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Etude patho-physiologique de patients atteints de myasthénie auto-immune : qualité de vie, activité physique habituelle, force et fatigue musculaire, et possibilité de participer à un entraînement individualisé à domicile.

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Physical Activity and Quality of Life in Auto-Immune Myasthenia Gravis

Thèse de doctorat de l'Université Paris-Est
École doctorale n°402 : Sciences de la Vie et de la Santé
Spécialité : Pathologie et recherche clinique

Thèse présentée et soutenue à Paris, le 7 Décembre 2018, par
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Resume

Physical Activity and Quality of Life in Auto-Immune Myasthenia Gravis

Physical inactivity is considered the 4th leading risk factor for death worldwide, linked to increased chronic disease and social isolation. Public health campaigns to encourage increased activity are rife. However, increasing physical activity levels and intensities may not be possible or advised in certain patient populations. Myasthenia gravis (MG) is a rare, auto-immune disease in which dysfunction at the neuromuscular junction causes weakness and fatigue. Symptoms can cause functional impairment and reduced activity, creating the increased burden of deconditioning in addition to primary disease symptoms. The present work investigated clinical symptoms, MG-specific health-related quality of life and activity levels in individuals with MG. Data presented here show that whilst some individuals lead a sedentary lifestyle, others participate in regular, high-intensity exercise. QoL does not seem to be related to physical activity patterns and is not improved with the addition of a structured exercise program. Exercise provides other benefits such as increased walking capacity and a possible increase in strength. Importantly, exercise has been shown to be safe in stabilized myasthenia. Finally, we reveal that whilst fatigue is a hallmark symptom in MG, formal testing demonstrated that muscle fatigue was not greater than healthy controls suggesting that perceived fatigue may be related to weakness. In light of these results we would recommend that subjects with MG are encouraged to reduce their daily sedentary behaviour and to undertake a regular exercise program to prevent deconditioning and potentially improve functional capacities. The optimal type and dosage of exercise remains to be elucidated.

Auto-immune myasthenia gravis, quality of life, physical activity, physical exercise, fatigue

Activité physique et qualité de vie dans la myasthénie auto-immune

L'inactivité physique est considérée comme le 4^{ème} facteur de risque de décès dans le monde. Aujourd'hui un défi de santé publique est d'augmenter l'activité physique (AP) des citoyens. Cependant, l'augmentation du volume et de l'intensité de l'AP peut être impossible ou déconseillée dans certaines populations. La myasthénie auto-immune (MG) est une maladie rare dans laquelle un dysfonctionnement de la jonction neuromusculaire provoque une faiblesse et une fatigue. Les symptômes peuvent entraîner une déficience fonctionnelle et une activité réduite, menant à un déconditionnement secondaire. Le présent travail a étudié les symptômes cliniques, la qualité de vie et l'activité physique dans une cohorte de sujets atteints de MG. Les données présentées ici montrent que certaines personnes mènent un mode de vie sédentaire mais d'autres participent à des activités physiques régulières et de haute intensité. La qualité de vie ne semble pas être liée aux comportements d'activité physique et n'est pas améliorée par l'ajout d'un programme d'exercice structuré. Notamment, il a été démontré que l'exercice est sans danger dans les cas de MG stabilisée. De plus, l'exercice procure d'autres avantages tels qu'une meilleure capacité de marche et une éventuelle augmentation sensible de la force. Enfin, nous révélons que même si la fatigue est un symptôme caractéristique de la MG, nous n'avons pas trouvé de fatigue musculaire supérieure à celle de témoins sains, ce qui suggère que la fatigue perçue pourrait davantage être liée à la faiblesse musculaire. En conclusion, nous recommandons qu'un programme d'exercice physique adapté et sur-mesure soit proposé aux personnes atteintes de MG afin de prévenir le déconditionnement et les comorbidités secondaires. Des recherches supplémentaires sont nécessaires pour définir le type et le dosage optimal de l'exercice.

Myasthénie auto-immune, qualité de vie, activité physique, exercice physique, fatigue

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Thesis aims

Physical inactivity represents an economic burden for society and a burden for the individual as it contributes to social isolation, increased risk of chronic disease and reduced life expectancy [1]. The negative effects of inactivity and positive effects of exercise in the general population are probably applicable to chronic diseases such as auto-immune myasthenia gravis (MG) [2]. Historically, exercise was contra-indicated in most neuromuscular diseases. Recent research demonstrates that not only does exercise seem to be safe but also beneficial in many patient populations. Research in MG is in its infancy with several new studies being published early this year.

The aims of this thesis were to evaluate the effects of exercise in auto-immune MG, to evaluate current activity levels in this patient population, to study the relationship between physical activity and quality of life and to evaluate the effects of adding an exercise program, on quality of life. An additional aim was to evaluate the presence of increased neuromuscular fatigue in this population to assist in understanding its possible contribution to reduced activity and/or performance limitations.

This manuscript begins with an introduction describing auto-immune myasthenia gravis, followed by a brief introduction at the beginning of each chapter and concludes with a general discussion reuniting all chapters.

List of papers

This thesis is based on the following papers

Published

- I Birnbaum S, Hogrel JY, Porcher R, Portero P, Clair B, Eymard B, Demeret S, Bassez G, Gargiulo M, Louet E, et al.: **The benefits and tolerance of exercise in myasthenia gravis (MGEX): study protocol for a randomised controlled trial.** *Trials* 2018, **19**:49.
- II Birnbaum S, Ghout I, Demeret S, Bolgert F, Eymard B, Sharshar T, Portero P, Hogrel JY: **Translation, cross-cultural adaptation, and validation of the french version of the 15-item Myasthenia Gravis Quality Of life scale.** *Muscle Nerve* 2017, **55**:639-645.
- V Birnbaum S, Sharshar T, Eymard B, Theaudin M, Portero P, Hogrel JY: **Marathons and myasthenia gravis: a case report.** *BMC Neurol* 2018, **18**:145.

Unpublished

Muscle and Nerve, under review

- III Birnbaum S, Sharshar T, Ropers J, Portero P, Hogrel JY: **Evaluation of neuromuscular fatigue in auto-immune myasthenia gravis using surface electromyography.**
Being finalized, to be submitted to Journal of Neuromuscular Diseases, IOS Press
- IV Birnbaum S, D Bachasson, Sharshar T, Porcher R, Hogrel JY, Portero P: **Free-living physical activity in auto-immune myasthenia gravis: a cross sectional study.**
In writing, data analysis incomplete
- VI Birnbaum S, Porcher R, Eymard B, Hogrel JY, Portero P, Gargiulo M, Louet E, Berrih-Aknin S, Le Panse R, Sharshar T and the MGEX Study Group: **The tolerance and benefits of a home-based physical exercise program in auto-immune myasthenia gravis: A randomized controlled trial.**

Co-author (Appendix 6)

Burns TM, Sadjadi R, Utsugisawa K, Gwathmey KG, Joshi A, Jones S, Bril V, Barnett C, Guptill JT, Sanders DB, et al: **An international clinimetric evaluation of the MG-QOL15, resulting in slight revision and subsequent validation of the MG-QOL15r.** *Muscle Nerve* 2016.

Table of contents

Resume.....	1
Acknowledgements.....	3
Thesis aims.....	4
List of papers.....	5
Table of contents.....	6
Abbreviations.....	7
Auto-Immune Myasthenia Gravis.....	9
I. Exercise in neuromuscular disease and myasthenia gravis.....	19
Exercise in auto-immune myasthenia gravis: protocol for a randomized controlled trial.....	29
II. Quality of Life in myasthenia gravis.....	44
Evaluating Quality of Life in myasthenia gravis: Introducing the MGQOL-15-F.....	44
III. Physical activity in myasthenia gravis.....	53
Free-living physical activity in auto-immune myasthenia gravis: a cross sectional study.....	55
IV. Fatigue in myasthenia gravis.....	80
Evaluation of neuromuscular fatigue in myasthenia gravis using surface electromyography.....	88
V. Exercise in myasthenia gravis.....	114
A home-based exercise program in stable myasthenia gravis: Preliminary results of a randomized, controlled trial.....	114
Marathons and Myasthenia Gravis.....	142
VI. General discussion.....	149
VII. Conclusions and future perspectives.....	155
Appendix.....	157
1. MG-ADL score (Score d'activité quotidienne) [18].....	157
2. Myasthenia Muscle Score (MMS) [16].....	158
3. MG-specific quality of life score (MGQOL-15-F) [19].....	159
4. Questionnaire destiné aux cliniciens.....	160
5. International revision of the MGQOL-15, MGQOL-15r.....	161
6. Scientific communications.....	168
References.....	169

Abbreviations

AChR	muscle nicotinic acetylcholine receptor
AChR+	seropositive for acetylcholine antibodies
Ach	acetylcholine
ACE	acetylcholinesterase
ACEi	acetylcholinesterase inhibitors
AT	aerobic training
BMI	body mass index
CMAP	compound muscle action potential
EPP	end plate potential
FVC	forced vital capacity
ICF	International Classification Functioning, Disability & Health
IgG	immunoglobulin G
IVIg	intravenous immunoglobulins
Lrp4	low density lipoprotein receptor-related protein 4
MET	Metabolic equivalent of task
MG	auto-immune myasthenia gravis
MG-ADL	MG Activities of Daily Living Scale
MGFA	Myasthenia Gravis Foundation of America classification
MGQOL-15-F	French version of the 15-item MG-specific quality of life scale
MMS	Myasthenia muscle score
MVPA	moderate-vigorous intensity physical activity
MVPA _{≥10 mins}	moderate-vigorous intensity physical activity lasting
MuSK	muscle-specific tyrosine kinase
MuSK +	seropositive for MuSK antibodies
NMD	neuromuscular disease
NMF	neuromuscular fatigue
NMJ	neuromuscular junction
PA	physical activity
PROM	patient-reported outcome measure

QoL	quality of life
RCT	randomized controlled trial
RNS	repetitive nerve stimulation
RT	resistance training
SB	sedentary behaviour

Auto-Immune Myasthenia Gravis

Auto-immune myasthenia gravis (MG), like other auto-immune diseases, is a complex, chronic disorder characterized by an inflammatory reaction against self-antigens. In MG, the thymus is the inflammatory organ but the target organ is the muscle [3]. Thymic abnormalities include follicular hyperplasia and thymoma. Regulatory T (T_{reg}) cells are important in preventing excessive inflammation in various organs and impairment of the suppressive function of T_{reg} cells has been reported in MG [3]. As with most auto-immune diseases, the cause of MG is multifactorial, its onset is a consequence of interactions between internal and external environmental and genetic risk factors [3].

Auto-immune MG can occur at any age, in both sexes, with a predominance in women for early onset and in men for very late onset (≥ 65 yrs) MG [4].

Altered neuromuscular transmission in MG

The cause of MG dysfunction lies in the peripheral nervous system. Auto-antibodies attack receptors on the muscle membrane at the neuromuscular junction (NMJ) [5]. The function of the NMJ is to evoke an action potential on the muscle fibre membrane in response to an impulse from its motor neuron [6]. A schematic representation of a normal NMJ modified from Gilhus, 2016 is presented in Figure 1. Neuromuscular transmission begins when an action potential arrives at the distal motor nerve triggering the opening of voltage-gated calcium channels causing an influx of calcium into the presynaptic terminal. The increased calcium concentration triggers acetylcholine (ACh) exocytosis. The ACh quanta travel across the synaptic cleft and bind to ligand-gated ACh receptors (AChRs) on the postsynaptic membrane, leading to a transient depolarization (endplate potential) along the postsynaptic membrane [7]. If large enough, this triggers the opening of voltage-gated sodium channels creating a transmembrane difference of potential, which, if the excitation threshold is exceeded, generates an action potential along the muscle fibres. The latter propagates along the transverse tubules leading to excitation-contraction coupling and ultimately muscle contraction.

Ach then detaches itself from the receptors and is hydrolysed by the enzyme acetylcholinesterase (AChE) (AChE inhibitors are a symptomatic treatment in MG, see below). In MG different mechanisms such as antibodies binding to AchRs, complement-mediated-damage of the endplate membrane causing elongation and loss of voltage-gated sodium channels and AchRs (destruction and accelerated internalization) take place. The resulting reduced surface area and reduced number of receptors causes a disruption in neuromuscular transmission. The resulting disruption of transmission is thought to cause symptoms of fatigue and weakness (see below).

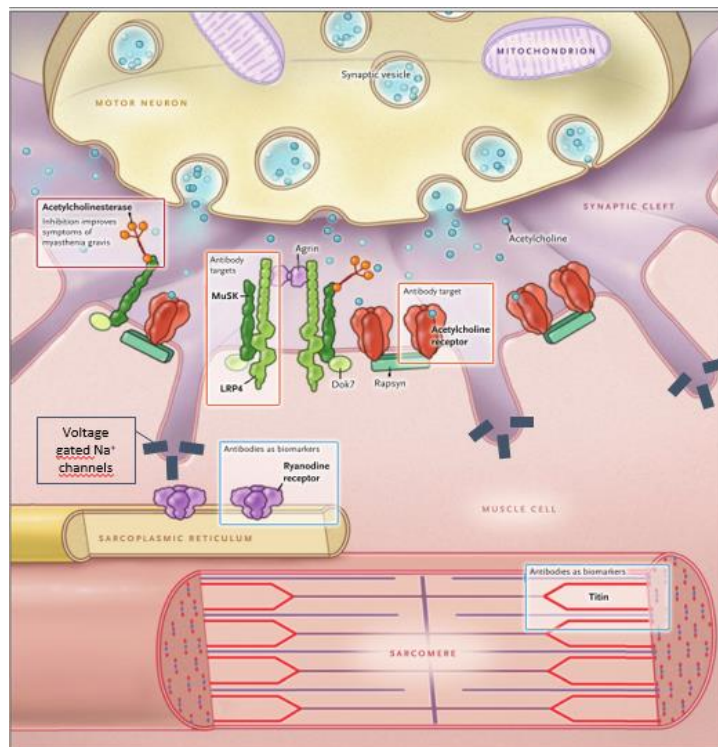


Figure 1 represents the location of AchRs and MuSK and LRP4 proteins on the postsynaptic membrane at the NMJ. Also depicted is Ach quanta being released from the presynaptic membrane and crossing the synaptic cleft. AChE is shown. The voltage-gated sodium channels are shown on the troughs of the synaptic folds. Titin and ryanodine receptor antibodies have been found to be relevant biomarkers in some subgroups of MG (modified from Gilhus, 2016 [8]).

Auto-antibodies and MG classifications

The majority (85%) of individuals with MG have immunoglobulinG1 (IgG1) antibodies directed towards the nicotinic acetylcholine receptors (AChR+), produced by T-cell dependent and B-cell mediated mechanisms which trigger inflammation by complement activation of the postsynaptic muscle membrane [9]. A smaller number have IgG4 antibodies towards muscle specific tyrosine kinase (MuSK+) and an even smaller number, have low density lipoprotein receptor-related protein (Lrp4) antibodies. Those without detectable serum antibodies are considered “seronegative”. The antibody subtype is one way of classifying MG, other classifications include age of onset; juvenile < 18 years early onset 18-50 years (EOMG) or late onset ≥ 50 years [9] and/or according to the distribution and severity of symptoms using the Myasthenia Gravis Foundation of America (MGFA) classification system. The MGFA classification differentiates between either ocular (MGFA I) or generalized MG (MGFA II-V) with predominately limb/axial (a) or bulbar (b) symptoms and MGFA V is reserved for intubation [10]. Although widely used this classification system remains somewhat subjective [10]. Clinical presentation and management can be different for the different subtypes with the additional challenge that current classifications systems are not mutually exclusive nor inclusive. MG subgroups can influence therapeutic decisions.

The majority of the work presented here (paper I, III, IV, V) includes subjects with generalized MG, i.e. they may present with visual signs or symptoms but in addition they also have manifestations elsewhere in the body (limb, axial, bulbar). They have differing antibody subtypes and varying age of onset.

Epidemiology of MG

MG is a rare disease, with an annual incidence rate varying between 1.7 and 21.3 cases per million persons and prevalence ranging from 15 to 179 per million [11]. Prevalence is increasing possibly due to both improved diagnosis and increased longevity. Exact numbers in France are currently unknown [12] however estimated prevalence is 1-9/100,000 [13].

Diagnosis of MG

Diagnosis of MG is based on clinical symptoms and specific antibody testing. When negative, repetitive nerve stimulation (RNS) or single-fibre electromyography (SFEMG) are performed [9]. For a positive result, RNS of a nerve-muscle pair at 3-5Hz should show a progressive reduction in size of the compound muscle action potentials (CMAPs) (a decrement $> 10\%$ between the 1st and 5th CMAP) as shown in Figure 2 and SFEMG reveals an elongated “jitter” (the time between the potentials of two muscle fibres of the same motor unit).

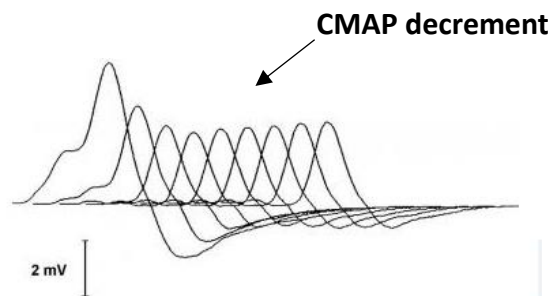


Figure 2: example of the reduction in compound muscle action potential (CMAP) amplitude i.e. “decrement” with repetitive stimulation seen in individuals with MG.

Clinical presentation of MG

As its name suggests, *myasthenia* is Greek for muscle weakness. Muscle weakness is a major sign and symptom in MG [9]. MG affects skeletal muscles to varying degrees and distribution. Commonly one of the first signs of MG is fluctuating ptosis or diplopia. In 15% of individuals with MG symptoms are confined to the ocular muscles [8]. For the majority, the MG becomes generalized and individuals experience weakness or fatigability of limb, respiratory, facial or bulbar muscles causing swallowing and speech difficulties (dysarthria, nasal voice, hypophonia). Typically, these symptoms tend to resolve or reduce with rest and then reappear with exertion or simply at different moments throughout the day. MG is a heterogeneous disease; its pathophysiology, clinical presentation, severity, evolution and response to treatment vary between individuals, although there are some common findings within each subtype. Respiratory problems coupled with bulbar dysfunction contribute to the gravity of this disease.

Clinical evaluation of MG

The World Health Organisation developed the International Classification of Functioning (ICF), Disability and Health which provides a framework and common language to categorise the different ways a disease can affect an individual and the interaction between them [14]. This model includes impairments of body function or structure (usually the signs and symptoms of a disease), activity limitations (the effects of the disease and its symptoms on activities of daily life) and participation limitations (the effects on social interactions, work). Additionally, personal and environmental factors, including social support and accessibility contribute to the level of disability (or ability) an individual can maintain despite their disease. In evaluating an individual, it is preferable to consider the different aspects of this framework and choose outcome measures accordingly where available. Figure 3 illustrates the ICF framework (modified from Barnett et al.) with several outcome measures used in MG. Mental health and well-being has been added to include QoL measures [15].

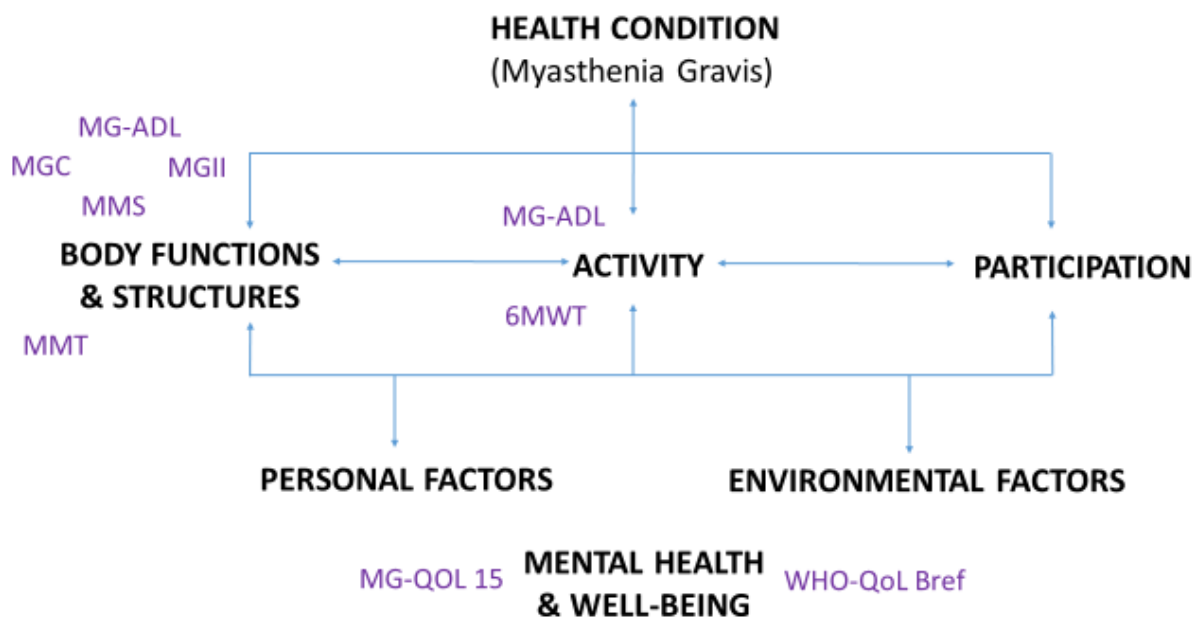


Figure 3: Schematic representation of the ICF framework showing outcome measures used in MG (modified from Barnett et al.) [15]. MG-ADL *MG Activities of Daily Living Scale*, MMS *Myasthenia Muscle Score*, MGC *MG Composite*, MMT *Manual muscle testing*, MGII *MG Impairment Index*, 6MWT *6-minute walk test*

Routine evaluation of MG usually consists of a physician evaluated MG-specific score such as the *Myasthenia Muscle Score* (MMS) commonly used in France [16] or the *Quantitative MG score* (QMG) which is commonly used in North America [17]. MMS: score range 0-100; lower scores suggest greater disease severity. These scores can be used to assess symptom severity. Due to the fluctuating nature of symptoms in MG (within the same day or from day to day), a clinical assessment which is based on a single point in time may be insufficient in capturing the extent of MG manifestations [15]. Thus, other measures which are based on longer time frames and which include the patient's perception are recommended. The *MG Activities of Daily Living Scale* (MG-ADL), an 8-item questionnaire is commonly used to understand how MG affects daily life [18]. MG-ADL: score range 0-24, higher scores suggest greater impact of MG symptoms on function. And finally, the *MG-specific quality of life scale, French version* (MGQOL-15-F) provides the self-perceived impact of MG on an individual's quality of life (QoL) [19]. MGQOL-15-F: 0-60, higher scores suggest lower self-perceived health-related QoL. The MMS, MG-ADL and MGQOL-15-F can be found in the Appendix. The *MG Composite* (MGC) scale is a mixed physician-assessed patient-report measure which measures both symptoms and signs of MG, MGC: 0-50, higher score suggests greater disease severity [20]. The MG Impairment Index is a relatively new outcome measure which combines both performance and patient-report items specifically addressing fatigability. Score range of 0-84, higher score = greater disease severity, it has been shown to be valid, reliable and sensitive to change [21, 22].

Below is a table summarizing some common outcomes measures used in MG. When choosing an outcome measure for research purposes the choice will depend on the intervention being tested and which aspect(s) of the disease the intervention may change. Also, importantly, and for clinical purposes also, the outcome measure should have robust psychometric properties (be valid, i.e. measure what it is supposed to measure and reliable i.e. reproducible) and be sensitive to change, ideally with a known minimal clinically important difference (i.e. the least change that is meaningful to a patient) or at least, the minimal detectable change (MDC) [15, 23]. Finally feasibility, in terms of time, equipment and space required and any training required for the evaluation are also factors to consider when choosing an appropriate outcome measure. The MGFA scientific board recommended the MGC as the primary outcome measure of choice for evaluating clinical improvement in MG trials because it has

the advantage over other outcome measures in that it is weighted for clinical significance and incorporates a patient-reported component. Global impression of change (patient or clinician), whilst not without bias, may be useful as a secondary outcome measure to provide an overall perspective [24].

	Performance-based	Patient-report	Mixed	MG-specific	Total items	Point-in-time measure	MDC
Myasthenia Muscle Score (MMS)	x			x	9	x	-
Manual Muscle Test (MG-MMT) [25]	x			x	30	x	-
MG Impairment Index (MGII)			x	x	28	-	8.1 group 5.5 individual
MG Composite (MGC)			x	x	10	x	3 points
MG-ADL		x		x	8	-	2 points
6-minute walk test	x			-	NA	x	-
MG-QOL-15-F		x		x	15	-	-

Mixed = both performance and patient-report; MDC = minimal detectable change; MG-MMT (0-120 higher score = greater disease severity); NA = Not applicable.

Table 1: Common outcomes measures used in MG.

Management of MG

Symptomatic treatment is aimed at reducing the breakdown of acetylcholine (ACh) by the enzyme acetylcholinesterase (AChE) with acetylcholinesterase inhibitors (ACEi) such as pyridostigmine bromide (*Mestinon*), neostigmine and ambenonium chloride (*Mytelase*) which increase the amount of acetylcholine or prolong the ACh availability at the NMJ and provide temporary relief of symptoms. ACEi are usually more efficacious for the AChR+ subtype. They have a half-life of approximately 3-4 hours or up to 6 hours for the slow release *Mestinon*.

Immunosuppressive drugs such as corticotherapy and azathioprine (*Imurel*) are initiated when symptoms persist despite symptomatic treatment. When necessary other immunosuppressive agents such as mycophenolate mofetil (*Cellcept*) or combinations are used for optimal management. Specific treatments such as plasma exchange or intravenous immunoglobulin (IVIg) are recommended in MG crisis (need for intubation) or some cases of refractory MG where other agents such as *Rituximab* (a monoclonal antibody that targets the CD20 antigen on B cells) or a more recent therapy, *eculizumab* (a monoclonal antibody that inhibits complement), can also be effective. Thymectomy is recommended in certain cases, particularly in the AChR+ subtype. Due to the heterogeneity of MG there is no one treatment that is best for all individuals with MG [26].

As an adjunct, physical activity can provide short-term and long-term benefits however no controlled studies have been published and recent guidelines do not provide information regarding participation in physical activity [9, 27, 28] (see chapter I). Twenty percent of a cohort of 250 patients reported using low impact aerobic exercise such as swimming and walking to help manage fatigue suggesting that activity may be useful in managing fatigue in MG [29].

Prognosis of MG

MG is a chronic disease. Full remission is rare in severe cases, although variation over time is common [9]. The evolution is unpredictable, and relapses are possible [5]. Known risk factors for exacerbation include infection and certain medications. Most cases of MG require long-term and even life-long drug treatment (immunosuppressors as well as symptomatic treatment). Prognosis is usually good [30]. Most patients with mild-to moderate symptoms can obtain remission or substantial improvement [9]. Figure 4 shows the reduction in mortality from MG in the last century [31].

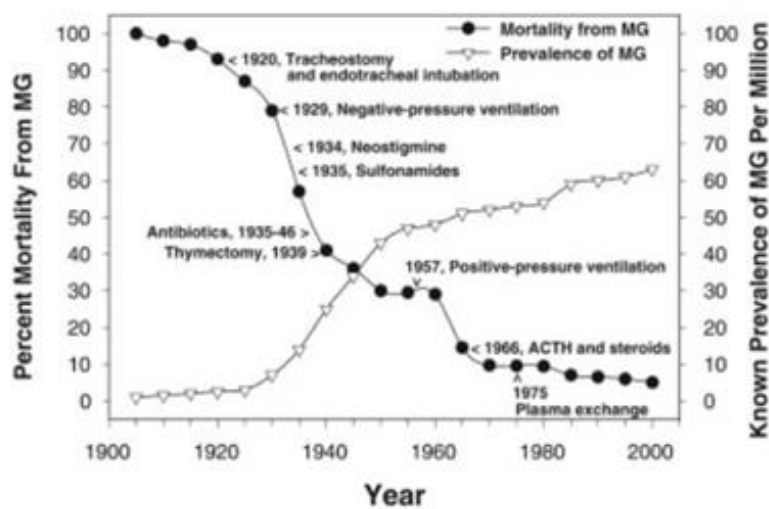


Figure 4: Mortality rates and prevalence of MG since 1900, Grob, 2008 [31].

Whilst life expectancy and quantity may no longer be reduced, quality, particularly physical aspects and daily function is often reduced [32, 33]. Reduced employment and income has been reported as well as reduced mental well-being including increased anxiety and depression [34-36].

I. Exercise in neuromuscular disease and myasthenia gravis

Neuromuscular disease (NMD) is the umbrella term given to disorders that are acquired or hereditary diseases of the anterior horn cell, peripheral nerve, NMJ and muscle [37]. A consequence of many NMDs is weakness, fatigue, disability and disuse which causes deconditioning and creates a vicious cycle of more weakness, more disuse and further deconditioning [38, 39]. MG is commonly referred to as a neuromuscular disease, however, reviews of exercise interventions in NMD seem to exclude MG [38, 40-43]. This may be due to its different underlying pathophysiology as an auto-immune disease and since in theory, MG affects the neuromuscular junction and not the muscle itself although as will be discussed in chapter IV, the muscle in MG is not just an innocent by-stander.

Exercise in MG

This thesis will not specifically treat respiratory aspects of MG, although it should be noted that several studies with varying methodology have found specific respiratory training to be effective in improving respiratory muscle endurance, strength or both in MG [44-47].

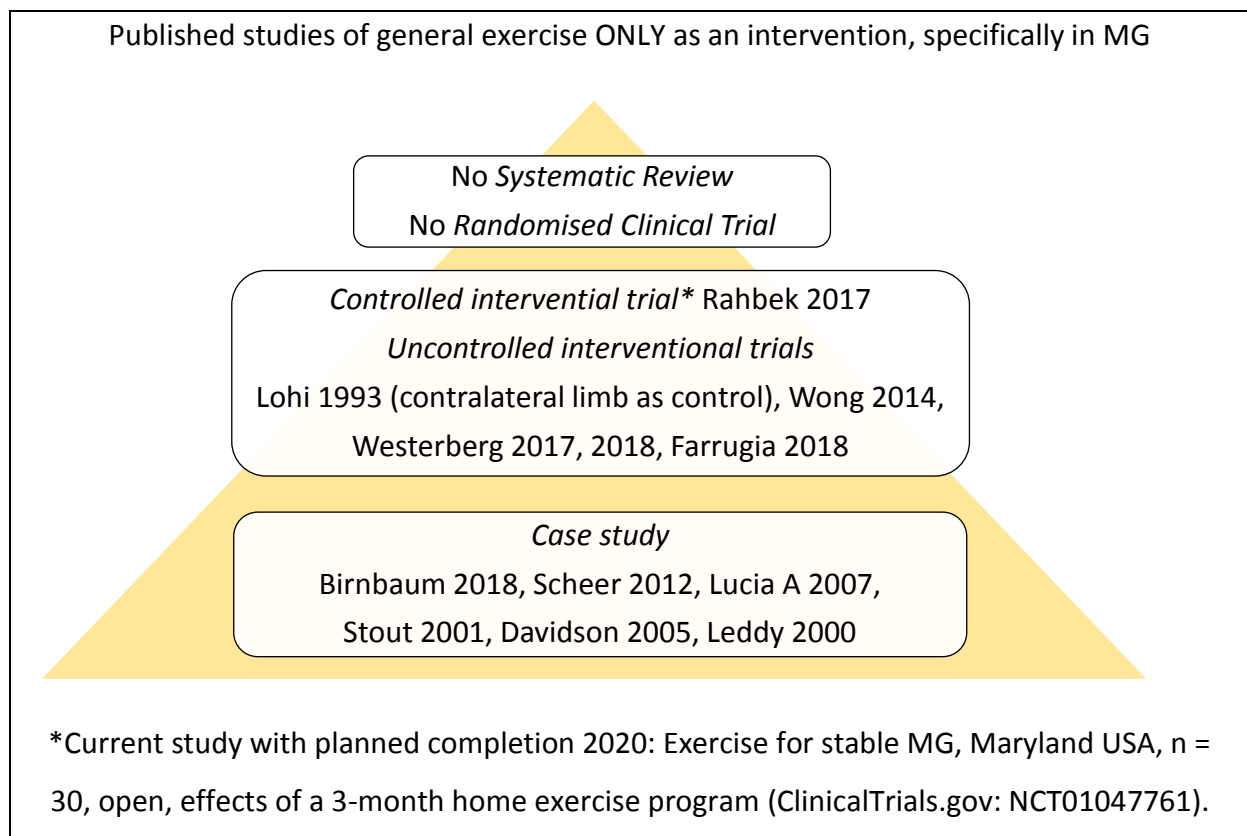
There is no one type of exercise program in the literature, exercise interventions have multiple dimensions and vary in type, intensity, duration and frequency. It is important to note that exercise interventions are complex interventions with a combination of factors including the exercise components as well as additional factors including whether the exercise is performed alone or in a group, the setting, the level of supervision or motivation (or lack of) provided, all of which can interplay and influence each other [48]. Some common terms used in the literature are described below before reviewing the current literature on exercise in MG.

Exercise is defined as physical activity that is planned, structured, repetitive and designed to improve or maintain physical fitness, performance, or health [49]. When describing an exercise intervention it is important to describe the intensity, the body part(s) involved, the duration, frequency and the aims of the exercise (to promote health, fitness and well-being or more specific strengthening, stretching, balance or functional goals). The American College of Sports Medicine categorises exercise as follows [49]:

Aerobic activity	Activity that is intense enough and performed long enough to maintain or improve an individual's cardiorespiratory fitness. Commonly includes the use of large muscle groups. Examples include walking, basketball, dancing.
Anaerobic activity	Activity that exceeds the capacity of the cardiovascular system to provide oxygen to muscle cells for the usual oxygen-consuming metabolic pathways. Anaerobic activity can be maintained for only a short period of time, about 2 to 3 minutes. Examples include sprinting and power lifting.
Muscle-strengthening activities	Physical activities that maintain or improve <u>muscular strength</u> (how much resistance can be overcome), <u>endurance</u> (how many times or for how long resistance can be overcome), or <u>power</u> (how fast the resistance can be overcome). Examples include weight machines, free weights, or elastic bands, climbing stairs, carrying/lifting objects.
Resistance training	Muscle-strengthening activity that involves the progressive use of resistance to increase one's ability to exert or resist force, can include isometric or dynamic (concentric/eccentric).
Flexibility training (stretching)	Activity that improves the range and ease of movement around a joint. Examples include static stretching, various poses of yoga, and some movements of tai chi.
Balance training	Movements that challenge postural control.
Mixed training	Can include different activity types within one program.

What does the literature on exercise in MG say?

Currently no exercise protocol exists to inform healthcare practitioners and patients with regards to exercise and MG. For some safety still remains a question, others seek answers concerning when to start once symptoms have been stabilized, which type of exercise is most beneficial, how to progress exercises and what physiological improvements can be expected [50]. Below is a schematic representation of the published research to date.



Narrative reviews

Several narrative reviews have been interested in the subject. Published in 2013 and 2014, Anziska et al. included MG in two review papers of exercise in NMD. They reported the seemingly positive and harmless effects of exercise although clearly stating that it is difficult to come to definitive conclusions due to the paucity of research and methodological limitations. Also, that exact benefits of different exercise types such as endurance and resistance remain to be determined [51, 52]. Although based on limited data,

recommendations were made for individuals with MG to exercise in cooler temperatures, avoiding prolonged endurance training and to train after adequate rest [51].

Mermier et al. focused specifically on MG in a narrative review and suggested that the mixed advice given to patients concerning exercise (some are told to refrain from exercise or strenuous activity whilst others are encouraged to be as physically active as possible) may stem from the fact that there is a broad range of severity of MG and those with a milder form can exercise at higher levels than those with severe MG [53].

The authors suggested that *“exercise can (and probably should) be prescribed to MG patients to combat muscle weakness and to maintain strength for activities of daily living”* and for the purpose of maintaining cardiovascular fitness [53]. As in the general population, lack of exercise leads to reduce muscle mass, increased body fat, exacerbating the weakness associated the disease [54]. However, a major difficulty in prescribing exercise in MG is the pre-existing fatigue. The authors reported that the overall effects of exercise in MG seem to mirror those in the general population, with improvements in strength, aerobic capacity and functional activities. They recommended that exercise programs be considered on a case to case basis with special considerations made with regards to *“over exercising”*.

The most recent review by Naumes et al. in 2016 concluded that is safe for patients with mild-moderate MG to exercise and improvements in physiological functioning such as decreasing fatigue, increasing strength and improving functional mobility are possible [50]. They suggest that MG symptoms should be controlled and stable prior to undertaking a new exercise program and they recommend professional supervision to individualise the program. For those with more severe symptoms they suggest lower intensity activities and more frequent rest breaks and they highlight the importance of modifying the program where necessary due to the variability of symptoms in MG. The authors acknowledge the lack of rigorous evidence, however they claim that the available research demonstrates that supervised exercise programs are safe for those with mild MG and that strength gains and improved functional abilities are possible with a skilled rehabilitation professional.

Experimental trials of exercise in MG

Since these reviews were written, three new studies have been published which have been integrated with the earlier studies in Table 1 and 2 below.

