UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE
„CAROL DAVILA“ DIN BUCUREȘTI

Str. Dionisie Lupu 37, sector 2, București, 020021, România, www.umfcd.ro, email: rectorat@umfcd.ro

“CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

DOCTORAL SCHOOL MEDICINE

Myasthenia Gravis – Individualization and Transdisciplinary Optimization of Treatment

PhD THESIS SUMMARY

PhD supervisor:

PROF. UNIV. DR. RIGA SORIN

PhD-Student:

MIHALACHE OANA ANTONIA

2024

Table of Contents

Introduction

The association of psychiatric comorbidities with neurological conditions represents a frequently encountered and complex clinical challenge, potentially affecting up to 50% of patients with neurological disorders (12). Patients who present with both a neurological disease and a psychiatric disorder may have more extended hospital stays, either due to reduced autonomy and compliance with treatment or due to the presence of additional symptoms that may delay discharge (3).

Recent studies indicate a high prevalence of psychiatric disorders such as depression and anxiety among patients with Myasthenia Gravis (MG) (4–6), which is even higher compared to other autoimmune diseases (7). These comorbidities can significantly complicate the clinical picture, negatively influencing the prognosis and patients' quality of life (8–10). Unfortunately, psychiatric pathologies are often underdiagnosed and inadequately treated, leading to worsening symptoms of both comorbidities (11-12).

The increased risk of depressive disorders in MG patients can be attributed to a variety of factors, such as the problematic management of an unpredictable and debilitating chronic disease that imposes multiple restrictions in daily life or the stress created by variable symptoms and the uncertainty felt living with a chronic condition, as well as the treatment options for the disease, which may cause psychiatric morbidity, all associated with the presence of pro-inflammatory mediators in MG specific to autoimmune diseases.

Managing MG becomes even more difficult due to the considerable variability in disease severity between individuals and within the same individual (13-14).

The study of the relationship between MG and psychiatric symptoms represents an integrated and holistic approach to these two medical conditions, which have been studied separately until now. The novelty element of the proposed doctoral research is combining knowledge from different fields and analyzing the correlation between MG and mental health.

My motivation to investigate the relationship between depression and MG arose from my professional experience in the MG Unit of the Neurology Department at Fundeni Clinical Institute. There, I had the opportunity to closely monitor patients' evolution and observe the mental state's influence on disease progression and treatment response. These findings prompted me to explore this interaction more deeply.

I. General Part

1. Myasthenia Gravis

MG is a rare chronic disease considered the most well-known autoimmune disorder of the neuromuscular junction (NMJ) (15–20). It is characterized by fluctuating muscle weakness caused by pathogenic autoantibodies of the immunoglobulin G (IgG) type and the complement system that binds to the NMJ's essential functional and structural proteins (14-21).

2.Depression

In the current context, where the prevalence of depression continues to increase and affects a vast segment of the global population, the diagnosis and treatment of depression represent a significant priority in mental health (22-23). This mental disorder not only affects the emotional well-being and quality of life of those suffering but also has repercussions on physical health, professional performance, and interpersonal relationships (24-25).

2.1. The Impact of Inflammation on Depression

Recent psychiatric studies have hypothesized that interactions between inflammatory pathways, neural circuits, and neurotransmitters are involved in the pathogenesis and pathophysiological processes of depression. Although inflammation cannot explain the entire pathophysiology of depression, it represents an essential pathogenic mechanism (26–29).

Clinical and epidemiological research has shown that patients suffering from depression have higher levels of inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α), which can modulate neurotransmitter activity, inhibit neurogenesis, and reduce synaptic plasticity (30-33).

Chronic inflammation also activates the hypothalamic-pituitary-adrenal (HPA) axis, which is responsible for cortisol production and can exacerbate depressive symptoms. Peripheral cytokines can act directly on neurons and support cells such as astrocytes and microglia after crossing the blood-brain barrier or through signals mediated by afferent pathways such as those from the vagus nerve (29, 34-35).

Some studies have revealed that depression is significantly more frequent in patients with autoimmune or infectious diseases than in the general population (26). These conditions are

associated with elevated levels of systemic inflammation, leading to continuous production of pro-inflammatory cytokines. These molecules cross the blood-brain barrier and can influence neuronal and synaptic function, negatively affecting neurotransmission and synaptic plasticity in the brain, thus contributing to the development of depressive symptoms (28, 36).

These findings underscore the close connection between the immune system and mental health. The data highlight a bidirectional relationship between depression and inflammation, indicating that depression can induce inflammation, and this, in turn, can be a risk factor for the development of depression (37-38). This interdependence emphasizes the importance of an integrated approach in the treatment and management of autoimmune and infectious diseases to reduce the risk of depression and improve patients' quality of life. Implementing therapeutic strategies that simultaneously address inflammation and depressive symptoms can lead to more favorable clinical outcomes and better long-term mental health.

3. Myasthenia Gravis and Depression - A Complex Connection

Depression is a common comorbidity in people with chronic autoimmune diseases, and MG is no exception (39). Research shows that there is a high prevalence of depressive and anxiety disorders among patients diagnosed with MG. This association between MG and mental health disorders not only exacerbates patient suffering but also complicates the overall management of the disease. Understanding this interrelationship is essential for developing effective treatment strategies and providing adequate psychological support (40).

Although depression and MG seem like two distinct diseases, recent research suggests that these pathologies share common inflammatory mechanisms that may contribute to maintaining the interrelationship (39). Inflammation caused by the autoimmune response plays a central role in the pathophysiology of MG (41-42), and the association between systemic inflammation and depression is increasingly described in the specialized literature (43-45).

Both MG and depression are associated with elevated levels of pro-inflammatory cytokines; the autoimmune response triggers the release of cytokines that sustain inflammation and promote muscle damage (46-48), while in depression, elevated levels of interleukins such as IL-6 can influence various brain functions, being associated with diurnal mood variations and sleep disturbances (49-50).

