Vaccinations in autoimmune myasthenia gravis

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Chapter 3

Translation, cross-cultural adaptation, and validating the Myasthenia Gravis Quality of Life Questionnaire (MG-QOL15)

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1. INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder of the neuromuscular junction in which patients experience fluctuating weakness that most often affects specific muscle groups. In the majority of patients, MG is caused by antibodies against the acetylcholine receptor (AChR) or the muscle-specific receptor tyrosine kinase (MuSK). Optimal treatment aiming to achieve mild disease manifestations or remission often requires the use of immunosuppressive medication [1]. Despite treatment, patients can experience restrictions in their daily activities and health related quality of life (HRQOL) [2]. This can be due to side effects of medication or to the disease itself. The impact of the disease on quality of life is best reported directly by the patient through Health-Related Patient Outcomes (HR-PROs) [2]. PROs are measurements of any aspect of a patient's health status that are evaluated from the patient's perspective without interpretation of the response by a clinician or anyone else [3]. Nowadays, the focus in the clinical setting is mainly on the effect of treatment in terms of clinical symptoms. Previously, outcome measures like the MG composite (MGC) and the Quantitative Myasthenia Gravis (QMG) score have been used. These outcome measures do not assess health-related quality of life. The 15-item myasthenia gravis quality of life scale (MG-QOL15) was constructed to measure the patient's perceived HRQOL, which covers broad domains like physical, social, and psychological well-being [4,5]. In order to use the MG-QOL15 as an outcome measure in clinical trials and standard care, it must be validated. At the moment, the MG-QOL15 has been validated in several languages [6,4,7-9]. We translated and validated it into Dutch and evaluated its measurement properties in terms of test-retest reliability and construct validity.

2. PATIENTS AND METHODS

2.1 Design

This study had a cross-sectional design. It was executed at the outpatient clinic of the Department of Neurology of a Dutch academic medical center between March 2015 and January 2016. Ethical approval was obtained from the Medical Ethics Committee of this university hospital. Informed consent was obtained of all patients. The Dutch version of the MG-QOL15 was tested among 50 patients with acetylcholine-receptor antibody positive (AChR) MG who participated in a study of tetanus revaccination in patients with MG. This study was performed in order to investigate the effectiveness and safety of a tetanus revaccination in patients with MG. To validate and evaluate the measurement properties of the Dutch MG-QOL15, we used the data from the 2 time points over a 1-week interval before the revaccination.

2.2 Translation and adaptation of the MG-QOL15

The English version of the MG-QOL15 consists of 15 items with a 5-point response scale (0= not at all, 4 = very much). The response categories represent how applicable

the statement is for the patient in the past few weeks. The total scale score is the sum score of all 15 items, ranging from 0 to 60, with higher scores indicating less quality of life. The questionnaire was translated independently by 2 persons, a native Dutch-speaking translator who was a non-medical, lay person and a translator who works in the biomedical research field. The 2 translations were compared and combined into 1 Dutch version by the investigators (Figure 1). No significant modifications were required.

2.3 Sampling and questionnaire administration

The most important inclusion criterion for the study was a confirmed diagnosis of MG, based on clinical symptoms and a positive serological test for AChR antibodies. Patients had to be age 18 years or older, with a maximum of 65 years at time of vaccination. The dosage of their immunosuppressive medication had to be stable over the preceding 3 months, with a maximum of 30mg prednisolone per day. The use of IVIg or plasmapheresis was not allowed in the 3 months before participation. The patient was excluded from the vaccination study in the patient had tetanus revaccination in the past year, had a thymoma, or if the patient had undergone thymectomy in the preceding year.

We recruited patients through the outpatient clinic of a Dutch university hospital and the national patient organization. Included patients received the questionnaires either by mail or during their hospital visits and returned them in person at the hospital.

2.4 Measurement instruments

2.4.1 SF-36

The SF-36 Health Survey is a generic patient-reported quality of life measure. It is composed of 36 items organized into 8 multi-item scales: physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (MH). From these scales, 2 sum scores can be calculated: the physical component score (PCS) and the mental health component score (MCS). All scale scores are converted to a 0 to 100 scale, with higher scores indicating higher levels of functioning or well-being10. In this study we used the 2 component scores.

