Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of the Neurological Sciences 436 (2022) 120225

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Flare of myasthenia gravis induced by COVID-19 vaccines

ARTICLE INFO

Keywords
Myasthenia gravis
Severe acute respiratory syndrome coronavirus 2
Coronavirus disease 2019
BNT162b2
mRNA-1273
ChAdOx1-S

Dear Editor,

To combat severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, coronavirus disease 2019 (COVID-19) vaccines are generally recommended for both patients with autoimmune diseases and healthy individuals [1]. Among the COVID-19 vaccines, the mRNA vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), and the viral vector vaccine, ChAdOx1-S (AstraZeneca), are available in Japan. However, it remains unclear whether these vaccines cause flare of existing myasthenia gravis (MG) [2–4].

Methods

We followed 343 MG patients at Keio University MG clinic between April 1 and September 30, 2021. The diagnosis of MG was based on clinical findings (fluctuating symptoms with easy fatigability and recovery after rest) along with the amelioration of symptoms after an intravenous administration of acetylcholinesterase inhibitors, decremental muscle response to a train of low-frequency repetitive nerve stimuli, or the presence of autoantibodies. We tracked their COVID-19 vaccine coverage through December 3, 2021 and evaluated the clinical features of MG and the patients' quality of life before and after vaccination. Clinical features were determined by the recommendations of the MG Foundation of America, MG composite, MG activities of daily living, and revised 15-item MG quality of life scales.

Vaccine-induced MG flare was defined as met all 3 criteria: (i) MG deterioration starting from the day of the first dose to 28 days after the second dose [5]; (ii) $\geq$ 7 days of disease relapse of $\geq$3 points on the MG composite scale compared to baseline and (iii) treatment escalation. This study was approved by the institutional review board of the ethics committee (no. 20211071) and followed the strengthening the reporting of observational studies in epidemiology guidelines.

Results

We enrolled 343 MG patients (M:F = 119:224; range 20-91 years; mean: 57 years), including 174 early-onset, 109 late-onset, and 60 thymoma-associated MG patients. Baseline clinical features are summarized in **Supplementary Table 1**. Among them, 294 patients (85.7%) received COVID-19 vaccines. Two patients were ineligible for vaccination due to a history of allergic reaction, and 47 patients refused vaccinations for personal reasons. Vaccines were BNT162b2 in 254 (86.4%), mRNA-1273 in 40 (13.6%) and ChAdOx1-S in no patients. Stratification of COVID-19 vaccine coverage by age revealed that younger MG patients tended to avoid vaccination (**Supplementary Fig. 1**). In fact, a one-third of MG patients younger than 40 years did not receive vaccination.

There were no patients reported fatal adverse events, including myocarditis, idiopathic thrombocytopenic purpura, anaphylactic shock or death. Of 294 MG patients receiving vaccination, 3 (1.0%) experienced flare of existing MG (Table 1). All 3 were female patients with early-onset MG: 2 with the generalized form and 1 with the ocular form. Although patient 1 and 2 had the episodes of moderate to severe generalized MG symptoms, their diseases were generally stable on vaccination. There was no contract of COVID-19 infection nor an alternative explanation for their relapse of these 3 patients. BNT162b2 and mRNA-1273 were used in 2 and 1 patients, respectively. Timing of onset varied from 2 days after the first dose to 14 days after the second dose. MG symptoms including bulbar and ocular muscles deteriorated over the several days post-vaccination. Mean scores of MG composite and MG activities of daily living were increased from 3 to 12 and from 2 to 9, respectively. MG worsening induced by vaccination severely impaired quality of life: the revised 15-item MG quality of life scale was increased from 4 to 15 in average. Patient 3 did not experience generalization during flare of ocular symptoms. Autoantibody titers including 2 anti-acetylcholine receptor and 1 anti-muscle-specific tyrosine kinase antibodies were unchanged. All 3 patients were admitted to our hospital and received intravenous immunoglobulin and/or methylprednisolone pulse therapy. They responded well and were discharged without further sequelae.

Discussion

As of December 3, 2021, 78.9% of the Japanese general population had received at least one COVID-19 vaccine. The vaccines delivered were BNT162b2, mRNA-1273, and ChAdOx1-S in 83.7%, 16.2%, and

https://doi.org/10.1016/j.jns.2022.120225
Received 10 January 2022; Received in revised form 11 February 2022; Accepted 7 March 2022
Available online 9 March 2022

Table 1
Clinal features of 3 patients presenting with flare of existing MG.

