Disease Severity Assessment and Short-Term Outcome in Patients with Myasthenia Gravis

Deepthi Vemuri, Butchi Raju Garuda, S. Gopi, T. Sateesh Kumar, U. Aruna Kumari

Department of Neurology, Andhra Medical College/King George Hospital, Visakhapatnam, Andhra Pradesh, India

Abstract

Background: Myasthenia gravis (MG) is an autoimmune disorder with a chronic fluctuating course**.** The outcome measures encapsulate disease severity, functional impact at diagnosis, and objective evaluation of clinical benefit from therapeutic interventions. **Aims and Objective:** To assess the disease severity, correlation between various outcome measures, and to evaluate the short-term outcome at 3 months and 6 months in a cohort of MG patients. **Materials and Methods:** Quantitative myasthenia gravis (QMG) score, myasthenia gravis composite (MGC) score, and myasthenia gravis quality of life-15 (MG-QoL-15) score were applied to 54 patients at first visit, 3 months and 6 months follow-up. **Results:** Mean quality of life-15 (QoL-15) score at base line was 15.241. Mean QMG and MGC scores at baseline were 14.63 ± 8.37 and 15.87 ± 9.14, respectively. QMG score showed a strong positive correlation with both MGC and MG-QoL-15 scores. QMG and MGC scores showed a moderate correlation with acetylcholine receptor antibody (AChR Ab) titers. Mean QMG at follow-up was 9.95 ± 5.49 at 3 months and 6.74 ± 4.74 at 6 months. Mean MGC at follow-up was 10.75 ± 5.58 at 3 months and 6.51 ± 4.36 at 6 months. **Conclusion:** The combination of physician-evaluated and patient-reported outcome measures provided a more discerning picture of patient status and response to treatment. Incorporating MG outcome measures into clinical practice would aid in modulating therapies.

Keywords: The Myasthenia Gravis Foundation of America), myasthenia gravis, myasthenia gravis composite score, myasthenia gravis quality of life-15 score, quantitative myasthenia gravis score

Introduction

Myasthenia gravis (MG) is a potentially serious but treatable autoimmune disorder of the neuromuscular junction characterized by fatigable weakness of skeletal muscle causing disability and impaired quality of life (QoL). The overall incidence rate of MG has been constant and is estimated at 2.1 to 5.0 per 100,000 people per year.[1]

The outcome measures provide a benchmark that encapsulates disease severity and functional impact at diagnosis. When applied consistently and regularly to each patient, the outcome measures also provide important information on trends in patient symptom load.[2]

Aims and objective

To study the disease severity indices, the correlation between the various indices in patients with MG, and their relation with short-term outcome at 3 and 6 months.

Materials and Methods

This prospective observational hospital-based study was carried out at the Department of Neurology, Andhra Medical College, Visakhapatnam. Fifty-four patients with MG were recruited between April 2017 and February 2019. A diagnosis of MG was based on clinical history, repetitive nerve stimulation (RNS) studies, positive neostigmine test, and the presence of acetylcholine receptor antibody (AChR Ab). The patients recruited included newly diagnosed patients as well as those who were being regularly followed up.

The AChR antibodies were measured by a standard radioimmunoassay (RIA) method with human 125 I-AChR as antigen and using AChR RIA kits. Quantitative assessment of AChR antibody titers was done, with titers greater than 0.40 nanomoles/liter considered positive.

The Myasthenia Gravis Foundation of America (MGFA) clinical classification was used for objective documentation of the severity of weakness.[3] Disease severity was assessed using quantitative myasthenia gravis (QMG), myasthenia gravis composite (MGC), and myasthenia gravis quality of life-15 (MG-QoL-15) at initial presentation.[4,5] QMG and MGC scores were noted at 3 months and 6 months follow-up.

The MGC scale was composed of individual items from outcome measures (including the QMG, the Myasthenia Gravis-Activities of Daily Living [MG-ADL] scale, and the Myasthenia Gravis Manual Muscle Test [MG-MMT]).