2.4.2 MG-ADL

The Myasthenia gravis activities of daily living (MG-ADL) profile is an 8-item patient-reported scale that is administered by a physician to assess MG symptoms and their effects on daily activities11. It has a 4-point response scale ranging from 0 (normal) to 3 (constant/gastric tube/ventilator dependence). The total score of the MG-ADL ranges from 0 to 24, and higher scores indicate more impact of MG on daily activities [11].

2.4.3 MG composite
The Myasthenia Gravis Composite (MGC) scale, a physician-administrated scale, consists of 10 items that measure symptoms and signs of MG, with weighted response options [12,13]. These 10 items were selected from existing MG-specific scales [MG-ADL, QMG, and the Manual Muscle Test (MMT)] [12,13]. For each item there are 4 response options ranging in general from 0 (normal) to 9 (severe). The sum score of the MGC ranges from 0 to 50, with higher scores indicating greater clinical severity of MG.

2.4.4. QMG
The Quantitative myasthenia gravis score (QMG) is a 13-item (3 ocular, 2 bulbar, 1 respiratory, 1 neck, and 6 limb) scale that measures muscle strength and endurance [14,15]. This scale is a physician-administrated scale, which contains 4 response categories ranging from 0 (none) to 3 (severe). The QMG score ranges from 0 to 39, with higher scores indicating more severe MG.

2.5 Analyses

2.5.1 Internal consistency of scale
Internal consistency is the degree of interrelatedness among items [2,16], indicated by the Cronhbach alpha. A Cronhbach alpha of 0.70 or above is regarded as sufficient [17].

2.5.2 Test-retest reliability
Reliability is the degree to which the measurement is free from measurement error [3, 14]. To evaluate the test-retest reliability, we assessed the level of agreement and measurement error. Test–retest reliability is the extent to which results for patients who have not changed are the same for repeated measurements over time [2,16]. One assumption for the test-retest reliability is that respondents have to be stable in their symptoms during the 2 measurement points. To guarantee stability of the disease symptoms as much as possible, we chose a 1 week interval between the 2 measurement points [2,16] .To assess test-retest reliability, the intraclass correlation coefficient (ICCagreement) was calculated for data from time 1 (T1) and time 2 (T2). The formula used was: ICCagreement = $\sigma 2p / (\sigma 2p + \sigma 2time + \sigma 2error)$. Good test-retest reliability was assumed for an ICC ≥0.70 [17].

The measurement error is the systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured [2,16]. Based on the Standard Error of Measurement (SEM), it is possible to conclude whether changed scores within 1 subject over the time is based on a real difference or based on measurement error (difference score<SEM [18]). The SEM was calculated using the formula: SEMagreement= $\sqrt{\sigma 2time + \sigma 2error}$.

2.5.3 Construct validity
Construct validity is the degree to which the scores of an HR-PRO instrument are consistent with hypotheses based on the assumption that the HR-PRO instrument is a valid measures of the measured construct [2,16]. We made the following hypotheses:

1. We hypothesized that the correlation of the MG-QOL15 with the MG-ADL is medium [5, 12], because this scale measures the influence of the disease on activities of daily living. Therefore, it overlaps in its content a fair amount with measures of HRQOL.

2. We hypothesized that the correlation of the MG-QOL15 with the QMG is medium [5], because the QMG measures only physical strength and function, but no factors of HRQOL.

3. We hypothesized that the correlation of the MG-QOL15 with the MGC is medium [5, 12].

4. We hypothesized a high negative correlation of the MG-QOL15 with the physical component score of the SF-36, because the measured construct overlaps to a great extent [19].

5. We hypothesized that the correlation of the MG-QOL15 with the SF-36 mental component score was lower than with the physical component score based on findings in an earlier study [19].

To test these hypotheses we calculated Pearson correlations between the MG-QOL15, MG-ADL, QMG, and MG-composite and the SF-36 scores (table 1). A correlation coefficient of r<0.3 was considered as low, between 0.3 and 0.5 as medium and >0.7 as high [20].

