Original Article

Assessment of Nonmotor Symptoms in Myasthenia Gravis: Fatigue and Disease Burden

Rahmi Tümay Ala, Onur Bulut[1], İhsan Şükrü Şengün[2]

Department of Neurology, Ermenek State Hospital, Karaman, [1]Department of Neurology and Clinical Neurophysiology, Konya City Hospital, Konya, [2]Department of Neurology, Faculİlty of Medicine, Dokuz Eylul University, İzmir, Turkey

Abstract

Background: Patients with myasthenia gravis (MG) experience fatigue throughout their lives, making it essential to distinguish fatigue from muscle weakness. We aimed to provide information about fatigue, its prevalence, its relation to personal and disease-specific factors, and the possible burden of the disease. **Subjects and Methods:** Fifty-three patients with MG who presented to our Neuromuscular Clinic between 2020 and 2022 were enrolled in the study. Patients were in pharmacologic remission or at the minimal manifestation stage according to the Myasthenia Gravis Foundation of America treatment status scale. A definitive diagnosis was based on a positive antibody test, a decrement response in repetitive nerve stimulation tests, and/or increased jitter or block on a single nerve fiber test in electromyography. To confirm a myasthenic exacerbation or crisis, the need for rescue treatment was assessed. Patients were divided into two groups based on whether they received rescue treatment. The Checklist for Individual Strength-Fatigue (CIS) questionnaire, the Quality of Life Questionnaire on Myasthenia Gravis (MG-QoL) assessment of fatigue, and the Quantitative Myasthenia Gravis Score for neurologic examinations were used. **Results:** The average fatigue score was 72, leading to 84% of patients being classified as fatigued, with a cutoff value of 40. The myasthenic crisis group exhibited worse CIS-total, CIS-physical fatigue, and CIS-subjective perception scores, as well as poorer quality of life scores, compared with the other patients. Opinions on the disease burden may vary because all the patients were in remission. **Conclusion:** Patients who experienced more crises throughout the course of the disease were in a more morbidity and had a greater disease burden compared with those who experienced fewer or no crises during remission periods. Fatigue represents a concept distinct from the muscle weakness detected during physical examinations; it significantly impacts patients' daily lives and serves as a strong indicator of disease burden.

Keywords: *Fatigue, global burden of disease, muscle weakness, myasthenia gravis, myasthenic exacerbation*

Submitted: 29-Jul-2024
Revised: 03-Dec-2024
Accepted: 03-Dec-2024
Published: 13-Jan-2025

Introduction

Myasthenia gravis (MG) is an autoimmune disease associated with antibodies against acetylcholine receptors and associated proteins at the neuromuscular junction.[1] The prevalence of MG is estimated to be around 20 per 100,000.[2] Muscle fatigability and fluctuation are hallmarks of the disease, and patients report variable symptoms based on the affected muscle groups. Ptosis, ophthalmoparesis, proximal muscle weakness, and bulbar and respiratory muscle involvement can lead to diplopia, inability to perform daily activities, dysphagia, and dyspnea.

Access this article online

Quick Response Code:

Website: www.nsnjournal.org

DOI: 10.4103/nsn.nsn_106_24

Address for correspondence: Dr. Onur Bulut, Department of Neurology and Clinical Neurophysiology, Konya City Hospital, Karatay, Konya, Turkey.
E-mail: bulut8286@yahoo.co.uk

How to cite this article: Ala RT, Bulut O, Şengün İŞ. Assessment of nonmotor symptoms in myasthenia gravis: Fatigue and disease burden. Neurol Sci Neurophysiol 2024;41:223-30.

The Myasthenia Gravis Foundation of America (MGFA) scoring system is used to grade the clinical severity of the disease; progression of disease severity to a higher level on the scale indicates a myasthenic exacerbation, and experiencing life-threatening respiratory failure signifies a myasthenic crisis.[3]

MG was initially considered a purely motor disease, but "nonmotor symptoms" such as headache, fatigue, sleep disorders, restless legs syndrome, and possible cognitive impairment are also being detected.[4] Studies have shown that patients with MG experience more of these symptoms compared with healthy individuals; patients experiencing "nonmotor symptoms" reported lower quality of life (QoL) scores compared with other patients.[4] QoL scores are good indicators of treatment response and adherence; therefore, nonmotor symptoms are crucial for MG.[5]

Fatigue is a subjective and complex phenomenon associated with disproportionate exhaustion and loss of energy caused by physical tasks.[5] Patients often report fatigue in daily life but it is important to differentiate fatigue from muscle weakness.

