Neurology Asia 2026; 31(2) : 585 – 596

Distinctive features and outcome-associated factors in generalized myasthenia gravis: A comparison of bulbar- and extremity-predominant subtypes

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Abstract

Background: Risk factors for the conversion of ocular-onset myasthenia gravis (MG) to generalized MG (GMG) have been studied, but the characteristics of initially generalized onset MG subtypes remain unclear. This study aimed to identify distinguishing features of GMG by classifying patients into bulbar-predominant (GMG-B) and extremity-predominant (GMG-A) subgroups, and to evaluate prognostic factors associated with poor treatment response. *Methods:* A retrospective analysis was conducted on patients between January 2009 and January 2024 who met predefined inclusion and exclusion criteria. Demographic, clinical, electrophysiological, laboratory, and treatment data were collected. Statistical analyses were performed to identify features of GMG subtype and markers of poor treatment response. *Results:* A total of 118 patients were included (58 GMG-A, 60 GMG-B). GMG-B was associated with older age at onset, late-onset MG (>50 years), and male gender, whereas GMG-A was more common in early-onset MG (<50 years), female patients, and those with thymic pathology. MuSK antibody positivity strongly predicted poor treatment response, while AChR antibody positivity was associated with favorable outcomes.
Conclusion: This study is the first to examine distinctive features of GMG subtypes without preceding ocular symptoms and prognostic factors. Demographic variables (age at onset, onset category, and gender) and thymic pathology were significant predictors of GMG subtypes. Among laboratory markers, MuSK antibody positivity was the only independent predictor of poor treatment response.

Keywords: Generalized myasthenia gravis, bulbar predominant, extremity predominant, clinical features, prognostic factors

INTRODUCTION

Myasthenia gravis (MG) is an antibody-mediated autoimmune disorder that affects the neuromuscular junction and is characterized by fluctuating, fatigable muscle weakness.[1-3] Clinically, MG is classified into two main forms: ocular MG (OMG) and generalized MG (GMG), with approximately 85% of patients developing generalized symptoms.[1,3] Although most patients initially present with ocular symptoms, between 12% and 80% of these individuals will progress to generalized disease. Conversely, 15–20% of patients present with generalized symptoms at disease onset.[3-5] While prognostic factors for conversion from ocular MG have been studied, little is known about patients with *de novo* generalized onset. It is well established that approximately 50–60% of patients with OMG will convert to GMG within the first 24 months.[6] The Myasthenia Gravis Foundation of America (MGFA) Clinical Classification is commonly used to categorize disease severity and distribution. Patients were categorised according to the MGFA clinical classification subclassifications (A: limb/axial predominance; B: bulbar predominance).[7] Patients with GMG may exhibit both bulbar and limb muscle involvement. In some cases, limb weakness predominates, whereas in others, bulbar symptoms are more prominent. Based

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Date of Submission: 13 November 2025; Date of Acceptance: 6 February 2026

https://doi.org/10.54029/2026vwd

on symptom predominance, GMG can be further categorized into extremity-predominant (GMG-A) and bulbar-predominant (GMG-B) subtypes.[7]

Several risk factors have been identified for the generalization of OMG.[8-11] However, there is a lack of data concerning the factors specifically associated with the development of GMG-B or GMG-A subtypes in patients with generalized-onset MG. Clinical parameters such as MGFA classification, attack frequency, hospitalization rates, and response to immunosuppressive therapy are commonly used to assess disease progression in GMG. Nevertheless, to date, no studies have directly compared prognostic factors associated with disease worsening in patients with bulbar-onset versus extremity-onset forms of MG.

This study aimed to characterize phenotypic profiles and factors associated with treatment response in a strictly defined cohort of patients with generalized-onset myasthenia gravis. Given the considerable variability in generalization timelines and the distinct pathobiological and clinical course associated with ocular-onset MG, these patients were excluded to minimize heterogeneity and to accurately capture the natural history of primary generalized disease. In this context, the analysis focused on determinants specifically associated with the GMG-B or GMG-A subgroups.

METHODS

This retrospective cross-sectional study included patients diagnosed with GMG who were followed for a minimum of two years between January 2009 and January 2024 at the Neuromuscular Outpatient Clinic of Manisa Celal Bayar University.

The study protocol was approved by the Manisa Celal Bayar University Medical School Ethics Committee (Reference No: 20.478.486/827) and conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Informed consent for the future use of medical data was obtained from all patients during their diagnostic evaluation, examination, and treatment at our institution.

