Autoimmune myasthenia gravis : the impact of heterogeneous patterns of muscle weakness on outcome measures and diagnosis

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Chapter 5

Activity limitations in myasthenia gravis and relation to clinical variables

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ABSTRACT

Introduction

It is unknown how fluctuations in muscle weakness affect activity limitations in myasthenia gravis patients and how the severity of these limitations compares with published data on other neuromuscular disorders (NMD).

Methods

We analyzed ACTIVLIM (acronym of 'ACTIVity LIMitations') and Quantitative Myasthenia Gravis (QMG) scores. We assessed the impact of QMG and other clinical variables on ACTIVLIM, using B coefficients.

Results

The mean ACTIVLIM score in 118 MG patients was 3.3. There was a correlation between QMG and ACTIVLIM (B coefficient = -0.206; $p < 0.001$) and between changes in both scores (B coefficient = -0.175; $p = 0.002$). Men and patients without another autoimmune disease had a better ACTIVLIM score (B coefficient = 0.785; $p = 0.015$ and B coefficient = 0.998; $p = 0.008$, respectively).

Discussion

The ACTIVLIM score in MG is higher than in other NMD. Fluctuations in QMG correlated significantly with changes in ACTIVLIM.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease characterized by fatigability and fluctuating muscle weakness. In contrast to many other neuromuscular disorders (NMD) that are irreversibly progressive, the disease severity in many MG patients may change markedly over time with both improvements and deteriorations. Furthermore, the clinical spectrum of MG is broad, ranging from mild ptosis to severe generalized weakness.[1] The Quantitative Myasthenia Gravis (QMG) test can be used to measure ocular, bulbar, and generalized muscle fatigability.[2] Several other measures have been developed to assess quality of life or impairments in activities of daily living (ADL) in patients with MG.[3-9] However, impairments in ADL have never been compared between MG patients and patients with other NMD. The systematic use of a quantitative measure of activity limitations for different NMD may be useful to compare the burden they impose on ADL and establish clinically relevant outcome measures for future clinical trials. In addition, it is not known how fluctuations of the severity of muscle weakness affect the limitations that MG patients experience in ADL. The ACTIVLIM (acronym of 'ACTIVity LIMitations') questionnaire is a validated measure of daily activity limitations for patients with NMD in general.[10] Clinically, it may be practical to use a generic outcome measure of ADL for all NMD to provide insight into the impact of different NMD on daily activities for individual patients. We measured the ACTIVLIM score in MG patients to estimate their ADL limitations. This enabled a comparison between the scores of our MG patients and previously published data from patients with other NMD.[11-14] We then investigated the relationship between several clinical variables and the ACTIVLIM score to identify which factors contribute to limitations in daily activities. Finally, we analyzed how changes in muscle strength and fatigability, as measured by the QMG test, affected the ACTIVLIM score over a longer period of time.

METHODS

Patients

We included MG patients under treatment at the Leiden University Medical Center between 2007 and 2013. The QMG and ACTIVLIM scores were recorded in all MG patients who visited the outpatient clinic as part of routine clinical care. Inclusion in this study required a combination of clinically confirmed fluctuating muscle weakness and the presence of serum autoantibodies to the acetylcholine receptor (AChR MG). Patients who were seronegative or had autoantibodies to muscle-specific kinase (MuSK MG) were excluded. Patients were classified as either oculobulbar or generalized on the basis of clinical characteristics retrieved from their charts. All data were gathered according to the same clinical protocol that is used for all MG patients who visit our outpatient clinic for routine clinical care. This study was approved by the Medical Ethics Boards of the Leiden University Medical Center.

Clinical variables

The primary endpoint was the ACTIVLIM score, which is a measure of self-reported activity limitations. The questionnaire assesses the perceived difficulty patients have in performing daily activities on a 3-level ordinal scale (0=impossible, 1=difficult, or 2=easy). It contains 22 daily activities designed for both children and adults with NMD. The ordinal total score was transformed into an interval level measure of activity limitations using a Rasch model. The Rasch model estimates the item difficulty and the patient activity level so that the resulting measure is linear and can therefore be treated as a continuous variable. A higher score indicates fewer activity limitations.[10] We performed a literature search to compare the ACTIVLIM scores in other NMD with our findings.