MG can present significant challenges in terms of early diagnosis, which is often delayed because myasthenic symptoms such as respiratory disorders, impaired facial muscles with hypomimia, loss of tone, and fatigue (21, 51-52) frequently overlap with those of psychiatric conditions such as mood changes, tachypnea, social withdrawal, anxiety, which can lead to diagnostic errors and, implicitly, to inappropriate or delayed treatments (39, 53). A significant number of patients may initially be diagnosed with depression due to common symptoms, only to be later diagnosed with MG as clinical manifestations become more evident and specific to the autoimmune disease (54-55).

Depression in MG patients is often under-treated and underestimated because mild myasthenic symptoms can overlap with the somatic symptoms of depression (10, 56).

Moreover, psychiatric symptoms that appear during the evolution of MG are frequently mistaken for signs of the disease, mimicking an exacerbation of MG and negatively affecting the patients' progression (53).

Another essential aspect in managing psychiatric disorders associated with MG is the selection of psychiatric treatment. Treating symptoms of depression and anxiety in this context requires special attention due to possible interactions between psychiatric medication and clinical manifestations of MG. Careful selection of drugs and close monitoring of their effects are essential to manage these conditions effectively. The choice of personalized strategies aims to alleviate psychiatric symptoms without aggravating the specific muscular weakness of MG (40, 57-58).

II. Personal Contributions

4. Working Hypothesis and General Objectives

This research aims to investigate and elaborate on the complex relationship between MG and depression to highlight the existence of a bidirectional link between the two medical conditions. This research hypothesizes that there are possible associations between the severity of MG and the presence of depressive and anxious symptoms, and an integrative and individualized approach to these may lead to an improvement in patient prognosis.

General Objectives of the Study:

- Identify socio-demographic and clinical factors that may be associated with depressive disorders in MG patients.

- Compare the evolution of myasthenic symptoms between MG patients diagnosed and treated for depression and those without a diagnosis of depression by evaluating scores: the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale and the Quantitative Myasthenia Gravis (QMG) score.
- Investigate possible associations between the severity of myasthenia symptoms and various clinical and demographic parameters.
- Analyze the relationship between anxious-depressive symptoms quantified by the Hamilton Depression Scale (HAM-D) and the Hamilton Anxiety Scale (HAM-A) and the severity of MG using indicators such as the number of exacerbations and their duration (in days).
- Identify how specific MG variables may influence mental health and, conversely, how mental health affects the clinical course of MG.

This research is structured into three distinct studies, each addressing specific and complementary aspects of the investigated problem. Together, they provide a comprehensive and complex perspective on the interaction between MG and psychiatric disorders.

- First Study: "Personal Contributions Regarding Depression as a Factor Contributing to the Clinical Evolution of MG Patients" - This study initially conducted a comparative analysis between the two groups of patients, examining socio-demographic factors, clinical variables, and treatment regimens, and then investigated the evolution of MG by measuring evaluation scores - MG-ADL and QMG at the initial time and after six months, individually in both groups of patients and comparatively between the two groups.
- Second Study: "The Association Between Depressive Disorders and MG Severity"—This study explored possible associations between the severity of MG and various predictors in both groups of patients. The predictors used were clinical and demographic parameters and QMG, MG-ADL, HAM-D, and HAM-A scores monitored at two different points in evolution.
- Third Study: "Exploring the Bidirectional Relationship Between MG and Psychiatric Comorbidities"—This study investigated possible associations between MG

progression, depression, and anxiety in patient group A and examined the treatment response in this group of patients, comparing QMG, HAM-D, and HAM-A scale values at the study entry point and six months later.

5. General Research Methodology

5.1. Study Design

"Myasthenia Gravis - Individualization and Transdisciplinary Optimization of Treatment" study was conducted through prospective longitudinal observational research. The Fundeni Clinical Institute Ethics Council approved the study according to specific procedures and regulations—No. 57523.

The study group included patients diagnosed with MG who were hospitalized in the Neurology Clinic II—Myasthenia Gravis Unit of the Fundeni Clinical Institute from January 2019 to December 2020. They were selected by consecutive sampling based on inclusion and exclusion criteria.

The research comprised two evaluations during the study. Patients were initially assessed during hospitalization at the time of inclusion in the study (T0) and later after six months (T1), this interval is chosen as it represents the average period at which MG patients are re-evaluated in our clinic.

Evaluations were conducted by a multidisciplinary team consisting of a neurologist and a psychiatrist.

Neurological evaluation included the following components:

- Anamnesis and neurological clinical examination
- Confirmation of MG diagnosis
- Specific scales for MG evaluation
- Documentation of specific MG treatment

The psychiatric evaluation included the following components:

- Semi-structured interview for the assessment of alcohol/substance abuse, mental retardation, dementia, schizophrenia, schizoaffective disorder, and bipolar disorder

- Diagnosis or confirmation of depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)
- Documentation of psychiatric treatment followed by the patient and compliance with it
- Specific scales for psychiatric evaluation.

After the psychiatric evaluation, patients who required psychiatric treatment were prescribed a therapeutic regimen. Patients were periodically monitored to assess treatment efficacy and adjust therapeutic interventions.

After evaluation, patients were divided into two distinct groups:

- **Group A**, which included 49 MG patients diagnosed with depressive disorder and who were undergoing antidepressant and/or anxiolytic and/or sleep-inducing treatment.
- **Group B**, which included 73 patients who did not meet the diagnostic criteria for depressive disorder.

5.2. Screening Criteria for Patient Selection

Inclusion Criteria:

- Age over 18 years
- Confirmed diagnosis of autoimmune MG
- Completion of the informed consent form

Exclusion Criteria:

- Incomplete anamnesis data
- Patients in MGFA class V
- History of psychiatric disorders (except for depression and anxiety)
- History of substance abuse or dependence
- History of steroid-induced psychosis
- Discontinuation of recommended psychiatric or neurological treatment during the six months

6. Personal Contributions Regarding Depression as a Factor Contributing to the Clinical Evolution of MG Patients

6.1. Introduction (Working Hypotheses and Specific Objectives)

The study's main objective was to investigate possible differences in the evolution of MG between patients in groups A and B.

