Prevalence and Risk Factors of Myasthenia Gravis Exacerbation Related to COVID-19 Vaccination at Siriraj Hospital

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ABSTRACT

Objective: To study the prevalence and risk factors of MG exacerbation in relationship to COVID-19 vaccination at Siriraj Hospital.

Introduction: Various risk factors contribute to MG exacerbation, including infections, medications, and vaccination. In Thailand, 2.5 million people were affected by COVID-19 infection by the end of 2022. After COVID-19 vaccine approval, reports emerged of adverse events, particularly neurological complications. Despite Thailand's diverse use of COVID-19 vaccines and regimens, documentation of adverse events in MG patients in Thailand is lacking.

Materials and Methods: Our team conducted an observational retrospective study at Siriraj Hospital, Mahidol University, Thailand, to answer this issue. The data of patients in our MG clinic database from the established clinic until 31 December 2023 was reviewed. All patients who met the inclusion criteria were interviewed in person or via phone for information regarding COVID-19 vaccination and MG symptoms after the vaccination.

Results: Data collected from 209 MG clinic patients who attended the clinic from December 2019 to December 2023 revealed three episodes of MG exacerbation within six weeks after vaccination from a total of 633 vaccine events, comprising 0.47% of all COVID-19 vaccination events. Notably, two episodes of MG exacerbation occurred after the second dose, and one arose after the first. The factors associated with MG exacerbation after COVID vaccination from univariate analysis of patients with thymic carcinoma and patients with higher prednisolone dosage

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Conclusion: From the results of our study, given the low prevalence of MG exacerbation, MG patients should be encouraged to have COVID-19 vaccination with only minor concerns for MG exacerbation.

Keywords: COVID-19 vaccination, Myasthenia Gravis exacerbation, COVID-19 vaccination and Myasthenia Gravis exacerbation, Risk factors of Myasthenia Gravis exacerbation

Introduction

Myasthenia Gravis (MG) is a neuromuscular junction disorder caused by an autoimmune response against the post-synaptic neuromuscular junction, which later disrupts neural transmission to muscles, leading to muscle weakness. The incidence of MG in Thailand is approximately 2.17 per 100,000 population. Signs and symptoms of MG vary from extraocular muscle weakness, limb weakness, and facial muscle weakness to respiratory and pharyngeal muscle weakness, which can lead to respiratory failure, resulting in myasthenic crisis with a high mortality rate. The symptoms and severity of MG are individualized for each patient, depending on the structure of the neuromuscular junction (NMJ) damaged by immune cells and the disease stage.

Various risk factors contribute to MG exacerbation and MG crisis, including infections, medications, poor compliance, and vaccination. COVID-19 infection or vaccination can also result in worsening MG and MG crisis.

In Thailand, more than 2.5 million people were affected by COVID-19 infection by the end of 2022, ranking 30th globally[1]. COVID-19 primarily affects the respiratory tract, and the severity differs between each patient depending on patient co-morbidities, immunosuppressive drugs that lead to severe disease, COVID-19 vaccination, and the strain of COVID-19. The vaccine's efficacy against COVID-19 infection was 82.51% after one month of the first dose and up to 93.74% after one month of the complete second dose[2].

After COVID-19 vaccine approval, reports emerged of adverse events, particularly neurological complications such as Guillain-Barre syndrome, acute disseminated encephalomyelitis, MG exacerbation, and acute stroke. There were a few studies about the prevalence of MG exacerbation after COVID-19 vaccination, and most of them showed low event rates. About 5% of patients from a large cohort experienced worsening MG after COVID-19 vaccination[3]. Despite Thailand's diverse use of COVID-19 vaccines and regimens, documentation of adverse events, especially in MG patients, is lacking, leading our team to this study.

Method

Study design and population

This was a single-center observational retrospective study in MG Clinic, Siriraj Hospital, Mahidol University. The data of patients in our MG clinic database from the established clinic until 31 December 2023 was reviewed. The inclusion criteria of our population were 1.) Patients diagnosed with MG for at least three months; 2.) Age 18 years old or above; 3.) Patients who follow up in the MG clinic without documented loss to follow up; 4.) Good drug adherence and well-controlled disease; 5.) Documented any COVID-19 vaccination. The exclusion criteria were patients who were lost to follow-up or had incomplete medical records.

The primary outcome is the prevalence of MG exacerbation within six weeks of the COVID-19

vaccination, which is defined as the patient's subjectively reported worsening of symptoms by increasing MGFA grading and objective evident by physician examination that needs to be increased immunosuppressive dosage to control the symptom compared with before vaccination. The secondary outcome is a risk factor associated with MG exacerbation after COVID-19 vaccination.