We aimed to investigate the impact of disease-related factors on fatigue, especially myasthenic exacerbation, which is a decisive factor in immunosuppressive treatment. We also assessed the fatigue phenomenon and its effect on QoL among patients with MG.

Subjects and Methods

Study population

All patients had clinical signs and symptoms consistent with MG (ocular, bulbar, or generalized muscle weakness that occurred or worsened with fatigue), as well as a diagnosis based on a positive antibody test, a decrement response in repetitive nerve stimulation tests, and increased jitter or block on a single nerve fiber test in electromyography. The antibody status of the patients (anti-acetylcholine receptor antibody [anti-AChRAb] or anti-muscle-specific kinase antibody [anti-MuSK]) was recorded. Those negative for both antibodies were classified as double seronegative. Disease duration, age of onset, and medical history were assessed, and demographic data were obtained from the patients' medical records.

In line with the methods used in other studies in the literature, patients who experienced an increase in disease severity sufficient to move up a level in MGFA scoring and who therefore received rescue treatments (intravenous immunoglobulin or plasmapheresis) were classified as experiencing an exacerbation. Patients with life-threatening respiratory insufficiency were categorized as having a myasthenic crisis.[6] Patients were categorized as "MG with exacerbation (MGwE)" or "MG without Exacerbation (MGwoE)" based on the presence or absence of a myasthenic exacerbation. Patients classified as having a crisis were also included in the exacerbation group. Patients who experienced at least one exacerbation and/or crisis throughout their lives were grouped as "MGwE," and patients who had never experienced any of these were grouped as "MGwoE." It was investigated whether there were significant differences between the two groups in terms of demographic and clinical characteristics, Quantitative Myasthenia Gravis (QMG) scores, handgrip strength, and Checklist for Individual Strength-Fatigue (CIS) scores. Then, to investigate the effect of the number of exacerbations and/or crises experienced by patients in the MGwE group throughout their lives on CIS scores, patients were divided into three groups: "One exacerbation," "two exacerbations," and "three or more exacerbations," and statistically significant differences between the mean CIS scores were measured.

Patients with a history of other neurologic disorders and major depressive disorder were not included in the study. Patients with symptoms of sleep apnea (chronic loud snoring and witnessed apneas) and excessive daytime sleepiness were also excluded from the study.

The informed consent form, approved by the XXX Non-Interventional Research Ethics Committee (Protocol Number: 6309-GOA, Decision Number: 2021/21-16), was explained to the participants who presented to XXX Clinic, before the clinical interview and test applications. Following this, written consent was obtained from the participants.

Questionnaires and examinations

All patients, regardless of whether they had an exacerbation, were examined and their clinical scales were performed while they were in remission and during outpatient clinic visits.

Neurologic examinations, scale scoring, and questionnaire administration were performed in the morning to externalize daily fluctuations; the QMG test in patients under pyridostigmine treatment was performed 2 h after taking the medication.

The questionnaires and scales used in the assessment were administered through face-to-face clinical interviews.

Myasthenia Gravis Foundation of America Clinical Classification and Myasthenia Gravis Foundation of America Postintervention Status

According to the Recommendations for Clinical Research Standards from the Task Force of the Medical Scientific Advisory Board of the MGFA, patients were classified using the MGFA Clinical Classification and

MGFA Postintervention Status.[3] Clinical classification has five stages based on grading patients according to muscle weakness distribution (ocular, bulbar, axial, and extremity) and severity. Remission status is determined using the MGFA-Post Intervention Scale.

Quantitative Myasthenia Gravis Score

The QMG score is used to determine the clinical status of patients with MG.[7] This scale has been in use since 2000 and provides consistency among physicians. There are 13 items on the QMG scale, which are based on the strength of the ocular, bulbar, respiratory, facial, and extremity muscles. Each muscle group is graded between 0 and 3, with a total score ranging from 0 to 39. A higher score indicates more severe weakness. We conduct a detailed examination with subgroups, including ptosis and diplopia for ocular scores; swallowing, dysarthria, and vital capacity for bulbar scores; and arm and leg strength, along with hand grip, for extremity scores.

