A Conceptual Framework for Evaluating Impairments in Myasthenia Gravis

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Abstract

Background: Myasthenia gravis is characterized by weakness and fatigability of different muscle groups, including ocular, bulbar and the limbs. Therefore, a measure of disease severity at the impairment level in myasthenia needs to reflect all the relevant impairments, as well as their variations with activity and fatigue. We conducted a qualitative study of patients with myasthenia, to explore their experiences and related impairments, aimed at developing a conceptual framework of disease severity at the impairment level in myasthenia gravis.

Methods: Twenty patients representing the spectrum of disease participated in semi-structured interviews. Interviews were recorded and the transcripts were analyzed by content analysis using an inductive approach with line-by-line open coding. Themes were generated from these codes.

Results: Two main themes were identified: the severity of the impairments and fatigability (i.e., triggering or worsening of an impairment with activity). The impairments were further classified within body regions (ocular, bulbar and axial/limbs). Fatigability was described as a phenomenon affecting the whole body but also affecting specific impairments, and was associated with fluctuation of the symptoms. Patients were concerned that clinical examination at a single point in time might not reflect their true clinical state due to fatigability and fluctuations in severity.

Conclusions: This conceptual framework reflects the relevance of both severity and fatigability in understanding impairment-based disease severity in myasthenia. This framework could inform the development of impairment measures in myasthenia gravis.

Introduction

Development of outcome measures begins with a thorough understanding of the concept that is being measured. This is not always simple since many clinically relevant outcomes represent complex phenomena. Including items that are not relevant to the construct of interest or worse, omitting relevant ones can undermine content validity [1]. The International Classification of Functioning, Disability and Health (ICF) [2] defines impairments as significant deviations or loss of body functions (e.g. muscle power, speaking, seeing, etc.) or body structures (e.g. arms, legs, eyes). In the case of Myasthenia Gravis (MG) it has been shown that, based on the ICF definition, impairments of body structures and function are most strongly correlated with the difficulties encountered by patients with MG in their daily life [3]. Therefore, quantifying impairment can provide a measure of disease severity.

The underlying defect of neuromuscular transmission in MG is manifested clinically by muscle weakness and fatigability, which can improve with rest and frequently results in fluctuation of symptoms [4]. MG can cause impairment of extra-ocular, bulbar, axial and limb muscles and these are variably affected in different patients, such that some have purely ocular disease while others have different combinations of bulbar, limb and ocular impairments [4,5]. All of these factors make measuring impairment challenging in MG patients. Currently available impairment measures in MG were mostly developed based on experts' consensus of relevant impairments [6–9]. These measures differ in both the impairments included and how they are measured demonstrating that there is no global consensus. Incorporating the patient's perspective provides invaluable information regarding which impairments are most relevant to patients as well as the patterns of impairment experienced by patients. While some of this information in MG has been gathered through patient surveys [10], or through structured interviews using the ICF checklist of
imperfections [3] these methods do not allow the depth of inquiry needed to understand complex phenomena. Furthermore, the use of structured response options doesn’t easily allow for the incorporation of individual patients’ experiences. Finally, some have found low reliability for the ICF codes used in some surveys [11]. Given these gaps in the literature, the aim of this study was to explore the experiences of patients with MG, specifically those related to their impairments, to guide the development of a new impairment measure in myasthenia.

Methods

Study Design

This qualitative study used in-depth interviews with content analysis to explore patient experiences. Content analysis is focused on unique themes that illustrate a given phenomenon, improving the understanding of subjective experiences [12], and thus provides the opportunity to explore the depth of patient experiences by systematically identifying themes and patterns. This approach is in keeping with the guidance document from the US Food and Drug Administration (FDA) [13] and the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) [14], which recommend the incorporation of patient input and encourage the use of a conceptual framework to design new patient reported outcomes (PRO).

