bozyaka Education and Research Hospital, Department of Neurology, İzmir, Turkey

ABSTRACT

Introduction: In this study, we aimed to investigate the clinical effects of COVID-19 infection and vaccines on Myasthenia gravis (MG) during the pandemic.

Methods: A total of 141 MG patients between April 2020 and December 2021 were retrospectively analyzed. Data including demographic and clinical characteristics of patients, COVID-19 test results, and vaccine types (mRNA-BNT162b2 and/or inactivated-CoronaVac) were recorded. All patients were followed by face-to-face interviews and/or phone calls. Worsening MG symptoms after COVID-19 infection or vaccines were noted.

Results: A total of 60 patients were diagnosed with COVID-19, and reverse transcriptase-polymerase chain reaction test results were COVID-19 positive in 54 (90%) patients. Twenty-eight (46.7%) patients had lung involvement, while 20(33.3%) patients were followed in the ward. Twelve (20%) patients were followed in the intensive care unit, and two of them (3.3%) died. Both deceased patients were unvaccinated. The most common symptoms were fatigue (78.3%), and 13(21.7%) patients were asymptomatic. Of the patients, 96(68%) received at least one dose BNT162b2 or CoronaVac, while 30.4% of the patients received ≥3 doses of vaccines. The local skin irritation and fatigue rate was significantly higher with BNT162b2 vaccine than CoronaVac (p<0.001 and p=0.004, respectively). No serious side effect was observed with either vaccine. Five patients had worsening MG symptoms after vaccination during a six-week follow-up. None of the patients experienced myasthenic crises.

Conclusion: Our study results suggest that COVID-19 infection affects MG similar to the general population and does not lead to worsening MG symptoms. Both mRNA and inactivated vaccines with proven efficacy can be used safely in MG patients.

Keywords: COVID-19, myasthenic crisis, myasthenia gravis, pandemic, SARS-CoV-2, vaccination

Cite this article as: Öcek L, Demir Özen T, Öcek Ö, Sarıteke A, Şener U. Evaluation of Clinical Effects of COVID-19 Infection and Vaccines on Myasthenia Gravis. Arch Neuropsychiatry 2024; 61:213–220.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease caused by the production of specific antibodies to certain neuromuscular junction (NMJ) proteins, particularly to acetylcholine receptor subunits (1,2). Most MG patients suffer from infectious diseases, which are the leading causes of worsening of the clinical status characterized by weakening of the eye, limb, bulbar, and respiratory muscles (1–5). The novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) which was first identified in December 2019 has tremendously affected all over the world. Several studies have demonstrated that COVID-19 is associated with neurological disorders such as headache, seizures, and stroke (6,7). Although recent studies have suggested that COVID-19 is correlated with worsening MG symptoms, Tuncer et al. reported that having well-controlled MG before COVID-19 infection and absence of comorbidities likely affected the course of the infection favorably (8). However, there is still a limited number of studies investigating the effects of COVID-19 on NMJ disorders such as MG in the literature (2–5,8).

There has been a great effort to develop vaccines against COVID-19 all over the world. Clinical studies have shown the efficacy and safety of COVID-19 vaccines (9,10). Inactivated vaccines have been proven to be both effective and safe with a favorable immunogenicity and low side effect profile (9–11). In Turkey, inactivated CoronaVac (Sinovac, China) was routinely applied in the early stages of the pandemic. Subsequently, the Pfizer-BioNTech messenger ribonucleic acid (mRNA) COVID-19 vaccine, also known as BNT162b2, was shown to be 95% effective in preventing COVID-19 infection and was applied in our country (9). However, with the rapid development of COVID-19 vaccines, some

Highlights

- **We investigated the effect of COVID-19 infection and vaccines on MG patients.**
- **No increase in worsening or crisis in MG patients was seen during COVID-19 infection.**
- **No serious adverse events were shown in MG patients after COVID-19 vaccines.**
- **While there were two (3.3%) death after COVID-19, no post-vaccines death was observed.**

Correspondence Address: Levent Öcek, İzmir Sağlık Bilimleri Üniversitesi, Tepecik Eğitim ve Araştırma Hastanesi, Nöroloji Kliniği, İzmir, Turkey • **E-mail:** leventocek66@yahoo.com
Received: 23.01.2023, **Accepted:** 17.05.2023, **Available Online Date:** 19.08.2024

concerns were raised regarding the efficacy and safety of these vaccines in MG patients or those using immunosuppressive drugs. It is unclear if COVID-19 immunizations increase the likelihood of worsening MG symptoms or whether immunosuppressive medicines decrease the serological response to vaccines. In the present study, we, therefore, aimed to investigate the effects of COVID-19 infection and COVID-19 vaccines on the clinical course of MG during the pandemic.

