Impact of the Covid-19 epidemic on a US sample of patients with myasthenia gravis

Gloria Gutierrez* (iD) **, Helen Girma*, Pierce Kuhnell, Maurizio Macaluso and Henry J. Kaminski**

Abstract

Introduction: The Covid-19 pandemic has devastated the world and demonstrated the inadequacy of health care in the United States. To assess its impact, the Rare Disease Clinical Research Network conducted a survey to assess the pandemic on the rare disease community of patients, including those with myasthenia gravis (MG).

Methods: A cross-sectional survey was designed to target people or their care givers who live in the United States, have a rare disease, and are under 90 years of age. Respondents logged onto a dedicated web page and completed the survey online, which requested demographic, disease-specific, drug treatment, and symptom information as well as assessment of Covid-19 impact on them. The survey was open from May 2020 to December 2020.

Results: Five hundred ninety-four with self-reported myasthenia gravis completed the survey, which was the largest number of respondents. Sixty percent of respondents were women with a mean age of 60 years. Eighty-nine percent identified as White. Respondents did not appreciate a worsening of symptoms after the pandemic. Only 7 respondents reported the diagnosis of Covid-19 but 11% indicated they had difficulty accessing care at the time of the survey.

Discussion and Conclusion: Patients with MG complained of worse access to medical care during the early months of the pandemic, including challenges in diagnosis of suspected Covid-19 infection. A major limitation of the survey is its inability to access minority populations. Nevertheless, the results of the Rare Disease Clinical Research Network (RCDRN) survey of patients with MG provide clear evidence that the pandemic has demonstrated the deficiencies in US healthcare.

Plain Language Summary

Impact of Covid-19 Pandemic on Patients with Myasthenia Gravis

Deeper understanding of the consequences of the Covid-19 pandemic on people with rare diseases is critically important in order to enhance health care in the future. The Rare Disease Clinical Research Network (RDCRN) performed a web-based survey of individuals with rare diseases in the first year of the pandemic utilizing questions to assess the impact of the pandemic on their symptoms, access to healthcare, and medication use. Five hundred and ninety-four respondents reported having myasthenia gravis (MG). The average age was 60 years and 60% were women. Nearly ninety percent were White. A large minority indicated difficulty accessing health care and nearly a third used telemedicine. Only seven respondents indicated a diagnosis of Covid-19 but many more had symptoms consistent with infection. Overall, there was no increase in symptoms of MG after the beginning of the pandemic. The pandemic has demonstrated the deficiencies in US healthcare, and these are appreciated in the results of the RCDRN survey of patients with MG. The RDCRN will continue to survey the rare disease community to understand the ongoing impact of the Covid-19 pandemic.

Correspondence to:
Henry J. Kaminski
Department of Neurology,
The George Washington
University, 2150
Pennsylvania Avenue NW,
Washington, DC 200037,
USA
hkaminski@mfa.gwu.edu

Gloria Gutierrez
Helen Girma
Department of Neurology,
The George Washington
University, Washington,
DC, USA

Pierce Kuhnell
Maurizio Macaluso
Division of Biostatistics
and Epidemiology,
Cincinnati Children's
Hospital Medical Center,
Cincinnati, OH, USA

*These authors
contributed equally.

Introduction

The Rare Disease Clinical Research Network (RDCRN) performed an online survey to assess the impact of the COVID-19 pandemic on individuals with rare diseases and their caregivers. The RDCRN is a National Institutes of Health's (NIH) initiative led by National Center for Advancing Translational Sciences (NCATS), in collaboration with nine other NIH Institutes and Centers, and is currently made up of 20 clinical research consortia focused on improving understanding of rare diseases including their clinical course and development of better diagnostic approaches and treatments. The Myasthenia Gravis (MG) Rare Disease Research Network (MGNet) focuses on patients with MG. These patients are treated commonly with corticosteroids and immunosuppressive agents, potentially placing them at greater risk for severe complications of SARS-Cov2 infection. Infection of any sort is a well-appreciated cause of exacerbation of weakness leading to hospitalization and death.[1] Thus, patients with MG would be expected to be vulnerable to anxiety and increased disease severity, and to experience greater impact of social and economic factors produced by the COVID-19 pandemic.

