scientific reports

Check for updates

OPEN

Factors associated with increased severity of generalized myasthenia gravis among patients in the United States and Europe

Jacqueline Pesa[1]✉, Zia Choudhry[1], Jonathan de Courcy[2], Sophie Barlow[2], Shiva Lauretta Birija[2], Emma Chatterton[2], Gregor Gibson[2], Bethan Hahn[3] & Raghav Govindarajan[4]

Among individuals with generalized myasthenia gravis (gMG), risk factors for increased severity over time are unknown. This study examined the association between demographic and clinical variables and patient progression to a more severe MG Foundation of America (MGFA) classification. Data were drawn from the Adelphi Real World myasthenia gravis Disease Specific Programme™, a cross-sectional survey capturing retrospective data from patients' medical histories. Among 421 individuals, 16% experienced increased gMG severity (progression to higher MGFA class between diagnosis and the time of the survey, 1–7 years later) and for 84%, gMG was stable/improved (MGFA class the same/lower). Logistic elastic net regression determined that increased severity was associated with the occurrence of prior misdiagnosis. Bivariate analyses indicated significant associations between increased severity and longer time between symptom onset and (a) the first consultation with a healthcare practitioner and (b) MG diagnosis. Increased severity was also associated with older age and presence of specific symptoms at diagnosis. gMG stability/improvement was associated with employment status and general fatigue at diagnosis. There is a need for prompt and accurate diagnosis and improved treatment options with the potential to increase the likelihood of stability/improvement for gMG patients.

Keywords Myasthenia gravis, Real-world evidence, Severity, Cross-sectional studies, Misdiagnosis, Outcome

Myasthenia gravis (MG) is a rare, chronic, autoantibody-driven disorder of the post-synaptic membrane at the neuromuscular junction, resulting in muscle weakness and fatigability. The majority of patients initially present with ocular MG, with conversion to generalized MG (gMG) in 50–80% of patients, usually within two years[1–3]. Risk factors associated with generalization include older age at MG onset, female sex, acetylcholine receptor antibody titer, thymoma or thymic hyperplasia, presence of other autoimmune diseases, and others[4–6], and early immunosuppressive treatment may reduce this risk[7].

Few studies, however, have considered risk factors for an increased severity among patients who already present with generalized symptoms at diagnosis. Severity can be measured using the Myasthenia Gravis Foundation of America (MGFA) classification, which allocates patients to one of five classes based on clinical features and severity of muscle weakness[8]. As MGFA class correlates with patient functional status, the occurrence of exacerbations and myasthenic crises, and all aspects of health-related quality of life (both generic and disease-specific)[9,10], it is imperative that individuals at greater risk of progression to a higher, more severe MGFA class are identified, and that effective management and treatment strategies are implemented to minimize the risk of deterioration. Furthermore, it is important to recognize any modifiable risk factors, as this may inform clinical practice and health policy.

The objective of this study was to examine the association between a broad range of demographic and clinical variables and patient progression to a more severe MGFA class, using real-world data from a large, multinational population of individuals with gMG. The MG disease course is highly variable, with studies describing an initial period of 1–2 years during which the disease reaches maximum severity[11] and others referring to an initial 'active

[1]Janssen Scientific Affairs, LLC, Titusville, NJ, USA. [2]Adelphi Real World, Bollington, UK. [3]Macclesfield, UK. [4]HSHS Medical Group Multispecialty Care - St. Elizabeth's, O'Fallon, IL, USA. ✉email: JPesa@its.jnj.com

stage' characterized by relapses and remissions lasting approximately 7 years[12]. Therefore, our study focused on the time period between 1 and 7 years after diagnosis.

Methods

Study design and data source

The patient population included in this study are part of the Adelphi Real World (ARW) MG Disease Specific Programme (DSP)™. ARW DSPs are cross-sectional surveys that also capture retrospective data from patients' medical histories. A complete description of the DSP methodology has been previously published and validated[13–16]. Patient inclusion is not based on detailed eligibility criteria; any individual with the condition of interest who visits the physician for a consultation may be included. Physician- and patient-reported information is then collected with a consistent approach across all countries, generating objective and impartial data.

The MG DSP recorded information about patients with MG in the United States (US) and five European countries (France, Germany, Italy, Spain and the United Kingdom [UK]) in June–September 2020. Physicians were hospital- or office-based with a primary specialty of neurology, primary care or geriatrics, who had personally treated ≥ 1 patient with a confirmed MG diagnosis in the prior 12 months. They were recruited by local fieldwork agents, with appropriate remuneration for their involvement.

Following informed consent, data were collected in three stages: (1) an online physician-completed survey about disease management; (2) an online physician-completed patient record form chart review about the next 1–10 consecutive consulting patients with MG seen in clinical practice; and (3) a pen-and-paper patient self-completion form.

Survey questions

This analysis included examination of physician-reported data only, as provided in the patient record form. These included the following patient sociodemographic characteristic: age, sex, body mass index, and employment status. They also included the following clinical characteristics: MGFA class (class II [mild weakness affecting muscles other than ocular muscles], class III [moderate weakness affecting muscles other than ocular muscles], class IV [severe weakness affecting muscles other than ocular muscles], class V [intubation with or without mechanical ventilation, except when employed during routine postoperative management), Charlson Comorbidity Index, presence of concomitant conditions, MG remission status (defined as 'not in remission [no substantial decrease in clinical manifestations], minimal manifestations [some weakness detectable on examination], in pharmacological remission [has been symptom-free but continues to take treatment for MG] or in complete stable remission [has been symptom-free and has not received any treatment for MG during this period]), MG symptoms at diagnosis, medical history (hospitalizations, myasthenic crises, thymectomy, maintenance/chronic treatment history), and features of the diagnostic journey (time from symptom onset to first consultation and to diagnosis, and occurrence of misdiagnosis).