METHODS

Study Design and Study Population

This single-center, retrospective study was conducted at the Neuromuscular Diseases Unit of the Department of Neurology of a tertiary care center between April 2020 and December 2021. A total of 330 patients aged >18 years who were diagnosed with acquired MG based on clinical, immunological, and electrophysiological diagnostic criteria and 141 patients who met the inclusion criteria were enrolled. Data including demographic (age, sex, body weight, height, education status, phone number) and clinical characteristics of the patients (age of onset of MG and disease duration) were retrieved from the hospital database. During the pandemic, all patients were followed via face-to-face interviews and/or phone calls. Early-onset MG (EOMG) was defined as onset at ≤50 years of age, while late-onset MG (LOMG) was defined as onset >50 years of age. Initial symptoms of MG were classified as ocular, bulbar, or limb weakness. The disease was divided into two main types generalized and ocular MG.

The patients were divided into two groups, those with and without COVID-19 infection. The diagnosis of COVID-19 was made based on clinical symptoms, plain chest X-ray or computed tomography (CT) and real-time reverse transcriptase-polymerase chain reaction (RT-PCR) tests using nasopharyngeal swabs. A written informed consent was obtained from MG patients. A questionnaire for COVID-19 symptoms was filled out by the patients and/or family members. In addition, the clinical status of MG patients after COVID-19 infection was noted.

Data Collection and Definitions

From the beginning of the pandemic, all patients were reached in outpatient settings or by phone calls, significant importance was attached to maintaining close touch. Among these patients, those were vaccinated against COVID-19 (mRNA-BNT162b2 or inactivated CoronaVac) between April 2021 and December 2021 in accordance with the National Immunization Program were re-evaluated. The type of vaccine was chosen by the patients on a voluntary basis.

Hospitalization was defined as the admission of patients due to COVID-19 infection or COVID-19 vaccine during follow-up. Intensive care unit (ICU) admission was defined as the admission of patients due to respiratory support induced by COVID-19 infection or COVID-19 vaccine. Mechanical ventilation (MV) requirement was evaluated during hospitalization for each patient. In addition, all patients were re-evaluated in detail based on the National Health System database, if they had hospital and/or ICU stay during and after COVID-19 infection or COVID-19 vaccine. Death events following COVID-19 infection or vaccine were retrieved from the National Death Notification Service.

The Myasthenia Gravis Foundation of America (MGFA) classification was used to evaluate the severity of the disease (12). Worsening MG was defined as increased muscle weakness (new-onset or coexisting) for more than 24 hours within six weeks of COVID-19 infection or COVID-19 vaccine and shift in at least one class of the MGFA A or B. Myasthenic crisis was defined as the involvement of respiratory muscles and the subsequent need for intubation and MV.

Ethical Considerations

The study protocol was approved by the institutional Ethics Committee (No: 01–23/Date: 2022) and Republic of Türkiye , Ministry of Health, General Directorate of Public Health, Study of Scientific Board. The study was conducted in accordance with the principles of the Declaration of Helsinki. The written informed consents were obtained from all participations.

Statistical Analysis

Statistical analysis was performed using the IBM Statistical Package for Social Sciences (SPSS) program version 26.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency, where applicable. The chi-square (χ^2) tests were used to compare categorical variables of two groups. Continuous variables were compared using the Student *t*-test or Mann-Whitney U test, where appropriate. Multivariate regression analyses were performed to identify the risks of ICU/MV and the following covariates were included. Age, sex, tobacco use, body mass index (BMI), age of onset of the disease (EOMG and LOMG), anti-AchR antibody status, thymectomy, and immunosuppression treatment and presented in the odds ratios (ORs) with 95% confidence intervals (CIs). A *p* value of <0.05 was considered statistically significant.

RESULTS

The study included 141 patients, 79 (56%) of whom were females and 62 (44%) of whom were males. The average age was 60.03±14.96 years (range: 28 to 86). The mean age of onset of MG was 49.2±16.3 (range, 28 to 86) years. Ninety-five (67.3%) patients with MG were seropositive. A total of 96 (68.1%) of the patients had ocular MG and 14 (25.9%) had thymoma. The initial symptoms were ocular weakness in 115 (81.2%) patients, bulbar symptoms in 34 (24.1%) patients, and limb weakness in 63 (44.6%) patients. Based on the clinical disease type, 44 (31.2%) patients were diagnosed with ocular MG during follow-up. Of the patients, there were ischemic risk factors such as hypertension (HT), diabetes mellitus (DM), and cardiovascular diseases in 53 (37.6%), 26 (18.4%), and 19 (13.4%) patients, respectively. Twenty-six (18.4%) patients had concomitant autoimmune disorders. Demographic and clinical characteristics of the patients are summarized in Table 1.

Sixty (42.5%) patients were diagnosed with COVID-19. Of these patients, 54 (90%) had RT-PCR positivity for COVID-19. Twenty-eight (46.7%) patients had pneumonia and 20 (33.3%) were hospitalized. Twelve (20%) patients were followed in the ICU, and two (16.7%) of these patients died. Six (10%) patients had worsening MG symptoms after COVID-19 infection, and three (5%) had myasthenic crisis (Table 2). Two patients in whom the infection was confirmed by a positive RT-PCR test died. Both had no vaccination. The first case was an 86-year-old female with HT and hypothyroidism and under treatment with pyridostigmine 180 mg/day. The official cause of death was pneumonia with septic shock. The second case was an 81-year-old male with seropositivity (anti-AchR antibodies) MG with pulmonary disease and was under treatment with pyridostigmine 240 mg/day and azathioprine 100 mg/day.