The diagnosis of myasthenia gravis was primarily established based on clinical presentation, supplemented by confirmatory diagnostic modalities. Presence of at least two of the following three criteria was required for the diagnosis: (1) typical clinical features of fatigable weakness, (2) serological positivity for AChR or MuSK antibodies, and (3) abnormal electrophysiological findings on RNS or SFEMG. Clinical improvement with pyridostigmine was considered supportive but not mandatory for diagnosis.

A summary of these findings is provided below.

1. A typical clinical history of fatigable, fluctuating muscle weakness (for GMG-B: predominantly dysphagia, dysphonia, or slurred speech, mild lower proximal extremity weakness symptoms might be seen; for GMG-A: predominantly proximal limb weakness, mild bulbar symptoms might be seen) with clinical deterioration during the day and a positive fatigue test.
2. Positive serum antibody levels for AChR or MUSK (for AChR-Ab: titer > 0.5 nmol/L; for MUSK-Ab: titer > 0.01 nmol/L).
3. Abnormal RNS (recorded from the trapezius) or Single-fiber electromyography (SFEMG) (recorded from the orbicularis oculi; RNS was considered positive if a decremental response of ≥10% was observed between the first and fourth or fifth compound muscle action potential. SFEMG was considered positive if increased jitter was detected in more than 10% of examined fiber pairs or if blocking was present, in accordance with established diagnostic criteria.

Inclusion criteria for patients in the study are (1) being diagnosed with GMG according to the above diagnostic criteria, (2) having sufficient disease-related data in the database, (3) presentation with generalized symptoms showing either a predominance of extremity or bulbar involvement.

The exclusion criteria were (1) secondary generalization after ocular onset, (2) anti-titin positivity (Patients with anti-titin antibody positivity were excluded due to the very limited number of such cases and the potential confounding effect of a suspected paraneoplastic syndrome.) (3) additional myopathy, and (4) presence of another underlying neurodegenerative disorders that could cause generalized weakness. Patients with secondary generalization after ocular onset were excluded to avoid heterogeneity arising from the variable

conversion timeline and immunopathogenic differences between ocular and generalized forms.

Patients were classified according to the MGFA clinical classification into two groups: bulbar-predominant generalized myasthenia gravis (GMG-B) and extremity-predominant generalized myasthenia gravis (GMG-A) based on the predominant pattern of muscle involvement at disease onset, in accordance with the MGFA clinical classification. Patients presenting with predominantly bulbar or respiratory involvement corresponding to MGFA classes IIb, IIIb, or IVb were classified as GMG-B, whereas those presenting with predominantly limb or axial muscle weakness corresponding to MGFA classes IIa, IIIa, or IVa were classified as GMG-A. In patients presenting with myasthenic crisis (MGFA class V), subtype classification was determined based on the predominant clinical phenotype preceding the development of respiratory failure. Patients with clear bulbar dysfunction (e.g., dysphagia, dysarthria, or impaired airway protection) were classified as GMG-B, whereas patients in whom respiratory failure developed in the context of generalized or limb-predominant weakness without prominent bulbar involvement were classified as GMG-A. Patients without a clearly predominant pattern of bulbar or limb involvement at disease onset were not included, in order to maintain distinct and reproducible subtype definitions. Demographic factors evaluated included age, age at disease onset (early onset as defined as < 50 years old and late onset as defined as > 50 years old), and sex.

Laboratory and imaging assessments included the presence of AChR antibodies, MuSK antibodies, thyroid autoantibodies, thyroid function tests, RNS, and thymic pathology detected by imaging. Clinical characteristics such as concomitant autoimmune and systemic diseases were also recorded.

Demographic, laboratory, and imaging data were analyzed to identify features associated with being in the GMG-B or GMG-A subgroups. Disease severity was assessed using the MGFA clinical classification score at onset and the MGFA-PIS score following treatment. Treatments administered included Cholinesterase inhibitors primarily pyridostigmine, corticosteroids, azathioprine, mycophenolate mofetil, rituximab, intravenous immunoglobulin and plasmapheresis. IVIG and PLEX were primarily administered as rescue therapy during myasthenic crises or episodes of clinically significant deterioration. In a smaller subset of patients, IVIG was also used in the context of insufficient response to ongoing immunosuppressive therapy.