Hypotheses		Confirmed
1.	The MG-QOL15 has a medium correlation with the MG-ADL	Yes
2.	The MG-QOL15 has a medium correlation with the QMG	No
3.	The MG-QOL15 had a medium correlation with the MGC	Yes
4.	The correlation of the MG-QOL15 with the SF-36 PCS is negative high.	Yes
5.	The correlation of the MG-QOL15 with the SF-36 PCS is higher negative than with the SF-36 MCS	Yes

Table 1. Hypothesis for the construct validity of the MG-QOL15

3. RESULTS

3.1 Study sample

Fifty AChR MG patients were enrolled. They had a median age of 56 years, and 37 (74%) were women. Almost half of the patients used some kind of immunosuppressive medication (46%). Four patients were scored as in remission (MGFA 0), 4 as ocular (MGFA 1), 40 as mild generalized (MGFA 2), and 2 as moderate-severe (MGFA 3). The mean disease duration was 14.6 years (SD 13 years). See Table 2 for an overview.

	N	(%)
Number of patients	50	-
Diagnosis AChR MG	50	(100)
Gender, women	37	(74)
Age, median (SD)	56	(11,5)
Duration of disease (SD)	14.6	(13)
MGFA classification*		
0	4	(8%)
1	4	(8%)
2	40	(80%)
3	2	(4%)
Use of immunosuppressive medication	23	(46%)
Thymectomy	29	(58%)

Table 2. Participant characteristics.
MGFA Myasthenia Gravis Foundation of America

3.2 Descriptive statistics of measurement outcomes

The mean MG-QOL15 score at T1 was 20.4 (SD 11.2). The mean MG-QOL15 score at T2 was 19.4 (SD 11.6). The mean score of the MGC, MG-ADL, and QMG were 5.5 (SD 4.9), 3.9 (SD 3.2), and 6.7 (SD 4.3), respectively.

3.3 Internal consistency

The internal consistency proved to be sufficient, as the Cronbach alpha was 0.928.

3.4 Test-retest reliability

We had a 100% response rate of these 50 AChR MG patients. Based on this stable sample, the ICC between measurements T1 and T2 was good: ICC (95% confidence interval) = 0.866 (0.776-0.922). The SEM was 4.1 (6.8% of the scale range of 0-60) with a 95% CI of 1.4 to 6.9.

3.5 Construct validity

The MG-QOL15 had a medium high correlation with the MG-ADL (r = 0.501) and MGC (r = 0.388). The correlation with the QMG (r= 0.224) was low. The hypothesis of a medium correlation with the QMG could therefore not be confirmed. The high

negative correlation of the MG-QOL15 with the SF-36 PCS score (r = -0.832) was confirmed. Also, the hypothesis that the correlation of the MG-QOL15 with the SF-36 PCS was stronger than with the SF-36 MCS (r= -0.743) was confirmed. See table 3 for the correlations.

MG-QOL15	Correlation	*P*-value
MGC	0.388	0.005
MG-ADL	0.501	<0.001
QMG	0.224	0.117
SF-36 PCS	-0.832	<0.001
SF-36 MCS	-0.743	<0.001

Table 3. Correlation of the MG-QOL15 with the MGC, MG-ADL and QMG and the SF-36 component scores at 4 weeks.

4. DISCUSSION

The original English version of the MG-QOL15 was translated into Dutch and evaluated in a test-retest design with 2 measurement points separated by a 1-week interval. The sample consisted of patients who had stable disease, based on the MGFA classification and the requirement for a stable medication regimen over in the preceding 3 months. The requirement for good test-retest reliability was fulfilled with an ICC of 0.866. From our predefined hypotheses, 4 of 5 (80%) were confirmed, which points to good construct validity [17].

We predefined hypotheses about the correlations with 3 frequently used MG-specific outcome measures, the MGC, QMG, and MG-ADL. As expected, we found medium correlations of the MG-QOL15 with the MGC and MG-ADL. However, its correlation with the QMG was low instead of the expected medium correlation. When formulating the hypothesis, we focused on the relationship between symptoms and HR-QOL, which would lead one to expect a medium-high correlation. The QMG objectively measures muscle strength and endurance, but strongly depends on patient effort during only a short time window. A patient can obtain a low score on the QMG, suggesting mild symptoms of MG, while in everyday life mild weakness might lead to a highly variable degree of limitations in different patients with MG. Also, the QMG does not take emotional or mental aspects into account. These differences in the measurement construct between the QMG and the MG-QOL15 might explain the low instead of medium correlation.