To determine concomitant conditions, physicians were asked to 'indicate any diagnosed concomitant conditions for this patient'. To determine misdiagnoses, in a separate section of the survey, physicians were asked the following: 'Prior to the diagnosis of myasthenia gravis, had the patient ever received any misdiagnoses that were later attributed to the patient's myasthenia gravis? Note: we are asking about misdiagnoses only and you should not include concomitant conditions in your answers'.

Treatment history was qualified using the following wording: 'For the purpose of the following questions we are only interested in the patient's maintenance/chronic therapy. Please do not include any acute treatments or rescue therapies in your answers'. Physicians also provided the number of lines of therapy; a line was defined as the addition, removal or switch of any individual pharmacological therapy. Pausing treatment or dose changes were not considered line changes.

Inclusion/exclusion criteria

This analysis was performed using survey results for a subset of the entire MG DSP population. Eligible patients had received a diagnosis of MG between 1 and 7 years prior to the survey date and had MGFA classification recorded both at diagnosis and at the time of survey. Patients had gMG, as indicated by being MGFA class II, III, IV or V at both time points.

Ethical approval

The MG DSP survey obtained ethics approval from the Western Institutional Review Board (WIRB; study protocol number: 1276240. Data were collected in such a way that patients and physicians could not be identified directly; all data were aggregated and de-identified before receipt. All methods relating to this research, including the DSP data collection, were undertaken in line with relevant legislation and guidelines including European Pharmaceutical Marketing Research Association (EPHMRA) guidelines[17], the US Health Insurance Portability and Accountability Act (HIPAA) 1996[18], and Health Information Technology for Economic and Clinical Health (HITECH) Act legislation[19].

Data analysis

Patients were allocated to one of two groups: (i) increased gMG severity: progression to a higher MGFA class between diagnosis and the time of the survey, or (ii) gMG stable or improved: MGFA class either the same at diagnosis and the time of the survey or lower between diagnosis and the time of the survey. Sociodemographic characteristics, clinical characteristics, medical history related to the diagnostic journey, and treatment history were then compared for patients in each group.

For numeric variables, sample size, mean, standard deviation, were calculated and compared using Student's t-test. For categorical variables, sample size and number/percent in each category were calculated and compared

using a Fisher's exact test (nominal categorical variables) or Mann–Whitney test (ordered categorical variables). Missing data were not imputed; therefore, the base of patients for analysis could vary from variable to variable.

To identify factors associated with increased gMG severity in this population, regression was performed using a logistic elastic net model. In this method, multiple potential factors or covariates are considered, and those that are deemed as having an impact on the outcome are selected. These selected important covariates then work simultaneously within the model to estimate the outcome, while all other covariates have a coefficient of 0. The assumption was made that the effects of the covariates were independent of each other, therefore no interaction terms were hypothesized. Covariates included in our model are listed in Supplementary Appendix 1. The model output included only the important predictors; i.e. the potential covariates that were found to have an association with gMG being stable/improved (*versus* worse) between diagnosis and the time of the survey, as measured by MGFA class.

Coefficients were exponentiated to produce odds ratios. An odds ratio of 1.0 indicated no difference in odds, a ratio > 1.0 indicated increased odds of an association between the covariate and gMG stability/improvement, and a ratio < 1.0 indicated decreased odds of an association between the covariate and gMG stability/improvement (i.e. interpreted as an association with increased gMG severity).

Analyses were performed using STATA v18 (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC).

Results

Patients

The overall MG DSP was completed by 222 physicians with respect to 1234 patients. Of these, a total of 421 patients had received a diagnosis of gMG 1–7 years prior to the survey date and had MGFA classification data available both at diagnosis and at the time of survey, making them eligible for inclusion in this analysis.

Mean age was 54.4 years, half of the patients were female (Table 1), mean Charlson Comorbidity Index was 0.5, and the most common concomitant conditions were hypertension, dyslipidemia, depression, anxiety and obesity (Table 2). Regarding the clinical burden related to the presence of gMG, patients had been hospitalized due to MG one time on average, 30.8% had experienced at least one myasthenic crisis, and one fifth of patients were not in remission (as opposed to having minimal manifestations or being in pharmacological or complete stable remission) (Table 2).

Change in gMG severity over time

At diagnosis, over half of patients (57.3%) were MGFA class II, 33.0% were class III, 8.1% were class IV and 1.7% were class V (Supplementary Table S1). At the time of the survey (which was conducted a mean [standard deviation, SD] of 35.3 [18.3] and a median [min, max] of 30.3 [12.1, 83.9] months after diagnosis), many individuals had moved between groups: for 69 patients (16.4%) gMG severity had increased and for 352 patients (83.6%) it was stable or had improved (though remaining generalized).

Variables associated with increased gMG severity: bivariate comparisons

The mean age of patients in the 'gMG severity increased' cohort was significantly higher compared with the 'gMG stable/improved' cohort (Table 1). Employment status also differed significantly; for example, 10.1% in the 'gMG severity increased' cohort and 27.8% in the 'gMG stable/improved' cohort were in full time employment whereas 46.4% and 28.4% were retired, respectively (Table 1).

	Overall (N = 421)		gMG severity increased[a] (N = 69)		gMG stable or improved[b] (N = 352)		
	n	Parameter	n	Parameter	n	Parameter	*p*-value
Age, years, mean (SD)	421	54.4 (15.0)	69	59.2 (13.1)	352	53.4 (15.2)	$p = 0.003$
Female, n (%)	421	210.0 (49.9)	69	31.0 (44.9)	352	179.0 (50.9)	$p = 0.430$
BMI, kg/m^2, mean (SD)	421	25.9 (4.2)	69	26.3 (3.7)	352	25.9 (4.3)	$p = 0.437$
Employment status, n (%)	418		69		349		
Retired		131.0 (31.3)		32.0 (46.4)		99.0 (28.4)	$p = 0.008$
Working full time		104.0 (24.9)		7.0 (10.1)		97.0 (27.8)	
Working part time		77.0 (18.4)		10.0 (14.5)		67.0 (19.2)	
On long term sick leave		39.0 (9.3)		8.0 (11.6)		31.0 (8.9)	
Homemaker		35.0 (8.4)		8.0 (11.6)		27.0 (7.7)	
Unemployed		26.0 (6.2)		4.0 (5.8)		22.0 (6.3)	
Student		6.0 (1.4)		0.0 (0)		6.0 (1.7)	

Table 1. Sociodemographic characteristics at the time of the survey for patients with gMG who were diagnosed 1–7 years prior to the survey, overall and stratified according to whether gMG severity has increased or remained the same/improved since gMG diagnosis. *BMI* body mass index, *gMG* generalized myasthenia gravis, *MGFA* Myasthenia Gravis Foundation of America, *SD* standard deviation. [a]Progression to a higher MGFA class between diagnosis and the time of the survey. [b]MGFA class either the same at diagnosis and the time of the survey or lower between diagnosis and the time of the survey.

