Identifying risk factors for exacerbation and symptom worsening—a retrospective cohort study of patients with myasthenia gravis in the United States

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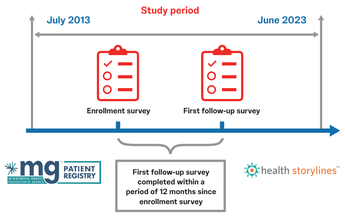
Background

- Myasthenia gravis (MG) is a rare autoantibody-driven disease in which antibodies target the structures of the neuromuscular junctions; this results in impaired or failed neuromuscular functions[1,2]
- The Myasthenia Gravis Foundation of America Global MG Patient Registry (MGFAPR) captures longitudinal patient-reported data that may facilitate understanding of risk factors associated with MG
  - The MGFAPR is an online patient-reported registry hosted on the Health Storylines platform, a proprietary mobile application of Alira Health
- A common outcome measure used to identify and track risk factors is the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale; this eight-item patient-reported outcome measure assesses MG symptoms and functional activities related to activities of daily living[3]
- The objective of this study was to identify risk factors for self-reported exacerbations and of ≥2 point increases in MG-ADL score

Methods

- This retrospective, cross-sectional, observational cohort study analyzed MGFAPR surveys completed between July 2013 and June 2023 by US-based adults with self-reported MG who had first follow-up data available within 12 months of enrollment (**Figure 1**)
- Exacerbations in the past 6 months and increase in MG-ADL score of at least 2 points between baseline and first follow-up were evaluated
- For statistical modeling, univariate analyses and multivariate logistic regressions were conducted
  - Multivariate logistic regression was performed after covariate selection using backward stepwise selection
  - In backward stepwise selection, the least significant variables (based on a chosen criterion, e.g., p-value) are iteratively removed to reduce overfitting and enhance statistical validity
- Statistics included:
  - Quantitative variables, summarized using means, medians, range (minimum, maximum), quartiles, and standard deviations
  - Qualitative variables, presented as counts and percentages
  - Statistical testing, where differences between groups were assessed using chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables

FIGURE 1: Overview of the study design



Results

Patients

- Overall, 1319 patients completed a follow-up survey within 12 months and were included in the study; 1187 reported on exacerbation and 1232 reported MG-ADL scores

Exacerbations of MG

- Characteristics of the 1187 patients who reported the presence or absence of an exacerbation at first follow-up are shown in **Table 1**
- Comorbid anxiety/depression, living alone, corticosteroid treatment, higher MG-ADL score at enrollment (≥2 vs <2), and MG symptoms worse compared with 6 months ago (vs no change) were factors associated with an increased risk of experiencing at least one self-reported exacerbation (**Figure 2**)

TABLE 1: Baseline characteristics[a] of patients reporting presence or absence of exacerbations

Characteristic	Reported 0 exacerbations (n=727)	Reported 1 exacerbation (n=225)	Reported 2 exacerbations (n=117)	Reported 3 exacerbations (n=45)	Reported ≥4 exacerbations (n=43)	All patients reporting on exacerbation (n=1187)
Age at first follow-up, years	61.3 (13.2)	57.5 (14.3)	53.9 (14.1)	52.8 (12.9)	52.3 (14.9)	59.1 (13.9)
Age at diagnosis, years	54.1 (16.8)	52.5 (16.4)	48.4 (15.9)	47.0 (13.2)	46.6 (15.5)	52.7 (16.6)
Male sex	49%	38%	29%	27%	33%	43%
Time since diagnosis at enrollment, years	6.7 (10.3)	4.4 (7.1)	4.8 (7.0)	5.2 (7.4)	5.1 (7.6)	5.9 (9.2)
Generalized symptoms of MG at first follow-up	85%	93%	98%	96%	100%	89%
Antibody status (unknown or missing not shown)						
AChR+	38%	38%	26%	24%	28%	36%
MuSK+	2.3%	3.1%	3.4%	2.2%	12%	2.9%
LRP4+	1.1%	2.0%	0%	6.7%	4.7%	1.5%
Double seronegative (AChR– and MuSK–)	5.5%	11%	21%	20%	19%	9.3%
Comorbidity[b]						
Autoimmune disorders	26%	29%	41%	47%	42%	29%
Respiratory disorders	16%	22%	30%	27%	28%	19%
Psychological disorders	55%	75%	85%	91%	95%	65%
Other comorbidities	60%	61%	68%	76%	74%	62%
MG treatment						
AChEIs	72%	82%	85%	84%	86%	76%
Corticosteroids	39%	52%	45%	49%	53%	43%
IVIg, rescue therapy excluded	14%	21%	21%	33%	26%	17%
PLEX, rescue therapy excluded	3.0%	5.1%	6.0%	2.2%	14%	4.1%
MG-ADL score at first follow-up	3.8 (3.2)	6.0 (3.8)	8.3 (3.4)	9.8 (3.7)	11.0 (4.1)	5.2 (4.0)
Feeding tube in the past 6 months	0.8%	7.1%	6.8%	8.9%	14%	3.5%
MG symptoms compared with 6 months ago						
Better	33%	38%	25%	13%	19%	32%
Worse	14%	36%	55%	53%	63%	26%
No change	53%	25%	21%	33%	19%	42%

