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Determinants of quality of life in Brazilian patients with myasthenia gravis

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OBJECTIVES: The aims of the current study were 1) to evaluate the reliability and validity of the Brazilian version of the 15-item Myasthenia Gravis Quality of Life Scale and 2) to investigate the quality of life of Brazilian patients with myasthenia gravis and its determinants.

METHODS: This cross-sectional study included 69 patients with myasthenia gravis who underwent neurological evaluation and completed questionnaires regarding quality of life (the 36-item Short Form of the Medical Outcomes Study and the 15-item Myasthenia Gravis Quality of Life Scale), anxiety and depressive symptoms.

RESULTS: The Brazilian version of the 15-item Myasthenia Gravis Quality of Life Scale showed high internal consistency and good concurrent validity with the 36-item Short Form of the Medical Outcomes Study and its subscales. Determinants of quality of life in Brazilian patients with myasthenia gravis included the current status of myasthenia gravis as assessed by the Myasthenia Gravis Composite, the current prednisone dose and the levels of anxiety and depression.

CONCLUSION: The Brazilian version of the 15-item Myasthenia Gravis Quality of Life Scale is a valid instrument. Symptom severity, prednisone dosage and anxiety and depression levels impact the quality of life of patients with myasthenia gravis.

KEYWORDS: Myasthenia Gravis; Quality of Life; Psychometrics; Neuropsychiatry.

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INTRODUCTION

Myasthenia gravis (MG) is characterized by fluctuating muscle weakness and fatigability, with great inter- and intra-individual variability (1-3). Due to its fluctuating course and clinical heterogeneity, the optimal approach to objectively evaluate the clinical profile, impact and treatment outcomes of MG has been discussed (4).

Measures of quality of life (QoL) have been widely used to follow patients with neuromuscular disorders, including MG (5). Tracking a disease via assessment of patients' perception of QoL may improve their care by promoting greater adherence to treatment and, ultimately, by leading to better clinical control and outcome (6,7).

Several studies have investigated the QoL of MG patients. Past studies employed the 36-item Short Form of the Medical Outcomes Study (SF-36), a non-disease-specific tool that assesses health-related QoL. However, SF-36 contains items not necessarily relevant to MG (*e.g.* bodily pain) and does not evaluate domains that are meaningful to MG (*e.g.* problems with vision, eating and speaking). Despite these limitations, QoL studies of MG patients that used the SF-36 demonstrated that patients with MG differed from healthy controls in all domains of SF-36, particularly in the rolephysical subscale (8,9). In addition, QoL scores modestly correlate with disease status among MG patients (8).

In 2008, a 60-item QoL questionnaire specific for MG (MG-QOL60) was developed and validated (10). This 60-item disease-specific instrument assesses the domains of mobility, symptoms, emotional well-being, general contentment, thinking and fatigue, family/social well-being, and additional concerns. However, as the authors themselves noted, a potential limitation of MG-QOL60 was the time required to complete the questionnaire. Accordingly, a 15-item MG-specific QoL scale (MG-QOL15) was recently developed from the MG-QOL60 as a more user-friendly instrument (11-13). The correlation coefficients for the

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Table 1 - Characteristics of the studied myasthenia gravis patients.

Characteristics	Patients (69)	
	N or Mean ± SD	% or Median (range)
Sex		
Male	14	20.3
Female	55	79.7
Age (years)	44.5 ± 10	45 (22-68)
Educational level (years of schooling)	8.6 ± 2.5	8 (4-13)
Disease duration	14.5 ± 10.5	12 (1-39)
Main symptom		
Ocular	23	33.3
Bulbar	21	30.4
Generalized	25	36.2
MGFA Classification		
I	13	18.8
IIA	14	20.3
IIB	2	2.9
IIIA	12	17.4
IIIB	7	10.1
IVA	4	5.8
IVB	3	4.3
V	14	20.3
MGC	7.5 ± 5	6 (0-23)
HAD Anxiety subscale score	7.7 ± 3.2	7 (2-16)
HAD Depression subscale score	4.6 ± 4.4	3 (0-17)
Thymectomized	42	60.9
Pyridostigmine	58	84.1
Prednisone	44	63.8
Azathioprine	30	43,5
Other immunosuppressant	9	13