Data collection and statistical analysis

We collected demographics data, MG clinical characteristics, COVID-19 vaccination information: gender, age, BMI, co-morbidities, age onset, age at diagnosis, the severity of symptoms at diagnosis and worst symptom by using MGFA, duration of follow-up, duration of follow-up to worst MGFA, MGFA at the beginning of 2020 through 2023, serological status, thymic pathology in patients undergoing thymectomy, adjuvant radiotherapy in patient experienced thymectomy, immunosup pressive and pyridostigmine usage, type of COVID-19 vaccines (inactivated virus, virus vector, mRNA), vaccine status (amount of vaccine that patient take, date of administration if possible, which vaccine that patients experience progression of MG symptom, duration from administration of vaccine to worsening MG symptom and severity of symptom, other precipitating factors that comprise to worsening of MG). The MGFA (Myasthenia Gravis Foundation of America) classification was used to classify the severity of the disease into five grades (I-V). All patients included in our study were interviewed in person or via phone for information regarding COVID-19 vaccination and MG symptoms after the vaccination.

Descriptive statistical analyses were performed to reveal qualitative data using percentages, frequencies and mean and standard deviations for quantitative data in a normal distribution. Median and IQR were utilized for quantitative data that were not in a normal distribution. Inferential analyses were applied to evaluate the prevalence of MG exacer bation after COVID-19 vaccinations. For the secondary outcome, Chi-square or Fisher's exact test was used for nominal scales such as gender. An independent t-test or Mann-Whitney-U test was applied for continuous data. P-value <0.05 was considered statistically significant.

Patient Consent and Protocol Approvals

All patients included in our study were informed consent via mobile phone or face-to-face before the interview session for information about COVID-19 vaccination and MG symptoms after getting the vaccination. The study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (Si402/2023).

Results

A total of 209 patients met the inclusion criteria, and the total number of events of COVID-19 vaccination received by 209 MG patients were 633 events. Fifty-four patients were male (25.8%), the mean BMI (SD) was 24.1(4.6), the mean age (SD) was 55.4(14.9) years, the mean age onset was 42.65(15.9) years, the median time (IQR) of follow up was 11(5,17.5) years, the median time (IQR) of follow up to worst MGFA was 18 (7.75,60) months. Medical comorbidities are shown in Table 1. MGFA at onset, worst MGFA, and MGFA baseline each year are shown in Table 1.

Ninety-one patients (43.5%) were Acetylcholine receptor antibody positive, seven patients (3.3%)

were anti muscle-specific tyrosine kinase antibody positive, twenty-three patients (11%) were serological negative, and the rest of the patients did not have the serological testing. One hundred and twenty-eight patients (61.2%) underwent thymectomy; thirty-three of them had thymic hyperplasia, thirty-nine patients had thymic involution, thirty-nine patients had thymoma, six patients had thymic carcinoma, and eleven patients the thymic pathology was not noted. The mean prednisolone dosage for 2020 to 2023 is shown in Table 1. One hundred and sixteen patients were taking oral immunosuppressive drugs, including 99 patients on azathioprine, seven on mycophenolate mofetil, and ten on other immunomo dulating agents such as rituximab. The baseline demographic and clinical characteristics of included patients are summarized in Table 1.

Table 1: Baseline characteristics of patients in this study.

Characteristics	Total (N=209)
Gender, n (%)	
Male	54 (25.8)
Female	155 (74.2)
Age, year, mean (SD)	55.4 (14.9)
BMI, kg/m2, mean (SD)	24.1 (4.6)
Onset age, year, mean (SD)	42.7 (15.9)
Comorbidity, n (%)	
Type 2 diabetes mellitus	51 (24.4)
Essential hypertension	83 (39.7)
Dyslipidemia	93 (44.5)
Cerebrovascular disease	19 (9.1)
Cardiovascular disease	13 (6.2)
Chronic kidney disease	8 (3.8)
Obesity	111 (53.1)
Malignancy at any organ	18 (8.6)
Other	102 (48.8)
MGFA at onset, n (%)	
MGFA1	74 (35.4)
MGFA2	99 (47.3)
MGFA3	20 (9.6)
MGFA4	4 (2)
MGFA5	12 (5.7)
Duration of follow up, year, median (IQR)	11 (5,17.5)
Duration of follow up to worst MGFA, months, median (IQR)	18 (7.75,60)
Serological status, n (%)	
Anti-Ach receptor	91 (43.5)
Anti-MusK	7 (3.3)
Seronegative	23 (11)
Not test	88 (42.1)
Thymectomy, n (%)	
Yes	128 (61.2)
No	81 (38.8)

Table 1: Baseline characteristics of patients in this study.