	Overall (N = 421)		gMG severity increased[a] (N = 69)		gMG stable or improved[b] (N = 352)		
	n	Parameter	n	Parameter	n	Parameter	*p*-value
Time of diagnosis, months prior to survey, mean (SD)	421	35.3 (18.3)	69	37.6 (20.2)	352	34.8 (17.8)	$p = 0.257$
Charlson Comorbidity Index	421	0.5 (1.2)	69	0.6 (1.2)	352	0.5 (1.2)	$p = 0.528$
Concomitant conditions[c], n (%)	421		69		352		
Hypertension		129.0 (30.6)		19.0 (27.5)		110.0 (31.3)	$p = 0.572$
Dyslipidemia		78.0 (18.5)		13.0 (18.8)		65.0 (18.5)	$p = 1.000$
Depression		77.0 (18.3)		18.0 (26.1)		59.0 (16.8)	$p = 0.087$
Anxiety		71.0 (16.9)		14.0 (20.3)		57.0 (16.2)	$p = 0.385$
Obesity		40.0 (9.5)		3.0 (4.3)		37.0 (10.5)	$p = 0.122$
Remission status	421		69		352		
Not in remission[d]		84.0 (20.0)		35.0 (50.7)		49.0 (13.9)	$p < 0.001$
Minimal manifestations[e]		314.0 (74.6)		34.0 (49.3)		280.0 (79.6)	
Pharmacological remission[f]		20.0 (4.8)		0.0 (0.0)		20.0 (5.7)	
Complete stable remission[g]		3.0 (0.7)		0.0 (0.0)		3.0 (0.9)	
Number of times ever hospitalized due to MG, mean (SD)	391	0.9 (1.2)	62	1.0 (1.2)	329	0.9 (1.2)	$p = 0.490$
Ever experienced myasthenic crisis, n (%)	409	126.0 (30.8)	67	25.0 (37.3)	342	101.0 (29.5)	$p = 0.247$
Number of myasthenic crises in prior 12 months, mean (SD)	390	0.3 (0.6)	64	0.3 (0.6)	326	0.3 (0.6)	$p = 0.382$
Has undergone thymectomy, n (%)	417	101.0 (24.2)	69	19.0 (27.5)	348	82.0 (23.6)	$p = 0.538$

Table 2. Clinical characteristics at the time of the survey for patients with gMG who were diagnosed 1–7 years prior to the survey, overall and stratified according to whether gMG severity has increased or remained the same/improved since gMG diagnosis. *gMG* generalized myasthenia gravis, *MGFA* Myasthenia Gravis Foundation of America, *SD* standard deviation. [a]Progression to a higher MGFA class between diagnosis and the time of the survey. [b]MGFA class either the same at diagnosis and the time of the survey or lower between diagnosis and the time of the survey. [C]Five most common. [d]No substantial decrease in clinical manifestations. [e]Some weakness detectable on examination. [f]In pharmacological remission (has been symptom-free but continues to take treatment for MG). [g]In complete stable remission (has been symptom-free and has not received any treatment for MG).

Approximately half of patients in the 'gMG severity increased' cohort had minimal manifestations and none were in remission, in contrast with the 'gMG stable/improved' cohort where values were 79.5% and 6.5%, respectively ($p < 0.001$; Table 2). There were also some differences in the specific symptoms recorded at diagnosis; weakness of the eye muscles and muscle ache following physical activity were significantly more common in the 'gMG severity increased' cohort, whereas impaired speech, slurred speech, shortness of breath, and arm weakness were less common in the 'gMG severity increased' cohort, relative to the 'gMG stable/improved' cohort (Supplementary Fig. S1). For all other indicators of clinical burden, values were comparable between cohorts (Table 2).

The typical patient journey from symptom onset to diagnosis differed between cohorts in numerous respects. Patients in the 'gMG severity increased' cohort experienced a significantly longer time between symptom onset and their first healthcare practitioner (HCP) consultation, a significantly longer time to diagnosis, and a significantly higher occurrence of misdiagnosis prior to their gMG diagnosis, relative to the 'gMG stable/improved' cohort (Fig. 1). The five most common misdiagnoses in the 'gMG severity increased' cohort were chronic fatigue syndrome, multiple sclerosis, connective tissue disease, amyotrophic lateral sclerosis, and chronic inflammatory demyelinating polyradiculoneuropathy (Fig. 1). Although there was no significant difference between cohorts in the HCP type at initial consultation or at diagnosis, a lower proportion of patients in the 'gMG severity increased' cohort were currently managed by a neurologist (*versus* all other HCP types combined), compared with the 'gMG stable/improved' cohort (Supplementary Table S2).

Across all patients in the analysis, the mean (SD) time between the date of the first consultation and gMG diagnosis was 2.76 (3.97) months for patients with no misdiagnoses, *versus* 13.40 (14.42) months for those with ≥ 1 misdiagnosis ($p < 0.001$) (N = 205 and N = 80, respectively).

Treatment history—including duration, number of consecutive maintenance/chronic treatment regimens received, and the type of treatment received—is shown in Table 3; there were no observable differences between patients in the 'gMG stable/improved' and 'gMG severity increased' cohorts.