The survey was open from May 2, 2020 to December 15, 2020, with 3414 complete submissions of which 594 by patients with MG. The questionnaire requested information on demographics, disease, co-morbidities, general symptoms, treatments, potential COVID-19 symptoms, and actual diagnosis of COVID-19. Thus, CRN COVID-19 survey provides an in-depth cross-sectional characterization of a large sample of patients with MG, which is only rivaled by the MG Patient Registry.[2]

Methods

The Rare Diseases Clinical Research Network (RDCRN), designed a cross-sectional survey through an iterative process with input by clinicians, epidemiologists and biostatisticians of the network (supplemental material). The need for this survey instrument began through discussions among researchers and patient advocacy organizations of the RDCRN in order to better understand the impact of the Covid-19 pandemic on patients with rare diseases. The present survey serves as a baseline assessment with the intention to carry out subsequent surveys of the respondents. We targeted people who live in the United States, have a rare disease and are under 90 years of age. The parents or caregivers could respond on behalf of the person with a rare disease, as needed. The respondents had the option to provide contact information and agree to receive information about future research or complete the survey anonymously.

We designed a survey instrument and implemented data collection in REDCap,[3] so that respondents could log onto a dedicated web page and complete the survey online. The instrument included introductory language equivalent to the information provided in an informed consent form, eligibility questions, checkboxes for agreement to participate, and basic demographics (age, gender, race and ethnicity, state of residence).

Respondents were asked to provide their rare disease diagnosis: the instrument included a facilitated search for any of the approximately 300 diagnoses included in the research conducted by the RDCRN, but persons with any of the over 7000 distinct rare disease diagnoses[4] could participate, and a free-text field allowed entering any diagnosis not covered by the RDCRN list.

RDCRN principal investigators compiled a list of symptoms and conditions commonly associated with the rare diseases studied by the network, and the respondent was asked to check whether they experienced the symptom/condition, and whether its occurrence and severity changed from before the beginning of the COVID-19 pandemic in the United States (January-February 2020) to the time of survey completion. The instrument employed the same layout to ascertain occurrence of COVID 19-related symptoms, and the respondent's use and dosage changes of select medications before and after the beginning of the pandemic.

The instrument also included questions on current use of tobacco and cannabis products. Finally, respondents were asked if they had been tested for COVID-19 infection and if they were diagnosed with COVID-19 infection. Those who replied that they had acquired the infection were also asked about aspects of the disease course and outcome (need for hospitalization, oxygen therapy or mechanically assisted ventilation, experimental therapy, length of stay). All respondents were asked questions about the psychological impact of the pandemic on themselves or family members, as well as whether the pandemic had affected their access to health care, medicines or special food, or rare disease related special treatment such as physical or speech therapy.

The Cincinnati Children's Hospital Institutional Review Board reviewed and approved the research protocol (protocol 2020_0299), the survey instrument and all recruitment materials on April 13, 2020, granting a waiver of documentation of informed consent.

The present report focuses on the information provided by respondents who reported that their condition was 'myasthenia gravis' or 'ocular myasthenia'. The analysis summarizes results on the sociodemographic characteristics of the respondents (gender, race/ethnicity, age), and their geographic and temporal distribution with respect to the course of the pandemic. We describe the prevalence of comorbidity, the impact of the pandemic on MG-related symptoms and treatments, and report the number of COVID-19 infections reported, their clinical characteristics and treatment approach. Finally, we report results on the impact of the pandemic on psychological/mental health outcomes and access to health care and treatment.

