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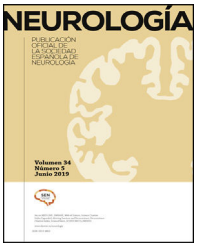

ORIGINAL ARTICLE

Myasthenia gravis in Spain: A survey of specialized neurologists to uncover unmet needs

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KEYWORDS
Myasthenia gravis;
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Abstract
Introduction: Myasthenia gravis (MG) is a neuromuscular autoimmune disease that requires prompt diagnosis and management by neurologists. The challenges of MG management are associated with the diagnostic process and the selection of an effective form of therapy enabling long-term remission of the disease. The objective of this study was to assess the state of MG in Spain to identify unaddressed needs in the clinical progression, diagnosis, and treatment approaches.
Methods: A survey was distributed via email between 19 July and 25 October 2022 to neurologists belonging to the Spanish Society of Neurology. A comprehensive descriptive analysis was conducted on all collected data.

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Results: In total, 69 completed surveys, representing 64 Spanish hospitals, were analyzed and included in the results. The study identified that economic difficulties, such as departmental budgets, have led to a lack of access to antibody testing during diagnosis. Furthermore, corticosteroids were found to achieve the best clinical response, despite also being associated with a higher frequency of adverse effects. The results show that 34% of patients with MG present active symptoms. Eighteen percent have symptoms that limit their daily activities. Additionally, 29% of patients have requested an unscheduled follow-up visit within the last year.
Conclusions: Several areas present unmet needs in terms of improving access to diagnostic assays, residual disease burden in treated patients, and the management and diagnosis of MG.

PALABRAS CLAVE
Miastenia gravis;
Necesidades no cubiertas;
Encuestas médicas;
Cuidado especializado;
Neurología

Miastenia gravis en España: una encuesta a neurólogos especializados para descubrir necesidades no cubiertas

Resumen
Introducción: La miastenia gravis (MG) es una enfermedad neuromuscular autoinmune que requiere un diagnóstico y tratamiento rápido por parte de neurología. Los desafíos en su manejo están asociados al proceso diagnóstico y a la selección de una terapia eficiente para la remisión a largo plazo. El objetivo fue evaluar el estado de la MG en España, para identificar las necesidades no cubiertas en el ámbito de la progresión clínica, diagnóstico y enfoques terapéuticos.
Métodos: Se distribuyó una encuesta entre el 19 de julio y el 25 de octubre de 2022 a los neurólogos miembros de la Sociedad Española de Neurología (SEN). Se realizó un análisis descriptivo exhaustivo de todos los datos recogidos.
Resultados: Se incluyeron los resultados de 69 encuestas en 64 hospitales. Este estudio identificó que existen razones económicas, como la capacidad financiera de los departamentos, que han provocado una falta de acceso a las pruebas de anticuerpos durante el diagnóstico. Además, los corticoides se identificaron como la terapia con la mejor respuesta clínica, a pesar de su asociación con una mayor frecuencia de efectos adversos. Se demostró que el 34% de los pacientes con MG experimentan síntomas activos. De ellos, un 18% presentan actividades diarias limitadas. Finalmente, un 29% de los pacientes han solicitado una visita de seguimiento no programada en el último año.
Conclusiones: La encuesta identificó áreas con necesidades no cubiertas en términos de mejorar el acceso diagnóstico a las pruebas, la carga residual de la enfermedad en los pacientes tratados, el manejo y el diagnóstico.

Introduction

Myasthenia gravis (MG) is a rare, multifactorial, autoimmune disease with a prevalence of 15—20 cases/100 000 population, and is characterized by complex pathophysiology, symptoms, diagnosis, and treatment.[1,2] MG is caused by the failure of neuromuscular transmission resulting from the binding of IgG autoantibodies to signaling proteins, mostly the nicotinic acetylcholine receptor (AChR) at the neuromuscular junction.[3] This induces muscle weakness that can differ between individual muscles and muscle groups. Extraocular muscles and muscles innervated by the cranial nerves are frequently affected, leading to intermittent ptosis, diplopia, reduced facial expression, speech, and swallowing weakness.[4] In the most severe cases, the respiratory muscles are also affected, causing breathing problems.[5] Approximately 10% of patients with MG have substantial symptoms and recurrent exacerbations that may necessitate hospitalization.[6,7]

MG requires prompt identification and treatment due to the high potential for improvement, and even remission in some cases. However, its diagnosis can be challenging and delayed because of the nature of muscle weakness and the overlap of signs and symptoms with other neuromuscular diseases.[8] Diagnosis is based on the patient's signs and symptoms, electrophysiological study results suggesting impaired neuromuscular transmission, and positive tests for pathogenic IgG autoantibodies. These include antibodies against AChR, muscle tyrosine kinase (MuSK), and lipoprotein-related protein 4 (LRP4). However, 10%—15% of patients with MG are double-seronegative for AChR and MuSK antibodies.[9]

The standard treatment is based on patient-specific characteristics and typically involves the administration of

Table 1 Number of years of experience of the neurologists participating in the survey.

