Brazilian-Portuguese translation, cross-cultural adaptation and validation of the Myasthenia Gravis Composite scale. A multicentric study

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Myasthenia gravis (MG), a chronic autoimmune disease, is characterized by progressive weakness and fatigue of skeletal muscle caused, in 85% to 90% of patients, by antibodies against the acetylcholine receptor (AChR) of the post-synaptic membrane of the neuromuscular junction¹. There is also a smaller number of patients showing autoantibodies against

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ABSTRACT

Objective: To perform the translation, cultural adaptation and validation of the Myasthenia Gravis Composite (MGC) scale in Brazil. Methods: The study was conducted at three neuromuscular disease research centers in accordance with the international ethical standards, following a multi-modal approach and was conducted in three steps consisting of translation, cultural adaptation, and validation according to international guidelines. The final version of the MGC was applied in a sample of 27 MG patients and the total score was compared to a Portuguese version of the MG-QOL-15. Results: The internal consistency verified by Cohen’s Kappa test was excellent (0.766). The correlation between the MGC and MG-QOL-15 was strong (R = 0.777; p = 0.000). No significant differences were found between the responses of patients in the first and second applications of the MGC. Conclusion: The MGC scale, validated into Brazilian Portuguese, has proven to be a reliable instrument that is easy to use, and is highly reproducible.

Keywords: myasthenia gravis; translating; surveys and questionnaires.

RESUMO

Objetivo: Realizar a tradução e a adaptação transcultural da escala composta de Miastenia Grave (ECMG) Myasthenia Gravis Composite (MGC) no Brasil. Métodos: O estudo foi realizado em três centros de investigação em doenças neuromusculares, de acordo com as normas éticas internacionais, consistindo em tradução, adaptação cultural e validação de acordo com as diretrizes internacionais. A versão final do MGC ECMG foi aplicada em vinte e sete pacientes com MG e a pontuação total foi comparada ao questionário MG-QOL 15. Resultados: A consistência interna verificada pelo teste Kappa de Cohen foi excelente (0,766) e a correlação entre o a ECMG MGC e MG-QOL 15 foi positiva (R = 0,777; p = 0,000). Não foram encontradas diferenças entre as respostas dos pacientes na primeira e segunda aplicação da MGC. Conclusão: A ECMG escala MGC validada para o Português do Brasil provou ser um instrumento confiável, de fácil aplicação e altamente reprodutível.

Palavras-chave: miastenia gravis; tradução; inquéritos e questionários.

Myasthenia gravis (MG), a chronic autoimmune disease, is characterized by progressive weakness and fatigue of skeletal muscle caused, in 85% to 90% of patients, by antibodies against the acetylcholine receptor (AChR) of the post-synaptic membrane of the neuromuscular junction. There is also a smaller number of patients showing autoantibodies against the acetylcholine receptor (AChR) of the post-synaptic membrane of the neuromuscular junction. There is also a smaller number of patients showing autoantibodies against...
the muscle-specific kinase (MuSK) or the low-density lipo-
protein-related protein 4 (LRP4) and even against agrin8.

The prevalence of MG varies from 1.7 to 21.3 cases per
million people per year in the general population, mainly
affecting individuals aged 20-40 years, and more women than
men (ratio 3:2). The mortality rate varies from 0.06 to 0.89 per
million people each year3,4.

Disease severity depends on the compromised mus-
cle groups, varying from mild, with purely ocular symp-
toms, to the most serious cases with generalized mus-
cle weakness and respiratory failure1. The Myasthenia
Gravis Committee Foundation of America (MGFA) cat-
egorizes MG into five levels of severity according to the
appearance of symptoms and the anatomical distribu-
tion of affected muscle groups5.

Health Related Quality of Life (HRQoL) is an important
cOMPONENT in the evaluation of MG patients, as the disease
severity can vary widely. the assessment instruments of
HRQoL and clinical progression can be generic or specific to
a particular group of diseases, such as MG6. Clinical trials to
test new therapeutic interventions require some scale of cli-
cinal evaluation to assess the level of disease severity and the
response to therapy7,8.