Sampling and Data collection

Adult patients with a confirmed diagnosis of MG attending the Neuromuscular Clinic at Toronto General Hospital (Toronto, Canada), who were fluent in written and verbal English, were invited to participate. Theoretical sampling was used to achieve maximum variation [13]. Hence, patients with varying disease localization (i.e. ocular or generalized) and symptomatic complaints were invited to participate. The Myasthenia Gravis Foundation of America (MGFA) classification [16] was used to

Figure 1. Interview Guide. This is the interview guide used for the interviews. It depicts the open questions and possible probes. doi:10.1371/journal.pone.0098089.g001
classify patients according to their symptom distribution and severity. This classifies patients in class I if purely ocular, and classes II, III, IV, and V for generalized patients with increasing severity. For patients in class II and higher, the subclass “b” indicates primarily bulbar impairments and “a” primarily limb or axial impairments.

There is no consensus on what constitutes a sufficient sample size for qualitative studies [17], however most researchers agree that once new themes are no longer being generated with subsequent interviews (i.e. data saturation), sufficient sample size has been reached for understanding the phenomenon of interest [18]. Therefore, we conducted interviews until data saturation was achieved. The University Health Network Ethics Board approved the study and all patients provided written informed consent.

Individual interviews were conducted following a semi-structured interview guide (Figure 1). Interviews were chosen as they allow in-depth exploration of individual participant’s experiences whereas focus groups rely more on group interaction to elicit information [18]. The interviews began with broad, open questions regarding the patients’ experiences with MG with probes used to facilitate more in-depth description. One author (CB) conducted all patient interviews after receiving training in interviewing techniques and performing pilot interviews using the interview guide. The interviews were conducted in person, audio tapped and transcribed verbatim. Additionally, memos were created after each interview to allow for interviewer reflection and consideration of any bias that might have influenced the interview. The transcripts were imported into HyperRESEARCH (version 3.5, Researchware, Inc) software for managing qualitative data. The transcripts were analyzed using content analysis which is a process whereby the data are systematically analyzed by classifying words or phrases that have the same meaning together, aiming to explain the phenomenon of interest through these categories or themes [19].

We used an inductive approach, thus assuming no previous knowledge of the phenomenon and used line-by-line open coding [19]. Two authors, (CB and AD) independently coded the first 6 transcripts and then discussed the codes to develop a coding framework. Coding then proceeded in a constant comparative manner to allow probing of arising topics, and the coding was compared to reach consensus. A third author (VB) also coded a sample of transcripts to further ensure that all relevant themes were identified. At bi-weekly meetings, two authors (CB and AD) discussed the transcripts and arising themes and revised the coding framework as appropriate. After the main themes were developed from the codes, sub-themes were created by further grouping similar codes, using the ICF classification [2].The ongoing discussions regarding the transcript codes and themes not only allowed the investigators to discuss their biases but importantly to discuss how themes were evolving from the codes and their potential relationships as the framework was developed.

Results

Twenty patients were interviewed, the median age was 62.5 years (range: 29 to 78); 11 (55%) patients were female and the median disease duration was 7 years (range: 1 to 27). Regarding localization and MGFA severity, 4 (20%) patients had purely ocular disease (MGFA class I). Of the patients with generalized disease, 5 (25%) were in MGFA class Ia, 8 (40%) were in class Ib, 1 (5%) in class Iia and 2 (10%) were type Iib at the time of the interview. The clinical characteristics of the patients participating in this study are summarized in Table 1.

Two main themes were identified that were common across anatomical sites of involvement: the severity of the impairments and fatigability of the impairments (i.e. change or triggering of an impairment with usual activities or onset/worsening of an impairment over the course of the day). Impairments were grouped in 3 sub-themes, based on their anatomical location: ocular, bulbar and axial/limbs. As shown in Figure 2, the impairments were further organized based on the ICF classification of body functions and structures within the sub-themes. The results below have been organized presenting an overview of each main theme with examples for each sub-theme.

Main Theme: Impairment Severity

Impairment severity refers to the variable extent to which a given impairment was experienced by the patients. The patients used different language to described different impairments within each sub-theme (additional quotes for this theme can be found in Table 2).

Ocular. In the case of ocular impairments, most of the patients reported double vision. “I was driving and all of a sudden, instead of one car coming at me there were two coming at me, one in my lane.” (P9, female, age 63). Some patients described a range of double vision, regarding the separation of the images: “…it varies from being very little off, so things just almost look a little blurry, to now, I can see two TVs: sitting side by side.” (P11, male, age 78).