#	Population	Adverse events	Improvements reported	No change	Compliance
Pre/post design					
1	7 (6F) mean 53.9 yrs (24-75) stable MG MGFA IIa + III	None reported	QMG: median change -28.6% (n=6) 4 wk F/U -41.2% TUG _{cognitive} median -18.9s Sway velocity ↓ displacement COP	6MWT TUG (s)	1 drop-out 2° work commitments
2	14 (8F) mean 60±18yrs stable MG mild-moderate MG	None reported	↑ CMAP (mV) RF 4.5 to 5.3; p=.016 ↑ MVIC (HHD, kg) knee ext: 25.2 to 30.2; p=.014 ↑ U/S muscle thickness (mm) RF: 19.6 to 23.0; p=.0098 VI: 18.0 to 22.0; p=.034 30SCST median +2, p=.0039 Median MGC ↓ (3 to 2), p = 0.04	12MWT MGQOL-15 BB: CMAP nor MVIC %PEF QMG TUG Handgrip strength	3 drop-outs (2 lack of time, work-related health problem) Compliance of 11 remaining: 75%-96%, mean 88±7%
3	10 (5F) Age 32-76yrs stable MG	None reported	VAFS post intervention (not maintained at 3-month F/U) MG-QOLr (37.8±10.9 to 31.2±7.6) HADS – anxiety	MGC, MG-ADL, MFIS, FSS, depression	1 drop out after 1 st session, 4 missed 1-2 sessions
4	13 (4F), 65±14yr Stable, mild MG (MGFA I-II)	None reported	↑ CMAP (mV): BB 6.3±4 to 8.2±3 RF 6.1±2 to 7.7±3 6MWT 486±91 to 561±67 30SCST 13.6±5.6 18.6±6.2 ↑ weight (kg) resistance training Exercise Self Efficacy Scale (ESES) median 36 to 29.5 ↓ miR-150-5p & miR-21-5p	MGC, PEF, TUG, CMAP APB, EDB MVIC (HHD), Handgrip strength, Romberg, Toe-rise test CRP, CK, myoglobin, Serum IL-6	3 drop outs spontaneous vertebral fracture, spinal stenosis, prescheduled thymectomy Of 10 remaining: 2 = 71% 8 = 95%
5	11 (10F) < 50yo. Mild-mod MG	None reported	↑ knee extension MVIC	elb FLX/EXT MVIC Fatigue (repetitive voluntary, poor test-retest reproducibility)	Elb ext – 9 could not manage reps, 8 could not ↑ load, elb flx 4 had prob with reps, 3 with load

Table 1: Experimental exercise trials in MG – population, results, adverse events and compliance. # 1. Wong et al. 2014 [55] 2. Westerberg et al. 2018 [56] 3. Farrugia et al. 2018 [57] 4. Westerberg et al. 2017 [58] 5. Lohi et al. 1993 [59]

study, F female, QMG Quantitative MG score, F/U follow-up, TUG Timed up and go test, COP centre of pressure, CMAP compound muscle action potential on repetitive nerve EMG testing 3Hz, RF rectus femoris, HHD handheld dynamometer, U/S ultrasound, VI vastus intermedius, 30SCST 30 second sit-to-stand test, MGC MG composite score, PEF Peak Expiratory Flow, BB Biceps Brachii, VAFS Visual analogue fatigue scale, MFIS fatigue modified fatigue impact scale, FSS fatigue severity scale, HADS Hospital anxiety and depression scale APB abductor pollicis brevis, EDB extensor digitorum brevis, BBS Berg Balance Scale

#	Population	Adverse events	Improvements reported	No change	Compliance
Randomised Trial – stratified to gender + QMG, evaluator-blinded, 2 active treatment groups (Resistance Training vs Aerobic Training)					
6	15 (8F) 55.6±17.2yr MGFA II (n = 14), MGFA III (n=1)	1 RT - bulbar symptoms requiring prednisolone 4 weeks into intervention → stopped. (NB : QMG ↑ prior to beginning RT) AT + RT grps reported temporary ↑ fatigue + bulbar symptoms	Within-grp analyses (pre-post n = 6) RT: ↑ MVIC knee extensor & shoulder abductor, Fatigability test : decline in strength smaller in RT group (p = 0.04) ↑ STS (AT + RT) RT ↑ B & B Between-group analyses SCT(s) (greater Δ RT) Deterioration MG-QOL 15 (within grp ↑ AT grp)	<u>Both grps</u> QMG MFIS MDI Aerobic power* Knee ext isokinetic MVIC knee, elb, hip FLX, hip EXT iEMG 6MWT <u>AT</u> no Δ MVIC AT no Δ fatigability test <u>RT</u> no Δ MGQOL-15	3 drop-outs (20%) 2 drop outs AT - lack of time, work injury 1 RT 2° adverse event Adherence: AT 91.7 ± 9.8% RT 98.3 ± 4.1%

Table 1: Experimental exercise trials in MG – population, results, adverse events and compliance. # 6. Rahbek et al. 2017 [60] *incremental cycle test at a fixed self-chosen cadence until exhaustion, VO₂ peak calculated

QMG Quantitative MG score, RT Resistance Training, AT Aerobic Training, MFIS Modified Fatigue Impact Scale, MDI Major Depression Inventory, STS 30-s sit to stand test, B & B Box and Blocks Test, SCT Stair Climb Test

#	Aerobic (AT)	Resistance (RT)	Mixed	Individual /Group	Other	Frequency / duration
1			x	Group	Balance training stations individually tailored e.g heel-toe walking, ball catching/ throwing <i>PT supervised</i>	16 sessions 1 (n=2) or 2 (n=4) per week Duration NR
2	Bike ergometer: 5min warm-up, 7 2min intervals high load (80% HR max, resistance adjusted continuously), 1min low load, 5min cool-down	2 sets, 10rep max, adjusted by PT (BB, latissimus dorsi pulldown, triceps pushdown, leg curl, cable rowing, sit-ups, leg press)	x	Individ	Individually tailored, <i>supervised</i> AT & RT + 2 balance & 6 stretching exercises	Twice weekly for 12 weeks (total 24 sessions) 90min per session
3			x	Group	Low intensity exercises in sitting + standing + stretches, breathing + relaxation + psychological therapy, at own pace determined by pt, <i>supervised</i>	Weekly for 10 weeks 20-35mins per session
4	Bike ergometer: 5min warm-up, 7 intervals of 2min cycling against high load, 1min cycling against minimum load, ending with 5min cool-down	BB curl, triceps pushdown, seated leg curl, cable pull-down exercise, leg extension, cable rowing, sit-ups, and leg press, each 2 sets, 10 rep max	x	Presumably individ	Individually tailored <i>PT supervised</i> AT & RT & balance (1-leg standing 1min, variable surfaces) Increasing bike load & RT weights as subjects improved.	Twice weekly for 12 weeks 75 mins PT setting
5		Randomised right arm + left leg or v.v. Elb FLX + knee EXT in sitting, elb EXT in supine, protocol with ↑ % force + modified number reps (submaximal, dynamic)		Individ	<i>supervised</i>	10 wks, 27-30 sessions (+ allowed to perform ≤ 5 sessions alone)
6	5min low-intensity warm-up 3 sets of 10–12 min cycling on a bicycle ergometer with 3-min rest periods. Intensity progressed from 70 to 85% of maximal heart rate.	5min low-intensity warm-up Full-body program; weighted step-up, Smith bench-press, leg-press, pull-down, hip flexion, lateral raises. All progressed from 3 sets 12 reps at 15 rep max (week 1), to 3 sets of 8 reps performed at 8 rep max (week 8) Sets interspaced by 90- to 120-s rest	x	Most individual, some overlapped so could have 2 at same time	Individually <i>supervised</i> by an exercise physiologist	5 sessions per 2 weeks over 8 weeks 20 sessions

Table 2: Experimental exercise trials in MG – exercise intervention type and dosage.

1. Wong et al. 2014 [55] 2. Westerberg et al. 2018 [56] 3. Farrugia et al. 2018 [57] 4. Westerberg et al. 2017 [58] 5. Lohi et al. 1993 [59] 6. Rahbek et al. 2017 [60]

RT Resistance Training, AT Aerobic Training, PT physiotherapist, BB Biceps Brachii, rep repetition, NR non-reported, SLR straight leg raise, FLX flexion, EXT extension, pt patient

As can be seen in Table 1; of the six studies, only one report an adverse event whereby the subject had to stop the exercise intervention and required immunosuppressor therapy [60]. The authors suggest that the worsening of the MG was likely prior to the beginning of the exercise as evidence by the deteriorating QMG score prior to commencing the intervention. In the same study subjects in both AT and RT groups reported temporary worsening of bulbar symptoms and fatigue which did not affect participation in the exercise interventions. The other 5 studies did not report any adverse events from the exercise interventions and drop-outs seem to be unrelated to the intervention including other health issues or time/professional constraints [55-59].

The exercise training vary with regards to the type of exercise; resistance, aerobic or mixed (resistance and aerobic), one focused on balance training and another on low-intensity stretches/gentle exercise mixed with psychological therapy. Dosage with regards to session duration, intensity and intervention period varied from a total of 10 to 30 sessions, some lasting 20 minutes, others 75 or even 90 minutes with sessions either once, twice or 3 times per week. In all studies the exercise was supervised. The population included was female and male adults with mild-moderate, stable (a priori - not all reported) MG. Cohort size was small ranging from n = 7-15 at inclusion to n = 6-12 at study completion.

Five studies were a pre/post design whilst the study by Rahbek et al. had a randomised design without a priori power analysis performed and analyses were performed within group as well as between groups probably due to the lack of a no exercise control group for comparison [60]. Outcome measures were numerous including MG-specific clinical measures, strength, fatigue questionnaires and functional measures. Whilst many outcomes remained unchanged several studies demonstrated improvements in MG score (MGC or QMG) [55, 56], knee extension strength [56, 59], functional measures such as the 6MWT [58] or the 30s sit to stand test [56, 58]. The MGQOL-15 was evaluated in two studies with an improvement in one [57] and a deterioration in another [60]. Westerberg et al. demonstrated improvements in the *exercise self-efficacy scale*, which may be interesting to consider due to the potential behavioural component involved in incorporating physical activity in daily life [58].

Finally, for those subjects remaining in the studies, when reported, compliance ranged from 71% to 98%, with one study reporting difficulties with the number of repetitions or load [59] however with the majority not providing reasons for reduced compliance.

Exercise in MG: what do the recommendations say?

No specific published recommendations with respect to exercise in MG exist today. Recent management guidelines for MG such as the *Association of British Neurologists' management guidelines of MG*, 2015 [28] and the *International formal consensus of MG experts intended to be a guide for clinicians caring for patients with MG worldwide*, 2016 [27] do not mention exercise at all.

On the contrary, the French Protocole National de Diagnostic de Soins (PNDS) for auto-immune MG discusses physiotherapy and exercise however the underlying message seems mixed [61]. A PNDS is aimed at guiding health professionals with respect to diagnosis, optimal patient management and care pathways for rare diseases [62]. On one hand progressive return to physical activity is advised to prevent MG-induced deconditioning and the secondary effects of long term corticotherapy, particularly when the disease is stable. On the other hand re-training and resistance exercises are contra-indicated. Two extracts are presented below [61].

*« La kinésithérapie comportant des exercices de ré-entraînement et de musculation est **contre-indiquée** chez les patients myasthéniques. Par contre la reprise progressive d'une activité physique (marche, vélo) est souhaitable pour lutter contre l'effet de désentraînement dû à la maladie». (p38)*

*« **L'activité physique**, luttant contre le désentraînement et les effets d'une corticothérapie au long cours, **est très souhaitable**, d'autant que la myasthénie est stabilisée. Les séances de kinésithérapie et de physiothérapie (massages, relaxation, exercices doux, piscine) sont souvent bénéfiques en cas de douleurs rachidiennes favorisées par la faiblesse axiale et pour amorcer le réentraînement progressif à l'effort. En cas de difficultés respiratoires, des séances de kinésithérapie respiratoire, peuvent également être mises en place. » (p44)*

Beliefs of clinicians working with individuals with MG (personal unpublished data):

An anonymous survey of a convenience sample of 40 researchers and clinicians (n = 28 neurologists, 9 neuropsychiatrists, 2 neurophysiologists and 1 rehabilitation consultant) working with MG who were attending a specialised conference (*XIII^{èmes} Journées de la Société Française de Myologie, 2015*) found that 37.5% believe that MG could be aggravated by intensive physical exercise, 40% didn't believe so and 22.5% weren't sure. The large majority (87.5%) advise patients with MG to undertake physical exercise with 77% of clinicians believing it is beneficial. Of those recommending exercise, most believe both endurance AND strength training should be carried out, a smaller number believe only endurance exercise should be performed and a minority advise strength training.

This data, although anecdotal demonstrates a lack of cohesion in the beliefs and practices of clinicians with regards to exercise and MG.

The limited existing research presents methodological shortcomings to make definitive conclusions regarding the efficacy of exercise for individuals with MG. That said, studies tend to show an absence of adverse effects and rather, some positive effects on muscle strength and clinical measures. Reasons for non-compliance should be considered in order to understand whether interventions are appropriate for all subgroups of MG or whether certain participants did not completely adhere due to difficulty or discomfort. Existing recommendations are insufficient to guide clinical practice and whilst clinician's beliefs are mixed, the majority advise patients to perform exercise with a preference for aerobic as opposed to resistance training.

Exercise in auto-immune myasthenia gravis: protocol for a randomized controlled trial

Whilst randomised, controlled trials (RCT) can have methodological limitations which expose them to bias ultimately they are considered superior to uncontrolled studies in assessing the effectiveness of treatment. Different features of an RCT contribute to its internal validity and robustness. This trial protocol was designed and received a grant in 2012.

Paper I describes the protocol of the first randomised control trial of exercise in myasthenia gravis.

Birnbaum S, Hogrel JY, Porcher R, Portero P, Clair B, Eymard B, Demeret S, Bassez G, Gargiulo M, Louet E, et al.: **The benefits and tolerance of exercise in myasthenia gravis (MGEX): study protocol for a randomised controlled trial.** *Trials* 2018, **19**:49.

STUDY PROTOCOL

Open Access



The benefits and tolerance of exercise in myasthenia gravis (MGEX): study protocol for a randomised controlled trial

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Abstract

Background: Research exploring the effects of physical exercise in auto-immune myasthenia gravis (MG) is scarce. The few existing studies present methodological shortcomings limiting the conclusions and generalisability of results. It is hypothesised that exercise could have positive physical, psychological as well as immunomodulatory effects and may be a beneficial addition to current pharmacological management of this chronic disease. The aim of this study is to evaluate the benefits on perceived quality of life (QOL) and physical fitness of a home-based physical exercise program compared to usual care, for patients with stabilised, generalised auto-immune MG.

Methods: MGEX is a multi-centre, interventional, randomised, single-blind, two-arm parallel group, controlled trial. Forty-two patients will be recruited, aged 18–70 years. Following a three-month observation period, patients will be randomised into a control or experimental group. The experimental group will undertake a 40-min home-based physical exercise program using a rowing machine, three times a week for three months, as an add-on to usual care. The control group will receive usual care with no additional treatment. All patients will be followed up for a further three months. The primary outcome is the mean change in *MGQOL-15-F* score between three and six months (i.e. pre-intervention and immediately post-intervention periods). The *MGQOL-15-F* is an MG-specific patient-reported QOL questionnaire. Secondary outcomes include the evaluation of deficits and functional limitations via MG-specific clinical scores (Myasthenia Muscle Score and MG-Activities of Daily Living scale), muscle force and fatigue, respiratory function, free-living physical activity as well as evaluations of anxiety, depression, self-esteem and overall QOL with the WHO-QOL BREF questionnaire. Exercise workload will be assessed as well as multiple safety measures (ECG, biological markers, medication type and dosage and any disease exacerbation or crisis).

Discussion: This is the largest randomised controlled trial to date evaluating the benefits and tolerance of physical exercise in this patient population. The comprehensive evaluations using standardised outcome measures should provide much awaited information for both patients and the scientific community. This study is ongoing.

Trial registration: ClinicalTrials.gov, NCT02066519. Registered on 13 January 2014.

Keywords: Myasthenia gravis, Physical exercise, Quality of life

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Background

Auto-immune myasthenia gravis (MG) is a rare, chronic, auto-immune disease of the neuromuscular junction. The incidence is estimated to be 30 per 1,000,000 people per year worldwide [1]. MG affects both genders and symptoms include fluctuating fatigue and weakness which vary in intensity and location (upper and/or lower limbs, axial, eyes and face, bulbar and respiratory muscles) [2]. These symptoms affect patients to varying degrees and while disease-induced mortality is rare nowadays, activities of daily function are affected and quality of life (QOL) is reduced [3–6]. Relapses are unpredictable and can be present throughout the disease course, especially in the initial stages when the disease may not yet be treated. Current treatment includes various pharmacological agents which are either symptomatic such as acetylcholinesterase inhibitors which act to temporarily relieve symptoms or disease-modifying immunosuppressors aimed at minimising the auto-immune response. As there is currently no known cure, the goal of treatment is to obtain remission; and where this is not possible, to obtain disease stability with the least symptoms.

While rest is recommended during an acute exacerbation of MG, evidence is lacking as to whether exercise is both feasible and beneficial in periods of disease stability. Anecdotal evidence from patients with MG suggests that those who participate in regular physical exercise feel better. According to them, it gives them confidence in their capacities and helps them understand their disease and their personal limits. Some even report experiencing symptom improvement and reduced levels of fatigue [7].

For the general population, it is widely accepted that regular physical exercise has multiple positive physical and psychological effects as well as being effective in the prevention of various non-communicable diseases such as stroke, heart disease and cancer and increasing longevity [8–10]. Recently, the use of exercise has been proposed in the management of various neurological diseases [11–13]. Exercise has even been compared to pharmacological treatment and has been found to be equivalent in some populations, supporting the recent notion that ‘exercise is medicine’ [14]. Traditionally, exercise was thought to exacerbate symptoms for patients suffering from MG as their muscle weakness and fatigue was thought to be brought on or worsened by physical exertion and improved with rest. Despite the increasing number of studies exploring exercise in various neuromuscular pathologies, to date, little research has explored physical activity in the context of MG [15, 16]. Several case studies exist which demonstrate that despite the disease patients can participate in sport and increase their strength, power or endurance with adequate training [17–20]. A within-subject

control study provided promising results, yet these limited data do not enable us to draw reliable conclusions concerning the safety and benefits of physical exercise for patients with MG [21]. Two new studies provide further information including different types of physical exercise [22, 23]. In the study by Rahbek et al., progressive resistance training appears to be beneficial however aerobic training seems to increase depression and fatigue and reduce knee extensor strength [22]. The mixed aerobic resistance program study carried out by Westerberg improved functional physical performance and exercise self-efficacy without strength improvements noted [23]. Exercise was well tolerated in both studies; however, due to small sample sizes and lack of control group, it is difficult to make firm conclusions about the various possible benefits. It is hypothesised that physical exercise is beneficial for adults with stabilised MG.

The primary aim of this study is to determine whether a regular moderate intensity physical exercise program improves perceived QOL for patients with stable, generalised MG. Secondary aims are to evaluate the effects of this exercise program compared to usual care on physical fitness, depression and self-esteem as well as on the immune system.

Methods/Design

Study design, ethics, consent and permission

This is a multi-centre, interventional, randomised, single-blind, parallel group, controlled trial with a planned duration of four years (nine months for each patient) (Figs. 1 and 2).

Safety evaluations are monthly; muscular and psychological evaluations are three-monthly (M0, M3, M6 and M9). The intervention period is between M3 and M6. The study has been approved by an ethics committee in accordance with French regulations (*Comité de Protection des Personnes Ile de France XI* under the CPP number #13064 on 13 December 2013 and authorised by the *Agence Nationale de Sécurité du Médicament et des produits de santé* on 11 October 2013). The trial is conducted in accordance with the Helsinki Declaration [24]. Each participating patient receives written and verbal explanations about the study and evaluation procedures. The trial is registered in the ClinicalTrials.gov registry (NCT02066519). Reporting of the study will adhere to the Consolidated Standards of Reporting Trials (CONSORT) guidelines and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [25–27]. The SPIRIT checklist is available as an Additional file 1.

Participating centres include the neuromuscular and neurological intensive care departments, Pitié-Salpêtrière

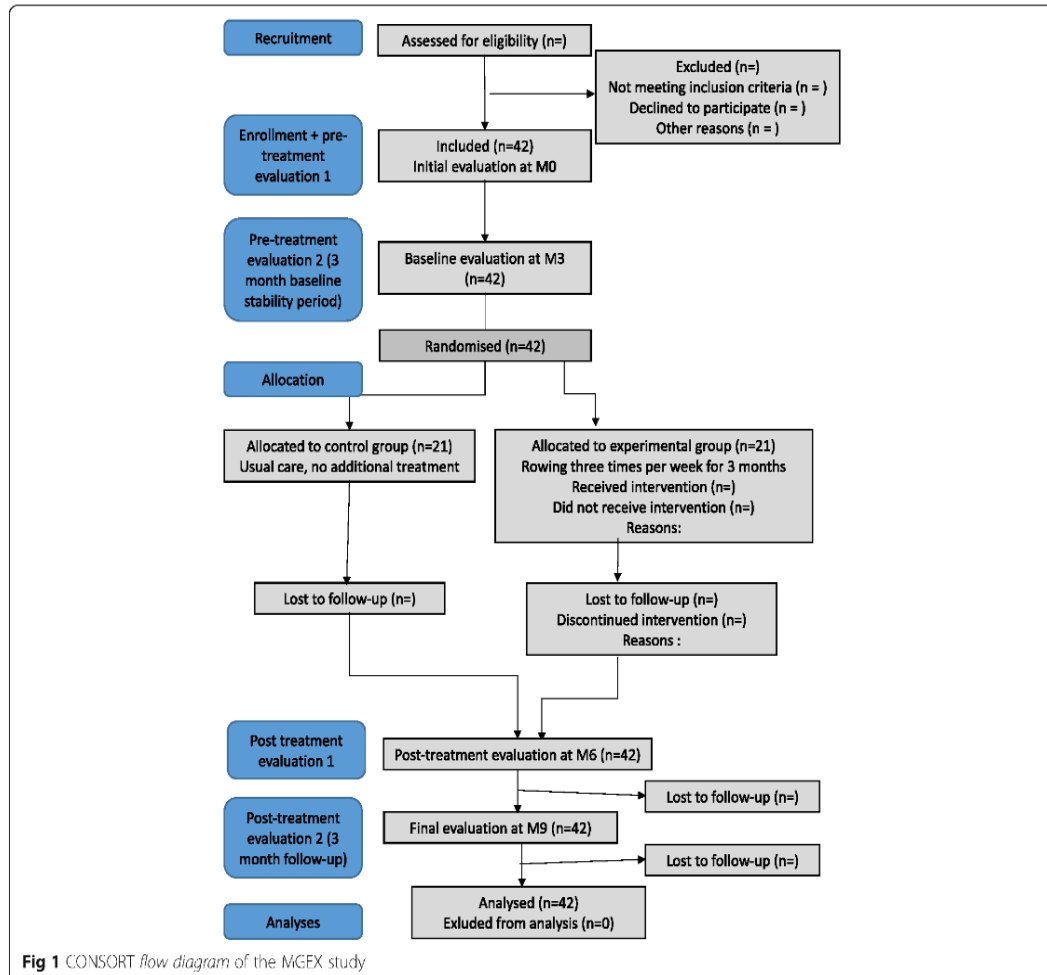


Fig 1 CONSORT flow diagram of the MGEX study

Hospital, Paris, the Raymond Poincaré Hospital, Garches (Paris region) and Rothschild Hospital, Paris.

Sample size calculation

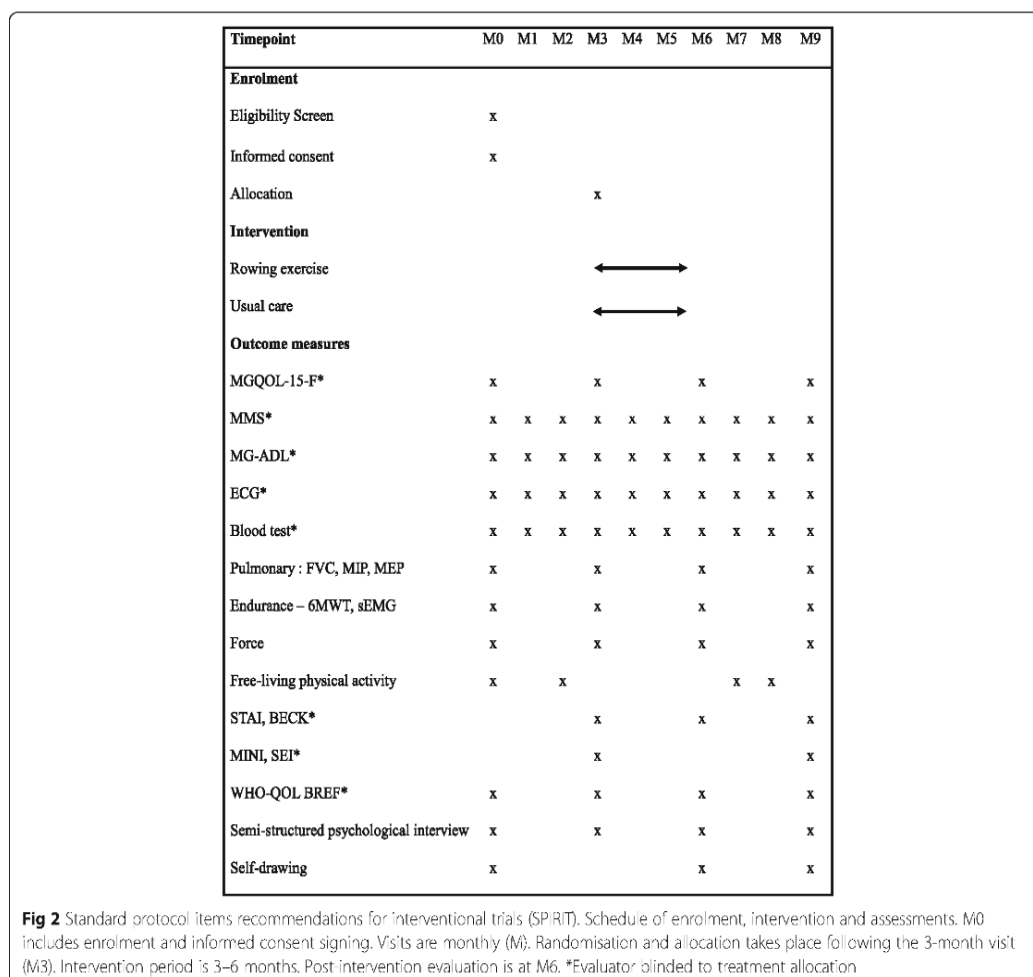
We estimated that 42 patients (21 in each arm with 1:1 randomisation) would be necessary to show a difference in changes in the *MGQOL-15-F* of 8 points between both arms with 80% power and a two-sided type I error rate of 5%, assuming the standard deviation of changes in the *MGQOL-15-F* is 9 points based on Burns et al. [28]. A difference in 8 points is considered to be a clinically meaningful change for this population. No increase in sample size for potential drop-outs was considered in the calculation.

Recruitment and trial participants

All patients presenting for a regular out-patient consultation with their neurologist in one of two university

hospitals in Île-de-France, France (Pitié-Salpêtrière, Paris and Raymond Poincaré, Garches), are screened for eligibility. Both hospitals are specialist centres for the management of MG. Eligible patients are invited to participate and a date is organised for study inclusion. Information about the study is also advertised by the French Association against Neuromuscular Disorders (AFM) myasthenia group and various social media patient groups. Information flyers are displayed in the two university hospital waiting rooms.

Adult patients with a diagnosis of mild or moderate generalised MG (II or III on the Myasthenia Gravis Foundation of America [MGFA] classification) are considered for eligibility [29]. Diagnosis should be confirmed by the presence of circulating antibodies against acetylcholine (AChR) or muscle-specific kinase (MuSK) or low density lipoprotein receptor-related protein 4 (LRP4) receptors or abnormal repetitive nerve



stimulation testing (decrement > 10%) on EMG or abnormal single fibre EMG (conduction block or jitter) or based on their clinical history and symptom improvement with acetylcholinesterase inhibitors. The MG must be stabilised for at least six months before entry into the study; thus, duration of the disease must be at least six months but is otherwise unrestricted. Both men and women aged 18–70 years are eligible for inclusion. For practical reasons (due to multiple visits and rowing machine delivery), participants should live in Paris or in the surrounding Paris region; they agree to be able to participate in the exercise program and can house the rowing machine for the three-month duration in their home. They should be affiliated with the national social security system.

Exclusion/non-inclusion criteria:

Patients participating in other interventional clinical trials in the preceding three months, patients for whom intensive physical exercise would be contraindicated

because of unstable coronary syndrome or myocardial infarction within the preceding three months, respiratory failure (vital capacity < 70% predicted value) or cardiac failure (ejection fraction < 50% predicted value), other neuromuscular pathology, disabling rheumatological disease (> 80% disability on the Barthel scale), chronic pain or disabling orthopaedic conditions, hospitalisation in the last three months for a serious medical or surgical condition, anaemia (haematocrit < 30%), stroke within the previous year. Pregnancy or patients with pure ocular or severe MG (MGFA class I, IV or V) or with severe cognitive impairment necessitating specific protection are not eligible for inclusion, nor are patients with a score < 15 on the *MGQOL-15-F*.

Randomisation, allocation and blinding

Figure 1 depicts the participants’ flow through the study according to the CONSORT guidelines [25, 26]. Figure 2

presents the timeline of assessments and intervention. Following study inclusion, there is a three-month observation period to ensure disease stability (in addition to the six-month stability required before inclusion). All consecutive participants are then randomly assigned to either the control or experimental group with a 1:1 allocation ratio as per a computer-generated randomisation schema stratified by centre using permuted blocks of randomly varying sizes. To ensure concealment, the block sizes are not disclosed. Group allocation is revealed via a computer software (CleanWeb) exclusively to the non-blinded physiotherapist once randomisation has been performed (concealed allocation). The physiotherapist then informs the patient verbally. The randomisation list was constructed prior to the beginning of the study by an off-site independent statistician with no clinical involvement in the study.

Clinical and psychological evaluations are performed by blinded assessors. As randomisation takes place three months after inclusion, the physiotherapist is unaware of group allocation for the first two evaluations (M0 and M3). Patients are informed not to disclose their allocation to their treating neurologist or psychologist. Throughout the study all participants are requested to maintain their regular lifestyle, the only difference being the three-month exercise period for the experimental group which is lacking for the control group.

Intervention

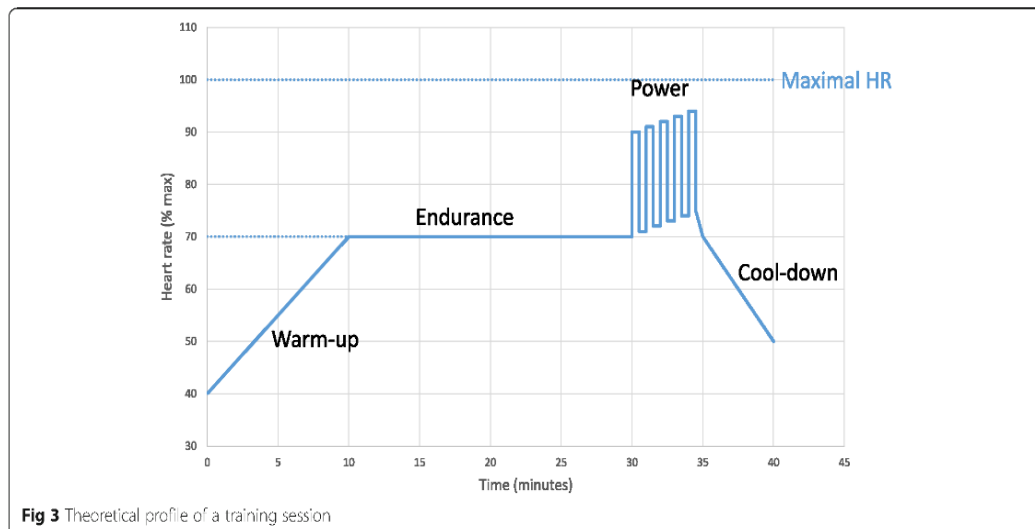
Patients randomised to the experimental group (EX) participate in two to three supervised exercise sessions to learn how to use the rowing machine (Concept2™) and follow the individualised exercise program. The Concept 2 rowing machine is a stationary ergometer

where the patient is seated and simultaneously exercises both upper and lower limbs and the trunk thus targeting the multiple muscles which can be affected in MG. The rowing exercise is impact-free so unlikely to cause pain or injury and the basic stroke is easy to learn even for those untrained and unexperienced with the technique. The machine is then delivered to their home where they continue the sessions three times a week for three months (total of 36 planned sessions). Figure 3 shows the theoretical training session profile.

Each 40-min moderate intensity training session consists of a 10-min warm-up to reach their individual target heart rate (i.e. 70% of their maximal heart rate [HR], using 220-age as HRmax), followed by an endurance plateau phase consisting of 20 min of constant aerobic activity rowing at their individual target heart rate, followed by a power interval phase (ten pulls at maximum effort every minute for 5 min) and finally a 5-min active cool-down period whereby the rowing exercise is continued at a slow pace. A heart rate monitor (Garmin®) is worn by the patient and data (rowing distance, session duration, HR) are recorded by the rowing machine for each training session. These will be analysed to evaluate tolerance and possible cardiovascular adaptations from exercising. Patients are advised to organise their training sessions on alternate days. The first home session is supervised when possible. Details will be presented as per current recommendations for reporting of exercise interventions [30]. Patients continue to benefit from usual care.

Control group

The control group does not participate in any organised physical exercise program. The control group



has no added intervention other than usual care and the scheduled monthly appointments as per the study protocol.

Compliance to the physical exercise program

Compliance is calculated as the number of completed sessions compared with the number of intended sessions. Session duration and rowing distance are recorded for each session onto a card via the rowing machine monitor. In addition, patients are requested to fill in a training log-book to record medication and any minor adverse effects related to training sessions (such as fatigue or any MG symptoms). Patients are informed to contact their general practitioner if there is any worsening of symptoms and to inform the physiotherapist of the study. Compliance is facilitated by weekly phone calls to check on progress and provide encouragement. Reasons for non-compliance are noted. The rowing machine is collected at the end of the intervention period (i.e. M6). Factors preventing or limiting completion of the exercise program are noted such as absence, unrelated illness, etc.

Criteria for discontinuing

Patients are advised to stop training if there is a clear exacerbation of their MG or if there is any other medical reason or new event for which the exercise program is contraindicated.

Outcome measures

Safety factors are evaluated monthly and muscular and psychological status is evaluated at baseline and at three, six and nine months (Fig. 2).

Training effect

Primary outcome measure

The various potential benefits of exercise training can be appreciated by a change in one's QOL which incorporates multiple dimensions of a person. A disease-specific QOL measure evaluates the perceived impact of the disease on one's QOL. The *MGQOL-15-F* is an MG-specific self-administered QOL scale. It evaluates the perceived impact of MG on one's QOL over the preceding weeks.

The *MGQOL-15-F* was translated from English and the French version has recently been validated in a large cohort of patients [31]. The questionnaire consists of 15 items scored on a 5-point Likert scale (from 0 to 4). Scores are in the range of 0–60 with a higher score indicating a lower QOL. It is both reliable and valid and considered to be an excellent measure of perceived QOL in MG [28]. The primary outcome is the mean change in total *MGQOL-15-F* score at 3–6 months, i.e. before and after the intervention period. The

questionnaire is given to and collected from participants by blinded assessors.

Secondary outcome measures

Clinical, biological and pharmacological assessment

MG medical history, including thymectomy, medications, duration of the disease, disease course (exacerbations and crisis) and symptoms, is noted at baseline. The severity and type of MG is classified according to the MGFA classification and the MGFA post-intervention status is used to describe current status of symptoms and treatment [29].

A monthly assessment performed by a blinded neurologist involves a general check-up including vital signs (blood pressure, HR) and cardiopulmonary auscultation, biological markers from venous blood samples and an electrocardiogram. A thorough subjective patient history is carried out including MG behaviour over the preceding month and any other symptoms such as muscle or joint or chest pain or other illness. The frequency and severity of exacerbations are noted, as part of the regular clinical assessment and reported as per the safety criteria of the study. Medication type and dosage is noted and changes are made as per the clinical judgement of the treating neurologist. All neurologists are specialised in managing MG.

Disease severity is evaluated with the Myasthenic Muscle Score (MMS), a performance-based measure of myasthenic symptoms [32, 33]. The score consists of nine items including strength and endurance of limbs, face, eyes and bulbar symptoms. The total maximum attainable score is 100 and a lower score indicates greater disease severity. The mean change in MMS score between three and six months will be evaluated. The impact of symptoms on daily activities is evaluated with the MG-ADL scale [34]. The MG-ADL is a patient-reported scale comprising eight items rated on a 4-point Likert scale evaluating the functional limitations due to myasthenic symptoms over the preceding eight days. The mean change in MG-ADL score between three and six months will be evaluated. Change in cumulated corticosteroid and anticholinesterase inhibitor dosage between three and six months is recorded as a secondary outcome measure.

Strength and endurance measures

All strength and endurance measures take place in the same neuromuscular evaluation laboratory (Neuromuscular Physiology and Evaluation Lab, Institute of Myology, Pitié-Salpêtrière Hospital, Paris) by the same trained physiotherapist.

Pulmonary function and respiratory strength

For all respiratory evaluations, patients are seated with a backrest and feet firmly on the floor. Forced vital capacity (FVC) is measured with a Micro Medical Spiro

USB spirometer and Spida 5 software or a Vitalograph spirometer (the same spirometer is used for all evaluations for each patient). Calibration is performed according to manufacturer's guidelines with a 3-L syringe before each evaluation. FVC in litres is measured from total lung capacity according to the ATS/ERS task force guidelines [35]. Patients are instructed to inhale completely and then exhale maximally until no more air can be expelled. For respiratory muscle strength evaluations, the MicroRPM device (Micromedical, Rochester, UK) is used. Maximal inspiratory pressure (MIP) is measured first, followed by maximal expiratory pressure (MEP). Both are expressed in cmH_2O . MIP is measured from residual lung volume and MEP from total lung capacity [36]. All measurements are repeated three times or until maximum values are reached if the patient continues to improve and remains clinically stable (no signs of fatigue). For MEP measures, patients are asked to place their hand around the mouthpiece to minimise air leaks. A tubed mouthpiece is used for both. Strong verbal encouragement is provided for all measures. A nose clip is used for FVC. The highest value from the three trials is used in data analysis. Secondary outcome measurements involve the mean change in FVC, MIP and MEP between M3 and M6.