Specific Objectives:

- Conduct a comparative analysis between the two groups of patients
- Investigate the reduction of MG-ADL and QMG evaluation scores after six months of treatment for both groups of patients
- Compare the differences between MG-ADL and QMG scores in the two groups of patients

Working Hypothesis:

MG patients with depressive disorders have a different disease course than MG patients without depressive disorders, and the presence of depression is associated with more severe forms of MG. Correct diagnosis and treatment of depressive disorders contribute to the improvement of MG-specific symptomatology.

6.2. Patients and Methods

The selection of patients and the methodology used in this study were presented in detail earlier in Chapter 5, "General Research Methodology."

The study's primary endpoints were the MG-ADL and QMG values measured at T0 and T1. Using bidirectional paired T-tests, it was investigated whether there was a reduction in both scores at T1 separately in both groups of patients.

Differences between the two scores were compared between the two groups of patients using a bidirectional Welch test.

A comparative analysis was performed between the two groups of patients. Welch t-tests were used for continuous variables, and chi-square or Fisher exact tests were used for categorical variables.

P-values less than 0.05 were considered statistically significant.

6.3. Results

Comparing the socio-demographic characteristics of patients in the two groups, we observe that the average age of patients in group A is significantly lower (47.27 years, SD = 14.88) compared to group B (58.97 years, SD = 14.67) with a p-value < 0.001. The gender distribution does not show a statistically significant difference (p = 0.081), although group A has a higher percentage of women (76%) compared to group B (60%). Regarding the level of education, there are no significant differences between groups (p = 0.56), with similar proportions of patients with medium and higher education in both groups. The environment of origin also does not differ significantly between groups (p = 0.19), although a higher percentage of patients in group B come from urban areas (63%) compared to group A (51%). These data suggest that despite significant age differences, the two groups are comparable in terms of gender distribution, education level, and environment of origin.

Comparing the two groups of patients in terms of clinical characteristics, we observe no statistically significant difference in the onset of the disease (p = 0.24). However, the average duration of the disease is significantly longer in group B (95.03 years, SD = 102.64) compared to group A (59.55 years, SD = 66.98) (p = 0.023). Also, group A has a higher average number of hospitalizations (1.55 SD = 1.08) than group B (1.12 SD = 0.37) (p = 0.01). Regarding myasthenic crises, these are much more frequent in group A (37%) compared to group B (5.5%) (p < 0.001). The distribution of MGFA classes shows significant differences, with more patients in group A in classes IIb and IIIb and in group B in classes IIa and IIb (p < 0.001). The proportion of patients who underwent thymectomy is higher in group A (55%) compared to group B (30%) (p = 0.006), and the incidence of thymoma is also higher in group A (31%) compared to group B (11%) (p = 0.007). The presence of anti-AChR antibodies does not differ significantly between groups (p = 0.99). These differences suggest significant variations in the evolution and management of the disease concerning the two groups of patients.

In the graph in Figure 6.1, a boxplot compares the differences in MG-ADL between the two groups of patients, and these are statistically significant (Group A vs. Group B); the bidirectional Welch T-test shows that the difference in means = 2.54, T-statistic = 3.83, degrees of freedom = 80.79, p = 0.0002, 95% confidence interval (CI) = (1.22 to 3.86). The median MG-ADL scores are considerably higher in group A, being approximately six compared to group B, where it is approximately 1. The variability of scores is also higher in group A, with a more comprehensive interquartile range (IQR), suggesting a greater dispersion of data. In contrast, group B shows more outlier values but generally lower variability. These observations indicate that depression significantly impacts daily activities and overall functioning, leading to higher and more variable MG-ADL scores.

The graph in Figure 6.2 shows the mean differences in QMG scores between the two groups are statistically significant (Group A vs. Group B). The bidirectional Welch T-test shows the difference in means = 4.68, T-statistic = 4.07, degrees of freedom = 88.82, $p < 0.0001$, 95% CI = (2.39 to 6.96). For patients in group A, the median difference in QMG scores is around 10, indicating a significant median reduction in symptoms, with a wide IQR from approximately 0 to 20, suggesting considerable variability in treatment responses. In contrast, for patients in group B, the median difference in QMG scores is close to 0, indicating a more modest reduction in symptoms, with a narrow IQR between -5 and 5, suggesting a more uniform and modest overall improvement. The presence of outliers in both groups indicates the existence of patients with atypical treatment responses. In conclusion, patients in group A experienced a more significant reduction in QMG scores, although with greater variability in responses, highlighting the need for personalized approaches to manage these patients' treatment.

