Lack of Relationship Between Myasthenia Gravis and COVID-19 Severity

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Introduction

Myasthenia gravis (MG) is the most common autoimmune neuromuscular junction disorder.[1,2,3] The course of MG is punctuated by exacerbations or frank crises leading to respiratory failure. MG patients are often immunosuppressed by immune modifying pharmacotherapy. As a result, it is conjectured that MG patients may be highly vulnerable to COVID-19 infection and its complications,[4] including respiratory involvement. Although MG is a rare disease with a prevalence of 36,000 to 60,000 cases in the United States,[5] the wide-spread nature and infectivity of SARS-CoV-2 mandate a greater understanding of the relationship between COVID-19 and MG. It is important to correlate the severity of MG with COVID-19 infection and to look at the impact of immunosuppression on MG severity.

As COVID-19 spread worldwide at a very high rate and capacity for mutations, there has been scant research on the relationship between viral infection and MG. A large study of 3,558 registered MG patients in France suggested a limited effect of COVID-19 on MG patients, although it did not use a MG severity measurement but instead relied on Myasthenia Gravis Foundation of America (MGFA) classification.[3] In contrast, Jakubíková, et al.[7] found that 38% of infected patients developed severe pneumonia and 11% died in a cohort of 93 MG patients in Czech Republic. Another study of CARE-MG registry identified a death rate of 24% of 91 MG patients due to COVID-19 without severity assessment of MG prior to COVID-19.[8] A study done by Ozlem, et al.[16] concluded that having well-controlled MG before infection and absence of comorbidities likely affected the course of the infection favorably and that immunosuppression did not influence the progression. Furthermore, a Brazilian study with 15 hospitalized MG patients showed that 73% needed mechanical ventilator support during MG, limiting the study to hospitalized patients and potentially obscuring general population representation.[9]

Our main objective is to study whether the baseline MG severity predicts complicated COVID-19 disease course and assess if immunosuppressive medications and MG severity are contributing factors.

Methods

Data Collection and Participants

This study is an IRB approved observational multicenter study done at seven neuromuscular centers within the United States of America (Table 1). MG patients with positive SARS-CoV-2 PCR virus testing were included. MG diagnosis was confirmed by immunological or neurophysiological testing. Immunological testing was considered positive if the patient had a positive acetylcholine receptor or MUSK serum antibody. Neurophysiological diagnosis of MG was based on >10% decrement on repetitive nerve stimulation study. Each subject was assigned a numerical identifier before being surveyed. The personal data of subjects was confidential and only accessible by the principal investigator and the study coordinator. All data was saved in the research center terminals with security firewall and password protection. Review of the deceased medical record was also confidential and accessible to only authorized personnel from the available electronic medical records. All subjects had signed a privacy practices acknowledgement and requested restrictions form. Before research conduction, all involved research personnel underwent a training session on handling private medical and personal information. A verbal informed consent was obtained from subjects by the surveyors. A detailed explanation of the purpose, design, and use of information was discussed with the subjects, as well as their ability to withdraw their responses from the research at any time. Patients were asked to respond to a questionnaire by phone calls or asked by surveyors to fill online forms of the questionnaire. The questionnaire is included in the appendix section and was performed after developing COVID-19 infection. The time duration between positive SARS-CoV-2 PCR testing and questionnaire administration was not limited or specified as the interviews were conducted in early 2022, but the time ranged from one month to two years. The aim of the questionnaire was to assess the severity of COVID-19 infection and MG status four weeks before testing positive for COVID-19. It included introduction, demographic data, vaccination status, COVID-19 symptoms, MG weakness type, immunosuppressive treatments received, and the MG-QOL15r questionnaire. MG severity was assessed based on the well validated MG-QOL15r questionnaire, which requires little time to administer and is easy to interpret. This questionnaire comprises 15 questions on

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how disease symptoms affect the patient's mood, ADLs, work, and social activities.[15] MG-QOL15r score of 0-9 is considered mild MG, 10-19 moderate MG, and 20-30 severe MG.

Questionnaire

Patient data was collected including patient's gender, age, date of myasthenia gravis diagnosis, SARS-CoV-2 virus PCR positive testing and SARS-CoV-2 vaccination status. Symptoms of COVID-19 infection were categorized as:

- No symptoms or mild category (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, and loss of taste and/or smell);
- Moderate category includes patients with pneumonia discovered during clinical assessment or chest imaging; or
- Severe category if patients were admitted to ICU, had SpO_2 <94% on room air at sea level, or were put on a ventilator (NIV included).