Upper and lower limb strength and fatigue

Voluntary strength testing is performed using a Biodex System 3 Pro dynamometer (Biodex Medical Systems, Shirley, NY, USA). For the upper limb, elbow flexion force is evaluated. The patient is seated in the adjustable Biodex chair with the shoulder in 90° flexion and 15° horizontal abduction. The upper arm is placed on a support, the elbow flexed to 90° and the forearm in full supination, with the strap placed at the wrist, leaving the hand free. The axis of the dynamometer is aligned with the joint axis of rotation of the elbow. Bilateral shoulder straps and a waist strap are used to stabilise the thorax and pelvis to avoid compensations. For the lower limb knee extension force is evaluated with the patient seated in the Biodex chair with the hips and knees flexed to 90° . The thorax, pelvis and right thigh are secured with straps. The axis of the dynamometer is aligned with the axis of rotation of the knee. Both positions are designed to avoid the influence of gravity on the muscle contraction.

Before each test, there is one test trial at submaximal force to ensure that the patient understands the instructions. Testing involves three isometric contractions at maximal voluntary isometric force (MVIC) followed by a 1-min rest between each MVIC trial. Maximal torque is presented in Nm. The highest value from the three trials of each muscle group is used in data analysis. Following the third MVIC there is a 5-min rest period where the patient remains in the same position. Fatigue testing comprises a sustained 40-s isometric contraction at 50%

of their best individual MVIC from the same day. A last MVIC is performed immediately after completing the fatigue exercise. Visual cues are provided to the patient via a computer screen to enable them to maintain the target level of force for the duration of the fatigue test. Strong verbal encouragement is provided by the evaluator for both force and fatigue testing. The details of the dynamometer position (chair position, height, depth, etc.) for each patient are noted for repeatability in successive testing. Measurements are performed on the right side only. Secondary outcome measure is the mean change in UL and LL strength between M3 and M6.

Electrophysiological measurements

Surface EMG (sEMG) is a non-invasive method of evaluating the electrical signals of muscles to gain insight into the physiological characteristics of a muscle contraction. It has been used to investigate peripheral muscle fatigue in various conditions [37, 38] Myoelectrical manifestations of fatigue can be studied during sustained submaximal contractions through changes in amplitude and frequency content of the sEMG signal. In this study, four aligned miniature, circular silver-silver chloride (Ag/AgCl) surface electrodes of 4 mm in diameter, 11 mm inter-electrode distance are used. Three signals are derived from this bipolar configuration. The electrodes are connected to an amplifier (bandwidth = 10–1000 Hz). Where necessary, hair is gently removed with a shaver and the skin is abraded slightly and cleaned with an alcohol solution to reduce inter-electrode resistance. To improve conduction electrolytic gel is placed on the electrodes which are then placed on the biceps brachii (BB) for elbow flexion and on the vastus lateralis (VL) for knee extension, parallel to the estimated direction of muscles fibres according to the Surface EMG for Non-Invasive Assessment of Muscles (SENIAM) recommendations [39]. A neutral reference electrode is placed on the ulnar styloid for the BB and the fibular head or patella for the VL.

Surface EMG recordings are performed for both force and fatigue tests at a sampling rate of 10 kHz and stored on the computer for further analysis. Surface EMG recordings will be processed using standard methods using the root mean square (RMS) as an estimate of the signal amplitude, notably indicating the level of motor unit recruitment during the contraction and the mean power frequency (MPF) as an estimate of the mean value of the power spectral distribution of the signal used to evaluate localised muscle fatigue. The onset of fatigue is identified by a decrease in the MPF. Where possible, muscle fibre conduction velocity will also be computed.

Grip strength

Handgrip strength of the dominant hand is measured via an isometric contraction using the Myogrip dynamometer

(Ateliers Laumonier, France), an electronic device specifically designed to measure grip strength in neuromuscular disorders [40]. Its handle can be adjusted to accommodate different hand sizes and the strength is displayed directly on the screen. Patients are seated on the edge of a plinth, their back in an upright position, hips and knees flexed to 90° and feet flat on the floor. The dominant arm hangs down the side of the body with the shoulder in neutral and the elbow extended. The patient is instructed to squeeze the handle as hard as possible; verbal encouragement is provided to motivate the patient to perform a maximal effort. The test is performed three times or until no further improvement. Maximal grip strength is recorded in kg. Mean change in grip strength between M3 and M6 is a secondary outcome.

Walking endurance

Walking endurance is measured via the 6-min walk test (6MWT), a simple, well tolerated and reliable quantitative measure of functional exercise capacity [41]. Patients are instructed to walk the longest distance possible in 6 min in a 25 m long, level surface indoor corridor. At each end of the 25 m they turn around a cone placed on the floor. There is a starting line marked on the floor on the right of the first cone. Instructions provided before the test and verbal guidance throughout the test are standardised according to the American Thoracic Society guidelines/recommendations [42]. The total distance (m) is recorded (6MWD) as well as the time every 25 m. The patient is advised to wear comfortable walking shoes for the test. An accelerometer (Locometrix) is worn around the lumbar spine during the test for possible more in-depth gait analyses. Mean change in 6MWD between M3 and M6 will be evaluated as a secondary outcome.

As anticholinesterase inhibitors can temporarily influence muscle strength and fatigue the timing of medication is recorded as well as the timing of each evaluation. Where possible the same timing is respected for consecutive evaluations.

Free-living physical activity

Free-living physical activity and sedentary behaviour are quantitatively measured at four time points during the trial. Patients wear a tri-axial seismic accelerometer (DynaPort Movemonitor, McRoberts) on their lumbar spine using the supplied elastic belt. The accelerometer weighs 55 g and measures 106.6 × 58 × 11.5 mm. It stores raw data on a microSD card and contains a USB connection to upload data to the software for preparation and analysis. The accelerometer measures acceleration in three axes at a sample rate of 100 samples per second. Algorithms developed by the manufacturer quantify physical activity and inactivity by measuring body posture and

movement intensity from acceleration signals [43]. Body postures include lying/sitting/locomotion/standing and shuffling where shuffling is defined as <3 consecutive steps or where the intensity or direction of motion doesn't comply with locomotion. Measurements begin at a pre-set time. Patients are instructed to wear the device during waking hours for seven consecutive days, except when bathing/showering or swimming. Multiple days are monitored to account for day-to-day variation.

Free-living physical activity is further evaluated via the completion of a Bouchard questionnaire at the beginning of the study [44]. The questionnaire enables an estimation of the daily energy expenditure over a three-day period by asking patients to record their physical activity over a 72-h period (two weekdays and one weekend day). The day is divided into 96 periods of 15 min and activities are quantified on a scale of 1–9 depending on their intensity. The questionnaire has the added benefit of providing a qualitative perspective on the activities performed which is lacking in the accelerometer data. Yet the accelerometer data, when worn correctly, lacks the problems of recall bias. Thus, the two can be considered complementary.

QOL and psychological state

At three, six and nine months anxiety is evaluated via the State Trait Anxiety Inventory (STAI) and depression is evaluated via the modified Beck Depression Inventory (BDI-13). Psychiatric disorders are evaluated by the Mini-International Neuropsychiatric Interview (MINI, French Version 5.0.0) and self-esteem via the Self-Esteem Inventory scale (SEI) at both three and nine months. Global QOL is measured via the World Health Organisation QOL-BREF scale and specific QOL via the MGQOL-15-F at zero, three, six and nine months. Semi-structured interviews are conducted at zero, three, six and nine months. We ask patients to draw themselves at zero, six and nine months. Evaluations are carried out during a face-to-face meeting with a clinical psychologist which lasts approximately 90 min. The mean change in the total score for each questionnaire will be compared between groups at M3 and M6 as secondary outcomes.

The STAI evaluates anxiety via a self-administered questionnaire consisting of two 20-item sub-scales: the STAI A evaluates the actual level of anxiety at the moment of the assessment (state anxiety); and the STAI B investigates more general and long-standing anxiety (trait anxiety) [45]. Scores are in the range of 20–80 for each questionnaire with higher scores indicating greater anxiety. The French version was validated by Bruchon-Schweitzer and Paulhan [46].

The SEI evaluates the judgment that an individual holds about themselves regardless of the circumstances. The self-administered questionnaire, adapted into French (ECPA, 1984), consists of 58 items with sentences describing

feelings, opinions or individual reactions with either a 'like me' or 'unlike me' response [47]. It investigates self-esteem in four domains: personal (26 items); social (eight items); family (eight items); professional (eight items); and contains a lie scale (eight items). A higher score indicates greater self-esteem.

Depression is evaluated via the self-administered BDI-13 (short version), consisting of 13 items validated in French by Collet and Cottraux [48]. Each item has four response choices (0–3) and provides a global score (0–39) corresponding to depression severity (0–4 = no depression, 4–7 = mild, 8–15 = moderate, ≥ 16 = severe depression).

The MINI is a short, structured, clinical interview organised in diagnostic modules [49]. It enables researchers to investigate 16 axis I DSM-IV disorders according to the DSM-IV or the CIM-10. For most modules, two to four screening questions are used to rule out the diagnosis when answered negatively. Positive responses to screening questions are explored by further investigation of other diagnostic criteria. The MINI is also used to confirm the diagnosis of depression if the Beck score is ≥ 4 .

Global QOL is evaluated by the WHOQOL-BREF [50]. The French translation was validated by Leplège et al. in patients with various neuromuscular diseases [51]. This self-administered questionnaire consists of 26 items (score of 0–5) and assesses QOL according to four domains: physical health; psychological health; social relationships; and environment. Myasthenia-specific QOL is evaluated by the French version of the Myasthenia Gravis QOL scale, the MGQOL-15-F as previously described (primary outcome measure) [31].

Semi-structured interviews are conducted by trained clinical psychologists to qualitatively assess the psychological impact of MG on patients' personal, marital, social, professional life and physical activities. The interviews are recorded to be qualitatively analysed with the NVivo software 7 as it allows a thematic analysis [52]. Finally, patients are asked to draw themselves. The instructions are: 'Can you draw yourself as you feel today?' This drawing is analysed as a projective test and considered as an index of the representation of the body and of its investment [53].

Other exploratory measures

Inflammatory and immunological markers

The level of pro- and anti-inflammatory cytokines is measured at three, six and nine months. A total of 50 mL of venous blood is collected and the serum and mononucleated cells are isolated. Blood samples of the same patients are operated simultaneously to avoid inter-experimental variability. The sera are conserved in a freezer at -80°C and the cytokines are analysed by ELISA or Bioplex technology. The cytokines to be studied in the sera include the

interleukin (IL)-6, IL-17, IL-21, interferon gamma and tumour necrosis factor alpha (pro-inflammatory cytokines) as well as IL-10 and IL-1RA (anti-inflammatory cytokines) [54]. The mononucleated cells are isolated using a Ficoll gradient. The cells are frozen in a freezing medium containing 10% dimethyl sulfoxide. The phenotype of the monocytes and lymphocytes will be investigated by flow cytometry using a combination of eight markers. The expression of cluster of differentiation (CD)14 coupled with CD16 and Toll-like receptor 4 of the monocytes will be analysed [54]. We will also determine the proportion of regulatory B cells (Breg) and regulatory T cells (Treg) in the lymphocytes. The percentage of Treg cells will be determined using the combined expression of CD4, CD25, CD127 and FoxP3 (a marker associated with the regulatory function) on permeabilised cells (as the FoxP3 marker is intracellular). The percentage of Breg cells will be determined by the combination of CD19, CD38, CD27 and CD24. The expression of chemokine receptors such as CXCR3 (pro-inflammatory) and CXCR5 (follicular helper cells) will also be determined. The flow cytometry experiments will be performed on a FACS-Canto (Becton-Dickinson) apparatus.

Levels of circulating specific MG antibodies (AChR or MuSK) are measured at inclusion, three, six and nine months.

Adverse event reporting

An adverse event (AE) is defined as any untoward medical occurrence in a participant which does not necessarily have a causal relationship with this study. These can be identified at any moment during the study. Eligibility criteria rule out patients with known contraindications to physical exercise. An ECG is performed monthly to monitor cardiac status. It is expected that patients in the experimental group may experience muscle soreness and fatigue in response to exercise, particularly for the more sedentary patients. However, this is not an AE as it is considered a normal response to exercise.

A serious adverse event (SAE) includes: death; risk of death; necessity or prolongation of existing hospitalisation; persistent or significant disability or incapacity; or any other undesirable event considered to be medically significant. MG exacerbation requiring modification of current therapeutic management during the intervention period is considered a possible AE. All suspected unexpected SAEs are to be notified without delay to the sponsor, as well as any worsening of the disease suspected to be related to the physical programme if a patients' treatment needs to be modified. In this case, unblinding can occur. Should a worsening occur without needing a change of the treatment, it is only to be recorded in the electronic database without mandating a direct report to the sponsor. The sponsor's vigilance unit is in charge of the causality

assessment as well as of its regulatory duties with regard to reporting obligations to the French Medicines Agency.

Data and statistical analysis

Data management

Data are recorded and managed through a dedicated web-based software (Cleanweb Telemedicine) with secured and restricted access. Access to the system is controlled for each investigator by an individual login/password and using a secured https connection. Data are stored on a centralised server. Participants also have paper files which are anonymised and only contain the participant's unique identification code. These are stored in a dedicated storage unit in each centre. Access to the complete final trial dataset will be restricted to the Clinical Research Unit statistician who will analyse the study data for the purpose of report and publication. Subsets of the final dataset may be shared with investigators if needed for discussion or additional analyses. Should the need arise, advice from the steering Committee will be sought and provided to the sponsor APHP who will retain ownership of the data as well as the final decision on authorising further access to data.

Monitoring

Clinical research assistants from the sponsors research unit regularly visit all centres for on-site monitoring to ensure protocol compliance and monitor data quality according to the data management unit guidelines and clarification forms. Data entered into Cleanweb should be complete and consistent with source documents. Eligibility criteria and consent forms are checked as well as outcome measures and adverse events. No interim analyses are planned.

Statistical analysis

The statistical analysis will be performed once the planned number of patients will have completed the study, according to the intention-to-treat principle. Each participant is analysed according to the group in which he/she was randomised. For the primary outcome (*MGQOL-15-F* at three or six months), missing values will be handled through multiple imputation by chained equations. No multiple imputation will be carried out for secondary outcomes. The main analysis of the primary and secondary outcome measures will not be adjusted. Adjusted analyses on the centre will be performed but considered as secondary analyses. As there are only two centres, the centre will be modelled as a fixed effect. Two-sided tests will be used with a 5% significance level.

Patient description and follow-up

A descriptive analysis of inclusions and follow-up will be performed (graph of inclusions and theoretical and actual visits). All patients will be included in the analysis

unless their consent is retracted and they are opposed to their data being analysed. Any drop-outs or patients having stopped the intervention early will be included in the analysis. A patient is considered a drop-out when he/she revokes his/her consent to participate in the study and thus all participation in the study will cease.

Epidemiological and clinical characteristics of patients at baseline will be described by group without statistical tests. Any violation to the protocol and reasons for drop out will be described.

The primary outcome measure, the changes in *MGQOL-15-E*, will be analysed via a Student's test and adjustment on the centre will use ANOVA. If the distribution of the changes in the *MGQOL-15-F* between the two groups is very asymmetrical, then a non-parametric approach based on the ranks will be used for statistical testing.

Secondary outcome measure analysis

For binary outcome measures a non-adjusted analysis will be carried out using Fisher's exact tests. The analysis will then be adjusted according to the centre via a logistic regression model. The quantifiable outcome measures will be analysed using a Student's test for the non-adjusted analysis and an ANOVA model for the analysis adjusted for the centre. A transformation (for example a logarithm) will eventually be envisaged if the distribution of variables is not compatible with the normal distribution assumption. If the envisaged transformations do not enable a symmetrical distribution, a non-parametric analysis will be used (Wilcoxon test and ANOVA on ranks).

The analysis will be performed using the R software (version 3.4.3 or later; The R foundation for statistical computing, Vienna, Austria).

Timeline

Recruitment and final inclusions are anticipated to be completed in June 2017 with final subjects completing the study in February 2018.

Dissemination

We will provide all participants with a summary of trial outcome once data analysis has been completed. The trial results will be widely disseminated to the scientific community and the general community via publications in international peer-reviewed journals and presentations in national and international conferences as well as disseminated to patients via patient groups.

Discussion

In this article, we describe the design and methods of MGEX, a multi-centre, two-arm, parallel group, randomised, controlled trial investigating the tolerance and potential benefits of a moderate-intensity, individualised,

home-based physical exercise program in adults with generalised, stable, MG. This is the first study to explore physical exercise in this population with such a large sample size and rigorous methodological design.

Another strength of this study is the comprehensive evaluation using robust outcome measures. Outcome measures are valid and reliable and explore the multiple facets of the disease including the psychological aspects, the various physical symptoms, from a clinical, functional and physiological perspective as well as the complex immunological aspects.

Eligibility criterion are broad enabling the inclusion of multiple MG phenotypes which is important for the external validity of results, particularly as MG is a heterogeneous disease.

Recommendations regarding the practice of physical exercise in this population are lacking. Both patients and clinicians are awaiting evidence-based guidelines. The results of this study have the potential to provide much awaited and needed insight into the feasibility, tolerability and potential beneficial effects of physical exercise for patients with stabilised MG. Another non-randomised trial evaluating multi-modal exercise in stable MG is underway (NCT01047761) and due for completion in 2020.

If safe, participating in regular physical exercise may not only contribute to minimising deconditioning but may also improve QOL and daily function for patients and contribute to secondary prevention of various chronic conditions such as cardiovascular disease, cancer and depression. Moreover, the possible immunomodulatory effects of exercise which have been investigated in other auto-immune diseases, may also play an important role in the management of this auto-immune disease.

As quantitative data will be collected from the physical exercise sessions in MGEX, there will be no recall bias problems in relation to adherence and tolerability evaluations. The exercise program is personalised and is carried out at home, unsupervised, which is also important for real-life transfer. Thus, patients can be more self-sufficient and autonomous in undertaking an active lifestyle.

Trial status

To date, 32 patients have been included. Recruitment began in October 2014 and remains open and we are optimistic that the required number of participants will be met. No AEs related to exercise have been reported at this stage. This is V3.0 of the protocol, last updated on 12 January 2017. Clinical research assistants are responsible for informing all necessary bodies of any protocol modifications.

Additional file

Additional file 1: SPIRIT checklist. (PDF 280 kb)

Abbreviations

ANOVA: Analysis of variance; CD: Cluster of differentiation; ECG: Electrocardiogram; FVC: Forced vital capacity; HR: Heart rate; IL: Interleukin; MEP: Maximal expiratory pressure; MG: Auto-immune myasthenia gravis; MG-ADL: MG activities of daily living; MG-QOL-15: MG quality of life; MIP: Maximal inspiratory pressure; MMS: Myasthenic muscle score; QOL: Quality of life; WHO-QOL BREF: World Health Organization Quality of Life 26-item questionnaire.

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The MGEX Study Group

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Availability of data and materials

Data sharing is not applicable to this dataset at this current time.

Authors' contributions

The study protocol was elaborated and carried out by the MGEX study group, with TS as the leading contributor and coordinator of the study. TS also designed the clinical measures. JYH designed the pulmonary and muscular evaluations. MG and EL designed the psychological evaluation. PP and JYH designed the exercise program. PT provided input into the exercise program. SBA planned the immunological marker evaluations. RP is the methodologist and statistician of the study. BC, GB, BE and SD are involved in recruiting and evaluating study participants. PA is the coordinator of the clinical research unit, his team ensures the regulatory follow-up of the study and the monitoring of the data. SB wrote the first draft of this manuscript, performs the pulmonary and muscle evaluations, organises patient visits and organises the exercise training. AJ assists in clinical assessments and organises patient follow-up. All authors read and approved the final manuscript.

Authors' information

Not applicable.

Ethics approval and consent to participate

Ethics approval for all participating centres has been provided by an ethics committee, *Comité de Protection des Personnes Ile de France XI*, in accordance with French regulations under the number #13064 on 13 December 2013 and authorised by the *Agence Nationale de Sécurité du Médicament et des produits de santé*, reference 131300B-32, on 11 October 2013. All patients are required to provide written informed consent before inclusion in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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II. Quality of Life in myasthenia gravis

Evaluating Quality of Life in myasthenia gravis: Introducing the MGQOL-15-F

A patient-reported measure (PROM) aims to capture what really matters for an individual with a particular health condition. It ensures the patients' voice is central to clinical decision making and facilitates understanding of the impact of the disease and its treatments on an individual's quality of life (QoL). It does not replace performance-based assessments, it accompanies them in collecting data about all aspects of the patient to ensure accurate and optimal management [63]. Health-related QoL can be evaluated using generic questionnaires such as the SF-36 or the WHOQOL-Bref or using disease-specific questionnaires.

A disease-specific PROM to evaluate health-related QoL for French-speaking individuals with MG was lacking. This was the chosen **primary outcome measure** for the MGEX trial (Paper I), evaluating the change in self-perceived quality of life with exercise in MG.

International guidelines stipulate that PROMs should undergo a specific cross-cultural validation if translated into a different language. **Paper II** describes the translation and cross-cultural validation of this 15-item self-reported, MG-specific quality of life scale for use with French-speakers. This questionnaire is used in routine practice in the *Centre de référence neuromusculaire Paris Est* (Appendix 4).

The MGQOL-15 has since been translated into Chinese, Italian, Polish, Dutch and Arabic. There was also the creation of a revised version, the MGQOL-15r although based on the literature the original MGQOL-15 is still largely in use today.

Paper II: Birnbaum S, Ghout I, Demeret S, Bolgert F, Eymard B, Sharshar T, Portero P, Hogrel JY: **Translation, cross-cultural adaptation, and validation of the french version of the 15-item Myasthenia Gravis Quality Of life scale.** *Muscle Nerve* 2017, **55**:639-645.

TRANSLATION, CROSS-CULTURAL ADAPTATION, AND VALIDATION OF THE FRENCH VERSION OF THE 15-ITEM MYASTHENIA GRAVIS QUALITY OF LIFE SCALE

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ABSTRACT: *Introduction:* Evaluation of quality of life (QOL) has become essential in healthcare. Currently no MG-specific QOL measure exists in French. The aim of this study was to translate, culturally adapt, and evaluate the psychometric properties of the French version of the 15-Item Myasthenia Gravis Quality of Life Scale (MG-QOL15) scale for French myasthenia patients. *Methods:* Translation and cross-cultural adaptation of the MG-QOL15 was performed, followed by reliability and validity evaluations. *Results:* One hundred and twenty-five patients were included. Internal consistency was excellent (Cronbach $\alpha = 0.92$) as was test-retest reliability (ICC = 0.92, 95% CI 0.86–0.96). Concurrent validity was good for both clinical scores (myasthenic muscle score: $\rho = -0.52$, $P < 0.001$; Myasthenia Gravis-Activities of Daily Living scale score: $\rho = 0.62$, $P < 0.001$). Correlations were strongest for overall QOL ($\rho = 0.62$, $P < 0.001$) and physical health ($\rho = 0.67$, $P < 0.001$) on the World Health Organization Quality of Life short score (WHO-QOL BREF). *Conclusion:* The French version of the MG-QOL15 is valid and reliable and is now available for use with French-speaking patients.

Muscle Nerve 55: 639–645, 2017

Myaesthesia gravis (MG) is a rare, chronic autoimmune disease in which abnormal neuromuscular transmission results in muscle weakness and fatigue. Disease evolution in terms of location of and severity of symptoms, presence or absence of exacerbations, and response to treatment is unpredictable and variable. Quality of life (QOL) is

Abbreviations: AChR, acetylcholine receptor; ADL, activities of daily living; HRQOL, health-related quality of life; MG, myasthenia gravis; MG-ADL, Myasthenia Gravis-Activities of Daily Living scale; MGFA, Myasthenia Gravis Foundation of America; MGQ, 25-item MG questionnaire; MMS, myasthenic muscle score; MMT, manual muscle testing; MG-QOL15, 15-item Myasthenia Gravis Quality of Life scale; MG-QOL60, 60-item Myasthenia Gravis Quality of Life scale; MuSK, muscle-specific tyrosine kinase; PROM, patient-reported outcome measure; QMG, quantitative myasthenia gravis score; QOL, quality of life; SF-36, Short-Form Health Survey; WHO-QOL BREF, World Health Organization Quality of Life short score

Key words: autoimmune myasthenia gravis; cultural adaptation; patient-reported outcome measure; quality of life; validation

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French Version of MG-QOL15

negatively affected for most patients to differing degrees, and the impact on QOL is difficult to determine with standard clinical evaluations. Clinical scores [such as the quantitative myasthenia gravis score (QMG), the myasthenic muscle score (MMS), or manual muscle testing (MMT)] or external observational impressions do not provide the same information as when a patient completes a questionnaire designed for this purpose. Thus, the use of patient-reported QOL measures that truly reflect the impact of the disease on an individual has become common practice in healthcare. These measures can be used to monitor the evolution of a disease and/or judge the efficacy of treatment. Multiple patient-reported outcome measures (PROMs) exist. Generic QOL questionnaires, such as the Short-Form Health Survey (SF-36) or the World Health Organization QOL short version (WHO-QOL BREF), have been used in myasthenia populations, but they are long and lack disease-specific items that are important to MG patients. Therefore, several specific health-related QOL (HRQOL) measures were developed, including the 25-item MG questionnaire (MGQ), developed in Italy and later validated in Swedish and Serbian populations.^{1–3} This was followed by the 60-item Myasthenia Gravis Quality of Life Scale (MG-QOL60), which included psychological factors⁴ lacking in the MGQ. The MG-QOL60 was then shortened to 15 items to reduce the completion time and has been used in both the clinical and research setting.⁵ It has proven to be user-friendly and reliable.^{6,7} It was successfully translated to Brazilian Portuguese and translated and tested in Japanese and Iranian populations.^{8–10}

Today no specific QOL measure exists for French-speaking patients with MG. For a PROM to be used reliably in another language and culture, it should undergo a careful translation and cultural adaptation process.¹¹ Using the same outcome measure can enable comparisons across countries and cultures, which is particularly important in rare diseases such as MG.

MUSCLE & NERVE May 2017 639

The purpose of this study was to translate and culturally adapt the English version of the MG-QOL15 into French and to evaluate its psychometric properties for use in a clinical and research setting.

METHODS

Subjects and Data Collection. This prospective validation study was conducted between June and December 2014 in Île-de-France, France. Patients were recruited when they presented for their regular outpatient neurology consultation at 1 of 2 hospitals, (Pitié Salpêtrière Hospital in Paris or Raymond Poincaré Hospital in Garches), both specialist centers for the management of MG.

Consecutive patients were included if they were French-speaking with a confirmed diagnosis of autoimmune MG and were ≥ 18 years of age. The diagnosis of MG was made by a neurologist based on clinical findings, including muscle fatigability that improves with rest, symptom improvement with anticholinesterases, abnormal repetitive nerve stimulation testing (decrement $> 10\%$) or abnormal single-fiber electromyography (conduction block or jitter), and/or the presence of circulating antibodies against the acetylcholine receptor (AChR) or muscle-specific kinase receptor (MuSK). Patients were excluded if they were unable to complete the French version of the questionnaire (MG-QOL15-F) because of lack of French fluency or because of cognitive impairment. In cases of severe visual impairment the questionnaire was read to the patient. Patients with severe MG who were ventilated [Myasthenia Gravis Foundation of America (MGFA) class V] were not included, as the MG-QOL15-F is unlikely to be appropriate and relevant for this subgroup of patients, and the original MG-QOL15 was not validated in this subgroup. All participants provided informed consent. This study was approved by the local ethics committee (Ref. No. 15-206).

Gender, age, presence or absence of specific antibodies (anti-AChR or anti-MuSK), and current MG status based on the MGFA classification¹² were documented. The myasthenic muscle clinical score (MMS) and the Myasthenia Gravis-Activities of Daily Living (MG-ADL) score on the day of consultation were recorded when possible, and patients were asked to complete the WHO-QOL BREF on days 1 or 3. The MMS is a clinical score routinely performed by neurologists in France to assess muscle force and fatigue at a moment in time.¹³ It evaluates limb, axial, and bulbar symptoms, and the maximum score (thus, no detectable deficit) is 100. The MG-ADL, which is also used routinely in clinical practice, consists of 8 items and measures the impact of MG on activities of daily living.¹⁴

Responses are based on the preceding week. A score of 0 corresponds to no ADL limitation, and 24 is the maximum score. The MGFA classification is a clinical classification of the type/localization (bulbar/facial or limb predominance) and severity of MG.¹² The WHO-QOL BREF, a generic, global measure of QOL, was completed when possible for criterion-related validity, as there is no existing "gold standard" QOL measure for MG in French for correlation with the MG-QOL15-F. The WHO-QOL BREF consists of 26 questions, including 1 general health and 1 general QOL item, as well as multiple items in 4 specific domains: physical health; psychological health; social relationships; and environment. It was chosen because it is a self-reported measure of QOL that has been tested in patients with neuromuscular disorders; it is freely available and has been validated in French.¹⁵

The MG-QOL 15. The MG-QOL15 is a 15-item self-administered questionnaire that evaluates the HRQOL of a patient with MG over the preceding few weeks. The objective of the MG-QOL15 is to provide an effective, reliable, and rapid means of evaluating self-perceived HRQOL of patients with MG in a clinical or research setting. Of the 15 items, 3 evaluate "symptoms," 2 evaluate "general contentment," 2 evaluate "emotional well-being," and 8 evaluate "mobility." Each item is scored from 0 to 4 on a 5-point Likert scale. A total score is calculated, with a maximum score of 60 and a minimum of 0. A higher score represents lower perceived QOL. The MG-QOL15 is simple and quick to fill out and has been shown to be valid and reliable.^{6,7} The only material required is the questionnaire and a pen to tick the boxes.

Translation and Cultural Adaptation. The translation and cross-cultural adaptation was conducted according to published international guidelines.^{11,16-18} This consisted of 3 independent forward translations completed by a professional linguistic translator, a neuroscientist, and an occupational therapist, who were selected for their ability to understand QOL concepts as well as neuromuscular diseases. All 3 were proficient in understanding written English. A common forward translation was then established via consensus. This was translated back to English by a native English-speaking, bilingual physiotherapist who was blinded to the original English MG-QOL15. This was then submitted to the developer of the English MG-QOL15 (Dr. T.M. Burns) for approval. A final version was established between the translators, which incorporated feedback from Dr. Burns. This version was presented to a multidisciplinary bilingual committee consisting of 3 MG experts, a psychologist, a methodologist, and the original

translators. Care was taken to ensure that equivalence was maintained with the original questionnaire while ensuring cultural and linguistic acceptability for French-speaking patients. The final approved French version was pilot tested with 10 MG patients for content validity verification. Patients were probed for their understanding and acceptability of the questionnaire. No changes were considered necessary. The original title of the questionnaire was kept for simplicity, and an F was added to identify the French version, MG-QOL15-F.

Psychometric Testing. Validity is the degree to which a HR-PRO instrument measures the construct it sets out to measure.¹⁹ Construct validity was evaluated by testing the *a priori* hypothesis that a lower HRQOL (higher MG-QOL15-F) would correlate with muscle weakness and fatigability (i.e., a lower MMS score) and greater functional disability (i.e., a higher MG-ADL score). As there is currently no other myasthenia-specific gold standard QOL measure for French-speaking patients, the WHO-QOL BREF was selected to measure criterion validity. Test-retest reliability refers to the scale's reproducibility and its capacity to provide consistent scores over time in a stable population. This was measured by comparing 2 questionnaires from the same patient over a 2-day interval. Participants completed the MG-QOL15-F during their medical consultation (day 1), then completed it a second time 2 days later (day 3), and returned it via post. As the analysis was anonymous, a code was written on the questionnaire to allow the test-retest comparison. Participants were asked to contact the project manager if their health status changed between days 1 and 3 (to ensure stability). Internal consistency, defined as the degree of interrelatedness among the items, was also evaluated. Cross-cultural validity describes the degree to which performance of the items on a translated or culturally

Table 1. Patients' characteristics ($N = 125$, except for severity data given for 121 patients)

Age in years (mean \pm SD)	52.9 \pm 18.5
Women	74 (59.2%)
Asymptomatic	20 of 121 (16.6%)
MGFA I	8 of 121 (6.6%)
MGFA IIa	54 of 121 (44.6%)
MGFA IIb	11 of 121 (9.1%)
MGFA IIIa	20 of 121 (16.6%)
MGFA IIIb	5 of 121 (4.1%)
MGFA IVa	2 of 121 (1.6%)
MGFA IVb	1 of 121 (0.8%)
Antibodies: AChR	94 (75.2%)
Antibodies: MuSK	8 (6.4%)
Seronegative (neither AChR nor MuSK)	22 (17.6%)
Antibodies: unknown	1 (0.8%)

French Version of MG-QOL15

Table 2. Missing items

MG-QOL15-F Item	Test ($n = 125$)	Retest ($n = 108$)
10 (driving)	11	7
8 (profession)	2	3
9 (talking)	1	1
2 (vision)	1	
4 (social life)	1	
13 (public places)	1	
6 (family obligation)		1
7 (planning)	1	

adapted HR-PRO instrument adequately reflect the performance of the items of the original version of the instrument. This was evaluated by comparing results for the MG-QOL15-F with results from the MG-QOL15 and the Japanese MG-QOL15. Floor and ceiling effects as well as acceptability of the questionnaire (the number of non-responses and missing items) were also evaluated.

Statistical Analysis. Construct and criterion validity were estimated via Spearman rank correlation coefficients between the MG-QOL15-F, the MMS, the MG-ADL, and the WHO-QOL BREF. Cronbach α was calculated to evaluate internal consistency and an intraclass correlation coefficient (ICC) for test-retest reliability. A confidence interval (CI) of 95% was used for both. A Bland-Altman plot was constructed to indicate absolute agreement for test-retest measurements with 95% limits of agreement, and Cohen weighted κ coefficients were calculated to evaluate agreement between individual items. All analyses were performed using R version 2.15 software (R Foundation for Statistical Computing, Vienna, Austria). $P < 0.05$ was considered statistically significant.

RESULTS

Among the 138 patients approached for inclusion, 7 were excluded due to lack of French fluency, 4 did not have a definite diagnosis of MG, 1 did not consent to participate, and 1 was being treated for an exacerbation that made the test-retest unlikely to be reliable due to expected clinical improvement. The characteristics of patients are shown in Table 1. A total of 125 patients completed the MG-QOL15-F, and 17 questionnaires were returned incomplete. The most frequent missing item ($n = 11$) was item 10 (driving), followed by item 8 (professional activity) ($n = 2$). Of the 108 retest questionnaires that were returned, there were 12 missing items, mostly concerning driving ($n = 7$) and professional activity ($n = 3$). Table 2 lists all of the missing items.

Women comprised 59% of the cohort, with a mean age of 53 (range 18–94) years. The majority (54%) had mild, generalized MG (MGFA II), and

MUSCLE & NERVE May 2017 641

Table 3. MG-QOL15-F score according to MGFA classification

MG classification	Score (mean ± SD)
Asymptomatic	6.3 ± 4.7
MGFA I	7.1 ± 5.2
MGFA IIa	14.9 ± 12.3
MGFA IIb	12.4 ± 7.2
MGFA IIIa	24.1 ± 11
MGFA IIIb	19.4 ± 16.4
MGFA IVa	42.0 ± 11.3
MGFA IVb	Missing data

1 out of 6 patients was asymptomatic. The majority (75%) had antibodies against AChR.

The mean MG-QOL15-F score from our cohort was 14.6 ± 12.2 (range 0–52, possible score 0–60). Mean scores, according to myasthenia type, and severity, according to MGFA classification, are shown in Table 3. Higher scores indicate lower perceived QOL. No ceiling or floor effect was observed, thus indicating that all items are relevant, and the scale is appropriate for a large population of myasthenic patients despite varied symptoms and severity.

Internal consistency was excellent (Cronbach coefficient $\alpha = 0.92$, 95% CI 0.89–0.94, $n = 108$). Test–retest reliability was evaluated in 90 patients and found to be excellent (ICC = 0.92, 95% CI 0.86–0.96) (Fig. 1A). Agreement between individual items was excellent; the lowest agreement (Cohen $\kappa = 0.75$) was for item 7, “need to make plans,” and the highest was for item 3, “trouble eating” (Cohen $\kappa = 0.85$). The Bland–Altman plot showed good agreement between the 2 tests

Table 4. Correlations between the MG-QOL15-F and the MMS, MG-ADL, and WHO-QOL BREF

	N	Score (mean ± SD)	Spearman ρ	P-value
MMS	91	90.9 ± 10.3	−0.519	<0.001
MG-ADL	47	2.8 ± 2.9	0.623	<0.001
WHO-QOL BREF				
QOL and general health	72	56.8 ± 19.3	−0.622	<0.001
Physical health	69	57.6 ± 17.8	−0.667	<0.001
Psychological health	66	68.7 ± 15.8	−0.411	<0.001
Social relationships	69	71.5 ± 15.2	−0.290	0.016
Environment	70	72.3 ± 18.8	−0.577	<0.001

(Fig. 1B). The average of the differences was close to 0 (0.63).

Construct validity was demonstrated by significant correlations between the MG-QOL15-F and the MMS and MG-ADL (Table 4). Significant correlations were found between the physical health domain of the WHO-QOL BREF and general quality of life, yet correlations were weaker for psychological health and the social life domain (Table 4).

