Author’s response to reviews

Title: Quantitative Motor Assessment of Muscular Weakness in Myasthenia Gravis: A pilot study

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Author’s response to reviews:

Subject: Resubmission of manuscript “Quantitative Motor Assessment of Muscular Weakness in Myasthenia Gravis: A pilot study” (MS ID#: NURL-D-15-00172)

Dear Dr. Murai,

Thank you for considering our manuscript for publication in BMC Neurology.

We would like to resubmit our thoroughly revised manuscript (NURL-D-15-00172) entitled “Quantitative Motor Assessment of Muscular Weakness in Myasthenia Gravis: A pilot study“. We have changed our manuscript according to the comments of the reviewers.
Upon receiving your response and the reviewer’s comments to the original manuscript (dated 16 November 2015), we were pleased to see that the reviewers found considerable merit and interest in our work. In addition, we felt that the detailed comments of the reviewer improved our manuscript substantially.

We hope that our revised manuscript has improved sufficiently to warrant publication in BMC Neurology. We greatly appreciate your and the reviewer’s time reconsidering the manuscript.

Sincerely yours,

Sarah Hoffmann

We would like to thank the reviewers for their helpful comments and have changed the manuscript according to their suggestions as follows:

REVIEWER #2

1. Does abnormal value of Q-IMA without decrease in grip force reflect the easy fatigability in upper extremities and/or hand grip of each MG patient? If so, did PI and OI correlate more significantly with items for arm-outstretch time and/or hand grip in QMG compared with total QMG

Response:

Like the reviewer states, we hypothesize that PI and OI as measures for involuntary movements in space are more sensitive parameters for detecting myasthenic muscle fatigability than isometric grip force as a measure for overt muscular weakness. While muscle strength can still be enough to hold the weight, it might not be enough to hold it steadily constant. Our visual comparison is that of a weightlifter starting to shake before dropping a weight (see Discussion). Unfortunately, a comparison of PI and OI correlations with subitems of the QMG score is not possible since only total QMG score was listed in our database. We feel, however, that the reviewer has raised an interesting issue and plan to assess QMG subitems in future studies on Q-Motor Assessment.

We added this drawback to our Discussion section and changed the manuscript as follows (page 14, line 2 ff.):
“Firstly, QGFA and QIMA assess only one body region whereas QMG score assesses 13 items involving different muscle groups. Future studies on Q-Motor Assessment should compare correlations with total QMG score and its subitems (i.e. arm outstretched, hand grip).”

2. What are "deficits in motor coordination in MG"? The reviewer feels that it would be better to comment on what Q-IMA reflect in MG patients with various distributions of symptoms

Response:

Though muscular weakness might result in subsequent deficits in motor coordination we agree with the reviewer that this choice of words might be misleading for the readers. We therefore restricted the presentation of our data to the assessment and quantification of muscular weakness. The term “motor coordination” was removed on page 10 line 1 and 5 and page 14, line 19.

3. Is there no difference in PI and OI between ocular and generalized MG.

Response:

The reviewer addresses an essential drawback of this study. Though OMG and GMG-patients showed significantly higher PI and OI values compared to healthy controls, no significant differences were seen between OMG and GMG-patients. We believe that there are two possible explanations for this finding: Firstly, the missing differences between OMG and GMG patients could be due to a hypothesized subclinical affection of limb muscles in OMG patients. Another explanation might be the patient selection. Though inclusion criteria encompassed all MG-patients independent of disease severity excluding only myasthenic crisis, the GMG-patients enrolled were only mildly affected (all patients but one patient had MGFA classification IIa/b). More severely affected patients might have declined the test battery due to their condition. Future studies on Q-Motor Assessment will have to include more severely affected patients to show plausible differences between OMG and GMG-patients.

We emphasized this drawback more clearly in our Discussion section and changed the manuscript as follows (page 13, line 11 ff.):

“No differences were seen for PI and OI between OMG and GMG-patients. There might be two possible explanations for this finding. The missing differences between OMG and GMG patients could be due to a hypothesized subclinical affection of limb muscles in OMG patients. Another explanation might be the patient selection. Though inclusion criteria encompassed all MG-
patients independent of disease severity excluding only myasthenic crisis, the GMG-patients enrolled were only mildly affected (all patients but one patient had MGFA classification IIa/b). Future studies on Q-Motor Assessment will have to include more severely affected patients to show plausible differences between OMG and GMG-patients.”

4. The authors commented that Q-Motor assessments are easily applicable methods, so I want to know how much time does Q-Motor assessment require.

Response:

We thank the reviewer to request this important information for the readers, which we have added accordingly to our Method section as follows (page 6, line 16f.):

“Completion of Q-motor tasks required 5 minutes per hand and weight.”

REVIEWER #3

1. What was special about the OMG patients who showed high value? Did they have diplopia rather than ptosis?

Response:

We reviewed the patient files and found that among our OMG-patients 1 patient had isolated ptosis, 2 patients had isolated diplopia and 4 patients suffered from ptosis and diplopia. We analysed possible differences between these subgroups. The only significant difference was found in OI for the light weight and dominant hand (p-value 0.46, patients with ptosis and diplopia showing the highest values). We specified the patients’ clinical characteristics in the results section as follows (page 8, line 11ff):

“Seven (17.5%) patients had clinically OMG (MGFA I, 1 patient with isolated ptosis, 2 patients with isolated diplopia and 4 patients with ptosis and diplopia).”

Due to the very low case number among OMG subgroups we abstained from including them into our analysis.

2. Do PI and OI values in OMG correlate with disease duration?
Response:

This is an interesting question, which the author’s had not considered yet. We assessed correlation between disease duration and PI and OI values in our OMG-patients and found no significant results. For the reviewer’s scrutiny, the correlation of PI and OI with disease duration in OMG patients are presented at the end of the revised cover letter (see upload).

We added this information in our discussion and changed the manuscript as follows (page 13, line 6ff.):

“Hence, it is unlikely that the shorter disease duration entirely explains the differences seen between OMG patients and HC. The fact that PI and OI values in OMG patients did not correlate with disease duration seems to support this assumption (data not shown).”

3. Authors mentioned that there were no differences in PI and OI value between MGFA IIa patients and IIb+IIIb patients. What would be the explanation for this?

Response:

According to the reviewers suggestion we have emphasized this issue more clearly in our discussion and changed the manuscript as follows (page 12, line 8ff.):

“No differences in PI and OI value were seen between patients with predominantly affected limb and/or axial muscles and patients with predominantly affected oropharyngeal and/or respiratory muscles. The explanation for this finding might be twofold: Firstly, to assess differences between subgroups of MG-patients, all patients were categorized into either MGFA IIa or MGFA IIb+IIIb. Categorization based on the clinical judgement of the study physician concerning the pattern of muscle weakness. Thereby, the predominantly but not exclusively affected muscle groups decided upon MGFA classification. The fluctuating extent and variable predominance of the muscle groups involved, makes it extremely difficult to classify MG patients and the inherent imprecision of the MGFA classification is widely accepted [3]. Secondly, Q-Motor might be able to detect subclinical affection of limb muscle weakness in patients with predominantly affected oropharyngeal and/or respiratory muscles the way it seems to do in patients with purely ocular symptoms.”
4. In Table 1 and 3, MGFA II+IIIb should be MGFA IIb+IIIb. In the footnote of Table 1, AchR should be AChR.

Response:

We thank the reviewer for carefully reading the manuscript. The misspellings were corrected according to the reviewer’s suggestions.