The most common signs and symptoms of MG patients infected with COVID-19 were fatigue (78.4%), fever (60%), cough (53.3%), headache (41.1%), loss of smell (23.3%), loss of taste (23.3%), myalgia (18.3%), and arthralgia (9%). Thirteen (21.7%) patients had no neurological symptoms. The number of patients with comorbidities such as HT and DM were significantly higher in COVID-19-positive patients (p=0.008 and p=0.026, respectively). The comparison of clinical and demographic characteristics of the MG patients with and without COVID-19 is shown in Table 3. There was no statistically significant difference in the demographic and clinical characteristics of the patients with and without COVID-19 in the multivariate analysis (Table 4).

Table 1. Demographic data of all patients

	MG patients (n=141)	(%)
Female/Male	79/62	56/44
Age (± sd) (years)	60.03 (±14.96)	
BMI (kg/m²)(± sd)	28.48 (±4.17)	
Tobacco		
Smoking	39	27.7
No smoking	102	72.3
Age at disease onset (years)	49.26 (±16.33)	
EOMG (<50)	68	48.2
LOMG (≥50)	73	51.8
Anti-AchR antibody status		
Seropositive (≥0.49 nM)	90	63.8
Seronegative (<0.49 nM)	51	36.2
Presenting symptoms at disease onset		
Ocular weakness	115	81.5
Bulbar weakness	34	24.1
Limb weakness	63	44.6
MG type		
Ocular MG	44	31.2
Generalized MG	97	68.8
Thymectomy		
Yes	54	38.3
No	87	61.7
Thymic pathology		
Thymoma (+)	14	25.9
Thymoma (-)	40	74.1
Concomitant autoimmunity		
Graves' disease	11	7.8
Hashimoto thyroiditis	14	9.9
Sjögren	1	0.7
Disease status before COVID-19		
Stable	104	73
MGFA I	26	18.4
MGFA IIA	10	7.1
Immunosuppression (IS) protocols		
Steroids monotherapy	35	24.8
IS monotherapy	38	27
Steroids + IS	9	6.4
No therapy	59	41.8
Types of immunosuppressive drugs		
Azathioprine	39	82.9
Mycophenolate mofetil	8	17.1
COVID-19 outcome	60	42.5
PCR (+)	54	90
Pneumonia	28	46.7
Hospitalization	21	35
ICU+MV	12	20

AchR: Acetylcholine receptor; BMI: Body mass index; EOMG: Early onset myastenia gravis; ICU: Intensive care unit; LOMG: Late onset myastenia gravis, MG: Myastenia gravis; MGFA: Myasthenia Gravis Foundation of America; MV: Mechanical ventilation; n: patients. PCR: Polymerase chain reaction; sd: standard deviation

Table 2. Characteristics of patients with MG worsening and/or MG crisis

	MG worsening						MG crisis		
Patients	1	2	3	4	5	6	1	2	3
Gender	F	M	F	M	F	F	F	M	F
Age	74	38	46	66	67	52	86	81	34
Age at disease onset (years)	66	34	48	59	52	41	50	60	34
Comorbid Disease	HT, DM	-	-	DM, Liver tumor	HT	-	HT, Hypothroid, Ovarian tumor	COPD	–
MGFA	IIA	I	IIA	IIA	I	IIA	I	IIA	IIA
Thymectomy	No	Yes	Yes	No	Yes	Yes	No	No	No
Antibody status	AchR	Seronegative	AchR	AchR	AchR	AchR	Seronegative	AchR	Musk
MG treatment	PYR+PR	PYR	PYR+AZA	PYR+AZA	PYR+AZA	PYR+AZA	PYR	PYR+AZA	PYR+AZA
MG worsening treatment	PYR dose increase +PR+ IVIG	PYR dose increase +PR	PYR dose increase +PR	PYR dose increase +PR	PYR dose increase +PR	PYR dose increase +PR	PYR dose increase +PR +IVIG	PYR dose increase +PR+ IVIG	PYR dose increase+PR+ IVIG+PE

AchR: Acetylcholine receptor; AZA: Azathioprine; COPD: Chronic Obstructive Pumoner Disease; DM: Diabetes mellitus; F: Female; HT: Hypertension, IVIG: Intravenous immunglobulin; M: Male; MG: Myastenia gravis; MGFA: Myasthenia Gravis Foundation of America; Musk: Muscle spesific kinase. PR: Prednisone; PYR: Pyridositgmin.