MGFA-PIS scores were routinely evaluated every six months. Patients were followed for a minimum of two years. At each follow-up visit, patients underwent a structured clinical assessment, including evaluation of bulbar symptoms (such as dysphagia, dysarthria, and nasal speech), limb and axial muscle strength, and respiratory function. Simple bedside measures, including single-breath counting, were routinely performed, and neuromuscular symptoms were systematically documented to guide clinical decision-making and treatment adjustments. Patients who experienced clinical worsening frequently underwent treatment intensification, including higher corticosteroid doses or additional immunosuppressive or rescue therapies. In our cohort, treatment was individualised according to disease severity and clinical course, reflecting real-world practice. Treatment response was not assessed based on specific drug regimens or dose changes, but instead categorised using the MGFA-PIS, which captures the net, sustained clinical effect of all therapeutic interventions. Immunosuppressive treatments, including corticosteroids and steroid-sparing agents, were analysed across two predefined time intervals: 0–6 months and 6–24 months after diagnosis. This stratification was chosen to reflect distinct phases of treatment, with the first 6 months representing the induction and early response period, during which treatment escalation, dose adjustments, or early tapering decisions are commonly made, and the subsequent 6–24 months reflecting longer-term maintenance therapy. Shorter treatment duration within the initial 0–6 month period therefore did not uniformly indicate clinical improvement but could also reflect early treatment escalation or modification due to insufficient response or adverse effects.

Treatment outcome was assessed using the Myasthenia Gravis Foundation of America Postintervention Status (MGFA-PIS) classification at the last available follow-up, with a minimum follow-up duration of 24 months in order to capture sustained clinical status rather than transient fluctuations. MGFA-PIS status was evaluated at regular follow-up visits, and the final outcome was determined based on the assessment performed at or beyond 24 months

after diagnosis. Given that all patients presented with a baseline status of MM-2 or MM-3 (minimal symptoms while receiving immunosuppressive treatment; MM-3 indicates prior thymectomy) or worse, the 'change in status' component of the MGFA-PIS was utilized to categorize treatment responses into three groups: improved, unchanged, or worsened.

Improvement was defined as achieving a better MGFA-PIS category compared with baseline, including minimal manifestations (MM), pharmacologic remission (PR), or complete stable remission (CSR). Lack of improvement was defined as persistence in the same MGFA-PIS category without improvement. Worsening was defined as transition to a worse MGFA-PIS category during follow-up. For analytical purposes, a poor outcome was defined as either lack of improvement or worsening according to MGFA-PIS classification. The terms 'improvement' and 'general treatment response' reported in Table 1 were defined according to MGFA-PIS–based outcome categories, as described above. Improvement reflects achievement of a better MGFA-PIS status compared with baseline, whereas general treatment response was determined based on MGFA-PIS assessment performed at or beyond 24 months of follow-up. Patients who were experiencing a myasthenic crisis at the time of the final outcome assessment were not classified according to MGFA-PIS at that visit; outcome evaluation was deferred until clinical stabilisation was achieved. Predictors of treatment response were also evaluated.

Statistical analysis was performed using SPSS 25 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics are presented as mean and standard deviation for parametric variables, and median (min-max) for non-parametric variables. The Independent Sample t-test was employed to compare numeric variables. Categorical variables were compared using the Chi-square test. For comparisons involving three groups, one-way analysis of variance (ANOVA) was used for normally distributed variables, and the Kruskal–Wallis test was applied for non-normally distributed variables. Post hoc analyses were performed when appropriate. Potential risk factors for GMG subtypes were further evaluated using odds ratios (ORs) with 95% confidence intervals (CIs) in univariate and multivariate analysis. Logistic regression analysis was applied to assess factors associated with outcomes. Significance was set at $p < 0.05$.

RESULTS

From January 2009 to January 2024, 655 patients had been diagnosed with MG in the Neurology department of our tertiary hospital. According to the inclusion and exclusion criteria 118 patients (71 women, 47 men, 18% of all patients) with generalized onset were included in the study. Flowchart of the study is presented in Figure 1. The mean age was 55.4±16.2 years (range 20-88). The follow-up period was a minimum of 24 months, extending to 180 months (mean±SD: 58.02±47.67 months).