The patients also reported drooping of the eyelids and difficulty opening their eyes, such as: “…there is something weird with my eye, it doesn’t appear to want to stay open….” (P10, female, age 70) and in some cases, they related their most severe experience of eyelid drooping “…I had to keep my eyelid open with my finger. They wouldn’t stay open far enough to actually see.” (P7, male, age 63).

Bulbar. The patients reported different impairments that were classified as bulbar, including problems while eating, speaking, breathing and problems with their facial muscles and expression.

Regarding ingestion functions, patients reported difficulties with chewing, especially with harder foods: “It’s changed dramatically from going to the point where I could not have any kind of solids, … to the point where I could eat anything semi-solid. I can’t really eat a steak per se okay or anything like these celery or chew a raw carrot or a raw apple, that’s still difficult.” (P2, male, age 58). Swallowing was also affected, patients reported different degrees of impairment from choking to difficulty swallowing certain foods: “…if something goes down the wrong way, I choke fast… before I thought nothing of it, but when I was chewing meat, I was having problems swallowing.” (P14, male, age 64). Some patients reported difficulties with swallowing fluids: “I couldn’t swallow water, as soon as I swallowed it, it would come back in my nose” (P4, male, age 60), and some patients had required a feeding tube at some point: “I wasn’t really eating so much… so they put me on a [feeding] tube at home for three years.” (P12, female, age 34).

The patients also reported two different problems when speaking: problems with the quality of the voice and problems with articulation. The voice quality was affected by low volume or changes in the tone. For example, a participant described the complexity of her voice problems: “I wasn’t able to speak, I wasn’t able to articulate my words. I literally wasn’t able to. I was just mumbling…” (P2, male, age 58).

Breathing impairments were also frequently reported, sometimes during physical activity: “…before, when I was walking, I couldn’t...
breathe. But, now it’s better.” (P9, female, age 62). A few patients had experienced a myasthenic crisis: “Then two or three days later I was having problems breathing so I came in the hospital, and they put me in a breathing machine because my breathing was very weak.” (P19, male, age 63).

Some patients reported changes in their facial muscles, in cases producing reduced expression, as this patient describes: “[they] were misreading a lot of my facial expressions as being angry or mean because my face wasn’t accurately reflecting my emotions. The muscles in my face, I always looked really angry and I also looked sort of tired.” (P1, female, age 39). Other patients reported impairments localized to their lower face and mouth muscles, for example: “I couldn’t drink from a cup or a straw, it would just run down my face. I had no control [of] muscles in my mouth whatsoever to even seal a straw” (P20, female, age 44).

Limb and axial muscles. The patients reported impairments in their arms, legs and also neck. In the case of the arms, a common impairment was weakness, as reflected in this example: “…If I were talking on the cell phone too, I wouldn’t be able to keep my arm lifted. Sometimes I would have to prop my arm up or something to keep the arm up all the way through [the call]. So, I guess it was the back of the arms. Hard to tie ponytails, hard to shampoo…” (P6, female, age 29). Some patients described leg weakness, for example: “I couldn’t go upstairs or in the car or the truck or something, I couldn’t … my legs, they would just give out, like cooked macaroni.” (P13, male, age 63). Some patients also described weakness in their neck, with difficulty holding up their head, such as: “But, honestly, it was so bad that I couldn’t hold my head up, every time I talked to somebody my head was kinked down like this” (P4, male, age 60). The following example illustrates the severity of the neck weakness: “My head, when I am walking, I have to sometimes keep my chin like that [holds chin with hand], because my head is falling forward. Maybe the muscles in my neck are very, very weak” (P9, female, age 62).

Main Theme: Fatigability

Fatigability refers to the triggering or worsening of an impairment with usual or normal activities, or onset/worsening of an impairment over the course of the day. This was reported by all patients and affected different body structures and functions. It was frequently described as weakness occurring right after physical effort: “Physical labour messes me right up. If I go out to mow the lawn, I’m done for two hours. I have to lie down.” (P8, female, age 63) And from a different patient, again illustrating the relationship between exertion and the symptoms: “It improved tremendously and it was almost normal but any exertion was a problem…But as I explained to you, exertion would again bring those things but if no exertion is done then I don’t feel it.” (P16, male, age 64).