Statistical analysis

We summarize select survey responses using simple descriptive statistics (frequencies and percentages for count variables, means and standard deviations for continuous variables), and provide 95% confidence intervals (CI) as a measure of the precision of the estimates when appropriate. As this was a descriptive survey, we did not perform power calculation as we had no specific hypothesis to test and statistical hypothesis testing is done only when warranted and is limited to a few comparisons.

We aimed to achieve a target sample size of 5000 to obtain information about 50–100 Covid-19 cases as initially the World Health Organization estimates suggested that the prevalence of Covid-19 infection may be between 1% and 2%. Although we may not have achieved the target sample size, we have identified 71 self-reported cases of Covid-19 which gave us a higher than expected precision in the study as a whole. In addition, while 71 respondents of the general survey indicated acquiring Covid-19, a true estimate is limited as significant number of respondents indicated that they were uncertain of their Covid-19 status due to lack of access to testing and health care. We compared the monthly observed COVID-19 cases among MG survey respondents to the cases expected on the basis of the New York Times data.[5] To compute the monthly expected number of cases we multiplied the national monthly infection rate by the number of survey respondents who according to the survey were at risk of acquiring a COVID-19 infection during that month. We plotted observed and expected COVID-19 cases over time.

Results

Demographics

Five hundred and ninety-four participants self-identified as having MG completed the survey, nearly all in the first 2 months of survey availability (Supplementary Figure 1) with a geographic distribution generally mimicking the population of the United States (Supplementary Figure 2). Demographic characteristics of the participants are listed in Table 1. Nearly 60% of participants were women, while three did not identify a gender or indicated other. Gender distribution of participants was consistent with previous studies of MG and similar to the MG Patient Registry.[2,5,6] The mean age of the sample was 60 years. Most respondents (97%) were 25 years old or older. Eighty-nine percent identified as being White. The Hispanic identification was also low compared to that of the general US population. The clinical manifestations of MG are broadly divided into ocular and generalized MG. Only three percent of respondents identified as having ocular myasthenia in contrast to expectations of upward of 20%.

Impact of COVID-19 pandemic on symptoms

The survey performed an extensive query of symptoms requesting participants to evaluate the

Table 1. Demographic characteristics of 594 survey respondents with MG.

	Percent
Gender	
Women	56
Men	41
Other	1
No response	2
Race	
White	89
Black	3
American Indian or Native Alaskan	1
Asian	1
Native Hawaiian or Pacific Islander	0
More than one race	1
Other	2
No response	4
Unknown	-
Ethnicity	
Hispanic/Latino	3
Non-Hispanic or Latino	82
Unknown	3
Choose not to answer	6
No response	6

impact of the pandemic (see Supplemental Table 1). MG subjects did not indicate an increased frequency after the pandemic with any of the symptom categories, but reported worsening of certain pre-existing symptoms (Table 2).

The survey asked about access to medical care, which was and remains a significant concern during the Covid-19 pandemic. Eleven percent (65) of respondents reported having trouble obtaining advice regarding being tested for Covid-19 infection. Seven patients indicated they had confirmed diagnosis of Covid-19 and 94 (16%) did not know. Taken together, the responses to these

access questions suggest there could have been patients who may have had Covid-19 but had not been detected. A temporal comparison of cumulative expected and observed cases is shown in Figure 1. The monthly cumulative number of cases observed was higher than the monthly cumulative number of cases expected based on the national infection rate, but this difference was not statistically significant.

Of the seven respondents who were diagnosed with Covid-19, four were hospitalized with three requiring intubation and mechanical ventilation. Four who reported confirmation of infection and a quarter of the 94 who could not confirm infection indicated that MG had complicated care for Covid-19. The patients who did not know whether they acquired Covid-19 reported high rates of increased shortness of breath (58%), headache (68%), muscle aches (62%), and weakness (50%). Of these patients, a quarter could not obtain an appointment for assessment and 39% (36) received care by telemedicine. Nearly 20% of respondents experienced treatment delays or treatment was interrupted which they attributed to the pandemic and close to 10% of surveyed indicated hospitalization was avoided because of the pandemic. Mood alteration or anxiety were attributed to the pandemic by about 20% of respondents. No patients received medications contraindicated for MG (Supplemental Table).