Myasthenia Gravis Quality of Life Questionnaire (MGQoL-15)

We used an MG-specific QoL questionnaire to determine the burden of the disease, its effect on daily activities, and the level of disability.[8] This questionnaire consists of 15 items related to social, physical, and psychological well-being, each rated between 0 and 4. Higher scores represent a lower QoL. The Turkish version of the test was used, which was validated by Taşcilar *et al*. in 2016.[9]

Checklist of Individual Strength (Checklist for Individual Strength-Fatigue)

The CIS questionnaire measures fatigue with four domains: fatigue severity, concentration problems, reduced motivation, and activity subscales.[10] Each item on CIS is rated on a 7-point scale, ranging from 1 to 7, with higher scores indicating more severe symptoms. The total CIS score can range from 20 to 140. Except for patients with cancer, adjusting the cutoff to 40 results in a better trade-off between sensitivity and specificity, leading to improved discrimination between severe fatigue and fatigue within normal ranges. We considered patients with fatigue scores of ≥40 to be fatigued. The Turkish version of the test was used, which was validated by Ergin and Yildirim in 2012.[11]

Data analysis and statistics

A *t*-test was performed for normally distributed variables and a Chi-square test for categorical variables to assess whether there were significant differences in demographic data between the groups. Mean and standard deviation (SD) are reported for normally distributed variables, and percentages are provided for categorical variables. For more than two independent groups, a one-way analysis of variance test was used to analyze whether there were significant differences in variables with normal distribution and homogeneous variance. Pearson's correlation was performed to investigate the correlation between variables that both showed normal distribution, and P and r values were reported. $P < 0.05$ was considered statistically significant.

Results

Demographic and clinical characteristics

A total of 53 patients, including 25 males and 28 females, aged between 17 and 83 years, were included in the study. Among the participants, 43 patients were AChRAb positive, 2 were MuSKAb positive, and 8 were double seronegative.

A total of 53 patients with MG participated (MGwE n = 22, MGwoE n = 31) in the study. Of the participants, 25 were male and 28 were female. The average age of the participants was 58.06 (SD 2.18) years, with a minimum age of 18 and a maximum age of 83 years. There were no significant differences between the two groups in terms of age (P = 0.174), sex (P = 0.062), alcohol consumption (P = 0.234), smoking (P = 0.365), and any antibody positivity (anti-AChRAb or anti-MuSKAb) (P = 0.561). Disease duration was longer in the MGwE group than in the MGwoE group (P = 0.012) [Table 1].

Table 1: The relationship between demographic and clinical characteristics and myasthenic exacerbation

	MGwE (n=22), n (%)	MGwoE (n=31), n (%)	P
Age	58.73±3.85	57.58±2.59	0.174
Sex (%)			
Male	7 (31.8)	18 (58)	0.062
Female	15 (68.2)	13 (42)	
Smoking (%)	10 (45.4)	18 (58)	0.365
Alcohol consumption	3 (13.6)	8 (25.8)	0.234
Disease duration "year", mean±SD	6.62±0.76	9.1±1.46	0.012
MGFA status			
MGFA 1	1 (1.88)	7 (13.2)	0.146
MGFA 2A	7 (13.2)	9 (16.98)	
MGFA 2B	2 (3.77)	6 (11.32)	
MGFA 3A	4 (7.54)	7 (13.2)	
MGFA 3B	8 (15.09)	2 (3.77)	
Antibody			
Anti-AChRAb positive	19 (86.3)	24 (77.4)	
Anti-MuSKAb positive	0	2 (6.4)	
Double seronegative	3 (13.6)	5 (16.1)	

SD: Standard deviation, MGFA: Myasthenia Gravis Foundation of America Status, Anti-AChRAb: Anti-acetylcholine receptor antibody, Anti-MuSKAb: Anti-muscle-specific kinase antibody, MGwE: Myasthenia gravis with exacerbation, MGwoE: Myasthenia gravis without exacerbation

Patients in the MGwE group were divided based on the number of exacerbations or crises they experienced: 10 patients had one, 5 had two, and 6 had three or more exacerbations or crises.