Years of experience	General neurology *n* (%)	Neuromuscular neurology *n* (%)	Pediatric neurology *n* (%)
<5 years	2 (5.3)	1 (3.3)	–
5–10 years	7 (18.4)	6 (20.0)	–
11–15 years	6 (15.8)	13 (43.3)	–
16–20 years	7 (18.4)	3 (10.0)	1 (100.0)
>20 years	16 (42.1)	7 (23.3)	–

acetylcholinesterase (AChE) inhibitors, immunosuppressive drugs, and thymectomy. MG crises are usually managed in an intensive care setting with ventilatory support and treatment with corticosteroids and intravenous immunoglobulins (IVIG) or plasma exchange.[8] A range of immunomodulatory therapies have conventionally been used to achieve clinical remission (previously published estimates of clinical remission rates ranged from 6.5% to 45.9%). Although currently available therapies control clinical symptoms reasonably well in most patients, health-related quality of life remains lower than expected due to the chronic, disabling nature of the disease, treatment-related adverse events, tolerability problems, and even treatment resistance, all of which contribute to the significant burden of the disease.[5,10–13] Additionally, different studies have shown that 8.5%–15% of patients with MG are unresponsive to conventional treatments.[14–16] Furthermore, new therapies with new mechanisms are emerging in the market, such as agents targeting B cells and plasmablasts, complement inhibitors, and neonatal fragment crystallizable receptor (FcRn) antagonists[17]; it is important to understand which patients could benefit from these to improve disease management and patient outcomes.[2] Due to the complex nature of MG, diagnosis and treatment are often limited to specialized neurologists.[18]

Management of the disease can present challenges including its diagnosis, treatment (resistance, adverse effects), coexisting immune conditions, lack of specialized medical care, and the lack of identification of unmet needs. Therefore, the objective of this study was to assess the state of MG management and unmet needs in Spain.

Methodology

This paper reports data from a survey completed by neurologists from Spanish hospitals. Scientific endorsement was obtained from the Spanish Society of Neurology (SEN, for its Spanish initials).

Participant selection and recruitment

Between 19 July and 25 October 2022, all neurologists belonging to the SEN ($n = 2000$) were invited to participate. Participants were sent a link to the online survey, with information about the aim and the importance of the study. Participants received no incentives or funding.

Survey questions

The online survey included 34 questions related to the number of patients observed, their symptoms, diagnostic approach, referrals, tools, and difficulty and disease management (the survey questions are provided in Supplementary table 1). The questions were written and validated by the authors of this article.

Data analysis

No formal sample size calculation was performed. A descriptive analysis was conducted.

Results

Eighty-one responses were received; however, 12 surveys were incomplete and therefore excluded from the final analysis. The final data included 69 surveys completed by neurologists from 64 Spanish hospitals (54 public and 10 private). Most respondents were general neurologists ($n = 38$, 55.1%) and neuromuscular neurologists ($n = 30$, 43.5%). One survey was completed by a pediatric neurologist (1.4%). One-third of respondents had more than 20 years' experience in clinical practice ($n = 23$); 15.9%, 25.5%, 18.8%, and 3.3% had 16–20, 11–15, 5–10, and <5 years of experience, respectively. A greater number of years of experience was observed among general neurologists (Table 1).

Diagnosis and referral characteristics

In the 64 hospitals included in this study, 890 patients with MG were estimated to be diagnosed each year (475 by neuromuscular neurology, 411 by general neurology, and 4 by pediatric neurology). Most patients were followed up by the neurology department (89.1%), by neuromuscular neurologists (61.34%), or by general neurologists (38.40%). On a global scale, most patients with MG (89.12%) are not referred to other medical departments, with only a minority (10.74%) being referred. However, when examining patient referrals by neurologist category, the data show a noteworthy contrast in referral rates across different areas of neurological expertise. Specifically, in pediatric neurology, a substantial proportion of patients (70.0%) were referred, whereas a considerably lower percentage of patients were referred by neuromuscular neurologists (3.27%) and general neurologists (15.8%).

Table 2 Patients referrals by order of importance (from 1, main source of referrals, to 9, residual).

Number of beds	Primary care	Ophthal-mology	External neurologist	Hospital neurology department	Emergency room	Critical care unit	Other hospital services	Electro-myography	Other
<200 beds	1.3	1.6	3.0	4.0	4.0	7.5	5.0	6.0	3.5
200—500 beds	3.2	4.4	4.3	3.8	3.6	5.4	5.7	6.6	7.4
500—1000 beds	4.2	4.1	4.2	3.6	2.9	5.5	6.4	5.4	7.0
>1000 beds	5.1	4.3	4.2	2.8	4.1	5.3	6.0	5.0	7.9
Total	3.8	4.0	4.2	3.5	3.4	5.5	6.0	5.8	7.2

The size of hospitals or centers that received patients was analyzed according to the number of beds at each institution. Most cases of MG were diagnosed at hospitals or centers with 501—1000 beds (57.6%), followed by those with more than 1000 beds (23.5%). The percentage of patients diagnosed in hospitals or centers with 200—500 beds or with fewer than 200 beds was 16.9% and 2.0%, respectively. The data indicated that a larger proportion of patients received follow-up care at hospitals with 501—1000 beds (46.1%), followed by those with more than 1000 beds (34.4%), 200—500 beds (18.6%), and fewer than 200 beds (0.9%). Furthermore, the analysis of patient referrals by hospital shows that a higher percentage of patients from hospitals with fewer than 200 beds are referred for further medical attention (44.3%), followed by hospitals with 200—500 beds (12.1%), hospitals with 501—1000 beds (4.1%), and finally, hospitals with more than 1000 beds (4.1%).

Patient referrals were described by order of importance (from 1, meaning the main source of referrals, to 9, residual) (Table 2). Overall, the most relevant units were the emergency room (scored as 3.4), the hospital neurology department (3.5), and primary care (3.8). In smaller hospitals (fewer than 200 beds) primary care stood as the most relevant unit (1.3), while for larger ones (more than 1000 beds) the neurology department was identified as the most important (2.8).