Overall, the questionnaire was well received, mostly due to the brief time needed to complete it and the fact that it involved patients self-evaluating the impact of symptoms that are specific and relevant to them. Item 10 (driving) presented difficulties for certain patients, as a large number of Parisians do not drive regularly (or at all), thus they did not know how to reply. Also, item 8, concerning professional capacities, was irrelevant for retired patients (as the questionnaire is based on

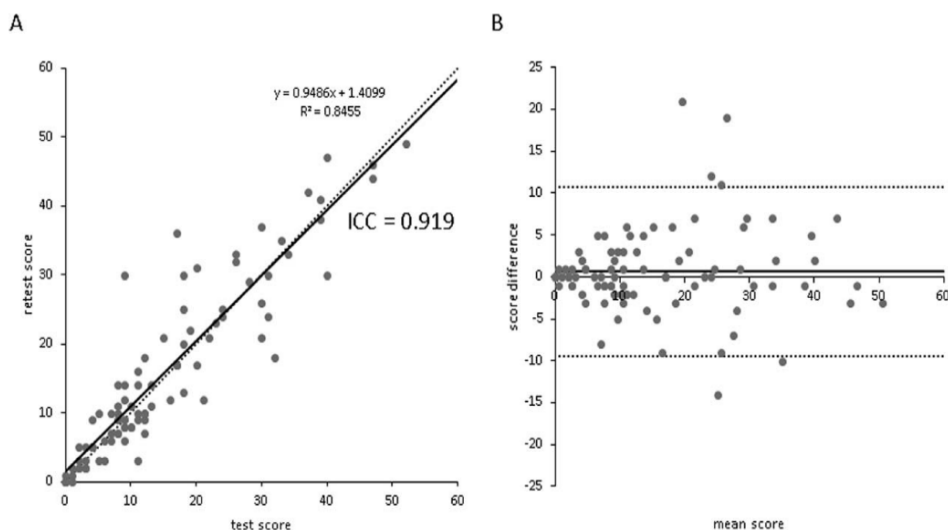


FIGURE 1. Test–retest reliability. (A) Retest score as a function of test score. Identity line is represented by a dotted line. (B) Bland–Altman plot. Dotted lines represent 95% limits of agreement.

current status and not on how the MG affected them at a time when they may have been working).

DISCUSSION

The MG-QOL15 was successfully translated and validated into French. Translation and cross-cultural adaptation did not present any major difficulties, thus a conceptually equivalent French version of the MG-QOL15, the MG-QOL15-F, was developed. Like the Japanese version, our results show that the MG-QOL15-F has demonstrated excellent reliability and satisfactory construct validity with myasthenia-specific clinical scores.

Our population was similar to that of the Japanese cohort and is representative of a typical myasthenic population.^{9,20} Compared with the original English version, reproducibility was only slightly inferior, and internal consistency was almost equal.⁶ A time period of 1–2 weeks is often used in the literature to assess reproducibility,²¹ but, because of the unpredictable and fluctuating nature of MG, a 2-day interval was chosen for our study to ensure that patients remained stable for reliability evaluation of the instrument. The same time frame was used in the Japanese validation study.⁹ An interval of 2–4 days was used for the original version.⁶

The most frequently missing item was item 10, which concerns driving, followed by item 8, concerning professional situation. As there is no recommended methodology for handling missing items in the original MG-QOL15, the statistical analysis was only conducted on scores with complete data. Removing the questionnaires with missing items is not thought to have significant effects on the results.

Despite being a generic QOL questionnaire, the WHO-QOL BREF, was chosen to evaluate criterion validity as no disease-specific “gold standard” QOL score for MG currently exists in French, and normative data from the WHO-QOL BREF exist for a French population.²² Not surprisingly, the most affected domain, and thus the highest correlation with the MG-QOL15-F, was the physical domain. This has been demonstrated in other cohorts.^{23,24} The social relationship domain had a very weak correlation.

Construct validity was evaluated via our *a priori* hypotheses that perceived QOL would be worse with a lower clinical score (MMS) as an indicator of greater disease severity and a higher MG-ADL score as an indicator of greater functional restriction. One of the reasons a QOL score is required in clinical studies today is that clinical scores and physical disability are not always interchangeable with patients’ perception of well-being and/or

satisfaction with their disease. This could be a reflection of the lack of specificity or sensitivity of the clinical score, or it could be that such scores do not evaluate exactly the same constructs as QOL scales and thus the 2 evaluations are usually complementary. It is not surprising that correlations with the clinical score, the MMS, a snapshot evaluation of muscle force and fatigue, were modest, and correlations with the MG-ADL, which evaluates real-life limitations in daily activities, were higher. It is important to note that the MMS suffers from a ceiling effect.

To further illustrate this concept, despite a lack of symptoms, patients in the asymptomatic category still reported that their QOL was negatively affected. This may have been due to side effects of treatment, the negative aspects of living with a chronic disease, or simply because perceived QOL is a complex construct with various and multiple dimensions. For example, despite the same mean score on the MG-ADL, perceived QOL, as expressed by the MG-QOL15, was lower in our cohort compared with a recent Iranian cohort.¹⁰

There was no significant effect of age or gender on MG-QOL15-F scores. This is in agreement with previous findings measured by the MG-QOL60 in an Australian cohort.²⁵ An American cohort found a weak inverse correlation (Pearson $r = -0.4$) between age and QOL as measured by the MG-QOL15.⁵ Unsurprisingly, as compared with normative data, QOL measured via the WHO-QOL BREF in our cohort was most greatly affected in the physical domain, yet psychological health was not inferior in our cohort.²²

In addition to psychometric properties when validating an instrument, cost and feasibility should also be addressed. The MG-QOL15-F will be freely available and only requires paper and a pen to complete. Feasibility refers to both the respondent and administrator burden. This is negligible, as it is very quick to fill out (≤ 3 minutes), with almost no added burden on the clinician or the patient. Furthermore, no specific skills or training are required to administer the scale. It is also very easy to interpret; the score requires a simple addition of all items and provides an immediate impression of QOL that can be directly compared with previous scores.

Due to the small number of patients affected by MG, it is not considered a major public health problem. However, as a chronic disease, MG can have a major financial impact on patients and the healthcare system, and successful care should incorporate reliable measures of QOL.²⁶ The fact that MG is a rare disease creates difficulty in recruiting sufficient patients into research trials.

Having common outcome measures increases the possibility of performing multicenter trials and meta-analyses of clinical trials.

As MG is variable and fluctuates for an individual over time, it is particularly useful for the clinician to have an objective/quantifiable measure of the impact of the disease on an individual's perceived QOL. The disease symptoms impact patients differently, and it is impossible to predict and difficult to understand or appreciate the consequences of the disease otherwise. As the developer of the scale has clearly stated, this questionnaire is not intended to replace discussions with the practitioner. It does enable a standardized follow-up in a disease that is often changing with medications or dosages being modified frequently. It gives patients a voice to express themselves while limiting subjective interpretation. Beyond research, one must also consider individual patients. Their point of view on how they are coping with their disease (and treatment) is crucial in order to adapt current treatments and to monitor disease evolution. To do this, we need objective measures. Now that the validity of the MG-QOL15-F has been evaluated, French patients have an objective tool to express themselves. From current experience with patients and clinicians, it is likely that the MG-QOL15-F will be easily integrated into clinical practice due to its simplicity, rapidity, and ease of interpretation.

Finally, as patients do not always have access to specialist myasthenia treatment centers in France, due to distance, it would be worthwhile to test the use of the MG-QOL15-F by telephone (as has been done with the English version) to assist in therapeutic decisions and ensure optimal treatment.²⁷ Also, as stated earlier, for the MG-QOL15-F to be useful in clinical research studies, sensitivity to change should be evaluated.

Limitations of this study include patient selection. Our sample seems to be representative of the population in terms of the demographics of patients with MG (majority anti-AChR antibodies, more women than men), but it was limited to a particular region in France. Patients from Ile de France may not necessarily be representative of the entire MG population in France. For example, many Parisian patients do not drive and, as MG can limit the ability to drive (item 10 on the MG-QOL15-F), this item would be less relevant. In another region in France where people depend on driving, this item would be particularly important and bear a greater impact on their QOL. In the Japanese MG-QOL15 validation study, internal consistency for this item was low, as many people do not drive in Tokyo.⁹ It also posed a problem for

the Persian version, as a large group of women do not drive in Iran.¹⁰ Another item on the MG-QOL15-F that may present difficulty is item 8, which concerns professional situation. For retired patients this item is irrelevant. Although we were aware of these 2 potentially problematic items, we did not want to modify the questionnaire to be able to compare data and contribute to a common international scientific language. It should be noted that these items have now been reviewed and modified in a recent international collaboration.²⁸

Generalizability of results also involves other French-speaking countries, as the population of myasthenic patients may be different in the context of different environments. There is hope that this version is useful to French-speaking patients around the world, despite slight differences in characteristics and social/environmental contexts. It is important to keep in mind, however, that both reliability and validity are continuous psychometric indices, where a greater amount of evaluation will provide more evidence to support the robustness of the scale.

It is important to note that, although the MG-QOL15-F has proven to be robust, as a PROM it is possible that certain patients respond differently at different time-points. This was the case in 2 of our patients who had very different scores on the retest. We cannot exclude the possibility of an exacerbation, but we believe the large difference is more likely due to changes in mood when completing the questionnaire.

Responsiveness, the ability of a measure to detect clinically meaningful change, is a very important characteristic of an outcome measure. We did not set out to measure this construct, as there were no changes expected for patients over the 2-day interval. However, to confirm the utility of the instrument as an outcome measure, responsiveness should be evaluated.

In conclusion, the French version of the MG-QOL15, the MG-QOL15-F, has demonstrated excellent reliability and satisfactory construct validity. It can thus be used reliably in both the clinical and research settings. Further evaluation of sensitivity to change and the minimal clinically relevant difference for this version is required to assist in interpreting research findings. Future studies should evaluate different modes of administration (e.g., by telephone) for patients who are more remote as a way of monitoring disease status and treatment efficacy.

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III. Physical activity in myasthenia gravis

Clinical presentation and severity of MG are variable from one person to another. Whilst some individuals present difficulties in performing basic activities of daily living (both personal and instrumental), others seem to be able to maintain a relatively “normal” lifestyle, including performing strenuous physical activity (PA) [64]. Reduced activity has been shown to be related to increased fatigue severity [65]. To what extent (volume and intensity) individuals with MG perform PA is currently unknown. Knowledge of activity levels and sedentary behaviour could assist in providing more appropriate and tailored advice and also help to understand any possible barriers or facilitators to being physically active in the quest to minimise the secondary effects of a sedentary lifestyle. In the general population higher levels of PA are associated with improved quality of life [66]. It has been suggested that PA may be helpful in MG but to what extent this relationship with quality of life exists has not been formally tested.

Objective monitoring of daily life PA, otherwise known as habitual PA or free-living PA has become simpler in the last decade, with the increasing and widespread availability of a variety of wearable technologies. On the contrary to common tests used during consultations with health professionals where an individual is required to execute an action, free-living PA is a measure of performance rather than capacity [67, 68]. Free-living PA encompasses any activity performed in a person’s natural environment. It is a direct measure as opposed to traditional self-report questionnaires or activity diaries which are indirect measures, susceptible to subjectivity and recall bias [68, 69]. Information obtained from wearable activity trackers or monitors is useful to identify whether altered activity behaviours are present and to establish appropriate doses of PA for specific populations. Keeping in mind, however, that activity behaviours are not a precise measure of the impact of a disease on one’s ability to be active [70]. Other factors such as social, personal and environmental factors can contribute to activity behaviours and should also be considered when interpreting data [71].

Paper III

Paper being finalised, planned submission to *Journal of Neuromuscular Diseases*

Birnbaum S, D Bachasson, Sharshar T, Porcher R, Hogrel JY, Portero P: **Free-living physical activity in auto-immune myasthenia gravis: a cross sectional study.**



The DynaPort (McRoberts) accelerometer was chosen for the MGEX study for measuring physical activity of the individual at home.

Title page

Free-living physical activity in auto-immune myasthenia gravis: a cross sectional study

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Ethics

The MGEX study was approved by the local ethics committee in accordance with French regulations (*Comité de Protection des Personnes Île-de-France XI* under the CPP number #13064 on 13 December 2013) and authorised by the *Agence National de Sécurité du Médicament et des produits de santé* on 11 October 2013. The study was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants.

Free-living physical activity in auto-immune myasthenia gravis: a cross sectional study

Abstract

Background

Muscle weakness and fatigability are prominent symptoms of auto-immune MG and impact negatively on daily function and quality of life (QoL). To what extent symptoms limit daily life physical activity is unknown. To date, data regarding physical activity (PA) patterns in individuals with auto-immune myasthenia gravis (MG) are lacking.

Objectives

This study aimed to describe daily life physical activity patterns of female adults with MG and explore associations between PA metrics, clinical presentation and QoL.

Methods

Females with confirmed MG and healthy participants wore a tri-axial accelerometer on their lumbar spine for 7 consecutive days. Recordings with ≥ 4 days with ≥ 12 hours daytime (between 7am-11pm) were considered for analysis. Wilcoxon rank-sum tests were used to study between-group differences. MG-specific evaluations as well as six-minute walk test, spirometry and knee extension strength were assessed in individuals with MG. Univariable analyses and Spearman rank correlation coefficient were performed to explore relationships between these parameters and PA metrics in MG.

Results

Thirty-three individuals with MG (lwMG) were compared to 113 age, gender and weight-matched control subjects. lwMG performed less physical activity (light, moderate and vigorous intensity) than control subjects ($p < 0.05$). Twenty-four percent of lwMG met PA recommendations for adults, undertaking, on average, 100 minutes (range 0-400) of bouts (≥ 10 minutes) moderate-vigorous intensity PA per week compared to 66% of controls who performed an average 250 minutes (range 0-677). For lwMG, quality of life was correlated with knee extension strength but not with habitual PA. Six-minute walk distance was

correlated with PA ($\rho = 0.581$, $p = 0.029$) and body mass index was negatively correlated with habitual PA ($\rho = -0.407$, $p = 0.19$) and positively with sedentary behaviour.

Conclusions

lwMG undertake lower levels of PA compared to the general population as measured using trunk accelerometry. PA is not related to self-perceived QoL. Clinical measures such as the six-minute walk test may provide some insight into PA patterns of lwMG. Increased body mass index is negatively associated with PA behaviour and with walking capacity in this population.

Free-living physical activity in auto-immune myasthenia gravis: a cross sectional study

Introduction:

Myasthenia gravis (MG) is an auto-immune disease in which antibodies modify the normal functioning of the neuromuscular junction of skeletal muscles causing reduced neuromuscular transmission efficiency. As a consequence, individuals experience fatigue and weakness which can be generalised or localised, and usually affects proximal more than distal muscles. Symptoms tend to vary over the course of a day and from day to day (1).

This fluctuating fatigue and weakness experienced by individuals with MG causes functional impairment which presumably contributes to a more sedentary lifestyle (2). Surprisingly, there is a paucity of research about physical activity (PA) patterns in individuals with MG (lwMG). The existing evidence from two studies does not provide clear information of PA levels in MG. Using a self-report questionnaire Vinge et al. reported similar daily MET scores between individuals with MG (median 40.5) and healthy controls (median 45.2) (3). Instrumented assessment of sedentary behaviour and steps taken per day in 14 lwMG found a median of 10 hours and 8801 steps, respectively (4). Physical activity in this study, however, was self-reported, with subjects reporting a median of < 30 min/week for strenuous exercise and 150-300 min/week for incidental exercise.

Recent research has proposed exercise programs as an adjunct therapy for individuals with MG (4-6). Before proposing additional exercise, it would seem plausible to understand current activity levels in MG to provide insight into feasibility and aid in designing appropriate interventions. Also, knowledge of PA patterns of lwMG could provide information regarding the functional capacities and impact of MG in daily life.

Physical activity is any body movement produced by skeletal muscles that results in energy expenditure and can include leisure-time activity, transportation such as walking or cycling, occupational and/or household work such as cleaning, lifting and carrying as well as sport (7). Typically, PA is defined by its duration, intensity and frequency or regularity. Activity intensity can be described in relation to energy expenditure, or metabolic equivalent units (METs) (8).

One MET is the rate of energy expenditure while sitting at rest which for most people approximates to an oxygen uptake of 3.5 ml/kg/min (9). The MET value of activity is calculated relative to rest and is expressed in multiples of METs. Sedentary behaviour (SB) is defined as lack of body movement during waking time that does not increase energy expenditure substantially above the resting level such as lying down, sitting, watching television, and reading (10).

Physical inactivity is responsible for increased risk of chronic diseases such as cardiovascular disease, type 2 diabetes, osteoporosis, and breast and colon cancer and for 9% of worldwide deaths (11). Public health recommendations for the general adult population advise a minimum of 150 minutes per week of moderate-intensity aerobic physical activity in bouts of at least 10 minutes, as well as strength training twice a week (12). Even if this target is not met, recommendations stipulate that individuals can still achieve substantial health gains by increasing their activity levels or reducing their inactivity. For example, replacing some sedentary behaviour with light-intensity PA reduces the risk of all-cause mortality, cardiovascular disease incidence and mortality, and the incidence of type 2 diabetes (11).

The use of accelerometers to assess PA and SB has become a preferable and feasible alternative to traditional self-report methods such as questionnaires which suffer from recall bias (13). Accelerometers are small, wearable devices that measure accelerations of the body continuously in real-time, capturing all movement performed whilst wearing the device. The signals are processed to obtain activity counts or accelerations due to body movement. The volume, intensity and duration of daily PA and SB are obtained by classifying activity into specific categories with intensity thresholds, providing quantitative and objective data.

In chronic disease, evaluating activity patterns outside of the clinical setting provides insight into real-life behaviour, particularly in a disease such as MG where symptoms fluctuate. Ultimately, the goal of treatment is to improve real-life activity and not performance on consultation-based clinical assessments. Consultation-based assessments only provide a snapshot to a specific instant which may be an under or over-estimation of an individual's capacity throughout the day or week (14). Habitual PA could potentially be used as an outcome measure to evaluate effectiveness of new or current treatments particularly for

higher functioning individuals who achieve maximal scores on current disease-specific evaluations.

Aim: This study aimed to describe habitual physical activity (PA) patterns of female adults with auto-immune myasthenia gravis in their regular, daily, community life and explore associations between PA, SB, clinical characteristics, quality of life (QoL) and clinic-based assessments.

Methods:

Design: cross-sectional

Subjects/participants:

Data presented in the current work are from a prospective clinical trial. Full details of participant recruitment, inclusion and exclusion criteria have been published elsewhere (6). Briefly, to be eligible subjects had a confirmed diagnosis of stable, generalised auto-immune MG without contra-indication to exercise. The MGEX study was approved by an ethics committee in accordance with French regulations (*Comité de Protection des Personnes Île-de-France XI* under the CPP number #13064 on 13 December 2013) and authorised by the *Agence National de Sécurité du Médicament et des Produits de Santé* on 11 October 2013. The study was conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from all participants. Only women were considered for this study due to the small number of men (3) to favourise homogeneity. Healthy control subjects were from the accelerometer manufacturer database self-reported to have no significant medical condition, were willing to wear the accelerometer for 7 days and provided consent for data use.

Physical activity monitoring:

Free-living physical activity and sedentary behaviour were quantitatively measured in daily life using a tri-axial accelerometer (Version 3.0 DynaPort Movemonitor, McRoberts, The Netherlands) attached to the lumbar spine with the supplied elastic belt. The accelerometer weighs 55 g and measures 106.6 × 58 × 11.5 mm. It stores raw data on a microSD card which is uploaded for analysis at the end of the planned wear period. The accelerometer measures acceleration in three axes at a sample rate of 100 Hz with a range of -6 g to + 6 g (15). Algorithms developed by the manufacturer first determine whether the accelerometer was worn based on threshold and frequency analysis of the raw signal and then identifies physical activity and inactivity by measuring body posture and movement intensity from acceleration signals (16, 17). To classify different activity intensities, proprietary energy expenditure algorithms were used which have been previously validated using indirect calorimetry (17). Maximal recording duration was 7 days. Subjects were asked to wear the device during waking hours for seven consecutive days, except when bathing/showering or swimming as the device

was not waterproof. Multiple days were monitored to account for day-to-day variation. Participants were asked to mail the device back to the coordinating centre in a pre-paid envelope after the 7-day monitoring period.

Recordings ≥ 4 days with ≥ 12 hours daytime wear-time (between 7am-11pm) were considered for analysis (18, 19). Daily PA data was then averaged over valid days to determine habitual daily activity. Non-wear time was based on a manufacturer algorithm meeting six different criteria based on the vertical, medial, lateral and anterior posterior accelerations (see supplementary data).

PA intensity was based on accelerometer activity and defined as multiples of the resting metabolic rate where light-intensity PA is within 1.5 and 3 METS, moderate-intensity is within 3 and 6 METS, vigorous-intensity PA is within 6 and 9 METS. Threshold for moderate to vigorous PA was 3 METS. Both unbouted (MVPA <10 min and bouted MVPA were computed. *Bouted* MVPA (MVPA $_{\geq 10}$ mins) was defined as sustained MVPA for at least 10 minutes with activity < 3 METs not lasting more than 1 minute over this period. Sedentary behaviour was defined as time spent < 1.5 METS. Vector magnitude (counts) was used as a proxy for total volume of PA (20). Steps were the number of steps per day including stairs.

Clinical assessment:

Information regarding clinical MG history, MGFA classification and current medications were recorded by an expert neurologist who also administered the Myasthenia Muscle clinical score (MMS) and the Myasthenia Gravis–Activities of Daily Living score (MG-ADL). The MMS is a clinical score routinely performed by neurologists to assess muscle force and fatigability at a moment in time (21). It evaluates limb, axial, and bulbar symptoms, and the maximum score (thus, no detectable deficit) is 100. The MG-ADL score which is also used in clinical practice, consists of 8 items and measures the impact of MG on activities of daily living, a zero indicates no functional impairment (22). Subjects also completed a self-reported MG-specific quality of life questionnaire. The MGQOL-15-F has been shown to be valid and reliable. Higher scores (with a maximum score of 60) represent a lower perceived QoL (23). A physiotherapist performed the following assessments: 6-minute walk test (6MWT), maximal isometric knee extension strength (right-side) using an isokinetic dynamometer (Biodex System 3 Pro, Biodex

Medical Systems, Shirley, USA) and spirometry including Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV1). Full details of the protocol have been described previously (6). To account for the effect of age, height and weight, predictive models were used for the 6MWD, knee extension strength, FVC and FEV1. Data were expressed as percentage of predicted values (24-26).

Statistics:

Demographic and clinical characteristics of subjects were described by group in terms of mean, and standard deviation or median, inter-quartile range for continuous variables and number for categorical variables. Between-group differences were tested using Wilcoxon rank-sum test. Within-group differences were tested using a Wilcoxin signed-rank test. Univariable analyses were performed to evaluate associations between habitual PA and; personal factors (BMI), disease characteristics (disease duration, severity: MMS), daily function (MG-ADL) and Quality of Life (MGQOL-15-F and WHO-QOL, physical domain), functional walking capacity (6MWD), knee strength and respiratory function (FVC, FEV1). Spearman-rank was used to assess strength of correlations between continuous variables. P values < 0.05 were considered as being significant for all analyses.

Results:

Thirty-three women with MG (lwMG) and one hundred and thirteen age, weight and gender-matched control subjects were included. Demographic characteristics are presented in Table 1. lwMG were shorter and had a higher body mass index (BMI) than control subjects.

	MG (n = 33)	Controls (n = 113)	P value
Age (years)	45.4 (10.6)	47.2 (12.7)	0.43
Height (cm)	163.3 (6.0)	168.1 (7.0)	< 0.001
Weight (kg)	73.7 (15.1)	71.8 (11.5)	0.58
BMI (kg/m²)	27.6 (5.0)	25.4 (3.9)	< 0.001

Table 1: Demographic information of individuals with MG (MG) and healthy controls, mean (SD).

For lwMG, average disease duration was 14 (12) years with average age onset at 32 (15) years old. The majority had early onset MG (EOMG). Clinical characteristics are presented in Table 2.

MG characteristics

Disease Onset: Juvenile < 18 yrs/EOMG/LOMG < 50 yrs	7/20/6
MGFA classification: IIa/IIb/IIIa/IIIb	12/6/10/5
Serum auto-antibodies: AChR+/MuSK+/ AChR- and MuSK-	28/1/4
Clinical scores	Median, (Q₁ to Q₃)
Disease severity: MMS total score (/100)	87 (81 to 96)
Impact on ADLs: MG-ADL total score (/24)	3 (1 to 4)
MG-specific QOL: MGQOL-15-F total score (/60)	23 (17 to 29)
Clinical measures	Mean (SD)
Functional walking capacity: 6MWD (m)	498 (82)
% of theoretical distance (%)	86 (13)
Knee extension strength (Nm)	108 (31)
% of theoretical knee extension strength (%)	94 (28)
Respiratory function: FVC (L, % predicted)	3 (0.5), 84 (11)
Other auto-immune disease: Hashimoto's disease/Vitiligo	5/1
Co-morbidities other:	
Osteoporosis/Hypertension/DM 2	8/7/3
Overweight (BMI ≥ 25)/Obesity (BMI ≥ 30)	23/7

Table 2: Clinical characteristics for lwMG, mean (SD), median (IQR), or number (n). Early onset MG (EOMG), Late onset MG (LOMG), Myasthenia Gravis Foundation of America (MGFA), muscle nicotinic acetylcholine receptor (AChR), muscle-specific tyrosine kinase (MuSK), Myasthenia Muscle Score (MMS), Activities of Daily Living (ADL), Quality of Life (QoL), Six-minute walking distance (6MWD), Forced Vital Capacity (FVC), Body Mass Index (BMI).

Main results from lower-trunk accelerometry are displayed in Figures 1-3 and Table 3.

	lwMG (n = 33)	Control (n = 113)	P value
Median daily wear-time (Q₁; Q₃), hrs/day	14.2 (13.7; 14.9)	15.9 (15.8; 15.9)	< 0.001
Mean (SD)	14.3 (0.8)	15.9 (0.1)	
Mean % of total (SD)	89.4%	99.1%	
Mean number of days worn [min; max]	5.8 [4; 7]	5.7 [5; 6]	0.199
Median sedentary time (Q₁; Q₃), hrs/day	11.5 (10.5; 12.3)	12.1 (11.4; 12.8)	0.005
Mean (SD)	11.4 (1.2)	12.1 (1.0)	
Median number of steps/day	6162	8192	<0.001
(Q₁; Q₃)	(4724; 7767)	(6690; 10718)	
Mean (SD)	6534 (2761)	8790 (2950)	

Table 3: Accelerometer wear-time data and sedentary behaviour, sedentary time spent in activity < 1.5 METs. Total daily recording time = 16hrs, between 7am and 11pm. SD = standard deviation, Q₁; Q₃ = Interquartile range.

lwMG undertook on average 75mins/day of light PA, 81 mins/day of moderate-intensity PA and 16 mins/day of vigorous-intensity PA (significantly less than control subjects, $p < 0.01$, see Figure 1. Within groups, both populations performed similar amounts of light-intensity and moderate-intensity PA, ($p = 0.145$ MG, $p = 0.230$ controls) however significantly less vigorous PA ($p < 0.001$). lwMG took significantly less steps per day compared to controls 6534 (2761) versus 8790 (2950), respectively; $p < 0.001$).

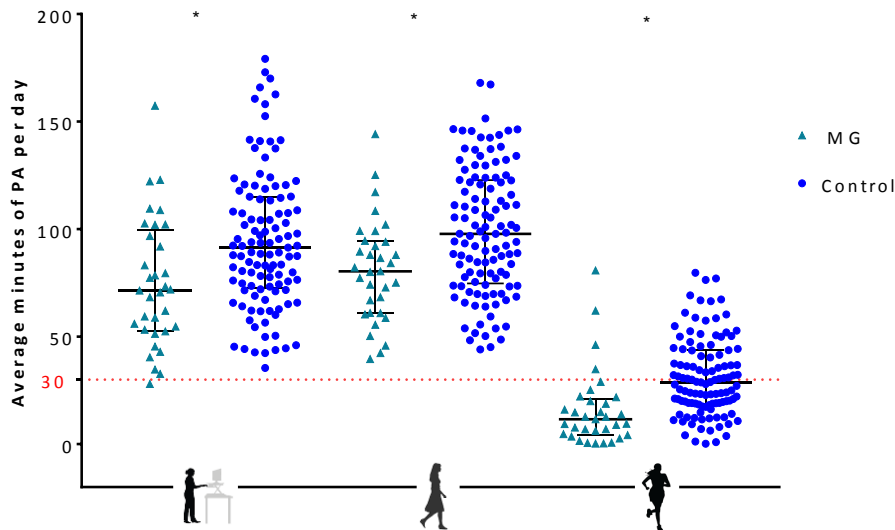





Figure 1: Average minutes per day of light-intensity PA , moderate-intensity PA  and vigorous-intensity PA  for lwMG and control subjects. * $p < 0.01$. Thick wide line = median, upper and lower line = IQR Data for light-intensity PA for two control subjects are not shown: 276 and 202 minutes.

The majority of lwMG did not meet current PA recommendations. As shown in Figure 2, 24% of lwMG compared to 66% of control subjects undertook at least 150 minutes/week of MVPA ≥ 10 mins. lwMG undertook an average of 100 (112) [range 0-400] mins/week and controls, 249 (150) [range 0-678min] mins/week.

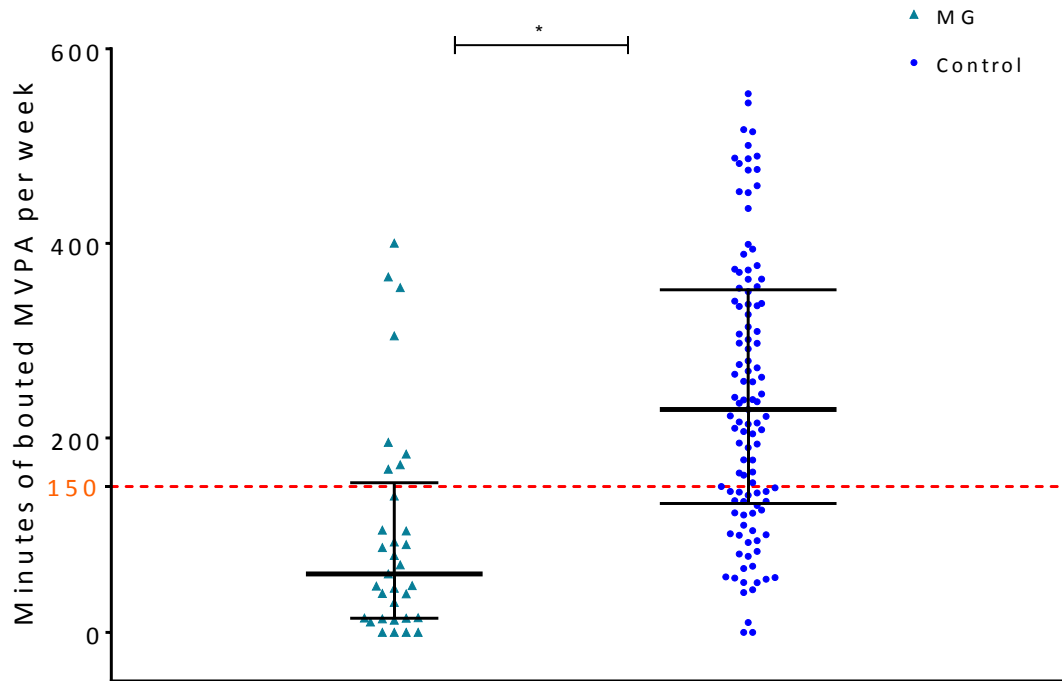


Figure 2: Minutes of $MVPA_{\geq 10 \text{ mins}}$ per week for each population ($p < 0.001$). Thick line = median, upper and lower line = IQR. Two data points are not shown for control subjects (644 and 678 minutes). The dashed line represents the recommendations for minimal amount of $MVPA_{\geq 10 \text{ mins}}$ per week for adults.

As shown in Figure 3, $MVPA_{\geq 10 \text{ mins}}$ in lwMG was on average 15% (median 12, 3 to 25) of total MVPA per day, 97(32) mins/day compared to 32% (median 40, 22 to 61) in control subjects who undertook an average of 130 (35) mins/day of MVPA ($p < 0.001$).

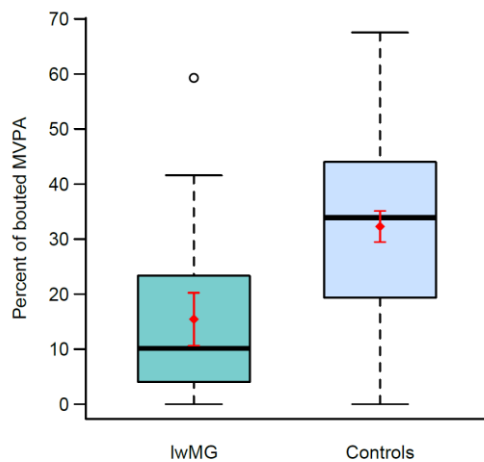


Figure 3: Distribution of the percentage of mean daily time spent in bouts of MVPA over mean daily total MVPA total in MG and control subjects. The box-and-whiskers plots present the median (thick black lines), the first and third quartiles (box). The whiskers represent data points that do not extend from the boxes by more than 1.5 times the interquartile (IQR) range, and outer circles data points that lie beyond 1.5 IQR from the box. The red diamond point and interval give the mean and its 95% confidence interval.

Relationship between habitual PA and clinical variables (Figures 4A-4D):

For lwMG, MG-specific QoL correlated with percentage of predicted knee extension strength ($\rho = -0.405$, $p = 0.021$) but we concluded no relation with habitual PA ($\rho = 0.217$, $p > 0.225$). The 6MWD correlated with vigorous PA, ($\rho = 0.511$, $p = 0.003$) and total volume PA, ($\rho = 0.387$, $p = 0.029$). The 6MWD also correlated with FVC, $r = 0.566$, and, FEV1, $\rho = 0.581$, both, $p < 0.01$, and negatively with BMI ($\rho = -0.509$, $p = 0.003$).

BMI negatively correlated with steps/day ($\rho = -0.355$, $p = 0.042$), vigorous PA ($\rho = -0.490$, $p = 0.004$) and total volume PA ($\rho = -0.407$, $p = 0.019$). BMI also negatively correlated with FVC, ($\rho = -0.384$, $p = 0.028$) and FEV1, ($\rho = -0.354$, $p = 0.043$) and positively with sedentary behaviour ($\rho = 0.354$, $p = 0.043$).

No relationship was found between sedentary behaviour and QoL nor with disease severity or function.

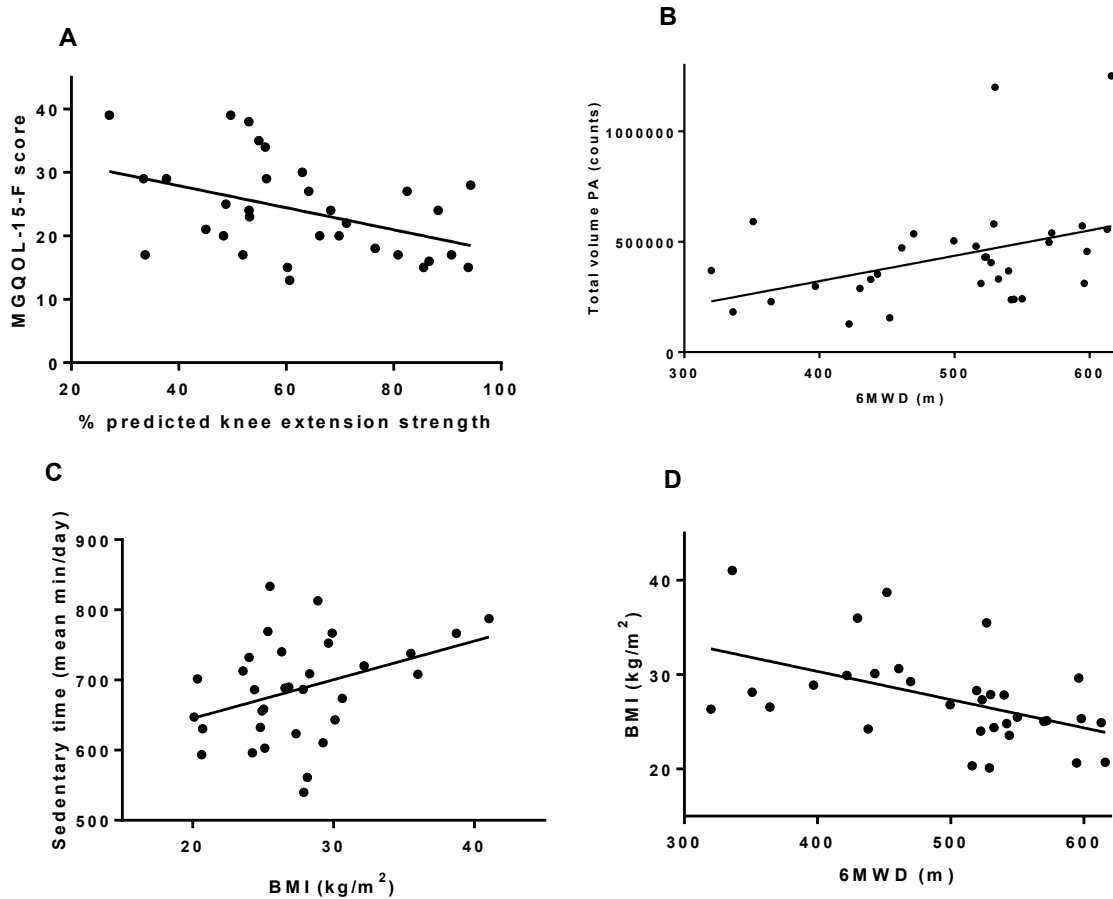


Figure 4: Panel A presents the negative correlation between quality of life (MGQOL-15-F) and knee extension strength (% of predicted strength) in IwMG. Panel B presents the positive correlation between total volume physical activity and six-minute walking distance (6MWD) in IwMG. Panel C presents the positive correlation between sedentary behaviour and Body Mass Index (BMI) in IwMG. Panel D presents the negative correlation between Body Mass Index (BMI) and six-minute walking distance (6MWD) in IwMG.

