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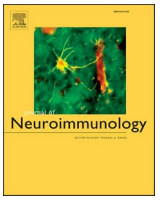

Short Communication

Seasonal variation in myasthenia gravis incidence

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ABSTRACT

Introduction: Environmental factors may contribute to myasthenia gravis (MG) development, sometimes with seasonal patterns of exposure. However, whether seasonality has an impact on MG incidence remains unclear. We aimed to investigate the association between seasonality and MG onset.

Methods: We reviewed data of MG patients with acetylcholine receptor (AChR)-IgG and disease onset between January 2010–December 2019, from two Italian cohorts: 1) an hospital-based cohort and 2) a population-based cohort. MG cases were assigned to four season-trimesters based on month of onset to determine seasonal association with MG incidence.

Results: We enrolled 316 patients:214 in the hospital-based and 102 in the population-based cohort. Median age at onset was 66 years (range, 8–92); Female accounted for 41.1 %. The median number of new MG cases per season-trimester was significantly higher in summer than other trimesters *($p = 0.009$),* and associated with higher environmental temperatures.

Discussion: Our findings suggest that MG onset may be more common in summer and at higher environmental temperatures. Identifying the determinants of this association may improve our understanding of disease pathophysiology.

1. Introduction

Autoimmune diseases are heterogeneous conditions characterized by loss of tolerance to self-antigens. The complex interplay of genetic susceptibility, epigenetic mechanisms, and environmental factors is crucial for the development of the disease. Myasthenia gravis (MG) is caused by antibodies (Abs) targeting proteins at the neuromuscular junction and thus resulting in abnormal muscle fatigability (Gilhus et al., 2019). Various environmental factors have been proposed to play a role in the pathogenesis of MG including infections (Leopardi et al., 2021), vaccinations (Schattner, 2005), low serum levels of vitamin D (Bonaccorso, 2023), and smoking (Maniaol et al., 2013). These factors exhibit seasonal variability that may impact MG onset and exacerbations. Although an association between seasonality and disease worsening has been described in different autoimmune neurologic disorders (Acosta-Ampudia et al., 2019; Watad et al., 2016; Akaishi et al., 2020), data on MG are still limited (Hamedani et al., 2023). We investigated whether seasonality may affect disease incidence in two Italian MG cohorts.

2. Methods

The study was approved by the Institutional Review Boards of the University of Cagliari and the Fondazione Policlinico Universitario Agostino Gemelli IRCCS. All involved patients consented to the use of their medical records for research purposes.

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2.1. Study population

We retrospectively identified MG patients with AChR-IgG positivity and disease onset between January 1, 2010 and December 31, 2019, from two different Italian cohorts: 1) a hospital-based cohort of consecutive patients seen at the Neurology Unit of the IRCCS Fondazione Policlinico Gemelli in Rome; and 2) a previously described population-based cohort of incident cases resident in the Sanitary District of Sassari, in the region of Sardinia (Sechi et al., 2024).

MG diagnosis was based on clinical features, Ab detection and neurophysiological findings. AChR-IgG positivity was assessed by radioimmunoassay (RIA) (RSR-LTD, Cardiff, UK) in all patients.

2.2. Data collection and seasonality assessment

For all included patients we reviewed medical records to determine month and year of MG presentation, age at MG presentation, sex, and presence of thymoma documented by pathology. Patients were classified as: 1) Early-onset (EOMG; age at MG onset <50 years); 2) Late-onset (LOMG; age at MG onset ≥50 years); and 3) Thymoma-associated (TAMG), regardless of the age at onset. MG cases were assigned to one of the four season-trimesters based on the month of MG onset: 1) Spring (March to May); 2) Summer (June to August); 3) Autumn (September to November); and 4) Winter (December to February). The environmental temperatures reported over the study period in the cities of Sassari and Rome were also collected from weather stations of Rome Ciampino and Alghero Fertilia.