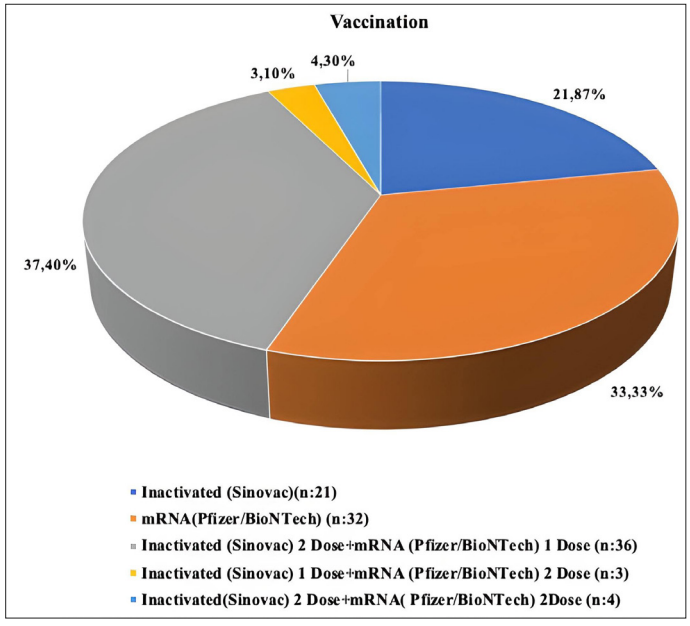

Figure 1. Distribution of COVID-19 vaccines in MG patients

A total of 96 (68%) patients received at least one dose BNT162b2 and/or inactivated CoronaVac vaccine, while 30.4% of the patients received ≥3 doses of vaccines (Figure 1). A total of 34.7% of the patients experienced mild side effects after the vaccine, and none of the patients had serious vaccine-related reactions. The rate of local skin irritation and fatigue was significantly higher with BNT162b2 vaccine than CoronaVac ($p<0.001$ and $p=0.004$, respectively) (Table 5). Five patients had worsening MG symptoms after vaccination during a six-week follow-up. None of the patients experienced myasthenic crises. Intravenous immunoglobulin (IVIG) was given to three patients with worsening MG symptoms, while pyridostigmine and corticosteroid treatment was administered to the remaining two patients, and symptoms resolved over time. A detailed analysis of the patients with worsening MG symptoms after the COVID-19 vaccine is depicted in Table 6.

DISCUSSION

In the present study, we investigated the effects of COVID-19 infection and vaccines on the clinical course of MG during the pandemic. The results we obtained were consistent with those of Tuncer et al., who discovered no significant increase in the rate of MG worsening and/or myasthenic crisis as a result of COVID-19 infection (8). In our study, none of the patients had any vaccine selection. In addition, none of the patients experienced serious vaccine-related side effects with either BNT162b2 or CoronaVac. However, the rate of acute and mild side effects was higher in the patients receiving BNT162b2. Based on these findings, we suggest that COVID-19 vaccines are safe for patients with MGFA Class I and II MG.

Viral and bacterial respiratory infections are common triggers for worsening MG or myasthenic crises. The SARS-CoV-2 infection has also been described as a trigger for MG exacerbation (13,14); however, MG exacerbation is rare in COVID-19 which only accounts for 10 to 15% of the patients (15,16)**.** On the other hand, mortality rates tend to decrease as COVID-19 is better understood with therapeutic developments. In the literature, for the first time in a Brazilian cohort, 87% of the MG patients with COVID-19 infection were admitted to the ICU and 73.2% required MV support with a mortality rate of 30% (13). At the onset of the COVID-19 pandemic, preliminary data indicated that patients with MG might be at an increased risk of experiencing severe COVID-19 infection and these patients might require more intensive care support. In the interim data of the CARE-MG study, Muppidi et al. reported that 36 out of 91 patients with MG (40%) required additional treatment (e.g., intravenous immunoglobulin, plasma exchange, or steroids) for MG worsening or crisis and 22 of these (24%) died due to COVID-19 (17). Afterwards, in a French cohort, Solé et al. evaluated clinical characteristics and outcomes of COVID-19 in 3.358 MG patients using

Table 3. Comparison of COVID-19 positive or negative groups in MG patients

	COVID-19(+) MG (n=60)	COVID-19(-) MG (n=81)	p*
Female/Male	34/26	45/36	0.895
Age (± sd) (years)	58.37 (±15.38)	61.26 (±14.58)	0.257
BMI (kg/m²) (± sd)	28.03 (±4.03)	28.58 (±4.29)	0.723
Tobacco			
Smoking	18 (30)	21 (25.9)	0.593
No smoking	42 (70)	60 (74.1)	0.364
Age at disease onset (years)	48.70 (±15.88)	49.68 (±16.75)	0.726
EOMG	29	39	0.983
LOMG	31	42	0.559
Anti-AchR antibody status			
Seropositive (≥0.49 nM)	39	51	0.803
Seronegative (<0.49 nM)	21	30	
Presenting symptoms at disease onset			
Ocular weakness	49	58	0.801
Bulbar weakness	14	20	0.802
Limb weakness	28	33	0.982
MG type			
Ocular MG	16	28	0.272
Generalized MG	44	53	0.327
Thymectomy			
Yes	27	27	0.203
No	33	52	
Thymic pathology			
Thymoma (+)	7	10	0.310
Thymoma (-)	20	17	
Comorbide disease			
Hypertension	15 (25)	38 (46.9)	**0.008**
Diabetes mellitus	6 (10)	20 (24.7)	**0.026**
CAD	6 (10)	8 (9.9)	0.981
Atrial fibrillation	3 (5.0)	2 (2.5)	0.360
COPD	4 (6.7)	8 (9.9)	0.499
Cerebrovascular Disease	1 (1.7)	0	0.244
Malignancy	3 (5.0)	6 (7.4)	0.416
Chronic infection	1 (1.7)	5 (6.2)	0.190
Autoimmune disease	10 (16.7)	16 (19.8)	0.640
Disease status before COVID-19			
Stable	45 (72.8)	60 (74.1)	0.920
MGFA I	11 (18.3)	15 (14.9)	0.431
MGFA IIA	4 (6.7)	6 (7.4)	0.324
Immunosuppression protocols			
Steroids monotherapy	15 (25)	20 (24.7)	0.967
Steroids + IS	6 (10.0)	3 (3.7)	0.653
IS monotherapy	15 (25)	23 (28.4)	0.123
No therapy	24 (40)	35 (43.2)	0.712
Types of immunosuppressive drugs			
Azathioprine	16 (26.7)	23 (28.4)	0.821
Mycophenolate mofetil	5 (8.3)	3 (3.7)	0.209