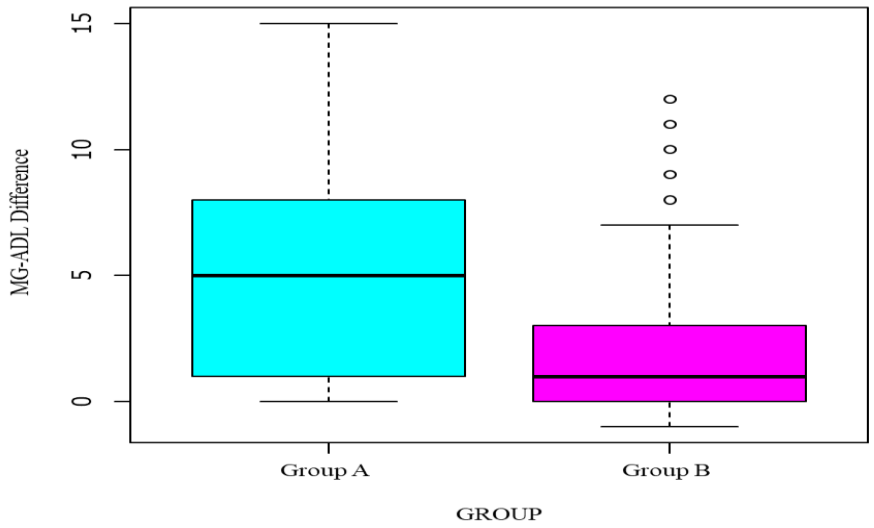

Fig. 6.1. Comparison of MG-ADL Differences

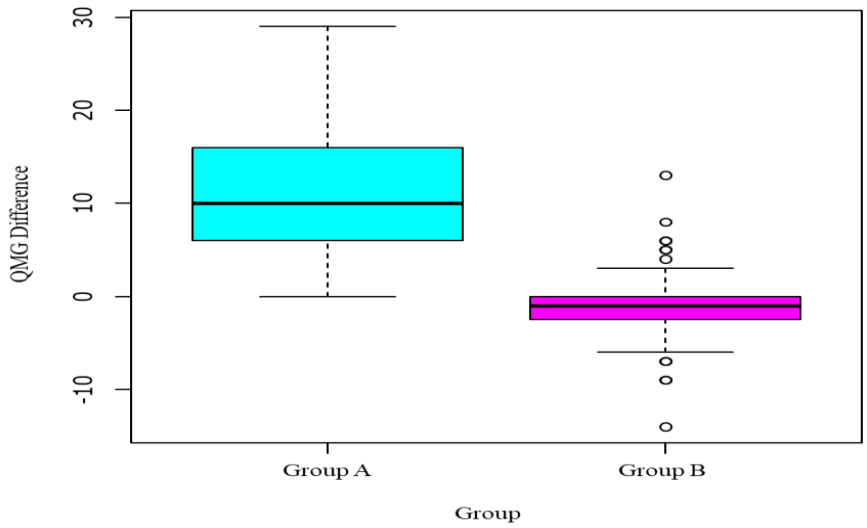

Fig. 6.2. Comparison of QMG Differences

7. The Association Between Depressive Disorders and MG Severity

7.1.Introduction

The main objective of this study was to investigate the associations between anxiety-depressive disorder and the severity of myasthenic symptoms.

Two variables quantified MG severity:

- Number of disease exacerbations (average number of exacerbations/year)
- Duration (in days) of exacerbations (average duration in days of the last exacerbation)

Specific Objectives:

- Investigate possible associations between myasthenia severity and various clinical and demographic parameters using a generalized linear model with a Poisson link function.
- Evaluate the evolution of QMG, MG-ADL, HAM-D, and HAM-A scores at two-time points and analyze them as predictors.

7.2. Patients and Methods

The selection of patients and the methodology used in this study were presented in detail earlier in Chapter 5 "General Research Methodology."

The first outcome is a variable that belongs to extended natural numbers with 0. Its mean (1.4) is approximately equal to the standard deviation (0.9), so the variable's distribution in the sample is approximately Poisson.

A generalized linear model with a Poisson link function (Poisson regression) was used to investigate the possible associations described earlier. The dependent variable was the number of exacerbations, and the independent variables were various clinical and demographic parameters monitored in the study.

The analysis for the total number of exacerbation days was similar to the previous outcome, but linear regression was used.

The QMG, MG-ADL, HAM-D, and HAM-A scores were monitored at two time points. To quantify this, a variable was created using the formula (Initial Value—Final Value) / Initial Value, which quantifies the evolution of the respective scores. The variable's initial value was also used as a predictor.

7.3. Results

The analysis of the impact of demographic and clinical factors on the average number of exacerbations revealed that age and the form of disease onset are the most influential factors.

It was observed that as age increases by one year, the average number of exacerbations decreases by 1%. Also, patients with ocular disease onset showed a 36% reduction in the average number of exacerbations compared to those with bulbar onset. On the other hand, factors such as sex, education level, environment of origin, disease duration, and previous treatment did not have a statistically significant impact on the average number of exacerbations.

The analysis of predictive factors on the average number of exacerbations in the study patients further included MGFA classification and QMG, MG-ADL, HAM-D, and HAM-A scores evaluated at two-time points. The data analysis showed that the following predictors had statistically significant influences on the average number of exacerbations: patients in MGFA class IIa had an almost 50% reduction in the average number of exacerbations compared to those in MGFA class III. A one-point increase in the initial QMG score was associated with a 2% increase in the average number of exacerbations. The initial MG-ADL score also suggested a 4% increase in the average number of exacerbations for each additional point, although this result was marginally insignificant. Similarly, the initial HAM-D score indicated a 3% increase in the average number of exacerbations for each additional point. Furthermore, a one-point increase in the initial HAM-A score was associated with a 1% increase in the average number of exacerbations, although this effect was also marginally insignificant.

The graph in Figure 7.1 illustrates the relationship between the HAM-D score at T0 and the average number of exacerbations. On the horizontal axis, the HAM-D score at T0 is represented, while on the vertical axis, the average number of exacerbations is shown. The red line in the graph shows a clear upward trend, indicating that as the HAM-D score at T0 increases, the average number of exacerbations also increases. This relationship is supported by the red-shaded confidence area, which widens as the HAM-D score increases, suggesting greater variability in the number of exacerbations estimates for higher scores. We conclude that a higher HAM-D score at T0 is associated with a higher average number of exacerbations, indicating that the severity of depression at T0 is correlated with an increased frequency of exacerbations.

The linear regression analysis of the total number of days of exacerbation revealed that the environment of origin and disease duration are significant predictors. Patients from urban

areas had an average of 3.1 fewer days of exacerbation compared to those from rural areas, and each additional day of disease was associated with an average decrease of 0.02 days of exacerbation.

The graph in Figure 7.2 illustrates the effect of the HAM-D score at T0 on the number of days of exacerbation. On the vertical axis, the number of days of exacerbation is represented, while on the horizontal axis is the HAM-D score at T0. The red line indicates a positive relationship between the HAM-D score at T0 and the number of days of exacerbation, showing that as the HAM-D score increases, the number of days of exacerbation also increases. The red-shaded area represents the confidence interval, indicating the variability of estimates. We observe that at a low initial HAM-D score (approximately 0-10), the average number of days of exacerbation is approximately 15 days, while at a high initial HAM-D score (approximately 40), the average number of days of exacerbation can exceed 25 days. This suggests that a higher initial HAM-D score, indicating a higher level of depression at onset, is associated with a greater number of days of exacerbation, reflecting a correlation between the severity of initial depression and the severity and duration of exacerbations.