Variables associated with increased gMG severity: elastic net regression

The elastic net regression model indicated that being in the 'increased severity' cohort was associated with the occurrence of prior misdiagnosis, as indicated by an odds ratio of 0.57 (Fig. 2). A ratio < 1.0 indicated decreased odds of an association between the covariate and gMG stability/improvement, i.e. an association instead with increased gMG severity. Increased severity was also associated with older age (odds ratio 0.99) and the presence of specific symptoms at diagnosis (odds ratios: muscle ache after physical activity 0.42, ptosis 0.68, weakness of

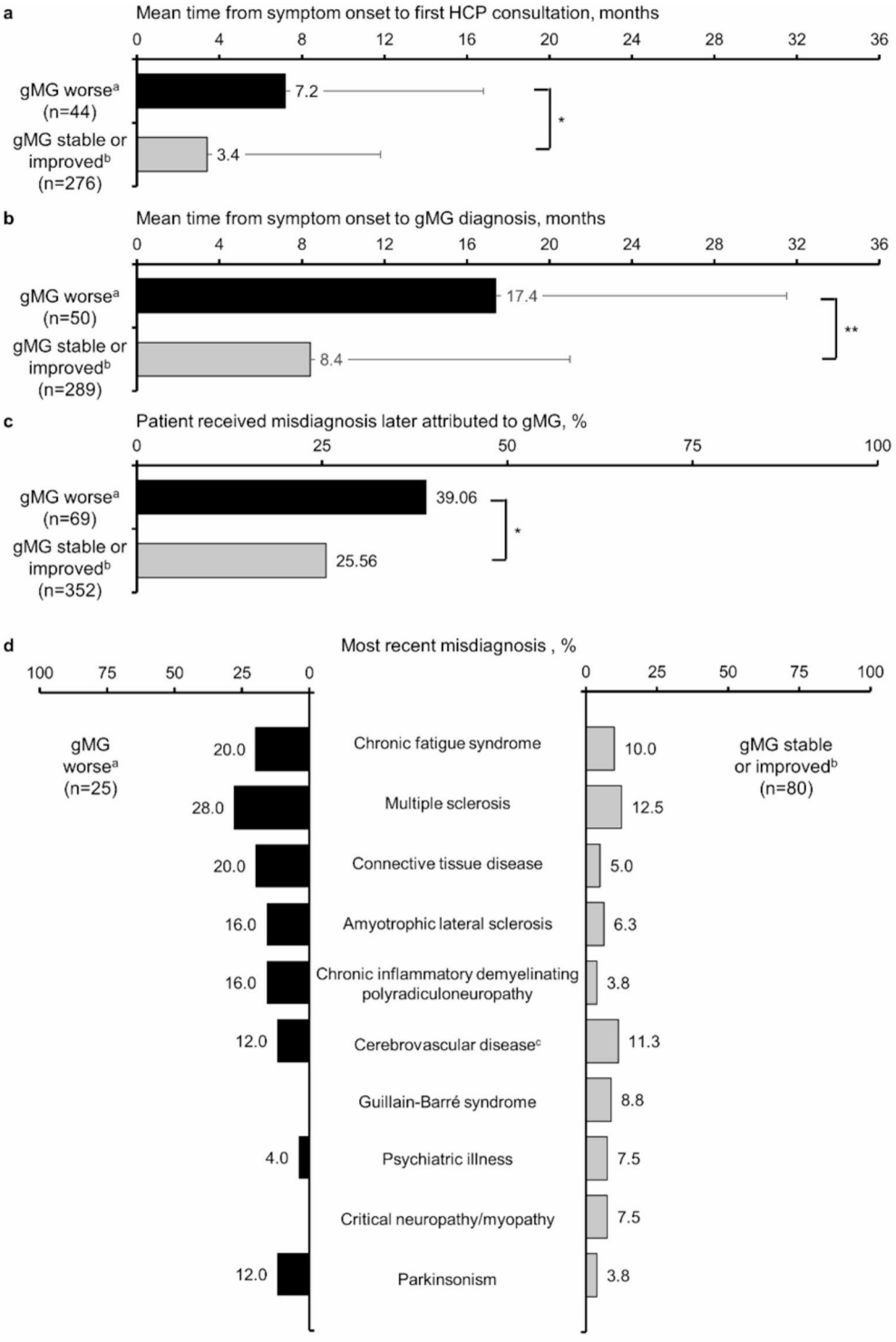

Fig. 1. Features of the diagnostic journey for patients with gMG who were diagnosed 1–7 years prior to the survey, stratified according to whether gMG severity had increased or remained stable/improved since gMG diagnosis: (**a**) time to first consultation, (**b**) time to diagnosis, (**c**) proportion of patients who received a misdiagnosis, and (**d**) condition incorrectly diagnosed prior to gMG diagnosis. gMG, generalized myasthenia gravis; HCP, healthcare practitioner. [a]Progression to a higher MGFA class between diagnosis and the time of the survey; [b]MGFA class either the same at diagnosis and the time of the survey or lower between diagnosis and the time of the survey; [c]This included transient ischemic attacks and posterior circulation stroke. *$p < 0.05$; **$p < 0.001$. Panels a and b show mean and standard deviation. Panel c shows percentage. Panel d shows conditions diagnosed in ≥ 5% of either cohort.