Characteristics	Total (N=209)
Thymus histopathology, n (%)	33 (15.8)
Hyperplasia	39 (18.7)
Involution	39 (18.7)
Thymoma	6 (2.9)
Carcinoma	11 (5.3)
No data	
Radiation, n (%)	23 (11)
Yes	186 (89)
No	
Prednisolone dosage, mg/d, mean (SD)	4.6 (5.4)
Prednisolone dosage in 2020	4.7 (5.3)
Prednisolone dosage in 2021	4.8 (4.8)
Prednisolone dosage in 2022	5 (5.2)
Prednisolone dosage in 2023	
Immunosuppressive drug, n (%)	99 (47.4)
Azathioprine	7 (3.3)
Mycophenolate mofetil	10 (4.8)
Others	93 (44.5)
None	
MG exacerbation, n (%)	3 (1.4)
Yes	0 (98.6)
No	
MGFA at exacerbation, n (%)	1 (33.3)
MGFA1	0
MGFA2	0
MGFA3	0
MGFA4	2 (66.7)
MGFA5	6.7 (7.6)
Prednisolone dosage at exacerbation, mg/d, mean(SD)	
Severity of exacerbation, n (%)	1 (0.5)
Worsening MG	1 (0.5)
Impending MG crisis	1 (0.5)
MG crisis	
Other precipitating factor, n (%)	2 (1)
Infection	0
Drugs	0
Surgery	0
Trauma	0
Others	1 (0.5)
None	

All patients included in our study received various vaccine regimens, varying from one to six doses

of vaccines and from one to multiple types of vaccines (Figure1). The vaccination information was gathered from a vaccine passport of each patient who received vaccine at the government healthcare service outside Siriraj hospital, and from the medical record of Siriraj in patients who received vaccine at Siriraj hospital. The prevalence of MG exacerbation after vaccination was found in 3 of 633 vaccine events (0.47%) from three different patients. MG exacerbation was documented by history and physical examination by neurologists in the MG clinic. The exacerbation was within the postulated risk period of 6 weeks from each vaccine administration (patients No.1-3 in Table 2). Two of three got exacerbation after the second dose of vaccine (patients no.1 and no.2) and one had exacerbation after the first dose of vaccine (patient no.3). All events occurred within 14 days after vaccination. Three events of MG exacerbation happened after mRNA, inactivated virus, and virus vector vaccination in Patients No.1,2,3, respectively. Patients no.1 and no.2 required hospitalization after an exacerbation, and patient no.3 needed to adjust the immunosuppressive drug to relieve symptoms without hospitalization.

For the secondary outcome of the study, the factors associated with MG exacerbation after COVID vaccination from univariate analysis of patients with thymic carcinoma and patients with higher prednisolone dosage as shown in Table 3.