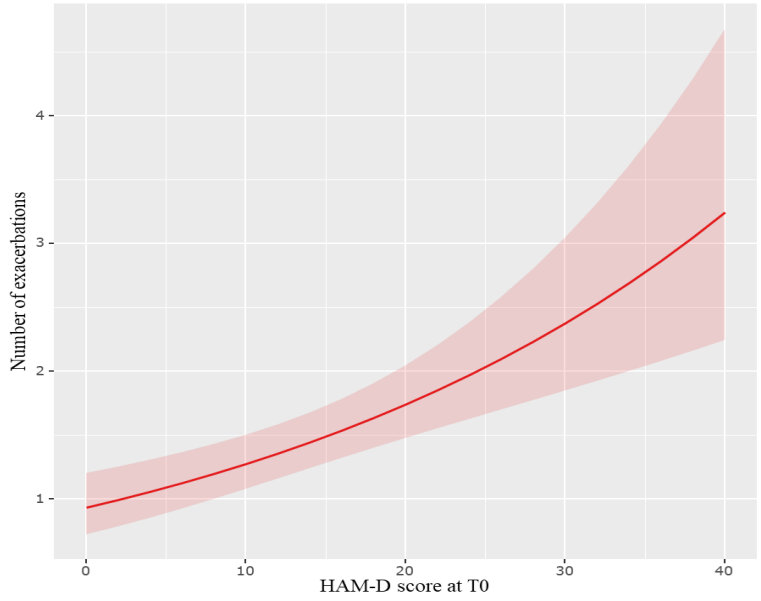

Fig. 7.1. Effect of HAM-D Score at T0 on the Average Number of Exacerbations

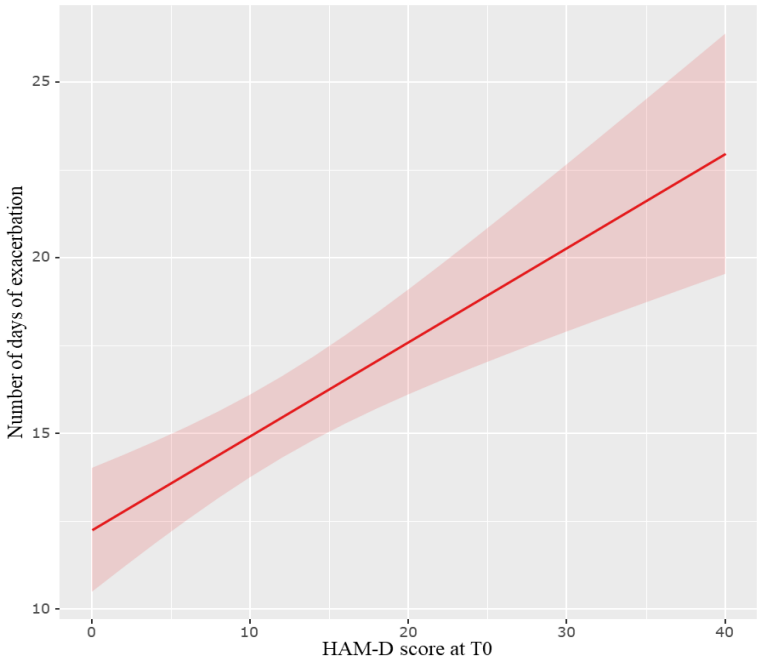

Fig. 7.2. Effect of HAM-D Score at T0 on the Number of Days of Exacerbation

8. Exploring the Bidirectional Relationship Between MG and Psychiatric Comorbidities

8.1.Introduction

The study aimed to investigate possible associations between MG progression, depression, and anxiety by analyzing the complex interaction between these conditions and identifying their mutual impact.

The secondary objective was to investigate the therapeutic response of MG patients with depression by comparing QMG, HAM-D, and HAM-A scale values at T0 and T1.

8.2. Patients and Methodology

The selection of patients and the methodology used in this study were presented in detail earlier in Chapter 5 "General Research Methodology."

The population included in this study consists only of group A, which comprised 49 MG patients diagnosed with depressive disorder and who were currently undergoing antidepressant and/or anxiolytic and/or sleep-inducing treatment.

The study's main endpoints were the QMG, HAM-D, and HAM-A values measured at T0 and T1.

To achieve the main objective, given that possible associations between variables measured in the same patient at two distinct times are being investigated, more precisely the investigation of possible associations between the QMG score and the HAM-D and HAM-A scales, a linear mixed model with random intercept was used using R packages, with the dependent variable being the QMG value measured at T0 and T1, while the independent variables were the HAM-D and HAM-A values measured at T0 and T1, as well as other demographic and clinical variables measured at the beginning of the study. For the secondary objective, Paired T-tests were used to compare QMG, HAM-D, and HAM-A scale values at T0 and T1.

The alpha significance level of the study was 0.05; p-values less than 0.05 were considered statistically significant.

8.3. Results

The study included a cohort of 49 patients diagnosed with MG and depressive disorder, with a mean age of 42.27 years, of whom the majority were women (76%). Almost half of the patients came from rural areas, and 59% had a medium level of education. The average duration of MG disease was 59.55 months. The majority of patients (90%) tested positive for anti-AChR antibodies, and 55% underwent thymectomy.

At the beginning of the study, 53% of patients were already on antidepressants, anxiolytics, or sleep inducers. After the initial evaluation, another 20 patients started antidepressant treatment during the six-month study period. The most frequently used antidepressants were escitalopram (51%) and sertraline (14%), and 65% of patients also received anxiolytics, primarily buspirone. Insomnia was treated in 24 patients using mirtazapine or trazodone.

The analysis of QMG, HAM-D, and HAM-A scores between the initial time (T0) and after six months (T1) showed a significant improvement in the physical and mental condition of patients, with all scores decreasing significantly ($p < 0.001$).

The study identified a positive correlation between the improvement of depressive symptoms (HAM-D) and the reduction in MG severity (QMG) as well as between the improvement of anxiety (HAM-A) and the improvement of MG symptoms. The simple linear

mixed model showed that a one-point reduction in the HAM-D score is associated with a 0.58-point decrease in the QMG score and a one-point reduction in the HAM-A score is associated with a 0.40-point decrease in the QMG score. The presence of anti-AChR antibodies was associated with a greater reduction in the QMG score.