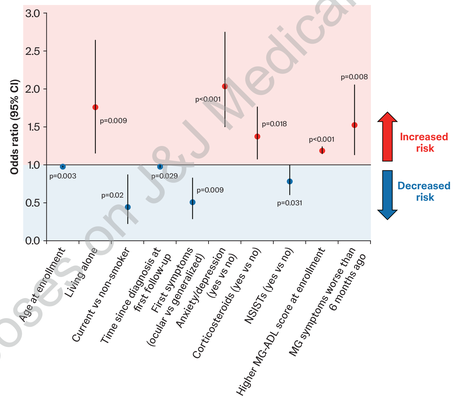
Data are mean (standard deviation) or percentage of patients.
[a]All variables captured at enrollment unless otherwise indicated.
[b]Comorbidity data were taken from enrollment and first follow-up.
AChEI, acetylcholinesterase inhibitor; **AChR**, acetylcholine receptor; **IVIg**, intravenous immunoglobulin; **LRP4**, low-density lipoprotein receptor-related protein 4; **MG**, myasthenia gravis; **MG-ADL**, Myasthenia Gravis Activities of Daily Living; **MuSK**, muscle-specific tyrosine kinase; **PLEX**, plasma exchange.

- Each additional year of age at enrollment, ocular versus generalized first MG symptoms, and nonsteroidal immunosuppressants at enrollment were associated with a decreased risk of experiencing at least one self-reported exacerbation (**Figure 2**)

MG-ADL score

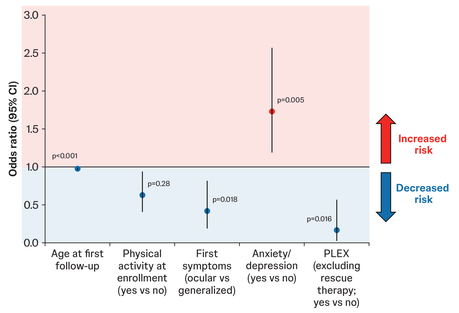
- A total of 1232 patients reported MG-ADL scores at enrollment and first follow-up; 210 (17%) had an increase in score of ≥2 points (**Table 2**)
- Comorbid anxiety/depression was associated with a heightened risk of a self-reported MG-ADL score increase of ≥2 points (**Figure 3**)

FIGURE 2: Factors associated with risk of exacerbation



Non-significant factors not shown: sex; race (vs White non-Hispanic): Black non-Hispanic, Hispanic (Black or White), Native American, Asian, Other (or more than one race); region type (rural vs urban); physical activity at enrollment (yes vs no); antibody status: MuSK+, double seronegative (AChR– and MuSK–), or unknown or missing; thymectomy (yes vs no); cardiometabolic disorders (yes vs no); autoimmune disorders (yes vs no); respiratory disorders (yes vs no); any family history of autoimmune conditions (yes vs no); PLEX (rescue therapy excluded; yes vs no); MG symptoms better compared with 6 months ago (vs no change).
AChR, acetylcholine receptor; **CI**, confidence interval; **MG**, myasthenia gravis; **MG-ADL**, Myasthenia Gravis Activities of Daily Living; **MuSK**, muscle-specific tyrosine kinase; **NSISTs**, nonsteroidal immunosuppressants; **PLEX**, plasma exchange.