	Overall (N = 421)		gMG severity increased[a] (N = 69)		gMG stable or improved[b] (N = 352)		
	n	Parameter	n	Parameter	n	Parameter	*p*-value
Total treatment duration, days, mean (SD)	162	688.0 (509.4)	26	617.9 (503.1)	136	701.4 (511.3)	p = 0.445
Number of consecutive maintenance/chronic treatment regimens received[c]							
Mean (SD)	421	1.6 (0.8)	69	1.6 (0.9)	352	1.6 (0.8)	p = 0.855
Number of regimens, n (%)	421		69		352		
0		14.0 (3.3)		3.0 (4.3)		11.0 (3.1)	
1		227.0 (53.9)		38.0 (55.1)		189.0 (53.7)	
2		124.0 (29.5)		17.0 (24.6)		107.0 (30.4)	
3		48.0 (11.4)		8.0 (11.6)		40.0 (11.4)	
≥ 4		8.0 (1.9)		3.0 (4.3)		5.0 (1.4)	
Type of treatment, n (%)	407		66		341		
Acetylcholinesterase inhibitors		331.0 (81.3)		51.0 (77.3)		280.0 (82.1)	p = 0.388
Nonsteroidal immunosuppressants		238.0 (58.5)		41.0 (62.1)		197.0 (57.8)	p = 0.586
Corticosteroids		206.0 (50.6)		32.0 (48.5)		174.0 (51.0)	p = 0.788
Biologics		65.0 (16.0)		15.0 (22.7)		50.0 (14.7)	p = 0.140
Intravenous/subcutaneous immunoglobulins or plasmapheresis		66.0 (16.2)		11.0 (16.7)		55.0 (16.1)	p = 0.857

Table 3. Treatments received (at any point) by patients with gMG who were diagnosed 1–7 years prior to the survey, overall and stratified according to whether gMG severity has increased or remained the same/improved since gMG diagnosis. *gMG* generalized myasthenia gravis, *MGFA* Myasthenia Gravis Foundation of America, *SD* standard deviation. [a]Progression to a higher MGFA class between diagnosis and the time of the survey; [b]MGFA class either the same at diagnosis and the time of the survey or lower between diagnosis and the time of the survey; [c]Including patients who had never received maintenance treatment.

eye muscles 0.69). In contrast, gMG stability/improvement was associated with employment status (odds ratio 2.22) and general fatigue at diagnosis (odds ratio 1.05).

Discussion

In this multinational, real-world study, 16% of individuals with gMG experienced an increase in gMG severity between diagnosis and a survey conducted 1–7 years later, as indicated by an increase in MGFA class. These patients were substantially more likely to be considered 'not in remission' by their physician. In an elastic net regression model, increased gMG severity was associated with the occurrence of prior misdiagnosis, and in bivariate analyses it was also associated with a longer time between symptom onset and both first HCP consultation and gMG diagnosis. This highlights an unmet need for prompt and accurate diagnosis of gMG in order to avoid 'lost time' when patients could be receiving MG-specific treatment and avoiding unnecessary and potentially harmful interventions. In addition, older age and the presence of specific symptoms at diagnosis (muscle ache after physical activity, ptosis, and weakness of the eye muscles) were associated with increased gMG severity, and employment status and fatigue at diagnosis were associated with gMG stability/improvement.

Our finding that accurate and timely diagnosis of gMG may be important for optimum disease control is consistent with a previous study where a diagnostic delay of ≥ 2 years was associated with higher disease activity[20]. However, change in disease activity over time was not measured, and the study was performed in a single country only. Other research suggests that long delays to diagnosis may be widespread; findings include diagnosis taking > 1 year for 56% of patients, with > 60% reporting that the process was long and complicated[21], average diagnostic delays of ~ 2 years[22,23], and a substantial proportion of patients receiving an MG diagnosis after 2–5 years[20].

Accurate diagnosis of MG can be challenging due to similarities with numerous other disorders, as well as symptom fluctuation and the frequent presence of comorbidities[12,24–26]. Our results point to a need for increased education around MG signs and symptoms, particularly among HCPs who come into contact with MG patients outside of a neurology setting. For example, primary care practitioners may see patients who have concerns about their muscular symptoms at a relatively early stage of the disease, and emergency physicians may encounter patients who are experiencing myasthenic crisis or severe exacerbations. In particular, the occurrence of chronic fatigue syndrome as a misdiagnosis may reflect a lack of awareness of fatigue as a prominent symptom of gMG[27].

There is, however, a need for improvement as prompt diagnosis and treatment may ultimately lead to better outcomes for patients with MG. The initial years following MG onset are generally the most 'active', with symptoms reaching maximum severity[11,12], and a plateau occurs after this point. Therefore, it is important to gain symptom control and thus improve quality of life during this period. Guidelines recommend thymectomy early in the disease course to improve clinical outcomes and minimize immunotherapy requirements and the need for hospitalizations for disease exacerbations[28].

Half of the patients included in this study had received corticosteroids, one sixth had received intravenous/subcutaneous immunoglobulins or plasmapheresis, and one sixth had received biologics. The data collected in this study do not allow us to determine an association between any particular aspect of treatment history and