During the four weeks before COVID-19 infection, the severity of MG was assessed as:

- Mild severity defined as weakness affecting the eye muscles (e.g., double vision or droopy eyelids);
- Moderate severity with weakness affecting the speech and swallowing muscles (e.g., choking or speech difficulty); or
- Severe severity by weakness affecting other parts of the body (e.g., breathing difficulty, severe leg and/or arm weakness, or death).

MG immunotherapeutic type and dose of medications during this period included steroids, non-steroidal immunosuppressive medications (azathioprine, mycophenolate, tacrolimus, cyclosporine, or methotrexate), rituximab, eculizumab, IVIG, plasma exchange, or none. The steroids dose was further classified as either low dose, considered to be equal to or less than 20 mg by mouth every other day, or high dose steroids, being greater than 20 mg by mouth every other day. The MG-QOL15r questionnaire included items that reflect physical, psychological, and social domains of patient well-being based on the impact MG has had on their quality of life over the four weeks prior to COVID-19 infection. Scoring as 0 if no symptoms, 1 if somewhat had symptoms and 2 if patients had a lot of symptoms in an item affecting QOL. The highest/worse total score was 75.[14]

Data Analysis

Baseline characteristics including age, sex, SARS-CoV-2 vaccination status of each participant were described in all seven centers based on the severity of COVID-19 infection and MG disease severity. For analyses, patients were grouped into four categories based on COVID-19 infection severity (mild, moderate, severe, and death) and MG disease severity was categorized as either mild, moderate, or severe. To evaluate variables that could affect the severity of COVID-19, a univariate logistic regression model analyses was performed with severity of COVID-19 as the dependent variable and the following factors as independent variables: risk factors for COVID-19 including age (≤65 years vs >65 years), sex, COVID-19 vaccination status, MG severity, MG weakness type (generalized vs ocular), MG medications, and high dose steroids groups (2 groups, yes or no). A multivariate ordinal model, wherein a p-value of <0.05 was considered statistically significant studied association between COVID-19 high severity and independent variables including age, sex, COVID-19 vaccination status, and MG severity. A subgroup analysis was done to study association between COVID-19 high infection severity and MG high disease severity in each group of MG weakness type (generalized or ocular), MG medication and high dose steroids (yes or no) based on logistic regression model.

Results

- Patients' Baseline Characteristics

A total of 90 patients from seven neuromuscular centers in the United States were included in this study between December 2021 and August 2023. The mean age of patients was 59.8 (+/- 17.2). Of the total patients included, 48 had an age >65 years and 42 patients had an age ≤65 years. There were more males recruited at four centers, whereas an equal sex distribution was observed in the remaining three centers. Overall, 52 patients were male patients and 38 were female patients (Table 1). Moreover, due to the limited number of participants in the COVID-19 partially vaccinated group number (n=2), we combined partially, and fully vaccinated groups as an ever-vaccinated group. There were 28 patients not vaccinated, and 62 patients were considered in ever vaccinated group. Six out of seven centers had higher percentage of patients who were ever vaccinated.

- COVID-19 Infection and MG severity

The severity of COVID-19 infection and concurrent myasthenia gravis disease severity was assessed as shown in Table 2. COVID-19 infection severity was considered either Mild (n=67 patients), Moderate (n=8), Severe (n=8), or "Death" (n=7). MG severity was categorized into mild, moderate, or severe. The highest percentage of patients was found under the mild categories of both COVID-19 infection and MG severity (49 patients).

Due to the limited number of participants in some COVID-19 severity groups, mild and moderate severity groups were combined as the "Low severity" group and severe and death severity groups as the "High severity" group. A total of 75 and 15 patients were considered to belong to "Low severity" and "High severity" COVID-19 infection groups, respectively. Likewise, due to the limited number of participants in some MG severity groups, moderate and severe groups were combined as a "High severity" group. Mild severity is defined as the "Low severity" group (Table 3). Upon cross tabulation of patients with COVID-19 infection severity and myasthenia gravis

severity, we found low MG severity to be comparable in frequency in the low severity (73.33%) and high severity (66.67%) COVID infection patient groups.