Most patients made a distinction between absolute weakness and reduced endurance, as in this example: “I can climb up the fabric [gym class] and I can do things like that, so I have very strong muscles, which I don’t know if that’s an indicator or not though because I feel like it’s not so much how strong your muscles are, as how intensely you’ve used them over a long period of time” (P6, female, age 29). Patients reported having to take frequent breaks, in order to perform tasks: “And as far as doing
anything, I can do anything but I just have to do it inconsistently, like I do a little bit and then I stop for a minute and take a break and do a little bit more.” (P4, male, age 60).

Participants also described fluctuations of the impairment that reflected fatigability: “Every time I went home after work, I was so drained. There were times that I was so weak and I couldn’t even get up but after having a rest again in the evenings, the day after again when I go to work, I’m okay” (P12, female, age 34). And from the same patient “…Some better days, bad days, I don’t know, I really can’t explain myasthenia. Sometimes I’m good. Sometimes I’m really bad.” In some patients, these changes were a source of concern regarding their clinical assessments, as this patient indicated: “It’s [the assessment] just such a quick snapshot of how I’m doing, really, at that very moment. And it seems so variable throughout the day. I could have a good hour where people wouldn’t even know that I have MG at all. I look like I have lots of energy and whatnot. But then, at a moment’s notice, it could completely change.” (P1, female, age 39). The following also reflects patients concerns during clinical examination: “I know I’m a lot weaker than what I normally am, what I’m capable of, I know that the muscles are fatigued. But somebody doing the physical test on me, looks at me and says, wow, you’ve got incredible strength. But it’s trying to make sure that the person realises that yes, I have MG at all. I look like I have lots of energy and whatnot. But then, at a moment’s notice, it could completely change.” (P1, female, age 39). The following also reflects patients concerns during clinical examination: “I know I’m a lot weaker than what I normally am, what I’m capable of, I know that the muscles are fatigued. But somebody doing the physical test on me, looks at me and says, wow, you’ve got incredible strength. But it’s trying to make sure that the person realises that yes, I have MG at all. I look like I have lots of energy and whatnot. But then, at a moment’s notice, it could completely change.” (P1, female, age 39).

Besides the descriptions of general fatigability above, the patients also described fatigability concerning specific impairments.

**Ocular.** Patients reported that their impairments (eyelid drooping and double vision) could be caused or worsened by prolonged activities with the eyes: “…And clearly, after a full day of office work, reading, being at my desk, my vision is worse so by the time I go to drive home from downtown [city name] at 5:00 p.m., my vision is probably at its worst that it will be during the day.” (P3, male, age 66). They also reported fluctuation of the eye impairments, particularly related to the duration of the episodes of double vision: “Oh, I’ll have to say sometimes hours, and sometimes minutes, but then there would be days with nothing.” (P11, male, age 78). The impact of specific activities and also of the time of day was also reported in drooping of the eyelids: “… and I would find that by 12:00 in the day time my eyes were like really down. I find out that it is pretty much mostly when I’m tired or especially if I’ve been staring at something or reading for a bit, then like it [eyelid] really droops.” (P17, male, age 61)

**Bulbar.** The patients reported a fatigability component with chewing, speaking and breathing. In chewing, fatigability was frequently reported: “I could chew for a while and then everything stopped, my muscles, I couldn’t chew anymore… I’d be getting into a good hamburger and it would just stop,” (P14, male, age 64) “I cannot chew gum because one, two or three times if I chew, my jaws I cannot move anymore. I’ve got to wait 5 or 10 minutes, and then I get a little bit stronger so I gave up chewing gum.” (P19, male, age 63). But also, some patients reported chewing problems occurring throughout the day: “I used to have quite difficulty chewing by the end of the day” (P6, female, age 29).