2.3. Statistical analysis

Continuous data were reported as medians with ranges and interquartile ranges (IQR), while categorical data were presented as numbers and percentages, as appropriate. Season variability at MG presentation was assessed by comparing the median number of incident cases per year in each season trimester over the 10-year study period using the Kruskal Wallis test. Mann-Whitney *U* test was employed to compare the number of new cases in summer with the mean of new cases in the other seasons. A multivariate logistic regression model was developed to identify factors associated with MG onset in summer. Generalized additive model (GAM) was applied to evaluate the relationship between temperature (assessed as average temperature in Rome and Sassari in each season-trimester per year) and new MG cases. *P*-values <0.05 were considered statistically significant. Statistical analyses were performed using GraphPad Prism 10.1.0 and JMP 18. Visualizations, including the heatmap and other graphs, were created using the R programming language with the ggplot2 package.

3. Results

A total of 316 patients were included: 214 from the hospital-based cohort, and 102 from the population-based cohort. The median age at MG onset was 66 (range, 8–92) years; and 130 (41.1 %) were female. Thirty-nine (12.3 %) cases were classified as EOMG, 219 (69.3 %) as LOMG, and 58 (18.4 %) patients had a thymoma. The characteristics of included patients and after stratification by hospital-based vs population-based cohort are summarized in Table 1.

Table 1
Characteristics of included patients stratified by cohort of origin.

	Combined cohort	Hospital-based cohort	Population-based cohort
N	316	214	102
Demographics			
Female:Male	130:186	88:126	42:60
Median age of onset (range)	66 (8–92)	65 (18–92)	70 (8–90)
MG subtype			
EOMG	39 (12.3 %)	28 (13.1 %)	11 (10.8 %)
LOMG	219 (69.3 %)	140 (65.4 %)*	79 (77.4 %)*
TAMG	58 (18.4 %)	46 (21.5 %)**	12 (11.8 %)**
Season-trimester at MG onset			
Winter (Dec-Feb)	75 (23.7 %)	53 (24.8 %)	22 (21.6 %)
Spring (Mar-May)	68 (21.5 %)	47 (22.0 %)	21 (20.6 %)
Summer (Jun-Aug)	108 (34.2 %)	72 (33.6 %)	36 (35.3 %)
Autumn (Sep-Nov)	65 (20.6 %)	42 (19.6 %)	23 (22.5 %)

* The frequency of late-onset MG was significantly higher in the population-based cohort compared to the hospital-based cohort; $p = 0.037$.

** The frequency of thymoma-associated MG was significantly higher in the hospital-based cohort compared to the population-based cohort; $p = 0.043$ (Fisher exact test). All other comparisons were not significantly different.

Abbreviations. EOMG: early-onset MG; LOMG: late-onset MG; TAMG: thymoma-associated MG.

3.1. Season variability at MG presentation

The seasonal MG incidence (the median number of new cases per season-trimester) was significantly higher in summer: 11 cases (range, 7–15; IQR 8.25–13.25) in summer ($p = 0.009$); 6 (3–11; IQR 5.5–8) cases in autumn; 8.5 (3–11; IQR 4.5–10.25) cases in winter; and 7 (2–10; IQR 4.25–7.25) cases in spring (The seasonal distribution of new MG cases per year is shown in Fig. 1-B and in Supplementary Table). MG incidence was significantly higher in summer also comparing the number of new cases in summer with the mean of new cases in the other seasons using Mann-Whitney *U* test ($p = 0.005$). Notably, in five of ten years examined, the number of new MG cases in summer was higher than 10 cases as shown in Fig. 1B.

The patterns of cumulative distribution of new MG cases across the four season-trimesters were similar after stratification by cohort of origin (hospital-based vs population-based) (Fig. 1-A). After stratification by MG subgroup, the highest MG incidence in the summer season-trimester was more evident in patients with LOMG (Fig. 1-C).

Gender, age at MG onset, presence of thymoma, type of MG onset (ocular versus generalized) were included in the multivariate logistic regression model. None of these factors was independently associated with MG onset in summer. GAM revealed a significant non-linear association between average temperature and MG cases ($p = 0.005$). The estimated smooth function showed fluctuations in the number of MG cases across the temperature range, suggesting that certain temperature range may influence MG incidence more strongly than others (Fig. 2).

4. Discussion

Our study suggests that the onset of AChR-MG may exhibit a distinct seasonal distribution, with a peak during the summer months. Investigating the factors contributing to this seasonal variability could enhance our understanding of MG pathophysiology, and assist in planning healthcare resource allocation and preventive strategies.

