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The Myasthenia Gravis-Specific Activities of Daily Living Profile

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The myasthenia gravis activities of daily living (MG-ADL) profile is an eight-item patient-reported scale developed to assess MG symptoms and their effects on daily activities. The MG-ADL profile correlated well with the Quantitative MG (QMG) score ($r = 0.58$, $P < 0.001$) in 254 consecutive patient visits. Further analysis during clinical trials confirmed the excellent correlation with the QMG test and provided additional evidence that the MG-ADL profile is responsive to clinical improvement. MG-ADL performance was further analyzed during a recent multicenter, prospective scale validation study for two new outcome measures. At the first visit, there was a strong positive correlation between the MG-ADL and the MG Composite ($r = 0.85$, $P < 0.0001$) and between the MG-ADL and the MG-Quality of life15 (MG-QOL15) ($r = 0.76$, $P < 0.0001$). Test–retest analysis demonstrated a high reliability coefficient. Sensitivity/specificity analysis revealed that a 2-point improvement has the best trade-off attributes to predict clinical improvement. The MG-ADL profile also performed well on Rasch analysis. The MG-ADL scoring system is useful as a secondary outcome measure and in routine clinical management.

Keywords: myasthenia gravis outcome measures; MG-ADL; MG Composite; MG QOL15

Introduction

Outcome measures when developed for various diseases are tested for multiple psychometric properties. Routine psychometric analysis of outcome measures includes validity (construct and concurrent), test–retest reliability, and responsiveness of the outcome measure to change, in addition to sensitivity and specificity analysis. Recently, advanced psychometric analysis such as Rasch analysis is also performed. Ideally, various psychometric properties of an outcome measure should be assessed before it is adopted into clinical practice or is used as an outcome measure in therapeutic trials since using a nonvalid or unreliable measure could potentially affect the outcome of the clinical trial or, in worst-case scenario, lead to incorrect conclusions about the drug or treatment effect. However, occasionally an outcome measure, in this case the myasthenia gravis-specific activities of daily living (MG-ADL) scoring system, might be adopted into clinical practice and research studies well before it is extensively studied and yet ultimately perform well on subsequent psychometric evaluation. In this review, we will address the initial creation of the MG-ADL profile, psychometric evaluation of the MG-ADL profile, and its use in research and clinical practice.

Over the last two decades, numerous MG outcome measures have been studied.[1] These vary in terms of time taken to complete, ease of use, and finally, whether a physician or patient completes them. Some outcome measures such as the Quantitative MG (QMG) score[2] will also require specialized equipment and training. The MG-ADL profile was developed in the late 1990s since there were no other outcome measures at that time that would reflect the effect of MG-related disability on patient's activities of daily living.[3] At that time, the QMG test was considered the gold standard and was routinely used as a primary outcome measure in MG clinical trials. The MG-ADL profile was partially derived from the QMG test, a 13-item linearly scored scale. The MG-ADL profile is an 8-item scale, with linear scoring from 0 to 3. The range of total MG-ADL score is

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Table 1. MG activities of the daily living scale

Items	Grade 0	Grade 1	Grade 2	Grade 3	Score (0,1,2,3)
1. Talking	Normal	Intermittent slurring of nasal speech	Constant slurring or nasal, but can be understood	Difficult to understand speech	
2. Chewing	Normal	Fatigue with solid food	Fatigue with soft food	Gastric tube	
3. Swallowing	Normal	Rare episode of choking	Frequent choking necessitating changes in diet	Gastric Tube	
4. Breathing	Normal	Shortness of breath with exertion	Shortness of breath at rest	Ventilator dependence	
5. Impairment of ability to brush teeth or comb hair	None	Extra effort, but no rest periods needed	Rest periods needed	Cannot do one of these functions	
6. Impairment of ability to arise from a chair	None	Mild, sometimes uses arms	Moderate, always uses arms	Severe, requires assistance	
7. Double vision	None	Occurs, but not daily	Daily, but not constant	Constant	
8. Eyelid droop	None	Occurs, but not daily	Daily, but not constant	Constant	
				Total MG-ADL SCORE (items 1–8)	

0–24. Completing the MG-ADL usually takes less than five minutes and is entirely reported by the patient. The eight items of the MG-ADL aim to assess disability secondary to ocular (2 items), bulbar (3 items), respiratory (1 item), and limb (2 items)-related effects from myasthenia gravis. There are no items to assess the disability from pure axial weakness such as neck extension weakness (See Table 1).