According to our respondents' experience, indicators of unstable disease in a patient with MG are (in order of importance): presence of persistent symptoms, need for rescue therapy, need for high-dose treatment, and occurrence of adverse effects. Moreover, 34.4% of patients presented active symptoms, with 18.2% presenting limiting symptoms with an impact on their daily lives. A total of 28.9% had requested at least one unscheduled visit per year. Scheduled visits were held every 3 months (13.0%) or every 6 months (18.8%), but in most cases there was no established frequency and/or it depended on the severity (68.1%).

Respondents reported that the most frequent comorbidities were other autoimmune diseases (73.9%), followed by diabetes (71.0%), hypertension (69.6%), anxiety/depression (55.1%), osteoporosis (40.6%), obesity (26.1%), infection (13.0%), cancer (10.1%), cataracts (8.7%), and liver or kidney alterations (7.2%).

Diagnostic management

Around 40.5% of patients arrived at neurological departments without a working diagnosis, 37.8% were referred with a working diagnosis, and 20.2% arrived with a confirmed diagnosis for treatment (Fig. 1). These percentages vary according to the hospital (Table 3), with the highest number of patients without a working diagnosis observed at smaller hospitals (<200 beds or 200—500 beds). Similar patterns were noted in both general neurology and neuromuscular neurology, where 43.9% of patients were initially referred to the neurology department with a working diagnosis, 27.9% without a working diagnosis, and 24.9% had already received a diagnosis and were referred for treatment.

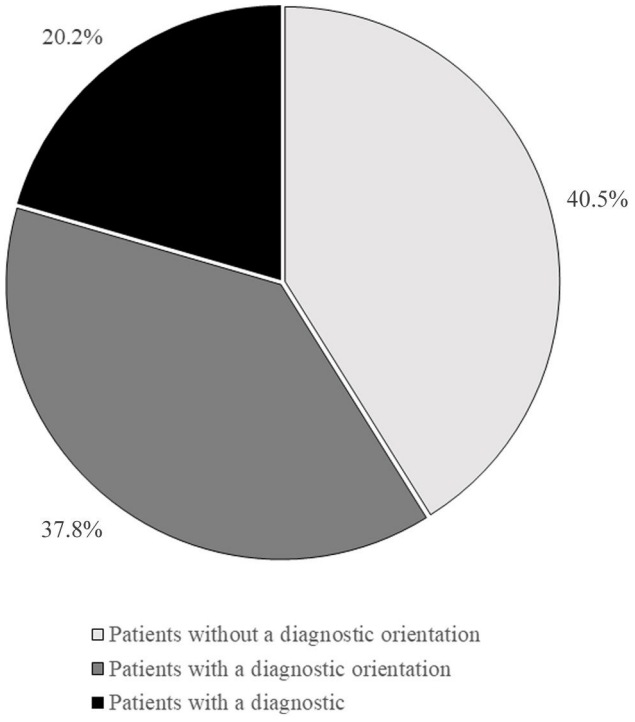

Figure 1 Diagnostic status of MG patients arriving at the neurology department. The graph demonstrates that most patients arrive at neurology departments without a working diagnosis.

Specialists rated the diagnostic difficulty of MG on a scale of 1—5 (where 1 is an easy and fast diagnosis and 5 is an extremely difficult diagnosis). On average, general neurologists rated the difficulty at 2.9 and neuromuscular neurologists rated it at 2.5.

Most neurologists requested antibody profiles ($n = 62$, 89.8%), in a sequential approach ($n = 45$, 72.6%). The protocol involves an initial analysis of anti-AChR antibodies,

Table 3 Working diagnoses of myasthenia gravis at first visit, by hospital size.

Number of beds	No working diagnosis (%)	Working diagnosis established (%)	Confirmed diagnosis, referred for treatment (%)
<200 beds	75.7	22.1	2.1
200—500 beds	45.8	37.6	16.6
500—1000 beds	34.2	40.4	25.4
>1000 beds	23.4	41.3	25.2
Total	40.5	37.8	20.2

Table 4 Percentage of patients with myasthenia gravis under treatment.

Treatment	General neurology (%)	Neuromuscular neurology (%)
AChE inhibitors	24.7	18.1
Oral corticosteroids*	27.5	25.2
Immunosuppressants*	24.6	23.7
Immunosuppressants plus corticosteroids*	17.4	24.3
IVIG**	8.9	6.0
Plasmapheresis**	3.6	2.7
Rituximab**	5.5	4.6

AChE: acetylcholinesterase: IVIG: intravenous immunoglobulins.
* With/without AChE inhibitors.
** With/without other treatments.

followed by anti-MuSK antibody testing in the event of negative results. If anti-MuSK antibody results are negative, further testing for anti-LRP4 antibodies is conducted. The remaining specialists who did not request these studies ($n = 7$, 10.2%) attributed this to a lack of economic resources at their departments.

Treatment management

More than one-third of patients (34.3%) underwent thymectomy in the past 2 years. Most were treated (72.7%) with immunosuppressants (30.5%), corticosteroids plus immunosuppressants (22.5%), or corticosteroids only (19.6%).

The treatment sequence followed by the specialists started with AChE inhibitors, followed by corticosteroids such as prednisone, and immunosuppressants such as azathioprine, tacrolimus, cyclosporine, cyclophosphamide, and rituximab.