Discussion:

To the best of our knowledge, this is the first study to present information of habitual PA patterns for individuals with MG measured with trunk accelerometry. Main results are as follows: (i) females with MG perform less PA (light, moderate and vigorous-intensity) than age-matched control subjects, (ii) although most do perform moderate-vigorously intense activities, they tend to fragment this activity more than control subjects (iii) quality of life for lwMG does not seem to be related to daily PA.

Regarding compliance wear-time during waking hours was superior to previous work and included a minimum of 4 valid days to account for possible day-to-day variation due to MG symptoms (27). Both lwMG and control subjects spent the largest amount of waking time, sedentary. For both populations this was longer than that reported in the literature despite similar device wear-time (28) This may be due to different algorithms, different devices, shorter wear-time as well as correction for wear-time in other studies (29, 30).

Almost a quarter of lwMG met current minimum recommendations for weekly aerobic PA (≥ 150 minutes of MVPA $_{\geq 10 \text{ mins}}$) compared to almost two-thirds of control subjects. This is the first time this has been reported. Westerberg et al., reported a median of 30 minutes of strenuous exercise per week which is half at that found in this cohort (4). Self-report often tends to over-estimate activity however maybe in this population the opposite could be true (31). Control subjects, on average undertook 2.4 times more bouts MVPA per day than lwMG. However, when considering unbouted MVPA this factor decreased to 1.4 times the amount for lwMG. Thus, the total volume of MVPA was smaller for lwMG but the difference was less when considering unbouted compared to bouts MVPA (MVPA $_{\geq 10 \text{ mins}}$). Our data do not provide a direct explanation for inferior PA in MG but we can speculate that fatigue may have contributed to promoting shorter bouts. In this study no fatigue-specific measure was used. Our results do not show an association with disease severity and PA. This data is important to consider when designing interventions for this population. Although more intense and longer durations of PA correlate directly with improved health outcomes, small amounts of PA provide protective health benefits and increased longevity (32, 33). In lwMG, shorter and more frequent bouts of MVPA may be more feasible. Especially considering the high sedentary behaviour, even small amounts of activity in exchange for sedentary time

should be encouraged and may be a more realistic goal particularly for the least active individuals.

There was wide variability in activity levels in lwMG. These results did not provide evidence of a determining factor for the difference in PA. It is important consider that even though habitual PA is linked to one's capacity, it is ultimately related to behaviour which is influenced by social, environmental, psychological and genetic factors and can not only be explained by MG-related factors. A clinical measure such as the 6MWT which may be closer to measuring actual functional capacity, was related to cardiorespiratory fitness as well as high volume and intensity of PA and negatively correlated with BMI.

Further research is warranted to explore the role of BMI in this population. The cross-sectional nature of our data does not enable us to determine whether the increased BMI is a cause or consequence of reduced walking capacity, reduced habitual PA and increased sedentary behaviour. Seventy percent of lwMG were overweight and 21% were obese. One explanation could be that increased BMI is related to corticotherapy treatment which could in turn be related to disease severity. However, we did not find any relationship between BMI and disease severity and current corticotherapy doses were fairly low (mean 7mg, n=6 with \geq 10mg, min 0, max 15) however previous corticotherapy-induced weight gain could still be present despite reduced actual doses. BMI was greater in lwMG although it is difficult to attribute this to MG and a possible sedentary lifestyle as differences in height were likely due to the fact that Dutch women are taller than French women (34). Twenty-four percent of lwMG had osteoporosis, again this may be related to corticotherapy treatment or menopause, and regardless of the cause this is another reason to encourage PA in this population.

Surprisingly, habitual PA was not related to QoL. In the general population beyond the physical health benefits previously presented, regular PA also reduces feelings of anxiety and depression, improves sleep and quality of life and increased volume of PA is associated with higher levels of happiness (35). In this cohort actual walking capacity was not related to QoL either. Self-perceived QoL is complex and multi-dimensional and it is difficult to predict influencing factors.

Several minor limitations should be considered. Due to the cross-sectional design of this study only associations can be observed but no causal relationships can be confirmed or refuted.

The MG cohort was heterogeneous, yet the moderate sample size did not allow subgroup analysis of, for example MG subtype.

With regards to PA measurement; accelerometer type and wearing location can influence results thus comparison with other studies should be performed with caution (36). A limit of assessment with accelerometry is differences in wear-time which can present. Wear-time variation can present a random bias if the subject takes off the device regardless of activity and a non-random bias if subjects remove the device before undertaking an activity (37). Non-wear time has been shown to mainly affect sedentary time estimates and due to the large wear-time inclusion criteria in this study we hope to have minimised any possible non-wear-time bias. Water-proof accelerometers are now available which can be worn non-stop which may help to eliminate variation and facilitate analyses in future studies.

Finally, the control population in this study were from Holland which has been shown to be the most active country in Europe, although activity levels in this group were well below what has been described elsewhere (38). Nonetheless, this and culture and environmental differences should be considered when comparing the two populations.

Conclusions

lwMG undertake overall lower levels of PA and shorter durations of cumulated MVPA than the general population as measured using trunk accelerometry. Habitual PA is not related to self-perceived QoL. Clinical measures such as the 6MWT may provide some insight into PA patterns of lwMG and BMI seems to play a central role in PA behaviour and walking capacity. PA monitoring in lwMG may be a useful tool to monitor treatment effectiveness and appropriately target interventions, keeping in mind that shorter duration PA also provides health benefits and may be more feasible and appropriate particularly for those who are largely inactive.

Abbreviations

AChR	muscle nicotinic acetylcholine receptor
BMI	Body mass index
FVC	Forced Vital Capacity
MuSK	Muscle-specific tyrosine kinase
MET	Metabolic equivalent of task
MMS	Myasthenia muscle score
MG-ADL	MG Activities of Daily Living Scale
MGQOL-15-F	French version of the 15-item MG-specific quality of life scale
MVPA	combined moderate-vigorous intensity physical activity
MVPA _{total}	total combined moderate-vigorous intensity physical activity
MVPA _{≥10 mins}	moderate-vigorous intensity physical activity lasting
MGFA	Myasthenia Gravis Foundation of America classification
PA	physical activity
SB	sedentary behaviour
QOL	quality of life
6MWT	6-minute walking test
6MWD	6-minute walking distance

Supplementary data

The detection of not worn periods is established by meeting six different criteria that are based on the vertical (VT), medial lateral (ML) and anterior posterior (AP) accelerations. The first two criterion assume that there is a relatively large amount of activity before and after the not worn period. This large activity represents the removal and refitting of the device. The third criteria is based on frequency analyses. It assumes that power of the present frequencies is almost zero. The fourth criterion is sensitive for the amount of perturbations present in the signal. When the device has been laid flat down on a table, almost no perturbations should be present. The fifth criterion assumes the acceleration signal to be a flat line. The sixth and last criteria concerns the orientation of the device. When the device is rolled more than roughly 60 degrees (relative to the device orientation when it is worn in the anatomical position, Figure 2) around the roll axis, it is assumed that the device is worn. For such orientations of the device it is very unlikely that the device is lying still. A combination of these 6 criteria determines if the device has been worn or not.

Carrying the device in a handbag and carrying the handbag with you when performing physical activity, will create tremendous amount of activity and will therefore not be classified as not worn.

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IV. Fatigue in myasthenia gravis

Fatigue

Fatigue can be described as an unpleasant sensation which can be normal and physiological, inciting one to sleep and rest, allowing for regeneration. On the other end of the continuum fatigue can be considered pathological, when it presents without warning, is unrelieved by usual means and interferes with daily functioning [29]. It is a complex construct, with both psychological and physiological components which can be influenced by behavioural, cognitive, physiological, social and emotional factors [72].

Due to its multiple dimensions which pose difficulties in evaluation and in understanding fatigue, several different models have been proposed. Kluger et al. proposes the terminology “*perceptions of fatigue*” and “*performance fatigability*”, to differentiate between the subjective, patient-reported symptoms of fatigue and the objective changes during or following an activity or movement (Figure 1) [73].

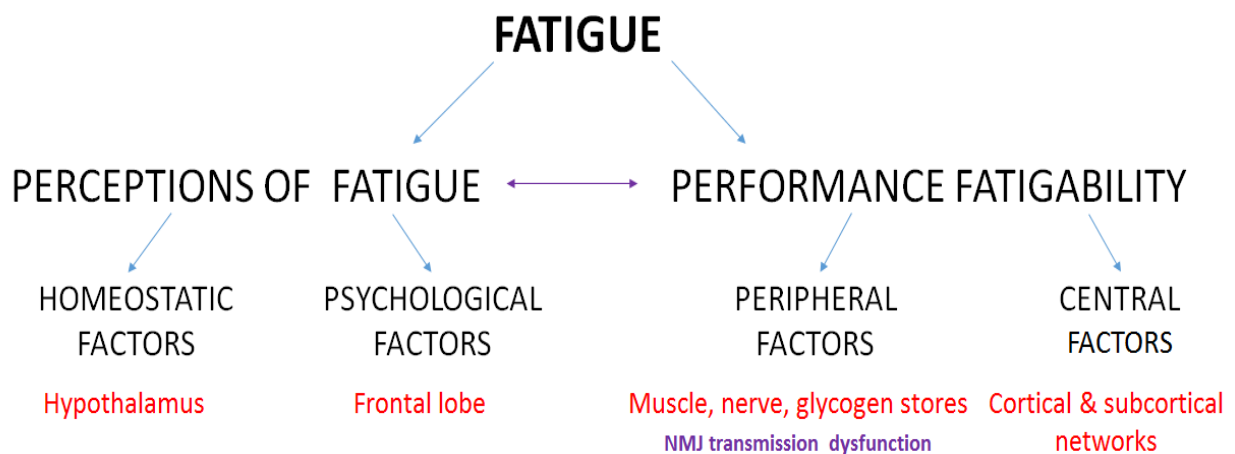


Figure 1 modified from Kluger et al. demonstrating the 2 domains of fatigue, their major contributing factors and in red, the known neuroanatomical sites mediating these factors [73]. In purple NMJ transmission dysfunction which takes place in MG.

The term neuromuscular fatigue which will be employed in this work is described below. It is important to note that perceived fatigue and performance fatigability or neuromuscular fatigue are not only different but they can be independent of one another [73]. In a clinical context for optimal patient management an assessment of both is preferable.

Perceived fatigue in MG

The presence, severity and/or impact of **perceived fatigue** in daily life can be evaluated using different patient-reported questionnaires. Examples used in MG include the Fatigue Severity Scale, the Visual Analogue Fatigue scale, the Modified Fatigue Impact Scale [57], the Myasthenia Gravis Fatigue Scale [65, 74, 75], the Fatigue Questionnaire [76], the Multicomponent Fatigue Index [77] as well as parts of broader scales such as the fatigue component of the Neuro-QOL [33, 78].

Fatigue, as reported by the individual is the most commonly reported symptom in MG and has said to dominate one's life [29]. It has been described as a physical tiredness [77], a lack of energy to complete tasks, exhaustion after usual activity, weakness and as mental and/or cognitive fatigue [65]. In a population of 28 subjects with generalized MG, 82% reported having fatigue [77]. Half reported having cognitive as well as physical fatigue [77]. In a survey of 250 individuals with MG, two thirds reported that fatigue limits participation in activities [29]. Self-reported fatigue is more common in MG than in the general population [79]. It has been shown to be associated with disease severity, anxiety and depression [78, 79]. Fatigue represents a significant problem for individuals and has an important negative impact on daily function and quality of life [80].

Performance fatigability

Performance fatigability concerns objective performance-based measures. Examples of evaluation methods in the literature are abundant. It is not the object of this work to discuss all techniques in depth however it is important to understand the underlying differences in order to interpret the results of and appreciate the gaps in the current evidence.

Neuromuscular fatigue (NMF) has been defined as an exercise-induced reduction in the ability of a muscle or muscle group to generate force or power or the ability to maintain the required or expected force [81-83]. There can be peripheral or central causes (or both) at any level along the pathway from the brain to skeletal muscle (Figure 2). Thus when evaluating NMF this must be kept in mind. Often the cause of NMF is differentiated into central (neural) or peripheral (muscle) however it is important to understand that these systems are mutually dependent [84]. Recruitment of firing motoneurons is dependent on descending drive but is also controlled by excitatory and inhibitory reflex inputs from muscle and cutaneous afferents.

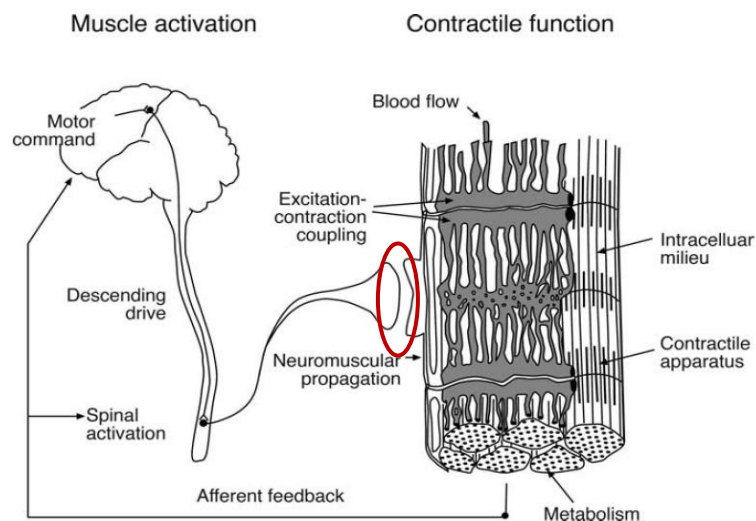


Figure 2 modified from Enoka and Duchateau, 2016, is a schematic representation of the physiological processes (central and peripheral) that can contribute to NMF [85]. The underlying cause of NMF in MG is peripheral, i.e. the NMJ, and in some cases the muscle, yet central psychological factors may also play a role.

Evaluating neuromuscular fatigue (NMF)

The evaluation of NMF is a large research field due to the various techniques and multiple anatomical and physiological processes involved along the pathway. In addition to voluntary effort, different combinations of artificial stimulation i.e. electrical and/or magnetic (peripheral, e.g. femoral or cortical e.g. TMS) can be used to provide insight into central and peripheral contributions to NMF, see Figure 3 [81]. The actual task performed is also of utmost importance, whether the contraction is dynamic or static, sustained or intermittent, the number of repetitions, the intensity or load, recovery time and the position, will all contribute to the specificity of the task.

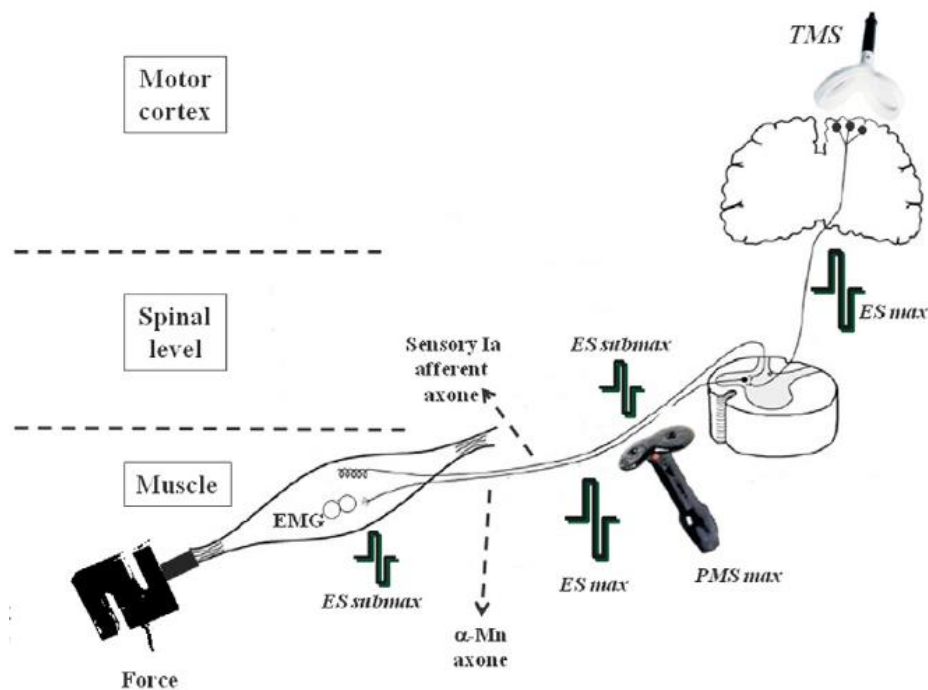


Figure 3 modified from Millet et al. presents the main electrical and magnetic stimulation techniques to investigate NMF. ES: electrical stimulation, TMS: transcranial magnetic stimulation; PMS: peripheral magnetic stimulation [81].

Neuromuscular fatigue in MG

Whilst studies of perceived fatigue in MG are multiple, investigating the prevalence, the consequences and possible contributing factors, the evaluation of NMF is sparse with fewer than five studies. The majority of these involve shoulder abductors, evaluating the decline in force with repetitive, intermittent voluntary isometric contractions, see Table 1 (below) for details.

#	Population	Task	Muscle grp	Results	NMF
1	20 MG AChR+ ND-MG (n=8 54.3yr), D-MG, (n=12 52.8yr) 21 controls, 53.8yr	Biodex, System 3: 3 MVICs – 3s each, 2min rest between. <u>Intermittent MVIC</u> - target highest baseline individual MVIC – <u>12 MVICs</u> – 4s on, 1s off. Recovery phase - single 3-second MVICs at 0.5, 1, 3, 5, 10, and 15 minutes following cessation of the fatiguing phase of contractions.	Shoulder abductors dominant side	All 3 grps force ↓ with time (p < 0.001). Although each grp had different initial MVIC force values, the grps did not fatigue differently. Strength MG < controls, ND-MG > D-MG	x
2	Pre/post design MG pre & post treatment 21 (8F) 65yr (19-80)	Biodex, System 3: <u>Intermittent 13 MVICs</u> , 5s separated by 5s rest intervals, followed by recovery phase consisting of 4 MVICs, each lasting 5s at 0.5, 1, 3, and 5 min following cessation of the fatigue phase.	Shoulder abductors	No difference in decline in strength post treatment, nor recovery phase. No non-MG control group for comparison	Inconclusive
3	90 MG (46F) 58±14.7yr, MGFA I-IV 50 Controls (29F) 59±6.2yr	Biodex, System 3 <u>13 intermittent</u> MVIC 5s duration, 5s rest intervals + restitution phase 4MVIC each 5s at 30s, 1,3,5 mins after “fatigue” phase	Shoulder abductors	MG < strength MG & controls similar decline in strength (19% & 20%, respectively). During restitution, strength increased by 17% in both groups.	x
4	32 stable MG (23F) 55.7±3yr 17 age + gender-matched controls	<u>Sustained</u> @ 80% MVC (holding time measured, s)	Handgrip	Fatigability MG ↔ controls Lower force MG	x

Table 1: Studies evaluating neuromuscular fatigue in MG. # 1. Symonette et al. 2010, Canada [74] 2. Vinge et al. 2016, Denmark [86] 3. Vinge et al. 2019 Denmark [87] 4. Jordan et al. 2016, Germany [75]

Study, F=female, ND-MG = non-decrementing MG, D-MG = decrementing MG MVIC = maximal voluntary isometric contraction, gMG = generalized MG

Three out of four studies have a similar experimental paradigm, evaluating the same muscle group and a similar task (repetitive intermittent MVIC) [74, 86, 87]. The age group was also similar. Study 1 and 3 did not find greater NMF in subjects with MG compared to matched controls [74, 87]. Study 2 evaluated the difference pre and post administration of medication in newly diagnosed MG and whilst NMF was unchanged post treatment, there was no control group to identify whether there was greater NMF in MG compared to control subjects [88]. Lohi et al. demonstrated high variability in repetitive intermittent MVIC in a cohort of MG subjects, thus raising the question as to whether this is the most appropriate task for evaluating NMF in MG [59]. Jordan et al. evaluated a sustained contraction (handgrip) at 80% of maximal force, again subjects with MG did not demonstrate greater NMF [75]. Importantly all studies demonstrated that MG subjects had reduced strength compared to control subjects and the specific “fatiguing task” in all studies was based on the individual’s MVC [74, 75, 86, 87]. All MVC’s were performed with no control or evaluation of central factors.

Performance fatigability in MG

Performance fatigability was evaluated by Jordan et al. by assessing the decline in performance of two tasks (6MWT and Arm movement Test) over time [75].

Population	Task	Results	PF
32 stable MG (23F) 55.7±3yr 17 age + gender- matched controls (C)	6MWT	Linear trend MG: -0.62±1.43 vs C: 0.24±0.73 (p < 0.005)	√
	Arm movement Test (AMT)	MG: -0.14±0.56 vs C: 0.32±0.38 (p < 0.005)	√

The authors concluded that there was increased fatigability in MG subjects (negative linear trend) compared to control subjects (positive linear trend). This performance fatigability was only weakly correlated with perceived fatigue for the AMT (r = -0.41) [75].

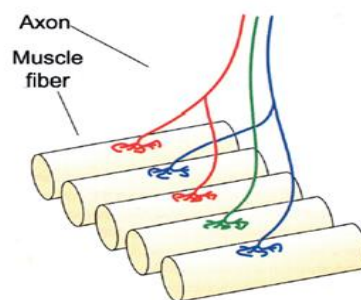
As mentioned earlier the notion of fatigue in MG comes from the perceived fatigue experienced by individuals and also from the electrophysiological response. Electrophysiological evaluation of individuals with MG shows a decrement of the compound muscle action potential on repetitive stimulation at low frequency. A higher decrement is usually associated with more affected muscles, clinically. This is due to the reduced safety margin at the NMJ in individuals with MG. However, this test provides no specific information on change in muscle strength or fatigability beyond the NMJ.

The methods used in previous studies did not result in evidence of increased NMF in individuals with MG [74, 75, 86, 87]. Surface electromyography (sEMG) has been extensively used to evaluate peripheral muscle fatigue; however to the best of our knowledge it has not been used as an investigative tool in MG [89]. The analysis of the EMG signal using indexes of fatigue in the time and spectral domains can provide a quantitative approach to measuring muscle fatigue during a sustained or repeated contraction [90].

Measuring neuromuscular fatigue in MG with surface electromyography

In **Paper III** neuromuscular fatigue was evaluated using surface electromyography and the post-exertion decline in maximal isometric strength in two limb muscle groups. Subjects with MG did not demonstrate greater NMF than gender and age-matched controls.

The figure below is an image modified from Slater, 2008 showing axon terminal branching innervating muscle fibres [7]. It serves as a reminder of the branching of terminal motor axons onto different muscle fibres. In MG muscle function will depend on the extent of the damage to respective NMJs.



Paper III, under review in *Muscle and Nerve*,

Birnbaum S, Sharshar T, Ropers J, Portero P, Hogrel JY: **Evaluation of neuromuscular fatigue in auto-immune myasthenia gravis using surface electromyography.**

Evaluation of neuromuscular fatigue in myasthenia gravis using surface electromyography

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Competing interests

None of the authors has any conflict of interest to disclose.

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Ethical publication statement

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Abstract: 127 words

Manuscript: 3991 words

Evaluation of neuromuscular fatigue in auto-immune myasthenia gravis using surface electromyography

Abstract

Introduction

Research findings of neuromuscular fatigue (NMF) in adults with MG are inconclusive.

Methods

In this cross-sectional study, we assessed maximal voluntary strength using fixed dynamometry and NMF fatigue 1) using surface EMG of the vastus lateralis and biceps brachii muscles during a sustained (40s), submaximal (50%MVC), isometric contraction and 2) the loss of maximal force following the sustained contraction. Relationships with MG-specific clinical scores were evaluated.

Results

Individuals with MG (n=41, mean age 41 years) displayed reduced limb strength ($p < 0.01$) without greater NMF than age-matched controls (n=18). Reduced QoL (MGQOL-15-F) was correlated with lower knee strength and higher post-effort fatigue but not with sEMG recorded fatigue.

Discussion

We suggest that strength deficits may contribute to the sensation of fatigue perceived by individuals with MG.

Keywords

Auto-immune myasthenia gravis, fatigue, surface electromyography, evaluation, quality of life

1. INTRODUCTION

With an incidence of 0.3-3 per 100,000 people worldwide, auto-immune myasthenia gravis (MG) is the most common disorder of the neuromuscular junction (NMJ) [1, 2]. The cardinal symptoms of MG are fluctuating fatigable weakness of ocular, bulbar, respiratory, axial and limb skeletal muscles. Fatigable weakness can be separated into fixed weakness which is a default in strength production during a maximal effort and, fatigue, which is defined as any exercise-induced reduction in the ability of a muscle to generate force [3, 4].

Neuromuscular fatigue (NMF), as defined above, should be distinguished from perceived fatigue which is the sensation of fatigue perceived by an individual [5, 6]. NMF and perceived fatigue have both been described in MG and they can, but do not have to be, present simultaneously [7, 8]. In this paper NMF will be referred to as fatigue.

Fatigue can be caused by impairment of any one or more of the multiple physiological processes leading to muscle contraction. It is often referred to as peripheral or central fatigue depending on its origin [4, 9]. The underlying cause of fatigue in MG is considered to be peripheral, i.e. outside the central nervous system, more specifically at the level of the NMJ. Specific auto-antibodies provoke complement-mediated lysis of the post-synaptic membrane [10], reducing the concentration of acetylcholine receptors (AChR) and voltage-gated sodium channels available for transmission between the nerve terminal and the muscle membrane [11]. It has also been suggested that the auto-immune process in MG affects satellite muscle cells and muscle regeneration with possible consequences on myogenic signaling pathways, at least in individuals with AChR auto-antibodies [12].

To the best of our knowledge, except for two studies in which grip strength was not significantly less than control subjects [7, 13], all of the recent literature has demonstrated reduced strength in individuals with MG [8, 14-17]. With respect to fatigue in MG, the literature presents conflicting results likely due to the different methods of evaluation. For example, intermittent isometric contractions of the shoulder abductors in 20 individuals with AChR positive MG did not induce greater fatigue compared to healthy controls. There was, however, reduced strength in SwMG [8]. Similarly, Cevjanovic et al. did not demonstrate greater fatigue with repeated isometric testing in a cohort of adult subjects with MG (SwMG), however strength was, on average, 28% less than controls [15]. Furthermore, in a cohort

(n=107) of subjects with generalized MG (gMG), Citirak et al. concluded an absence of fatigue due to no reduction in strength with repeated isometric contractions. Reduced maximal strength was present, however, particularly in shoulder abductors, hip flexors and knee extensors [14]. Finally, endurance measured via a sustained handgrip contraction (80% of maximal voluntary contraction) failed to demonstrate fatigue or reduced strength in 32 adults with stable, gMG. In fact MG had a longer holding time than controls [7].

On the contrary, in the same study Jordan et al. demonstrated greater fatigue with a negative linear trend on the six-minute walk and arm movement test in SwMG compared to healthy controls who maintained a stable performance [7]. Vinge et al. demonstrated the presence of fatigue with a reduction of shoulder abduction strength with repetitive intermittent contractions in untreated MG and a similar reduction in the same cohort post-treatment [18]. However, there were no control subjects in this study for comparison. Finally, a pilot study by Hoffman et al. (2015) showed evidence of subclinical fatigue during handgrip evaluation even though strength was not different in SwMG compared to healthy controls [13].

It seems that further evaluation is necessary to understand fatigue in MG. Past studies have shown evidence of fatigue originating from the muscle itself, i.e. beyond the NMJ, suggesting impairment of excitation-contraction coupling and contractility [19-21]. With direct intercostal muscle stimulation (bypassing the NMJ) muscle tension decreased greater and more quickly in MG than control subjects [19]. It is possible that individuals with MG suffer from both primary and secondary fatigue. Primary fatigue refers to fatigue resulting directly from the disease process and secondary fatigue is due to disease-related consequences such as reduced activity, deconditioning and/or side effects of medication [5, 22]. As with perceived fatigue, due to the non-specificity or overlap of symptoms it can be difficult to differentiate between primary and secondary fatigue.

Whilst various methods exist to evaluate fatigue, surface electromyography (sEMG) has the advantages of being non-invasive and particularly useful as it provides information of changes in the muscle prior to task failure [23]. The sEMG signals represent the electrical activity generated in muscles in response to their activation by motor neurons [24]. This information could provide additional insight which previous studies were lacking and may help understand the sensation of difficulty felt by individuals with MG *whilst* performing a task before being obliged to cease the activity.

The aim of this study was to investigate the presence of accentuated limb fatigue in individuals with generalized MG compared to healthy controls. A secondary aim was to assess possible relationships between fatigue and strength, perceived quality of life, function and disease severity, in SwMG.

2.0 METHODS

2.1 Design

Observational cross-sectional study.

2.2 Subjects

Data from baseline evaluations of female subjects included in a prospective clinical trial [25] were analysed. Briefly, to be included in the MGEX study subjects had to be between 18-70 years old, with a confirmed diagnosis of mild or moderate, generalised auto-immune MG (MGFA II or III) [26], stabilized for at least 6 months. The MG diagnosis was made by an expert neurologist, based on clinical signs and symptoms of fluctuating, fatigable muscle weakness, presence of specific MG auto-antibodies against acetylcholine receptor (AChR) or muscle-specific tyrosine kinase (MuSK) and/or EMG evidence of neuromuscular transmission defect as a decrement of > 10% in the amplitude of the compound muscle action potential on low rate repetitive nerve stimulation or jitter on single-fibre EMG and/or positive response to acetylcholinesterase inhibitors (AChEi). Subjects with cardiac or respiratory failure, other neuromuscular pathology, rheumatological or orthopaedic conditions in which exercise was contra-indicated were ineligible. Female subjects only were considered for this study as there were only 3 male subjects included in the MGEX trial and physiological differences in strength and fatigue between genders would complicate analyses and interpretations [27]. Control data was collected from females of similar age without known neuromuscular disorder. For the present study we did not perform a separate sample size calculation.

The MGEX study was approved by an ethics committee in accordance with French regulations (Comité de Protection des Personnes Île-de-France XI: CPP number #13064, 13/12/2013) and authorised by the Agence National de Sécurité du Médicament et des produits de santé on 11/10/2013. The study was conducted in accordance with the Helsinki Declaration [28]. Consent was obtained from all participants before study participation.

2.3.1 MG-specific evaluations

Information regarding clinical history (disease onset, thymectomy), disease severity (MGFA classification), presence or absence of MG-specific auto-antibodies and current medications were recorded by an expert neurologist who also administered the Myasthenia Muscle score (MMS) and the Myasthenia Gravis–Activities of Daily Living (MG-ADL) scale to all participants. The MMS is a clinical score routinely performed by neurologists in France to assess function and fatigue at a moment in time [29]. It evaluates limb, axial, and bulbar symptoms, and the maximum score (thus, no detectable deficit) is 100. The MG-ADL scale, which is also used routinely in clinical practice, consists of 8 items and measures the impact of MG on activities of daily living [30]. The minimum score representing no impact on ADLs is zero. Participants also completed the MGQOL-15-F, a 15-item self-administered MG-specific questionnaire that evaluates self-perceived health related quality of life (QoL) of an individual with MG over the preceding few weeks. It has been shown to be valid and reliable [31]. Higher scores (with a maximum score of 60) represent a lower perceived QoL.

2.3.2 Strength and fatigue measurements

All evaluations took place in the Neuromuscular Physiology and Evaluation Laboratory, Institute of Myology, Pitié Salpêtrière, Paris, France. To motivate subjects to perform their maximal effort strong verbal encouragement was provided by the evaluator for all evaluations. Height and weight were measured prior to evaluations and age noted for use in predictive models.

Voluntary elbow flexion and knee extension strength testing were performed using a Biodex System 3 Pro dynamometer (Biodex Medical Systems, Shirley, NY, USA). Measurements were performed on the right side only; the axis of the dynamometer was aligned with the axis of rotation of the joint. Bilateral shoulder straps and a pelvis strap were used to stabilize the thorax and pelvis to avoid compensations and/or movement throughout the evaluation. For elbow flexion subjects were seated in the adjustable Biodex chair with the shoulder in 90° flexion and 15° horizontal abduction. The upper arm was placed on a support, the elbow flexed to 90° and the forearm in full supination, with the strap placed at the wrist, leaving the hand free. Knee extension was evaluated with the participant seated in the Biodex chair with the

hips and knees flexed to 90°. An additional strap was placed over the right thigh to stabilize it. Both positions were designed to avoid the influence of gravity on the contraction.

A graphic representation of the evaluation protocol is presented in supplementary material S1. Testing involved three isometric contractions at maximal voluntary strength ($MVIC_{pre}$) with a 1-minute rest between each $MVIC_{pre}$ trial. The highest value from the three trials for each muscle group was used in data analysis. Torque in Newton meters (Nm) was expressed as a percentage of theoretical strength using predictive models [32].

As shown in S1, following the third $MVIC_{pre}$ there was a 5-minute rest period where the subject remained in the same position. This was followed by a sustained 40 second isometric contraction at 50% of the highest individual $MVIC_{pre}$. Visual feedback was provided via a computer screen to maintain the target level of strength for the duration of the contraction. A last MVIC was performed immediately after this sustained contraction, called the $MVIC_{post}$. Post-effort fatigue was the decline in peak torque calculated using the equation $100 * [(MVIC_{post} - MVIC_{pre})/MVIC_{pre}]$ for elbow flexion and knee extension.

Myoelectrical indicators of fatigue were evaluated using surface electromyography (sEMG). Standards for reporting sEMG data were followed [33]. A plastic rectangular bar with four aligned miniature, circular silver-silver chloride surface electrodes of 4mm in diameter, 11mm inter-electrode distance, was used. Where necessary, hair was gently removed with a shaver and the skin was abraded and cleaned with an alcohol/acetone solution to minimize resistance. Inter-electrode impedance was kept below 100k Ω [34]. Electrolytic gel was placed on the electrodes which were then positioned on the right Biceps Brachii (BB) for elbow flexion and on the right Vastus Lateralis (VL) for knee extension, parallel to the estimated direction of muscle fibres according to the SENIAM recommendations [35]. Electrodes were fixed to the skin using adhesive tape and connected to an isolated amplifier (bandwidth 10-1000Hz) and the gain was individually adjusted to a suitable level. A neutral reference electrode was placed on the ulnar styloid for the BB and the fibular head or patella for the VL. Surface EMG recordings were performed at a sampling rate of 10 kHz. A data acquisition processor (DAQ board) recorded the analog signals which were converted digitally after the evaluation and analysed using a window epoch overlap of 50%, window size 0.5s after filtering (bandpass between 6 and 350Hz and 50 Hz rejection).

Surface EMG recordings were processed using the root mean square (RMS) as an estimate of the signal amplitude and the mean power frequency (MPF) as an estimate of the mean value of the power spectral distribution of the signal. This was calculated using the Fast Fourier Transform algorithm. Increased RMS and decreased MPF representing a shift to the lower frequencies is used as an indicator of localized muscle fatigue [36, 37]. Change in RMS and MPF over time were calculated from the initial 2 seconds (i) and final 2 seconds (f) of the sustained contraction (see Figure S2) using the following equations: $100 * [(RMS_f - RMS_i) / RMS_i]$ and $100 * [(MPF_f - MPF_i) / MPF_i]$. If the contraction was not maintained (task failure), values were taken from the final 2s of the stable contraction.

The time of pyridostigmine intake and evaluations were noted to consider possible effects of anticholinesterase inhibitors on strength output and fatigue.

2.4 Statistical analysis

Demographic and clinical characteristics of subjects were described by group with mean and standard deviation. Mann-Whitney tests were used to study between-group differences. To compare data from the same population a paired Wilcoxon signed-rank test was used. Relationships between strength and fatigue and quality of life, function and disease severity were explored graphically using scatterplots and estimated using Spearman correlations [38]. A $p < 0.05$ was considered significant for all analyses. Data analysis and graphs were performed using Graphpad Prism 7.

3.0 RESULTS:

3.1 Subjects

Forty-one females with generalized, auto-immune myasthenia gravis (SwMG) were included and compared to 18 age and gender-matched control subjects. Subject characteristics are presented in Table 1. SwMG had a significantly higher weight and body mass index (BMI) than control subjects.

	SwMG	Control subjects	p value
Female (n)	41	18	N/A
Age, years	44.3 ± 10.5	46.7 ± 9.7	p = 0.340
Weight, kg	76.2 ± 16.5	65.7 ± 13.4	p = 0.018
Height, cm	164.1 ± 5.7	163.2 ± 6.9	p = 0.645
BMI, kg/m²	28.2 ± 5.3	24.8 ± 5.5	p = 0.013

Table 1: Subject characteristics, BMI = body mass index. Results are expressed as mean ± standard deviation (SD).

3.2 Clinical characteristics of subjects with MG

Clinical characteristics of SwMG are presented in Table 2. Fifty-six percent had mild (MGFA II) and 44% moderately-severe MG (MGFA III), with the limb/axial muscles being predominantly affected (MGFA a) in both the mild and moderately-severe categories. Average disease duration was 15 years. Daily function was mildly affected (average MG-ADL score was 2.6/24) as was motor function as subjects scored 86/100 on average on the clinical Myasthenia Muscle Score (MMS). Quality of life was reduced with a mean score of 25/60 on the MGQOL-15-F. Eighty-five percent took acetylcholinesterase inhibitors (AChEi), the mean time interval between pyridostigmine intake and strength and fatigue evaluations was 220 ± 90 minutes for elbow flexion and 257 ± 93 minutes for knee extension.