*The chi-square (χ^2) test was used for non-continuous variables. Continuous variables were compared between the groups by the Student's t-test. P value of <0.05 was considered as significant and indicated bold in the table.
AchR: Acetylcholine receptor; BMI: Body mass index; CAD: Coronary arter disease; COPD: Chronic obstructive pumoner disease; EOMG: Early onset myastenia gravis; ICU: Intensive care unit; LOMG: Late onset myastenia gravis, MG: Myastenia gravis; MGFA: Myasthenia Gravis Foundation of America; MV: Mechanical ventilation; n: patients; sd: standard deviation.

Table 4. Multivariable regression models evaluating risk factors for severe Covid-19

	Multivariable analysis (n=141)	**p**
	OR (95% CI)	
Age (years)	1.014 (0.961–1.069)	0.610
Sex (Male&Female)	0.326 (0.034–3.124)	0.331
Tobacco (smoke&not smoke)	0.613 (0.116–3.237)	0.565
BMI (kg/m²)	1.012 (0.853–1.201)	0.889
Age at disease onset (EOMG&LOMG)	0.454 (0.86–2.403)	0.353
Anti-AchR antibody (Seropositive& Seronegative)	0.958 (0.248–3.697)	0.950
Thymectomy (Yes&No)	1.413 (0.307–6.50)	0.657
Treatment		
No therapy	Ref	Ref
Steroids	0.612 (0.39–9.729)	0.728
IS monotherapy	0.280 (0.19–4.129)	0.354
Steroids+ IS	0.808 (0.68–9.527)	0.865

*Severe Covid-19:need for ICU or MV.
AchR: Acetylcholine receptor; BMI: Body mass index; EOMG: Early onset myastenia gravis; IS: Immunosuppressive; LOMG: Late onset myastenia gravis.

Table 5. Adverse effects observed after COVID-19 vaccines

	Total	**Inactivated (Sinovac)**	**mRNA (Pfizer/BioNTech)**	**p***
Adverse effects, n (%)	67 (34.7)	19 (17.9)	48 (55.2)	**<0.0001**
Local arm tenderness, n (%)	31 (16.1)	7 (6.6)	24 (27.6)	**<0.0001**
Headeche, n (%)	4 (2.1)	2 (1.9)	2 (2.3)	0.612
Myalgia, n (%)	10 (5.2)	6 (5.7)	4 (4.6)	0.512
Fatigue, n (%)	10 (5.2)	1 (0.9)	9 (10.3)	**0.004**
Weakness, n (%)	5 (2.6)	1 (0.9)	4 (4.6)	0.129
Fever, n (%)	5 (2.6)	1 (0.9)	4 (4.6)	0.129
Vomiting n (%)	1 (0.5)	0	1 (1.1)	0.451
Metallic taste, n (%)	1 (0.5)	1 (0.9)	0	0.549

*The chi-square (χ^2) test was used for non-continuous variables. P value of <0.05 was considered as significant and indicated bold in the table.

Table 6. Characteristics of MG patients with worsening after COVID-19 vaccines

Patients	1	2	3	4	5
Gender	F	M	M	M	F
Age	74	38	72	49	67
Age at disease onset (years)	69	23	65	37	52
Comorbid Disease	COPD, HT, DM	-	HT	DM, HT, CRI	HT
MGFA	Stable	I	Stable	IIA	I
Thymectomy	No	Yes	No	No	Yes
Antibody status	AchR	AchR	AchR	Seronegative	AchR
MG treatment	PYR+PR	PYR+	PYR+PR	PYR+PR	PYR+AZA
Vaccine type	Pfizer/BioNTech	Pfizer/BioNTech	Pfizer/BioNTech	Pfizer/BioNTech	Sinovac
MG symptoms	Ptosis, diplopia	Limb weakness	Ptosis, limb weakness, bulbar weakness,	Ptosis, diplopia	Ptosis, diplopia
MG worsening treatment	PYR dose increase+PR	PYR dose increase +PR	PYR dose increase +PR+ IVIG	PYR dose increase +PR	PYR dose increase+PR