A higher percentage of patients received corticosteroids with or without AChE inhibitors: 27.5% and 25.2% in general neurology and neuromuscular neurology, respectively (Table 4). Among general neurologists, 24.7% of patients were receiving AChE inhibitors alone. This percentage decreased to 18.1% of patients for neuromuscular neurologists. A total of 24.6% and 23.7% of the patients from general neurology and neuromuscular neurology, respectively, were receiving immunosuppressants with or without AChE inhibitors. IVIG was administered in 8.9% and 6.0% of general neurology and neuromuscular neurology patients. Rituximab was used as an immunosuppressant in 5.5% and 4.6%, and plasmapheresis (plasma exchange) alone or combined with other systemic treatments was prescribed to 3.6% and 2.7% of general neurology and neuromuscular neurology patients, respectively.

Neurologist experience with MG treatments

Neurologists were invited to provide an account of their experiences with a range of pharmacological treatments, specifically AChE inhibitors, corticosteroids, azathioprine, mycophenolate, methotrexate, cyclosporine, tacrolimus, IVIG, plasmapheresis, rituximab, and cyclophosphamide (Table 5).

In relation to the positive impact of treatment on patients' quality of life following treatment, AChE inhibitors received the highest score (61 responses, 88.4% of participants agreed). Corticosteroids were found to be the most effective treatment for managing symptoms of MG according to the experience of neurologists (58 responses, 84.1%). Azathioprine was considered the most convenient treatment option for administration and dosage, obtaining the highest score with 49 responses (71.0%). Based on the respondents' experience, the highest percentage of patients who responded well to treatment were those managed with corticosteroids (59 responses, 85.5%). In terms of the frequency of adverse effects resulting from treatment, corticosteroids were found to induce the highest percentage of adverse effects, with 60 responses (90.0%). IVIG was considered the treatment with the fastest onset of action, receiving 57 responses (82.6%). The least commonly used treatment option included in this study was cyclophosphamide, with

Table 5 Neurologists' experience with myasthenia gravis treatments. Number of neurologists and percentage that agreed with each statement.

Treatment	Positive effect of treatment on patient quality of life *n* (%)	Most effective treatment to control MG symptoms *n* (%)	Convenience of administration and dosing *n* (%)	Highest percentage of patients who respond to the treatment *n* (%)	Frequently induces adverse effects *n* (%)	Rapid onset of action *n* (%)	Least frequently used treatment *n* (%)	Patient satisfaction with treatment *n* (%)
AChE inhibitors	61 (88.4)	41 (59.4)	47 (69.1)	41 (59.4)	19 (27.5)	55 (79.7)	1 (1.5)	46 (66.7)
Corticosteroids	54 (78.3)	58 (84.1)	41 (59.4)	59 (85.5)	60 (90.0)	47 (69.1)	1 (1.5)	16 (23.2)
Azathioprine	53 (76.8)	44 (63.8)	49 (71.0)	37 (53.6)	18 (26.1)	1 (1.5)	5 (7.3)	51 (79.9)
Mycophenolate	44 (63.8)	37 (53.6)	40 (58.0)	30 (43.5)	13(18.8)	2(2.9)	14 (20.2)	33(47.8)
Methotrexate	15 (21.7)	7 (10.1)	11 (15.9)	5 (7.3)	10 (14.5)	0 (0.0)	40 (58.0)	7 (10.1)
Cyclosporine	20 (30.0)	15 (21.7)	13 (18.8)	14 (20.3)	23 (33.3)	5 (7.3)	39 (56.5)	6 (8.7)
Tacrolimus	30 (43.5)	27 (39.1)	26 (37.7)	21 (30.4)	18 (26.1)	11 (15.9)	24 (34.8)	22 (31.9)
IVIG	54 (78.3)	50 (72.5)	21 (30.4)	53 (76.8)	5 (7.3)	57 (82.6)	3 (4.3)	48 (69.6)
Plasmapheresis	34 (49.3)	38 (55.1)	10 (14.5)	41 (59.4)	9 (13.0)	47 (68.1)	12 (17.4)	19 (27.5)
Rituximab	40 (58.0)	38 (55.1)	23 (33.3)	29 (42.0)	9 (13.0)	17 (24.6)	16 (21.2)	30 (43.5)
Cyclophosphamide	7 (10.1)	8 (11.6)	3 (4.3)	5 (7.3)	19 (27.5)	5 (7.3)	58 (84.1)	2 (2.9)

AChE: acetylcholinesterase; IVIG: intravenous immunoglobulins; MG: myasthenia gravis.

58 responses (84.1%). According to neurologists' experience, azathioprine exhibited the highest level of patient satisfaction, as evidenced by 51 responses (79.9%).

Management of double-seronegative patients (AChR and MuSK antibodies)

Most neurologists (70.3% in general neurology and 80.0% in neuromuscular neurology) managed double-seronegative MG patients the same way as seropositive patients. This percentage increased with the years of experience of the respondents: 66.7%, 69.2%, 81.8%, and 81.8% for physicians with <5 years, 5—10 years, 11—15 years, and 16—20 years of experience, respectively.