SD: standard deviation; MGFA: Myasthenia Gravis Foundation of America; HAD: Hospital Anxiety and Depression; MGC: Myasthenia Gravis Composite.

associations of the scale score with disease severity and quality of life were similar between MG-QOL15 and MG-QOL60 and MG-QOL15 outperformed SF-36, notably by demonstrating a stronger correlation with changes in disease severity and in activities of daily living. MG-QOL15 also demonstrated longitudinal construct validity and test-retest reliability (12,13).

Most studies of the QoL of patients with MG were conducted in the United States and Europe, and there are scarce data on this topic from developing countries. Recently, we translated and adapted the Brazilian-Portuguese version of the MG-QOL15 (14). The aim of the current study was to evaluate the reliability and validity of MG-QOL15 in a clinical setting. Furthermore, we aimed to identify factors associated with perceived QoL among Brazilian patients with MG.

PATIENTS AND METHODS

Patients

This was a cross-sectional study that investigated MG patients receiving attention at the Center for Neuromuscular Diseases, University Hospital, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil. Socio-demographic and clinical information was obtained via clinical evaluation and chart review.

Diagnosis of MG was based on the following criteria: clinical history of fatigability with recovery after resting, clinical response to the administration of anticholinesterase drugs, presence of autoantibodies and/or decreased electrical activity upon repetitive nerve stimulation and exclusion of alternative neurological diagnoses (15).

Clinical instruments

The Myasthenia Gravis Composite (MGC) was used to assess the current status of MG (16). The MGC comprises 10 items evaluating ocular (3 items), bulbar (3 items), respiratory (1 item), neck (1 item), and limb (2 items) signs and symptoms. Patients were classified according to the Clinical Classification of the Myasthenia Gravis Foundation of America (MGFA) (15). This classification was developed to identify subgroups of patients with MG who share similar clinical features, possibly indicating similar prognoses and/or therapeutic responses. The MGFA classification system separates patients with purely ocular involvement from those with generalized or bulbar muscle weakness and categorizes the degree of weakness as mild, moderate or severe (17).

MG-QOL15 has a maximum score of 60, and there is no pre-specified cutoff for classifying the QoL of MG patients (12). The higher the MG-QOL15 score, the poorer the QoL of the MG patient. In this study, we used the Brazilian-Portuguese version of MG-QOL15 (14), and SF-36 was used to assess the concurrent validity of this version of MG-QOL15.

SF-36 is a multidimensional questionnaire composed of 36 items that provide information related to eight domains of health: physical functioning (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role-emotional (RE) and mental health (MH). The two summary measures are the physical health and mental health components. The calculation of the physical health component score positively weights the PF, RP, BP and GH domain scores and negatively weights the RE and MH domain scores. Conversely, to calculate the mental health component score, positive weights are placed on the MH, RE, SF and VT domain scores, whereas substantial negative weights are placed on the PF and RP domain scores. The total scores for each of the eight domains are converted to a 0-100 scale, with a higher score representing better health (18). SF-36, which has previously been validated in Brazil (19), is the most commonly used QoL instrument nationwide. Here, SF-36 was considered as the gold standard for construct validation of MG-QOL15 (11-13).

Variables that may impact QoL in MG patients include the following: a) demographic variables: age and gender; b) clinical variables: disease duration, main symptoms, MG classification, and treatments; and c) anxiety and depressive symptoms. The Hospital Anxiety and Depression (HAD) scale was used to evaluate the presence and/or severity of anxiety and depressive symptoms (20).

Procedure

The local ethics committee approved this study, and all patients signed a written consent form. Participants completed MG-QOL15, SF-36 and the HAD questionnaire and underwent a neurological examination (MGC) on the day of their routine neurological appointment. Medical records of the patients were also revised to classify the disease according to the MGFA system.