The other clinical variables included in this study were QMG score, age, age at onset of first symptoms below age 50 or older, presence of one or more additional autoimmune disease(s) (AID), thymectomy with or without the presence of thymoma, and exacerbations or emergency treatments within the last year. These variables were chosen based on previous studies, potential clinical relevance, and reliability with which these data could be analyzed retrospectively.[1, 15-20] For the analysis of the correlation of changes in QMG and ACTIVLIM we also subdivided the QMG into an oculobulbar (first 5 items of the QMG) and a generalized domain (remaining 8 items). An exacerbation was defined as a clinical deterioration of MG that required starting with or an increase of at least 20 mg of prednisone daily or led to an emergency treatment. An emergency treatment was defined as the administration of intravenous immunoglobulin, plasmapheresis, or mechanical ventilation.[18]

Statistical Analysis

We assessed the impact of multiple clinical variables on the ACTIVLIM score by analyzing only the first visit in all patients. In addition, we investigated the correlation between changes in QMG and ACTIVLIM scores by taking into account multiple measurements in the same patient. We used generalized estimating equations (GEE) with an unstructured correlation model to account for the dependence between repeated measurements in the same individual. To account for missing values in clinical variables, we used a 5-fold multiple imputation (for which we included all clinical variables). Results are expressed as B coefficients, which represent the slopes of the regression lines, and 95% confidence intervals (CI). For the association between changes in QMG and ACTIVLIM, these regression lines are shown in figures. *P*-values < 0.05 were considered significant. Statistical analyses were performed using SPSS version 23 (IBM Corp., Armonk, NY).

RESULTS

We included 118 consecutive patients with AChR MG. Of this group, 63 underwent multiple assessments, ranging up to 6 assessments per patient. Baseline characteristics of all patients are shown in table 1. The mean ACTIVLIM score in our cohort was 3.3 (standard deviation [±] 2.2), and subdivided by weakness pattern 3.6 ± 2.1 for oculobulbar MG patients and 2.7 ± 2.3 for generalized MG patients. Before missing data imputation, the pattern of weakness was missing on 21 of 252 measurements and the presence of an exacerbation or emergency treatment in the last year was unknown on 47 occasions. An overview of mean ACTIVLIM scores in MG patients and patients with other NMD is shown in table 2.

Table 1. Baseline characteristics of 118 patients with MG included in this study

	All patients N=118	**Oculobulbar N=84**	**Generalized N=34**
Age, y	51.9 ± 18.9	54.1 ± 19.7	46.2 ± 15.6
Age at onset, y	41.5 ± 20.3	44.7 ± 20.9	33.8 ± 17.0
<50	73 (62)	49 (58)	24 (71)
≥50	45 (38)	35 (42)	10 (29)
Gender			
Male	43 (36)	37 (44)	6 (18)
Female	75 (64)	47 (56)	28 (82)
Additional AID			
Yes	18 (15)	14 (17)	30 (88)
No	100 (85)	70 (83)	4 (12)
Thymectomy			
Yes, with thymoma	15 (13)	10 (12)	5 (44)
Yes, without thymoma	25 (21)	11 (13)	14 (41)
No	78 (66)	63 (75)	15 (15)
QMG	9.2 ± 5.3	8.5 ± 5.3	10.9 ± 4.7
ACTIVLIM	3.3 ± 2.2	3.6 ± 2.1	2.7 ± 2.3

Baseline characteristics of 118 patients with MG included in this study are shown. Row 3 and 4 show the data subdivided by oculobulbar and generalized weakness patterns. Data are presented as number of patients (%) for categorical variables and as mean ± SD for continuous variables.

QMG was strongly and inversely associated with ACTIVLIM (B coefficient = -0.206, 95% CI = -0.250; -0.163; $p < 0.001$). Thus, high performance on quantitative muscle tests and therefore a low QMG score was associated with fewer activity limitations, which is reflected in a high ACTIVLIM score. In addition, men had a higher ACTIVLIM score than women (B coefficient = 0.785, CI = 0.153; 1.416; $p = 0.015$), and patients without another autoimmune disease had fewer limitations in ADL (B coefficient = 0.998, CI = 0.262; 1.733; $p = 0.008$). Outcomes of the multivariate analysis for ACTIVLIM are shown in table 3.