Two prior studies conducted in the United States have examined the influence of seasonality on MG exacerbations. The first study, based on ICD-9 diagnoses of hospitalized patients from a single electronic health record in New York City, reported an increased incidence of MG worsening during late winter and late summer (Melamed et al., 2014). A more recent analysis using the National Inpatient Sample in the USA also identified a summer peak in MG hospitalizations (Hamedani et al., 2023). These findings are consistent with our results.

The observed seasonal variability in MG onset was similar among patients from two geographically and genetically distinct regions in Italy, suggesting that the association is unlikely to be due to chance and pointing to a significant role for environmental factors in triggering MG symptoms. Additionally, the patients included in our study were drawn from a reference Centre for MG and a population-based cohort, reducing the likelihood of selection bias. Importantly, this seasonal pattern was evident across all patients' subgroups, despite the known genetic

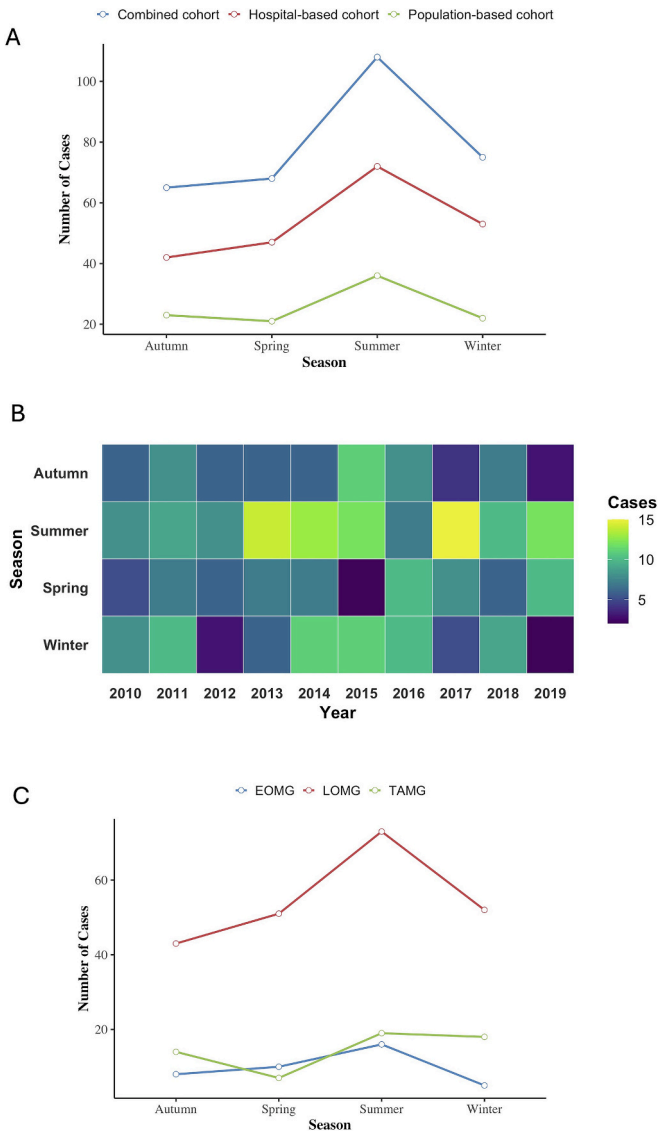

Fig. 1. Number of included patients at MG onset across season-trimesters and seasonal distribution per year.
The graphs show the different number of new MG cases per season-trimester, stratified by cohort of origin (A) and MG subtype (C). The heatmap shows the seasonal distribution of new MG cases per year (B).
Abbreviations. EOMG: early-onset MG; LOMG: late-onset MG; TAMG: thymoma-associated MG.

differences between EOMG and LOMG (Chia et al., 2024), while TAMG is considered a paraneoplastic disorder. The summer peak was more evident in patients with LOMG, likely due to their predominance within the population sample.