The patients reported fatigability of their voice triggered by prolonged activity: “One of the symptoms was that your voice gets tired or

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**Figure 2. Conceptual Framework for Evaluating Impairments in Myasthenia Gravis.** This diagram depicts our proposed framework of disease severity at the impairment level, in myasthenia gravis patients. The main themes (impairment severity and fatigability) were further sub classified by body region, using the ICF classification.

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Discussion

This work provides a framework for understanding and evaluating impairments from Myasthenia Gravis based on patient experiences. Patients’ descriptions suggest that not only the severity but importantly the fatigability are major drivers of their overall impairment (Figure 2). Of current measures, the MG impairment scale [20] has two components: fatigability and strength/function which is in keeping with our two main themes. However, although the specific impairments and their severity related to ocular, bulbar, limb and axial muscles have been incorporated in most MG tools, the inclusion of fatigability has been variable among current measures of impairment [6–9,20–23] as shown in table 4. Hence, the main difference between our framework and most current impairment tools in MG is the incorporation of fatigability as a main theme across impairments.

Fatigability has been defined as exercise-induced reduction in the ability of muscles to produce power [24], or as the magnitude of change in a performance criterion relative to a reference value over a given time of task performance [25]. Fatigability can result in disability if individuals are unable to complete tasks or take longer to do them, limiting daily life activities [24,25]. Fatigability should be differentiated from fatigue which is a broader concept that includes a mental component [25], and which has been defined as a subjective lack of physical and mental energy that interferes with usual activities [24]. In the case of MG patients, the clinical and electrodiagnostic examinations can provide objective evidence of muscle weakness occurring with activities [4,5], and this performance fatigability was reported by all our patients. The differentiation between muscle power and fatigability or muscle endurance, can affect how the patients’ impairments are perceived when assessed clinically. This might impact clinical decision-making as relevant impairments might be missed by single, fixed point in time measurement without evaluation of fatigability. The result is that some patients might seem to be doing better on a single assessment than their true clinical state measured over the course of their daily activities. Even when the patients used the word fatigue, the probes used to deepen that concept during the interviews usually resulted in descriptions of fatigability, further supporting its importance in understanding impairment in MG.
The importance of the concept of fatigability and reduced endurance was also demonstrated in a study of 102 patients with MG which used the ICF checklist to quantify the prevalence of impairments in body structures and function (and activities and limitations and environmental factors) [26]. The results showed that muscle endurance impairments were more prevalent (77.5%) than impairments of muscle power (54.9%). This further supports our interpretation of our qualitative data.

The reason for the variable inclusion of fatigability in current measures is unclear.

Quantification of fatigability can be challenging and it is possible that is why it has not been widely included in current measures. Although some measures provided limited information on criteria for including and reducing items, in the case of the MGC [9], items were selected from a pool of several available measures used in a clinical trial. Items were chosen based on correlations with quality of life scales and clinical change, such that they represent different phenomena.

Additionally, our findings differ somewhat from those of the study by Leonardi et al. regarding the impairments described [26], and this is likely due to a difference in overall purpose. The aim of the current study was to conceptualize impairments directly caused by MG, as a measure of disease severity. Hence, we did not include impairments that can be caused by other factors such as sleeping functions, which can be secondary to respiratory muscle weakness, medications or depression. This is in contrast to the study by Leonardi et al. [26] that included secondary causes and, using the ICF checklist, found that energy and drive, sleep functions, which can be secondary to respiratory muscle weakness, were relevant to patients with MG, in addition to the pain were relevant to patients with MG, in addition to the pain were relevant to patients with MG.

Our framework, as shown in figure 2, includes as sub-themes the following body functions: extra-ocular muscles and the eyelids, ingestion functions (chewing and swallowing), voice and speech functions (articulation and voice quality), respiratory functions, function of facial muscles (lower), and functions of the arms, neck and legs. Currently available measures of impairment have differences among them in terms of the impairments measured as well as with our framework (Table 4). For example, the QMGS [8] includes only swallowing to assess ingestion functions, while the Myasthenia Gravis Composite (MGC) [9] includes swallowing and chewing, in keeping with what our patients reported. Most scales assess speech based on clarity (stuttered speech or dysarthria) alone or in combination with tonal changes (nasal voice or hypophonia) within a single item. However, our findings suggest that patients distinguish between tonal and speech articulation impairments such that they represent different phenomena.