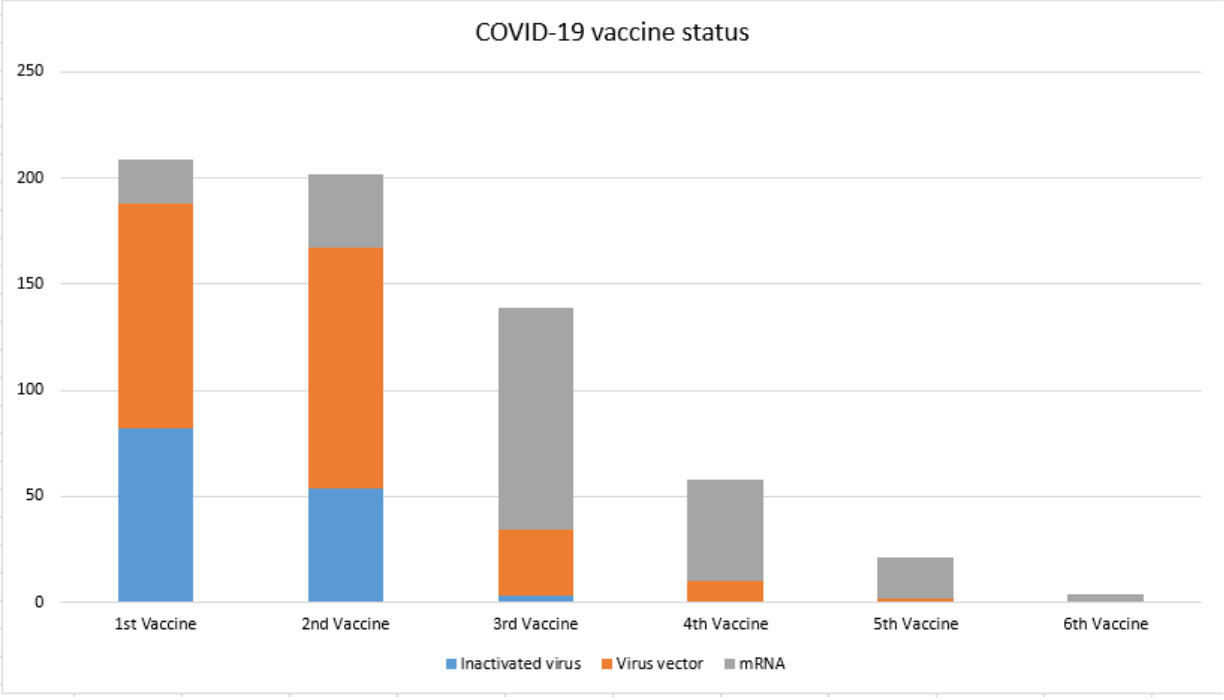

Figure 1 : COVID-19 vaccine status.

Table 2: Characteristics of the cases with MG exacerbation.

Pt	Sex	Age	BMI	Comorbidity	Age onset (Years)	MGFA at onset	Worst MGFA	Duration of follow up (months)	Duration from follow up to worst MGFA (years)	Serology	Thymectomy
1	M	44	18.9	Others	21	1	5	23	48	Anti-Ach	Yes
2	M	41	18.7	Others	33	1	5	8	60	Anti-MusK	No
3	F	59	24.7	Essential hypertension, Dyslipidemia	45	5	5	14	At onset	Seronegative	Yes

PtP	Thymic pathology	Radiation	MGFA during follow up	Mean prednisolone dosage (mg/d)	IS	Vaccine dose before exacerbation	MGFA at exacerbation	Vaccine type	Days from vaccine (ds)	Prednisolone dosage at exacerbation , mg/d	Symptom severity	Other precipitating factor
1	Thymic carcinoma	No	2020 : 1 2021 : 5 2022 : 1 2023 : 1	2020 : 5.5 2021 : 17 2022 : 16.4 2023 : 8.8	AZA	2nd dose	5	mRNA	3	15	MG crisis	Infection
2	-	No	2020 : 1 2021 : 2 2022 : 1 2023 : 1	2020 : 4.9 2021 : 13.5 2022 : 13.8 2023 : 8.6	AZA	2nd dose	5	Inactivated virus	10	5	MG crisis	Infection
3	Thymic carcinoma	Yes	2020 : 1 2021 : 1 2022 : 1 2023 : 1	2020 : 0 2021 : 0 2022 : 6.9 2023 : 4.4	None	1st dose	3	Virus vector	13	0	Worsening MG	None

Table 3: Comparison of multiple factors between exacerbation and non-exacerbation groups.

Characteristics	No exacerbation (N=206)	Exacerbation (N=3)	P-value (95% CI)
Gender, n (%)	52/54 (96.3)	2/54 (3.7)	
Male	154/155 (99.4)	1/155 (0.6)	0.164
Female	55.5 (14.9)	48 (9.6)	0.388
Age, year, mean (SD)	24.1 (4.6)	21.8 (3.7)	0.393
BMI, kg/m2, mean (SD)	42.8 (16)	33 (12)	0.292
Onset age, year, mean (SD)			
Comorbidity, n (%)	51 (100)	0	1
Type 2 diabetes mellitus	82/83 (98.8)	1 (1.2)	1
Essential hypertension	92/93 (98.9)	1 (1.1)	1
Dyslipidemia	19 (100)	0	1
Cerebrovascular disease	13 (100)	0	1
Cardiovascular disease	8 (100)	0	1
Chronic kidney disease	110/111 (99.1)	1/111 (0.9)	0.601
Obesity	18 (100)	0	1
Malignancy at any organ	100/102 (98)	2/102 (2)	0.614
Other			
MGFA at onset, n (%)	72/74 (97.3)	2/74 (2.7)	0.286
MGFA1	99 (100)	0	1
MGFA2	20 (100)	0	1
MGFA3	4 (100)	0	1
MGFA4	11/12 (91.7)	1/12 (8.3)	0.163
MGFA5			
Worst MGFA during follow up, n (%)	43 (100)	0	1
MGFA1	101 (100)	0	1
MGFA2	21 (100)	0	1
MGFA3	5 (100)	0	1
MGFA4	36/39 (92.3)	3/39 (7.7)	0.006(0.989-1.186)
MGFA5	11 (5,17)	14 (8,23)	0.447
Duration of follow up, year, median (IQR)			
Duration of follow up to worst MGFA, year, median (IQR)	12 (7.5,60)	60 (48,72)	0.197
Serological status, n (%)			
Anti-Ach receptor			
Anti-MusK	90/91 (98.9)	1/91 (1.1)	1
Seronegative	6/7 (85.7)	1/7 (14.3)	0.098
Not test	22/23 (95.7)	1/23 (4.3)	0.296
	88 (100)	0	0.265
Thymectomy, n (%)			
Yes			
No	126/128 (98.4)	2/128 (1.6)	1
	80/81 (98.8)	1/81 (1.2)	1

