Clinical and therapeutic features of myasthenia gravis in adults based on age at onset

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Abstract

Objective

To describe the characteristics of patients with very-late-onset myasthenia gravis (MG).

Methods

This observational cross-sectional multicenter study was based on information in the neurologist-driven Spanish Registry of Neuromuscular Diseases (NMD-ES). All patients were >18 years of age at onset of MG and onset occurred between 2000 and 2016 in all cases. Patients were classified into 3 age subgroups: early-onset MG (age at onset <50 years), late-onset MG (onset ≥50 and <65 years), and very-late-onset MG (onset ≥65 years). Demographic, immunologic, clinical, and therapeutic data were reviewed.

Results

A total of 939 patients from 15 hospitals were included: 288 (30.7%) had early-onset MG, 227 (24.2%) late-onset MG, and 424 (45.2%) very-late-onset MG. The mean follow-up was 9.1 years (SD 4.3). Patients with late onset and very late onset were more frequently men ($p < 0.0001$). Compared to the early-onset and late-onset groups, in the very-late-onset group, the presence of anti-acetylcholine receptor (anti-AChR) antibodies ($p < 0.0001$) was higher and fewer patients had thymoma ($p < 0.0001$). Late-onset MG and very-late-onset MG groups more frequently had ocular MG, both at onset (<0.0001) and at maximal worsening ($p = 0.001$). Although the very-late-onset group presented more life-threatening events (Myasthenia Gravis Foundation of America IVB and V) at onset ($p = 0.002$), they required fewer drugs ($p < 0.0001$) and were less frequently drug-refractory ($p < 0.0001$).

Conclusions

Patients with MG are primarily ≥65 years of age with anti-AChR antibodies and no thymoma. Although patients with very-late-onset MG may present life-threatening events at onset, they achieve a good outcome with fewer immunosuppressants when diagnosed and treated properly.

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Glossary

AChR = acetylcholine receptor; **ICU** = intensive care unit; **MG** = myasthenia gravis; **MGFA** = Myasthenia Gravis Foundation of America; **MGFA-PIS** = Myasthenia Gravis Foundation of America postintervention status; **MuSK** = muscle-specific tyrosine kinase; **NMD-ES** = Spanish Registry of Neuromuscular Diseases; **SNMG** = seronegative myasthenia gravis.

Myasthenia gravis (MG) is an autoimmune disease produced by antibodies against postsynaptic antigens at the neuromuscular junction.^{1,2} It is a heterogeneous disorder.^{3,4} From an immunologic point of view, around 80% of patients with MG present antibodies against the acetylcholine receptor (AChR)^{5,6} and about 5% present antibodies against muscle-specific tyrosine kinase (MuSK).^{7,8} Around 15% present no antibodies against either AChR or MuSK and are known as seronegative (SNMG).^{9,10} Recently, new antibodies, such as anti-LRP4¹¹ and anti-Cortactin,^{12,13} have been described in SNMG. From a clinical point of view, MG differs among patients in terms of distribution of muscle weakness, presenting as either ocular or generalized MG,¹⁴ and in terms of severity, ranging from mild to severe or life-threatening.¹⁵ It also differs regarding thymus pathology, varying from normal to hyperplasia or thymoma,¹⁶ and regarding response to immunosuppressive and immunomodulatory therapies, with some patients becoming refractory to conventional drugs.^{17,18} Classifying patients in accordance with their clinical and immunologic characteristics allows a better understanding of the disease and helps to select the most appropriate treatment.^{19–21}

MG was initially considered a disorder in women under 40 years of age but in recent decades the incidence has increased in both men and women over 65.^{22–24} Patients are now generally classified into 2 subgroups according to age at onset: early-onset MG, when they are under 50 at disease onset, and late-onset MG, when they are aged 50 or older at onset.⁴ However, some studies have used other age cutoffs, making it difficult to compare results.^{25–27}

Several studies suggest that clinical characteristics differ between age groups. Early-onset MG seems more frequent among women with thymic hyperplasia and high titers of anti-AChR antibodies,²⁸ while late-onset MG has been associated with the presence of thymoma and more severe forms of the disease.²⁹ It has also been observed that positive anti-AChR antibodies and ocular forms of the disease are more frequent in late-onset patients and that the therapeutic management of this group is more complex because of a higher frequency of comorbidities³⁰ and drug side effects.³¹ However, systematic studies are lacking.