Patients of the GMG-B group were older than the patients of the GMG-A group (59.4±16.9 years versus 51.5±17.6 years (p=0.011). In addition, the age of disease onset was higher in the GMG-B group than the GMG-A group (52.4±17.5 years versus 43.1±18 years (p=0.008). When the age of disease onset was divided into two categories as early (<50 years) and late (≥50 years), it was observed that 67.2% of the GMG-B group had late onset disease, when this rate was 38.3% in the GMG-A group (p=0.002). Female gender was more prominent in the GMG-A group than in the GMG-B group (75% versus 44.8% (p=0.002). The clinical and laboratory features of the two groups is given in Table 1.

In terms of laboratory, radiological, electrophysiological features and treatment responses, it was observed that thymus pathologies were higher in the GMG-A group than in the GMG-B group (37.3% versus 19.3%, (p=0.022). Although not statistically significant, MUSK positivity was observed at a higher rate in the GMG-B group than in the GMG-A group (19.4% vs 7.7%; p=0.171). No statistically significant differences between the two groups were recorded regarding other laboratory, radiological or treatment parameters The relatively low rate of improvement attributed to cholinesterase inhibitor therapy reflects the restriction of the cohort to patients with primary generalised-onset disease, in whom symptomatic treatment alone is typically insufficient and immunosuppressive therapy is required early. Although IVIG and PLEX were numerically more frequent in the GMG-B subgroup, the difference did not reach statistical significance. This likely reflects the early and protocol-driven use of rescue therapies in both subgroups, particularly in patients with severe generalised weakness or impending crisis. (Table 1).

On univariate analysis, the feature associated

Table 1: Comparison of demographic, clinical, laboratory, and treatment findings of bulbar versus extremity predominant generalized myasthenia gravis groups

Characteristics	Generalized myasthenia gravis				p
	N	GMG-A (N=60)	N	GMG-B (N=58)	
Age (mean±SD)	60	51.5±17.6	58	59.4±16.9	**0.011**
Disease onset age (mean±SD)	60	43.1±18	58	52.4±17.5	**0.008**
Onset age group (%)					
Early (<50)	37	61.7	19	32.8	
Late (≥50)	23	38.3	39	67.2	**0.002**
Gender (%)					
Female	45	75	26	44.8	
Male	15	25	32	55.2	**0.002**
AChR antibody group (%)					
Positive	25	52.1	25	73.5	
Negative	23	47.9	9	26.5	0.083
MUSK antibody group (%)					
Positive	3	7.7	6	19.4	
Negative	36	92.3	25	80.6	0.171
Thyroid autoantibody positivity (%)	17	37.8	8	22.2	0.206
RNS group (%)					
Positive	28	48.3	32	65.3	
Negative	30	51.7	17	34.7	0.116
Thymus pathology group (%)					
Thymoma	4	7.8	6	10.5	
Thymic hyperplasia	15	29.4	5	8.8	
Normal	32	62.7	46	80.7	**0.022**
Thymectomy (%)					
Positive	16	26.7	10	17.2	
Negative	44	73.3	48	82.8	0.311
Time of Thymectomy					
0-6 month	9	56.3	5	50	
6-24 month	7	43.7	5	50	1.000
Improvement with ChEI (%)	8	13	7	12	0.801
CS use (%)					
0-6 month	23	38.3	29	50	0.202
6-24 month	16	26.7	15	25.9	0.921
Total	39	65.8	44	75.9	0.276
Improvement with CS and ChEI (%)	14	33	21	48.2	0.193
Immunosuppressant use with CS and ChEI (AZA, MMF, other %)					
0-6 month	10	16.7	11	18.9	
6-24 month	29	48.3	29	50	
Total	32	53.3	33	56.9	0.697
Improvement with immunosuppressant with CS and ChEI	22	68	25	75	0.911

Table 1: (continued)

Characteristics	Generalized myasthenia gravis				p
	N	GMG-A (N=60)	N	GMG-B (N=58)	
Additional IVIG usage (%)	44	73.3	49	84.5	0.209
Improvement with additional IVIG (%)	35	79	35	71.5	0.627
Additional PE usage (%)	2	3.3	6	10.3	0.159
Additional RTX usage (%)	3	5	6	10	1.000
Improvement with additional RTX (%)	2	66	4	66	1.000
General treatment response (%)					
Remission	45	75	37	63.8	
Stable or progression	15	25	21	36.2	0.262