AchR: Acetylcholine receptor; AZA: Azothiopirin; COPD: Chronic Obstructive Pumoner Disease; CRI: Chronic renal insufficiency: DM: Diabetes mellitus; F: Female; HT: Hypertension, IVIG: Intravenous immunglobulin; M: Male; MG: Myastenia gravis; MGFA: Myasthenia Gravis Foundation of America; Musk: Muscle spesific kinase. PR: Prednisone; PYR: Pyridositgmin.

the French database for rare disorders and reported that only 34 (0.96%) patients had COVID-19 (18). At the end of the study period, 29 (85%.3) patients recovered from COVID-19 and five (14.7%) died. In another study including 93 MG patients infected with COVID-19, 34 required hospitalization and none of these patients had myasthenic crisis during or after COVID-19 infection (15). According to the study conducted by Tuncer et al., SARS-CoV-2 infection was detected in 19 (13.5%) out of 140 patients with MG. In this study, they reported that it was impossible to evaluate the myasthenic status in two of the three elderly MG patients who had severe COVID-19 and were followed up in the ICU, while the third patient recovered from COVID-19 with severe MG exacerbation. Moreover, three patients who experienced moderate COVID-19 symptoms were controlled by increasing corticosteroid dose. The remaining 13 patients had mild COVID-19 and their myasthenic status did not change. Therefore, in this study, it was suggested that COVID-19 did not significantly affect in patients with MG (8). Businaro et al. reported that three of 11 MG patients with COVID-19 infection required MV support, and one of these patients in whom corticosteroid dose was up titrated died during follow-up (16). Similarly, in a study using real-world data, Digala et al. confirmed COVID-19 in 24 of 91 MG patients, and only four (4.4%) patients had worsening MG (19). In the present study, 60 (42.5%) of the patients had COVID-19, and hospital admission and ICU admission were needed in 20 (33.3%) and 12 (20%) patients, respectively. Consistent with the literature, six (10%) patients had worsening MG and three (5%) patients had myasthenic crisis. Two (3.3%) of these patients died, while the remaining patients became clinically stable with IVIG and/or corticosteroid treatment. Moreover, the advanced ages of these two patients might have potentially augmented the probability of COVID-19-related mortality.

Previous studies have demonstrated that uncontrolled symptoms, prolonged use of corticosteroids, advanced age, malignancies, and rituximab treatment are independent risk factors for COVID-19-related mortality in MG patients (15). However, worsening MG has been reported in a few numbers of patients, and mortality is mostly related to viral or secondary pneumonia. In their case series, Rodrigues et al. reported a mortality rate of 50% for patients suffering from myasthenic crises following COVID-19 infection (20). On the other hand, in a meta-analysis including 19 studies, Abbas et al. reported a mortality rate of 11.8% in MG patients infected with COVID-19 (21). In our study, the rate of myasthenic crisis and mortality was relatively low. Three (5%) patients who were clinically stable before COVID-19 infection died from myasthenic crisis, while two (3.3%) from secondary pneumonia and septic shock. The low mortality rate in our study can be attributed to the fact that the majority of the patients had low MGFA class and were clinically stable before COVID-19 infection.

Regardless of gender, the prevalence of MG patients over the age of 65 is higher (22). In our study, the mean age of the patients was 60.03±14.96 years and the mean age of onset of MG was 49.2±16.3 years. We did not observe a high incidence in any age range in our MG and COVID-19 patients. In addition, the most common symptoms were fatigue, fever, and cough among MG patients with COVID-19, consistent with the literature (23,24). Comorbidities such as cardiovascular diseases, HT, DM, and respiratory diseases may increase the risk of complications in COVID-19 patients (6,25). In our study, similar to previous findings, the rate of hospitalized patients with COVID-19 was significantly higher in those having HT and cardiovascular diseases. However, the multivariate analysis revealed no significant correlation between the presence of comorbidities and COVID-19-related hospital and/or ICU admission and mortality.

Furthermore, chronic immunosuppressive drugs for the treatment of MG may affect the clinical course of COVID-19. In the literature, one study has demonstrated that high-dose corticosteroids and rituximab might increase mortality, while azathioprine, mycophenolate mofetil, and cyclosporine have no effect on mortality (15). Unfortunately, multivariate analysis was not performed in this study. Therefore, it is not possible to fully distinguish whether the severity of MG prior to infection or the dosage of corticosteroids has a greater impact on the course of COVID-19 in patients with MG. In our study, one of the deceased patients was receiving azathioprine treatment, while the other one did not receive any immunosuppressant drug. This patient was seronegative for COVID-19 and had no myasthenic crisis but had more than one comorbidity. In the multivariate analysis, there was no significant correlation between the use of corticosteroid and immunosuppressive treatment, and worsening MG and/or myasthenic crisis due to COVID-19 infection.