The aim of our study was to describe clinical, immunologic, and therapeutic characteristics in a subgroup of patients with very-late-onset MG, defined as patients with onset at 65 years or older, and compare them to the early-onset and late-onset MG subgroups. For this purpose, we used the data from the nationwide neurologist-driven Spanish Registry of Neuromuscular Diseases (NMD-ES).

Methods

Data source: NMD-ES project

The MG registry was founded in 2010 as part of NMD-ES and designed in accordance with current Spanish legislation on biomedical research and data protection. Neurologists from 30 neuromuscular units at university hospitals in Spain participate in the collection of MG-specific data. The Registry includes 60 items concerning demographic, clinical, immunologic, and therapeutic data. Follow-up information is updated annually and whenever a significant clinical event occurs. The Registry is reviewed at least once a year to ensure the quality of the data collected. Data from the Registry have been used in a previous publication.¹⁵

Patients and clinical evaluation

In this observational cross-sectional multicenter study, we selected all patients in the MG registry who had onset of MG between January 1, 2000, and December 31, 2016. Patients with onset <18 years of age were not included because they were considered to have juvenile autoimmune MG. We also excluded patients lost to follow-up and those for whom relevant information was missing. We classified patients into 3 age subgroups: early-onset MG, when they were younger than 50 years at onset; late-onset MG, when they were 50–64 years of age at onset; and very-late-onset MG, when they were 65 years or older at onset. This third group was established based on epidemiologic data showing that the incidence of MG has increased in this group of patients in our media.^{22,23} Follow-up ended on December 31, 2018.

We analyzed the following variables: demographic characteristics (sex, age at onset, date of diagnosis); AChR and MuSK antibody positivity and titer at onset; severity and distribution of muscle weakness according to the Myasthenia Gravis Foundation of America (MGFA) clinical classification³² at onset and at maximal worsening; frequency of life-threatening events, defined as MGFA IVB and V, at onset; frequency of myasthenic crises and days in the intensive care unit (ICU) to achieve weaning from mechanical ventilation; generalization, defined as patients with a focal ocular form of the disease at onset (MGFA I) but generalized (MGFA II or higher) afterwards; mortality and causes of death; thymoma, defined by pathologic study in patients undergoing thymectomy and by thoracic CT in the others; treatment required and frequency of drug side effects; clinical outcome according to the MGFA postintervention status (MGFA-PIS)³²; frequency of refractory MG, defined as MGFA-PIS unchanged or worse after

Figure 1 Flowchart shows patients included in the study

MG = myasthenia gravis.

steroids and at least 2 other immunosuppressive therapies, according to previous definition¹⁷; diagnostic delay, defined as the difference between the date of diagnosis and the date of onset; and follow-up time, defined as the difference between the follow-up deadline or date of death and the date of diagnosis.

Standard protocol approvals, registrations, and patient consents

All participating centers obtained approval to participate from their corresponding ethics committees and all patients signed an informed consent form.

Statistical analysis

A descriptive data analysis was performed. The frequencies of symptoms are reported as percentages. Demographic characteristics are reported as means and SD. Differences in baseline characteristics between patient subgroups were evaluated using the χ^2 test and Fisher exact test to compare categorical variables, and analysis of variance or the Mann-Whitney U test to compare quantitative variables. A significant difference was defined as $p < 0.05$. Missing data were dropped as they were less than 5% of the sample for the relevant variables. Statistically significant variables were analyzed within each sex group. Data analysis was carried out using the STATA 13 software for Windows (StataCorp LP, College Station, TX).

