Challenges Managing Myasthenia Gravis: An International Perspective

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ABSTRACT

There have been increasing breakthroughs in the diagnosis and treatment of myasthenia gravis over the past decades. However, most published research in myasthenia is conducted in developed regions, such as the US, Canada and Europe. The challenges faced in these regions may be different from other areas of the world, often under-resourced, such as having fewer neurologists, limited or no access to specialised testing for myasthenia, and poor access to some therapeutic interventions. During the 14th International Conference for Myasthenia Gravis and Myasthenic Disorders, we organized a panel of neurologists and researchers who work with people living with myasthenia in different world regions. The goal was to stimulate discussion around common challenges as well as those that are specific for given areas. Ultimately, we aimed to develop networks of clinicians caring for people living with myasthenia gravis around the world, to improve patient care. We present a summary of challenges using a case format by region, and a discussion around common threads and potential next steps.

Key words: Myasthenia gravis, low-resource settings, global health

Introduction

Over the past century, the prognosis of myasthenia gravis (MG) has dramatically changed. From a described mortality close to 90% in the early 1900s to ≤ 10% in the 2000s, MG is a treatable disease where approximately 90% of patients improve with available treatment[1]. We have also seen an increase in the incidence of MG over the last decades, likely a combination of greater awareness and improved diagnostic abilities, as well as a probable increase in incidence with recognition of late and very-late onset of disease.[2–4] Causative antibodies can be found in up to approximately 90% of people with autoimmune MG, and genetic testing for congenital myasthenic syndromes is more readily available in developed countries. However, we know that there is still a large number of patients who, despite available treatments, live with high disease burden.[5, 6] Newly approved treatments for MG, such as eculizumab and efgartigimod, have the potential to further improve patient care due to rapid onset of benefits and good safety profiles;[7, 8] however, there are marked limitations to their implementation in practice, in large part due to their very high costs.[9]

These challenges have been recognized in well-resourced, developed countries, heavily biased towards the US, Canada and Europe; however, the perspectives from other populations are not usually incorporated. To understand gaps in MG care around the world, we assembled a panel of neurologists caring for people with MG in Argentina, United Arab Emirates, South Africa and South Korea, as well as a social scientist researching MG patient experiences in China. During the meeting, each panelist presented cases representing specific challenges they face in their countries. Other panelists commented on how that situation would present in their respective countries, and the impact of resource limitations. Additionally, we had rich audience interactions from participants from different countries. We will present a summary of challenges by country, as presented by each panelist, followed by a discussion of common and divergent issues discussed during the meeting.

Perspectives from South Africa

Treatment-refractory ophthalmoplegia in MG is increasingly recognised as an indication for urgent attention.[10, 11] We have reported several cases with AChR-antibody positive (AChR-pos) moderate to severe generalized MG, who showed excellent responses to MG immune regimens except for their extraocular muscles (EOMs), which remain paretic and treatment refractory. Observational data collected in our clinic previously showed that patients with MG-associated ophthalmoparesis who are treated with higher doses of prednisone within 12 months of symptom onset, compared to those who start prednisone >12 months, have a significantly higher chance of resolution of the weak EOMs.[10]

We discussed a case with AChR-pos MG who started immune treatment for MGFA class IVB within 6 months; the patient received steroids, azathioprine, underwent a thymectomy and subsequent cyclophosphamide pulses, but remained with refractory ophthalmoplegia/ptosis for which he was referred for further management 3.5 years later. Thyroid function was normal. MRI of the orbits showed normal EOM STIR sequence intensities. As the referral occurred during the COVID-19 pandemic, he received a vaccination (uncomplicated) three months in advance of a planned single rituximab infusion. Despite residual partial ophthalmoplegia on examination, the patient's EOMs showed substantial functional improvement which remained stable for seven months on continued maintenance azathioprine alone.[12] However, within a week of receiving a COVID-19 vaccination booster, the extraocular muscles/ptosis decompensated. The case raised discussion around treatment-resistant MG-related ophthalmoplegia, which appears to be more common among Chinese and African children and adolescents with AChR-pos MG,[13] although we have reported cases in older patients and those with and without MuSK-antibody positive MG.[14] Longitudinal observations of MG patients with severe EOM involvement, likely in the setting of genetic susceptibility, have shown that earlier immune treatment to prevent prolonged loss of muscle contractility as a result of antibody-mediated 'functional denervation', will impact the activation of atrophy pathways in EOMs and thereby clinical reversibility.[11] MG patients with refractory ophthalmoplegia may benefit from the use of crutch glasses and prisms. Moreover, in selected cases, surgical correction may be considered, although the success of treatment-refractory ptosis surgery is far better than EOM re-alignment surgery.