- Factors associated with COVID-19 severity

We studied factors associated with COVID-19 high severity using the univariate logistic regression model (Table 4). In the COVID-19 high severity group, 11 patients (73.33%) were older than 65 years of age and four patients (26.67%) were 65 years or younger, whereas an almost equal proportion of each age group was distributed among patients with COVID-19 low severity. Age as a continuous variable was not shown to be significantly associated with COVID-19 infection severity (p=0.098). Similarly, no significant association was found between sex and COVID-19 severity (p=0.703). Ever being vaccinated against COVID-19 showed an association with low severity COVID-19 infection (p=0.003) as 57 patients (76%) were ever vaccinated and had low severity COVID-19 infection and 10 patients (66.67%) were never vaccinated against COVID-19 and had high severity COVID-19 infection.

The majority of both high (n=10 or 66.67%) and low (n=55 or 73.33%) severity COVID-19 infection groups had low MG severity. There was no significant association (p=0.569) between COVID-19 high/low infection severity and MG high/low disease severity. Similarly, we found no association between COVID-19 severity and MG weakness type (generalized vs ocular) and whether high dose of MG medication was taken or not (p=0.199 and 0.475, respectively).

After controlling for potential confounding variables, including age [≤65 vs. >65], sex, and vaccination status, there was no association (p=0.691) between COVID-19 high infection severity [Severe and Death] and MG high disease severity (Table 5). A subgroup analysis using the logistic regression model with adjustment for sex, age, and COVID-19 vaccination status showed no association between the COVID-19 infection severity and MG disease severity for all patients and each of the two subgroups: MG weakness type [generalized vs ocular] and MG high dose medication (Table 6).

Discussion

This is one of the largest multicenter studies aiming to investigate the association between COVID-19 infection severity, MG disease severity, and MG immunosuppressive medications. Except for an association of vaccination with low severity COVID-19 infection and of older age with severe COVID-19 outcomes (Table 5), we could not identify any association between COVID-19 infection severity and that of MG or its treatment.

A prior smaller study of 15 patients reported that all patients who did not require mechanical ventilation were using prednisone and a second immunosuppressant drug, suggesting a favorable course and a protective role in patients using MG drugs at baseline.[9] In the current study however, we could not replicate this finding as dose of MG medications was not associated with COVID-19 severity. Also, a French cohort[6] showed that immunosuppressants are associated with poor COVID-19 outcomes on univariate analysis but not on multivariate analysis. Univariate analysis in the French study only identified immunosuppressants use and severe MG at COVID-19 onset as risk factors, not age.[6]

These data are not contradictory and can be explained based on the results of the RECOVERY,[18] study. In it, dexamethasone was an effective treatment for severe COVID-19 and ARDS but did not benefit patients who did not require ventilatory support.[3] In our study, COVID-19 vaccination status and age were the only risk factors associated with COVID-19 disease course severity.

We could not identify an association of MG severity or its treatment with COVID-19 severity. One study concluded that clinical course and outcomes in patients with MG and COVID-19 are highly variable.[9] Another study, which might be biased towards reporting poorer outcomes, showed that MG patients with COVID-19 severe acute respiratory syndrome were frequently admitted to hospital, had disease exacerbations, and had a higher mortality than the general population with COVID-19.[5] In an International Neuromuscular COVID-19 Registry including 315 patients from 13 countries, 18% (56) of these neuromuscular cases had MG. In these 56 MG cases, 33 did not require hospitalization. Of the remaining 23 cases, 3 were hospitalized but did not require ventilation/oxygenation, 13 needed ventilation/oxygenation and survived, and 7 died. They did not find MG to be associated with higher odds of severe COVID-19.[13]

Our study has several limitations. The study design allowed for an investigation of association but not causation. A control group would have permitted us to directly compare COVID-19 patients with and without MG. Furthermore, no data analysis was performed to compare immunosuppressant dosing in MG patients who didn't develop COVID-19 with those who did develop COVID-19 infection. In a future study, this comparison would be helpful to relate the possible effect of immunosuppressant dose treatment and COVID-19 infection development. Also, given MG rarity and the limited number of study sites, our study population sample size was midsize. We relied on the MG-QOL15r questionnaire to gauge MG severity. Since it is patient-reported and has subjectivity, it might have introduced some bias. Also, the time duration between positive SARS-CoV-2 virus PCR testing and questionnaire administration was not limited or specified, and may have limited patients' ability to recall the specific details of the sickness event and to correctly answer the questionnaires, raising possible recall bias. In addition, other covariate parameters, such as hypertension or diabetes, were not studied as cofounders for high risk COVID-19 infection or MG severity. Collecting patients' comorbidities and their effects would be helpful to conclude true association

between both severities. One study showed that elderly patients with diabetes are more likely to suffer from severe COVID-19 illness, however there was no evidence of association between diabetes and COVID-19 severity.[17] Moreover, our dose cutoff value for prednisone high dose may have been too low. Despite these limitations, this study informs future design into this complex interaction between MG and COVID-19 infection.