GMG-A: Generalized Myasthenia gravis extremity-predominant, GMG-B: Generalized Myasthenia gravis bulbar-predominant AChR: acetylcholine receptor, MUSK: muscle-specific kinase, RNS: Repetitive nerve stimulation, EMG: electromyography, ChEI: cholinesterase inhibitor CS: corticosteroids, AZA: azathioprine, MMF: mycophenolate mofetil, IVIG: intravenous immunoglobulin, PE: plasma exchange, RTX: rituximab

with bulbar onset in GMG patients was older age at disease onset (OR: 3.87, 95% CI: 1.77–8.17, p<0.001). Cut-off values for age was 59.5 (specificity: 65%, sensitivity: 67%, AUC: 0.63 (in suboptimal area), p=0.011). On the other hand, features associated with extremity onset in GMG were early onset disease (<50 years of age) (OR: 3.30, 95% CI: 1.50–7.03, p = 0.001), female gender (OR: 3.69, 95% CI: 1.21–8.05, p = 0.001), and the presence of an additional thymic pathology (OR: 2.05, 95% CI: 1.09–3.84, p = 0.016). Thymic hyperplasia occurred predominantly in early-onset GMG-A. Among 10 thymoma cases, six improved while four remained stable/worsened. Further multivariate analysis revealed older age of disease onset as a predictive factor for GMG-B (p=0.003) whereas early onset disease, female gender and additional thymus pathology were predictive factors for GMG-A (p=0.004, p=0.008 and p=0.023 respectively). Results of the univariate and multivariate analyses is given in Table 2.

In order to evaluate prognostic factors, the patients included in the study were divided

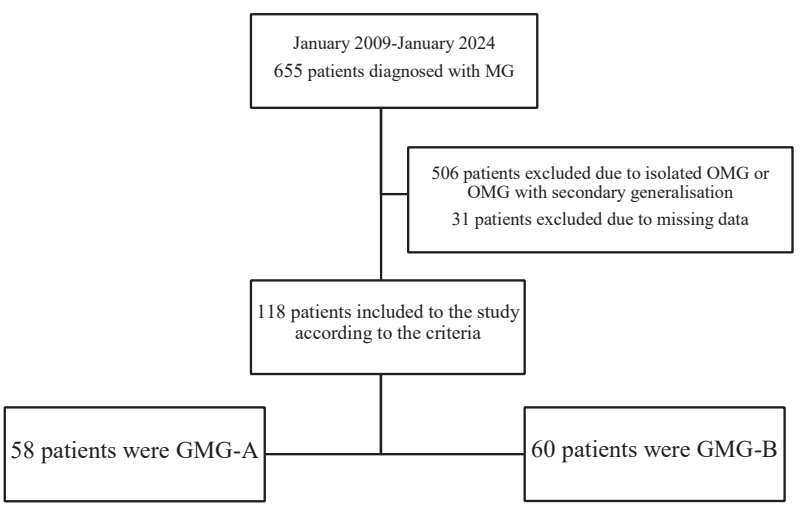

Figure 1. Flowchart of study
MG: myasthenia gravis, GMG-A: Generalized Myasthenia gravis extremity-predominant and bulbar, GMG-B: Generalized Myasthenia gravis bulbar-predominant and extremity, OMG: ocular myasthenia gravis.

Table 2: Univariate and multivariate logistic regression model for predictive risk factors for GMG onset type

	Univariate Analyses		Multivariate Analyses	
	ORR (95%CI	**p**	**ORR (95%CI**	**p**
GMG-A risk>GMG-B				
Early vs late onset	3.30 (1.50-7.03)	**0.001**	3.19 (1.42-7.01)	**0.004**
Gender female vs male	3.69 (1.21-8.05)	**0.001**	3.02 (1.34-6.81)	**0.008**
Additional hypothyroidism	3.60 (1.38-9.42)	**0.006**	2.72 (0.33-7.90)	0.065
Additional thymus pathology	2.05 (1.09-3.84)	**0.016**	2.96 (1.15-7.60)	**0.023**
GMG-B risk>GMG-A				
Age of disease onset (numerically older onset)	3.87 (1.77-8.17)	**<0.001**	4.02 (1.61-10.02)	**0.003**

GMG-A: Generalized Myasthenia gravis extremity-predominant, GMG-B: Generalized Myasthenia gravis bulbar-predominant, ORR: Odds Ratio, CI: confidence interval,

into three groups in terms of overall treatment response: (1) those improved with treatment (IWT), and (2) those did not change with treatment (UWT), and (3) those worsened with treatment (WWT) as defined in the Materials and Methods section. Comparison of the three groups revealed that MUSK positivity was higher in the UWT and WWT groups ($p<0.001$) whereas AChR positivity was higher in the IWT group ($p=0.025$). Other features including demographic, clinical, electrophysiological, radiological, and treatment parameters were not different between the three groups. Table 3 summarizes the characteristics of GMG patients according to their response to treatment.