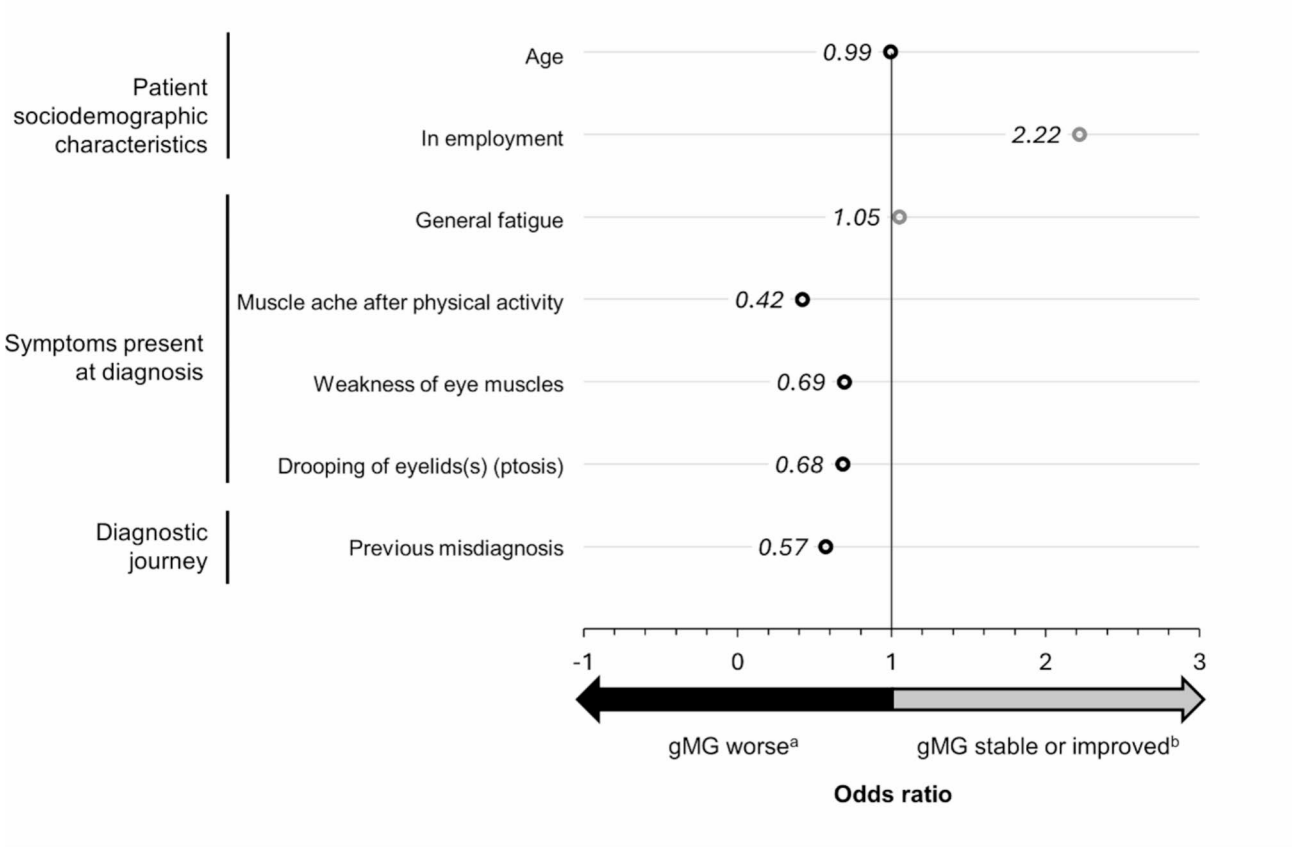

Fig. 2. Positive associations between patient sociodemographic/clinical variables and the likelihood of increased gMG severity (versus remaining the same/improving) since diagnosis, among patients with gMG who were diagnosed 1–7 years prior to the survey. gMG, generalized myasthenia gravis. [a]Progression to a higher MGFA class between diagnosis and the time of the survey; [b]MGFA class either the same at diagnosis and the time of the survey or lower between diagnosis and the time of the survey.

increased gMG severity. Of note, however, bivariate analysis indicated that patients with increased gMG severity were less likely to have a neurologist involved in their disease management. Additional research is required to further investigate gMG treatment and management approaches and the impact they have on disease course over time.

In addition to our findings related to the diagnostic process, a strong association was observed between increased gMG severity and employment status. Substantial work impairment is experienced by individuals with MG, particularly if they are at a higher MGFA class[29], and this finding reflects an important aspect of the lived experience and wider disease burden for individuals with gMG. Similarly, an association has been shown between increased impairment over a period of 10 years and the likelihood that a person with MG has retired from employment[30].

Older age was also associated with increased gMG severity, albeit to a minor extent. Older age has previously been associated with poorer outcomes of myasthenic crisis[9] and increased likelihood of exacerbations[31]. Thus, the treating physician may consider closer monitoring of older patients. Decisions around appropriate treatment will be particularly nuanced, potentially taking into account multiple comorbidities, impaired functional capacity/frailty, cognitive impairment, and complex care needs[32]. The systemic side effects of long-term corticosteroid therapy may be markedly undesirable in the older patient.

The presence of particular symptoms at diagnosis was associated with the likelihood of increased gMG severity over time. Increased severity was associated with muscle ache and ocular symptoms (ptosis, weakness of eye muscles); this is perhaps unexpected as one may expect such typical MG symptoms to elicit prompt diagnosis and treatment initiation. A possible explanation is that patients presenting with these symptoms are not treated as aggressively as those with generalized symptoms (such as speech impairment, arm weakness, or respiratory symptoms), increasing the likelihood of subsequent increased disease severity. In contrast, gMG stability/improvement was associated with general fatigue (though it should be noted that the odds ratio was close to 1); this is also perhaps unexpected as one may anticipate a higher likelihood of misdiagnosis among these patients. However, patients commonly report fatigue to be among the most bothersome of symptoms[33,34], which may elicit a physician response and treatment change, including more aggressive treatment. The fact that all of the above symptoms were among the most frequently observed may also affect results. It is clear that additional analysis is required to further elucidate these findings and their clinical significance. This may include

multivariate analysis of differences in the diagnostic pathway (including but not limited to the likelihood of prior misdiagnosis) and/or treatment strategy according to presenting symptoms. In our study, no relationship was observed between the presence of comorbid hypertension or depression/anxiety, or patient prognosis due to the presence of comorbidities (i.e. CCI), and increased gMG severity. Similarly, a previous study found no relationship between the presence of comorbidities and conversion from ocular to gMG[35]. In a study focussing on individuals with MG onset > 65 years of age, no association was identified between the presence of comorbidities and symptom severity or outcome[36]. However, for some specific comorbid conditions, associations have been observed with patient response to treatment[37,38].

The study has some limitations. Though there were no formal patient selection verification procedures, the DSP is not a true random sample of physicians/patients; participation is influenced by willingness and frequency of physician consultations (though the instruction to complete surveys for the next 1–10 patients with MG is representative of a physician's classification of their patients in usual clinical practice). It is possible that patients with the least impairment are the most likely to participate. As with all surveys, recall bias may influence physician responses (though data were collected during appointments, when physicians would be expected to have access to medical records, reducing the likelihood of bias). As missing data were not imputed, the base of patients for analysis could vary between variables. Although included as a survey question, antibody status was not provided by the responding physician for a large majority of patients (presumably reflecting the real world scenario) and was therefore not reported here; this information would be valuable to aid interpretation of results.