Conclusion

Though there has been a general concern that COVID-19 infection-associated respiratory failure may trigger MG worsening and thus producing severe MG, the relationship between severity of COVID-19 infection and that of MG disease remains unknown. We could not confirm an association between severity of MG and that of COVID-19. We suspect the relationship between both diseases, if any, to be complex and multifactorial. Data from larger worldwide longitudinal studies using objective outcome measures assessed before and after emergent infection are ideally suited to provide better insight into the complex interaction between COVID-19 infection and MG clinical course.

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Appendix:

The questionnaire is previewed below:

Hello, my name is _____. I am contacting you to ask several questions as a part of a study being conducted by our center in order to understand the relationship between: the severity of COVID-19 infection and the severity of myasthenia gravis (MG) disease, the degree of immunosuppression, and prior COVID-19 vaccination. Your contribution will help us understand the effect of COVID-19 infection on patients suffering from MG. The questionnaire will only take few minutes of your time.

All your personal information is confidential, and your replies will be handled and analyzed strictly by authorized research staff.

Do you agree to participate in this study?

Yes (Subject accepted to participate verbally)

No (Subject refused to participate)

Patient died from COVID19. Date of death:

Interviewer initials:

Date of interview: / / (Month/Day/Year)

Center:

ID#:

Subject's Initials:

DOB: / / (Month/Day/Year)

Gender: Male Female Other

1- When were you diagnosed with MG? / (Month/Year)

2- Have you ever tested positive for COVID19?
   a. Yes, Date: / (Month/Year)
   b. No

3- COVID-19 vaccination status:
   a- Fully vaccinated
   b-Partially vaccinated
   b- Not Vaccinated

4- If you have tested positive for COVID-19, which of the following applies to you (*if negative, skip to question 5*)
   a. I had no symptoms or mild symptoms (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell)
   b. I had Pneumonia discovered during clinical assessment or chest imaging)
   c. I was admitted to the ICU, had SpO_2 <94% on room air at sea level or I was put on a ventilator (NIV included)..

5- During the four weeks before COVID19 infection, what type of weakness did you have from myasthenia gravis? And if you did not have COVID-19, what level of weaknesses have you had in the last 4 weeks?
   a. My weakness was mainly affected the eye muscles (double vision, droopy eyelids, etc.)
   b. My weakness affected the speech and swallowing muscles (choking, speech difficulty, etc.)
   c. My weakness affected other parts of the body (leg or arm weakness, breathing difficulty, etc.)

6- During the four weeks before COVID-19 infection, what immunotherapeutic medications were you taking for MG? And if you did not have COVID-19, what medications have you been taking in the last 4 weeks?
   a. Low dose steroid (equal to or less than 20mg by mouth every other day)
   b. High dose steroid (more than 20 mg by mouth every other day) and/or non-steroid immunosuppressive medications (Azathioprine (Imuran), Mycophenolate (Cellcept), Tacrolimus (Prograf), Cyclosporine, Methotrexate, etc.)
   c. Rituximab
   d. Eculizumab
   e. IVIG or plasma exchange
   f. I was not on any immunotherapeutic medications

7- MG-QOL15r

Please complete the following quality of life survey, grading your myasthenia gravis during the 4 weeks before COVID19 infection or 4 weeks from now if you did not get COVID-19 infection	Not at all 0	Somewhat 1	Very much 2
1. I was frustrated by my MG			
2. I had trouble with my eyes because of my MG (e.g., double vision)			
3. I had trouble eating because of MG			
4. I had limited social activity because of my MG			
5. My MG limited my ability to enjoy hobbies and fun activities			
6. I had trouble meeting the needs of my family because of my MG			
7. I had to make plans around my MG.			
8. I was bothered by limitations in performing my work (including work at home) because of my MG.			
9. I had difficulty speaking due to MG			
10. I had lost some personal independence because of my MG (e.g., driving, shopping, running errands)			
11. I was depressed about my MG			
12. I had trouble walking due to MG			
13. I had trouble getting around public places because of my MG			
14. I felt overwhelmed by my MG			
15. I had trouble performing my personal grooming needs due to MG			
Total Score:			