In terms of accompanying diseases, thyroid autoantibody positivity and hypothyroidism were significantly higher in the GMG-A group than in the GMG-B group (33% versus 12%; $p=0.005$ table 4, OR:3.60, 95%CI:1.38-9.42, $P=0.006$ Table 2). There was no difference between the groups (GMG-A versus GMG-B) regarding the presence of other systemic disorders including atherosclerotic or other autoimmune diseases ($p>0.05$). The rates of both additional systemic diseases and additional autoimmune diseases including hypothyroidism were similar between the patient groups regarding the treatment response ($p>0.05$, Table-4).

DISCUSSION

This study is distinguished by its inclusion of patients who presented with generalized symptoms—either extremity-predominant or bulbar-predominant—without preceding ocular manifestations, a novel approach within the existing literature. To the best of our knowledge, this study is among the few that specifically compare factors associated with outcomes in patients with generalized-onset myasthenia gravis. Between 2009 and 2024, 18% of patients in our cohort presented with primary generalized-onset MG, without preceding ocular involvement (comprising both GMG-A and GMG-B subgroups). This frequency aligns with previously published data.3,12

Previous studies investigating the conversion from OMG to secondary GMG have reported varying results regarding patient demographics. Some studies have identified older age as a risk factor for conversion[13-15], while others did not confirm this association.[13,6-19] Additionally, female gender has been reported as a risk factor for a higher frequency of myasthenic exacerbations in AChR-positive OMG and GMG patients.[20,21] In the present study, demographic analysis revealed that older age at disease onset (mean 59.5 years), late-onset disease (>50 years), and male gender were the features associated with the GMG-B subgroup. In contrast, early-onset disease (<50 years) and female gender were features of the GMG-A subgroup. Among patients who presented with generalized symptoms at onset, AChR antibody positivity was identified as being associated with a more favorable treatment response, while MuSK antibody positivity was associated with poorer outcomes.

Hehir *et al.* (2018) reported AChR antibody positivity in approximately 85% of GMG patients, MuSK positivity in 7%, and seronegativity in 7%, including those with ocular onset MG.[3] The literature also supports higher rates of MuSK positivity in late-onset patients[22] and MuSK-positive individuals are more likely

Table 3: Characteristic features of GMG patients according to their response to treatment

Characteristics	Generalized Myasthenia Gravis						
	N	IWT	N	UWT	N	WWT	p
Age (mean±SD)	82	56.37±17.86	31	52.90±17.76	5	54.40±15.53	0.646
Disease onset age (mean±SD)	82	47.96±18.50	31	46.45±18.51	5	50.00±16.77	0.889
Onset age group (%)							
Early (<50)	28	63.6	14	31.8	2	4.5	0.616
Late (≥50)	54	72.9	17	22.9	3	4.0	
Gender (%)							
Female	47	66.2	19	26.8	5	7	0.165
Male	35	74.5	12	25.5	0	0	
Type of generalized symptom							
GMG-A	42	70	15	25	3	5	0.884
GMG-B	40	69	16	27.6	2	3.4	
AChR antibody group (%) (nmol/L)							
Positive	37	74	13	26	0	0	**0.025**
Negative	18	56.3	10	31.3	4	12.5	
MUSK antibody group (%) (nmol/L)							
Positive	1	11.1	5	55.6	3	33.3	**<0.001**
Negative	44	72.1	16	26.2	1	1.6	
Thyroid autoantibody positivity (%)	18	72	5	20	2	8	0.697
RNS group (%)							
Positive	42	70	14	23.3	4	6.7	
Negative	32	68.1	14	29.8	1	2.1	0.450
Thymus pathology group (%)							
Thymoma	6	60	3	30	1	10	
Thymic hyperplasia	16	72.7	5	22.7	1	4.5	
Normal	53	67.9	22	28.2	3	3.8	0.891