The stratification of patients into severity change categories is also subject to a limitation: to be classed as 'increased severity', patients were required to have increased MGFA class from diagnosis to time of survey, making it impossible for class II patients at diagnosis to have improved. In contrast, patient who were class III-IV at diagnosis could improve. Similarly, a patient who was class V at diagnosis could not to experience increased severity as this is the most severe grouping.

For the analysis of misdiagnoses in particular, there are limitations related to recall (as many misdiagnoses occurred a number of years prior to the survey) and availability of chart data (as misdiagnoses or suspected conditions may not all have been recorded). Future studies may collect additional data regarding the complete diagnosis journey, and analyse the HCP type responsible for misdiagnosis to enable targeted education.

In conclusion, this analysis of a large, multinational population of individuals with gMG suggests that progression to a more severe disease state over time may be associated with particular variables. These include the occurrence of prior misdiagnosis and long delays between symptom onset and both HCP consultation and MG diagnosis, highlighting an unmet need for prompt and accurate diagnosis of gMG in order to avoid 'lost time' when patients could be receiving MG-specific treatment and avoiding unnecessary and potentially harmful interventions. They also include older age–aligning with the findings of previous studies–which may indicate a need for closer monitoring of older patients. Finally, increased gMG severity was associated with employment status, highlighting an important aspect of the lived experience and burden of gMG. Taken together, these findings reflect an unmet need for prompt and accurate diagnosis of gMG to reduce the risk of increased severity, and also more broadly highlight a need for improved gMG management options that help patients achieve disease stability or improvement.

Data availability

All data, i.e. methodology, materials, data and data analysis, that support the findings of this survey are the intellectual property of Adelphi Real World. All requests for access should be addressed directly to Gregor Gibson at gregor.gibson@adelphigroup.com. Gregor Gibson is an employee of Adelphi Real World.

Received: 27 November 2024; Accepted: 6 March 2025
Published online: 01 April 2025

References

1. Bever, C. T. Jr., Aquino, A. V., Penn, A. S., Lovelace, R. E. & Rowland, L. P. Prognosis of ocular myasthenia. *Ann Neurol.* **14**, 516–519 (1983).
2. Oosterhuis, H. J. The natural course of myasthenia gravis: A long term follow up study. *J Neurol Neurosurg Psychiatry.* **52**, 1121–1127 (1989).
3. Guéguen, A. et al. Generalization of ocular myasthenia gravis 10 years after onset. *J Neurol.* **269**, 6597–6604 (2022).
4. Li, F. *et al.* Prediction of the generalization of myasthenia gravis with purely ocular symptoms at onset: a multivariable model development and validation. *Ther. Adv. Neurol. Disord.* **15**, 17562864221104508 (2022).
5. Ruan, Z. et al. Development and validation of a nomogram for predicting generalization in patients with ocular myasthenia gravis. *Front Immunol.* **13**, 895007 (2022).
6. Fang, C. E. H., Bokre, D. & Wong, S. H. Clinical characteristics associated with secondary generalization in patients with ocular myasthenia gravis: A systematic review and meta-analysis. *Neurology.* **101**, e1594–e1605 (2023).
7. Li, M. et al. Do early prednisolone and other immunosuppressant therapies prevent generalization in ocular myasthenia gravis in Western populations: A systematic review and meta-analysis. *Ther Adv Neurol Disord.* **12**, 1756286419876521 (2019).
8. Jaretzki, A. *et al.* Myasthenia gravis: Recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. *Ann. Thorac. Surg.* **70**, 327–334 (2000).
9. Nelke, C. et al. Independent risk factors for myasthenic crisis and disease exacerbation in a retrospective cohort of myasthenia gravis patients. *J Neuroinflammation.* **19**, 89 (2022).
10. Dewilde, S. et al. Patient-reported burden of myasthenia gravis: baseline results of the international prospective, observational, longitudinal real-world digital study MyRealWorld-MG. *BMJ Open.* **13**, e066445 (2023).
11. Grob, D., Brunner, N., Namba, T. & Pagala, M. Lifetime course of myasthenia gravis. *Muscle Nerve.* **37**, 141–149 (2008).
12. Juel, V. C. & Massey, J. M. Myasthenia gravis. *Orphanet J. Rare Dis.* **2**, 44 (2007).
13. Anderson, P., Benford, M., Harris, N., Karavali, M. & Piercy, J. Real-world physician and patient behaviour across countries: Disease-Specific Programmes - a means to understand. *Curr Med Res Opin.* **24**, 3063–3072 (2008).