None of our patients reported eye closure weakness, which is measured in most impairment tools in MG. This is in keeping with...
the post-intervention status classification by the MGFA, which allows the presence of isolated eye closure weakness as the only clinical sign in patients in remission (no signs or symptoms for more than 1 year) [16]. Together with our findings, this suggests that eye closure weakness is not clinically significant in this population and that it is not informative to measure this impairment in MG patients. In contrast, patients did report lower facial weakness and reduced facial expression, suggesting that those impairments should be measured.

We used a patient-centered approach in developing this framework that will be used to develop a measure of impairment severity. Therefore, it is not surprising that we found some differences compared to current measures given that these were developed mostly based on clinicians’ experiences [8,9,20,22,23,29], pre-dating current standards for developing patient-reported outcomes that require incorporation of the patient perspective [13].

Incorporating Patient Reported Outcomes (PROs) can be of great value in the case of MG where the impairments fluctuate, as PROs can assess the impairments over longer periods of time than in a typical clinical examination, and thus can be more sensitive to detect clinical change. Further, PROs can assess impairments and their relationship with daily life activities, therefore assessing fatigability, which is harder than with the clinical examination alone. Clinical tests for fatigability typically measure endurance or weakness after repetitive exercise [8,30], but time constraints might obscure fatigability in patients that require longer activity to trigger their impairments. Therefore combining clinical examination with PROs might be more sensitive to measure overall impairment.

While the qualitative studies are not meant to be generalizable, we do acknowledge that recruitment from a single centre may increase the chances of not identifying relevant impairments. However, while our recruitment site is a large academic centre with more than 300 patients assessed each year, certain experiences such as access to care and treatment patterns and side effects might differ from patients in different settings. Since we were focused on the impairments, which are not related to the treatment environment and are mostly dependent on the patients’ individual factors, this might not be an issue. Additionally, we purposely sampled to achieve maximum variation, including a heterogeneous sample of purely ocular and generalized patients with different degrees of severity, to represent the breadth of MG presentation. Further, we did not find any missing themes when looking at the available measures, supporting the main themes and sub-themes incorporated in our framework. Additionally, the investigator who conducted the interviews (CB) had clinical involvement with some of the patients before the interview, and

### Table 4. Characteristics of Current Impairment Tools for Myasthenia Gravis in Relationship with Proposed Framework.

| Measure Name     | Fatigability Measures Included               | Impairments Not Included     | Patient Reported Items |
|------------------|---------------------------------------------|------------------------------|------------------------|
| QMGS [7,8]       | Endurance: arms, neck, legs                 | Chewing                      | None                   |
|                  | Time to diplopia and ptosis                 | Voice quality                |                        |
|                  | Speech articulation                         | Lower facial muscles         |                        |
| MGC [9]          | Time to diplopia and ptosis                 | Speech articulation and voice | Chewing                |
|                  | Chewing                                     | Lower facial muscles         | Swallowing             |
|                  | Breathing                                    | Speech and voice             |                        |
|                  |                                            |                              |                        |
| MMT [23]         | None                                        | Chewing                      | None                   |
|                  |                                            | Swallowing                   |                        |
|                  |                                            | Speech articulation          |                        |
| MMS [6,30]       | Endurance: arms and legs                    | Ptosis and diplopia          | None                   |
|                  |                                            | Speech articulation and voice |                        |
|                  |                                            | Lower facial muscles         |                        |
| MG Impairment [20] | Endurance: arms, legs, neck                 | Speech articulation          | Chewing                |
|                  | Time to ptosis                              |                              | Swallowing             |
|                  | Chewing                                     |                              |                        |
|                  | Voice Quality                                |                              |                        |
|                  | Tongue                                      |                              |                        |
|                  | Swallowing                                   |                              |                        |
| MG Score [22]    | Arms                                        | Upper and lower facial muscles | Swallowing             |
|                  | Legs                                        | Ptosis and diplopia          | Speech articulation and voice |

1Both impairments are combined in a single item.
2Unclear whether it is patient reported.
QMGS: Quantitative Myasthenia Gravis Score.
MGC: Myasthenia Gravis Composite.
MMT: Manual Muscle Test.
MMS: Myasthenic Muscle Score.
MG: Myasthenia Gravis.
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this is a potential source of bias. However, a different investigator (AD), who has no connection to the patients, actively participated in the coding and content analysis, helping to minimize any bias.