Table 2. Overview of ACTIVLIM scores in MG and other NMD

NMD	N	Age	Gender (% male)	ACTIVLIM
CMD				
Meilleur et al.[92]	24[a]	11.4 (5-22)	41	0.6 ± 3.0
Vuillerot et al.[95]	42[b]	10.8 (5-19)	55	-1.1 ± 2.9
HN				
Vandervelde et al.[94]	44	(8-80)	100	2.0 ± 2.1
MD				
Vandervelde et al.[94]	37	(16-72)	-	2.7 ± 2.1
ALS				
Vandervelde et al.[94]	18	(46-80)	-	0.4 ± 2.31
SMA				
Vandervelde et al.[94]	14	(9-61)	-	-0.5 ± 3.4
FSHD				
Vandervelde et al.[94]	12	(12-67)	-	1.6 ± 2.0
Other				
Vandervelde et al.[93]	132[c]	31 (6-80)	67	1.2 ± 2.7
Vandervelde et al.[94]	45[d]	(6-72)	-	-1.1 ± 3.1
AChR MG				
Current study	118	51.9 (13-88)	36	3.3 ± 2.2

Overview of mean ACTIVLIM scores in MG patients (this study) and in patients with other neuromuscular diseases (other studies). Data are shown subdivided by neuromuscular disease. Age (range), % male and ACTIVLIM ± SD are shown for each study separately.

[a] Within the group of CMD patients, 53% had COL6-RD and 47% had LAMA2-RD.

[b] Group of 42 CMD patients included patients with COL6-RD, LAMA2-RD or unclassified CMD. The exact distribution of these subgroups has not been specified.

[c] Group consisted of 27 DMD patients, 17 MD patients, 20 CMT patients and 68 patients with another neuromuscular disease.

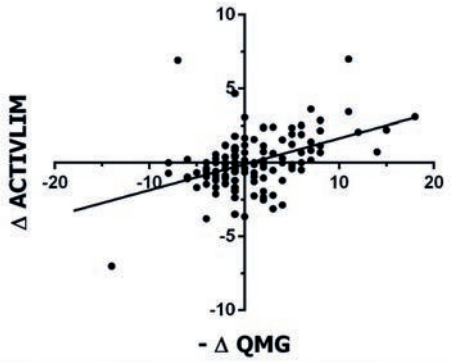
[d] Group consisted of DMD, BMD and LGMD patients. The exact distribution of these subgroups has not been specified.

In individual patients who underwent repeated assessments, changes in QMG (Δ QMG) and ACTIVLIM (Δ ACTIVLIM) were strongly and inversely correlated (B coefficient = -0.175, CI = -0.284; -0.066; $p = 0.002$). Thus, improvement in quantitative muscle tests was associated with fewer activity limitations (figure 1). Generalized MG patients had a strong correlation between Δ QMG and Δ ACTIVLIM on both the generalized items of Δ QMG (B coefficient = -0.353, CI = -0.505; -0.202; $p < 0.001$) and total Δ QMG (B coefficient = -0.222, CI = -0.334; -0.109; $p < 0.001$). In patients with oculobulbar MG there also was a correlation between Δ QMG and Δ ACTIVLIM on both the generalized items of Δ QMG (B coefficient = -0.199, CI = -0.337; -0.062; $p = 0.005$) and total Δ QMG (B coefficient = -0.137, CI = -0.252; -0.021; $p = 0.020$). In both oculobulbar and generalized MG patients there was no significant correlation between the oculobulbar items of Δ QMG and Δ ACTIVLIM. Results of the analysis of the correlation between Δ QMG and Δ ACTIVLIM divided by subgroups are shown in figure 2.