Seventeen patients were on azathioprine, seven were on mycophenolate mofetil therapy, and six were not receiving any immunosuppressive treatment in the MGwoE group. There were 5 patients on rituximab, 11 on mycophenolate mofetil, and 6 on azathioprine in the MGwE group.

Results of the scales and questionnaires

QMG-total, QMG-bulbar, and QMG-extremity scores were significantly higher in the MGwE group than in the MGwoE group (P = 0.002, P = 0.025, and P = 0.003, respectively). The MGwE group had lower QoL scores than the MGwoE group based on MGQoL-15 (P = 0.011). As part of the QMG-extremity score, hand grip strength was found to be statistically significantly lower in the group with myasthenic worsening compared with the group without worsening (P = 0.013). The MGwE group had significantly higher CIS-total and CIS-physical activity scores than the MGwoE group (P = 0.046 and P = 0.027, respectively). The mean CIS-total score was 72.2. With a cutoff value of 40, 45 out of 52 patients were fatigued. Six patients in the MGwoE group and one patient in the exacerbation group were not fatigued [Table 2].

As the number of myasthenic exacerbations or crises increased, patients reported higher CIS-total fatigue and subjective perception scores in the MGwE group [Table 3].

Table 2: The relationship between the scale and questionnaire results and myasthenic exacerbation

	MGwE (n=22)	MGwoE (n=31)	P
QMG scores, mean±SD			
Total	12.5±1.33	7.29±0.97	0.002
Ocular	2.18±0.39	1.67±0.33	0.304
Bulbar	2.45±0.43	1.22±0.25	0.025
Extremity	7.1±0.83	4±0.59	0.003
Hand grip strength (kg/W), mean±SD	25.67±2.08	32.86±1.82	0.013
CIS scores (mean)			
Total	80.81	65.82	0.046
Fatigue severity	37	30.82	0.090
Concentration problems	17.36	15.13	0.375
Reduced motivation	12.59	11.72	0.412
Activity	13.45	10.93	0.027

SD: Standard deviation, QMG: Quantitative Myasthenia Gravis Score, CIS: Checklist of Individual Strength, MGwE: Myasthenia gravis with exacerbation, MGwoE: Myasthenia gravis without exacerbation

The relationship between disease-related factors and the CIS questionnaire was also investigated. Patients were grouped according to the age of onset (early or late), antibody type (AChRAb positive, MuSKAb positive, or seronegative), immunosuppressive treatment (azathioprine, mycophenolate mofetil, and rituximab), and disease duration (≤years, 6–10 years, or >11 years). The CIS total and subscale scores for each group were analyzed and no statistically significant relationships were found.

QMG scores were evaluated as an indicator of disease severity, and this correlation analysis was performed to demonstrate the association of fatigue scales (CIS) with disease severity. The relationships between patients' QMG and CIS scores (both total scores and subtypes separately) were examined. A high level of correlation was found between CIS-Total and QMG-Total scores (P < 0.001), a low level of correlation between QMG-Ocular and CIS-Total scores (P < 0.032), a moderate level of correlation between CIS-Total and QMG-Bulbar scores (P < 0.001), and a moderate level of correlation between CIS-Total and QMG-Extremity scores (P < 0.001). For the relationship between CIS scores and MGQoL-15 scores, CIS-Total and CIS-Subjective Perception had a high correlation, and CIS-Fatigue Severity scores showed a moderate level of correlation with MG-QoL [Table 4].

Discussion

The concept of the global burden of disease has been proposed in recent years to provide a broader perspective on the outcomes of diseases and better calculate their consequences. In the 1990s, the World Health Organization, the World Bank, and Harvard University expressed it as "disease burden is, in effect, the gap between a population's actual health status and some "ideal" or reference status."[12] Currently, there is no consensus among medical professionals as to how chronic fatigue syndrome may be definitively diagnosed. It may include chronic, profound, disabling, and unexplained fatigue with coinciding symptoms such as sleep problems or postexertional malaise.[13] It signifies muscle weakness that resolves with rest and a multidimensional picture involving more chronic, diverse symptoms, necessitating a more comprehensive pathophysiologic explanation. Respiratory disorders during sleep and deterioration in QoL related to sleep,[14] restless leg syndrome,[15] and depression and anxiety[16] are symptoms that occur more frequently in patients with these conditions than in healthy populations and contribute to fatigue. There are also studies based on hypotheses regarding the role of acetylcholine in the pathophysiology of rapid eye movement sleep, but they