Address for correspondence: Dr. Butchi Raju Garuda, Department of Neurology, 2nd Floor, Superspeciality Block, King George Hospital/Andhra Medical College, Maharanipeta, Visakhapatnam - 530 002, Andhra Pradesh, India.
E-mail: rajugarudabr@gmail.com

Submitted: 28-Apr-2019 **Revised:** 19-Jun-2019 **Accepted:** 26-Jun-2019
Published: 25-Feb-2020

DOI: 10.4103/aian.AIAN_243_19

The domains of these 10 items include ocular (three items), bulbar (three items), respiratory (one item), neck strength (one item), and limb strength (two items). The MGC scale contains a total of six physician-evaluated items and four patient-reported items.[6] A three-point improvement in the total MGC score is optimal for signifying clinical improvement.[6]

QoL was assessed using the MG-QoL-15 scale. This is a self-administered disease-specific questionnaire comprised of 15 items.[7] These items were read out to the patients in their local language, and their responses were marked. This study was approved by the Institutional Ethics Committee.

The data was incorporated into Microsoft Excel spreadsheet for analysis and was analyzed by using the Statistical Package for the Social Sciences (SPSS) software. Chi-square test was done to determine the significance of association for categorical variables. Correlation analysis was done to find out association between two quantitative variables using Pearson correlation coefficient ($r \geq 0.8$ strong correlation; $r = 0.3$–0.7 moderate correlation; $r \leq 0.3$ poor or weak correlation).

Results

The cohort comprised of 54 patients, and the age range was 8–74 years. In the majority of patients, the onset was ocular-40 (74.1%). Bulbar onset was seen in seven patients (13%); presentation as general crisis was seen in one patient; and limb-girdle onset was seen in six patients. The majority of patients in this study had their onset of MG <50 years of age, i.e., early-onset MG in 79.6% of the patients.

AChR antibodies were positive in 3 out of 13 ocular myasthenia patients (23%) and 23 out of 41 generalized myasthenia patients (56.1%). Mean AChR antibody titer was 6.13.

All patients received pyridostigmine in appropriate doses based on symptom severity. The mean daily requirement of pyridostigmine was 285.81 ± 144.4 mg (range: 90–540 mg/day). The investigations and treatment details are summarised in Table 1. Sixteen patients received oral steroids; 24 patients received azathioprine and oral steroids; one patient received mycophenolate mofetil (MMF); one patient received oral steroids and MMF. Three patients with ocular MG were treated with pyridostigmine alone with which they had symptomatic improvement. Five patients received oral prednisolone for 1 month; 12 patients received for 2 months; five patients received for 3 months; eight patients received for 4 months; 13 patients received for 6 months. Two patients who were started on oral prednisolone were lost to follow-up. Thymectomy was performed in five patients, of whom four had thymoma and one had thymic hyperplasia and all were AChR Ab positive.

Disease Severity Indices

Mean QoL-15 score at base line was 15.241. Mean MG-QoL-15 scores for subjects with MGFA grades I, II, III, IV were 5.23, 12.42, 19.67 and 27.66, respectively. The QoL scores correlated significantly with the MGFA grade ($P = 0.01$).

QMG Score and MGC Score

The mean QMG score at the time of first visit was 14.63 ± 8.37. Based on QMG score at base line, 18 patients had mild disease (QMG 0–9), 14 patients had moderate disease (QMG 10–16), and 22 patients had severe disease (QMG > 16). There was a decline in mean QMG at follow-up by 9.95 ± 5.49 at 3 months and by 6.74 ± 4.74 at 6 months. The mean MGC score at the time of first visit was 15.87 ± 9.14. There was a decline in mean MGC at follow-up by 10.75 ± 5.58 at 3 months and 6.51 ± 4.36 at 6 months.

Correlation between QMG, MGC, and MG-QoL-15 Scores [Table 2]

1. Correlation between the QMG and MGC score was strong ($r = 0.90$; $P = 0.01$) [Figure 1].
2. Correlation between the QMG and MG-QoL-15 score was strong ($r = 0.84$; $P = 0.01$) [Figure 2].
3. Correlation between the MGC and MG-QoL-15 score was strong ($r = 0.80$; $P = 0.001$).

There was only a moderate correlation between the disease severity indices and AChR antibodies.

Follow-up of Patients at 3 Months

Forty-five out of fifty-four patients were followed up at the end of 3 months. One patient died during the follow-up due to respiratory failure. Five patients were lost to follow-up. According to assessment by QMG score, a minimal clinically important change was observed in 7 patients (63.63%) with ocular MG and in 26 patients (76.47%) with generalized MG. According to assessment by MGC score, a clinically significant change (≥3 point decrease) was observed in 1 patient (9%) with ocular MG and in 25 patients (73.52%) with generalized MG [Table 3].