Data availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Results

At the time of the study, the MG Registry included 1,510 patients. Of these, 1,178 patients were diagnosed with MG

Figure 2 Percentage distribution of myasthenia gravis (MG) cases by sex and age at diagnosis grouped in decades

Table 1 Comparison of clinical features of patients with early-onset, late-onset, and very-late-onset myasthenia gravis (MG) and *p* values from statistical analysis

	Early-onset MG (≥18 to <50) (n = 288)	Late-onset MG (≥50 to <65) (n = 227)	Very-late-onset MG (≥65) (n = 424)	<i>p</i> Value
Sex, male, n (%)	91 (31.6)	146 (64.3)	259 (61.1)	<0.0001
Diagnostic delay, y, mean (SD)	1.1 (1.3) (n = 275)	1.0 (1.2) (n = 218)	0.9 (1.2) (n = 395)	0.0573
Antibodies, n (%)	AChR 223 (77.4)	AChR 182 (80.2)	AChR 394 (92.9)	<0.0001 ^a
	MuSK 12 (4.2)	MuSK 9 (4.0)	MuSK 4 (0.9)	
	SNMG 52 (18.1)	SNMG 36 (15.9)	SNMG 25 (5.9)	
	AChR + MuSK 1 (0.3)	AChR + MuSK 0	AChR + MuSK 1 (0.2)	
Antibodies titer at onset, mean (SD)				
AChR	165.8 (640.9) (n = 203)	61.9 (240.5) (n = 172)	29.5 (48.1) (n = 372)	0.0554
MuSK	39.5 (69.1) (n = 12)	16.0 (18.4) (n = 8)	25.9 (28.3) (n = 4)	0.5866
Ocular onset, n (%)	86 (31.3) (n = 275)	108 (48.6) (n = 222)	180 (43.0) (n = 419)	<0.0001
Bulbar onset, n (%)	108 (39.3) (n = 275)	72 (32.4) (n = 222)	180 (43.0) (n = 419)	0.034
Life-threatening event at onset, n (%)	16 (5.8) (n = 275)	7 (3.2) (n = 222)	44 (10.5) (n = 419)	0.002 ^a
Myasthenic crisis, n (%)	22 (8.2) (n = 267)	13 (6.0) (n = 215)	31 (7.7) (n = 402)	0.640
At onset, n (%)	7 (2.5) (n = 275)	3 (1.4) (n = 222)	14 (3.3) (n = 419)	0.323
Mean days in ICU (SD)	30.6 (39.0) (n = 17)	20.4 (23.1) (n = 12)	11.5 (8.6) (n = 28)	0.1282
MGFA stage at onset				<0.0001
I	86	108	180	
IIA	61	32	45	
IIB	61	51	91	
IIIA	19	7	13	
IIIB	31	14	45	
IVA	1	3	1	
IVB	9	4	30	
V	7	3	14	
MGFA stage at maximal worsening				<0.0001
I	50	69	121	
IIA	50	30	32	
IIB	43	44	69	
IIIA	35	11	31	
IIIB	45	31	77	
IVA	7	6	4	
IVB	15	11	37	
V	22	13	31	
Generalization, n (%)	32 (40) (n = 80)	35 (34) (n = 103)	47 (28.3) (n = 166)	0.177
Thymoma, n (%)	65 (23.1) (n = 281)	36 (16) (n = 225)	22 (5.3) (n = 415)	<0.0001 ^a
Refractory MG, n %	62 (21.5)	31 (13.7)	20 (4.7)	<0.0001 ^a
Treatment required, n %				<0.0001

Continued

Table 1 Comparison of clinical features of patients with early-onset, late-onset, and very-late-onset myasthenia gravis (MG) and *p* values from statistical analysis (*continued*)

	Early-onset MG (≥18 to <50) (n = 288)	Late-onset MG (≥50 to <65) (n = 227)	Very-late-onset MG (≥65) (n = 424)	<i>p</i> Value
No IS therapy	81 (28.1)	73 (32.2)	117 (27.6)	
Steroids	61 (21.2)	50 (22.0)	118 (27.8)	
Steroids +1 IS	65 (22.6)	61 (26.9)	129 (30.4)	
1 IS	15 (5.2)	12 (5.3)	35 (8.3)	
Steroids + ≥2 IS	62 (21.5)	31 (13.7)	20 (4.7)	
2 IS	4 (1.4)	0	5 (1.2)	
Deceased, n (%)	9 (3.1)	14 (6.2)	91 (21.5)	<0.0001 ^a
Causes of death				0.357
MG crisis	0	1	2	
Thymoma	1	1	1	
Infection	2	3	19	
Cancer	1	3	17	
Nonrelated	1	5	32	
Unknown	4	1	20	

Abbreviations: AChR = acetylcholine receptor; ICU = intensive care unit; IS = immunosuppressant; MGFA = Myasthenia Gravis Foundation of America; MuSK = muscle-specific tyrosine kinase; SNMG = seronegative myasthenia gravis.