Clinical characteristics	SwMG (n = 41)
MGFA classification : (n)	
Ila/IIb	17/6
IIIa/IIIb	12/6
MG disease duration (years)	14.6 ± 11.2 [1, 44]
Disease onset: n, (%)	
Juvenile (< 18yo)/Early onset/Late onset (> 50yo)	8 (20)/28 (68)/5 (12)
MG-specific auto-antibodies: n, (%)	
AChR/MuSK/neither AChR nor MuSK	35 (85)/2 (5)/4 (10)
MG-ADL score [0-24] (mean ± SD) [min, max]	2.6 ± 1.7 [0, 7]
MMS [0-100] (mean ± SD) [min, max]	86.1 ± 12.3 [54, 100]
MGQOL-15-F [0-60] (mean ± SD) [min, max]	25.2 ± 7.7 [13, 39]
Current MG medications: n, (%)	
Acetylcholinesterase inhibitors (AChEI)	35 (85)
Prednisone	17 (41)
- Dose (mg) mean, [min, max]	7.6 ± 3.3 [2, 13]
Immunosuppressors:	
- Azathioprine/Mycophenolate mofetil/Cyclosporine	21/6/2
Rituximab/Plasma Exchange	1/1
Thymectomy, n (%)	28 (67)

Table 2: Clinical characteristics for SwMG. Results are expressed as mean ± standard deviation (SD), [minimum, maximum] and number and percentage % as appropriate. MGFA = Myasthenia Gravis Foundation of America Classification (II = mildly severe, III = moderately severe, a = limb predominance, b = bulbar predominance). Acetylcholinesterase inhibitors = pyridostigmine bromide or ambenonium chloride

3.3 Strength and fatigue

Elbow flexion and knee extension strength expressed in % of predicted values for age, gender and weight were significantly lower in SwMG compared to controls (Table 3). There were no significant correlations between strength and fatigue, disease severity, nor with daily function (not shown).

Strength	SwMG (n = 41)	Control (n = 18)	p value
Elbow flexion	79.4% ± 18.2	97.3% ± 22.1	p = 0.005
Knee extension	93.8% ± 25.7	124.1% ± 27.2	p < 0.001

Table 3: Percentage of predicted strength values for right-sided elbow flexion and knee extension. Results are expressed as mean ± standard deviation.

Post-effort fatigue was present in both muscle groups in both populations (Figures 1A and 1B) with no significant difference in the mean relative difference between the two populations in either muscle group (Table 4). For SwMG post-effort fatigue (elbow and knee) were correlated with each other ($r = 0.486$, $p = 0.003$). Myoelectrical indicators of fatigue represented by the increase in RMS (Figures 2A and 2B) and the decrease in MPF during the sustained submaximal contraction (Figures 3A and 3B) were present in both populations without a between-group difference (Table 5). Electromyography changes for VL correlated with post-effort knee extension fatigue in SwMG ($r = -0.383$, $p = 0.023$, for RMS change and; $r = 0.538$, $p = 0.001$ for MPF change). RMS change in VL weakly correlated with item 6 of the MG-ADL - difficulty standing up from a chair $r = -0.351$, $p = 0.026$. There were no significant correlations between fatigue and disease severity (MMS).

Post-effort fatigue	SwMG (n = 35)	Controls (n = 12)	p value
Elbow flexion	- 12.5% ± 11.5	- 11.4% ± 3.4	p = 0.819
Knee extension	- 21.6% ± 13.4	- 16.0% ± 8.1	p = 0.186

Table 4: *Post-effort fatigue* for elbow flexion and knee extension. Results are expressed as mean ± standard deviation (SD)

Myoelectrical indicators of fatigue	SwMG (n=41)	Control (n=18)	p value
RMS change:			
Biceps Brachii	36.4% ± 36.0	60.9% ± 43.0	p = 0.058
Vastus Lateralis	38.4% ± 30.1	42.3% ± 33.1	p = 0.924
MPF change:			
Biceps Brachii	-9.7% ± 5.9	-13.3% ± 6.6	p = 0.066
Vastus Lateralis	-13.5% ± 7.6	-14.5% ± 8.9	p = 0.822

Table 5: Difference between mean RMS and mean MPF change for each muscle between SwMG and control subjects. RMS = root mean square, MPF = mean power frequency. Results are expressed as mean ± standard deviation. CON = control

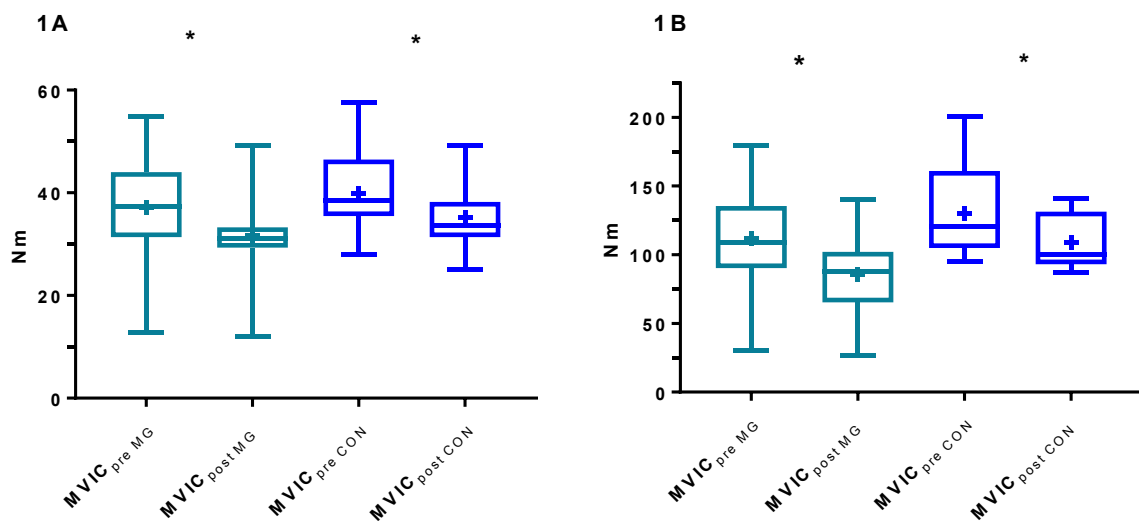


Figure 1: A: MVIC_{pre} and MVIC_{post} showing *post-effort fatigue* for elbow flexion (*SwMG: p = 0.0005, Control: p < 0.001). + = mean. CON = control. **B:** MVIC_{pre} and MVIC_{post} showing *post-effort fatigue* for knee extension (*SwMG: p = 0.0005, Control: p < 0.001). + = mean. CON = control

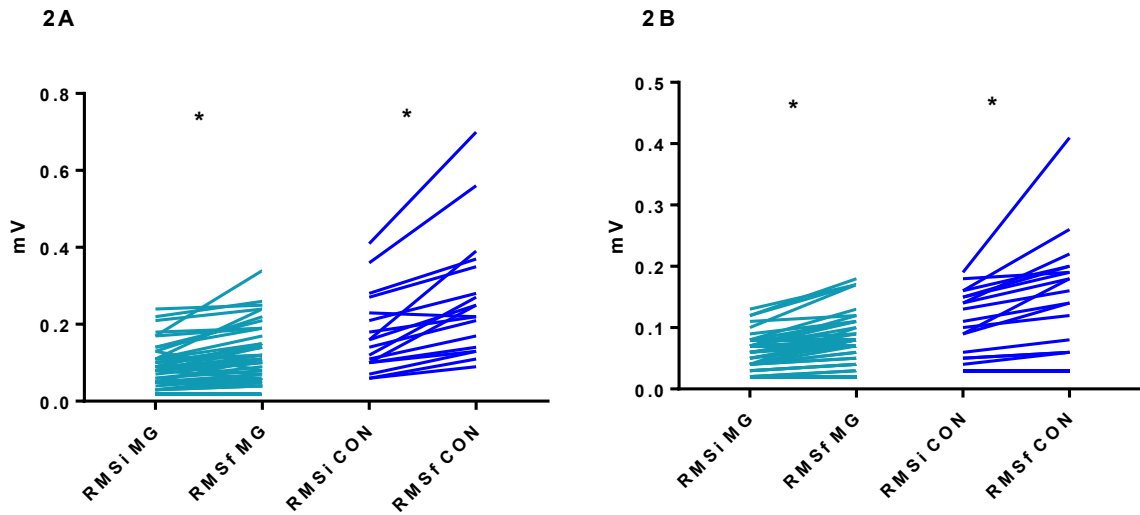


Figure 2: A: RMS change between the beginning (RMSi) and end (RMSf) of the fatigue task for the biceps brachii (* $p < 0.001$). RMS = root mean square. CON = control. **B:** RMS change between the beginning (RMSi) and end (RMSf) of the fatigue task for the vastus lateralis (* $p < 0.001$). RMS = root mean square. CON = control

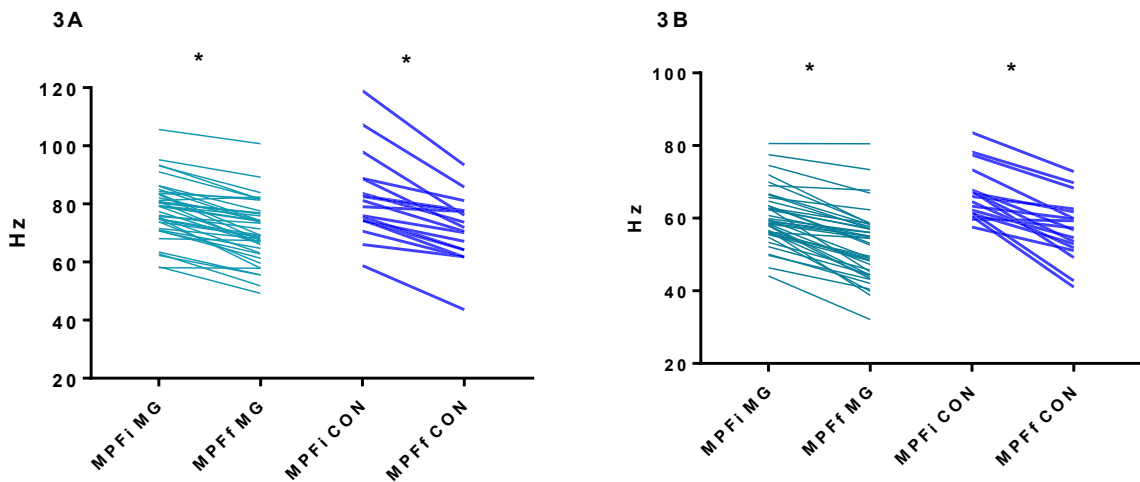


Figure 3: A: MPF change between the beginning (MPFi) and end (MPFf) of the fatigue task for the biceps brachii (* $p < 0.001$). MPF = mean power frequency. CON = control. **B:** MPF change between the beginning (MPFi) and end (MPFf) of the fatigue task for the vastus lateralis (* $p < 0.001$). MPF = mean power frequency. CON = control

3.4 Quality of life

Weak but significant negative correlations were present between quality of life (MGQOL-15-F) and knee extension strength (% predicted, $r = -0.360$, $p = 0.021$). Quality of life correlated with post-effort fatigue for both knee extension ($r = 0.357$, $p = 0.035$,) and elbow flexion ($r = 0.482$, $p=0.003$,). No significant correlations were found between QoL and disease severity nor with elbow strength or myoelectrical indicators of fatigue of the BB or VL.

4. DISCUSSION

This study investigated strength output and fatigue in two limb muscle groups in women with MG compared to control subjects. Quality of life (MGQOL-15), function (MG-ADL) and disease severity (MMS) were also evaluated in SwMG.

The main findings in this study are that SwMG produce less maximal voluntary strength than control subjects in isometric elbow flexion and knee extension. Fatigue, as defined by a post-effort decline in maximal voluntary strength was present in SwMG to the same degree as in control subjects for both elbow flexion and knee extension. Myoelectrical indicators of muscle fatigue of the BB and VL were not present to a greater extent in SwMG compared to control subjects.

The reduced strength found in SwMG is in agreement with previous findings in the literature [8, 14, 15]. A reduction in knee extension strength has previously been reported in SwMG [15, 39]. Other authors have reported weakness predominating in proximal muscles such as shoulder abductors and hip flexors [8, 14]. Selective triceps brachial weakness has also been reported in the literature as has distal weakness [16, 40, 41]. The cause of this “fixed weakness” in auto-immune MG remains poorly understood [14]. It may be due to damaged junctional folds of the NMJ which create less surface area for AChRs and sodium channels resulting in less depolarization and muscle action potentials. This will affect strength as well as endurance [14].

Earlier studies suggested a possible extra junctional defect. Botelho observed changes in muscle tension without changes in compound muscle action potentials, suggesting a defect in muscle contractility [20, 42]. Pagala et al. found greater decreased muscle-evoked tension, with shorter duration of stimulation despite the same fiber composition in SwMG and control

subjects [19]. Even though dysfunction at the NMJ is considered to be the main underlying cause, potential defect in excitation-contraction coupling and contractility may play a role in enhancing fatigue and/or weakness in MG [19, 43]. Muscle biopsy studies of SwMG reveal a smaller number of fibres, with a smaller diameter [43-46], both of which will contribute to reduced strength generation.

Preferential atrophy of type 2 fibres has been reported in MG which could explain a greater difficulty to produce strength yet preserved function in endurance tasks if type 1 fibres are unchanged [44-46]. A recent study has proposed the hypothesis of fewer myofibres potentially due to a delay of maturation during the regeneration process [12]. Whilst further studies are required to confirm this hypothesis this could potentially alter the strength generating capacities of myasthenic muscles. Finally, reported neurogenic changes could be related to pharmaceutical treatment [47-49].

Abnormal and exaggerated fatigue is a clinical hallmark of MG. However, our findings did not illustrate increased muscle fatigue compared to control subjects. Whilst surprising this can be explained by several factors. The cohort in this study had mild or moderately-severe MG, with disease stability for at least 6 months prior to inclusion. Whilst all were still symptomatic, stability of the disease process may have meant less transmission inefficiency at the NMJ thus making fatigue more difficult to detect. Secondly, whilst not all subjects took ACEi and for those that did, most evaluations took place towards the end or beyond the estimated four-hour duration of effect of the molecule, the artificial prolonged presence of supplemental acetylcholine at the NMJ may have increased transmission efficiency and masked possible fatigue which may have been detectable without the medication. Future studies will hopefully provide further information concerning the specific effects of ACEi on muscles in MG (ClinicalTrials.gov Identifier: NCT03510546). Thirdly, the sEMG findings were recorded during a submaximal contraction where only a fraction of the total motor neuron pool is recruited [9]. This is important as it is unlikely that all motor neurons of a muscle are affected in stabilized MG. Thus, it may be possible that the motor neurons recruited during the fatigue task had intact or unaffected NMJs and thus the muscles did not show elevated signs of fatigue. These hypotheses remain to be confirmed.

Finally, it is important to note that the fact that accentuated fatigue was not found in this study does not rule out its presence in SwMG. Maximal voluntary strength is implied however

without performing a twitch interpolation it is impossible to know whether subjects were at their true maximum, i.e. whether the cortical drive was capable of exciting the entire motoneuron pool [50]. One hundred percent activation is not always achieved with voluntary activation in healthy controls [51] and other reasons related to MG could exist such as central activation failure [52] from fear or “muscle wisdom” whereby afferent input limits maximal strength being produced with the aim of protecting the muscle structure [53]. Thus the sustained submaximal 50%MVC contraction may have been overestimated. Also, during a sustained contraction central factors regulate motor drive to match altered contractile properties and strong encouragement may not be enough to remove central inhibitions [3].

Whilst not specific for SwMG, it should be noted that other muscle synergists may have contributed to maintaining the contraction and as a result less fatigue and changes in myoelectrical parameters of the BB or VL muscle would be recorded. The lack of EMG monitoring of the relative contribution of synergists does not allow us to verify this hypothesis. In healthy individuals with neuromuscular fatigue the central nervous system finds strategies to share the load between muscles to complete a desired task [54].

We did not find any relationship between strength and fatigue. Whilst this was unexpected it has previously been suggested that they are distinct features of motor dysfunction [55]. The idea that perceived fatigue is related to weakness as has been suggested could still hold true as functionally weakness may induce a sensation of fatigue [56].

As expected, reduced QOL (total score MGQOL-15-F and more specifically Item 12 and 13, related to walking and mobilizing) was associated with reduced knee extension strength. Post-effort fatigue for both limbs correlated with reduced QOL. Fatigue has previously been associated with reduced QOL however most studies have evaluated perceived fatigue and not NMF [57]. Whilst we may like to assume that perceived fatigue is related to neuromuscular fatigue, the specific relationship remains unclear and may differ between individuals [8, 58].

No relationship was found between QOL and disease severity however the MMS suffered a ceiling effect in some subjects. A more sensitive outcome measure may provide different results. QOL did not correlate with sEMG measurements. However as abnormal fatigue was not detected in this cohort this finding should be interpreted with caution.

4.1 Limitations of this study

As discussed previously, evaluations were all voluntary thus it is impossible to differentiate the role of central fatigue or central deactivation. It is possible that subjects recruited below their actual “maximal” strength which may have made the fatigue task more “achievable”. This phenomenon could be present in control subjects too however SwMG may be more prone to central activation failure [52] or muscle wisdom phenomena [53] than control subjects. Further studies should include direct measures of central activation.

Fatigue is task-dependent, it can be argued that sustained isometric contractions of phasic muscles are not very common in daily life. Repeated intermittent contractions may have preferentially demonstrated the fatigue that SwMG feel. However, isometric contractions provide a more optimal sEMG recording environment and previous research failed to demonstrate fatigue in intermittent contractions in SwMG [8, 14, 15].

Finally, due to the cross-sectional nature of this study it is impossible to confirm that differences between populations are solely due to MG. And, even though different MG phenotypes were included, results cannot be generalised to the entire MG population. This cohort had mild or moderately-severe, gMG, with an altered QoL due to their MG. In including a large panel of SwMG there is also the inconvenience of mixing together different phenotypes which may have different fatigue/strength mechanisms. Sample sizes were too small for subgroup comparisons.

5.0 CONCLUSION

In conclusion, our study confirms the recent literature showing the presence of fixed limb weakness in SwMG, poorly related to disease severity and function as measured with disease-specific scales. On objective assessment greater limb fatigue was not present in this cohort of SwMG when compared to control subjects. Reduced quality of life was associated with reduced knee extension strength and post-effort fatigue but not sEMG recorded fatigue. Further studies are required to identify simple and reliable methods to measure fatigue in MG. Interventions aimed at increasing strength may contribute to improving quality of life in individuals with MG, regardless of disease severity.

Supplementary Figures

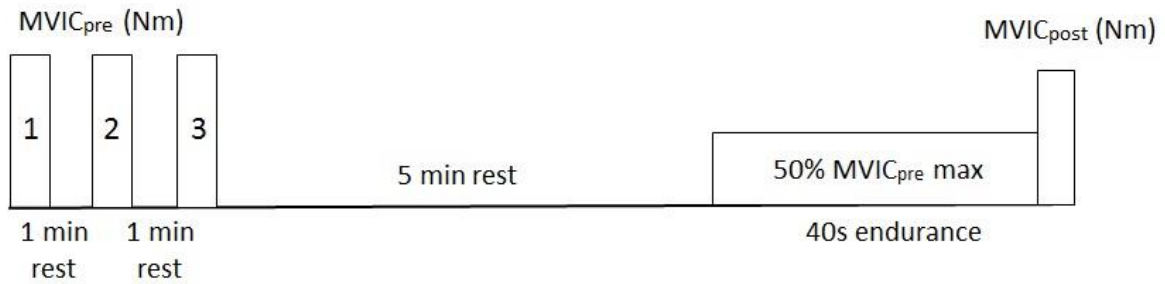


Figure S1: A graphic representation of the evaluation protocol is presented in supplementary material S1.

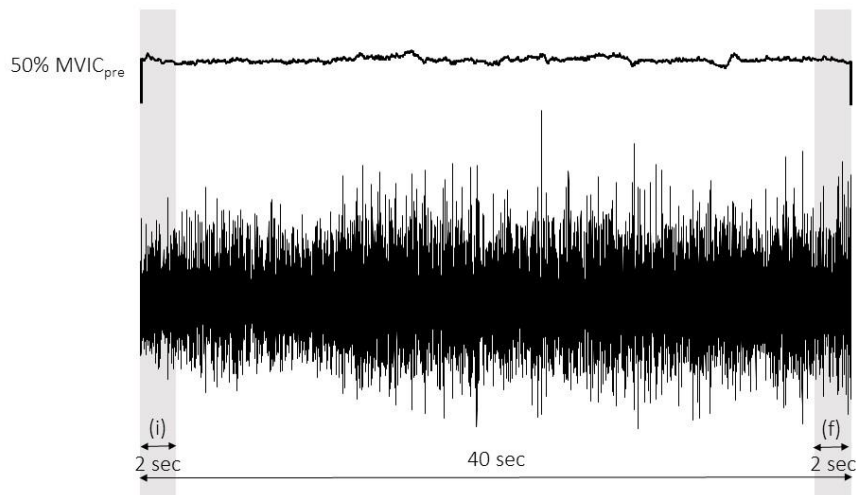


Figure S2: Example of a sEMG recording and torque signal

Author contributions

SB collected and analysed data and drafted the manuscript. JR assisted in data analysis. JY and PP designed and assisted in evaluations and data analysis. TS assisted in participant recruitment, performed physician evaluations and assisted in data interpretation. All authors read and approved the final manuscript.

Abbreviations

AChEi	Acetylcholinesterase inhibitors
AchR	Muscle nicotinic acetylcholine receptor
BMI	Body mass index
MG	Auto-immune myasthenia gravis
MG-ADL	MG Activities of Daily Living Scale
MGFA	Myasthenia Gravis Foundation of America classification
MGQOL-15-F	French version of the 15-item MG-specific quality of life scale
MMS	Myasthenia Muscle Score
MPF	Mean power frequency
MuSK	Muscle-specific tyrosine kinase
MVIC	Maximal voluntary isometric contraction
Nm	Newton metres
NMF	Neuromuscular fatigue
NMJ	Neuromuscular junction
RMS	Root mean square
sEMG	Surface electromyography
SwMG	Subjects with MG
QoL	Quality of life

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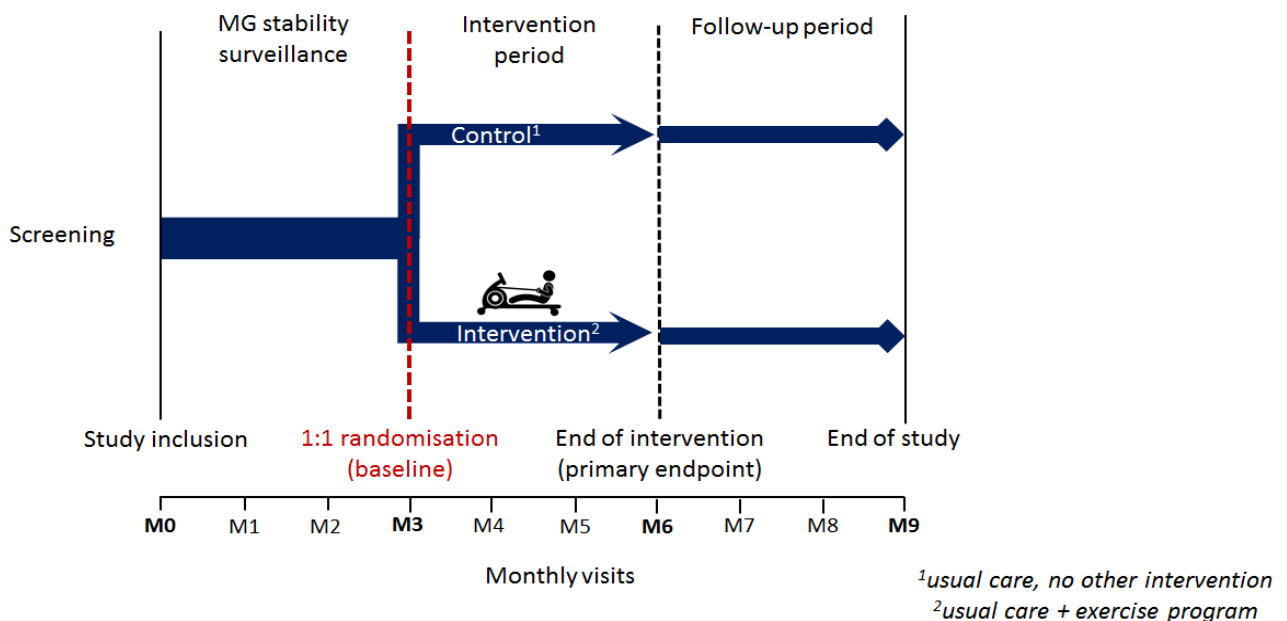
V. Exercise in myasthenia gravis

A home-based exercise program in stable myasthenia gravis: Preliminary results of a randomized, controlled trial

Paper VI : Birnbaum S, Porcher R, Eymard B, Hogrel JY, Portero P, Gargiulo M, Louet E, Berrih-Aknin S, Le Panse R, Sharshar T and the MGEX Study Group.

All analyses presented here are preliminary, the database has not yet been finalized. All data are **confidential**. Writing of the paper has begun and is in process. Writing follows the CONSORT guidelines for non-pharmaceutical clinical trials [91]. Below is the methods section, preliminary results and discussion.

Schematic representation of the trial (protocol details in Paper I)



OBJECTIVES

The **primary aim** of this study was to determine whether a regular home-based physical exercise program improves perceived QoL for individuals with stable, generalized MG.

Secondary aims were to evaluate the effects of this intervention compared to usual care on physical performance, depression and self-esteem as well as on immune system markers.

METHODS

Trial design:

A full description of the methods is available in our previously published protocol paper [92]. Briefly, the study was a two-arm, parallel-group, randomized controlled trial conducted in two university hospitals in Ile-de-France, France. Ethics approval was granted by the French regulatory board (*Comité de Protection des Personnes Ile de France XI* under the CPP number #13064 on 13/12/2013 and authorized by the *Agence National de Sécurité du Médicament et des produits de santé* on 11/10/ 2013). The trial was conducted in accordance with the Helsinki Declaration [93]. All participants provided written, informed consent prior to enrolment. The trial was prospectively registered in the ClinicalTrials.gov registry (NCT02066519).

Changes to trial design:

Modifications to V3.0 protocol publication [92] include change of place of practice of the principal investigator. Changes were made to the cytokine analyses; specific details can be found in supplementary information. Briefly, the sera were conserved in a freezer at – 80 °C and the cytokines were analysed using the Bioplex technology.

Participants:

Participants were recruited during regular out-patient consultations and from patient groups. Participants were eligible if they were between 18 and 70 years old and had a confirmed diagnosis of mild-moderately-severe, generalized auto-immune MG. The MG had to be stable for at least 6 months prior to inclusion. Any contra-indication to physical exercise which precluded participation in the experimental arm was considered an exclusion criterion. Inclusion and exclusion criteria are presented in Table 1.

Table 1: Study eligibility criteria

Inclusion criteria	Exclusion criteria
Age 18-70 yrs old	Score < 15 on the MGQOL-15-F
Mild or moderately-severe generalized autoimmune MG stable \geq 6 months	Any contra-indication to physical exercise including: unstable coronary syndrome or myocardial infarction within the preceding 3 months, respiratory failure (VC < 70% predicted value), cardiac failure (ejection fraction < 50% predicted value), other neuromuscular pathology, disabling rheumatological disease (> 80% disability on the Barthel scale), chronic pain or disabling orthopaedic conditions, hospitalisation in the last 3 months for a serious medical or surgical condition, anaemia (haematocrit < 30%), stroke within the previous year.
Affiliated with the national security system	Pure ocular MG (MGFA I) or severe MG (MGFA IV or V)
	Pregnancy
	Severe cognitive impairment necessitating specific protection
	Participation in other interventional clinical trial in previous 3 months

Setting:

Two university hospitals in Ile-de-France, France (Pitié Salpêtrière, Paris and Raymond Poincaré, Garches).

Randomisation, allocation concealment, blinding and implementation:

Following the 3-month visit, consecutive participants were randomized to either the intervention or control group with a 1:1 allocation ratio as per a computer-generated randomization schema stratified by centre using permuted blocks of randomly varying sizes. To ensure concealment, the block sizes were not disclosed. Group allocation was revealed via a software (CleanWeb) exclusively to the non-blinded physiotherapist once randomization had been performed (concealed allocation). The randomisation list was constructed prior to

the beginning of the study by an off-site independent statistician with no clinical involvement in the study. All evaluators were blinded except the physiotherapist performing the respiratory, force and endurance measures and managing the training program.

Intervention:

The control group received usual care and evaluations as per the study protocol. The intervention group were invited to participate in a 12-week home-based exercise program. The program comprised of 3 sessions per week, including a total of 36 sessions over the intervention period. Initially two or three supervised exercise sessions were provided to teach subjects how to use the rowing machine (Concept2™) and how to follow their individualised exercise program. The Concept 2 rowing machine is a stationary ergometer where the participant is seated and simultaneously exercises both upper and lower limbs and the trunk thus targeting the multiple muscles which can be affected in MG. The rowing machine was then delivered to their home. Supplementary data Figure S1 shows the theoretical training session profile. Each 40-min moderate-intensity training session consisted of a 10-min warm-up to reach their individual target heart rate (i.e. 70% of their maximal heart rate [HR], using the equation $220 - \text{age}$ as HRmax), followed by an endurance plateau phase consisting of 20 min of constant aerobic activity rowing at their individual target heart rate, followed by a power interval phase (ten pulls at maximum effort every minute for 5 min) and finally a 5-min active cool-down period whereby the rowing exercise is continued at a slow pace. A heart rate monitor (Garmin®) was worn by the subject and data (rowing distance, session duration) were recorded by the rowing machine for each training session. Participants were advised to organise their training sessions on alternate days. Subjects continued to benefit from usual care. Table 2 details the exercise program as per Slade et al. [94].

Table 2: Description of exercise intervention

Material	Stationary rowing machine Concept2™
Provider	Two-three individual training sessions supervised and provided by a trained physiotherapist.
Delivery	Subjects completed the exercise program individually and unsupervised, with telephone contact possible with the physiotherapist for any technical problem solving and/or advice and for motivation where necessary. A logcard recorded completed training sessions (time, distance, heart rate at the end of each interval). Any adverse events were reported to the physiotherapist via telephone and a medical doctor if necessary. Serious adverse events were declared to the trial safety monitoring staff.
Location	Initial physiotherapy supervised training sessions took place at the Rothschild hospital, Paris, the remainder took place at the subject's home.
Dosage	Thirty-six forty-minute sessions (3 per week) were planned over a period of 3 months. Each session consisted of: 10-minute warm-up, 20 minutes at 70% max HR, 5 minutes high intensity interval work (10 maximum pulls every minute), 5-minute cool-down. Subjects could decide the time of day and the day of the week, ideally on alternate days.
Individual tailoring	Target heart rate for the plateau phase = 70% maximal heart rate where maximal heart rate = 220 – age.
Compliance	Compliance was recorded via the logcard inserted into the rowing machine. Reason for non-compliance were to be reported in a logbook by subjects.

Study schedule and evaluations:

Supplementary data Table S1 shows the outline for all assessments. Briefly, the study was divided into 3 parts, the initial 3-month baseline period (M0-M3) followed by the 3-month intervention period (M3-M6) and then the 3-month post-intervention follow-up period (M6-M9).

Statistical methods and analysis:

Sample size calculations have been described previously [92]. Analyses were performed according to the intention-to-treat principle as planned (all participants were included in the groups to which they were randomly assigned even if the intervention was not completed). And *compliers average causal effect*, CACE analysis was also performed.

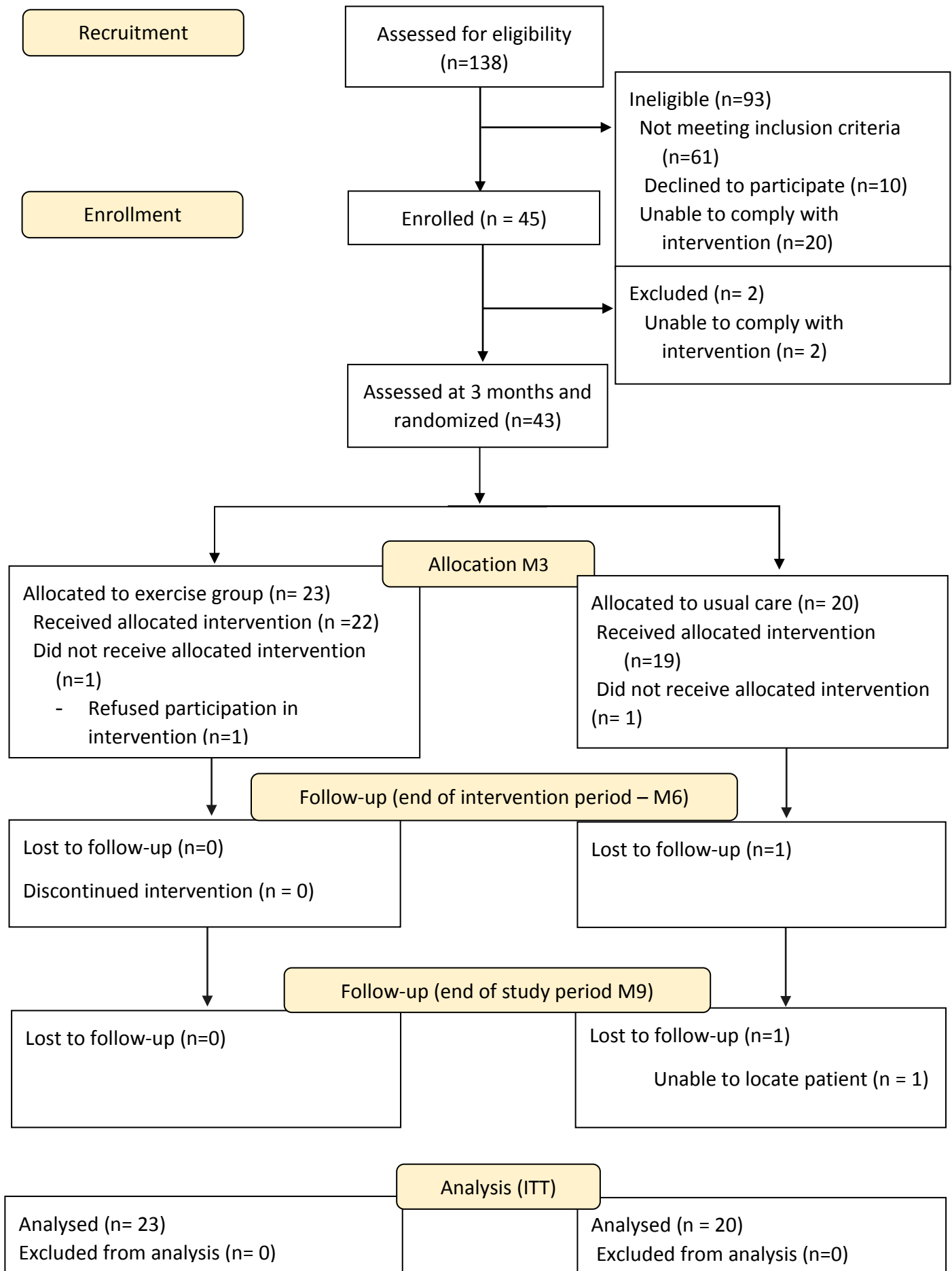
All outcome measures were tested with superiority analyses. As planned, a multiple imputation by chained equations model was used for missing data. The model included all outcomes measured at all time points. The imputation was performed independently within each group [95]. Continuous variables were imputed with the *predictive mean matching* method. A logistic model was used for binary variables and a multinomial model for qualitative variables. As recommendations are scarce, the number of imputations was based on the percentage of observations with missing data [96].

Variations in scores at M3, M6 and M9 for continuous variables were compared between the 2 groups, adjusted to the score at M3 using a covariance model (ANCOVA). A mixed model was used for monthly measures, SMM and MG-ADL [97]. Medication dose was compared using a student's test. Adverse events were described and Fishers exact tests were used to compare the 2 groups.

Two-sided tests were used with a 5% significance level for all analyses. All analyses were performed with the software R, version 3.5.0 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS:

Participant flow: Consort diagram



Role of the funding source:

This study was sponsored by the *Assistance Publique – Hôpitaux de Paris* who received a grant from the French Ministry of Health after selection in the 2012 call for projects (*Programme Hospitalier de Recherche Clinique-PHRC régional 2012*, AOR12149) and conducted in collaboration with the Institute of Myology, monitoring and data management being performed by the *Unité de Recherche Clinique Paris Île-de-France Ouest (URCPO)*.

RESULTS

Screening, eligibility, recruitment (Consort flow diagram), numbers analysed:

Of 138 patients screened for participation, 77 met eligibility criteria, 10 individuals declined to participate, 20 were unable to comply with the intervention. Between October 2014 and June 2017 45 participants were included in the study, composing of 42 women and 3 men. Between M0 and M3 two women withdrew as they were unable to comply with the intervention. Twenty-three subjects (all women) were randomly assigned to the intervention group and 20 to the control group. One participant refused to participate in the exercise program but remained in the trial, the other 22 subjects participated in the exercise program although compliance was variable. Two participants, both in the control group were lost to follow-up, one following randomization (M3) and the other at M8. All participants were included in the analyses (intention-to-treat).

At baseline (M3) 43 participants were included, mean age 45.5 (10) years. Baseline characteristics are presented in Table 3. Disease duration was on average 14.3 (11) years. Eighty-one percent had auto-antibodies directed against the AChR, 7% against MuSK and the remaining 12% did not have auto-antibodies for either proteins. Sixty-five percent were treated with immunosuppressors (not including corticotherapy), 42% with corticotherapy and 86% took ACEi. Thirteen were obese (BMI \geq 30), 10 subjects had osteoporosis, eight had hypertension and four had Type 2 diabetes mellitus.

Table 3: Demographic, disease characteristics and medical history of participants at baseline (M3) with mean (SD) ± range.