The other point of discussion was related to the "MG decompensation" noted within days of an mRNA COVID-19 vaccine. A prospective clinic cohort of 91 stable MG patients, of whom 79% were on a single immunosuppressant, were followed after receiving an mRNA COVID-19 vaccination; at 7 days, 58% developed transient non-specific vaccine-related symptoms, but only 2 experienced mild emergence of MG symptoms.[15] Surveillance groups/networks in the United Kingdom identified seven new MG cases developing symptoms within 2-14 days of a COVID-19 vaccination, although two cases only developed their MG symptoms after a 3rd vaccine dose.[16] Most of these patients developed generalised MG with significant bulbar symptoms. The authors reviewed seven other published cases from elsewhere in whom five developed MG symptoms after the second vaccine dose.[16] Therefore, although MG symptoms emerged in rare cases within days of a COVID-19 vaccine, most known MG patients on treatment tolerated the vaccine well.[15]

An adolescent with double seronegative (AChR- and MuSK-antibody negative by radioimmunoassay (RIA)) and moderately-severe refractory MG (MGFA class 3B) was discussed. She remained with moderately-severe and fatigable leg weakness which was refractory to >2 years each of azathioprine and cyclosporine, in addition to dependence on 30mg daily prednisone. A single infusion of 600mg rituximab resulted in >50% reduction in prednisone and pyridostigmine dosing and minimal leg fatigability (MGFA class IIA) after 3 months, which was sustained for > 12 months similar to previous cases.[12]. This case highlights the cost-effectiveness of a single dose of rituximab in resource-limited settings, and is in keeping with a recent trial of low-dose rituximab in AChR-pos MG.[17]

Accessibility to diagnostic assays other than RIA vary from country to country and can make a difference in the therapeutic management of "seronegative" by RIA MG patients.

Perspectives from South Korea

This is a fictional case of refractory AChR-pos MG. A 52-year-old male with Masaoka stage IVa WHO type B2 thymoma. Due to severe bulbar palsy, he often developed aspiration pneumonia, which led to myasthenic crisis. The dose of corticosteroids could not be lowered to less than 15 mg/day. Immunosuppressant agents including azathioprine, cyclosporine, and tacrolimus were not effective. IVIG and rituximab showed only partial effect. Due to prolonged use of corticosteroids, CMV retinitis, osteoporosis, iatrogenic Cushing's syndrome occurred.

For refractory MG patients, newly developed therapeutic agents such as complement inhibitors can be a good treatment option.[7] In South Korea, National Health Insurance (NHI) is mandatory and covers almost all of the population. The reimbursement and price of drugs is strictly regulated by the government.[18] After approval of new drugs by Ministry of Food and Drug Safety (MFDS), major factors that hinder access to the new drugs are delays in drug pricing negotiations between the National Health Insurance Service (NHIS) and the relevant drug manufacturer and in process of determining whether to reimburse the drugs or not.[19] Eculizumab was approved by MFDS in 2019; however, reimbursement and eculizumab pricing negotiations have been stalled for a long time. The NHIS is concerned about the financial risk from introducing the expensive new drug that costs more than $400,000 a year per a patient, whereas the manufacturer wants to maintain its drug price internationally. In the treatment of MG, eculizumab is available but not accessible in South Korea. Because policymakers may refer to a drug price information from other countries in their own negotiation on the drug price, low price of a drug in one country can lead to price cuts in other countries.[20] Therefore, a country's low drug pricing policy may force some manufacturers to abandon the market of the country. This situation seriously hinders refractory MG patients in the country from accessing new treatment options. In order to improve accessibility to new

treatment, patient-oriented approaches with reasonable policies and drug prices are needed.

A second case was a 49 year-old AChR-pos MG patient with Masaoka stage I WHO type AB thymoma in stable condition with MG-ADL 1 or 2. However, about two weeks after COVID-19 infection, MG exacerbation occurred. He was not vaccinated for COVID-19. He was treated with plasma exchange in the intensive care unit.