Information about clinical evaluation and HRQoL,
obtained through specific instruments, enable a better
understanding of the patient’s needs, and allow provision of
adequate clinical support6. the more specific the instrument,
the more relevant it becomes for evaluation and monitoring
of disease progress.

The HRQoL and clinical status measures, obtained
through patient-oriented instruments, are considered
essential in the evaluation of neurological diseases, espe-
cially in those diseases that may affect a patient’s general
status, such as MG. Patient-derived tools have added a
new dimension to clinical outcome evaluation. these are
important, both for assessing individual patients in the
neurology clinic, and for international comparisons, mul-
ticenter trials and other types of collaborations9. Previous
studies have described a significant correlation between
HRQoL and severity of MG10,11,12.

We found only three specific tools for evaluating
HRQoL in MG patients in the international scientific lit-
erature (Myasthenia Gravis Questionnaire13, Myasthenia
Gravis-specific Activities of Daily Living Profile14,15,
Questionnaire of Life Quality Specific for Myasthenia
Gravis – 15 items (MG-QOL-15)16) and two instruments
to assess the clinical evaluation of patients with MG
(Quantitative Myasthenia Gravis Score17 and Myasthenia
Gravis Composite scale (MGC)18). From these instru-
m ents, only the MG-QOL-15 has been translated into
Brazilian Portuguese19. Therefore, it was important to
study the translation, cultural adaptation and validation
of the MGC in Brazilian patients.

METHODS

The study was conducted at three neuromuscular dis-
ease research centers in accordance with the ethical stan-
dards established in the 1961 Declaration of Helsinki (as
revised in Hong Kong in 1989 and Edinburgh, Scotland in
2000) and complied with the Regulatory Guidelines and
Norms for Research Involving Human Subjects of the
National Health Board of the Brazilian Health Ministry
issued in December 2012. This study is part of a research
protocol that was approved by the Human Research Ethics
Committee of Nove de Julho University (Brazil) under pro-
cess no. 360.488 and is registered with the World Health
Organization (WHO) under Universal Trial Number (UTN)
U1111-1147-7853 and the Brazilian Registry of Clinical
Trials (REBEC) RBR-7ckpdd. A written informed con-
sent was obtained, and subjects were allowed to withdraw
from the study at any time without consequence.

The study included patients with a clinical diagnosis of
MG according to the MGFA, aged 18–75 years, both genders,
who were clinically stable and who agreed to participate by
signing the informed consent form. We excluded patients
with other neuromuscular disorders, episodes of acute clin-
cal decompensation in the two months prior to consider-
ation for inclusion, and those with a history of stroke, mental
instability, or drug or alcohol abuse.

The Instrument

The MGC scale is a valid and reliable instrument used
to evaluate the clinical status of patients with MG both
in clinical practice, and in scientific research. The scale
was validated through tests conducted in 2008 and 2009
in 11 research centers in the United States of America
and Europe20. The MGC is an ordinal scale, consist-
ing of 10 items, each representing a function commonly
affected by MG. the response categories of MGC items
are weighted. For example, ‘ptosis’ scores 3 points, while
‘severe weakness of hip flexion’ is equivalent to 5 points,
and severe respiratory weakness (i.e. ventilator-dependent
patients) equates to 9 points. the maximum MGC score
is 50, and directly relates to patient condition i.e., a high
score reflects severe disease. A reduction of 3 points in
the score may indicate a significant and reliable clinical
improvement in patients with MG.

Translation, cross-cultural adaptation, and
validation

The study design followed a multi-modal approach and
was conducted in three stages consisting of translation, cul-
tural adaptation, and validation of the MGC according to
international guidelines proposed and developed in other
linguistic and socio-cultural contexts21,22,23,24,25. Figure 1 dis-
plays the flowchart of the study.