Multivariate analysis confirmed the predictive significance of the HAM-D and HAM-A scores on MG evolution, with a 0.50-point reduction in the QMG score for each point decreased in the HAM-D. Although the association between HAM-A and QMG was positive, it was not statistically significant.

9. Conclusions and Personal Contributions

9.1. Conclusions

The study confirms that depressive symptoms are frequently encountered among individuals diagnosed with MG, with a depression prevalence of 40.16% in the studied patient cohort.

The research highlighted the importance of a transdisciplinary approach in the treatment of MG, emphasizing the need to integrate psychiatric treatments into the management of MG patients. The results suggest that treating depression can significantly improve the clinical course of MG, providing a new direction for optimizing therapeutic strategies.

The general objectives of the study were achieved as follows:

- Identifying socio-demographic and clinical factors that may be associated with depressive disorders in MG patients:

  Patients in group A diagnosed and treated for depressive disorder are younger and have more severe clinical characteristics compared to those in group B.

  Despite a shorter duration of the disease, patients in group A required more hospitalizations and experienced myasthenic crises more frequently. Also, group A had a higher incidence of thymoma.

  In group A, there were more women and a higher percentage of patients living in rural areas, although these differences were not statistically significant.

  Our study highlighted significant differences in the treatment of MG patients between groups A and B. Group A patients required higher doses of corticosteroids and

pyridostigmine at the initial time and maintained an increased need for pyridostigmine at the six-month evaluation.

- Comparing the evolution of myasthenic symptoms between MG patients diagnosed and treated for depression and those without a diagnosis of depression by evaluating MG-ADL and QMG scores:

  Patients in group A had higher initial disease severity scores on the MG-ADL and QMG evaluation scales at T0.

  The analysis of MG-ADL and QMG scores reveals a general improvement in patient condition, with a significant reduction in scores in both groups of patients. Patients with depression recorded a greater median reduction in scores, although with greater variability, indicating heterogeneous treatment responses.

  Patients without depression showed a more uniform but modest improvement in scores, starting from lower initial disease severity scores than those in group B.

- Investigating possible associations between myasthenia severity and various clinical and demographic parameters:

  The following effects related to MG severity, evaluated by the average number of disease exacerbations per year, were observed:

  - Disease Onset: Compared to spinal onset, bulbar onset is associated with an average increase of 13% in the number of exacerbations. In contrast, ocular onset is associated with an average decrease of 17% in the number of exacerbations.
  - MGFA Classification: Compared to stage IIb MGFA, stage III MGFA of the disease is associated with an average increase of 13% in the number of exacerbations, while stage IIa MGFA is associated with an average decrease of 6% in the number of exacerbations.
  - MG-ADL Score: No significant impact of the MG-ADL score on the number of exacerbations was identified.
  - Thymic Tumor: Patients with thymoma had an average increase of 9% in the number of exacerbations.
  - Cortisol: The dose of cortisol did not have a significant effect on the number of exacerbations.

- Sleep Inducer: Patients who received sleep inducers showed an average increase of 20% in the number of exacerbations.

  The following effects related to MG severity, measured by the average duration of the last exacerbation (in days), were highlighted:
- Environment of Origin: Patients from rural areas had an average duration of exacerbations two days longer compared to patients from urban areas.
- MGFA Classification: Compared to stage IIb MGFA, in stage IIa MGFA, the average duration of exacerbations was 0.90 days shorter, while in stage III MGFA, it was 0.90 days longer.
- Initial QMG Score: A one-unit increase in the initial QMG score is associated with an average increase of 0.1 days in the duration of exacerbations.
- Initial MG-ADL Score: A one-unit increase in the initial MG-ADL score is associated with an average increase of 0.2 days in the duration of exacerbations.
- Sleep Inducer Administration: In patients who received sleep inducers, the average duration of exacerbations was 0.02 days longer.

- Analyzing the relationship between anxious-depressive symptoms evaluated by HAM-D and HAM-A scores and MG severity measured by the number and duration of exacerbations revealed the following conclusions:
  - HAM-D Score: A one-unit increase in the initial HAM-D score is associated with an average increase of 3% in the number of disease exacerbations. Additionally, a one-unit increase in the initial HAM-D score is associated with an average increase of 0.12 days in the duration of exacerbations.
  - HAM-A Score: The initial HAM-A score did not have a significant impact on the number of exacerbations or the duration of exacerbations.

- Identifying mutual influences between specific MG variables and mental health:
  - Association between QMG and HAM-D scores: The analysis revealed a statistically significant positive association between QMG and HAM-D scores. Specifically, a one-point reduction in the HAM-D score is correlated with a 0.50-point decrease in the QMG score, suggesting that improving depressive symptoms may have a beneficial effect on the physical symptoms of MG.

- Association between QMG and HAM-A scores: A positive association between QMG and HAM-A scores was observed, but this effect was not statistically significant. Specifically, a one-point reduction in the HAM-A score is associated with a 0.21-point decrease in the QMG score, but this correlation did not reach statistical significance.

9.2. Personal Contributions

This original study evaluates various aspects of MG patients that are often underestimated but have direct implications in clinical practice. This research analyzes multiple relevant outcomes for patients, including numerous variables and clinical scales to assess potential interrelationships.

The personal contributions of this study consist of clarifying the complex relationships between MG severity and anxious-depressive symptoms:

- The research highlights the significant impact of depression on the clinical evolution of MG patients, demonstrating that depressive patients exhibit greater symptom severity and reduced quality of life. Through a comparative analysis of two distinct groups of patients, it was found that depression worsens MG-ADL and QMG scores (Chapter 6.3.3).
- The research suggests that initial scores on depression (HAM-D) and anxiety (HAM-A) assessment scales are strongly correlated with the subsequent severity of MG symptoms, being associated with a higher frequency and longer duration of exacerbations (Chapter 7.3.1. Chapter 7.3.2.).
- The research results confirmed that not only does MG influence patients' mental state, but depression can also exacerbate MG symptoms, suggesting that improving depression, evaluated by HAM-D scores, is associated with a statistically significant reduction in MG physical symptoms, measured by the QMG score (Chapter 8.3.2.).
- The research also provided clarifications on the influence of bulbar onset and advanced MGFA stages on the number of exacerbations compared to ocular onset and early MGFA stages (Chapter 7.3.1).