Follow-up of Patients at 6 Months

Forty-three out of fifty-three patients were followed up at the end of 6 months. Five patients were lost to follow-up. Five patients did not complete 6 months following their inclusion into the study. According to assessment by QMG score, a minimal clinically important change from the baseline score was observed in eight patients (72.72%) with ocular MG and in 28 patients (87.50%) with generalized MG. According to assessment by MGC score, a clinically significant change (≥3 point decrease) from baseline score was observed in six patients (54.54%) with ocular MG and in 30 patients (93.75%) with generalized MG.

Discussion

Despite effective immunotherapy, MG requires lifelong follow-up and treatment. Understandably, it significantly affects daily living and QoL. Several scales have been developed and validated to assess the severity of neuromuscular weakness and the response to treatment in MG. No data is available

Table 1: Investigations and treatment details of the patients (n=54)

PARAMETERS	OBSERVATIONS
Neostigmine test positivity	51 (94.4%)
RNS positivity	47 (87%)
AChR antibody positivity	26 (48.20%)
Mean AChR antibody titers in MFGA Class I/II/III/IV	0.49/3.24/8.59/26.35
CECT CHEST	
Normal	
Thymoma	44 (81.48%)
Thymic hyperplasia	5 (9.2%)
TREATMENT	5 (9.2%)
IVMP	13 (24.1%)
IVIG	7 (13%)
ORAL STEROIDS	45 (83.3%)
AZATHIOPRINE	28 (51.9%)
MMF	2 (3.7%)
THYMECTOMY	5 (9.25%)

RNS=Repetitive nerve stimulation; AChR Ab=Acetylcholine receptor antibody; IVMP=Intravenous methylprednisolone; IVIG=Intravenous immunoglobulins; MMF=Mycophenolate mofetil

Table 2: Correlation between various disease severity indices, disease severity indices with AChR Ab titers and with age

CORRELATION PARAMETERS	*r* and *P*	Inference
QMG score and MGC score	r=0.90; P=0.01	Strong correlation
QMG score and MG-QoL-15 score	r=0.84; P=0.01	Strong correlation
MGC and MG-QoL-15	r=0.80; P=0.001	Strong correlation
QMG SCORE vs. AChR Ab titers	r=0.57; P=0.01	Moderate correlation
MGC score vs. AChR Ab titers	r=0.57; P=0.01	Moderate correlation
MGFA grade vs. AChR Ab titers	r=0.43; P=0.01	Moderate correlation
QMG score vs. Age	r=0.15; P=0.2	Weak correlation
MGC score vs. Age	r=0.15; P=0.2	Weak correlation

r=correlation coefficient; QMG=Quantitative Myasthenia gravis; MGC=Myasthenia Gravis Composite; MG-QoL-15=Myasthenia Gravis Quality of life-15

from India that applies these validated scores in assessing the outcome.

MG-QoL-15 Score

QoL is affected by physical restrictions due to disease-related symptoms and effects of long-term treatment. Mean QoL-15 score in this study was 15.241 and in Kumar *et al.*'s[8] study (n = 50) was 10.34. QoL score in Kumar *et al.*'s study correlated significantly with the MGFA grade as in the current study. Age, gender, thymectomized status, thymoma, and steroid therapy did not affect QoL scores. In addition to experiencing