Unmet medical needs

Neurologists were asked to select the two most relevant unmet medical needs in MG management, from the following options: (*1*) drugs with better tolerance/fewer adverse effects; (*2*) reducing the use/doses of the drug; (*3*) fast-onset drugs; (*4*) biomarkers for disease progression; and (*5*) achieving a response in refractory patients (Fig. 2). Overall, achieving a response in patients with drug-resistant disease and the need for drugs with better tolerance or fewer adverse effects appear to be the most relevant unmet medical needs, identified by 55.1% and 53.6% of respondents, respectively. Among general neurologists, 59.5% considered there to be a need for new drugs with better tolerance and fewer adverse effects, and 45.9% considered it necessary to offer a solution to patients with drug-resistant disease. Additionally, 18.9% of general neurologists considered it important to reduce the use/doses of treatments. Neuromuscular neurologists, on the other hand, prioritized the need to achieve a response in patients with drug-resistant disease (66.7%) and to have drugs with better tolerance or fewer adverse effects (50.0%).

Discussion

MG management is a complex and challenging process that demands a multidisciplinary approach to cater to the unique needs of each patient. A comprehensive understanding of the current status is crucial in identifying areas for improvement and ensuring optimal patient care. This survey represents a preliminary study to better understand the status of MG management in Spain and identify the most relevant unmet medical needs.

The first description of MG in Spain dates from 1892,[19] and the most recent epidemiological studies in the Iberian Peninsula reported a substantial increase in its prevalence in the elderly population.[20] Early diagnosis by general practitioners and better access for elderly patients to specialized care are essential.[21] However, patient referral from primary care was relatively low in our study, with only 1.3% of patients at small hospitals being referred from primary care.

Treatment-related adverse effects and tolerability problems contribute to the disease burden, especially in refractory phenotypes. Neurologists reported that 30.4% of patients presented active symptoms, and 18.2% presented self-limiting symptoms. A large cross-sectional study including 1660 patients with MG in Germany showed that the disease burden includes economic and social aspects, as well as patients' emotional well-being. Moreover, 20% of patients with MG included in that study perceived no improvement in myasthenic symptoms after therapy. These results may be explained by lack of response to treatment or lack of access to experienced neurologists.[12]

Diagnosing MG in seronegative patients remains a challenge, particularly among those with double seronegativity

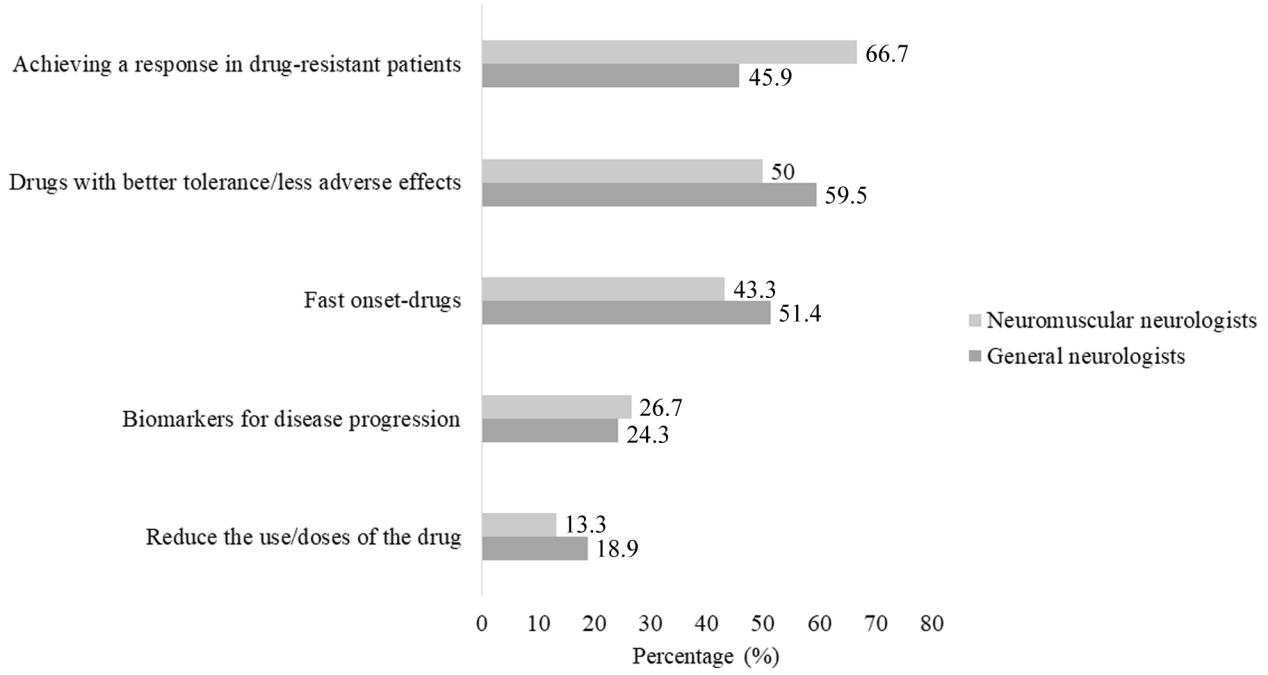

Figure 2 Unmet needs identified by each participant group. The graph demonstrates that 66.7% of the neuromuscular neurologists prioritized the need to achieve a response in patients with drug-resistant disease. On the other hand, the majority of general neurologists identified the development of new drugs with better tolerance or fewer adverse effects as an unmet need.

for anti-AChR and anti-MuSK antibodies. Additionally, certain patient populations, such as those with anti-MuSK MG, thymomatous MG, refractory MG, and pregnant women, need particular attention.[22] Both general and neuromuscular neurologists considered MG diagnosis to be somewhat challenging (2.9 and 2.5/5 respectively). A lack of antibody testing during MG diagnosis due to economic reasons was reported by 7 neurologists in our study. However, antibody detection is not only useful for diagnostic purposes, but also very important for immunophenotyping of patients to select the most appropriate therapy. For instance, MuSK-positive patients do not benefit from thymectomy,[23] and rituximab is particularly effective in this subgroup of patients when they are refractory to other therapies.[24] Therefore, accurate, timely diagnosis (using antibody testing) is crucial for organizing healthcare services and implementing preventive measures.[25,26]