In summary, this is the first qualitative study looking at impairments in patients with Myasthenia Gravis. The resulting conceptual framework of disease severity aids to the understanding of the complexity of the impairments, their severity, and fatigability triggered by specific activities and throughout the day. This framework provides the basis for developing new outcome measures or modifying existing ones to better reflect the impairments and symptom burden in patients with Myasthenia Gravis.

**Author Contributions**

Conceived and designed the experiments: CB VB MK AK AD. Performed the experiments: CB. Analyzed the data: CB AD. Contributed reagents/materials/analysis tools: CB VB AD. Wrote the paper: CB AD. Reviewing and editing the manuscript: CB VB MK AK AD. Final approval of the manuscript: CB VB MK AK AD.

**References**

1. De Vet HCW, Terwee CB, Mokkink LB, Knol DL. (2011) Measurement in Medicine. Cambridge Univ Pr; 2011. pp 30-64.
2. World Health Organization (2001) International Classification of Functioning, Disability and Health (ICF). 1st ed. World Health Organization.
3. Leonardi M, Raggi A, Antozzi C, Confalonieri P, Maggi L, et al. (2009) Disability and functional profiles of patients with myasthenia gravis measured with ICF classification. Int J Rehab Res 2009;32: 167–172. doi:10.1097/ MRR.0b013e3282a1e2f77.
4. Howard JF (2012) The diagnosis of myasthenia gravis and other disorders of neuromuscular transmission. In Engel AG (2012) Myasthenia Gravis and Myasthenic Disorders. Oxford University Press. pp 108–129.
5. Kaks JMB, Oosterhuis HJGH (2009) Clinical presentation and epidemiology of myasthenia gravis. In Kaminski HJ (2009) Myasthenia Gravis and Related Disorders. Springer. pp 93–114.
6. Gajdón P, Simon N, de Rohan-Chabot P, Goulon M (1983) Effets à long terme des échanges plasmatiques au cours de la myasthenie. Résultats d’une Etude randomisée. Presse Med 12: 939–942.
7. Tindall RS, Rollins JA, Phillips JT, Greenwood RG, Wells L, et al. (1977) Preliminary results of a double-blind, randomized, placebo-controlled trial of cyclosporin in myasthenia gravis. N Engl J Med 316: 719–724. doi:10.1056/NEJM198703193161205.
8. Barohn RJ, McIntire D, Herbelin L, Wolfe GI, Nations S, et al. (1998) Reliability testing of the quantitative myasthenia gravis score. Ann N Y Acad Sci 841: 769–772.
9. Burns TM, Conaway MR, Cutter GR, Sanders DB, Muscle Study Group (2008) Construction of an effective evaluative instrument for myasthenia gravis: the MG composite. Muscle Nerve 38: 1533–1562. doi:10.1002/mus.21185.
10. Twork S, Wiesnef S, Klowerw J, Poldau D, Kugler J (2010) Quality of life and life circumstances in German myasthenia gravis patients. Health Qual Life Outcomes 8: 129.
11. Okochi J, Utsunomiya S, Takahashi T (2005) Health measurement using the ICF: test-retest reliability study of ICF codes and qualifiers in geriatric care. Health Qual Life Outcomes 3: 46. doi:10.1186/1477-7525-3-46.
12. Zhang Y, Wildenhus BM (2009) Qualitative analysis of content. In Wildenhus BM (Ed.) Applications of social research methods to questions in information and library science. pp308–319. Westport, CT: Libraries Unlimited.
13. U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health (2006) Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims: draft guidance. Health Qual Life Outcomes 8: 129.
14. Mokkink LB, Terwee CB, Knol DL, Stratford PW, Alonso J, et al. (2010) The COSMIN checklist for evaluating the methodological quality of studies on measurement properties: A clarification of its content. BMC Med Res Methodol 10: 22.