	Patient 1	Patient 2	Patient 3
Age/sex	21 years/female	45 years/female	48 years/female
Disease duration	3.8 years	18.1 years	9.6 years
Disease subtype[a]	Early-onset MG	Early-onset MG	Early-onset MG
MG Foundation of America classification[b] (worst condition during entire course)	Generalized (Class IIIb)	Generalized (Class IVb)	Ocular (Class I)
Baseline regimen (daily)	PSL 10 mg, tacrolimus 3 mg	PSL 10 mg, tacrolimus 3 mg, pyridostigmine 180 mg	Pyridostigmine 180 mg
Thymectomy	No	Yes	No
Vaccines	mRNA-1273	BNT162b2	BNT162b2
Onset of flare	3 days after the first dose	2 days after the first dose	14 days after the second dose
MG symptoms	Dysarthria, dysphagia, diplopia	Dysphagia, nasal voice, limb weakness	Ptosis, diplopia
Disease scales (pre- and post-vaccination)			
MG composite[c]	3, 17	5, 13	1, 6
MG activities of daily living[d]	2, 13	3, 8	1, 7
Revised scale of 15-item MG quality of life[e]	5, 19	6, 16	2, 10
Autoantibodies	Anti-muscle-specific tyrosine kinase	Anti-acetylcholine receptor	Anti-acetylcholine receptor
Titers, nM (pre and post vaccination)	36.6, 33.0	1.7, 2.7	0.2, 0.3
Additional treatment	IVIg, IVMP	IVIg	PSL 20 mg/day, IVMP
Outcome	Improved	Improved	Improved

Abbreviations: MG, myasthenia gravis; PSL, prednisolone; IVMP, methylprednisolone pulse therapy; IVIg, intravenous immunoglobulin.

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[e] Muscle Nerve. 2016;54(6):1015–1022. doi: https://doi.org/10.1002/mus.25198.

0.1% of cases, respectively [6]. Our MG cohort resembled the general population in this regard. It is likely that younger people tend to keep COVID-19 vaccines away due to inappropriate information through the social media. Adverse events, such as pain, redness at the injection site, and headache were common between healthy individuals and MG patients. Although fatigue is one of common adverse events, it is difficult to discriminate whether fatigue was attributed to vaccination or MG.

Disease flare with treatment escalation induced by COVID-19 vaccines was observed in 1.0% of our patients with MG, compared to 3.5% of patients with autoimmune inflammatory rheumatic diseases [7]. This discrepancy may be due to pharmacological therapies such as molecular targeting drugs that are frequently used in patients with rheumatic disorders. In our cohort, 8 MG patients had an episode of SARS-CoV-2 infection, including 6 before vaccination and 2 after vaccination (breakthrough infection). However, there were no cases of flare of existing MG during SARS-CoV-2 infection.

Among 343 MG patients, 31 (9%) were admitted to our hospital and received intravenous immunoglobulin and/or methylprednisolone pulse therapy before worsening of MG over a 6 month-period. It potentially suggests the background rate of MG exacerbation unrelated to vaccination. Thus, the relative risk of COVID-19 vaccines is exceedingly low as well as other vaccination for herpes zoster, hepatitis B and human papillomavirus. Nonetheless, we observed that flare of existing MG was preferentially observed in younger patients with a variety of disease classifications, autoantibody statuses and onset timing. If MG patients suffer from severe involvement such as severe bulbar symptoms and myasthenic crisis, COVID-19 vaccination may be safe to postpone. Therefore, before initiating additional treatment, MG symptoms and signs of transient worsening or disease fluctuation should be carefully monitored especially for 7 days post-vaccination.

Author contributions

Dr. Suzuki had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Takizawa and Suzuki.

Acquisition, analysis, or interpretation of data: Ishizuchi, Sekiguchi, Motegi, Oyama.

Drafting of the manuscript: Ishizuchi, Suzuki.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Ishizuchi, Suzuki.

Administrative, technical, or material support: Nakahara, Suzuki.

Supervision: Nakahara, Suzuki.

Funding/support

This work was supported by JSPS KAKENHI Grant Number JP20H03592.

Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2022.120225.

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