In our study, thymectomy was performed in 34.3% of patients. Similar results were observed in an epidemiological study performed in the Spanish province of Ourense, where thymectomy was performed in 31.6% of cases.[27] MG is induced by thymoma in 10% of patients, and thymectomy should always be performed, if technically possible, in this group. Moreover, thymectomy is a treatment option for patients with MG and thymic hyperplasia.[28] Thymectomy for MG should only be performed when the patient is in a stable condition and it is deemed medically safe to perform this procedure, which may result in postoperative pain and limitations in respiratory function.[29] In the study by Al-Bulushi et al.,[30] the authors observed that, post-thymectomy, 21% of patients presented complete clinical remission, 76% presented significant clinical improvement, and 3% showed no apparent improvement in their clinical status.[30]

Wolfe et al.[23] conducted a randomized trial to compare extended trans-sternal thymectomy plus alternate-day prednisone against the latter treatment alone, in 126 patients. The results showed that patients undergoing thymectomy had a lower time-weighted average quantitative MG score over a 3-year period compared to those who received prednisone alone (6.15 vs 8.99; $P < .001$). Patients in the thymectomy group also had a lower average requirement for alternate-day prednisone. Moreover, fewer patients in the thymectomy group required immunosuppression with azathioprine or were hospitalized due to exacerbations.[23] In our study, at 3 years post-thymectomy, most patients are under some pharmacotherapy including immunosuppressants or corticosteroids. Pharmacotherapies included (*1*) AChE inhibitors, (*2*) immunosuppressants, and (*3*) immunomodulatory treatments. The sequences of different treatment options selected by the neurologists included in this study are in line with the international guidelines, and the clinical and immunological characteristics of each patient.[31] AChE inhibitors such as pyridostigmine constitute the most widely used symptomatic therapy. According to the experience of our study participants, AChE inhibitors had the greatest positive effect on the quality of life of patients with MG. In line with international recommendations,[29] respondents considered azathioprine as a first choice when immunosuppression was needed. Corticosteroids were considered the most effective treatment, but were also the therapy that caused the most adverse effects, according to respondents' clinical experience. These results are consistent with those reported in the literature: although the effectiveness of corticosteroids in MG is documented, one of the main weaknesses of the treatment is the fact that patients may experience symptom worsening after

corticosteroid treatment initiation (first 2 weeks), and time-dependent side effects.[29,32,33] In this study, rituximab was considered as the last option in a sequence of treatments, with a lower percentage of patients receiving this treatment (5.5% and 4.6% of the patients reported by general neurologists and neuromuscular neurologists, respectively). According to the International Consensus Guidance for Management of MG, rituximab should be considered as an early therapeutic option in patients with anti-MuSK MG who have an unsatisfactory response to initial immunotherapy.[29] The lower percentage of patients receiving treatment with plasmapheresis in this study can be explained by this treatment mainly being used for myasthenic crises, and the fact that plasma exchange is not available at all centers. Moreover, one of the disadvantages noted by some specialists is that plasmapheresis is excessively invasive to be used as a chronic treatment.[34] Cyclophosphamide was the least frequently used treatment among the neurologists that participated in this survey. Although this drug has shown effective results in inducing remission, some data suggest a lack of effectiveness in the long term,[35] and there is high risk of severe adverse effects. Some studies recommend long-term follow-up, alternative immunomodulation, and careful monitoring for adverse events when cyclophosphamide is used.[36]

Most of the participating neurologists followed the same therapeutic strategy for double-seronegative patients as for seronegative patients (70.3% in general neurology and 80.0% in neuromuscular neurology). Although seronegative patients represent around 10%—15% of all patients with MG, there are only very limited data on the clinical management and outcomes of these patients. Mergenthaler et al.[37] observed that, although disease crises in seronegative MG affect younger patients after a longer duration of the disease, crisis treatment efficacy and outcomes do not differ compared to patients with anti-AChR MG.[37]

According to the general and neuromuscular neurologists that participated in this study, the two most urgent unmet needs in MG management are the development of new drugs with fewer adverse effects and better tolerance (59.5% and 50.5%, respectively), and achieving a response in refractory patients (45.9% and 66.7%, respectively). General neurologists and neuromuscular neurologists have different areas of expertise and training, which may have led to differences in their opinions about the most urgent unmet needs in MG management. While their opinions may differ on this subject, their ultimate goal is the same: to provide the best possible care for their patients with MG.

This study has some important limitations. Firstly, the questionnaire was unevenly distributed nationwide to members of the SEN, and the sample size is relatively small. Thus, our results may not be representative of all neurologists treating MG in Spain. Furthermore, the numbers and percentages cited in this study are estimated by the respondents, and do not correspond to real data. For instance, whereas the number of new cases diagnosed annually was estimated at 890, the incidence of MG is 8—10 new cases/million population/year; therefore, in Spain we would expect around 470 new cases/year. Nevertheless, we estimated that there are around 110 neurologists treating patients with MG, and obtained answers from 69. Moreover, this is the first study to specifically analyze the situation of MG in Spain.