Statistical Analysis

To evaluate the item-specific internal consistency of MG-QOL15, we calculated Cronbach's alpha coefficients and corrected the item-total correlations. A Cronbach's alpha between 0.60 and 0.70 indicates acceptable reliability, and

Table 2 - Mean score and internal reliability of the Brazilian-Portuguese version of MG-QOL15.

Questions:		Mean (SD)	Median (range)	Corrected item-total correlation	Cronbach 's alpha coefficient if the item is removed (αC)
1. I'm frustrated by my myasthenia gravis.	1. Eu estou frustrado por causa da Miastenia Gravis.	1.3 (1.5)	1 (0-4)	0.81	0.74
2. I have trouble using my eyes because of my myasthenia gravis.	2. Eu tenho dificuldade para usar meus olhos por causa da Miastenia Gravis.	1.4 (0.9)	2 (0-3)	0.78	0.75
3. I have trouble eating because of my myasthenia gravis.	3. Eu tenho dificuldade para comer por causa da Miastenia Gravis.	1.6 (0.9)	2 (0-4)	0.81	0.75
4. I have limited my social activity because of my myasthenia gravis.	4. Eu limitei a minha atividade social por causa da Miastenia Gravis.	1.6 (1.2)	1 (0-3)	0.89	0.74
5. My myasthenia gravis limits my ability to enjoy hobbies and activities.	5. A Miastenia Gravis limita minha capacidade de ter divertimento e atividades de lazer.	1.9 (0.9)	2 (0-4)	0.92	0.75
6. I have trouble meeting the needs of my family because of my myasthenia gravis.	6. Eu tenho dificuldade para atender as necessidades da minha família por causa da Miastenia Gravis.	1.9 (1)	2 (0-4)	0.85	0.75
7. I have to make plans around my myasthenia gravis.	7. Eu tenho que fazer os meus planos em torno da Miastenia Gravis.	2 (1)	2 (0-4)	0.80	0.75
8. My occupational skills and job status have been negatively affected by my myasthenia gravis.	8. Minhas habilidades profissionais e minha posição no trabalho (cargo) foram afetadas negativamente por causa da Miastenia Gravis.	2.1 (1.1)	2 (0-4)	0.84	0.75
9. I have difficulty speaking due to my myasthenia gravis.	9. Eu tenho dificuldade para falar por causa da Miastenia Gravis.	1.8 (1.1)	2 (0-4)	0.73	0.75
10. I have trouble driving due to my myasthenia gravis.	10. Eu tenho problemas para dirigir por causa da Miastenia Gravis.	1.3 (1.3)	1.5 (0-3)	0.08	0.77
11. I am depressed about my myasthenia gravis.	11. Eu estou deprimido por causa da Miastenia Gravis.	1 (1)	1 (0-3)	0.77	0.75
12. I have trouble walking due to my myasthenia gravis.	12. Eu tenho dificuldade para andar por causa da Miastenia Gravis.	1.9 (0.9)	2 (0-3)	0.77	0.75
13. I have trouble getting around public places because of my myasthenia gravis.	13. Eu tenho dificuldade de passear em lugares públicos por causa Miastenia Gravis.	2 (1.2)	2 (0-4)	0.91	0.74
14. I feel overwhelmed by my myasthenia gravis.	14. Sinto-me sobrecarregado por causa da Miastenia Gravis.	1.6 (1)	1 (0-4)	0.90	0.75
15. I have trouble performing my personal grooming needs because of myasthenia gravis.	15. Eu tenho dificuldade para realizar meus cuidados pessoais (higiene) por causa da Miastenia Gravis.	1.1 (0.7)	1 (0-3)	0.79	0.75
TOTAL:		23.8 (12.2)	21 (4-48)	1	0.95*

SD: standard deviation of the mean.
* Cronbach's alpha coefficient

a value above 0.80 indicates good reliability. Pearson's correlation coefficients were used to evaluate concurrent validity between MG-QOL15 and subscales of SF-36.