^aSignificantly different in the very-late-onset group compared to the early-onset and late-onset MG groups.

between January 1, 2000, and December 31, 2016. Twenty-two patients were excluded because they were younger than 18 years at onset and 217 patients were excluded because relevant information was lacking. A total of 939 patients from 15 hospitals were therefore included (figure 1). Mean age at onset was 57.9 years (SD 18.2), 52.8% were men, 799 (85.1%) were anti-AChR-positive, 25 (2.7%) were anti-MuSK-positive, 113 (12%) had SNMG, and 2 (0.2%) were anti-AChR and anti-MuSK double-positive. A total of 123 (13.4%) presented a thymoma and 113 (12%) were drug-resistant. A total of 288 patients (30.7%) were classified as early-onset MG, 227 patients (24.2%) as late-onset MG, and 424 (45.2%) as very-late-onset MG (figure 1). Figure 2 shows the distribution of the patients according to sex and age, grouped in decades, at diagnosis.

Table 1 shows clinical data about the patients in the 3 subgroups. The frequency of men was higher in the late-onset MG and very-late-onset MG groups than in the early-onset MG group ($p < 0.0001$). Antibodies against AChR ($p < 0.0001$) and no thymoma ($p < 0.0001$) were more frequent in the very-late-onset MG group. Patients with very-late-onset MG also presented more life-threatening events (IVB or V) at onset ($p = 0.002$) (figure 3A). Late-onset MG and very-late-onset MG groups more frequently had ocular MG, both at onset (<0.0001) and at maximal worsening ($p = 0.001$). No differences were observed among the 3 age groups regarding generalization frequency ($p = 0.177$) or

mean diagnostic delay ($p = 0.057$). Although this did not reach statistical significance, patients with very-late-onset MG with myasthenic crises spent fewer days in the ICU to reach weaning ($p = 0.128$) than patients with early-onset MG and patients with late-onset MG. Patients with very-late-onset MG also required fewer drugs for disease control ($p < 0.0001$) and showed a lower frequency of drug resistance ($p < 0.0001$). The frequency of drug side effects with mycophenolate was higher in the very-late-onset MG group ($p = 0.031$) but no differences were observed for the other drugs (table 2). Mycophenolate side effects were recorded in 6 patients: 1 early-onset patient and 5 very-late-onset patients. The early-onset patient presented severe abdominal pain when treated with mycophenolate mofetil. One of the very-late-onset patients had a pulmonary thromboembolism while receiving treatment with mycophenolate sodium. The other 4 very-late-onset patients were receiving mycophenolate mofetil and the side effects were insomnia and muscle pain in 1 and a cutaneous rash, cellulitis, and herpes zoster L4, respectively, in the other 3. No differences were found between groups in MGFA-PIS at the last visit ($p = 0.165$) (figure 3B). Statistically significant variables analyzed to determine differences within each sex subgroup (table 3) showed no significant differences.

Patients were followed for a mean of 9.1 years (SD 4.3). During this time, 114 patients died. Mortality was higher in the very-late-onset MG group ($p < 0.0001$) but there were

Figure 3 Clinical classification of patients with generalized myasthenia gravis (MG) at onset and after treatment

no differences between groups in terms of causes of death ($p = 0.357$). Three patients (2.6%) died because of an MG crisis: 2 patients with very-late-onset MG and 1 patient with late-onset MG. Through a living will, 1 of the patients with very-late-onset MG explicitly stated not wanting orotracheal intubation, so no exhaustive treatment was given, and the other had multiorgan failure as a complication. The patient with late-onset MG had a severe MG crisis triggered by nivolumab treatment for lung metastasis from a parotid carcinoma. The cause of death was recorded as complications related to thymoma in 3 patients (2.6%), infectious

complications in 24 (21.1%), cancer in 21 (18.4%), and other causes (such as heart disease, stroke, or trauma) in 38 (33.3%). The cause of death was not recorded in 25 patients (21.9%) (table 1).