Table 3: The relationship between Checklist of Individual Strength scores and the number of myasthenic exacerbations

CIS scores (mean)	One exacerbation	Two exacerbations	Three or more exacerbations	*P*
Total	68.5	75.6	102.14	0.034
Fatigue severity	31.5	33.8	47.14	0.017
Concentration problems	15.2	13.6	23.14	0.052
Reduced motivation	10.9	12	15.42	0.085
Activity	12.1	12	16.42	0.264

CIS: Checklist of Individual Strength

Table 4: The relationships between patient's Quantitative Myasthenia Gravis Scores and the results of the Checklist of Individual Strength-fatigue questionnaire

CIS scores (mean)	QMG-total (*P*; *r*)	QMG-ocular (*P*; *r*)	QMG-bulbar (*P*; *r*)	QMG-extremity (*P*; *r*)	MGQOL-15 (*P*; *r*)
Total	<0.001; 0.604	0.032; 0.300	<0.001; 0.530	<0.001; 0.573	<0.001; 0.745
Fatigue severity	<0.001; 0.696	<0.001; 0.488	<0.001; 0.546	<0.001; 0.614	<0.001; 0.740
Concentration problems	0.003; 0.406	0.251; 0.164	0.002; 0.424	0.006; 0.381	<0.001; 0.552
Reduced motivation	0.017; 0.332	0.422; 0.115	0.103; 0.231	0.012; 0.351	0.51; 0.008
Activity	<0.001; 0.543	0.161; 0.199	<0.001; 0.480	<0.001; 0.477	<0.001; 0.530

The *P* and *r* values were obtained from the Pearson correlation analysis. QMG: Quantitative Myasthenia Gravis Score, CIS: Checklist of Individual Strength, MGQOL-15: Myasthenia Gravis Quality of Life Questionnaire

have not been able to present significant arguments due to being conducted on a small number of patients.[17]

There are many studies demonstrating the impact of fatigue on the burden of illness. In these studies, the relationship between disease severity, clinical subtype, symptoms, antibody status, treatment, social factors, and fatigue has been investigated. In a comprehensive study involving 1660 patients, female sex, older age, low income, partnership status, lower activities of daily life, symptoms of depression, anxiety, and fatigue, as well as self-perceived low social support, were associated with a lower health-related QoL in patients with MG.[18] In a survey conducted with 196 patients, correlation analysis adjusting for body mass index and sleep apnea revealed a moderate positive correlation between MGQoL-15, Myasthenia Gravis Activities of Daily Living (MG-ADL), and Fatigue Severity Scale.[19] Jordan *et al*. concluded that patients with long-standing MG reported experiencing more fatigue despite the absence of weakness.[20] In a study involving 200 patients, which evaluated age, sex, duration of illness, antibody status, treatment, thymectomy status, and other medications used for various reasons, fatigue was found in 56.1% of patients. Disease severity, depressive mood, and anti-MuSK antibody status were shown to be associated with fatigue.[21]

In 2020, a systematic review was conducted including 21 studies.[5] In this review, the lowest fatigue rate was 44%[22] and the highest was 82%.[23] In our study, 84% of our patients were fatigued, similar to earlier studies. Participants were in remission according to MGFA treatment status, which is an approving factor. This situation raises questions about the origin of fatigue and the factors that may affect it.

Fatigue is a multidimensional factor with many associated factors. We divided these into two groups, demographic and disease-related factors. Grohar-Murray *et al*. demonstrated that female patients showed much more fatigue in tests.[24] Sex, age, early- or late-onset MG, smoking, and alcohol consumption may play a role in fatigue, and our groups did not differ in these regards.

Disease severity was the primary factor investigated in earlier studies; MGFA classification,[25] MG-ADL, MG-QoL,[21] and QMG[26] are used for this. These studies showed that disease severity was correlated with fatigue. In our study, QMG scores were also strongly correlated with CIS scores. Disease duration is another aspect that could be related to fatigue. According to Kittiwatanapaisan *et al*., disease duration was the most impactful factor of fatigue despite QMG's correlation with fatigue; however, Tran *et al*. found the opposite.[26,27] In our study, disease duration was shorter in the exacerbation group (6.62 vs. 9.1 years). In the exacerbation group, CIS scores were higher; accordingly, disease duration alone does not solely affect fatigue and raises other questions about disease-related factors.