All continuous data are expressed as means and standard deviations (SDs). The Mann-Whitney test was used to compare continuous variables between two groups, and the Kruskal-Wallis test was used to compare more than two groups. Correlations were assessed using Pearson's correlation coefficients or Spearman's correlation coefficients according to the data distribution. Factors with correlations showing statistical significance ($p<0.05$) based on univariate analysis were included in a multivariate linear regression analysis to identify factors independently affecting the QoL of MG patients. Regression tree analysis was performed to examine the influence of each factor on QoL. A value of $p<0.05$ was considered statistically significant.

Statistical analyses were performed using SPSS, version 18.0 (SPSS Inc., Chicago, Illinois).

RESULTS

Most participants were female and middle aged (Table 1). Regarding disease, most participants were classified as Class IIA or V (n=14 for each), followed by Class I (n=13) and IIIA (n=12). Regarding treatment, most patients were using pyridostigmine and two-thirds of the patients were using prednisone.

MG-QOL15 showed good internal consistency (Table 2). Most items displayed a good item-total correlation, with the exception of item 10. MG-QOL15 scores negatively correlated with SF-36 scores and with the scores of most of its subscales (Table 3). The score for the pain domain of SF-36 was the only subscale that did not correlate with the MG-QOL15 score.

The mean MG-QOL15 score was 23.8; this value suggests that the MG patients generally reported a good perceived QoL. This result was corroborated by a mean SF-36 score 99.3. Regarding the physical health component, the mean subscale scores were below 55. Regarding the mental health component, the mean subscale scores were above 60, except for the MH domain score.

The current status of MG (MGC; rho=0.60, $p<0.01$), the dosage of prednisone (rho=0.36, $p=0.02$) and the levels of anxiety (rho=0.38, $p<0.01$) and depression (rho=0.45, $p<0.01$) negatively correlated with QoL based on univariate analysis (Table 4). Those four variables were included in a

multivariate linear regression analysis, and the regression model retained all of the factors. An adjusted coefficient R2 of 0.48 was calculated; this value indicates that the model explains nearly half of the variance in QoL among MG patients (Table 5).

DISCUSSION

Several studies have observed that MG worsens the QoL of people suffering from this disorder. However, few studies have used disease-specific instruments and QoL has not been investigated previously in Brazilian MG patients.

MG-QOL15 was developed from MG-QOL60 and it has been thoroughly evaluated regarding its reliability, validity and usefulness (10-13). The Brazilian version of MG-QOL15 has shown good internal consistency and concurrent validity with SF-36. A low item-total correlation for item 10 ("I have trouble driving") probably resulted from the presence of non-drivers in the sample. The Japanese version of MG-QOL15 also found low item-total correlation for item 10 due to heavy traffic and the high cost of parking spaces in the Tokyo metropolitan area (21). Analysis of the correlation between MG-QOL15 and the domains of SF-36 revealed that only the pain domain does not correlate with MG-QOL15. This finding is expected, as muscle pain is not frequent in MG patients. Notably, when pain is present, it significantly impacts QoL (22,23).

The mean scores on MG-QOL15 and SF-36 suggest good perception of physical, psychological and social well-being among MG patients. In line with this finding, Paul et al. previously observed that QoL and well-being measures were not significantly different between MG patients and the general population (9).

The current study did not reveal any association between QoL and MGFA classification of the disease, which reflects the worst episode of MG during a patient's life. However, MG-QOL15 positively correlated with MGC, a measure of current disease severity. This result corroborates the view that the MGFA classification does not actually reflect current clinical severity or associated QoL (15). The negative correlation between the severity of current MG symptoms and QoL has been well established in the literature (12,16). The disease duration did not influence perceived QoL among MG patients due to the fluctuating nature of MG symptoms. Accordingly, patients with a longer disease duration did not necessarily have more symptoms or poorer QoL. There is evidence that as the disease duration increases, patients are more likely to experience remission of MG signs and symptoms (24).

Although some reports described that the mental health component of SF-36 is not significantly affected in MG patients, other reports suggested that the QoL of MG patients is similarly affected by physical and mental health factors (6,8,9). In the current study, the levels of anxiety and depression negatively correlated with QoL. As patients with MG have an elevated frequency of psychiatric disorders, particularly depression and anxiety, psychological symptoms must not be overlooked in clinical practice (25). Importantly, these symptoms typically predict poorer QoL both in the general population and among patients with other neurological disorders (6,26).