Comorbid conditions and medication use

The survey queried patients on common co-morbid conditions (Supplemental Table). High blood pressure, diabetes, hypothyroidism, reflux, and asthma were the most commonly identified conditions (Table 3). The frequency of tobacco and marijuana use was less common than the general US population.

Participants were queried on use of a range of medications (Supplementary Table), including ones used for treatment of MG. Fifty-seven percent were taking pyridostigmine with a slight increase after the start of the pandemic, perhaps suggesting a worsening of symptoms consistent with the large number of respondents ($N = 54$) reporting more severe weakness. Forty-one percent of participants were taking prednisone with an equal distribution taking more or less at the time of survey compared with prior to pandemic.

There was no greater use of immunoglobulin therapy or immunosuppressants. Seventeen percent indicated use of immunoglobulin treatment before and after the start of pandemic.

The survey provided additional insights in general care of patients with MG. Given the common use of prednisone in the sample, medications used to prevent bone loss were only used by 3 percent of respondents. Use of medications for gastric irritation was not increased despite the frequency of prednisone treatment, and over-the-counter medications used for headache were not different before and after the pandemic despite the frequency in headache complaints. Anxiolytics use was not increased despite the increase in complaints of anxiety.

The survey findings do not indicate if confirmed COVID-19 diagnoses worsened the course of MG directly, but patients with COVID-19 and those with suspected diagnoses identified that their overall course of treatment was complicated due to having a rare disease. Most notably, patients indicated that COVID-19 impacted their health and treatment course as a result of increasingly limited access to care, abbreviated appointment availability and hesitation to risk exposure

Table 2. Symptoms which worsened after the pandemic.

Symptom[a]	More severe (n, % (CI)) N% CI	
Difficulty breathing	30	25 (18%–34%)
Nausea	13	35 (20%–53%)
Abdominal pain	19	46 (31%–63%)
Inability to walk more than 25 feet	12	31 (17%–48%)
Headache	23	36 (24%–49%)
Weakness	59	31 (24%–38%)
Incoordination	11	29 (15%–46%)
Joint swelling	32	31 (22%–41%)
Muscle aches	32	29 (21%–39%)

CI, confidence interval.
[a]For each of these symptoms, the number of respondents who experienced the symptom more severely was significantly larger than the number of participants who experienced the symptom less severely (test of the null hypothesis that the number of respondents whose symptoms were more severe equaled the number of respondents whose symptoms were less severe).