Initial MG-ADL analysis

Initial analysis of the MG-ADL was conducted at a single center.[3] Patients with MG were prospectively evaluated for this study. The study included 254 unique evaluations (156 patients, 90 were women), in patients with confirmed diagnosis of myasthenia gravis irrespective of clinical severity of MG. A single examiner performed a QMG test and asked the patient to complete the MG-ADL questions. The mean MG-ADL score was 4.80 ($\pm$3.63) with a range of 0–18. The mean QMG score was 10.80 ($\pm$5.70) with a range of 0–27. The Pearson correlation coefficient was 0.583 ($P < 0.001$). Authors correctly concluded that the MG-ADL was an easy to administer outcome measure and that the MG-ADL profile correlates well with QMG scores. Based on the above findings, the authors suggested that the MG-ADL profile may be used as a secondary endpoint in clinical trials in MG and because it does not require any specialized equipment could be easily adopted into routine clinical practice.

Enthusiastic adoption of the MG-ADL profile

After the above initial analysis, because of the ease of use and lack of similar MG outcome measures, the MG-ADL profile was used as a tool in both routine patient care and as an outcome measure in research studies. In the early 2000s, the MG-ADL

was used as a secondary outcome measure in multiple therapeutic clinical trials evaluating the benefit of etanercept,[4] IVIG,[5] and tacrolimus.[6–8] Improvements in MG-ADL scores in these studies mirrored improvements in QMG scores.

Further analysis of the MG-ADL profile

Even though the MG-ADL continued to be used in clinical practice and in various clinical trials as a secondary outcome measure, further psychometric testing was not performed until the mycophenolate mofetil (MMF) clinical trials.[9,10] One of these prospective randomized placebo-controlled studies completed by the Muscle Study Group[10] evaluated the effectiveness of MMF and prednisone as initial therapy in MG. The study was double blinded for the first 12 weeks followed by an open-label extension phase for 36 weeks. Eighty patients were randomized to either MMF or placebo in addition to 20 mg of prednisone. The primary outcome measure was the improvement in QMG scores at 12 weeks. The MG-ADL and MG manual muscle tests (MG-MMT) were secondary outcome measures. Importantly, MG-ADL and MG-MMT scores were not available to the QMG scorers and physicians who would assess global impression of change in patients and this allowed for unbiased evaluation of psychometric properties of the MG-ADL test. During the study period, patients in both groups improved, and there was no significant difference between the two treatment arms in this study, but a subset of patients had significant improvement. This provided an opportunity to assess one of the key psychometric properties: the responsiveness of the MG-ADL to clinically significant improvement in MG status.[11]

Similar to initial analysis, MG-ADL scores correlated well with QMG scores at baseline and throughout the double blind study period of 12 weeks. The correlation coefficients ranged from 0.51 to 0.65 ($P < 0.0001$). Correlation of the change in QMG and MG-ADL scores was also good, 0.55 at 12 weeks and 0.44 at 36 weeks ($P < 0.001$). Since a subset of patients improved significantly, responsiveness of the MG-ADL to change in clinical status was analyzed. This revealed a mean change of 3.66 points at 12 weeks and 5.48 at 36 weeks. The effect size was 1.16 at 12 weeks and 1.59 at 36 weeks. Interestingly, in this study MG-ADL scores were more sensitive to change in clinical status than were QMG scores.[11] Finally, the most important finding was that improvement in MG-ADL score was incremental. Patients with significant improvement had greater decrease in their MG-ADL score than those with mild improvement or no improvement. There was no significant change in MG-ADL scores in patients who did not improve at 12 weeks. MG-ADL scores improved by 3.29 at 12 weeks in patients with improvement on global assessment of MG and by 4.83 in patients with marked improvement on global assessment of MG. This analysis provided clear evidence that the MG-ADL test was sensitive to clinical change in MG status and reinforced continued usage of the MG-ADL profile in clinical practice and in research studies.

The final assessment of MG-ADL came with a multicenter study of two new MG outcome scales, the MG Composite (MGC)[12] and the MG-Quality of life15 (MG-QOL15).[13] Eleven centers participated in the multicenter validation studies for the MGC and the MG-QOL15, and out of these five centers also simultaneously assessed the MG-ADL. This provided a unique opportunity to perform validity and reliability testing of the MG-ADL profile. Unlike previous therapeutic trials with narrow inclusion criteria, all patients with confirmed MG seen in routine clinical practice were recruited and this allowed us to assess the MG-ADL as an outcome measure in clinical practice. Patients with MG seen in clinics or hospitals had baseline evaluation of MGC, MG-QOL15, and MG-ADL scores at the first visit and again within six months. Eighty-seven patients completed the MG-ADL profile on the first visit and 76 returned for second visit.[14] Most patients had some improvement in MG-ADL scores between visits. Correlation of MG-ADL and MGC scores was robust during the first ($r = 0.846$, $P < 0.0001$) and second ($r = 0.869$, $P < 0.0001$) visits. Since the MGC shares a number of items with the MG-ADL profile, concerns about inflated correlation were raised, but a similar degree of correlation was seen with the MG-QOL15 ($r = 0.763$, $P < 0.0001$). Correlation of the delta in the MG-ADL score and physician impression of change in MG status between the two visits was also strong ($r = 0.70$, $P < 0.0001$).[14]