In the literature, there is no clinical study specifically investigating the efficacy and safety of COVID-19 vaccines on MG. However, there are several case reports showing worsening MG after COVID-19 vaccination (2). Nevertheless, no report is available showing an increased rate of vaccine-related side effects and worsening MG (26,27). In a single-center study investigating the safety of inactivated COVID-19 vaccine, Ruan et al. reported no worsening MG in 20 of 22 patients after two doses of vaccine (27). These two patients experienced worsening MG (mild neck muscle weakness) after the first dose of vaccine and symptoms resolved with the increased dose of pyridostigmine. In another multi-center study, Farina et al. found worsening MG in eight (7.7%) of 104 MG patients after mRNA COVID-19 vaccine administration. The symptoms spontaneously resolved in six of these patients (28). In our study, five (4.8%) patients had worsening MG after COVID-19 vaccine, while no mortality was observed. All worsening MG cases were reported after the second dose of vaccine at four to six weeks. Four (80%) of these patients received BNT162b2, and clinical stabilization was achieved with corticosteroid and/or IVIG in all patients.

There are several reports regarding the local and systemic side effects of mRNA or inactivated vaccines (29–31). In our relatively large cohort, vaccine-related side effects were observed in 34.7% of the patients, and all resolved with symptomatic treatment and follow-up. Of note, the rate of side effects was higher in the patients receiving BNT162b2 than those receiving inactivated CoronaVac. The most common side effects in both groups were local pain in the injection site (16.1%) and myalgia (5.2%), consistent with previous studies. None of the patients experienced serious side effects, in line with the literature (27,31).

Nonetheless, there are some limitations to this study. First, the study has a single-center, retrospective design which may have led to bias in reporting COVID-19 symptoms and severity, although we attempted to reduce bias by checking patient data using the hospital database. Second, data were retrieved from hospital records in most of the hospitalized patients; however, there may have been misleading information for non-hospitalized patients. Third, no efficacy data for COVID-19 vaccines were able to be collected and no serological tests were carried out in this study. However, we believe that the large sample size of the study would provide additional contribution to the body of knowledge on this topic in the literature. In addition, the fact that none of the MG patients, even those having a high complication risk, experienced serious side effects after COVID-19 infection supports the efficacy and safety of COVID-19 vaccination with a favorable tolerability profile in this patient population.

In conclusion, our study results showed that COVID-19 infection did not worsen the clinical course of MG or cause poor prognosis. In addition, immunosuppressive treatment did not change the clinical severity or outcomes of COVID-19 in these patients. Based on these findings, we suggest that both mRNA and inactivated COVID-19 vaccines are safe for this patient population and recommend vaccination of MG patients during and after the pandemic. Moreover, multicentre, large-scale,

prospective studies should be carried out for a better understanding of the relationship between clinical symptoms of MG and COVID-19 infection and vaccines.

Acknowledgment: This article was presented as an oral presentation at the 12th Neuroimmunology Symposium held between May 12-15 2022 in Antalya,Turkey.

Ethics Committee Approval: This study was approved by the Izmir University of Health Sciences Tepecik Education and Research Hospital Ethics Committee with the Approval No: 2022/01-23.

Informed Consent: The written informed consents were obtained from all participations.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept- LÖ, TDÖ, UŞ; Design- LÖ, TDÖ, ÖÖ, UŞ; Supervision- LÖ, TDÖ, ÖÖ, AS, UŞ; Resource- LÖ, TDÖ, UŞ; Materials- (-); Data Collection and/or Processing- LÖ, TDÖ, ÖÖ, AS; Analysis and/or Interpretation- LÖ, ÖÖ; Literature Search- LÖ, TDÖ, ÖÖ; Writing- LÖ, TDÖ, ÖÖ; Critical Reviews- LÖ, ÖÖ, AS, UŞ.

Conflict of Interest: The authors declared that there is no conflict of interest.

Financial Disclosure: This study received no specific grant from any funding agency in the public, commercial or not for profit sectors.