Earlier studies assessed thymectomy, autonomic impairment, immunosuppressive therapy, sleep disorders, depression, and antibody types. Westerberg *et al*. found that all thymoma-status patients reported fatigue.[28] We had six patients who had undergone thymectomy with fatigued status (CIS total score >40). Sleep disorders and depression evoke controversial opinions. Studies

on MG have not been able to clarify the relationship between fatigue and depression, leaving it uncertain whether depression is a cause or a consequence of fatigue. The similarities between fatigue and depression questionnaires further complicate distinguishing between the two conditions.[21,29] The relationship between depression and anxiety with fatigue in patients is controversial, and there are data indicating varying results.[30,31] Comorbidities including sleep disorders and depression may be impacting factors; therefore, we excluded patients with these conditions.

There was no difference in fatigue scores among patients receiving azathioprine, mycophenolate mofetil, or rituximab. Antibody type is a determinant factor for disease progression. We found no relationship between antibody type and the subtype of fatigue. Despite the anti-MuSK antibody correlation with fatigue in the literature, we did not have enough information in our study. There may be other factors contributing to fatigue; for example, Elsais *et al*. identified a strong correlation between fatigue and autonomic dysfunction.[22]

Ultimately, it is all about disease severity. The myasthenic exacerbation rate is a new way of evaluating disease severity. Myasthenic exacerbations and their impact on fatigue were not assessed in earlier studies, and our findings illustrate that they have an explicit effect. As stated in the method, all patients were evaluated in remission periods, regardless of whether they had an exacerbation, that is, the examination findings and scales reflect the patients' status in remission. The fact that patients who had exacerbations and/or crises in their past were different from those who had not, and those who had more were different in the remission period to those who had less, shows that exacerbations and/or crises constitute a morbidity burden. Although symptomatic treatment is also important, keeping the disease under good control and preventing exacerbations and/or crises will also bring about a better condition for patients in the long term. As far as we know, there is no study evaluating patients with MG using exacerbation rates in terms of life quality and fatigue scores.

Effective immunosuppressive treatment improves fatigue, but there is no information about exacerbations.[32] The postsynaptic membrane is not a passive immunologic target. Studies show that immunologic activation against the neuromuscular junction results in atrophic changes, reduced synaptic cleft volume, and decreased acetylcholine receptor clustering.[33] Rat models with myasthenic crisis show reduced sarcolemmal nitric oxide, which could be related to fatigue and muscle weakness.[34] According to these findings, we aimed to assess the relationship between fatigue and myasthenic exacerbations. CIS-total and CIS-physical activity scores were higher in the exacerbation group. Furthermore, as the patients received more rescue treatment, their fatigue questionnaire scores worsened.

Fatigue is multidimensional, and it has physical and mental aspects. The CIS scale has four subgroups, severity and physical activity, representing physical fatigue, and concentration and motivation, which better represent mental fatigue. CIS-physical activity was the only subgroup that showed a meaningful difference between the groups, indicating that fatigue has a primarily peripheral origin (13.45 vs. 10.93). Although not statistically significant, the exacerbation group had worse concentration and motivation scores, which raises questions about central fatigue. Feeling a lack of energy and concentration problems can be explained by central activation failure.[22,35] This has also been proposed as a defense mechanism.

The MGQoL questionnaire is a major tool used to assess clinical outcomes and disease burden.[32] Fatigue scores are strongly correlated with MGQoL scores, as in our study.[21,32] The strongest correlation was observed between subjective perception of fatigue and MGQoL. MG impacts fatigability and influences patients' perception of fatigue. Exacerbations directly increase fatigue and MGQoL, which can be explained as disease burden, or poor medication adherence indirectly.[36]

The limitation of our study is the small number of patients. The patient number was naturally limited because it was conducted face to face with patients during neurologic examinations. However, the fact that the study was conducted face to face with the patients is a strength because it increases its reliability. Since the aim of the study is to make a comparison between different patient types, there is no healthy control group.