Oliveira EF et al. Brazilian validation of the MGC scale
Translation

According to the established protocol previously published, two qualified Brazilian translators, one a professional scientific English translator who is unfamiliar with the area of expertise, the other a bilingual neurologist, performed independent Brazilian Portuguese translations. Then, a committee of four neurologists and two physiotherapists, all bilingual, compared these two initial translations, creating a new, first version of the scale in Brazilian Portuguese. All members of this committee were bilingual university professors and researchers with clinical experience in neuromuscular diseases and had advanced knowledge of the English language.

![Flow chart of the methodological approach.](image-url)
Reverse-translation

Two native English speakers, a layperson and a professional translator, subsequently performed two reverse-translations of the preliminary Brazilian Portuguese version of the scale. These translators were not informed about the study objectives and had no access to the original version. This reverse-translation aimed to prove that the new version was equivalent to the original.

Another expert committee, comprising one methodologist, six health professionals, two native-speaking professionals and the translators, compared the two reverse-translation versions with the original English version of the MGC, made necessary adjustments, and generated the final version in Portuguese. The second Portuguese version of the scale was established after consensus was reached among committee members on each item.

Cross-cultural adaptation

The second version of the scale, translated into Portuguese, underwent a semantic analysis, and was analyzed by twenty health professionals, specializing in clinical neurology and rehabilitation medicine (10 physicians and 10 physiotherapists), to determine whether the terms used were easy to understand. This step was performed to ensure that the translated items were equivalent to the original, and included an assessment of the degree of understanding of the issues proposed.

Health professionals involved in this research phase made comments about the understanding of the scale. Any ambiguous terms were highlighted and discussed by the members of the study committee, and were replaced by other terms with semantic equivalence, appropriate to Brazilian culture, thereby generating a third version in Portuguese, without compromising the original version.

Psychometric evaluation

Reliability

To check inter-rater reliability, the third Portuguese version was administered by 10 health professionals to 20 patients with a confirmed diagnosis of MG (15 women), on two different occasions, at the same time of the day, with an interval of 48 hours, to assess test-retest reliability. These results were used to determine the level of semantic understanding to consolidate the final version of the MGC scale. The final version of the MGC scale translated into Brazilian Portuguese is presented in Figure 2.

Pre-test

The content validity was assessed qualitatively in a pilot study, in which the patients provided critical feedback on the design, content, and structure of the questionnaire, and in consultation with specialized clinicians in the field. The validity of the questions on the clinical characteristics and disease severity of MG were evaluated retrospectively by the two main investigators. They were blinded to the questionnaire results when registering the symptoms in the medical records of the 20 patients who participated in the pre-test stage.

The self-reported clinical characteristics of the disease at onset were compared with the symptoms reported in the patient’s medical record, and the clinical symptoms reported in the medical records were considered to be the closest to a gold standard evaluation of the patients’ symptoms.

Validation

Forty patients (29 women) with a confirmed diagnosis of MG, and classified according to MGFA, were invited to participate in this step of the study. Twenty-seven patients (21 women) accepted, comprising 11 patients from Setor de Investigação de Doenças Neuromusculares da Universidade Federal de São Paulo (UNIFESP), 11 patients from Departamento de Neurologia da Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSC), and five patients from Departamento de Neurologia do Hospital do Servidor Público Estadual (HSPE).

Demographic and clinical data were collected, along with details of current MG-related symptoms and therapeutic strategies. We excluded nine patients due to cognitive impairment, illiteracy and/or other chronic diseases and four patients because of a diagnosis of congenital myasthenic syndrome. The final version of the MGC was administered to in a final sample of 27 MG patients and the total score was compared to a Portuguese version of the MG-QOL-15, validated in Brazil, and commonly used to assess quality of life in MG19.

The MG-QOL-15 is an effective, quick, and easy-to-use instrument, consisting of 15 items, graded on a scale of 0-4, evaluating three dimensions of the HRQoL. The highest possible score is 60 points, indicating a poor quality of life as perceived by the patient. These 15 items efficiently evaluate physical, social, and psychological aspects of life, which are essential components for the interpretation of the HRQoL. The instrument does not have a specific cut-off value16,19.