The underlying causes of the increased MG incidence during the summer months warrant further investigation. A plausible hypothesis is that high temperatures may impair neuromuscular transmission. The detrimental effects of heat on MG symptoms and electrophysiological findings are well documented. Several processes at the neuromuscular junction, including calcium influx into the nerve terminal, vesicles binding for acetylcholine (ACh) release, ACh binding on the post-synaptic membrane, endplate potential formation and Ach hydrolysis by acetylcholinesterase are all worsened by heat (Rutkove, 2001). Rutkove et al. demonstrated a significant enhancement of the decrement of compound muscle action potentials induced by repetitive nerve stimulation at elevated temperature in MG patients (Rutkove et al., 1998). Furthermore, seasonal infections (e.g., adenoviruses or varicella zoster

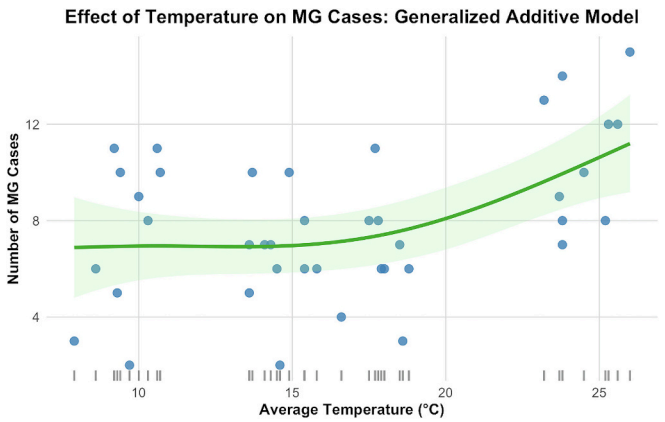

Fig. 2. Generalized Additive Model (GAM) depicting the non-linear relationship between temperature and myasthenia gravis (MG) cases.
The blue curve represents the estimated smooth function of temperature's effect on MG cases, modeled with a cubic spline. The shaded region indicates the 95 % confidence interval. The rug plot at the bottom displays the distribution of observed temperature values. The smooth term for temperature was statistically significant ($p = 0.005$), indicating a non-linear association between temperature and MG cases. The model explains 34.3 % of the deviance, underscoring the role of temperature in influencing MG case incidence. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

virus in summer) or use of antibiotics may also play a role in triggering MG worsening. The predominance of LOMG patients in our study suggests a higher susceptibility to seasonal variations in this group, aligning with demographic shifts in MG observed over the past two decades (Rostedt et al., 2022).

Our study has certain limitations. Firstly, the retrospective design did not permit the investigation of other potential risk factors associated with MG onset such as infections, vaccinations or use of drugs. Secondly, the study is limited to an Italian population, and our findings may not be generalizable to other countries, although similar seasonality patterns have been reported in the US, as discussed. Further research on larger populations is needed to confirm our data and explore new hypotheses regarding environmental factors in MG development. Identifying the environmental triggers underlying the association between seasonality and MG onset could provide opportunities for the development of new preventive and treatment strategies.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

CRediT authorship contribution statement

Silvia Falso: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Pietro Zara:** Investigation, Formal analysis, Data curation. **Sofia Marini:** Methodology, Investigation, Data curation. **Mariangela Puci:** Methodology, Formal analysis, Data curation. **Eleonora Sabatelli:** Methodology, Investigation, Data curation. **Giovanni Sotgiu:** Methodology, Formal analysis, Data curation. **Martina Marini:** Methodology, Investigation, Data curation. **Gregorio Spagni:** Methodology, Formal analysis, Data curation, Conceptualization. **Amelia Evoli:** Methodology, Investigation, Data curation, Conceptualization. **Paolo Solla:** Methodology, Investigation, Data curation. **Raffaele Iorio:** Writing – review & editing, Visualization, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Elia Sechi:** Writing – review & editing, Visualization, Supervision, Methodology, Investigation,

Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

RI has received consultancy fees and speaker honoraria from Alexion, Argenx, UCB and Dianthus Therapeutics. ES has received speaker honoraria and support for attending scientific meetings from Alexion, Horizon and Roche. He serves as an editorial board member for BMC Neurology and Frontiers in Neurology. The remaining authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jneuroim.2025.578524.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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