FIGURE 3: Factors associated with risk of MG-ADL worsening



The non-significant factors are: sex, race, smoking status, summer months, time since diagnosis, antibody status, cardiometabolic disorders, autoimmune disorders, respiratory disorders, AChEI, Biologics, MG symptoms compared to 6 months ago.
AChEI, acetylcholinesterase inhibitor; **CI**, confidence interval; **MG**, myasthenia gravis; **MG-ADL**, Myasthenia Gravis Activities of Daily Living; **PLEX**, plasma exchange.

- Each additional year of age at first follow up, ocular versus generalized first MG symptoms, plasma exchange (excluding rescue therapy), and physical activity at enrollment were associated with a decreased risk of a self-reported MG-ADL score increase of ≥2 points (**Figure 3**)

TABLE 2: Baseline characteristics[a] of patients reporting MG-ADL scores

Characteristic	Patients with increase in MG-ADL score of ≥2 points between enrollment and first follow-up (n=210)	Patients with increase in MG-ADL score of <2 points (n=1022)	All patients reporting MG-ADL scores (n=1232)
Age at first follow-up, years	55.8 (14.5)	59.8 (13.5)	59.1 (13.8)
Age at first symptom, years	45.1 (18.6)	49.3 (18.3)	48.6 (18.4)
Age at diagnosis, years	49.3 (17.0)	53.4 (16.2)	52.7 (16.4)
Male sex	41%	44%	43%
Body mass index, kg/m²	32.1 (7.4)	30.9 (7.4)	31.1 (7.4)
Engaging in physical activity at enrollment	17%	28%	26%
Generalized symptoms of MG	96%	89%	90%
Comorbidity[b]			
Autoimmune disorders	36%	28%	29%
Respiratory disorders	27%	19%	20%
Psychological disorders	79%	64%	67%
PLEX, rescue therapy excluded	1.0%	4.7%	4.1%
Treatment class changes (from enrollment to first follow-up)	64%	49%	52%
MG-ADL score at enrollment	5.4 (3.5)	6.3 (3.9)	6.1 (3.9)
MG-ADL score at first follow-up	8.4 (3.8)	4.7 (3.7)	5.3 (4.0)
Exacerbations in the past 6 months	57%	33%	37%
Feeding tube in the past 6 months	6.2%	2.9%	3.5%
MG symptoms compared with 6 months ago			
Better	16%	35%	32%
Worse	51%	22%	27%
No change	33%	42%	41%
Number of ER visits in the past 6 months	0.8 (1.7)	0.5 (1.1)	0.5 (1.2)
Myasthenic crisis	9.5%	4.5%	5.4%

Data are mean (standard deviation) or percentage of patients.
[a]All variables captured at enrollment unless otherwise indicated.
[b]Comorbidity data were taken from enrollment and first follow-up.
ER, emergency room; **MG**, myasthenia gravis; **MG-ADL**, Myasthenia Gravis Activities of Daily Living; **PLEX**, plasma exchange.

Key takeaways

- These analyses from a large US registry indicate that age, lifestyle factors, disease presentation, disease duration, and comorbidities of anxiety and depression could all be significant factors for predicting future worsening in MG disease
- This study demonstrated that many patients with MG report uncontrolled disease despite available treatment options

Conclusions

- Findings from these MGFAPR-based analyses suggest that many US individuals with MG experience exacerbations or worsening of MG-ADL scores despite available treatment options
- Younger age, shorter disease duration, and generalized first symptoms predicted more aggressive disease, suggesting a more efficacy-focused treatment plan may be important for these patients
- As anxiety and depression are common comorbidities with MG, and our results suggest both are important predictors of future MG disease worsening, further research to better understand the interactions between anxiety/depression and MG is warranted

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Disclosures

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