Statistical analysis

Initially, the Shapiro-Wilk test was used to verify the normal distribution of the sample data. Parametric data were expressed as mean and standard deviation, including anthropometric values, age, and the circumferences of the neck and abdomen. Non-parametric data were expressed by standard error.

In the pre-test, we used Cohen’s Kappa coefficient for ordinal measures. The Kappa statistic is frequently used to test inter-rater reliability. Rater reliability is important as it reflects the accuracy of the data collected. Measurement of the extent to which data collectors (raters) assign the same score to the same variable is called inter-rater reliability.
Pearson’s rank correlation coefficient was used for correlation of the subjective assessment of MGC and MG-QOL 15. A p value < 0.05 was considered significant. Statistical analyses were performed with the StatView 5.0 (SAS Institute, Cary, N.C., USA), and SPSS software (version 23.0, SPSS Inc. Chicago, IL, USA).

**RESULTS**

There were 27 patients (21 women) with a confirmed diagnosis of MG acquired autoimmune form, and a mean age of 46.55 ± 11.71 years, range 32–74 years, enrolled in this study. The average duration of illness in these patients was 11.33 ± 8.49 years. According to the classification of MGFA, two patients were class I, 17 were class II, eight were class III, and none were in classes IV and V. Ninety-eight percent of patients were taking cholinesterase inhibitors and 28% were taking an immunosuppressant. Clinical and demographic features of the MG patients are presented in the Table.

**Reliability and validity**

The average time required for completing the MGC by patients was 32 minutes. The expression "ptosis, ascending naturally", in the original version, was replaced by "ptosis, looking up easily". Items used in the evaluation of muscle strength of neck flexion/extension, hip flexion, and shoulder abduction generated the greatest difficulty. Specifically, the grading of muscle weakness as moderate weakness posed problems. The original version emphasizes that moderate weakness should

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**Table**: Myasthenia Gravis Composite Scale (MGC)

<table>
<thead>
<tr>
<th>Item</th>
<th>Normal</th>
<th>Moderate weakness</th>
<th>Severe weakness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Muscle strength</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neck flexion/extension</td>
<td>Normal</td>
<td>Moderate weakness</td>
<td>Severe weakness</td>
</tr>
<tr>
<td>Hip flexion</td>
<td>Normal</td>
<td>Moderate weakness</td>
<td>Severe weakness</td>
</tr>
<tr>
<td>Shoulder abduction</td>
<td>Normal</td>
<td>Moderate weakness</td>
<td>Severe weakness</td>
</tr>
<tr>
<td><strong>Vision</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ptosis (looking up easily)</td>
<td>&gt;45 segundos</td>
<td>11–45 segundos</td>
<td>1–10 segundos</td>
</tr>
<tr>
<td>Double vision</td>
<td>&gt;45 segundos</td>
<td>11–45 segundos</td>
<td>1–10 segundos</td>
</tr>
<tr>
<td><strong>Fertilization</strong></td>
<td>Normal</td>
<td>Moderate weakness</td>
<td>Severe weakness</td>
</tr>
<tr>
<td><strong>Respiration</strong></td>
<td>Normal</td>
<td>Moderate weakness</td>
<td>Severe weakness</td>
</tr>
<tr>
<td><strong>Swallowing</strong></td>
<td>Normal</td>
<td>Moderate weakness</td>
<td>Severe weakness</td>
</tr>
<tr>
<td><strong>Speech</strong></td>
<td>Normal</td>
<td>Moderate weakness</td>
<td>Severe weakness</td>
</tr>
<tr>
<td><strong>Dyspnea</strong></td>
<td>Normal</td>
<td>Moderate weakness</td>
<td>Severe weakness</td>
</tr>
</tbody>
</table>

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**Figure 2.** Portuguese-Brazil version of Myasthenia Gravis Composite Scale.

Nota: Observe que “fraqueza moderada” para os itens pescoço e membros deve ser interpretada como fraqueza equivalente a 50%±15% do esperado para uma força normal. Qualquer fraqueza mais leve do que isto seria classificada como leve e qualquer fraqueza mais grave seria classificada como grave.