Conclusion

Due to the global prevalence of MG and its negative consequences for individuals and society, it seems necessary to take measures to achieve better therapies or to use supportive therapies to alleviate symptoms. The limitations associated with the diagnosis, such as the absence of a definitive diagnostic test and the overlap with other conditions, highlight the need for improvement in the field. Moreover, these results reinforce the importance of implementing new treatments that can effectively manage symptoms and improve outcomes for patients with MG.

CRediT authorship contribution statement

All authors participated in the planning and execution of the study. All participating authors have read and approved the paper as it is submitted here.

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Conflict of interest

Elena Cortés-Vicente has participated in advisory boards/consultation activities or as speaker for Argenx, UCB, Alexion, and Janssen. The other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version available at https://doi.org/10.1016/j.nrl.2025.501912.

References

1. Huijbers MG, Marx A, Plomp JJ, Le Panse R, Phillips WD. Advances in the understanding of disease mechanisms of autoimmune neuromuscular junction disorders.

Lancet Neurol. 2022;21:163—75, http://dx.doi.org/10.1016/S1474-4422(21)00357-4.
2. Verschuuren JJ, Palace J, Murai H, Tannemaat MR, Kaminski HJ, Bril V. Advances and ongoing research in the treatment of autoimmune neuromuscular junction disorders. Lancet Neurol. 2022;21:189—202, http://dx.doi.org/10.1016/S1474-4422(21)00463-4.
3. Sánchez-Tejerina D, Sotoca J, Llaurado A, López-Diego V, Juntas-Morales R, Salvado M. New targeted agents in myasthenia gravis and future therapeutic strategies. J Clin Med. 2022;11:6394, http://dx.doi.org/10.3390/jcm11216394.
4. Gilhus NE, Tzartos S, Evoli A, Palace J, Burns TM, Verschuuren JJGM. Myasthenia gravis. Nat Rev Dis Primers. 2019;5:30, http://dx.doi.org/10.1038/s41572-019-0079-y.
5. Boldingh MI, Dekker L, Maniaol AH, Brunborg C, Lipka AF, Niks EH, et al. An up-date on health-related quality of life in myasthenia gravis — results from population-based cohorts. Health Qual Life Outcomes. 2015;13:115, http://dx.doi.org/10.1186/s12955-015-0298-1.
6. Mantegazza R, Antozzi C. When myasthenia gravis is deemed refractory: clinical signposts and treatment strategies. Ther Adv Neurol Disord. 2018;11, http://dx.doi.org/10.1177/1756285617749134, 1756285617749134.
7. Wendell LC, Levine JM. Myasthenic crisis. Neurohospitalist. 2011;1:16—22, http://dx.doi.org/10.1177/1941875210382918.
8. Ciafaloni E. Myasthenia gravis and congenital myasthenic syndromes. Continuum (Minneap Minn). 2019;25:1767—84, http://dx.doi.org/10.1212/CON.0000000000000800.
9. Gotterer L, Li Y. Maintenance immunosuppression in myasthenia gravis. J Neurol Sci. 2016;369:294—302, http://dx.doi.org/10.1016/j.jns.2016.08.057.
10. Winter Y, Schepelmann K, Spottke AE, Claus D, Grothe C, chröder R, et al. Health-related quality of life in ALS, myasthenia gravis and facioscapulohumeral muscular dystrophy. J Neurol. 2010;257:1473—81, http://dx.doi.org/10.1007/s00415-010-5549-9.
11. Ariatti A, Stefani M, Miceli P, Benuzzi F, Galassi GAT Prognostic factors and health-related quality of life in ocular myasthenia gravis (OMG). Int J Neurosci. 2014;124:427—35, http://dx.doi.org/10.3109/00207454.2013.853664.
12. Lehnerer S, Jacobi J, Schilling R, Grittner U, Marbin D, Gerischer L, et al. Burden of disease in myasthenia gravis: taking the patient's perspective. J Neurol. 2022;269:3050—63, http://dx.doi.org/10.1007/s00415-021-10891-1.
13. Bacci ED, Coyne KS, Poon JL, Harris L, Boscoe ANAT Understanding side effects of therapy for myasthenia gravis and their impact on daily life. BMC Neurol. 2019;19:335, http://dx.doi.org/10.1186/s12883-019-1573-2.
14. Suh J, Goldstein JM, Nowak RJ. Clinical characteristics of refractory myasthenia gravis patients. Yale J Biol Med. 2013;86:255—60 [PMID: 23766745].
15. Rath J, Brunner I, Tomschik M, Zulehner G, Hilger E, Krenn M, et al. Frequency and clinical features of treatment-refractory myasthenia gravis. J Neurol. 2020;267:1004—11, http://dx.doi.org/10.1007/s00415-019-09667-5.
16. Cortés-Vicente E, Álvarez-Velasco R, Pla-Junca F, Rojas-Garcia R, Paradas C, Sevilla T, et al. Drug-refractory myasthenia gravis: clinical characteristics, treatments, and outcome. Ann Clin Transl Neurol. 2022;9:122—31, http://dx.doi.org/10.1002/acn3.51492.
17. Sánchez-Tejerina D, Sotoca J, Llaurado A, López-Diego V, Juntas-Morales R, Salvado MAT New targeted agents in myasthenia gravis and future therapeutic strategies. J Clin Med. 2022;11:6394, http://dx.doi.org/10.3390/jcm11216394.