Discussion

In our series of patients, MG was more frequent in patients with very-late-onset disease than in the other groups. Furthermore, most of these patients were men without

Table 2 Frequency of side effects of immunosuppressive and immunomodulatory therapies by age group

	Early-onset MG (n = 288)	Late-onset MG (n = 227)	Very-late-onset MG (n = 424)	p Value
Steroids (n = 597)	2 (1.1) (188, 65.3)	9 (6.3) (142, 62.6)	6 (2.2) (267, 63)	0.013
Azathioprine (n = 315)	8 (7.6) (105, 36.5)	9 (12.9) (70, 30.8)	22 (15.7) (140, 33)	0.162
Mycophenolate (n = 129)	1 (1.9) (54, 18.8)	0 (0) (31, 13.7)	5 (11.4) (44, 10.4)	0.031
Cyclosporine (n = 84)	9 (22.5) (40, 13.9)	4 (16) (25, 11)	0 (0) (19, 4.5)	0.061
Rituximab (n = 35)	0 (20, 6.9)	0 (9, 4)	0 (6, 1.4)	
Tacrolimus (n = 48)	3 (10.7) (28, 9.7)	3 (25) (12, 5.3)	1 (12.5) (8, 1.9)	0.461
Methotrexate (n = 7)	0 (5, 1.7)	0 (1, 0.4)	0 (1, 0.2)	
Cyclophosphamide (n = 8)	0 (5, 1.7)	0 (3, 1.3)	0	
IV immunoglobulin (n = 239)	3 (3.2) (94, 32.6)	1 (1.9) (54, 23.8)	1 (1.1) (91, 21.5)	0.604

Abbreviation: MG = myasthenia gravis.
Values are n (%) (n, % patients treated).

thymoma and with anti-AChR-positive antibodies. Although a higher percentage of patients in this subgroup presented a life-threatening event at onset, they required fewer

maintenance medications and showed less drug resistance. Interestingly, these patients had a shorter time to weaning in the ICU after a myasthenic crisis. This finding was not

Table 3 Analysis of statistically significant variables within each sex subgroup, comparing early-onset, late-onset, and very-late-onset myasthenia gravis (MG) groups and p values from statistical analysis

	Early-onset MG (n = 288)		Late-onset MG (n = 227)		Very-late-onset MG (n = 424)		
	Females (n = 197)	Male (n = 91)	Females (n = 81)	Male (n = 146)	Females (n = 165)	Male (n = 259)	<i>p</i> Value
Antibodies							
AChR	158 (80.2)	65 (71.4)	55 (67.9)	127 (87)	149 (90.3)	245 (94.6)	♀ 0.002
MuSK	9 (4.6)	3 (3.3)	8 (9.9)	1 (0.7)	4 (2.4)	0	♂ <0.0001
SNMG	29 (14.7)	23 (25.3)	18 (22.2)	18 (12.3)	12 (7.3)	13 (5)	
AChR + MuSK	1 (0.5)	0	0	0	0	1 (0.4)	
Thymoma	38 (19.8) (n = 192)	27 (30.3) (n = 89)	17 (21.5) (n = 79)	19 (13) (n = 146)	14 (8.8) (n = 160)	8 (3.1) (n = 255)	♀ 0.006 ♂ <0.0001
Life-threatening event at onset	13 (7) (n = 187)	3 (3.4) (n = 88)	2 (2.5) (n = 80)	5 (3.5) (n = 142)	21 (13) (n = 161)	23 (8.9) (n = 258)	♀ 0.013 ♂ 0.049
Refractory MG	47 (23.9)	15 (16.5)	14 (17.3)	17 (11.6)	14 (8.5)	6 (2.3)	♀ 0.001 ♂ <0.0001
Treatment required							
No IS	63 (32)	18 (19.8)	30 (37)	43 (29.5)	46 (27.9)	71 (27.4)	♀ 0.001
Steroids	31 (15.7)	30 (33)	10 (12.3)	40 (27.4)	48 (29.1)	70 (27)	♂ 0.001
Steroids+1 IS	42 (21.3)	23 (25.3)	24 (29.6)	37 (25.3)	39 (23.6)	90 (34.7)	
1 IS	10 (5.1)	5 (5.5)	3 (3.7)	9 (6.2)	14 (8.5)	21 (8.1)	
Steroids + ≥2 IS	47 (23.9)	15 (16.5)	14 (17.3)	17 (11.6)	14 (8.5)	6 (2.3)	
2 IS	4 (2)	0	0	0	4 (2.4)	1 (0.4)	