Total de pontos: ______________________
...be equal to approximately 50% ± 15% of the expected normal force. Accordingly, we added a note explaining how to grade moderate muscle weakness to the final version of the scale.

The internal consistency verified by Cohen’s Kappa test was excellent (0.766). Patients scored an average of 12.93 ± 6.92 in the MGC scale and an average of 21.38 ± 12.07 in the MG-QOL-15 scale. The correlation between the MGC and MG-QOL-15 was strong (R = 0.777; p = 0.000). No significant differences were found between the responses of patients in the first and second applications of the MGC.

DISCUSSION

In recent years, disease-specific, patient-derived questionnaires have become important measures to describe disease severity when compared with generic, patient-derived instruments.

According to our knowledge, this is the first study of the translation and validation of the MGC scale to a language other than English. Translation of the MGC to Brazilian Portuguese was successful, and reverse-translation to English corresponded very well with the original version. The MGC scale was properly translated and culturally adapted following a defined sequence of actions in accordance with the standards for cultural adaptation.

In 2012, a Task Force of the Medical Scientific Advisory Board of the MGFA recommended using the MGC as the quantitative measure for determining improvement or deterioration in patients with generalized MG.

The MGC can be used in daily practice and in clinical trials. This instrument differs from most scales in that it is a hybrid of patient-reported and physician-reported test items. It is not surprising that certain patient-reported test items perform better than their physician-reported examination counterparts, and thus justify inclusion in the MGC.

The validity and reliability of the MGC for measuring disease severity in MG was previously demonstrated using conventional psychometric tests.

The evaluation of the HRQoL of a patient can influence therapeutic decisions and provide a better understanding of their needs, allowing the adoption of an appropriate therapeutic strategy. A disease-specific instrument may be the most relevant clinical and functional assessment of the disease state, avoiding ineffective approaches.

In the validation phase, the Brazilian version of the MGC was very well understood and accepted by patients and by health professionals. Neither patients nor professionals had difficulties completing the questionnaire. In the validation phase of our study, the MGC was compared with the MG-QOL-15, considered the gold standard HRQoL assessment instrument in MG, with a positive correlation. This result corroborates other studies that validated the use of the MGC as an evaluation tool in patients with MG.

Factors related to the disease can influence HRQoL in MG, such as the predominant symptoms, the frequency of myasthenic crisis and the therapeutic strategy adopted. The frequency and severity of MG symptoms also influence the perception of HRQoL. Therefore, it is expected that a poor clinical situation will lead to a poor HRQoL result.

In conclusion, the original version of the MGC scale, having been translated, culturally adapted, and validated into Brazilian Portuguese has proven to be a reliable instrument that is easy to use, highly reproducible, and can be used in both clinical practice and clinical trials in the evaluation of patients with MG.

### Table. Clinical and demographic features of the patients with myasthenia gravis.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n = 27) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>21/6</td>
</tr>
<tr>
<td>Age (years)</td>
<td>46.55 ± 11.71</td>
</tr>
<tr>
<td>Disease classification</td>
<td></td>
</tr>
<tr>
<td>Acquired autoimmune</td>
<td>27</td>
</tr>
<tr>
<td>MGFA</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>2</td>
</tr>
<tr>
<td>IIA</td>
<td>15</td>
</tr>
<tr>
<td>IIIB</td>
<td>2</td>
</tr>
<tr>
<td>IIIA</td>
<td>4</td>
</tr>
<tr>
<td>IIIB</td>
<td>4</td>
</tr>
<tr>
<td>MGC score</td>
<td>12.8 ± 7</td>
</tr>
<tr>
<td>MG QOL – 15 score</td>
<td>21.7 ± 12.2</td>
</tr>
</tbody>
</table>

MGFA: Myasthenia Gravis Foundation of America Clinical classification; MGC: Myasthenia Gravis Composite scale; MG-QOL: Questionnaire of Life Quality Specific for Myasthenia Gravis – 15 items.

**References**

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