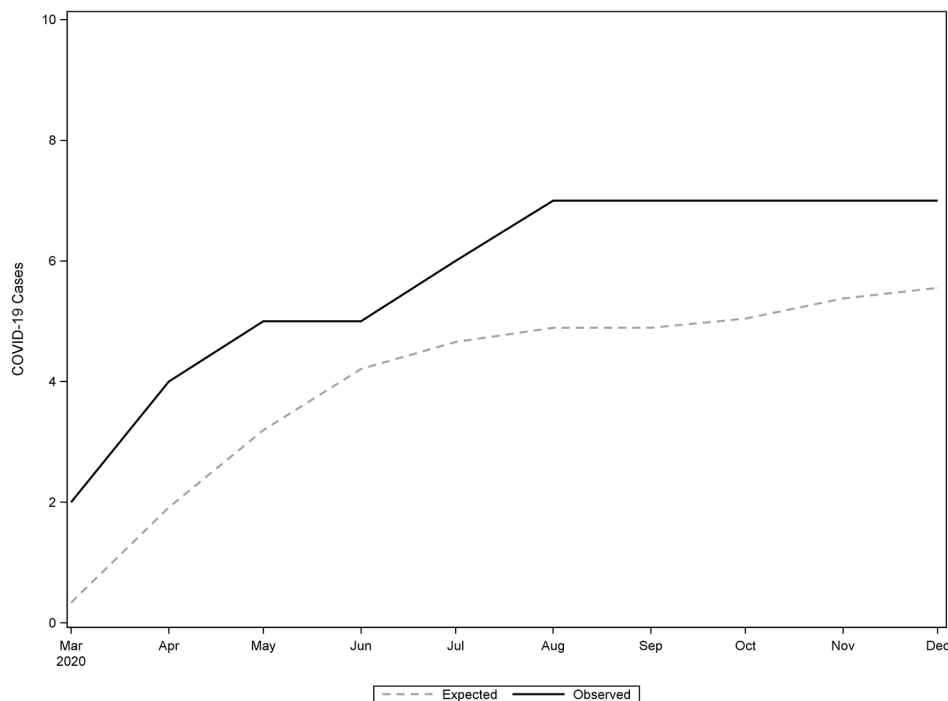to COVID-19 in clinical settings, compromising their routine MG treatment.

Figure 1. Cumulative expected and observed cases of Covid-19 in survey respondents.

Table 3. Most common co-morbid conditions.

Condition	Number (%)
Hypertension	79 (30%)
Hypothyroidism	64 (24%)
Asthma	62 (24%)
Reflux	60 (23%)
Diabetes	53 (20%)

Discussion

The results of the RDCRN survey reflect the challenges appreciated by the respondents with MG and were consistent with those of the general population with compromised access to care, use of telemedicine, and confusion regarding diagnosis of Covid-19 infection.[7] A significant minority of patients indicated that they had a disruption of treatment and some specifically avoided hospitalization because of the pandemic. In addition, some respondents could not access Covid-19 testing. Slightly over a third of patients were able to obtain care through telemedicine. This reduction of health care utilization was a general phenomenon across the population needing access to health care, and in particular among patients with common chronic diseases[8] but could have been more impactful on a rare disease in which patients are immunocompromised by treatment.[9] Respondents reported increased pyridostigmine use after the start of the pandemic suggesting a perception of increased weakness, but there was no increase in immunosuppressant use. Patients tend to modify the relatively benign pyridostigmine treatment, while leaving prednisone adjustments only to their physicians. Therefore, at the time of the survey there was no suggestion of an exacerbation of disease severity based on medication use. As of this writing, existing literature does not unequivocally identify a disproportionate impact of Covid-19 infection on the MG patient population.[10–12] Additional studies assessing the physiologic impact of Covid-19 infection on MG would provide further insight on whether or not this population is at risk of worse prognosis, though this study reveals worsening MG symptoms among the small number patients who reported confirmed Covid-19 related hospitalizations.

Uncertainty exists about the frequency of actual symptomatic and asymptomatic Covid-19 infection.[13] Only seven patients reported that they had been diagnosed with Covid-19; however, since 65 respondents indicated an inability to access testing, this could be an underestimate. On the other hand, our analysis comparing self-reported cases in the survey with the number expected using a national database is consistent with a degree of underestimation among MG cases that was not higher than in the general population. In the early months of the pandemic, many individuals suspected that an infection with Covid-19 had occurred instead of other viral illnesses.[13] This is supported by the responses of those who had not been diagnosed with Covid-19 but had symptoms suggestive of the diagnosis with shortness of breath, headache and muscle ache. The small group who were hospitalized with Covid-19 had worsening of MG symptoms. Fortunately, despite advocacy for use of hydroxychloroquine and azithromycin, which are contraindicated as treatments for Covid-19, none of the MG patients reported their use. Respondents to the survey are being asked to participate in a seroprevalence study and an updated survey, which may provide a valid estimate of the infection rate. A follow-up survey is underway, which will provide information on the experience of people who live with rare diseases and their families in relation to the changing dynamics of the pandemic.