Table 3. Association of clinical factors with ACTIVLIM score

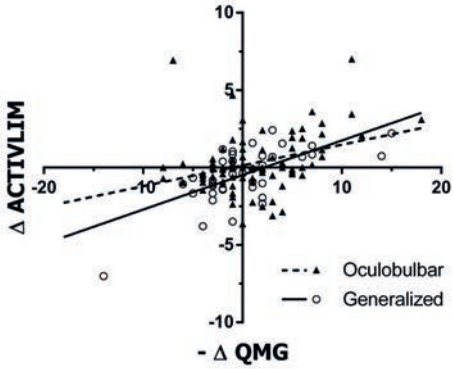
ACTIVLIM	No. of patients	B coefficient	95% CI	*p*-value
Age, y	118	-0.020	-0.044; 0.005	0.118
Age at onset, y				
<50	66	0.561	-0.296; 1.418	0.200
≥50	52	0		
Gender				
Male	41	0.785	0.153; 1.416	**0.015**
Female	77	0		
Additional AID				
Yes	14	0		
No	104	0.998	0.262; 1.733	**0.008**
Thymectomy				
Yes, with thymoma	23	0		
Yes, without thymoma	19	-0.122	-0.896; 0.652	0.758
No	76	-0.258	-0.949; 0.432	0.463
Exacerbations <1 y				
Yes		0		
No		0.209	-0.465; 0.882	0.543
Emergency treatments <1 y				
Yes		0		
No		-0.061	-0.965; 0.843	0.894
QMG	118	-0.206	-0.250; -0.163	**<0.001**

Multivariate analysis of ACTIVLIM score according to clinical variables. Data are presented as B coefficient and 95% confidence interval (CI). Boldfaced *p*-values indicate significant differences ($p < 0.05$).



Correlation Δ ACTIVLIM to:	No. of patients	B coefficient	95% CI	*p*-value
Δ QMG total	63	-0.175	-0.284; -0.066	**0.002**

Figure 1. Correlation of **Δ** QMG with **Δ** ACTIVLIM in all MG patients
Correlation of **Δ** QMG with **Δ** ACTIVLIM in 63 MG patients. Data are shown as B coefficient (slope) and 95% confidence interval (CI). The **Δ** QMG score is shown inverted on the x-axis so that a higher value on both the y- and the x-axis represents an improvement on the scale.



Correlation Δ ACTIVLIM to:	No. of patients	B coefficient	95% CI	*p*-value
Oculobulbar patients				
Δ QMG total	43	-0.137	-0.252; -0.021	**0.020**
Δ QMG oculobulbar	43	-0.151	-0.376; 0.074	0.189
Δ QMG generalized	43	-0.199	-0.337; -0.062	**0.005**
Generalized patients				
Δ QMG total	20	-0.222	-0.334; -0.109	**<0.001**
Δ QMG oculobulbar	20	-0.208	-0.457; 0.040	0.101
Δ QMG generalized	20	-0.353	-0.505; -0.202	**<0.001**

Figure 2. Correlations of **Δ** QMG with **Δ** ACTIVLIM in oculobulbar and generalized MG patients
Correlations of **Δ** QMG with **Δ** ACTIVLIM are shown for oculobulbar and generalized MG patients separately. Data are shown as B coefficient (slope) and 95% confidence interval (CI) for the correlations of the total **Δ** QMG and the oculobulbar and generalized items of the **Δ** QMG separately with **Δ** ACTIVLIM. **Δ** QMG score is shown inverted on the x-axis so that a higher value on both the y- and the x-axis represents an improvement on the scale.

DISCUSSION

In a series of 118 consecutive MG patients, we found that the mean ACTIVLIM score in MG patients is relatively high, indicating fewer limitations in daily activities in comparison with other NMD and that the ACTIVLIM score in MG patients is associated with QMG score, gender, and the presence of other autoimmune diseases. Fluctuations in QMG score were associated with changes in activity limitations in individual patients as well.

The mean ACTIVLIM score was higher in our cohort of MG patients (3.3) than in patients with other NMD in previous studies (-1.13 to 2.71).[11-14] MG appears to cause fewer activity limitations than a number of other NMD, such as hereditary neuropathy, congenital muscular dystrophy, myotonic dystrophy, and amyotrophic lateral sclerosis as reported in previous studies. This difference in ADL limitations is probably explained by a number of factors, including the availability of treatment options and the temporary and fluctuating nature of weakness in MG in comparison to NMD that are irreversibly progressive. The ability to quantify the activity limitations caused by different NMD on the same scale may

be useful for health care policy makers who want to compare the burden imposed by different NMD on ADL. Furthermore, our results may help establish clinically relevant outcome measures in future clinical trials involving MG and other NMD.

