



COVID-19 vaccination in myasthenia gravis: safe, but predictors of disease exacerbation yet to be determined

Sohyeon Kim¹ · Mi-Yeon Eun² · Hung Youl Seok¹

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Dear Editor,

We have read with interest a paper by Trinchillo et al. on the safety of the coronavirus disease 2019 (COVID-19) vaccine in patients with myasthenia gravis (MG) and predictors of MG exacerbation after COVID-19 vaccination [1]. The authors found that only 8 of 113 patients with MG (7.1%) who received the third dose of the BNT162b2 mRNA vaccine experienced MG exacerbation. Their results suggest that the risk of MG exacerbation after COVID-19 vaccination is low, which further suggests that COVID-19 vaccines are safe for patients with MG. They also reported young age at onset, anti-muscle-specific receptor tyrosine kinase (MuSK) antibody positivity, thymic pathology, and treatment with corticosteroids as possible predictors of MG exacerbation after COVID-19 vaccination, although the results were not statistically significant. We agree that COVID-19 vaccines are a safe treatment option for patients with MG. However, several issues require further discussion regarding the predictors of MG exacerbation after COVID-19 vaccination.

The first issue concerns the causality between the COVID-19 vaccine and MG exacerbation, which is a prerequisite for studying the predictors of MG exacerbation after COVID-19 vaccination. A recent study investigated the risk of MG exacerbation after COVID-19 vaccination by comparing the number of patients with MG exacerbation during the risk period after COVID-19 vaccination with that during the parallel period in the year before vaccination [2].

This study showed no difference in MG exacerbation rates between the two periods, indicating that COVID-19 vaccination did not increase the risk for MG exacerbation. Another study of 200 patients with MG who completed the second dose of the COVID-19 vaccine also found that COVID-19 vaccination did not cause exacerbation of MG [3]. As such, studies on predictors of MG exacerbation after COVID-19 vaccination cannot be established from the beginning if MG exacerbation is not directly caused by COVID-19 vaccination but simply by a small number of random events among a large number of vaccinated patients. The authors' study lacked other objective evidence to prove a causal relationship between COVID-19 vaccination and MG exacerbation other than temporal proximity. Moreover, they did not define the risk interval for MG exacerbation after COVID-19 vaccination in their study.

Second, the number of patients with MG who experienced worsening symptoms was too small ($n=8$) to analyze the predictors of MG exacerbation after COVID-19 vaccination. This small number of subjects, 8, is not suitable for analysis with adequate statistical power and may lead to experimenter or expectation bias. A glimpse into the possibility of this bias is that the authors proposed some possible predictors of MG exacerbation after COVID-19 vaccination based on common risk factors of MG exacerbation already known in the previous literature despite no statistical significance.

Finally, previous studies on the predictors of MG exacerbation after COVID-19 vaccination have shown conflicting results [4–6]. Eleven (10.3%) experienced MG exacerbation in a previous study of 107 patients with MG who had received at least one COVID-19 vaccine [4]. The only factor associated with MG exacerbation in logistic regression in this study was the interval since the last aggravation ≤ 6 months. Age at onset, thymoma, and MuSK antibody status were not associated with MG exacerbation. A recent study reported that 8 of 104 patients with MG (7.7%) who received the COVID-19 vaccine had MG exacerbation

Sohyeon Kim and Mi-Yeon Eun contributed equally to this work as the first authors.

✉ Hung Youl Seok
shy2354@gmail.com

¹ Department of Neurology, Dongsan Hospital, Keimyung University School of Medicine, 1035 Dalgubeol-daero, Dalseo-gu, Daegu 42601, Republic of Korea

² Department of Neurology, School of Medicine, Kyungpook National University, Kyungpook National University Chilgok Hospital, Daegu, Republic of Korea

[5]. They also reported that MuSK antibody-positive patients with MG were more susceptible to exacerbation of MG symptoms after vaccination. Another study showed MG exacerbation in 5 of 86 (5.8%) patients with MG who received the COVID-19 vaccine [6]. Factors statistically significantly associated with MG exacerbation after vaccination were the use of non-steroidal immunosuppressants and experimental study drugs. The total number of patients with MG was approximately 100, and approximately 10% showed MG deterioration after COVID-19 vaccination in all these previous studies. Particularly, the number of patients who experienced MG exacerbation was approximately 10, which is too small for proper analysis as in this study. This may be the reason for the conflicting previous results on the predictors of MG exacerbation after COVID-19 vaccination. The predictors of MG exacerbation after COVID-19 vaccination require further study in a larger number of patients.

This study showed important results regarding the safety of COVID-19 vaccines in patients with MG. However, their results on the predictors of MG exacerbation after COVID-19 vaccination may still be inconclusive. Therefore, a cautious approach is needed until more consistent results are obtained in a larger number of patients in the future.

Data Availability Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Ethical approval None.

Conflict of interest The authors declare no competing interests.

Informed consent Not applicable.

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