18. Stein M, Hoffmann S, Gerischer L, Stascheit F, Legg D, Meisel A, et al. Myasthenia gravis — a retrospective analysis of e-mail inquiries made to a patient organisation and specialized center to uncover unmet needs from patients and caregivers. BMC Neurol. 2022;22:455, http://dx.doi.org/10.1186/s12883-022-02981-y.
19. Morales B, Maestre JF, Garcia Ruiz PJ. First description of myasthenia gravis in Spain. J Neurol Neurosurg Psychiatry. 1991;54:846, http://dx.doi.org/10.1136/jnnp.54.9.846.
20. García-Estévez DA, Fraga-Bau A, García-Sobrino T, Mederer-Hengstl S, Pardo-Fernández JAT Epidemiology of myasthenia gravis in the Iberian Peninsula and Latin America. Rev Neurol. 2023;76:59—68, http://dx.doi.org/10.33588/rn.7602.2021201.
21. Aragonès JM, Altimiras J, Roura P, Alonso F, Bufill E, Munmany A, et al. Prevalence of myasthenia gravis in the Catalan county of Osona. Neurologia. 2017;32:1—5, http://dx.doi.org/10.1016/j.nrl.2014.09.007.
22. Nguyen T, Phan CL, Supsupin E Jr, Sheikh KAT Therapeutic and diagnostic challenges in myasthenia gravis. Neurol Clin. 2020;38:577—90, http://dx.doi.org/10.1016/j.ncl.2020.03.005.
23. Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, et al. Randomized trial of thymectomy in myasthenia gravis. N Engl J Med. 2016;375:511—22, http://dx.doi.org/10.1056/NEJMoa1602489.
24. Díaz-Manera J, Martínez-Hernández E, Querol L, Klooster R, Rojas-García R, Suárez-Calvet X, et al. Long-lasting treatment effect of rituximab in MuSK myasthenia. Neurology. 2012;78:189—93, http://dx.doi.org/10.1212/WNL.0b013e3182407982.
25. Salari N, Fatahi B, Bartina Y, Kazeminia M, Fatahian R, Mohammadi P, et al. Global prevalence of myasthenia gravis and the effectiveness of common drugs in its treatment: a systematic review and meta-analysis. J Transl Med. 2021;19:516, http://dx.doi.org/10.1186/s12967-021-03185-7.
26. Mahic M, Bozorg A, Rudnik J, Zaremba P, Scowcroft AAT Healthcare resource use in myasthenia gravis: a US health claims analysis. Ther Adv Neurol Disord. 2023;16, http://dx.doi.org/10.1177/17562864221150327, 17562864221150327.
27. García Estévez DA, López Díaz LM, Pardo Parrado M, Pérez Lorenzo G, Sabbagh Casado NA, Ozaita Arteche G, et al. Epidemiology of myasthenia gravis in the province of Ourense (Galicia, Spain). Neurologia (Engl Ed). 2022, http://dx.doi.org/10.1016/j.nrleng.2020.06.013. S2173-5808(22)00013-X.
28. Gilhus NE, Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol. 2015;14:1023—36, http://dx.doi.org/10.1016/S1474-4422(15)00145-3.
29. Narayanaswami P, Sanders DB, Wolfe G, Benatar M, Cea G, Evoli A, et al. International consensus guidance for management of myasthenia gravis: 2020 update. Neurology. 2021;96:114—22, http://dx.doi.org/10.1212/WNL.0000000000011124.
30. Al-Bulushi A, Al Salmi I, Al Rahbi F, Farsi AA, Hannawi SAT The role of thymectomy in myasthenia gravis: a programmatic approach to thymectomy and perioperative management of myasthenia gravis. Asian J Surg. 2021;44:819—28, http://dx.doi.org/10.1016/j.asjsur.2020.12.013.
31. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, et al. International consensus guidance for management of myasthenia gravis: executive summary. Neurology. 2016;87:419—25, http://dx.doi.org/10.1212/WNL.0000000000002790.
32. Lotan I, Hellmann MA, Wilf-Yarkoni A, Steiner IAT Exacerbation of myasthenia gravis following corticosteroid treatment: what is the evidence? A systematic review. J Neurol. 2021;268:4573—86, http://dx.doi.org/10.1007/s00415-020-10264-0.
33. Pascuzzi RM, Coslett HB, Johns TR. Long-term corticosteroid treatment of myasthenia gravis: report of 116 patients. Ann Neurol. 1984;15:291—8, http://dx.doi.org/10.1002/ana.410150316.
34. Guptill JT, Oakley D, Kuchibhatla M, Guidon AC, Hobson-Webb LD, Massey JM, et al. A retrospective study of complications

of therapeutic plasma exchange in myasthenia. Muscle Nerve. 2013;47:170—6, http://dx.doi.org/10.1002/mus.23508.

35. Gomez-Figueroa E, Garcia-Trejo S, Bazan-Rodriguez L, Cervantes-Uribe R, Chac-Lezama G, López-Hernández JC, et al. Intravenous cyclophosphamide monthly pulses in refractory myasthenia gravis. J Neurol. 2020;267:674—8, http://dx.doi.org/10.1007/s00415-019-09622-4.
36. Nagappa M, Netravathi M, Taly AB, Sinha S, Bindu PS, Mahadevan AAT Long-term efficacy and limitations of cyclophosphamide in myasthenia gravis. J Clin Neurosci. 2014;21:1909—14, http://dx.doi.org/10.1016/j.jocn.2014.03.019.
37. Mergenthaler P, Stetefeld HR, Dohmen C, Kohler S, Schönenberger S, Bösel J, et al. Seronegative myasthenic crisis: a multicenter analysis. J Neurol. 2022;269:3904—11, http://dx.doi.org/10.1007/s00415-022-11023-z.