QMG was strongly and inversely associated with ACTIVLIM, which shows that quantified muscle testing as measured by the QMG is directly relevant for activity limitations in MG patients. We also found that men had a significantly higher ACTIVLIM. This finding is in agreement with several large international studies in which a higher health-related quality of life (HRQoL) was found in men with MG.[5, 7, 21] Furthermore we found that patients with an additional AID had significantly more limitations in ADL. A potential explanation could be that the disease course of MG itself is more severe in patients with other AID. Indeed, the presence of an additional AID is associated with a higher risk of future exacerbations and emergency treatments.[18] However, the most likely cause for this finding is that these AID have a negative impact on ADL independent of MG, as QMG scores between patients with additional AID and patients without additional AID did not differ significantly in our study population (mean scores were 8 and 9, respectively).

Changes in QMG and ACTIVLIM were strongly and inversely correlated in individual patients. Our findings also showed that both oculobulbar and generalized MG patients had changes in activity limitations that were most clearly associated with changes in the generalized items of the QMG score. This finding suggests that we might underestimate the effect of subclinical generalized muscle weakness in patients who are clinically diagnosed with pure oculobulbar MG. This is in line with a previous study that described subclinical generalized weakness in ocular MG patients.[22] A previous study has shown that the ACTIVLIM score shows a good degree of responsiveness: in patients with a wide range of NMD undergoing repeated measurements, a self-reported deterioration in ACTIVLIM score corresponded to a decrease in functional status.[12] However, this study included progressive NMD in which only a deterioration of function was expected. Our study shows a good responsiveness of the ACTIVLIM score for both deteriorations and improvements in muscle strength.

Besides the ACTIVLIM described here, several measures for patient-oriented outcomes that assess ADL and quality of life (QoL) have been developed.[23] The MG-ADL is an ADL measure specifically for MG that correlates well with the QMG score, and improvements in QMG scores correlated well with changes in MG-ADL during a trial of mycophenolate mofetil.[8, 9] As the MG-ADL contains mainly oculobulbar items and only 2 extremity items, ACTIVLIM may be a useful addition for assessing generalized impairments in MG patients. It should be noted, however, that the ACTIVLIM score may underestimate the impact of oculobulbar symptoms on activity limitations. Indeed, of all the items on the MG-ADL, the items "chewing" and "swallowing" have the greatest impact on self-reported health, and these items are not assessed in the ACTIVLIM questionnaire.[4]

QoL in MG patients can be assessed with the Myasthenia Gravis Questionnaire and the MG-QOL15, in which the 60 item MG-QOL has been reduced to 15 items.[3, 6] A high cor-

relation was found between QMG score and MG-QOL15.[3] Although these disease-specific outcomes can be very useful in clinical trials, a questionnaire for all NMD in general such as ACTIVLIM may be practical in routine clinical care and allow for comparison of multiple NMD as well.

The strengths of this study are the large cohort of consecutive AChR MG patients, the analysis of repeated measurements to determine within-patient fluctuations in disease severity, and the systematic assessment of validated, quantitative measures for both muscle weakness (QMG) and activity limitations (ACTIVLIM).

Limitations of this study include the single center of inclusion, no assessment of ocular and bulbar weakness in our ADL measure, and the retrospective analysis of data. The ACTIVLIM questionnaire has been validated for NMD in general, although not specifically for MG patients. In addition, our data on the MG patient cohort was compared to historical data from previous publications on NMD. Potential differences in the selection of patients and evaluation points between studies could limit the validity of this comparison. Future studies could combine or compare assessment of activity limitations with ACTIVLIM and MG-ADL to gain a more complete view of oculobulbar and generalized impairments. We aimed to minimize the limitation of retrospective analysis by only including variables that could reliably be analyzed afterwards. Finally, our study population is from a tertiary referral center and may not fully reflect the total MG population due to a referral bias.

In conclusion, we have shown that MG patients report fewer activity limitations in comparison with other NMD, and that changes in the QMG score were associated with changes in activity limitations in individual MG patients. It may be useful to study the ACTIVLIM score and MG-ADL in the same group of MG patients to analyze whether the ACTIVLIM provides additional information or is more responsive to changes in generalized weakness in MG.

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