Sensitivity and specificity analysis

Since previous analysis did not provide an opportunity to perform sensitivity and specificity testing, during this new MG scale validation study we

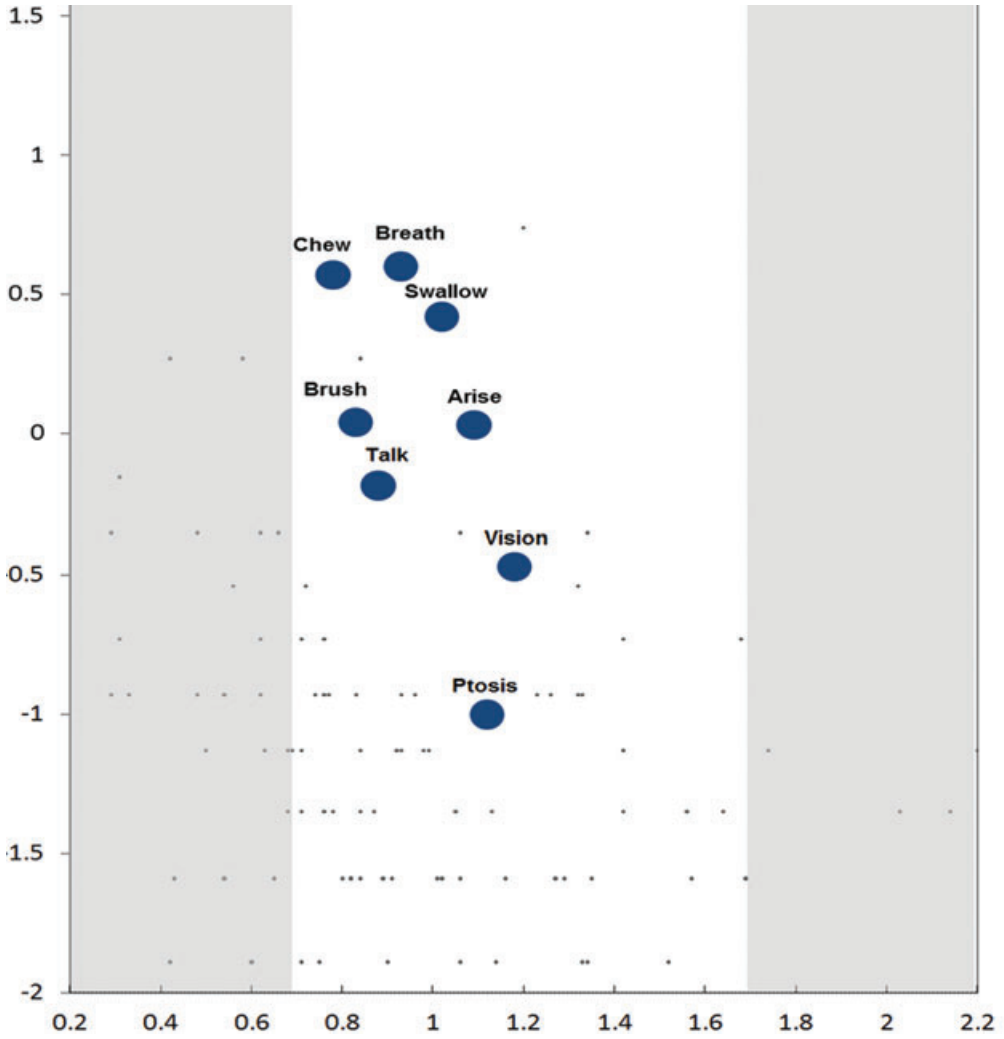

Figure 1. This figure depicts item difficulty and person ability measures (on the vertical logarithmic axis) and item fitting (on the horizontal logarithmic axis) for the MG-ADL profile. Each dot represents a subject and each circle represents an item. The vertical spacing approximates the items' placement on the linear probabilistic Rasch model. None of the items in the MG-ADL are misfitting, as they do not fall outside into the gray zone.