REFERENCES

1. Gilhus NE, Romi F, Hong Y, Skeie GO. Myasthenia gravis and infectious disease. J Neurol. 2018;265(6):1251–1258. [Crossref]
2. Singh S, Govindarajan R. COVID-19 and generalized myasthenia gravis exacerbation: a case report. Clin Neurol Neurosurg. 2020;196:106045. [Crossref]
3. Delly F, Syed MJ, Lisak RP, Zutshi D. Myasthenic crisis in COVID-19. J Neurol Sci. 2020;414:116888. [Crossref]
4. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):683–690. [Crossref]
5. Ramaswamy SB, Govindarajan R. COVID-19 in refractory myasthenia gravis -a case report of successful outcome. J Neuromuscul Dis. 2020;7(3):361–364. [Crossref]
6. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91–95. [Crossref]
7. Parrotta E, Kister I, Charvet L, Sammarco C, Saha V, Charlson RE, et al. COVID-19 outcomes in MS. Observational study of early experience from NYU Multiple Sclerosis Comprehensive Care Center. Neurol Neuroimmunol Neuroinflamm. 2020;7(5):835. [Crossref]
8. 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. [Crossref]
9. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–2615. [Crossref]
10. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384(5):403–416. [Crossref]
11. Keech C, Albert G, Cho I, Robertson A, Reed P, Neal S, et al. Phase 1-2 trial of a SARS-CoV-2 recombinant spike protein nanoparticle vaccine. N Engl J Med. 2020;383(24):2320–2332. [Crossref]
12. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, 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;55(1):16–23. [Crossref]
13. Camelo-Filho AE, Silva AMS, Estephan EP, Zambon AA, Mendonça RH, Souza PVS, et al. Myasthenia gravis and COVID-19: clinical characteristics and outcomes. Front Neurol. 2020;11:1053. [Crossref]
14. Anand P, Slama MCC, Kaku M, Ong C, Cervantes-Arslanian AM, Zhou L, et al. COVID-19 in patients with myasthenia gravis. Muscle Nerve. 2020;62(2):254–258. [Crossref]
15. Jakubíková M, Týblová M, Tesař A, Horáková M, Vlažná D, Ryšánková I, et al. Predictive factors for a severe course of COVID-19 infection in myasthenia gravis patients with an overall impact on myasthenic outcome status and survival. Eur J Neurol. 2021;28(10):3418–3425. [Crossref]
16. Businaro P, Vaghi G, Marchioni E, Diamanti L, Arceri S, Bini P, et al. COVID-19 in patients with myasthenia gravis: Epidemiology and disease course. Muscle Nerve. 2021;64(2):206–211. [Crossref]
17. Muppidi S, Guptill JT, Jacob S, Li Y, Farrugia ME, Guidon AC, et al; CARE-MG Study Group. COVID-19-associated risks and effects in myasthenia gravis (CARE-MG). Lancet Neurol. 2020;19(12):970–971. [Crossref]
18. Solé G, Mathis S, Friedman D, Salort-Campana E, Tard C, Bouhour F, et al. Impact of coronavirus disease 2019 in a French Cohort of Myasthenia Gravis. Neurology. 2021;96(16):2109–2120. [Crossref]
19. Digala LP, Prasanna S, Rao P, Qureshi AI, Govindarajan R. Impact of COVID-19 infection among myasthenia gravis patients -a Cerner Real-World DataTM study. BMC Neurol. 2022;22(1):38. [Crossref]
20. Rodrigues CL, de Freitas HC, Lima PRO, de Oliveira Junior PH, Fernandes JMA, D'Almeida JAC, et al. Myasthenia gravis exacerbation and myasthenic crisis associated with COVID-19: case series and literature review. Neurol Sci. 2022;43(4):2271–2276. [Crossref]
21. Abbas AS, Hardy N, Ghozy S, Dibas M, Paranjape G, Evanson KW, et al. Characteristics, treatment, and outcomes of myasthenia gravis in COVID-19 patients: a systematic review. Clin Neurol Neurosurg. 2022;213:107140. [Crossref]
22. Carr AS, Cardwell CR, McCarron PO, McConville J. A systematic review of population based epidemiological studies in myasthenia gravis. BMC Neurol. 2010;10:46. [Crossref]
23. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061–1069. [Crossref]
24. Yue H, Bai X, Wang J, Yu Q, Liu W, Pu J, et al; Gansu Provincial Medical Treatment Expert Group of COVID-19. Clinical characteristics of coronavirus disease 2019 in Gansu province, China. Ann Palliat Med. 2020;9(4):1404–1412. [Crossref]
25. Guan WJ, Liang WH, Zhao Y, Liang HR, Chen ZS, Li YM, et al; China Medical Treatment Expert Group for COVID-19. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. Eur Respir J. 2020;55(5):2000547. [Crossref]
26. Živković SA, Gruener G, Narayanaswami P; AANEM Quality and Patient Safety Committee. Doctor-Should I get the COVID-19 vaccine? Infection and immunization in individuals with neuromuscular disorders. Muscle Nerve. 2021;63(3):294–303. [Crossref]
27. Ruan Z, Tang Y, Li C, Sun C, Zhu Y, Li Z, et al. COVID-19 vaccination in patients with myasthenia gravis: a single-center case series. Vaccines (Basel). 2021;9(10):1112. [Crossref]
28. Farina A, Falso S, Cornacchini S, Spagni G, Monte G, Mariottini A, et al. Safety and tolerability of SARS-Cov-2 vaccination in patients with myasthenia gravis: a multicenter experience. Eur J Neurol. 2022;29(8):2505–2510. [Crossref]
29. Shimabukuro T. COVID-19 vaccine safety update. Advisory Committee on Immunization Practices (ACIP) meeting. Available at: https://stacks.cdc.gov/view/cdc/108329
30. Gargano JW, Wallace M, Hadler SC, Langley G, Su JR, Oster ME, et al. Use of mRNA COVID-19 vaccine after reports of myocarditis among vaccine recipients: update from the advisory committee on immunization practices - United States, June 2021. MMWR Morb Mortal Wkly Rep. 2021;70(27):977–982. [Crossref]
31. Menni C, Klaser K, May A, Polidori L, Capdevila J, Louca P, et al. Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID symptom study app in the UK: a prospective observational study. Lancet Infect Dis. 2021;21(7):939–949. [Crossref]