Table 3: Comparison of multiple factors between exacerbation and non-exacerbation groups.

Characteristics	No exacerbation (N=206)	Exacerbation (N=3)	P-value (95% CI)
Thymus histopathology, n (%)			
Hyperplasia	33 (100)	0	1
Involution	39 (100)	0	1
Thymoma	39 (100)	0	1
Carcinoma	4/6 (68.7)	2/6 (33.3)	**0.002(0.02-0.14)**
No data	11 (100)	0	1
Radiation, n (%)			
Yes	22/23 (95.7)	1/23 (4.3)	
No	184/186 (98.9)	2/186 (1.1)	0.296
Prednisolone dosage, mg/d, mean(SD)			
Prednisolone dosage in 2020	4.6 (5.5)	3.5 (3)	0.728
Prednisolone dosage in 2021	4.6 (5.3)	10.2 (9)	0.072
Prednisolone dosage in 2022	4.7 (4.7)	12.4 (4.9)	**0.006(-13.08,-2.28)**
Prednisolone dosage in 2023	4.9 (5.2)	7.3 (2.5)	0.438
Immunosuppressive drug, n (%)			
Azathioprine	97/99 (98)	2/99 (2)	0.604
Mycophenolate mofetil	7 (100)	0	1
Others	10 (100)	0	1
Other precipitating factor, n (%)			
Infection	0	2 (100)	**<0.001(0.001-0.34)**
Drug	0	0	-
Surgery	0	0	-
Trauma	0	0	-
Others	0	0	-
None	0	1 (100)	0.014(0.002-0.038)

Discussion

After the COVID-19 vaccine was introduced, reports about adverse events, especially neurological symptoms, raised concern in neurological patients. Individuals with pre-existing health conditions such as MG who were on immunosuppressive agents were potentially at higher risk for developing severe forms of infection requiring hospitalization and may lead to unfavorable outcomes[4-10].

There were only a few studies regarding the prevalence of neurological adverse events after COVID-19 vaccination in MG patients. One prior study found that as high as approximately 5% of all MG patients experienced worsening MG after COVID-19 vaccination[3]. In this study, we aimed to look for the prevalence of MG exacerbation after COVID-19 vaccination and risk factors associated with COVID-19 vaccination in a single medical center. From our study, there were only 3 MG exacerbation events out of 633 vaccination events that comprised only 0.47%, which was not a high prevalence. Two of three cases had MG exacerbation after the second dose of the vaccine, similar to the large cohort study of Sansone et al[2] and Patone et al.[8], in which most of the events

occurred after the second dose of the vaccine. When looking into the clinical characteristics between non-exacerbated and exacerbated groups, this study found that patients using higher doses of prednisolone and patients with confirmed thymic carcinoma had higher tendencies to get MG exacerbation after COVID-19 vaccination. This may be explained by poor disease control and higher severity of disease in patients with thymic carcinoma; these findings correlate with a study by Kato et al.[11] that found a high-grade thymoma was an independent risk factor of MG exacerbation after surgery. The strength of our study was the opportunity to study the prevalence of MG exacerbation after the various types of COVID-19 vaccination, given the fact that in Thailand, there were many types of COVID-19 vaccine. The other strength was that in our study, we personally interviewed each patient for the type of COVID-19 vaccination and symptoms of MG after the COVID-19 exacerbation. However, the main limitation of our study was the small number of patients, which limited the analysis of clinical risk factors for MG exacerbation after the COVID-19 vaccination.

Conclusion

Our study's results were correlated with previous studies that the prevalence of MG exacerbation after COVID-19 vaccination was low, although the drawback of our study was the small population, which has limitations on the analysis for clinical risk factors for MG exacerbation after COVID-19 vaccination. From the results of our study, given the low prevalence of MG exacerbation, the benefits of COVID-19 vaccination appeared to outweigh the risks, and MG patients should be encouraged to have COVID-19 vaccination with only minor concerns for exacerbation.

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