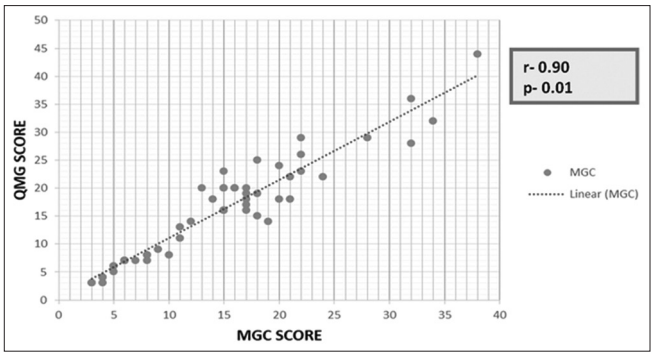

Figure 1: Correlation between QMG and MGC score

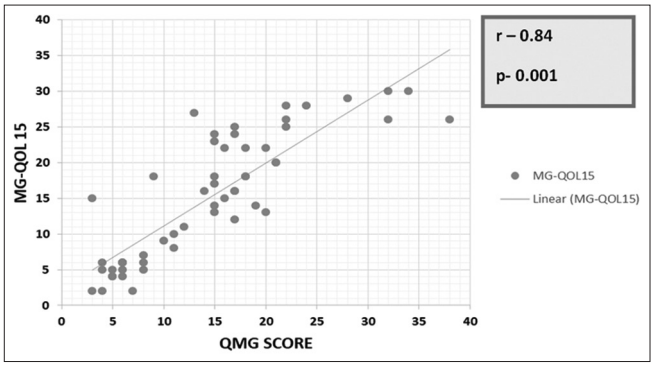

Figure 2: Correlation between QMG and MG-QoL-15 score

symptoms of weakness, symptomatic MG patients are frequently frustrated by their MG and find that it limits their ability to enjoy hobbies and fun activities. More severely affected patients very frequently report trouble walking, getting around, and meeting family needs. These concerns and complaints may not come up during clinical evaluation. However, they are relevant to the patient and are easily captured by the MG-QoL-15. This score correlates strongly with the MGC score (r = 0.80; P = 0.001) in this study. In like manner, Burns *et al.*'s[9] (n = 175) study also observed a strong correlation between MGC score and MG-QoL-15 (r = 0.67; P < 0.01).

Correlation between Various Outcome Measures

In the present study, the correlation between the QMG and MGC score was strong as well as between the QMG score and MG-QoL-15 score which correlated with Oliveira *et al.*'s[10] study. In a study by Barnett *et al.*[11] (n = 135), the QMG score showed a good correlation with the QoL-15 (r = 0.41; P = 0.0007). In Hoffmann *et al.*'s[12] study, QMG is a useful objective tool for assessing motor impairment and generalized subclinical signs in ocular MG. In a study by Burns *et al.*,[6] correlation between MGC and MG-QoL-15 scores was similar to the present study (r = 0.68). The MGC score took an average of 7 mins to administer in the present study whereas the QMG score took an average of 25 mins.

MGC was developed by combining items from other MG measures, based on their performance in two clinical trials of mycophenolate in MG.[13,14] Newer outcome measures

Table 3: Short-term outcome based on QMG and MGC scores at 3 months and 6 months

QMG 3 MONTHS FOLLOW-UP			
Category of MG	**IMPROVEMENT**	**NO IMPROVEMENT**	**TOTAL**
OCULAR	7	4	11
GENERALIZED	26	8	34
TOTAL	33	12	45
MGC 3 MONTHS FOLLOW-UP			
Category of MG	**IMPROVEMENT**	**NO IMPROVEMENT**	**TOTAL**
OCULAR	1	10	11
GENERALIZED	25	9	34
TOTAL	26	19	45
QMG 6 MONTHS FOLLOW-UP			
Category of MG	**IMPROVEMENT**	**NO IMPROVEMENT**	**TOTAL**
OCULAR	8	3	11
GENERALIZED	28	4	32
TOTAL	36	7	43
MGC 6 MONTHS FOLLOW-UP			
Category of MG	**IMPROVEMENT**	**NO IMPROVEMENT**	**TOTAL**
OCULAR	6	5	11
GENERALIZED	30	2	32
TOTAL	36	7	43

QMG=Quantitative myasthenia gravis; MGC=Myasthenia gravis composite score

like MGC incorporate more input from patients and have undergone more rigorous psychometric analysis.[15] The MGC was recommended as the primary outcome measure of choice in MG trials by the MGFA Scientific Advisory Board.[16]

Assessment of Short-Term Outcome at 3 Months and 6 Months

According to consensus guidance treatment statements, the pyridostigmine dose should be adjusted based on symptom severity and tolerability.[17] Expert consensus and some randomized controlled trial (RCT) evidence support the use of azathioprine as a first-line non-steroidal immuno-suppressive agent in MG.[17] One of the patients developed alopecia and elevated liver enzymes following a three-day treatment with azathioprine, so she was switched to MMF. Another patient developed pancytopenia following azathioprine therapy and was switched over to MMF following recovery from pancytopenia. MMF therapy had a favorable tolerability profile, but it is not cost effective so it could not be used widely in our hospital setting.[18]

The application of the QMG score in patients who did not show minimal clinically important change (12 patients) had the following results: the score remained same in seven patients, increased by 1 point in one patient, and a not clinically significant decrease was observed in four patients. The application of the MGC score in patients who did not show minimal clinically important change (19 patients) had the following results: the score remained same in 9 patients and a not clinically significant decrease was observed in 10 patients. This might reflect the need for a lower threshold to assess improvement in patients with lower MGC scores.