Most of previous studies about effects of COVID-19 infection on MG were performed in the early stages of the COVID-19 pandemic, when COVID-19 vaccination was not available.[21, 22] The situation in South Korea in early 2022 was different from those in other countries at the time. Most COVID-19 infections have occurred since February 2022. Almost of all COVID-19 infections are caused by SARS-CoV-2 Omicron variants, of which severity is milder than the other previous variants.[23] As of May 2022, full vaccination rate was about 86% of the population and booster was given to more than 63% of the population.[24] Therefore, a substantial number of MG patients had been vaccinated against COVID-19. In an analysis of 40 Korean MG patients infected with COVID-19, 28 patients were vaccinated before COVID-19 infection and 12 patients were not. The comparison between the vaccinated and unvaccinated MG patients are summarized in Table 1. The vaccinated MG patients had lower frequency of hospitalization for COVID-19 and MG worsening or exacerbation after COVID-19 infection than the unvaccinated MG patients. This is in keeping with previous studies showing that severe COVID-19 outcomes are less frequent in vaccinated than unvaccinated individuals.[25,26] Because the severity of infection can influence the disease activity of MG, vaccination against COVID-19 may have preventive effect of MG worsening or exacerbation through protection against severe COVID-19 infection. Although there have been studies showing the safety of vaccination against COVID-19 in MG patients,[27–30] no studies have evaluated the effect of the vaccination on MG deterioration after COVID-19 infection. Further large-scale studies are necessary to investigate the preventive effect of COVID-19 vaccination on MG worsening or exacerbation triggered by COVID-19 infection.

Perspectives from the United Arab Emirates

A 42-year-old woman who has been diagnosed with generalized seronegative MG (negative AChR, MuSK and LRP4 antibodies) for almost 10 years. Her disease started with ocular and bulbar manifestations followed by limb weakness. Her diagnosis was supported by the significant decrement response (> 60%) with 3Hz repetitive nerve

Table 1. Comparison between vaccinated and unvaccinated against COVID-19 MG patients who infected with COVID-19 in Korea

	Vaccinated (n = 28)	Unvaccinated (n = 12)	P-value
Age at COVID-19 infection	49.50 [38.25 – 61.5]	46 [41.25 – 56.5]	0.873
Age at MG onset	35 [24.25 – 48.5]	39 [32 – 47]	0.192
Sex			1.000
Male / Female			
Body mass index	24 [22.5 – 27]	23 [18 – 26]	0.118
Antibody status			0.833
AChR-Ab	22	9	
MuSK-Ab	1	1	
No detectable Abs	5	2	
Generalized Disease	23	11	0.648
MGFA at nadir			0.827
I	5	1	
II	8	4	
III	7	4	
IV	2	1	
V	6	2	
MG-ADL score at last visit before COVID-19 infection	2 [0.75 – 5]	3 [0.5 – 5]	0.425
Hospitalization for COVID-19 infection			0.001
Non-hospitalized	27	6	
Hospitalized	1	6	
Change in MG status			0.021
Worse or Exacerbation	5	7	
Improved or Unchanged	23	5	
Recovery after COVID-19 infection			1.000
Completely recovered	22	9	
Partially recovered	6	3	

stimulation. Over the years, she has been on different immunosuppressive medications with either poor response, or significant adverse events. IVIG was not effective; she developed significant psychiatric side effects, elevated liver enzymes and intolerance to steroids, methotrexate and azathioprine respectively. The patient was eventually started on rituximab, which resulted in subjective 30% improvement in her strength and respiratory function, and over 18 months she received 3 cycles. During this period, her MG-ADL score ranged between 9-12 points, and her MG-QoL15 score between 19-21 points, without significant objective benefit after rituximab. Patient declined to try other medications such as tacrolimus, eculizumab or efgartigimod, despite severe limitations to her daily life activities, preferring to stick with the medication that is "keeping me out of trouble" (patient's words).

Discordance between physician and patient perception of disease control and symptom severity has been a subject in research, especially in prevalent chronic conditions such as asthma[31] and rheumatoid arthritis.[32] Presence of patient-physician discordance contribute to poor symptom control while concordance leads to better clinical and patient reported outcomes.[33] Several factors had been implicated in patient-physician discordance, these include health literacy, race/ethnic minority, poor communication and use of anti-depressant medications (Hirsh & Kenney-Riley).[34,35]

MG is a chronic and potentially disability condition. Studying patient-physician discordance (or concordance) in disease control is an important step in improving the care for MG patients, especially in the current era of emerging new therapies.