Future studies may better illuminate the relationships between fatigue, which is a general concept, and many different parameters, and the individual relationships between the components of fatigue and the disease. The main goal of the treatment is to improve QoL; therefore, we need appropriate research criteria focused on QoL to evaluate the treatments. Advancing diagnostic tests may provide additional insight into seronegative participants who could not be included in our study.

Conclusion

Most patients with MG have both fatigue and a deterioration in QoL. Nonmotor symptoms that may not be included in routine neurologic evaluations have a significant impact on QoL. These effects increase as the number of disease flares (myasthenic crises) increases.

The fatigue experienced by patients with MG is a complex and multidimensional phenomenon, distinct from simple muscle weakness or fatigability.

Contribution details

Concept: R.T.A. and İ.Ş.Ş. Design: R.T.A. and İ.Ş.Ş. Definition of intellectual content: R.T.A., O.B., and İ.Ş.Ş. Literature search: R.T.A., O.B., and İ.Ş.Ş. Clinical studies: R.T.A. and İ.Ş.Ş. Data acquisition: R.T.A. and İ.Ş.Ş. Data analysis: R.T.A., O.B., and İ.Ş.Ş. Statistical analysis: R.T.A., O.B., and İ.Ş.Ş. Manuscript preparation: R.T.A., O.B., and İ.Ş.Ş. Manuscript editing: R.T.A., O.B., and İ.Ş.Ş. Manuscript review: R.T.A., O.B., and İ.Ş.Ş.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Gilhus NE. Myasthenia gravis. N Engl J Med 2016;375:2570-81.
2. Breiner A, Widdifield J, Katzberg HD, Barnett C, Bril V, Tu K. Epidemiology of myasthenia gravis in ontario, Canada. Neuromuscul Disord 2016;26:41-6.
3. Jaretzki A 3rd, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, *et al.* Myasthenia gravis: Recommendations for clinical research standards. Task force of the medical scientific advisory board of the myasthenia gravis foundation of America. Neurology 2000;55:16-23.
4. Tong O, Delfiner L, Herskovitz S. Pain, headache, and other non-motor symptoms in myasthenia gravis. Curr Pain Headache Rep 2018;22:39.
5. Ruiter AM, Verschuuren JJ, Tannemaat MR. Fatigue in patients with myasthenia gravis. A systematic review of the literature. Neuromuscul Disord 2020;30:631-9.
6. Rodrigues CL, de Freitas HC, Lima PR, de Oliveira Junior PH, Fernandes JM, D'Almeida JA, *et al.* Myasthenia gravis exacerbation and myasthenic crisis associated with COVID-19: Case series and literature review. Neurol Sci 2022;43:2271-6.
7. Bedlack RS, Simel DL, Bosworth H, Samsa G, Tucker-Lipscomb B, Sanders DB. Quantitative myasthenia gravis score: Assessment of responsiveness and longitudinal validity. Neurology 2005;64:1968-70.
8. Burns TM, Conaway MR, Cutter GR, Sanders DB, Muscle Study Group. Less is more, or almost as much: A 15-item quality-of-life instrument for myasthenia gravis. Muscle Nerve 2008;38:957-63.
9. Taşcilar NF, Saraçli Ö, Kurçer MA, Ankarali H, Emre U. Reliability and validity of the Turkish version of myastheniagravis-quality of life questionnaire-15 item. Turk J Med Sci 2016;46:1107-13.
10. Worm-Smeitink M, Gielissen M, Bloot L, van Laarhoven HW, van Engelen BG, van Riel P, *et al.* The assessment of fatigue: Psychometric qualities and norms for the checklist individual strength. J Psychosom Res 2017;98:40-6.
11. Ergin G, Yildirim Y. A validity and reliability study of the Turkish Checklist individual strength (CIS) questionnaire in musculoskeletal physical therapy patients. Physiother Theory Pract 2012;28:624-32.
12. Murray CJ, Lopez AD, editors. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020 (Summary). Harvard School of Public Health; 1996.
13. World Health Organization. Frequently Asked Questions About Chronic Fatigue Syndrome. Available from: https://www.who.int/standards/classifications/frequently-asked-questions/chronic-fatigue-syndrome. [Last accessed on 2024 May 18].
14. Oliveira EF, Nacif SR, Urbano JJ, Silva AS, Oliveira CS, Perez EA, *et al.* Sleep, lung function, and quality of life in patients with myasthenia gravis: A cross-sectional study. Neuromuscul Disord 2017;27:120-7.
15. Sieminski M, Bilińska M, Nyka WM. Increased frequency of restless legs syndrome in myasthenia gravis. Eur Neurol 2012;68:166-70.
16. 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;13:e2840.
17. Papazian O. Rapid eye movement sleep alterations in myasthenia gravis. Neurology 1976;26:311-6.
18. Lehnerer S, Jacobi J, Schilling R, Grittner U, Marbin D, Gerischer L, *et al.* Burden of disease in myasthenia gravis: Taking the patient's perspective. J Neurol 2022;269:3050-63.
19. Yang S, Miglis MG, Jaradeh S, Muppidi S. Myasthenia symptom burden, fatigue, and sleep: Are they related? J Clin Neuromuscul Dis 2021;22:123-8.
20. Jordan B, Mehl T, Schweden TL, Menge U, Zierz S. Assessment of physical fatigability and fatigue perception in myasthenia gravis. Muscle Nerve 2017;55:657-63.
21. Hoffmann S, Ramm J, Grittner U, Kohler S, Siedler J, Meisel A. Fatigue in myasthenia gravis: Risk factors and impact on quality of life. Brain Behav 2016;6:e00538.
22. Elsais A, Wyller VB, Loge JH, Kerty E. Fatigue in myasthenia gravis: Is it more than muscular weakness? BMC Neurol 2013;13:132.
23. Paul RH, Cohen RA, Goldstein JM, Gilchrist JM. Fatigue and its impact on patients with myasthenia gravis. Muscle Nerve 2000;23:1402-6.
24. Grohar-Murray ME, Becker A, Reilly S, Ricci M. Self-care actions to manage fatigue among myasthenia gravis patients. J Neurosci Nurs 1998;30:191-9.
25. Alekseeva TM, Gavrilov YV, Kreis OA, Valko PO, Weber KP, Valko Y. Fatigue in patients with myasthenia gravis. J Neurol 2018;265:2312-21.
26. Kittiwatanapaisan W, Gauthier DK, Williams AM, Oh SJ. Fatigue in myasthenia gravis patients. J Neurosci Nurs 2003;35:87-93, 106.
27. Tran C, Bril V, Katzberg HD, Barnett C. Fatigue is a relevant outcome in patients with myasthenia gravis. Muscle Nerve 2018;58:197-203.
28. Westerberg E, Landtblom AM, Punga AR. Lifestyle factors and disease-specific differences in subgroups of Swedish myasthenia gravis. Acta Neurol Scand 2018;138:557-65.
29. Paul RH, Cohen RA, Gilchrist JM. Ratings of subjective mental fatigue relate to cognitive performance in patients with myasthenia gravis. J Clin Neurosci 2002;9:243-6.
30. 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;41:271-91.