GMG-A: Generalized Myasthenia gravis extremity-predominant, GMG-B: Generalized Myasthenia gravis bulbar-predominant, IWT: improved with treatment; UWT: unchanged with treatment; WWT: worsened with treatment; AChR: acetylcholine receptor, MUSK: muscle-specific kinase, RNS: Repetetive nerve stimulation, EMG: electromyography,

to develop GMG, often presenting with bulbar symptoms.[23,24] Furthermore, MuSK positivity is linked to an increased risk of myasthenic crisis or exacerbation, regardless of initial symptom presentation.[16] In our study, antibody testing was performed in 82% of patients. Among them, AChR and MuSK antibody positivity were found in 61% and 10% of cases, respectively, while 29% were seronegative. Although the overall rate of MuSK positivity did not differ significantly between subgroups, it was more prevalent in the GMG-B group.

The diagnostic sensitivity of RNS in GMG remains controversial. Some studies have reported higher sensitivity of RNS in AChR-positive GMG patients[25], while others did not find a significant association.[26] In our study, RNS positivity was similar across GMG subgroups and showed no statistically significant difference.

Thymic abnormalities, including hyperplasia and thymoma detected via thoracic CT, are established risk factors for secondary generalization in OMG, particularly in early-onset cases.[3,8,13,27] In this study, thymic pathologies were identified in 48% of early-onset patients, compared to 9% of late-onset patients ($p < 0.001$), with thymic hyperplasia being significantly more common in the GMG-A subgroup ($p=0.022$). The higher prevalence of thymic hyperplasia among GMG-A patients may reflect the overall younger

Table 4: Demonstration of comorbidities of GMG patients according to GMG subtype and general treatment response

Accompanying Diseases (%)	Type of GMG					Treatment response						
	N	GMG-A	N	GMG-B	p	N	IWT	N	UWT	N	WWT	p
Autoimmune diseases	20	33.3	21	36.2	0.893	25	61	13	31.7	3	7.3	0.250
Hypothyroidism	20	33	7	12	0.005	23	85.2	3	11.1	1	3.7	0.102
DM	10	16.7	16	27.6	0.227	17	65.4	8	30.8	1	3.8	0.840
HT	14	23.3	16	27.6	0.750	22	73.3	7	23.3	1	3.3	0.863
Heart disease (HD)	5	8.3	4	6.9	1.000	7	77.8	2	22.2	0	0	0.752
Hyperlipidemia	4	6.7	1	1.7	0.365	3	60	2	40	0	0	0.718
MAD (DM+HT+HD+HL)	20	33.3	26	46.8	0.138	49	68.1	19	26.4	4	5.6	0.666

GMG-A: Generalized Myasthenia gravis extremity-predominant, GMG-B: Generalized Myasthenia gravis bulbar-predominant, N: number of patients, IWT: improved with treatment; UWT: unchanged with treatment; WWT: worsened with treatment; DM: diabetes mellitus; HT: hypertension; HD: heart disease; HL: hyperlipidemia; MAD: multiple atherosclerotic diseases.

age distribution in this subgroup, as thymic abnormalities are more frequently encountered in early-onset MG. Most thymoma-associated cases were classified as GMG-B, consistent with previous reports.In MG patients, particularly women, autoimmune diseases are more common compared to the general population. Among these, thyroid disorders are the most frequently associated comorbid conditions.[28] A recent meta-analysis reported thyroid disorders in 10.1% of MG patients.[29] In our cohort, both clinical and subclinical hypothyroidism were observed, with significantly higher prevalence in patients with GMG-A compared to those with GMG-B (p=0.005). Given the higher prevalence of thyroid autoimmunity among GMG-A patients, routine thyroid-function screening may be advisable in this subgroup. A recent study also suggested that type 2 DM may be a potential risk factor for MG.[30] Hypertension, as well as cardiac and respiratory diseases, have been reported to occur more frequently in MG patients than in healthy controls.[31] In our study, the most common systemic comorbidities were hypertension, DM, and coronary artery disease. However, the prevalence of these conditions did not differ significantly between GMG-B and GMG-A patients.

This study also evaluated factors associated with outcomes by analyzing treatment response. MG management includes symptomatic treatment with cholinesterase inhibitors, corticosteroids, non-steroidal immunosuppressants, plasma exchange, and monoclonal antibodies.[32,33] The interpretation of treatment response in generalised myasthenia gravis is inherently complex due to the heterogeneous disease course and the individualised nature of therapy escalation. In this retrospective cohort, patients who experienced clinical worsening frequently underwent treatment intensification, including higher corticosteroid doses or additional immunosuppressive and rescue therapies. Accordingly, the observed associations should be interpreted as descriptive relationships rather than causal or prognostic effects.