Characteristic	All (n=43)	Exercise (n=23)	Control (n=20)
Age (years) - Mean (SD)	45.5 (10.0) 29 to 70	47.1 (9.0) 34 to 64	43.7 (10.9) 29 to 70
Women - n (%)	40 (93)	23 (100)	17 (85)
BMI (kg/m ²) - Mean (SD)	28.4 (5.5) 20 to 45	27.1 (4.7) 20 to 39	29.9 (6.0) 21 to 45
MGFA class - n (%)			
Classe II a / Classe II b	17 (40)/6 (14)	9 (39)/4 (17)	8 (40)/2 (10)
Classe III a / Classe III b	14 (33)/6 (14)	5 (22)/5 (22)	9 (45)/1 (5)
Autoantibody profile - n (%)			
AChR /MuSK /AChR- and MuSK-	35 (81)/3 (7)/ 5(12)	20(87)/1(4)/2(9)	15(75)/2(10)/3(15)
MG onset - n (%)			
Juvenile (<18y)	7 (16)	6 (26)	1 (5)
Early	30 (70)	13 (57)	17 (85)
Late (>50 y)	6 (14)	4 (17)	2 (10)
Disease duration (yrs)-Mean (SD)	14.3 (11.0) 1 to 44	17.6 (13.0) 1 to 44	10.4 (6.6) 2 to 26
Thymectomy - n (%)	28 (65)	18 (78)	10 (50)
Treatment at randomization			
AchE inhibitor - n (%)	37 (86)	19 (83)	18 (90)
Glucocorticoid - n (%)	18 (42)	10 (43)	8 (40)
Prednisone dose (mg)-Mean (SD)	3.2 (4.3)	3.2 (4.3)	3.1 (4.4)
Immunosuppressor - n (%)	28 (65)	13 (57)	15 (75)
Co-morbidities			
Obese (BMI ≥ 30 kg/m ²) – n (%)	13 (32)	5 (24)	8 (40)
Hypertension – n (%)	8 (19)	5 (22)	3 (15)
Diabetes Type II - n (%)	4 (9)	2 (9)	2 (10)
Osteoporosis – n (%)	10 (23)	6 (26)	4 (20)

Table 4 presents function, QoL and psychological status of subjects at baseline (M3). Average MGQOL-15-F score was 22 (9) [5-44], MMS score was 86.3 (10.9) and MG-ADL score was 2.6 (2.4). The physical domain was the lowest of the WHO-QOL Bref scores, 12.1 (1.9) followed by the social domain 13.6 (3.8). Subjects suffered from mild depression (BDI) and mild anxiety (STAI A and B).

Table 4: QoL and psychological status at baseline (M3). Scores with Mean (SD) and range.

Score	All (n=43)	Exercise (n=23)	Control (n=20)
MGQOL-15-F score - Mean (SD)	22.0 (9.0) 5 to 44	20.0 (8.8) 6 to 35	24.4 (8.9) 5 to 44
MMS score - Mean (SD)	86.3 (10.9)	85.3 (10.6)	87.4 (11.4)
MG-ADL score - Mean (SD)	2.6 (2.4)	2.7 (2.6)	2.4 (2.2)
WHO-QOL score - Mean (SD)			
Domain 1: Physical	12.1 (1.9)	12.2 (1.8)	11.9 (2.0)
Domain 2: Psychological	14.2 (2.7)	14.2 (2.7)	14.2 (2.7)
Domain 3: Social relationships	13.6 (3.8)	13.1 (4.0)	14.2 (3.7)
Domain 4: Environment	15.0 (2.1)	15.0 (2.2)	15.0 (2.1)
STAI-Y State anxiety - Mean (SD)	35.7 (13.8)	35.5 (14.9)	35.8 (12.8)
STAI-Y Trait anxiety- Mean (SD)	42.3 (11.2)	42.8 (11.7)	41.6 (10.8)
Beck Depression Inventory - Mean (SD)	7.2 (5.7)	7.5 (5.6)	6.9 (6.0)
Self-Esteem Inventory - Mean (SD)	37.5 (8.4)	35.8 (9.5)	39.4 (6.7)

Intervention compliance and implementation:

Compliance was defined as having completed $\geq 20/36$ sessions (frequency) $\geq 30/40$ minutes (duration). Seventy percent of participants were compliant. Twenty-four (range 0-38) full sessions were completed on average (Table 5). Reasons for non-compliance included work commitments including travel, unplanned overseas travel for family death, holidays, moving houses and lack of motivation. Reasons for missing occasional sessions included: the flu,

weekend away, menstrual pain/tiredness. Characteristics were similar between compliers and non-compliers (supplementary data Table S1).

Table 5: Compliance to exercise

Compliance to exercise	Exercise (n=23)
Meeting the compliance criteria (≥ 20 sessions ≥ 30 minutes) –n (%)	16 (70)
N of sessions ≥ 30 minutes - Mean (range)	25.4 (0 to 38)
N of 40 minutes sessions - Mean (range)	24.0 (0 to 38)

Outcomes:

Safety - adverse events

Two serious adverse events (hospitalization for exacerbation of MG) were declared for two participants, both in the control group. Seventy-four adverse events were declared. Common adverse events included musculoskeletal symptoms, infections and MG symptoms.

Table 6: Adverse events. P values based on Fisher’s exact tests except * where P value is based on Poisson regression.

Variable	Exercise (n=23)	Control (n=20)	p value
No. of adverse events*	41	33	0.74
Allergic reaction	1	1	
Cardiac disorder	1	0	
Cephalalgia	3	1	
Infection or infestation	5	6	
MG exacerbation	3	2	
MG symptoms	9	3	
Musculoskeletal symptoms	5	13	
Other	11	7	
Respiratory symptoms	3	0	
≥1 event — no. of participants (%)	17 (74)	14 (70)	>0.99
Serious adverse events			
Death or life-threatening event — no. participants (%)	0 (0)	0 (0)	>0.99
Disability or incapacity - no. participants (%)	0 (0)	0 (0)	>0.99
Hospitalization - no. participants (%)	0 (0)	2 (10)	0.21
Hospitalization for MG exacerbation - no. participants (%)	0 (0)	2 (10)	0.21
Other significant event — no. participants (%)	0 (0)	0 (0)	>0.99

Medication:

There was no significant between-group difference in change in prednisone ($p = 0.63$) nor ACEi dose ($p = 0.62$) between the pre and post-intervention period (M3-M6), nor for the 3-month follow-up (M6-M9), $p = 0.75$ and $p = 0.87$, respectively.

Efficacy analyses:

Primary outcome:

The primary efficacy endpoint showed an adjusted between-groups mean decrease of 0.9 points on the MGQOL-15-F score (95%CI -5.6 to 3.8) at the end of the intervention period (M6) without a statistically significant difference between the two groups.

Table 7: Primary analysis of the primary outcome. Analyses of imputed data. MD: mean difference; 95% CI: 95% Confidence Interval. M3 = Randomisation. M6 = end of intervention period

Score	Exercise	Control	Adjusted MD (95% CI)	p value
MGQOL-15 score at M3	20.0 (8.8)	24.7 (9.0)
MGQOL-15 score at M6	18.8 (10.7)	23.5 (9.6)
Changes in MGQOL-15 score at M6	-1.1 (7.4)	-1.2 (6.1)	-0.9 (-5.6 to 3.8)	0.70
MGQOL-15 score at M9	19.9 (12.4)	20.3 (9.5)
Changes in MGQOL-15 score at M9	-0.0 (9.3)	-4.4 (8.1)	3.8 (-2.0 to 9.6)	0.20

Secondary outcomes:

No statistically significant between-group differences were found for secondary outcomes between M3 and M6 except for the six-minute walk distance where there was a mean adjusted between-group difference of 27.7m ($p = 0.012$, 95%CI 7.2-48.1) and a significant difference in the MG-ADL score ($p = 0.005$) however no meaningful treatment effect could be estimated. For both outcomes at M9 differences were no longer significant (Table 7). Knee extension strength increased in the EX group without reaching statistical significance (%95 CI 0.1-17.5). Further details of secondary outcomes can be found in supplementary data.

Table 8: Analysis of strength and walking performance. MD: mean difference; 95% CI: 95% Confidence Interval.

Outcome	Exercise		Control		Adjusted MD (95% CI)	p value
	N	Mean (SD)	N	Mean (SD)		
Grip strength (kg)						
Value at M3	23	23.8 (4.7)	20	26.4 (8.0)
Value at M6	23	25.1 (5.8)	19	26.4 (8.2)	1.3 (-1.2 to 3.9)	0.31
Elbow flexion (Nm)						
Value at M3	23	36.8 (7.1)	20	39.2 (11.5)
Value at M6	23	37.6 (8.3)	19	40.8 (11.7)	-0.8 (-3.5 to 1.9)	0.57
Knee extension (Nm)						
Value at M3	23	107.5 (27.9)	20	115.5 (43.8)
Value at M6	23	114.0 (33.3)	19	115.7 (45.9)	8.8 (0.1 to 17.5)	0.056
Value at M9	23	109.3 (33.0)	17	118.1 (48.6)	-4.0 (-18.6 to 10.6)	0.60
6MWD (m)						
Value at M3	22	502.1 (72.8)	20	493.8 (95.5)
Value at M6	23	516.8 (77.8)	19	486.0 (88.2)	27.7 (7.2 to 48.1)	0.012
Value at M9	23	508.0 (80.1)	16	499.0 (92.5)	-7.5 (-29.8 to 14.9)	0.52
6MWD (% predicted)						
Value at M3	22	86.5 (10.0)	20	83.6 (12.5)
Value at M6	23	90.1 (12.1)	19	82.7 (13.1)	4.8 (1.1 to 8.6)	0.015
Value at M9	23	88.7 (13.4)	16	85.6 (14.1)	-1.6 (-5.9 to 2.7)	0.48

Analyses presented above were analysed as intention to treat (ITT), i.e. based on allocation and not on whether the intervention was carried out or not. The ITT analysis responds to a real-world scenario where an intervention is available and some take advantage of it and others do not or do not fully adhere.

The following analyses, complier average causal effects (CACE) are aimed at identifying the causal effects of actually receiving a treatment and thus the “true” impact of the intervention.

The following tables report results where the exercise group has been separated between compliers and non-compliers. A compliers average causal effects (CACE) analysis using instrumental variables has been used to formally estimate the treatment effect among compliers, i.e. those who met the formal pre-defined compliance criteria of having completed at least 20 rowing sessions (out of 36) with a duration of 30 minutes (out of 40).

Table 9: Analysis of strength according to compliance status. CACE: compliers average causal effect expressed as an adjusted mean difference. %pred = % predicted, knee ext = knee extension.

Score	Exercise		Compliers		Control		CACE (95% CI)	p value
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)		
Grip strength (kg)								
Value at M3	7	23.8 (5.4)	16	23.8 (4.5)	20	26.4 (8.0)		
Value at M6	7	24.0 (7.0)	16	25.5 (5.3)	19	26.4 (8.2)	2.0 (-1.2 to 5.1)	0.22
Grip strength (% pred)								
Value at M3	7	71.4 (15.7)	16	77.0 (17.1)	20	75.8 (21.3)		
Elbow flexion (Nm)								
Value at M3	7	37.5 (7.7)	16	36.6 (7.1)	20	39.2 (11.5)		
Value at M6	7	36.1 (8.2)	16	38.2 (8.5)	19	40.8 (11.7)	-1.2 (-5.3 to 2.9)	0.58
Elbow flexion (% pred)								
Value at M3	7	85.4 (15.0)	16	82.9 (15.2)	20	74.4 (19.3)		

Score	Exercise				Control	CACE (95% CI)	p value	
	Non-compliers		Compliers		N			Mean (SD)
	N	Mean (SD)	N	Mean (SD)				
Knee ext (Nm)								
Value at M3	7	107.2 (31.1)	16	107.6 (27.4)	20	115.5 (43.8)		
Value at M6	7	105.1 (30.6)	16	117.9 (34.7)	19	115.7 (45.9)	13.0 (1.4 to 24.5) 0.034	
Value at M9	7	106.1 (35.9)	16	110.7 (32.8)	17	118.1 (48.6)	-5.9 (-28.6 to 16.7) 0.61	
Knee ext (% pred)								
Value at M3	7	97.9 (28.1)	16	96.1 (22.7)	20	87.4 (29.3)		
Value at M6	7	97.1 (26.4)	16	105.4 (29.1)	19	88.2 (31.7)	10.3 (0.5 to 20.1) 0.047	
Value at M9	7	98.3 (31.1)	16	99.8 (29.1)	17	90.4 (31.2)	0.9 (-13.3 to 15.0) 0.90	
6MWD (m)								
Value at M3	6	524.2 (67.3)	16	493.9 (75.1)	20	493.8 (95.5)		
Value at M6	7	531.6 (66.8)	16	510.3 (83.4)	19	486.0 (88.2)	39.0 (10.1 to 68.0) 0.012	
Value at M9	7	504.0 (65.6)	16	509.8 (87.7)	16	499.0 (92.5)	-10.6 (-37.1 to 15.9) 0.44	
6MWD (% pred)								
Value at M3	6	88.7 (7.6)	16	85.7 (10.9)	20	83.6 (12.5)		
Value at M6	7	92.8 (9.2)	16	89.0 (13.3)	19	82.7 (13.1)	6.7 (1.7 to 11.7) 0.013	
Value at M9	7	88.3 (11.4)	16	88.9 (14.6)	16	85.6 (14.1)	-2.2 (-7.4 to 3.0) 0.41	

Adaptation to exercise:

Analysis of 20-minute period of exercise program (at target heart rate, 70% of HRmax), of compliant subjects showing cardiorespiratory adaptation to exercise. For the same heart rate, distance increased on average 13%.

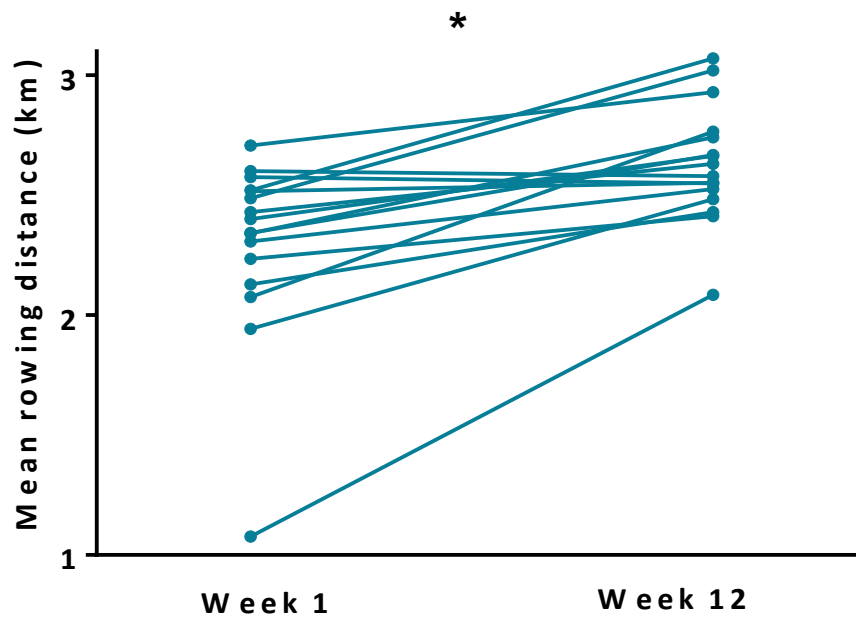


Figure 1: Average distance of first 3 training sessions ($2293\pm383\text{m}$) compared to average distance of last 3 training sessions ($2632\pm245.3\text{m}$) for compliant subjects ($n=16$), $*p=0.002$.

DISCUSSION

This is the first randomised controlled trial evaluating the effects of a general exercise program in MG. Retention was good with only two subjects (control group) withdrawing from the study. Blinding was maintained for all evaluators except the physiotherapist as planned in the protocol. For reasons unrelated to MG, one subject (exercise group) did not carry out the assigned intervention 7 subjects did not perform at least 20 sessions of at least 30 minutes in duration (compliance criteria). Recruitment was from two specialist centres.

Results did not show any significant between-group difference of the home-based exercise program on the primary outcome measure, self-perceived MG-specific QOL between 3 and 6 months (prior to and following the 3-month exercise program). Quality of life was reduced in

this cohort, the physical domain scored lowest of the different domains of general QoL. MG-specific quality of life was lower (i.e. higher MGQOL-15F score) than has previously been reported in a French cohort who scored a mean of 15 ± 12 but were slightly older than subjects in this study [98]. This could be due the fact that the large majority were women, all had generalized MG and the presence of mild depression, all factors which have been shown to be associated with reduced QoL [99, 100].

QoL measures are important in healthcare as they provide information about how satisfied one is with their current level of functioning compared to what they perceive to be possible or ideal [101]. The MG-QOL-15-F is a health related measure of QoL, specifically measuring the impact of MG on one's perception of QoL. It is not surprising that if the exercise program did not modify disease behaviour (no change in MMS) then the MGQOL-15 did not change.

An important finding in this study was the absence of deterioration in the exercise group. In fact, the two MG exacerbations with hospitalization during the study were both in the control group. Change in medication dosage was not different between the two groups.

With regards to secondary outcomes, there was a significant between-group difference in the six-minute walking distance at 6 months in favour of the exercise group. Whilst the 6MWT is reliable in this population, minimal clinically important difference or minimal detectable change for the 6MWT in MG remains to be studied [102]. However, based on results in subjects with mild multiple sclerosis, the improvement in this cohort exceeded the smallest real change (group) and the minimally important change [103]. It should also be noted that 6MWDs were relatively high priori to intervention making it more difficult to have a greater change. In fact, despite a greater BMI in this cohort, distance walked was greater than that described elsewhere for subjects of similar age (mean 465 ± 87) [102]. The difference was no longer present at 9 months, strengthening the possibility that gains were exercise-induced.

When adjusting for non-compliers (CACE), knee extension strength was also found to be significant in the exercise group but not elbow flexor strength. This phenomenon whereby there are gains in the lower limb but not in the upper limb with exercise in MG, has been reported previously [56, 59]. It remains difficult to explain other than that the training program may have solicited knee extensors more than elbow flexors or the upper limbs may

have been more affected by MG and had less capacity for improvement, but this is pure speculation.

Although aerobic capacity was not directly tested, cardiorespiratory gains were made in compliers, demonstrated by the increased rowing distance performed for the same target heart rate, this could also explain gains in the 6MWT. Surprisingly grip strength did not change despite having to hold the handlebar of the rowing machine, an endurance test may have been more sensitive to change in this case. This would be worth exploring further as it is two items of the commonly used quantitative myasthenia score [104].

The very modest improvements demonstrated in this study could be related to exercise type. The rowing machine was selected as it exercises both upper and lower limbs in a comfortable position with minimal risk of injury. Exercise type was aerobic with a very short period of increased power output. The improvement seen in the 6MWT is likely due to improvements in muscle metabolism and efficiency as well as small improvement in strength. At this stage more research is required to answer questions concerning the type of exercise, intensity, duration and frequency and the impact of each aspect on individuals or MG subgroups.

Results could also be related to compliance. Compliance of the exercise program was variable and should be considered in the design of future studies. However it should be kept in mind that compliance was acceptable considering the exercise was home-based and unsupervised. Also, considering a large number of subjects with juvenile MG were randomized to the exercise group, many of whom had spent most of their life not participating in exercise.

Whilst reported reasons for not participating were unrelated to the exercise program this raises the question of the effectiveness of the intervention. Frequency and duration may have been too much for some although there were no differences in clinical status between compliers and non-compliers (supplementary data). Prior studies have also shown similar compliance levels for exercise interventions [105]. And, this was exercise intervention was unsupervised which are reported to have lower adherence than supervised programs. Additionally, group exercise may increase compliance as opposed to individual exercise in our study [106]. Lack of compliance may be due to a lack of belief in or a lack of perception of benefits of the intervention which may in turn have impacted on self-report measures [107].

Participants subjective feedback is lacking for now but may provide insight for future studies. Some participants described the exercise program as giving them renewed confidence in themselves and their abilities. Whilst self-esteem was measured in this study, self-efficacy may have been more sensitive to change as self-esteem may be unlikely to change without specific targeted intervention.

This study presented some minor methodological limitations. Whilst this is the largest study of exercise in MG so far, the sample size was modest and statistical power was reduced [108]. Due to the type of intervention, blinding of participants was impossible and some improvement could be related to *positive expectation bias* particularly for those who were motivated to perform exercise [109]. There was an imbalance between the number of men and women in this study and all men were randomly assigned to the control group.

Supplementary data

Table S1: Baseline characteristics associated with compliance.

Characteristic	Non-compliant (n=7)	Compliant (n=16)	p value
Age (years) — Mean (SD)	48.5 (11.3)	46.5 (8.2)	0.62
BMI (kg/m ²) — Mean (SD)	26.0 (1.0)	27.4 (5.4)	0.84
FVC (% predicted) — Mean (SD)	78.5 (11.6)	83.7 (10.4)	0.38
MGFA class — no. (%)			0.52
Classe II a/ Classe II b	4 (57)/ 0 (0)	5 (31)/ 4 (25)	
Classe III a/ Classe III b	2 (29)/ 1 (14)	3 (19)/ 4 (25)	
Disease duration (yrs) Median (Q ₁ to Q ₃)	9.4 (3.7 to 17.0)	16.0 (9.6 to 30.5)	0.17
MG onset — no. (%)			0.15
Juvenile (<18 y)	1 (14)	5 (31)	
Early (18–50 y)	3 (43)	10 (62)	
Late (> 50 y)	3 (43)	1 (6)	
MGQOL-15-F score — Mean (SD)	16.1 (11.6)	21.6 (7.0)	0.17
MMS score — Mean (SD)	84.9 (10.8)	85.5 (10.9)	0.81
MG-ADL score — Mean (SD)	2.9 (3.9)	2.7 (1.9)	0.54

Table S2: Analysis of pulmonary function. MD: mean difference; 95% CI: 95% Confidence Interval. FVC = Forced Vital Capacity. MIP = maximal inspiratory pressure MEP = maximal expiratory pressure.

Outcome	Exercise		Control		Adjusted MD (95% CI)	p value
	N	Mean (SD)	N	Mean (SD)		
FVC (% predicted)						
Value at M3	23	82.1 (10.8)	20	87.4 (15.2)
Value at M6	23	80.7 (10.6)	19	84.9 (15.0)	0.1 (-2.6 to 2.9)	0.93
Value at M9	23	79.8 (13.7)	18	83.5 (15.3)	0.7 (-3.6 to 5.0)	0.75
MIP (% predicted)						
Value at M3	23	88.7 (33.1)	20	98.7 (28.9)
Value at M6	22	90.7 (36.3)	19	98.5 (35.0)	-0.7 (-11.2 to 9.8)	0.90
Value at M9	23	92.7 (35.9)	17	93.4 (34.5)	5.3 (-6.1 to 16.6)	0.37
MEP (% predicted)						
Value at M3	23	89.2 (30.1)	20	104.2 (31.4)
Value at M6	23	97.0 (31.3)	19	103.0 (31.5)	2.6 (-10.7 to 15.9)	0.71
Value at M9	23	96.6 (33.8)	17	101.5 (32.8)	4.4 (-7.6 to 16.5)	0.47

Table S3: Analysis of cytokine immuno-fluorescence. Results of the analysis of logged values, adjusted for baseline value and centre. ARGM: adjusted ratio of geometric means; CACE: compliers average causal effect expressed as an adjusted ratio of geometric means; 95% CI: 95% Confidence Interval. *p values were obtained on rank analysis of covariance to limit influence of extreme data points.

Cytokine	Month 6		Month 9	
	ARGM (95% CI)	P value	ARGM (95% CI)	p value
IL-6	1.09 (0.97 to 1.23)	0.15	1.07 (0.95 to 1.21)	0.35
TNF- α	0.97 (0.86 to 1.10)	0.53	1.02 (0.91 to 1.13)	0.45

Cytokine	Month 6		Month 9	
	CACE (95% CI)	P value	CACE (95% CI)	p value
IL-6	1.14 (0.98 to 1.33)	0.093	1.11 (0.94 to 1.31)	0.29
TNF- α	0.96 (0.81 to 1.14)	0.50	1.02 (0.88 to 1.19)	0.41

Table S4: Primary outcome according to compliance status. CACE: compliers average causal effect expressed as an adjusted mean difference. Results are pooled over imputed data

Score	Exercise		Control	CACE (95% CI)	p value
	Non-compliers	Compliers			
No. participants	7	16	20		
MGQOL-15 score at randomization (M3)	16.1 (11.6)	21.6 (7.0)	24.7 (9.0)		
MGQOL-15 score at M6	14.9 (13.4)	20.6 (9.3)	23.5 (9.6)		
Changes in MGQOL-15 score at M6	-1.3 (7.2)	-1.1 (7.7)	-1.2 (6.1)	-1.2 (-7.9 to 5.4)	0.72
MGQOL-15 score at M9	14.0 (10.3)	22.5 (12.6)	20.3 (9.5)		
Changes in MGQOL-15 score at M9	-2.1 (2.8)	0.9 (11.0)	-4.4 (8.1)	5.1 (-3.2 to 13.5)	0.23

Marathons and Myasthenia Gravis

Clinical presentation, severity, evolution and pathophysiology in MG is heterogeneous. Individual capacities also vary.

This case report describes a 36-year-old female who began long-distance running whilst experiencing her first symptoms of MG. Although advised against exercise by her treating neurologist and family, she realized she needed to exercise to help maintain a healthy body and healthy mind. Despite being symptomatic, Ms N managed to complete several marathons and achieve disease stability with cholinesterase inhibitors. Interestingly she refused a thymectomy despite being AChR+. The possible positive immunomodulatory role of exercise is discussed in this paper.

Birnbaum S, Sharshar T, Eymard B, Theaudin M, Portero P, Hogrel JY: **Marathons and myasthenia gravis: a case report.** *BMC Neurol* 2018, **18**:145.

NB: Ms N recently successfully climbed the Mont Blanc (4810m) and will soon run in the Amsterdam marathon.

CASE REPORT

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Marathons and myasthenia gravis: a case report



Simone Birnbaum^{1,2,3*} , Tarek Sharshar^{4,5,6}, Bruno Eymard¹, Marie Theaudin⁷, Pierre Portero² and Jean-Yves Hogrel¹

Abstract

Background: The cardinal symptoms of auto-immune myasthenia gravis are fatigue and weakness. Endurance events such as marathon running would seem incompatible with this chronic disease. Many patients stop sport altogether. There is limited literature of patients with auto-immune myasthenia gravis undergoing regular endurance exercise.

Case presentation: We report the case of a 36-year-old female who began long-distance running whilst experiencing initial symptoms of myasthenia gravis. She was diagnosed with auto-immune myasthenia gravis and whilst advised to stop all sport, her way of fighting and living with this chronic and unpredictable disease was to continue running to maintain a healthy body and mind. Despite suffering from ocular, bulbar and localized limb fatigability, she managed to complete multiple marathons and achieve disease stability with cholinesterase inhibitors.

Conclusions: Marathon and half-marathon running lead to distinct changes in mediators of inflammation in an exercise-dose-dependent manner. Despite symptoms of weakness and fatigue in certain muscles in myasthenia gravis, physical exertion remains possible and may not worsen symptoms as demonstrated in this case and recent studies. The immunomodulatory role of exercise could be considered in this case however this hypothesis remains to be confirmed in future studies with quantitative data.

Keywords: Myasthenia gravis, Marathon, Auto-immune disease, Health, Endurance exercise

Background

Auto-immune myasthenia gravis (MG) is a chronic disease whereby dysfunction at the neuromuscular junction causes symptoms of fatigue and weakness [1]. Endurance events such as marathon running would seem incompatible with MG. Many patients stop sport altogether, finding activities of daily living to be challenging enough in themselves [2]. Even for the general public, marathon running is not practiced by a large majority, one must train regularly and have a high endurance capacity.

There are only three case studies combining sport and MG reported in the literature. Scheer et al. (2012) describe a 52 year old ultra-endurance athlete with mild MG (MGFA IIa), treated with 10 mg of prednisone who completed a 220 km ultra-marathon over 5 days [3].

Fatigue, leg weakness, dysphagia and breathing problems were reported, relieved by rest, shade and 60 mg of pyridostigmine every 90 min (max daily dose 720 mg). He began running 5 years prior to MG diagnosis and maintained a combined weekly running distance of 70 km. Stout et al. (2001) report a 26 year old athletic (baseball and weight lifting) student who suffered from extreme weakness and atrophy due to his MG, he was unable to do a single push-up at diagnosis [4]. Once stabilized he began exercising again at low levels which prevented further weakness but he struggled to regain force until undergoing a 15-wk upper and lower limb resistance training program, with oral creatine supplementation and he was able to make force gains (37% leg extension) and increase training volume (34–40% upper limb). Finally, Leddy et al. (2000) describe a 17 year old college football player with mild generalized MG (antibody-negative, 15% decrement RNS-EMG), treated with 60 mg prednisone every other day and 60 mg pyridostigmine q.i.d [5]. Following an initial period of weakness at the time of diagnosis, his strength returned to normal after

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6 weeks and aside from a relapse associated with a period of non-compliance with medication, he became stable without treatment and was able to participate in full football practice.

Three recent uncontrolled trials have demonstrated benefits and tolerance of supervised physical activity (resistance or aerobic) programs for patients with stable MG [6–8]. Additionally, using the contralateral limb as a control, Lohi et al. found improvements in lower limb force following dynamic training and no deterioration nor negative side effects in a group of 11 subjects with mild MG [9]. A review article has suggested that risk factors for exacerbation of MG include prolonged exercise, running uphill and activity with stairs, however no specific data was provided to support these claims [10]. Currently there are no official guidelines regarding participation in sport and MG [11, 12].

Case presentation

Here we report a 36-year-old female nurse, working full-time 12-h night shifts in a busy intensive care service, with generalized (MGFA IIb) auto-immune MG, symptomatic and dependent on cholinesterase inhibitors. Past medical history includes eczema in her teens, she is a carrier for sickle disease (sickle cell trait (SCT)) and she carried two pregnancies to term. Red blood cells have slightly reduced mean corpuscular volume and mean corpuscular hemoglobin concentration, 75.5 fl and 25.7 pg, respectively. She has no clinical symptoms of anemia and no specific treatment or monitoring. Surgical history includes 1 cesarean (2004), linea alba repair (2011) and breast implant (2014). She is a nonsmoker and does not drink

alcohol. She is right-handed. She has a normal body mass index, 20.3 kg/m², weighing 52 kg for 1.60 m.

Despite already experiencing abnormal weakness, she began running a year before being diagnosed with MG. Prior to running, she played amateur level basketball however this became incompatible with working night-shifts. MG diagnosis was based on clinical signs (right hand weakness - difficulty brushing teeth and hair, carrying light loads, cutting meat, a heavy head, nasal voice, ptosis, diplopia, dysphagia and difficulty masticating and articulating), serum auto-antibodies against nicotinic acetylcholine receptors (AChR) (> 100 nmol/l) and significant decrement on repetitive nerve stimulation (3 Hz) EMG (50% right trapezius, 24% right anconeus, 15% left anconeus, 43% tongue/mouth (CN V/XII)). Myasthenic muscle score (MMS) was 65/100. Initial treatment consisted of intravenous immunoglobulins (2 g/kg over 3 days (100 g)) and 60 mg pyridostigmine (t.i.d). Thoracic CT scan did not show thymoma but was in favour of thymic hyperplasia. Thymectomy was not performed as per the patient’s request.

Despite the patient being informed at diagnosis that sport was contra-indicated, she kept running. Training consisted of 1–2 10 km weekly runs with the beginning being the most difficult. MG symptoms persisted including fatigue, dysphagia and episodes of diplopia at the end of pyridostigmine dose thus aziathoprine (100 mg) was introduced. She performed a half marathon 2 months later, followed by a full marathon and another half marathon. No major difficulty was experienced and performances significantly improved: 5h13mins (8.1 km/h) for a marathon pre-diagnosis to 4h51mins (8.7 km/h) post diagnosis (and treatment), Figs. 1 & 2.

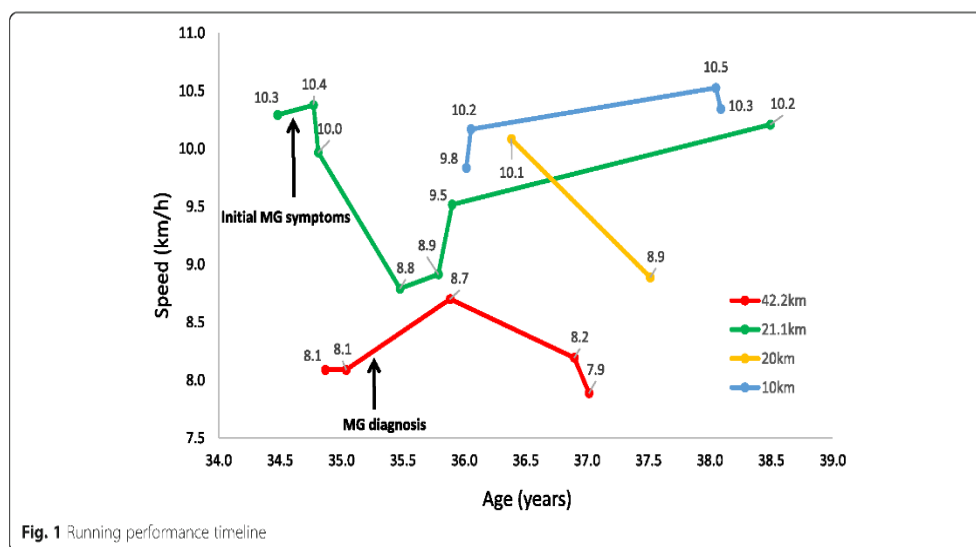
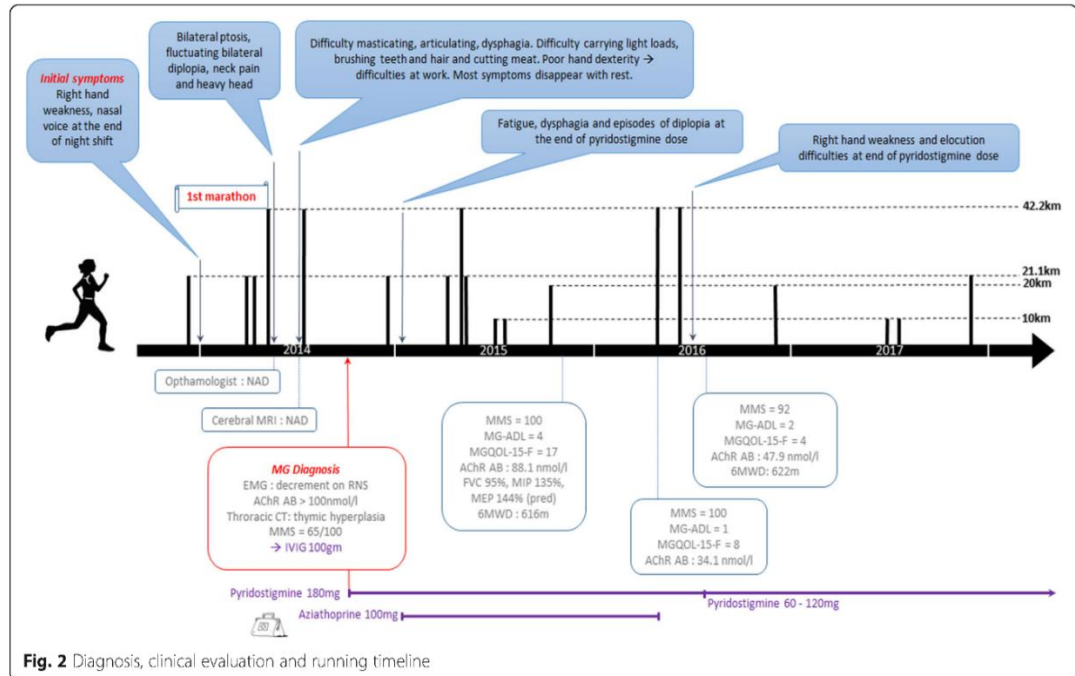


Fig. 1 Running performance timeline



On clinical evaluation 1 year after MG diagnosis, she had above average respiratory strength (MIP and MEP 135% and 144% of theoretical) and normal respiratory function (FVC 95% of theoretical). On maximal voluntary testing, limb strength was normal (knee extensors and elbow flexors: 128% and 101% of theoretical, respectively and right handgrip strength: 88%). Walking endurance was also considered normal (92% of theoretical 6MWD). The MMS suffered from a ceiling effect with the patient achieving the maximal score of 100 and a score of 4 on the MG-ADL due to episodes of dysphagia, dyspnea with effort and UL fatigue with brushing her teeth and hair. She reported recurrent MG symptoms including loss of hand dexterity (difficulty manipulating medication at work), bulbar symptoms such as dysphagia on her own saliva, a nasal voice and ocular symptoms (ptosis and diplopia). MG-specific quality of life (MGQOL-15-F) was reduced (17/60) particularly with regards to professional and social aspects, reflected in the WHO-QOL Bref with the social relationship and physical health domains being reduced, 11/20 and 13/20 respectively [13, 14].

She continued regular running without any particular changes in her MG, recurrent right hand weakness persisted and she experienced occasional ocular and bulbar symptoms primarily at the end of pyridostigmine dose. Quality of life improved significantly over time (Fig. 2) and strength remained stable (knee extensors and elbow flexors: 128% and 100% of theoretical, respectively, right

handgrip strength: 93%). She discontinued aziathoprine (treatment duration 14 months) and remained exclusively treated with cholinesterase inhibitors (60 mg, b.i.d).