14. Anderson, P. et al. Real-world evidence generation from patients, their caregivers and physicians supporting clinical, regulatory and guideline decisions: an update on Disease Specific Programmes. *Curr Med Res Opin.* **39**, 1707–1715 (2023).
15. Babineaux, S. M., Curtis, B., Holbrook, T., Milligan, G. & Piercy, J. Evidence for validity of a national physician and patient-reported, cross-sectional survey in China and UK: The Disease Specific Programme. *BMJ Open.* **6**, e010352 (2016).
16. Higgins, V. et al. Trends in medication use in patients with type 2 diabetes mellitus: a long-term view of real-world treatment between 2000 and 2015. *Diabetes Metab Syndr Obes.* **9**, 371–380 (2016).
17. European Pharmaceutical Market Research Association. Code of Conduct https://www.ephmra.org/sites/default/files/2022-03/2021%2520EPHMRA%2520Code%2520of%2520Conduct%25202.11.21.pdf (2021).
18. US Department of Health & Human Services. Summary of the HIPAA Privacy Rule http://www.hhs.gov/sites/default/files/privacysummary.pdf (2020).
19. US Department of Health & Human Services. Health Information Technology Act https://www.hhs.gov/sites/default/files/ocr/privacy/hipaa/administrative/enforcementrule/enfifr.pdf?language=es (2009).
20. Petersson, M. et al. Patient-reported symptom severity in a nationwide myasthenia gravis cohort: Cross-sectional analysis of the Swedish GEMG study. *Neurology.* **97**, e1382-1391 (2021).
21. Sobierajski, T., Lasek-Bal, A., Krzystanek, M. & Gilhus, N. E. Diagnosis and therapy of myasthenia gravis—the patients' perspective: a cross-sectional study. *Front. Neurol.* **14** (2023).
22. Lehnerer, S. et al. Burden of disease in myasthenia gravis: taking the patient's perspective. *J Neurol.* **269**, 3050–3063 (2022).
23. Yacouba, K., Kouda, D., Affognon, K., Bugeme, M. & Mourabit, S. Therapeutic itinerary of the patients followed for myasthenia in Dakar. *J. Neurol. Sci.* **405**, 316 (2019).
24. Spillane, J., Higham, E. & Kullmann, D. Myasthenia gravis. *BMJ (Clinical research ed.).* **345**, e8497 (2012).
25. Gilhus, N. E. et al. Myasthenia gravis. *Nat Rev Dis Primers.* **5**, 1–19 (2019).
26. Al-Asmi, A., Nandhagopal, R., Jacob, P. C. & Gujjar, A. Misdiagnosis of myasthenia gravis and subsequent clinical implication: a case report and review of literature. *Sultan Qaboos Univ Med J.* **12**, 103–108 (2012).
27. Ruiter, A. M., Verschuuren, J. J. G. M. & Tannemaat, M. R. Prevalence and associated factors of fatigue in autoimmune myasthenia gravis. *Neuromuscular Disorders.* **31**, 612–621 (2021).
28. Narayanaswami, P. et al. International consensus guidance for management of myasthenia gravis: 2020 update. *Neurology.* **96**, 114–122 (2021).
29. Pesa, J. et al. The impact of myasthenia gravis severity on work and daily activities. *Muscle Nerve.* **69**, 428–439 (2024).
30. Bozovic, I. et al. Long-term outcome in patients with myasthenia gravis: One decade longitudinal study. *J Neurol.* **269**, 2039–2045 (2022).
31. Bae, J. S., Go, S. M. & Kim, B. J. Clinical predictors of steroid-induced exacerbation in myasthenia gravis. *J Clin Neurosci.* **13**, 1006–1010 (2006).
32. Roller-Wirnsberger, R., Thurner, B., Pucher, C., Lindner, S. & Wirnsberger, G. H. The clinical and therapeutic challenge of treating older patients in clinical practice. *Br J Clin Pharmacol.* **86**, 1904–1911 (2020).
33. Jackson, K. et al. Understanding the symptom burden and impact of myasthenia gravis from the patient's perspective: A qualitative study. *Neurol Ther.* **12**, 107–128 (2022).
34. Narayanaswami, P. et al. Identifying a patient-centered outcome measure for a comparative effectiveness treatment trial in myasthenia gravis. *Muscle Nerve.* **65**, 75–81 (2022).
35. Guo, R. J. et al. Risk factors for generalization in patients with ocular myasthenia gravis: A multicenter retrospective cohort study. *Neurol Ther.* **11**, 73–86 (2022).
36. Vijayan, J. et al. Clinical profile and impact of comorbidities in patients with very-late-onset myasthenia gravis. *Muscle Nerve.* **64**, 462–466 (2021).
37. Ozdemir, H. N., Karasoy, H., Yuceyar, A. N. & Ekmekci, O. Effects of comorbid diseases on clinical outcomes in patients with myasthenia gravis. *Neurol Sci.* **44**, 2923–2931 (2023).
38. Harris, L., Graham, S., MacLachlan, S., Exuzides, A. & Jacob, S. A retrospective longitudinal cohort study of the clinical burden in myasthenia gravis. *BMC Neurol.* **22**, 172 (2022).

Acknowledgements

The authors of this paper would like to thank the physicians and patients for taking part in this study and providing the information included.

Author contributions

Material preparation, data collection and initial analyses were performed by Jonathan de Courcy, Sophie Barlow, Shiva Lauretta Birija, Emma Chatterton, and Gregor Gibson. Analysis and interpretation of data was performed by all authors. Formal statistical analysis was performed by Sophie Barlow. The first draft of the manuscript was written by Bethan Hahn and all authors reviewed and commented on subsequent drafts of the manuscript. All authors read and approved the final manuscript.

Funding

Janssen Scientific Affairs, LLC did not influence the original survey through either contribution to the design of questionnaires or data collection. The analysis described here used data from the Adelphi Real World Myasthenia Gravis DSP. The DSP is a wholly owned Adelphi Real World product. Janssen Scientific Affairs, LLC is one of multiple subscribers to the DSP. Publication of survey results was not contingent on the subscriber's approval or censorship of the manuscript.

Declarations

Competing interests

Jacqueline Pesa and Zia Choudhry are employees of Janssen Scientific Affairs, LLC and Johnson and Johnson stockholders. Jonathan de Courcy, Sophie Barlow, Shiva Lauretta Birija, Emma Chatterton, and Gregor Gibson are employees of Adelphi Real World. Bethan Hahn received payment as a contractor from Adelphi Real World for involvement in this manuscript, and also receives payment as a contractor from Janssen (Pharmaceutical Companies of Johnson and Johnson), Amiculum Limited, and McCann Health Medical Communications. Raghav Govindarajan serves on the advisory board for Argenx, Janssen, and UCB, and on the speakers bureau for Argenx and Alexion.

Consent to participate

Participating patients and physicians provided informed consent to participate.

Ethics declaration

The MG DSP survey obtained ethics approval from the Western Institutional Review Board (WIRB; study protocol number: 1276240). Data were collected in such a way that patients and physicians could not be identified directly; all data were aggregated and de-identified before receipt. Data collection was undertaken in line with relevant legislation and guidelines including European Pharmaceutical Marketing Research Association (EMPHMRA) guidelines[17], the US Health Insurance Portability and Accountability Act (HIPAA) 1996[18], and Health Information Technology for Economic and Clinical Health (HITECH) Act legislation[19].

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-025-93464-w.

Correspondence and requests for materials should be addressed to J.P.

Reprints and permissions information is available at www.nature.com/reprints.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.