Regarding treatment, all our patients received cholinesterase inhibitor drugs. In contrast to ocular or mild generalised MG, patients with primary generalised-onset disease rarely achieve sustained clinical control with cholinesterase inhibitors alone. The low response rate observed in our cohort therefore reflects disease severity and treatment strategy rather than reduced efficacy of ChEI therapy. Despite partial symptomatic improvement with high-dose cholinesterase inhibitor therapy in most patients, the frequent requirement for additional immunosuppressive treatment during follow-up was notable. Although overall rates of treatment response were comparable between GMG-A and GMG-B subgroups, patients with bulbar-predominant disease achieved remission less frequently. This difference likely reflects

the use of a more restrictive definition of remission (limited to pharmacologic remission or complete stable remission) and the greater clinical severity at presentation in GMG-B patients, rather than a true lack of responsiveness to corticosteroid therapy. In addition, treatment response analyses may be influenced by a more aggressive therapeutic approach in patients with prominent bulbar symptoms, given the increased risk of aspiration and respiratory complications. Early escalation of immunosuppressive or rescue therapies in this subgroup may modify apparent response patterns and complicate direct comparisons with limb-predominant disease. This observation may also be influenced by the higher prevalence of MuSK antibody positivity in the bulbar-predominant subgroup, as MuSK-positive myasthenia gravis is characteristically associated with prominent bulbar involvement and has been reported to show a less robust response to conventional corticosteroid-based therapy.

Comparable rates of IVIG and plasmapheresis use between bulbar-predominant (GMG-B) and limb-predominant (GMG-A) subgroups likely reflect contemporary, protocol-driven management strategies rather than an absence of phenotypic severity differences. Current guidelines recommend early initiation of IVIG or plasmapheresis in any patient with generalised myasthenia gravis who develops rapid clinical deterioration or impending myasthenic crisis, irrespective of symptom distribution.[34] Accordingly, in our study population, rescue therapies are commonly instituted based on clinical severity and risk of respiratory compromise rather than bulbar or limb predominance, which may attenuate expected differences in IVIG/PLEX utilisation between subtypes. Importantly, despite differences in initial clinical presentation, no significant differences were observed between GMG-A and GMG-B subgroups with respect to the use of corticosteroids, additional immunosuppressive agents, or rescue therapies such as intravenous immunoglobulin or plasma exchange. This finding suggests that early and appropriately escalated immunotherapy may attenuate potential differences in treatment response between bulbar- and limb-predominant disease phenotypes. Similar observations have been reported in previous studies, indicating that while bulbar involvement is associated with greater clinical severity at presentation, long-term treatment response is largely driven by immunological profile and treatment intensity rather than symptom distribution alone.[35,36]

AChR antibody positivity was associated with a favorable treatment response. Conversely, MuSK antibody positivity was significantly more common in the non-responder group, aligning with existing literature that identifies MuSK positivity as a poor prognostic factor, possibly reflecting limited access to targeted therapies during early years.[30] Additionally, the presence of autoimmune or systemic comorbidities did not significantly impact treatment outcomes.

The single-center, retrospective design of our study and the presence of incomplete data represent its main limitations. Antibody testing was performed in 82% of the cohort. Missing data in earlier cases reflected limitations of retrospective record availability rather than patient selection bias. Additionally, the retrospective nature of the analysis resulted in heterogeneous, non-standardized treatment regimens, which may confound interpretation of therapeutic responses and disease course. Moreover, the limited number of MuSK-positive patients precludes definitive subgroup analysis; therefore, MuSK-related observations should be considered hypothesis-generating and their generalizability remains restricted. The retrospective design and lack of systematically collected patient-reported outcome measures, such as the MG-ADL, represent an important limitation of the study. To obtain more accurate and comprehensive insights, multicenter prospective studies with standardized diagnostic and therapeutic protocols are warranted.

In conclusion our findings highlight male gender and late-onset disease as characteristic features of the GMG-B subgroup, while female gender, early-onset disease, and thymic pathology were more common in the GMG-A subgroup. Among generalized-onset MG patients, only AChR and MuSK antibody positivity were found to be associated with treatment outcomes.

DISCLOSURE

Data availability: The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Financial support: None

Conflict of interest: None

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