compared the changes in MG-ADL scores with the presumed gold standard, that is, physician impression of change plus improvement in MG-QOL15 for improvement in MG status. An MG-ADL score change of 2 points seemed to have the best balance between sensitivity and specificity. A 2-point change had a sensitivity of 77 and specificity of 82.[14] A 3-point improvement had much higher specificity of 90, but the sensitivity was diminished to 62. A receiver operating curve analysis was also performed. This revealed an area under the curve of 0.90, suggestive of high accuracy of the MG-ADL test to assess clinical improvement.[14]

Test and retest reliability analysis

After the above study, at a single center, test–retest reliability for the MG-ADL profile was performed. Twenty-six patients completed MG-ADL in clinic and were asked to repeat this again at home after one week. Twenty out of the 26 patients completed the second MG-ADL at home and mailed it back to the physician. A one-week interval was chosen to complete the MG-ADL profile again as it was considered too short a period to be affected by therapeutic changes made during the clinic visit but long enough that patients might not

remember their individual item score. Patients who were on plasma exchange were excluded. Reliability coefficient was 93.7, suggesting excellent test–retest reliability,[14] and the repeat MG-ADL scores did not differ by more than 2 points 85% of the time.

Rasch analysis

Psychometric testing of outcome measures usually includes tests to evaluate reliability, validity, sensitivity and specificity analysis, and responsiveness to change. By these measures, the MG-ADL profile performed well. However, these traditional methods do not measure the overall estimate of an individual item (or question) score to the total score and do not measure the behavior of an item in relation to others in an outcome measure. To understand these properties, item response theory (IRT) models are used. Among the types of IRT models, Rasch analysis is commonly used. In Rasch analysis, the two important features of item measures tested are item difficulty and person ability. *Item difficulty* refers to ability of an item to differentiate patients with worse MG manifestations from those who are not as affected, whereas *person ability* refers to how difficult it is for a person to respond to an item in an outcome measure. Rasch analysis can assess the item difficulty and person ability, identify any misfitting items and effects of these items on the unidimensionality of the outcome measure, and assess category response functioning. Questions related to ptosis and vision were easy items, and questions about chewing and breathing were difficult items. Category probability functioning testing revealed that the empirical category response probability ascends for all items in MG-ADL except for the vision item. Developmental pathway analysis revealed that none of the items in MG-ADL fall into the misfitting category (see Fig. 1). These findings suggest that MG-ADL performed well on Rasch analysis without any misfitting items and does not require any major revisions.

Discussion

Since development of the MG-ADL numerous other outcome measures have been created and are being used in clinical care of patients with MG and in research trials. Recently the task force of the Medical Scientific Advisory Board (MSAB) of the Myasthenia Gravis Foundation of America (MGFA) suggested that the MGC be used as a primary outcome measure in clinical trials. Going forward, the MG-ADL profile may still be used a secondary outcome measure and it is currently used in the MGTX study[15] and the study to assess the efficacy of Methotrexate in MG (http://clinicaltrials.gov/show/NCT00814138). The MG-ADL test has one unique feature that differentiates it from the other MG outcome scales: it is completed solely by the patient. Since it does not require a physician or nurse to administer this test, the MG-ADL test could potentially be used as an outcome measure in long-term MG studies. In addition, with the advent of electronic records and electronic communication with patients, the MG-ADL test could potentially be completed by the patient between and during the clinic visits. For example, many patients are now receiving maintenance intravenous immunoglobulin therapy at home for myasthenia gravis and a test like the MG-ADL profile might provide information about their ongoing MG clinical state. One could also foresee the MG-ADL test as a valuable tool in observational studies or clinical trials with long-term follow-up of years where it is not feasible to have frequent clinic visits, since patients can provide their MG-ADL score in-between clinic visits.

For all its positive attributes, the MG-ADL test has two important deficiencies as an outcome measure. One, there is no item to measure the effect of axial weakness (such as neck extension weakness). This is important because neck extension weakness when significant can cause head drop, a very disabling manifestation, and yet the MG-ADL score will not reflect this limitation on a patient's activity level. Secondly, items in the MG-ADL test are linearly scored and are not weighted. Linear scoring would suggest that degree of disability or effect on daily living activities of various individual items is the same. For example, if a patient has constant double vision, he would score 3 for diplopia item, but at the same time, being on ventilator for respiratory assistance would also score 3 for breathing item. Even though the contribution to the final MG-ADL score is the same, the degree of disability experienced by the patient on ventilator is many times higher than the disability of the patient with constant double vision. Newer MG scales such as MGC are weighted to correct for this limitation. Despite the above deficiencies, the MG-ADL self-test profile continues to be a useful tool and will probably have a role as an outcome measure going

forward in clinical trials and patient care, in myasthenia gravis.

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Conflicts of interest

The author declares no conflicts of interest.

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