Perspectives from China

Our presentation focuses on preliminary findings from a patient journey study on myasthenia gravis patients in China. Ethical approval of this study was obtained from the Survey and Behavioral Research Ethics Committee of the Chinese University of Hong Kong (approval no: SBRE-21-0260). The purpose of the study is to identify the factors contributing to MG relapse in China and to provide insight on how to improve care for MG patients. The findings were based on semi-structured in-depth interviews conducted between January 2022 and May 2022, with 28 MG patients or their main caregivers, 3 neurologists, 2 thoracic surgeons, and 2 Traditional Chinese Medicine practitioners in China.

According to a recent study, after adjusting age and sex, the incidence of MG in China is 0.68 per one-hundred thousand. The disease can occur at all ages but occurs most frequently between the ages of 30 to 50. There is a slightly higher incidence rate among females (0.76 per 100,000) than males (0.60 per 100,000).[36] The in-hospital mortality rate is 14.69%, with the main causes of death being respiratory failure and pulmonary infection. More than 64% of the MG patients with thymomas had thymectomy. Consistent with previous research, the majority of our MG patient participants were female aged between 18 and 65. All our participants had generalized MG, and 70% of them had undergone thymectomy. Eight of them self-identified as refractory cases.

Our study revealed that, although most of the patient participants were AChR-pos, 26 out of 28 patients experienced relapses, or even recurrence of crises, with varying reasons. Patient compliance was identified as the most common cause of relapse among MG patients in China. Many patients took medication not prescribed by their doctor, or made changes to the dosage of their medication at their own discretion. This was often due to ineffective or inefficient communication with their doctors, deteriorated doctor-patient relationships, or a lack of regular follow-ups. This is a significant problem as it can lead to the worsening of the patient's condition and even to a crisis.

Another factor contributing to the relapses of MG patients in China was the lack of a regular doctor or medication plan for migrant workers who had to work inter-provincially. These patients often had to seek medical help from different hospitals and doctors, making it difficult to establish a consistent treatment plan. This highlights the need for more coordinated care and better understanding of the unique challenges faced by migrant workers in the management of MG.

Overwork and emotional impact were also identified as significant factors that led to MG relapses. Patients who continued to work after the onset of their symptoms, or who were overworked due to household chores, childcare, and other factors were more likely to experience relapse. Emotional stressors, such as death of relatives, problems with family or spousal relationships, economic and psychological pressures, were also identified as potential causes of relapse. This highlights the need for a more holistic approach to the management of MG, which should not just focus on the physical symptoms but also on the emotional and psychological well-being of the patient.

Other factors contributing to MG relapse in China included seasonal flu, or, for female patients, menstrual periods, pregnancy and childbirth. Some patients did not allow family members to participate in disease management due to their strong personalities, which might further contribute to MG relapse. These findings emphasize the need for multidisciplinary teams for managing pregnancy and childbirth, stronger social support in disease management, as well as the importance of patient education to increase awareness of the disease.

There was one patient whose patient journey could mostly illustrate many of the factors we discussed above. The patient was a 37-year-old female who experienced multiple relapses while trying to reduce the dosage of steroids, as per her doctor's advice. As the quote indicates, the patient, after the several relapses, lost trust in doctors and frequently changed her attending doctors, often

increasing or decreasing her medication according to her own assessment of her condition. She would only go to her hometown hospital to receive IVIG when her symptoms worsened, as the doctors there did not know much about the disease. The patient had to dictate the dose and infusion method for the IVIG treatment to the doctors.

In conclusion, the study highlights the various factors that contribute to MG relapse in China. It emphasizes the need for effective communication between patients and their doctors, especially in terms of medication compliance, regular follow-up, and multidisciplinary teams for managing pregnancy and childbirth. The study also underlines the importance of social support, as well as patient education to increase awareness of the disease.