The demographics of the respondents are consistent with previous studies of MG patients with a slight overall preponderance of women. The general demographic information is consistent with that of MG generally and that of the patient reported information of the United States-based MG Patient Registry. The MG Patient Registry is a large registry established in 2011 and generated significant insights into the patient experience with MG related to disability and gender differences in disease severity and treatment.[2,5,6] The survey and the MG Patient Registry share similarities with web-based portals for completion and advertising largely through the patient advocacy groups and general web searches.

Despite there being no data to support large differences in frequency of MG based on race or ethnicity, 89% of respondents were white while the remainder self-identified as Black and non-Hispanics composed 82% of respondents.[14] There are several potential reasons that may contribute to the lack of diversity. The survey was distributed through multiple avenues to the rare disease

community, including MG patient advocacy groups, which acknowledge a general lack of diversity in their membership (personal communication). To be completed, the survey required Internet access, which is known to be reduced for minority populations.[15,16] Within the context of the COVID-19 pandemic, the social and economic consequences had a predominant impact on minority populations.[17,18] Economically disadvantaged individuals may not have had the luxury of time and resources to complete the survey. Whereas a Spanish version of the survey was made available and advertised through the same venues, only a few individuals overall and none with MG took advantage of the data entry tool in Spanish. These same barriers apply to the MG Patient Registry with more than 80% of respondents describing themselves as White. Three percent of respondents were Black Americans, which is again similar to the MG Patient Registry studies.

The RDCRN Covid-19 survey offered a unique snapshot of patients with MG. Consistent with established association with autoimmune thyroid disease, about a quarter of respondents indicated having thyroid disease.[19,20] Other comorbidities were related to the age of respondents but also adverse effects of the most common treatment, prednisone, with high levels of hypertension, diabetes, and gastric reflux. Medications to treat these disorders were also common. Although there were increased rates of anxiety, anxiolytics were not reported at high levels. Asthma, which is not considered to be associated with MG, was commonly reported.

Conclusion

Our investigation contributes to ever increasing characterization of the impact of the Covid-19 pandemic on all aspects of society, including the rare disease community. Patients with MG complained of worse access to medical care, including challenges in diagnosis of suspected Covid-19 infection, and movement to telemedicine evaluations. The study highlights the risk of health disparities among vulnerable populations such as those with rare diseases whose complex care is compromised by the pandemic. Though further study is necessary to assess the physiologic impact of Covid-19 on MG progression, there is evidence to suggest that Covid-19 can lead to exacerbation of MG symptoms among those with a confirmed infection. Even among those without Covid-19, the indirect effect of the pandemic led to deficits in overall quality of care. The survey further mirrors the lack of a voice by minority populations. The pandemic has demonstrated the deficiencies in US healthcare and these are evidenced in the results of the RCDRN survey. Ultimately, we hope the survey will not only highlight the impact of Covid-19 but also help to respond to the needs of the rare disease community through its large network of scientists, clinicians, and patient advocacy groups.

Author contributions

Gloria Gutierrez: Data curation; Formal analysis; Investigation; Writing – original draft; Writing – review & editing.

Helen Girma: Formal analysis; Project administration; Visualization; Writing – review & editing.

Pierce Kuhnell: Data curation; Formal analysis; Methodology; Resources; Visualization; Writing – review & editing.

Maurizio Macaluso: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Visualization; Writing – review & editing.

Henry J. Kaminski: Conceptualization; Formal analysis; Project administration; Supervision; Writing – original draft; Writing – review & editing.

Ethics statement

Cincinnati Children's Hospital–protocol number is 2020_0299, initial approval on April 13, 2020. Informed consent was taken from all participants as part of the survey questions.

ORCID iD

Gloria Gutierrez https://orcid.org/0000-0002-3150-7440

Supplemental material

Supplemental material for this article is available online.