The MQ-QOL15 aims to measure HR-QOL, and therefore we hypothesized a strong relationship with a generic HR-QOL measure, the SF-36. The high correlations with the SF-36 component scores we found are opportune, because they prove that the intended construct is indeed what the MG-QOL15 measures. In line with results of an earlier study that describes the development of the MG-QOL1519, we expected

a lower correlation for the mental component score compared to the physical component score. This hypothesis is confirmed, and although the correlation with the mental component score is lower than with the physical component score, it still is high (r=-0.74). The high correlation we found can be explained by the 3 items of the MQ-QOL15 (items 1, 11, and 14) that focus on emotions and distress experienced by the patient, which clearly overlap with the content of the items of the SF-36 mental component score.

These results allow us to assume that that it is necessary to pay attention to psychological distress that MG patients can experience, such as frustration, depression, or an overwhelmed feeling due to the disease. The MG-QOL15 might be suitable to signal any distress in MG patients, but its discriminative ability for this aim should be studied further. Signalling any signs of distress in MG patients is a prerequisite for helping the patient and improving these complaints. The role of psychological distress in MG patients has not been studied. For the future it would be important to study the prevalence of distress, its causes, and possible interventions for this patient group, as well as the role that treatment with corticosteroids or other immunosuppressive drugs plays in the psychological well-being of MG patients.

Overall, the low to medium correlations of the MG-QOL15 with the 3 MG-specific outcome measures and the high correlations with the generic QOL measure, the SF-36, confirms that QOL is measured well by the Dutch MG-QOL15. At the same time these results confirm the additional value of this MG specific quality of life outcome measure. As is typical for a HR-QOL outcome measure, its score is based on patient self-report, and it takes the physical and mental limitations in everyday life due to the disease into account. A benefit of the MG-QOL15 compared to existing generic HR-QOL measures, such as the SF-36, is that it is disease specific and therefore provides more detailed information about MG relevant limitations. The total score of the MG-QOL15 is easier to calculate than the SF-36, since calculation of the total scores are less complex. Furthermore, the MG-QOL15 is shorter than the SF-36, which makes it more feasible and less burdensome for patients to complete the questionnaire.

With its good test-retest reliability and construct validity, the MG-QOL15 is suitable as a MG- specific quality of life measure for research purposes. The MQ-QOL15 might be suitable for monitoring individual patients as well. There is a trend in healthcare to use patient reported outcomes in clinical practice to inform the patient and clinician about development of symptoms and limitations in individual patients [21]. The scores on the MG-QOL 15 might provide a starting point for the clinician and patient to discuss factors that contribute to the burden of disease in MG patients and to subsequently adapt patient care to these factors. With the Cronbach alpha exceeding 0.90 it fulfils the requirement for use on the individual level, [22] and with its short length and disease-specific character, we consider it to be very feasible for application in clinical practice. When comparing MG with other diseases, the SF-36 can be used, because it is a generic quality of life questionnaire, and it showed a high correlation with the MG-QOL15.

A limitation of our study is the relatively small number of included patients. Myasthenia gravis is a rare disease, which makes it challenging to establish a larger homogeneous population. Furthermore, in our study, we aimed to sample a stable population. Our inclusion and exclusion criteria were quite narrow , which challenged patient recruitment even more. The requirement for stable dosing of the immunosuppressive medication and the prednisone were the main recruitment challenges. However, we were able to include 50 patients, which is considered to be the least number of patients needed for a questionnaire validation17. A strength of our study is that we used predefined hypotheses to test the construct validity of the MG-QOL15, by which we tried to make the risk of bias as small as possible17. Another strength is that we included 4 comparison measures in the hypothesis testing, based on 3 frequently used MG-specific outcome measures.

To use the Dutch MG-QOL15 as an outcome measure in intervention studies, changed scores need to be interpreted well. For this, the smallest detectable change value is relevant, which can be based on the SEM we have calculated in this study. Additionally, the minimal clinically important change (MCIC) score for improvement would be of relevance. The MCIC is a score on the scale range of the instrument that indicates the lowest change score that is regarded as high enough to be considered clinically relevant. This score is crucial in indicating change. For calculating the MCIC, it is necessary to have a patient sample that experiences improvement in quality of life [23]. Therefore, it was not possible in our study. The MCIC calculation should be focus of further evaluation studies of the MG-QOL15.

5. CONCLUSION

The Dutch version of the MG-QOL15 demonstrates good test-retest reliability and good construct validity. This version of the MG-QOL15 now can be used in the research setting to measure disease-specific health related quality of life in MG patients. Furthermore, it may be suitable for follow-up of disease-specific quality of life in individual MG patients.

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