31. Gelinas D, Parvin-Nejad S, Phillips G, Cole C, Hughes T, Silvestri N, *et al.* The humanistic burden of myasthenia gravis: A systematic literature review. J Neurol Sci 2022;437:120268.
32. Andersen H, Mantegazza R, Wang JJ, O'Brien F, Patra K, Howard JF Jr., *et al.* Eculizumab improves fatigue in refractory generalized myasthenia gravis. Qual Life Res 2019;28:2247-54.
33. Vilquin JT, Bayer AC, Le Panse R, Berrih-Aknin S. The muscle is not a passive target in myasthenia gravis. Front Neurol 2019;10:1343.
34. Meinen S, Lin S, Rüegg MA, Punga AR. Fatigue and muscle atrophy in a mouse model of myasthenia gravis is paralleled by loss of sarcolemmal nNOS. PLoS One 2012;7:e44148.
35. Kartika L, Subadi I, Pawana IP, Andriana M, Sugianto P. Correlation of fatigue on walking ability in myasthenia gravis patients: A cross-sectional study. Ann Med Surg (Lond) 2024;86:115-20.
36. Law N, Davio K, Blunck M, Lobban D, Seddik K. The lived experience of myasthenia gravis: A patient-led analysis. Neurol Ther 2021;10:1103-25.