References

1. Gilhus NE. Myasthenia gravis. *N Engl J Med* 2016; 375: 2570–2581.

2. Cutter G, Xin H, Aban I, *et al.* Cross-sectional analysis of the myasthenia gravis patient registry: disability and treatment. *Muscle Nerve* 2019; 60: 707–715.

3. Harris PA, Taylor R, Thielke R, *et al.* Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009; 42: 377–381.

4. Haendel M, Vasilevsky N, Unni D, *et al.* How many rare diseases are there? *Nat Rev Drug Discov* 2020; 19: 77–78.

5. Lee I, Kaminski HJ, Xin H, *et al.* Gender and quality of life in myasthenia gravis patients from the myasthenia gravis foundation of America registry. *Muscle Nerve* 2018; 58: 90–98.

6. Lee I, Kaminski HJ, McPherson T, *et al.* Gender differences in prednisone adverse effects: survey result from the MG registry. *Neurol Neuroimmunol Neuroinflamm* 2018; 5: e507.

7. World Health Organization. The impact of the COVID-19 pandemic on noncommunicable disease resources and services: results of a rapid assessment. *Global Health Report*, 2020, https://www.who.int/publications/i/item/9789240010291

8. Nunez A, Sreeganga SD and Ramaprasad A. Access to healthcare during COVID-19. *Int J Environ Res Public Health* 2021; 18: 2980.

9. Chowdhury SF, Sium SMA and Anwar S. Research and management of rare diseases in the COVID-19 pandemic era: challenges and countermeasures. *Front Public Health* 2021; 9: 640282.

10. Menon D, Alnajjar S, Barnett C, *et al.* Telephone consultation for myasthenia gravis care during the COVID-19 pandemic: assessment of a novel virtual myasthenia gravis index. *Muscle Nerve* 2021; 63: 831–836.

11. Guidon AC, Muppidi S, Nowak RJ, *et al.* Telemedicine visits in myasthenia gravis: expert guidance and the myasthenia gravis core exam (MG-CE). *Muscle Nerve* 2021; 64: 270–276.

12. Businaro P, Vaghi G, Marchioni E, *et al.* COVID-19 in patients with myasthenia gravis: epidemiology and disease course. *Muscle Nerve* 2021; 64: 206–211.

13. Norrie J. Some challenges of sparse data necessitating strong assumptions in investigating early COVID-19 disease. *EClinicalMedicine* 2020; 26: 100499.

14. Dresser L, Wlodarski R, Rezania K, *et al.* Myasthenia gravis: epidemiology, pathophysiology and clinical manifestations. *J Clin Med* 2021; 10: 2235.

15. Early J and Hernandez A. Digital disenfranchisement and COVID-19: broadband internet access as a social determinant of health. *Health Promot Pract* 2021; 22: 605–610.

16. Whitacre B and Gallardo R. State broadband policy: impacts on availability. *Telecomm Policy* 2020; 44: 102025.

17. Khanijahani A. Racial, ethnic, and socioeconomic disparities in confirmed COVID-19 cases and deaths in the United States: a county-level analysis as of November 2020. *Ethn Health* 2021; 26: 22–35.

18. Holuka C, Merz MP, Fernandes SB, *et al.* The COVID-19 pandemic: does our early life environment, life trajectory and socioeconomic status determine disease susceptibility and severity? *Int J Mol Sci* 2020; 21: 5094.

19. Mao ZF, Yang LX, Mo XA, *et al.* Frequency of autoimmune diseases in myasthenia gravis: a systematic review. *Int J Neurosci* 2011; 121: 121–129.

20. Green JD, Barohn RJ, Bartoccion E, *et al.* Epidemiological evidence for a hereditary contribution to myasthenia gravis: a retrospective cohort study of patients from North America. *BMJ Open* 2020; 10: e037909.