Following the analyses, the need for personalized treatment for MG and depression patients was highlighted, suggesting that including antidepressant and anxiolytic treatments in

the therapeutic regimen of MG patients can significantly improve disease progression. This contribution underscores the need for a personalized and interdisciplinary approach to managing this complex condition and provides a new direction for optimizing treatment strategies tailored to individual patient needs.

Future research should focus on developing holistic treatment plans involving collaboration between neurologists, psychiatrists, psychologists, social workers, and other healthcare specialists. These plans should provide emotional support and address the adaptation to the working and living conditions of patients.

Additionally, special attention should be given to the continuous education of patients and their families to ensure efficient and comprehensive disease management. The ultimate goal is to improve the quality of life and emotional well-being of those affected by MG.

Selective Bibliography

1. MOREIRA DG OLIVEIRA EML de COELHO FM dos S FERRAZ HB FRANCISCO S BORGES V et al. What can be expected to be seen in a Neurology ward? Eleven-year experience in a Brazilian university hospital. Arq Neuropsiquiatr. 2021 Jun;79(6):478–82.

2. Lu E Pyatka N Burant CJ Sajatovic M. Systematic Literature Review of Psychiatric Comorbidities in Adults with Epilepsy. Journal of Clinical Neurology. 2021;17(2):176.

3. Gonçalves-Pinho M Martins B Costa A Ribeiro JP Freitas A Azevedo E et al. Psychiatric Comorbidities in Neurologic Hospitalizations in Portugal: A Nationwide Retrospective Observational Study. Acta Med Port. 2024 Jun 3;37(6):455–66.

4. Chu HT Tseng CC Liang CS Yeh TC Hu LY Yang AC et al. Risk of Depressive Disorders Following Myasthenia Gravis: A Nationwide Population-Based Retrospective Cohort Study. Front Psychiatry. 2019 Jul 9;10.

5. Marbin D Piper SK Lehnerer S Harms U Meisel A. Mental health in myasthenia gravis patients and its impact on caregiver burden. Sci Rep. 2022 Nov 11;12(1):19275.

6. Dewilde S Phillips G Paci S De Ruyck F Tollenaar NH Janssen MF. The Burden Patients with Myasthenia Gravis Experience in Terms of Breathing Fatigue Sleep Mental Health Discomfort and Usual Activities in Comparison to the General Population. Adv Ther. 2024 Jan 3;41(1):271–91.

7. Nadali J Ghavampour N Beiranvand F Maleki Takhtegahi M Heidari ME Salarvand S et al. Prevalence of depression and anxiety among myasthenia gravis (MG) patients: A systematic review and meta-analysis. Brain Behav. 2023 Jan 10;13(1).

8. Yang Y Zhang M Guo J Ma S Fan L Wang X et al. Quality of life in 188 patients with myasthenia gravis in China. International Journal of Neuroscience. 2016 May 3;126(5):455–62.

9. Braz NFT Rocha NP Vieira ÉLM Barbosa IG Gomez RS Kakehasi AM et al. Muscle strength and psychiatric symptoms influence health-related quality of life in patients with myasthenia gravis. Journal of Clinical Neuroscience. 2018 Apr;50:41–4.

10. Gavrilov Y V. Alekseeva TM Kreis OA Valko PO Weber KP Valko Y. Depression in myasthenia gravis: a heterogeneous and intriguing entity. J Neurol. 2020 Jun 5;267(6):1802–11.

11. Vitturi BK Kim AIH Mitre LP Pellegrinelli A Valerio BCO. Social professional and neuropsychiatric outcomes in patients with myasthenia gravis. Neurological Sciences. 2021 Jan 26;42(1):167–73.

12. Dawood S Poole N Fung R Agrawal N. Neurologists' detection and recognition of mental disorder in a tertiary in-patient neurological unit. BJPsych Bull. 2018 Feb 30;42(1):19–23.

13. Estephan E de P Baima JPS Zambon AA. Myasthenia gravis in clinical practice. Arq Neuropsiquiatr. 2022 May;80(5 suppl 1):257–65.

14. Berrih-Aknin S Frenkian-Cuvelier M Eymard B. Diagnostic and clinical classification of autoimmune myasthenia gravis. J Autoimmun. 2014 Feb;48–49:143–8.

15. Hehir MK Silvestri NJ. Generalized Myasthenia Gravis. Neurol Clin. 2018 May;36(2):253–60.

16. Gilhus NE Verschuuren JJ. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol. 2015 Oct;14(10):1023–36.

17. Gilhus NE Tzartos S Evoli A Palace J Burns TM Verschuuren JJGM. Myasthenia gravis. Nat Rev Dis Primers. 2019 May 2;5(1):30.

18. Lazaridis K Tzartos SJ. Autoantibody Specificities in Myasthenia Gravis; Implications for Improved Diagnostics and Therapeutics. Front Immunol. 2020 Feb 14;11.

19. Pascuzzi RM Bodkin CL. Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome: New Developments in Diagnosis and Treatment. Neuropsychiatr Dis Treat. 2022 Dec;Volume 18:3001–22.

20. Ciafaloni E. Myasthenia Gravis and Congenital Myasthenic Syndromes. CONTINUUM: Lifelong Learning in Neurology. 2019 Dec;25(6):1767–84.

21. Gilhus NE. Myasthenia Gravis. New England Journal of Medicine. 2016 Dec 29;375(26):2570–81.

22. Malhi GS Mann JJ. Depression. The Lancet. 2018 Nov;392(10161):2299–312.

23. Rehm J Shield KD. Global Burden of Disease and the Impact of Mental and Addictive Disorders. Curr Psychiatry Rep. 2019 Feb 7;21(2):10.

24. Alonso J Liu Z Evans-Lacko S Sadikova E Sampson N Chatterji S et al. Treatment gap for anxiety disorders is global: Results of the World Mental Health Surveys in 21 countries. Depress Anxiety. 2018 Mar;35(3):195–208.