Abbreviations: AChR = acetylcholine receptor; IS = immunosuppressant; MuSK = muscle-specific tyrosine kinase; SNMG = seronegative myasthenia gravis. Values are n (%).

statistically significant, most likely due to the low number of patients who presented a myasthenic crisis. Another difference of note was that patients with very-late-onset MG had more side effects when treated with mycophenolate mofetil than did patients with late-onset and patients with early-onset MG. This difference was not observed with other drugs.

The highest percentage of patients in the MG registry corresponded to those over 65 years of age. This might be due to the increasing life expectancy and the improved detection of MG in this previously underdiagnosed group,³³ but it could also be associated with an increased susceptibility to autoimmunity in the elderly. The immune system undergoes a series of changes during aging, a process known as immunosenescence or immune dysregulation. Essentially, this process includes 3 events: (1) a reduction in immune response; (2) an increase in the inflammatory background; and (3) a higher production of autoantibodies.³⁴ It is a system-wide process involving both the innate and the adaptive system and can result in the selection of a more self-reactive repertoire and the conversion of self-reactive naive T cells into memory-like cells.³⁵ Our results indicate that most patients with very-late-onset MG share a common phenotype that is clearly different from that in the early-onset and late-onset MG age groups. This suggests differences between groups in the pathogenic processes.

Despite signs of increased autoimmunity with age, autoimmune diseases are usually mild in the elderly and can be controlled with the right treatment. In our study, we observed that patients with very-late-onset MG had a better outcome than patients with early-onset and patients with late-onset MG in terms of drug requirements, drug refractivity, and mean time to achieve weaning when they present a myasthenic crisis, even though a significant percentage of these patients had a life-threatening event at onset. A possible explanation for this is the expansion of many protective regulatory mechanisms in the elderly, such as the higher production of peripheral T-regulatory cells.³⁶

We recommend continuing treatment in senior patients who present a myasthenic crisis or life-threatening events if they had a previously good quality of life because our results show they reached weaning faster than younger patients and usually responded favorably to conventional treatments.

Previous studies have suggested that patients with late-onset MG, defined as onset later than 50 years, are more frequently men, with antibodies against AChR and ocular forms of the disease as the main phenotype.³⁰ Other studies have indicated that patients with late-onset MG are more likely to have a thymoma and that their disease is more severe and more difficult to treat.^{29–31} Our findings extend these observations and modify current knowledge regarding MG in seniors. We found that thymoma is not frequent

in the very-late-onset group and that patients respond favorably to treatment, even if their onset is severe. Moreover, we endorse classifying patients into 3 age groups because early-onset MG and very-late-onset MG show clearly different phenotypes, and the late-onset MG group shows an intermediate phenotype between the two. In addition, the sample size in our study is considerably larger than that in former published works and with its registry-based multicenter design, we were able to review many variables from patients from many regions of the country.

The main limitation of our study is that the sample may be biased in terms of disease severity as data collected in the MG Registry were mainly recorded at tertiary university hospitals. Criteria based on age for patient referral to tertiary hospitals could also lead to sampling bias. Very elderly patients, for instance, may not be referred to tertiary hospitals for further treatment in a specialized unit. However, the use of standardized, updated information from a large number of patients with MG and systematically recorded by neurologists specialized in neuromuscular disorders allows systematic and structured research.³⁷ Moreover, the design of the MG Registry enabled the quality of the data to be monitored and validated before any analysis was conducted.

Patients with very-late-onset MG are mainly men who have antibodies against AChR and no presence of thymoma. MG diagnosis should be considered in seniors with suggestive symptoms as they usually achieve a good outcome if diagnosed and treated appropriately even if their onset is severe and shows bulbar signs or myasthenia crisis.

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Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

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