Perspectives from Argentina

Case 1 is about a 46-year-old patient who at 33 years old was diagnosed with MG, AchR-pos, associated with thymoma, MGFA class IIA at onset. He underwent a video-assisted thymectomy (VATS), with pathology consistent of thymoma WHO type AB, Masaoka-Koga Stage I. Afterwards, he was diagnosed with Morvan Syndrome, with positive leucine-rich glioma inactivated 1 (LGI1) and contactin-associated protein like-2 (CASPR2), and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR) antibodies. In two opportunities, he presented a crisis/exacerbation of both conditions simultaneously. He remained with invasive mechanical ventilation dependence despite IVIG, steroids and azathioprine. Successively and/or concurrently, different organisms were isolated in the sputum. The impossibility to eradicate the respiratory infection led to a reduction of the dose of azathioprine, with worsening of MG. A chest MRI showed images suspicious of pulmonary neoplasia in the right inferior lobe, previously interpreted as pneumonia. The biopsy showed a recurrence of the thymoma.

Thymomatous patients can have a more severe presentation and a higher risk of death. In one series, ~35% of the deaths were attributable to thymoma recurrence and dissemination.[37] Of these recurrences, 48% coincided with an MG flare-up or crisis. In our case, the red flags for tumor recurrence were antibodies positivity, symptom worsening when azathioprine was reduced, and antecedent of VATS (not the gold-standard procedure for thymoma).

This case highlights many issues, including managing the coexistence of two autoimmune neurological disorders, and the difficulties managing adequate immunosuppressive treatment when there are chronic infections that contribute to MG exacerbations. Finally, this case highlights the difficulties in managing patients with refractory MG.

The second case is about a 38-year-old woman diagnosed with AChR-pos MG at 16 years-old. The initial MGFA class was IIB. Since her diagnosis, she receives pyridostigmine and prednisone. She had several therapeutic failures, and was considered as refractory MG. She suspended azathioprine because of the elevation of liver enzymes and presented three myasthenic crises. She received cyclophosphamide IV, and 18 months later, she developed her fourth crisis. In this opportunity, treatment was initiated in three steps with IVIG followed by rituximab. She then received tacrolimus for a long time. She miscarried her first pregnancy, then she had her only daughter, who suffered from neonatal MG. Later, there was an important reduction in the steroid dose and QMG score. During the puerperium and the following years, she presented frequent exacerbations. She suffered a fifth and a sixth myasthenic crisis, in the context of a renal abscess, and discontinued tacrolimus. Later, and after numerous difficulties with the health system, and many years after her initial diagnosis, she started treatment with eculizumab.[7] Her MGFA-Post-intervention status was improved.

In patients with refractory MG, the therapeutic decision is conditioned by the availability and access to medications and interventions in the health system. Difficulty in monitoring, controlling, and acquiring the drug can perpetuate the refractory or pseudo-refractory status in these patients.

Discussion

A common thread across different presentations was the difficulty accessing new therapeutics for MG, especially in low-resource settings. This is especially relevant for treating patients with MG who are refractory to first-line treatments that are more commonly available. We discussed the use of rituximab that, as an older drug, is less costly than newer medications and maybe more accessible. During the panel discussion it also became evident that access to diagnostic testing for MG varies by region, such as variable access to antibodies, including RIA and cell based-assay for AChR, as well as for MuSK, and variable access to specialised electrophysiology testing such as single fiber EMG. There are also major differences in access to genetic panels for patients with suspicion of congenital myasthenia syndromes, for example in refractory seronegative patients.

Another common thread among presenters was the management of chronic infections and the relationship between infections and MG exacerbations, especially as people with MG have a higher risk of infections—especially respiratory.[38] This has become more relevant with the COVID-19 pandemic, where clinicians had to make therapeutic decisions early in the pandemic before evidence specific to MG became available.

The factors associated with MG relapse in China are also present in other countries, and during discussion the importance of communication between patients and physicians was emphasized, although it was also noted that there can be discrepancies in the assessment of disease status. The lack of detectable autoantibodies may raise diagnostic uncertainties, which may further compromise patients' trust in the physician. Of note, patients with seronegative

MG represent a small— but not negligible— proportion of MG cases. The importance of multidisciplinary teams for managing pregnancy and childbirth was highlighted in the presentation from China, but was also reflected in cases from other panelists.

In summary, our international panel identified many aspects of MG care that are hindered in different countries. In some cases it is due to lower resources overall, but sometimes it has to do with health policies around access to expensive medications, access to high risk perinatal care and overall robust multidisciplinary health teams. The importance of studying infections in MG and developing related guidelines, can help prepare for future epidemics. Developing networks of clinicians who care for people living with MG in different regions will be important to help overcome some of these limitations and improve patient care.

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Figure 1. Clinical course of patient with MG and Morvan Syndrome