25. Albert KM Newhouse PA. Estrogen Stress and Depression: Cognitive and Biological Interactions. Annu Rev Clin Psychol. 2019 May 7;15(1):399–423.

26. Jeon SW Kim YK. Inflammation-induced depression: Its pathophysiology and therapeutic implications. J Neuroimmunol. 2017 Dec;313:92–8.

27. Suneson K Lindahl J Chamli Hårsmar S Söderberg G Lindqvist D. Inflammatory Depression—Mechanisms and Non-Pharmacological Interventions. Int J Mol Sci. 2021 Feb 6;22(4):1640.

28. Li Z Ruan M Chen J Fang Y. Major Depressive Disorder: Advances in Neuroscience Research and Translational Applications. Neurosci Bull. 2021 Jun 13;37(6):863–80.

29. Miller AH Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol. 2016 Jan 29;16(1):22–34.

30. Pryce CR Fontana A. Depression in Autoimmune Diseases. In 2016. p. 139–54.

31. Köhler CA Freitas TH Stubbs B Maes M Solmi M Veronese N et al. Peripheral Alterations in Cytokine and Chemokine Levels After Antidepressant Drug Treatment for Major Depressive Disorder: Systematic Review and Meta-Analysis. Mol Neurobiol. 2017 Jun 13.

32. Kim Y Pang Y Park H Kim O Lee H. Cytokine associated with severity of depressive symptoms in female nurses in Korea. Front Public Health. 2023 Aug 10;11.

33. Lindqvist D Dhabhar FS James SJ Hough CM Jain FA Bersani FS et al. Oxidative stress inflammation and treatment response in major depression. Psychoneuroendocrinology. 2017 Feb;76:197–205.

34. Li B Yang W Ge T Wang Y Cui R. Stress induced microglial activation contributes to depression. Pharmacol Res. 2022 May;179:106145.

35. Innes S Pariante CM Borsini A. Microglial-driven changes in synaptic plasticity: A possible role in major depressive disorder. Psychoneuroendocrinology. 2019 Apr;102:236–47.

36. Serafini G Costanza A Aguglia A Amerio A Trabucco A Escelsior A et al. The Role of Inflammation in the Pathophysiology of Depression and Suicidal Behavior. Medical Clinics of North America. 2023 Jan;107(1):1–29.

37. Bica T Castelló R Toussaint LL Montesó-Curto P. Depression as a Risk Factor of Organic Diseases: An International Integrative Review. Journal of Nursing Scholarship. 2017 Jul 10;49(4):389–99.

38. Chan VKY Luo H Chan SSM Lau CS Yeung WWY Peng K et al. Treatment-resistant depression and risk of autoimmune diseases: evidence from a population-based cohort and nested case-control study. Transl Psychiatry. 2023 Mar 3;13(1):76.

39. Liu Y Tang X. Depressive Syndromes in Autoimmune Disorders of the Nervous System: Prevalence Etiology and Influence. Front Psychiatry. 2018 Sep 25;9.

40. Mihalache OA Vilciu C Petrescu DM Petrescu C Manea MC Ciobanu AM et al. Depression: A Contributing Factor to the Clinical Course in Myasthenia Gravis Patients. Medicina (B Aires). 2023 Dec 28;60(1):56.

41. Duan L Rao X Sigdel KR. Regulation of Inflammation in Autoimmune Disease. J Immunol Res. 2019 Feb 28;2019:1–2.

42. Huda R. Inflammation and autoimmune myasthenia gravis. Front Immunol. 2023 Jan 30;14.

43. Patil CR Suryakant Gawli C Bhatt S. Targeting inflammatory pathways for treatment of the major depressive disorder. Drug Discov Today. 2023 Sep;28(9):103697.

44. Wijaya MT Jin RR Liu X Zhang R Lee TMC. Towards a multidimensional model of inflamed depression. Brain Behav Immun Health. 2022 Dec;26:100564.

45. Kitzbichler MG Aruldass AR Barker GJ Wood TC Dowell NG Hurley SA et al. Peripheral inflammation is associated with micro-structural and functional connectivity changes in depression-related brain networks. Mol Psychiatry. 2021 Dec 17;26(12):7346–54.

46. Uzawa A Kanai T Kawaguchi N Oda F Himuro K Kuwabara S. Changes in inflammatory cytokine networks in myasthenia gravis. Sci Rep. 2016 May 13;6(1):25886.

47. Bahauddin A Ivannikov M Wang Z Jamaluddin M Curtis K Ibtehaj N et al. Histone Deacetylase Isoforms Differentially Modulate Inflammatory and Autoantibody Responses in a Mouse Model of Myasthenia Gravis. Front Neurol. 2022 Feb 10;12.

48. Uzawa A Kuwabara S Suzuki S Imai T Murai H Ozawa Y et al. Roles of cytokines and T cells in the pathogenesis of myasthenia gravis. Clin Exp Immunol. 2021 Feb 10;203(3):366–74.

49. Chu AL Stochl J Lewis G Zammit S Jones PB Khandaker GM

List of scientific publications

1. **Mihalache OA,** Vilciu C, Petrescu D-M, Petrescu C, Manea MC, Ciobanu AM, Ciobanu CA, Popa-Velea O, Riga S. Depression: A Contributing Factor to the Clinical Course in Myasthenia Gravis Patients. *Medicina*. 2024; 60(1):56. https://doi.org/10.3390/medicina60010056 https://www.mdpi.com/1648-9144/60/1/56

Chapter 6.

2. **Mihalache Oana-Antonia**, Vîlciu Crisanda, Petrescu Diana, Petrescu Cristian, Ciobanu Adela, Ciobanu Constantin, Riga Sorin. (2024). Exploring the bidirectional relationship between myasthenia gravis and psychiatric comorbidities. Psihiatru.ro. 2. 23. 10.26416/Psih.77.2.2024.9742. https://www.medichub.ro/reviste-de-specialitate/psihiatru-ro/exploring-the-bidirectional-relationship-between-myasthenia-gravis-and-psychiatric-comorbidities-id-9742-cmsid-66

Chapter 8.