Regarding treatment, prednisone and pyridostigmine were the most commonly used treatments; this result is similar to the findings reported in the literature (21,27,28). A negative correlation was observed between QoL and the current dosage of prednisone. It is uncertain whether this correlation is due to the side effects of prednisone or to the association of a higher prednisone dosage with increased MG severity (28). There was no difference in QoL between thymectomized and non-thymectomized patients; this observation was consistent with the findings of other studies (28-30).

Future studies must investigate how variables not included in this study may impact QoL, coping strategies and resilience among MG patients. Follow-up studies may

Table 3 - Correlation of the score on the Brazilian-Portuguese version of MG-QOL15 with the scores on SF-36 and its domains.

Continuous variables	Rho	*p*-value
SF-36	-0.63**	<0.01
SF-36 Physical Function	-0.45**	<0.01
SF-36 Role—Physical	-0.75**	<0.01
SF-36 Bodily Pain	-0.12	0.32
SF-36 General Health	-0.46**	<0.01
SF-36 Vitality	-0.46**	<0.01
SF-36 Social Functioning	-0.24*	0.04
SF-36 Role—Emotional	-0.23*	0.04
SF-36 Mental Health	-0.22	0.06

Table 4 - Analyses of the associations and correlations between dependent variables (patient background and clinical factors) and the scores on the Brazilian-Portuguese version of MG-QOL15.

Variables	Rho or Z	*p*-value
Gender	-0.14*	0.87
First symptom	<0.01**	0.76
Main symptom	<0.01**	0.23
MGFA Classification	<0.01***	0.29
Thymectomy	-0.81*	0.41
Myasthenic crisis	-0.81*	0.41
Age	-0.01	0.88
Treatment time	0.06	0.60
MGC	0.60	<0.01
Pyridostigmine (dose)	-0.14	0.22
Prednisone (dose)	0.36	<0.01
Azathioprine (dose)	0.01	0.90
HAD Anxiety subscale score	0.38	<0.01
HAD Depression subscale score	0.45	<0.01

Abbreviations: MGC: Myasthenia Gravis Composite; HAD: Hospital Anxiety and Depression.
Tests used: Pearson's correlation (parametric continuous variables); Z score (normality test); * Mann-Whitney U test (nonparametric categorical variables - two variables); ** Kruskal-Wallis test (non-parametric categorical variables - three variables); *** one-way ANOVA (parametric categorical variables - three variables).

Table 5 - Multivariate linear regression analysis of MG-QOL15 scores representing the effect of each independent variable on QoL.

Continuous variables	B coefficient	*p*-value	95% confidence interval
MGC	0.93	<0.01	0.45 – 1.41
Prednisone (dose)	0.12	0.04	0.03 – 0.24
HAD Anxiety subscale score	0.77	0.03	0.05 – 1.49
HAD Depression subscale score	0.69	<0.01	0.18 – 1.21

MGC: Myasthenia Gravis Composite; HAD: Hospital Anxiety and Depression.
Test used: Automatic Linear Modeling

overcome the limitation of the cross-sectional design of the current study and may enable causal assumptions.

In conclusion, this study provides evidence that the Brazilian version of MG-QOL15 is a valid and reliable instrument. Disease severity, anxiety level, depression level and prednisone dosage were negatively associated with the QoL of MG patients. Physicians must be aware of these determinants of poorer QoL, as most of these factors are clinically manageable.

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■ AUTHOR CONTRIBUTIONS

Mourão AM, Gomez RS, Barbosa LS, Freitas DS, Comini-Frota ER were involved in subject recruitment, data collection and interpretation of the results. Kummer A, Lemos SM and Teixeira AL designed the research, supervised data collection and assisted in statistical analyses. Mourão AM, Kummer A and Teixeira AL drafted the original manuscript, which was read and amended when necessary. The final manuscript was approved by all authors.

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