The application of the QMG score (at 6 months) in patients who did not show minimal clinically important change (seven patients) had the following results: the score remained same in two patients, increased in two patients, and a not clinically significant decrease was observed in three patients. The application of the MGC score in patients who did not show minimal clinically important change (seven patients) had the following results: the score remained same in two patients, increased in two patients, and a not clinically significant decrease was observed in three patients. In this study, follow-up of patients was for a short period of 6 months. Therefore, pharmacological remission, complete remission, and minimal manifestation status could not be assessed. The limitations of this study are small sample size and that other autoantibodies (anti-MuSK antibodies, anti-striational antibodies) were not performed. The outcome with different treatment strategies could not be compared because of the small sample size.

Conclusion

Studying the short-term outcome at 3 and 6 months while incorporating the newer outcome measures (QMG, MGC and MG-QoL-15) provided quantification of the improvement in terms of patients who achieved minimal clinically important change. Incorporating MG outcome measures into clinical practice would aid in modulating therapies.

The combination of physician-evaluated and patient-reported outcome measures (QMG, MGC and MG-QoL-15) provided a more discerning picture of patient status and response to treatment. From India, this study is the first of its kind objectively assessing short-term outcome in MG based on newer outcome measures.

Acknowledgements

All the patients and their family members for participating in this study and for their cooperation.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Vincent A. Unravelling the pathogenesis of myasthenia gravis. Nat Rev Immunol 2002;2:797-804.
2. Muppidi S. Outcome measures in myasthenia gravis: Incorporation in to clinical practice. J Clin Neuromuscul Dis 2017;18:13546.
3. Jaretzki A, 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. Barohn RJ, McIntire D, Herbelin L, Wolfe GI, Nations S, Bryan W.

Reliability testing of the quantitative myasthenia gravis score. Ann NY Acad Sci 1998;841:769-72.
5. Katzberg HD, Barnett C, Merkies ISJ, Bril V. Minimally clinically important difference in myasthenia gravis: Outcomes from a randomized trial. Muscle Nerve 2014;49:661-5.
6. Burns TM, Conaway M, Sanders DB, MG Composite and MG-QoL-15 Study Group. The MG Composite: A valid and reliable outcome measure for myasthenia gravis. Neurology 2010;74:1434-40.
7. 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.
8. Kumar R, Nagappa M, Sinha S, Taly AB, Rao S. MG-QoL-15 scores in treated myasthenia gravis: Experience from a university hospital in India. Neurol India 2016;464:4405-10.
9. Burns TM, Grouse CK, Conaway MR, Sanders DB. Construct and concurrent validation of the MG-QoL-15 in the practice setting. Muscle Nerve 2010;41:219-26.
10. Oliveira EF, Valério BCO, Cavalcante V, Urbano JJ, Silva AS, Polaro MN, *et al*. Quantitative myasthenia gravis score: A Brazilian multicenter study for translation, cultural adaptation and validation. Arq Neuropsiquiatr (Brazilian Academy of Neurology) 2017;75:457-63.
11. Barnett C, Katzberg H, Nabavi M, Bril V. The quantitative myasthenia gravis score: Comparison with clinical, electrophysiological, and laboratory markers. J Clin Neuromusc Dis 2012;13:201-5.
12. Hoffmann S, Siedler J, Brandt AU, Piper SK, Kohler S, Sass C, *et al*. Quantitative motor assessment of muscular weakness in myasthenia gravis: A pilot study. BMC Neurol 2015;15: 265.
13. Sanders DB, Hart IK, Mantegazza R, Shukla SS, Siddiqi ZA, De Baets MH, *et al*. An international, phase III, randomized trial of mycophenolate mofetil in myasthenia gravis. Neurology 2008;71:400-6.
14. Muscle Study Group. A trial of mycophenolate mofetil with prednisone as initial Immunotherapy in myasthenia gravis. Neurology 2008;71:394-9.
15. Barnett C, Herbelin L, Dimachkie MM, Barohn RJ. Measuring clinical treatment response in myasthenia gravis. Neurol Clin 2018;36:339-53.
16. Benatar M, Sanders DB, Burns TM, Cutter GR, Guptill JT, Baggi F, *et al*. Recommendations for myasthenia gravis clinical trials. Muscle Nerve 2012;45:909-17.
17. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, *et al.* International consensus guidance for management of myasthenia gravis: Executive summary. Neurology 2016;87:419-25.
18. Farmakidis C, Pasnoor M, Dimachkie MM, Barohn RJ. Treatment of myasthenia gravis. Neurology Clinics 2018;36:311-37.