Discussion and conclusion

It is well known that MG does not affect all muscles to the same extent and whilst some muscles may clearly be affected, other muscles may function normally and can be trained without adverse effects. Thus, continuing activities and daily life seems important for maintaining “unaffected” muscles and for psychological benefits. With regards to physical activity a close link between endurance running and the immune system activity has been demonstrated [15]. During sustained physical activity, repeated muscle contractions stimulate the production of inflammatory cytokines such as Interleukin-6 (IL-6) by myocytes. IL-6 may act as an inhibitor to pro-inflammatory cytokines such as TNF- α which is a potent mediator of tissue damage [16, 17]. IL-6 also stimulates the production of IL-10 (an anti-inflammatory cytokine) and IL-1ra, generating an anti-inflammatory environment. Whether these effects can modify disease activity in MG currently remains unclear. These exercise-induced mediators of inflammation are susceptible to exercise dose, with greater increases seen following a marathon as compared to a half marathon, for example [16]. A disease-specific response has been suggested for the change in cytokine kinetics in relation to exercise [18].

Whilst evidence of exercise-induced change of cytokines remains sparse in MG, there is growing evidence of the presence of inflammation and modulation of the immune response by cytokines in MG pathogenesis [19, 20]. Certain cytokines are upregulated (IL-17, IL-21, IL-6, IL-10) and others downregulated (IL-4) compared to control subjects [19, 21–23]. A recent study evaluated serum IL-6 before and after a twice-weekly, 3 month training program in subjects with ocular or mild, generalized MG. Serum IL-6 levels remained unchanged [7]. However, circulating microRNAs (miR150-5p and miR21-5p) decreased [7]. These immuno-microRNAs have been suggested as new biomarkers in AChR MG, notably miR150-5p as a marker for disease severity [24, 25].

Another factor which warrants consideration here is the localized role of IL-6 in triggering satellite cells in the myogenic process [26]. Whilst research has demonstrated the role of IL-6 in muscle atrophy, this has predominantly involved pathological situations such as cancer cachexia and ageing [27] where there is chronic inflammation. When released at low concentration into satellite cell niches IL-6 could promote repair and regenerate skeletal muscle tissue [27]. It seems that IL-6 is deregulated in the muscles of MG patients, possibly due to AChR antibodies deregulating the IL-6 pathway [28].

In the case of this patient, weakness induced by MG mechanisms tends to affect the same muscles which were initially affected, regardless of increased exertion. Whether this patient has benefitted from protective effects of exercise or not is difficult to determine, however, this case study demonstrates that an endurance sport such as running marathons and MG are not mutually exclusive. The immunosuppressor treatment likely played an essential role in attenuating the autoimmune attack enabling the patient to improve and optimize her physical capacities. Clinical scores improved and remained stable and running performance improved and remained relatively consistent (Figs. 1 and 2). The level of antibodies against AChR decreased over time (Fig. 2) however this also coincided with immunosuppressor treatment.

In stabilized MG there are no clear arguments to fear adverse effects of physical activity and as well as positive psychological effects, patients will benefit from cardiovascular and muscular adaptations as well as possible immunomodulatory effects. It is important to consider each individual case and weigh up the benefits and risks and possibly put into place a supervised or specific return to sport program where necessary. As can be expected in the absence of disease, inter-individual variation is likely with strenuous physical exercise.

It seems important to discuss the possible consequences of exercise and sickle cell trait which are not currently clear in the literature. Case-control studies have found an increased prevalence of sudden death on

exertion, often called “exercise collapse associated with sickle trait” however a direct causal relationship has not been confirmed [29]. It has been suggested that a combination of factors [30] such as high altitude or severe dehydration combined with intense physical activity could cause red blood cells to become deformed or sickled and cause complications such as rhabdomyolysis. This may be due to lower capillary density and tortuosity, reduced small vessels and a higher percentage of broader micro vessels [31]. Microvascular remodeling may be a compensatory mechanism to facilitate normal blood flow [29] which may be present in this patient considering the raised but not excessive elevation of CK following a marathon (data not presented). SCT may not be a completely benign carrier state nor a true disease entity but rather a potential risk factor which could be monitored. Maintaining physical fitness may be a protective agent by decreasing the endothelial activation through improvements in nitric oxide and antioxidant availability [32, 33]. Precautions would be the same as for exercise with MG i.e.; adequate hydration, control heat exposure and monitor exertion intensity [34].

This case report demonstrates that despite being in the first 2 years of MG disease onset in which exacerbations and instability are most common, and despite regular intense endurance running, the MG has remained stable. A growing body of literature suggests that regular physical exercise may lead to anti-inflammatory effects in chronic auto-immune diseases. The immunomodulatory role of exercise could be considered in this case study. However, further studies regarding the specific effects of exercise on disease activity in MG are necessary to confirm these speculations.

Patient perspective

“I am myasthenic and marathonian, running allows me to take time for myself, to evacuate stress and to think. It’s a real therapy”.

Abbreviations

6MWD: Six-minute walk distance; AChR: Acetylcholine receptor; b.i.d: Twice a day; CN: Cranial nerve; EMG: Electromyogram; IL-6: Interleukin-6; MG: Auto-immune myasthenia gravis; MG-ADL: Myasthenia Gravis Activities of Daily Living score; MGFA: Myasthenia Gravis Foundation of America disease classification; MGQOL-15-F: Myasthenia Gravis 15 item French Quality Of Life scale; MIP/MEP: Maximal inspiratory pressure/Maximal expiratory pressure; MMS: Myasthenic Muscle Score; SCT: Sickle cell trait; t.i.d: Three times a day; TNF- α : Tumour Necrosis Factor alpha; UL: Upper limb; WHO-QOL Bref: World Health Organisation Quality Of Life short questionnaire

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All data analysed in this case report are included in this published article.

Disclaimer

This is a case report and is by no means a reflection of common practice. Several factors may have contributed to disease stability in this subject.

Authors' contributions

SB contributed to the concept, drafting and reporting of the case. MT, BE and SB acquired clinical data and revised the manuscript. TS, PP, JY, contributed to reporting and revising the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

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VI. General discussion

The work presented here includes:

I. the protocol of a randomised controlled trial evaluating the benefits and tolerance of general exercise in auto-immune MG (MGEX),

II. the validation study of a French MG-specific patient-reported outcome measure of quality of life in a cohort of 125 participants, which was the primary outcome of the MGEX trial,

III. a cross-sectional study of physical activity patterns in 33 women with generalised MG, relationships with disease severity, duration, functional walking capacity and quality of life,

IV. an evaluation of limb muscle strength and neuromuscular fatigue in 41 women with generalized MG, and relationships with disease characteristics and quality of life,

V. preliminary results of the MGEX trial,

VI. a case report of a 36 year-old female who performs long-distance running despite MG, with a discussion of the immunomodulatory benefits of exercise.

Auto-immune MG is a chronic, unpredictable disease. Whilst diagnosis and treatment prospects have largely improved and mortality from MG has reduced, persistent and fluctuating symptoms can have significant consequences on QoL and daily living, and may limit participation in physical activity.

Research evaluating the effects of exercise in MG has been sparse however in the last two years four new studies have been published, a common trend in other neuromuscular diseases in this “exercise is medicine” era. For health professionals and/or patients no guidelines or recommendations exist and there does not seem to be a common consensus amongst specialists with regards to exercise.

When assessing the literature, of the five experimental studies only one reported significant adverse events, likely occurring prior to the commencement of the exercise intervention [60]. Thus, when considering safety, exercise seems possible in stable disease. When considering the type or quantity of exercise there is currently not enough information to conclude. One resistance training protocol reported subjects not being able to complete prescribed repetitions or meet increasing load [59]. A large range of outcome measures have been used in the various studies, including tests evaluating body structure and function as well as participation and two studies included a quality of life measure. There is currently no gold standard for measurement in MG, the MGFA Task Force recommends the MG-Composite for use in clinical trials which combines a physician assessment with a patient-report whereby a ≥ 3 point difference is considered clinically meaningful [24].

In 1946 the World Health Organisation introduced the broadened definition of health as “a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity”. Quality of life as opposed to simply quantity of life has become a large research interest and QoL measures are being used as endpoints in clinical trials, particularly of chronic diseases more often nowadays. It is desirable to ask patients directly about the impact of disease and treatment on their daily lives [110], putting the patient at the centre and seeking effects that are meaningful to them. However, this is not without difficulty as health-related QoL is a broad-ranging concept influenced by a person’s experiences, expectations and perceptions [111].

MGEX, the randomized clinical trial presented here selected a HRQoL measure, as its primary endpoint in evaluating the benefits and tolerance of an unsupervised, home exercise aerobic training program compared to usual care [92]. This disease-specific HRQoL measure was translated and “validated” in French prior to beginning the study to ensure its psychometric properties were robust for research purposes [92]. The MGQOL-15-F is rapid and simple to use and it is now part of routine clinical practice to provide additional insight into how an individual lives with their MG and its treatment. It is complementary to the point-in-time clinical measures commonly used in MG.

No difference was found in HRQoL between the two groups (paper V). Several secondary measures such as the MG-ADL, the impact of MG on activities of daily living, knee extension strength (CACE analysis) and functional walking capacity measured with the 6MWT showed greater improvements in the group randomised to exercise. There were presumably muscular and cardiovascular adaptations also as subjects improved their performance (mean 13% increase in rowing distance) whilst maintaining the same target heart rate during the exercise program. Although not formally tested, qualitatively, participants reported reduced pain, improved sleep and increased confidence. A recent study reported improved exercise self-efficacy which was not evaluated in MGEX but may be an important factor to consider as some individuals with MG may have fear or negative beliefs with regards to exercise e.g. that exercise may increase symptoms or worsen the disease [58]. Having the opportunity to participate in a structured exercise program, organised by health professionals, without experiencing adverse events may be useful in shifting beliefs and attitudes.

With regards to daily life, individuals with MG are more sedentary than control subjects, however our results demonstrate that they do undertake physical activity. They perform overall less vigorous physical activity. When considering combined moderate-vigorous intensity physical activity in bouts of at least 10 minutes, only 30% satisfy the current recommendations of 150 minutes per week [112]. The remaining 70% perform 150 minutes of moderate-vigorous intensity physical activity however the activity is more fragmented into shorter bouts i.e. < 10 minutes at a time. Whether this is learned behaviour or due to actual capacity is currently unknown. This is important to consider when designing individualised training programs and guidelines. The 12-minute walk test, in association with an evaluation of free-living physical activity may provide further insight and assist in stratifying subgroups.

Evaluating an individual's baseline activity with wearable activity trackers would provide valuable information even in routine practice as devices become accessible in terms of cost and data access.

The MGEX trial demonstrated that exercise can improve functional walking capacity. Walking capacity has been shown to be positively correlated to daily physical activity behaviour (paper III). Whilst MG-specific QoL did not improve with a structured-home based exercise program, this was consistent with daily activity not being related to HRQoL. Thus, concepts which may be largely accepted in the general population may not be applicable to this population, or rather to this subgroup of MG. It should be noted that the majority of these studies included females only, with stable disease yet a reduced HRQoL (inclusion criteria for MGEX, MGQOL-15-F ≥ 15) and relatively high body mass index. Thus, results here cannot be applied to all individuals with MG. However, these results do provide us with some insight into this population.

The MGEX trial also raises the problem of compliance. Whilst reasons unrelated to "ability" or "tolerance" were cited as reasons for non-compliance, we cannot rule out the possibility that the exercise program could have been considered too difficult for some, this has been a limiting factor in a past study for certain exercises [59]. Importantly this was the first unsupervised study of exercise in MG demonstrating a clear motivation of subjects to participate. Whilst compliance was lower than previous studies, it was still acceptable however it may not have been sufficient to induce expected changes. Whilst an unsupervised program may present with additional logistic and adherence difficulties it may be more effective in empowering individuals and enabling them to more easily make the transition from participating in exercise within the context of a clinical study and participating in real life exercise for themselves. Many factors influence compliance in exercise and physical activity, factors can be intrinsic such as personal motivation, attitudes and personal experiences or extrinsic such as one's social and physical environment.

Whilst fatigue is a hallmark symptom of MG, contrary to our hypothesis, we failed to demonstrate greater neuromuscular fatigue in individuals with MG compared to gender and age-matched controls in this cohort study (paper IV). It is important to consider these results within this particular experimental paradigm where there was no control of central factors and the type and intensity of the task (submaximal, 40 second sustained contraction) may

have been inadequate. Perceived fatigue is highly prevalent and impacts on both function and QoL in MG however its cause remains unclear. Studies evaluating neuromuscular fatigue in MG are sparse and fail to demonstrate greater NMF in individuals with MG compared to control subjects or methodological shortcomings limit conclusions. The concept of fatigue in MG stems from the fact that there is a reduced response (decrement) with repetitive stimulation on electrophysiological testing. Surprisingly, perceived fatigue has been found in individuals with and without decrement whilst neuromuscular fatigue did not differ between the 2 groups (decrement or non-decrement MG), nor with controls [74]. Importantly, there was a difference in strength.

It has been suggested that perceived fatigue is related to weakness and our findings are in line with this possibility. As we did not evaluate perceived fatigue, we could not draw conclusions however we did find subjects with MG to be weaker than control subjects. In line with the literature this was unrelated to disease severity nor disease duration in our cohort [74, 86, 113, 114].

In the quest for finding a complementary tool for evaluating performance fatigability in MG and considering the recent work done in other neurological diseases, we performed an analysis of the evolution of the 6MWT in women with MG and age, gender and height-matched controls (unpublished personal data). We found that the global walking distance was 21% (on average) less, however the walking pattern was similar ($p=0.407$). Both groups walked the furthest distance in the first minute and whilst the control group stabilised from the 2nd minute, the MG group stabilised from the 3rd minute and like controls, then maintained a steady pace until the end. We conclude that this simple clinical test is useful for evaluating global performance but not as a measure of performance fatigability in MG.

We demonstrated that reduced strength in individuals with MG was correlated with reduced QoL (paper IV). It would be worthwhile to evaluate the effects of a specific resistance program in a controlled trial to explore whether improved strength could lead to a decrease in perceived fatigue and a potential increase in self-perceived HRQoL. Rahbek, et al. recently demonstrated strength gains, reduced performance fatigability and improved HRQoL with progressive resistance training, despite methodological limitations, these results are promising [60].

This work reinforces the notion that MG is not only a heterogeneous disease in terms of pathophysiology/immunological profile. Physical activity patterns were varied, with some subjects performing beyond the minimal recommendations for physical activity for adults in the general population and others maintaining a highly sedentary lifestyle (paper III). These behaviours were unrelated to disease severity nor duration. Body mass index does seem to play a role. Whether it is a possible cause or the result of reduced activity remains to be elucidated. This would be worth investigating in this population particularly as increased body mass index was associated with reduced walking capacity (6MWD) thus creating a potential vicious cycle.

At this stage whilst the hypothesis that exercise could play a role in the immune response (due to the underlying auto-immune dysfunction in MG) was suggested in the case report, current analyses from the MGEX trial did not confirm this hypothesis. Analyses are still preliminary and results may be due to the choice of cytokines or due to compliance and dose-relationship factors or timing of serum collection with regards to exercise.

In conclusion, the work presented here demonstrates that exercise in stable MG is without danger and has beneficial effects on functional walking capacity likely due to improved aerobic capacity and muscle metabolism. The specific type of exercise as well as optimal intensity and duration for increased benefits is still unclear. One indicator to help guide decisions may be baseline activity levels. Instrumented measurement can assist in characterising a person's current activity volume and intensity. This could help in adapting programs according to current abilities and lifestyle particularly due to the heterogeneity in this population as seen in Paper III.

Further research and reflection should focus on not what is possible but what will actually be performed and consider any specific (or general) barriers or enablers to participation in exercise interventions or physical activity. Further studies of neuromuscular fatigue are warranted to understand its role in the perception of fatigue. Evaluations such as the MG Impairment Index may assist in differentiating between weakness and fatigability experienced by an individual [21]. Studies should use the interpolated twitch technique to measure any reduction in voluntary activation [81]. Careful consideration should also be given to the muscle selected with respect to individual symptoms.

VII. Conclusions and future perspectives

An updated review on exercise and MG is warranted to clearly incorporate all of the latest research since the last review published in 2016. This could be used as a guide to develop clear and specific recommendations for physical activity and exercise in MG which are currently lacking and long overdue.

Reflection with respect to clinical evaluation is warranted and whether a simple test such as the 30-second sit-to-stand should be incorporated into routine clinical practice particularly for individuals in which the Myasthenia Muscle Score suffers a ceiling effect. Even though it is more time (and space) consuming, where possible, the 6MWT could also be useful for further studying relationships with free-living physical activity and potentially for use in stratifying individuals into different functional categories. Identification of the minimal clinically important difference of the six-minute walking distance in this population is necessary for incorporating the 6MWT as an outcome measure in future clinical trials of exercise interventions and physical activity behaviours. Wearable activity trackers could also be used as future outcome measures and could be useful as complementary information in a National database to stratify individuals and further assist in understanding relationships between structure and function.

Another clinical trial, taking into account these results and the recently published literature and addressing the remaining questions is warranted. This should aim to confirm current findings and further understand group and individual barriers (and facilitators) to participation in exercise and consider dose and specific types of exercise. More sophisticated testing of neuromuscular fatigue is necessary in order to understand its role in the experience of fatigue and potentially aid in treatment strategies, including exercise interventions.

Whilst premature mortality is usually no longer a problem in treated MG, a lack of physical activity and excessive sedentary behaviours can increase the risk of other comorbidities such as cardiovascular disease which cause early mortality. Attitudes and beliefs can be a barrier to participation in exercise thus, it is crucial that clear guidelines and recommendations concerning physical activity for individuals with MG are established to inform and guide health professionals and patients. There is no longer reason to believe that individuals with MG cannot participate in physical activity.

Appendix

1. MG-ADL score (Score d'activité quotidienne) [18]

L'interrogatoire sur les 8 derniers jours précédant celle-ci.

Items	0	1	2	3	Score
Elocution	Normale	Voix nasonnée ou dysarthrie intermittente	Voix nasonnée ou dysarthrie permanente	Dysarthrie majeure empêchant d'être compris	
Mastication	Normale	Fatigue avec les aliments solides	Fatigue avec les aliments semi-liquides	Sonde nasogastrique	
Déglutition	Normale	Troubles épisodiques	Troubles fréquents imposant de changer de régime	Sonde nasogastrique	
Respiration	Normale	Dyspnée d'effort	Dyspnée de repos	Ventilation mécanique	
Difficulté à se brosser les dents ou à se peigner	Aucune	Nécessite un effort mais sans requérir de repos	Repos nécessaire	Ne peut accomplir aucun de ces gestes	
Difficulté à se relever d'une chaise	Aucune	Nécessite parfois l'aide des bras	Nécessite toujours l'aide des bras	Nécessite une assistance	
Diplopie	Aucune	Survenue épisodique mais pas quotidienne	Survenue quotidienne mais transitoire	Permanente	
Ptôsis	Aucun	Survenue épisodique mais pas quotidienne	Survenue quotidienne mais transitoire	Permanente	
Total					

2. Myasthenia Muscle Score (MMS) [16]

Membres supérieurs étendus à l'horizontale en antéroposition

1 point/10 secondes Max. 15 points
Min. 0 point

Membres inférieurs, malade en décubitus dorsal, cuisses fléchies à 90° sur le bassin, jambes à 90° sur les cuisses
1 point/5 secondes Max. 15 points
Min. 0 point

Flexion de la tête, le malade en décubitus dorsal

- contre résistance 10 points
- sans résistance 5 points
- impossible 0 point

Passage de la position couchée à la position assise

- sans l'aide des mains 10 points
- impossible 0 point

Oculomotricité extrinsèque

- normale 10 points
- ptôsis isolé 5 points
- diplopie 0 point

Occlusion palpébrale

- complète 10 points
- diminuée (signe des cils) 7 points
- incomplète avec recouvrement cornéen 5 points
- incomplète sans recouvrement cornéen 0 point

Mastication

- normale 10 points
- diminuée 5 points
- nulle 0 point

Déglutition

- normale 10 points
- dysphagie sans fausse route 5 points
- dysphagie avec fausse route 0 point

Phonation

- voix normale 10 points
- voix nasonnée 5 points
- aphonie 0 point

Score: |_|_|_| / 100

3. MG-specific quality of life score (MGQOL-15-F) [19]

MGQOL-15-F

Pour chacun des items suivants, cochez la case décrivant le mieux votre situation (au cours des dernières semaines)	pas du tout	un peu	moyennement	beaucoup	énormément
	0	1	2	3	4
1. Ma myasthénie est un poids pour moi					
2. J'ai des difficultés à voir à cause de ma myasthénie					
3. J'ai des difficultés à manger à cause de ma myasthénie					
4. J'ai limité ma vie sociale à cause de ma myasthénie					
5. Ma myasthénie m'empêche de profiter pleinement de mes loisirs					
6. J'ai des difficultés à remplir mes obligations familiales à cause de ma myasthénie					
7. Ma myasthénie m'oblige à planifier mes activités					
8. Ma myasthénie a affecté ma situation et mes aptitudes professionnelles					
9. J'ai des difficultés à parler à cause de ma myasthénie					
10. J'ai des difficultés à conduire à cause de ma myasthénie					
11. Je suis déprimé(e) à cause de ma myasthénie					
12. J'ai des difficultés à marcher à cause de ma myasthénie					
13. J'ai des difficultés à me déplacer dans les lieux publics à cause de ma myasthénie					
14. Je me sens dépassé(e) par ma myasthénie					
15. J'ai des difficultés à effectuer certaines activités quotidiennes (me laver, m'habiller, me coiffer..etc)					

Nom : _____

Date : _____

Score total : /60

4. Questionnaire destiné aux cliniciens

Pratiques et croyances : exercice physique et myasthénie auto-immune

Ce questionnaire ne concerne que les patients atteints d'une **myasthénie auto-immune**.

Le questionnaire sera anonyme mais afin de nous aider à décrire la population nous vous demandons votre:

Age : 20-29 ans 30-39 ans 40-49 ans 50-59 ans 60-69 ans 70-79 ans ≥ 80 ans

Sexe : Femme Homme

Profession : Neurologue Médecin généraliste Médecin physique et réadaptation
Kinésithérapeute Autres

Secteur de travail : Publique Privé

Combien de patients atteints de myasthénie auto-immune voyez-vous par mois en moyenne ?

0 1-4 5-9 10-14 15-19 ≥ 20

1. Pensez-vous qu'une pratique d'exercice physique intense (en dehors d'une poussée myasthénique) peut aggraver l'état de santé du patient ?

Oui Non Ne sait pas

2. En dehors d'une poussée myasthénique, conseillez-vous la pratique de l'exercice physique modéré et régulier à vos patients? (en plus de l'activité physique spontanée – déplacements, tâches ménagères, etc)

Oui Parfois Non

Si oui, quel exercice conseillez-vous de préférence ?

Plutôt endurance Plutôt renforcement musculaire Les deux

A quelle fréquence?

≤ Une fois par semaine Trois fois par semaine Tous les jours

A quelle intensité ?

Douce Modérée Intense

Si non, pourquoi ?

Fatigue Risque d'exacerbation/aggravation Pas de raison particulière

3. Pensez-vous que l'exercice physique pourra être bénéfique pour vos patients myasthéniques?

Oui Non Ne sait pas

Commentaires (facultatif) :

5. International revision of the MGQOL-15, MGQOL-15r

INTERNATIONAL CLINIMETRIC EVALUATION OF THE MG-QOL15, RESULTING IN SLIGHT REVISION AND SUBSEQUENT VALIDATION OF THE MG-QOL15R

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ABSTRACT: *Introduction:* The MG-QOL15 is a validated, health-related quality of life (HRQOL) measure for myasthenia gravis (MG). Widespread use of the scale gave us the opportunity to further analyze its clinimetric properties. *Methods:* We first performed Rasch analysis on >1,300 15-item Myasthenia Gravis Quality of Life scale (MG-QOL15) completed surveys. Results were discussed during a conference call with specialists and biostatisticians. We decided to revise 3 items and prospectively evaluate the revised scale (MG-QOL15r) using either 3, 4, or 5 responses. Rasch analysis was then performed on >1,300 MG-QOL15r scales. *Results:* The MGQOL15r performed slightly better than the MG-QOL15. The 3-response option MG-QOL15r demonstrated better clinimetric properties than the 4- or 5-option scales. Relative distributions of item and person location estimates showed good coverage of disease severity. *Conclusions:* The MG-QOL15r is now the preferred HRQOL instrument for MG because of improved clinimetrics and ease of use. This revision does not negate previous studies or interpretations of results using the MG-QOL15.

Muscle Nerve 54: 1015–1022, 2016

“Never neglect an opportunity for improvement.”

– Sir William Jones

Health-related quality of life (HRQOL) outcome measures are designed to measure a patient’s

Abbreviations: HRQOL, health-related quality of life; MG, myasthenia gravis; MG-QOL15, 15-item Myasthenia Gravis Quality of Life scale; MG-QOL15r, revised MG-QOL15; PCA, principal component analysis
Key words: MG-QOL15; MG-QOL15r; myasthenia gravis; myasthenia; quality of life; Rasch analysis; revised MG-QOL15
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Validation of the MG-QOL15r

appraisal and tolerability of a disease and its treatments.¹ Patient-reported outcomes, such as HRQOL measures, are particularly well-suited for myasthenia gravis (MG), because the manifestations of MG: (1) fluctuate over time, (2) may worsen later in the day (i.e., fatigue), and (3) are often more evident to the patient than to the physician (e.g., dysphagia and chewing fatigue).^{2,3} Thus, the physician’s examination of an MG patient is only a snapshot of a “video” that is the patient’s disease-related everyday life.^{2,3} The 15-item Myasthenia Gravis Quality of Life scale (MG-QOL15) is a disease-specific HRQOL instrument derived from a previously validated 60-item MG-QOL measure.^{4,5} The 15 items of the MG-QOL15 were selected based on performance, especially treatment responsiveness and reliability.⁴ The MG-QOL15 has been validated in a 175-subject, multicenter validity study.^{2,6} It is useful for: (1) learning the patient’s perspective during a clinical evaluation; (2) following patients over time^{2,7}; (3) comparing groups of patients, such as in a clinical trial^{7–9}; and (4) studying the HRQOL of cohorts of patients with MG.^{2,6,10–13}

The 15 items of the MG-QOL15 are designed to assess important aspects of the patient’s experience related to MG⁴ that should be considered during evaluation of clinical status. If, for example, a patient has mild to moderate symptoms that are stable and not particularly troublesome, one might be less inclined to escalate treatment and the associated attendant risks. On the other hand, if those manifestations are bothersome to the patient, the clinician

MUSCLE & NERVE December 2016 1015

may be more likely to consider treatment changes. In other words, an integral part of the risk-benefit calculation for management and treatment decisions includes disease-specific HRQOL considerations.

There has been recent interest in use of item response theory models such as Rasch analysis for clinometric evaluation of patient reported outcome measures. These models evaluate individual test item response pattern in relation to overall response as well as a hypothetically linear “expected” (i.e., ideal) model. These models also explore patient response patterns and allow comparison between groups (e.g., disease subtypes or gender).

The MG-QOL15 has been translated into Japanese, Spanish, French, Portuguese, Danish, Persian, Chinese, Malay, Thai, Indonesian, Hindi, Marathi, and other languages (personal communications).¹⁰⁻¹⁵ It is in use around the world, both in everyday practice and in clinical trials. Worldwide use of the MG-QOL15 over the past 7 years has given us the opportunity to: (1) evaluate its validity in other populations, (2) determine if any items should be revised, (3) investigate if the original 5-response-choice design (“not at all,” “a little bit,” “somewhat...”) is optimal, and (4) explore cultural or population differences in MG-QOL. We were able to evaluate scale results for populations in the United States, Canada, Scotland, France, Iran, Japan, and China, from which we performed the following analyses.

MATERIALS AND METHODS

The partial credit Rasch model was conducted using Winsteps software (version 3.92.1) to explore data for item-person targeting (item difficulty and person ability comparison), item-person stability (fit statistics and dimensionality), item dependency, category response functioning, and differential item functioning. Fit statistics were calculated measuring the variability between actual and expected response patterns for each item using chi-square (represented as mean square unstandardized average value of squared differences). Principal component analysis (PCA) of the differences between observed and expected scores (residuals) of misfitting items was performed to disclose potential items measuring different or contrasting items (such as items measuring a different concept).

Correlation analyses of patient responses for different items were performed to determine if 2 items are significantly measuring similar range or concept of disability. The partial credit model also compared the probability of a certain category response with other category responses; higher category responses are expected to have significantly higher probabilities in more severely affected patients. Expected model estimates were used to possibly modify scaling and improve test sensitivity. Differential item func-

tioning was also analyzed to compare response patterns among groups for each item individually and in relation to other items.

RESULTS

Phase I Results: Retrospective Analysis of MG-QOL15

Scale Scores. MG-QOL15 surveys were completed on consecutive MG patients seen in 19 participating clinics during various time periods from 2008 to 2013. (Results of some of these surveys have been published previously.^{2,6,10-14}) We analyzed scores from 1,362 MG-QOL15 surveys completed by 954 MG patients, some of whom completed the surveys at 2 consecutive clinic visits. Six hundred twenty-six patients were from eastern Japan (mean age 58.7 years \pm 16.4; disease duration 11.9 years \pm 9.4), 175 from centers in the United States (8.3 years \pm 16.6; 6.6 years \pm 7.9), 107 from Glasgow, Scotland (64.1 years \pm 16.4; 6.9 years \pm 7.1), and 46 from Toronto, Canada (56.3 years \pm 16.8; 5.7 years \pm 8.3). Mean MG-QOL15 scores were: Japan, 14.1 (\pm 12.7); United States, 16.5 (\pm 14.3); Scotland, 18.6 (\pm 16); and Canada, 33 (\pm 12.3).

Item-Person Targeting. “Trouble speaking” and “trouble eating” items were more likely scored abnormal in severe disease and, therefore, were best able to differentiate between different levels of severity in more severely affected patients. In contrast, “I am frustrated,” “affects ability to enjoy hobbies,” “make plans around my MG,” “trouble with vision,” and “affects my ability to be social” items were more appropriate for milder disease (Fig. 1, left panel)

Item-Person Stability. Fit statistics revealed that “trouble driving” and “trouble with vision” were the most misfitting items, followed by the work/occupation item (Fig. 1, left panel). Category response functioning of the 5-response version of the MG-QOL15 found the following items to be disordered: “occupation,” “driving,” “overwhelmed,” “grooming,” and “eating.” We revised the response system so that there were only 3 options: the previous 0 remaining 0 (“not at all”), the previous 1 and 2 becoming 1 (“a little bit” and “somewhat” = “somewhat”), and the previous 3 and 4 becoming 2 (“quite a bit” and “very much” = “very much”). After the response categories had been thus amalgamated from 5 to 3 options, all 15 items were found to be ordered (i.e., none were disordered). Re-scoring also improved the fit statistics of the 15 items, with all 15 items fitting the model.

Differential item functioning analysis identified only slight differences in items “frustration” and “trouble getting around public places” between Japanese and non-Japanese responses. It is worth mentioning that the “public places” item had been modified in the Japanese version of the MG-QOL15 because of difficulties with direct

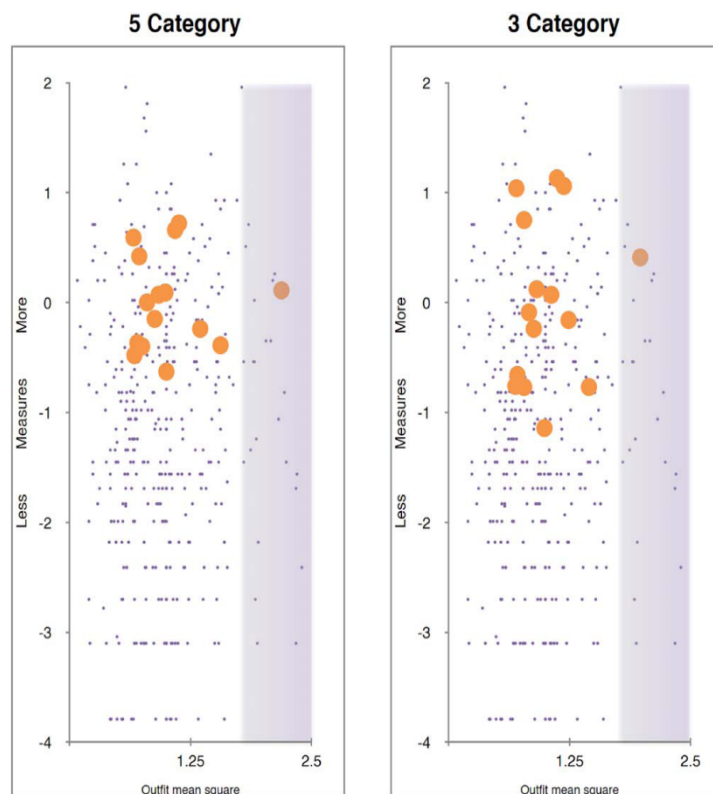


FIGURE 1. Developmental pathway map of the original MG-QOL15 before re-wording of 3 items. The left panel maps out items (circles) with a 5-response option organization. The right panel maps out items when a 3-response option system is used retrospectively. Item difficulty is mapped on the vertical axis, with more difficult items (e.g., bulbar items) located near the top and easier items near the bottom (e.g., “I am frustrated”). The horizontal axis maps how well the items fit under a uniform construct. For the original 5-option scale, the driving item was most misfitting; the driving item was only borderline misfitting with the 3-option scale. Furthermore, the items were less clustered on the vertical axis using the 3-option scale.

translation.¹⁰ In the Japanese version of the MG-QOL15, this item had previously been re-worded to read, “I have trouble getting around as my peers do (for example, in public places).”

The phase I results were reviewed and discussed during a conference call of investigators from each site in 2014. Consensus decisions were based on clinical experience, considerations about face and content validity, cultural and geographic concerns, and results from this analysis.

The committee concluded: (1) The MG-QOL15 was validated in the enrolled cohorts, and remains a useful and valid scale; nevertheless, we would undertake minor modifications that might improve the performance of the scale. (2) We would strive for a single scale that could be used in the countries represented on the committee, and as well as other countries, rather than create language- or country-specific versions. (3) We would prospectively compare the performance of scales having 3, 4, or 5-

response categories. (4) The “driving” item merits slight re-wording because of concerns about limited disease specificity, cultural, and geographic differences in driving habits and our phase I Rasch analysis showing slight misfitting. The committee decided that it was important to include this item in the final scale, largely because of concerns about content validity. That is, we believed that the ability to drive is an integral aspect of HRQOL for most patients, and removing this item would negatively impact the scale. Thus, the item was kept, but re-worded, mostly to be less task-specific, by including the phrase “loss of independence.” (5) Work/Occupation item: This item was believed to merit slight re-wording because of concerns about limited specificity (e.g., unemployment, retirement, or student status, age or other economic considerations unrelated to MG) and our Rasch analysis that indicated item slight misfitting. The item was re-worded to reflect activity beyond occupational work, “including work at home.” The

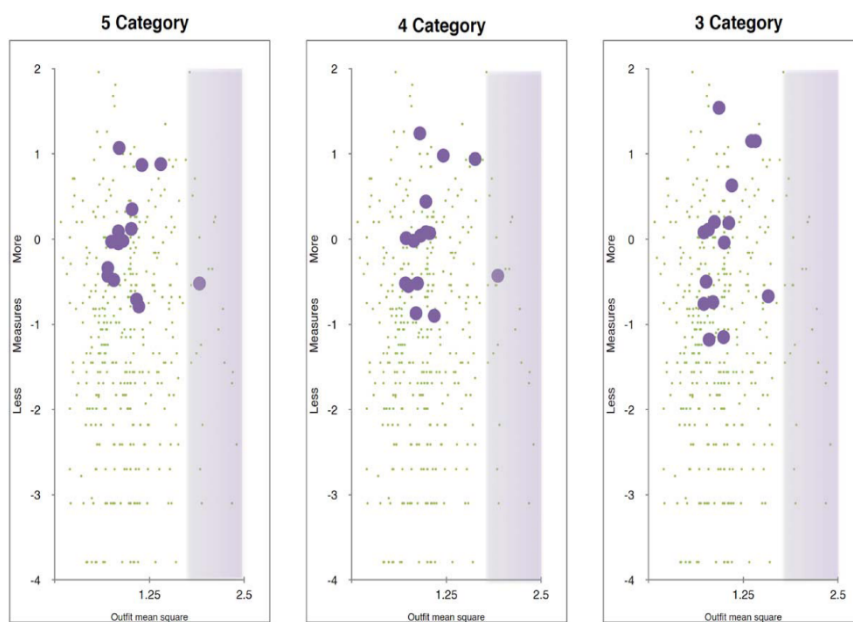


FIGURE 2. Developmental pathway map of the MG-QOL15r after re-wording of 3 items, tested prospectively. The left panel maps out items (circles) with a 5-response option organization, the middle panel with 4-options and the right panel using a 3-response option system. Item difficulty is mapped on the vertical axis, with more difficult items (e.g., bulbar items) located near the top and easier items near the bottom (e.g., “I am frustrated”). The horizontal axis maps how well the items fit under a uniform construct. For the original 5-option scale, the ocular item was most misfitting; the ocular item was only borderline misfitting with the 4-option scale and not misfitting with the 3-option scale. The driving item, which had been re-written, was no longer misfitting for any of the MG-QOL15r scales. Overall, the items were more aligned on the horizontal axis. Furthermore, the items were less clustered on the vertical axis using the 3-option scale, demonstrating better range for discerning various levels of severity. The MG-QOL15r uses the 3- response option system (right panel).

revised item was paraphrased from a similar item in the Neuro-QOL scale.¹⁶ (6) Vision item: The committee believed this item should also be slightly reworded by adding “(e.g., double vision)” to improve its disease specificity. This decision was based predominantly on our clinical experience, as vision changes from other etiologies (e.g., presbyopia, cataracts) are common and were sometimes mentioned by patients when completing the scale.

Phase II Methodology, Based on Results of PHASE I ANALYSES: Selection of Optimal Response-Options and Validation of Revised Scale. We prospectively studied the revised MG-QOL15 as a 3-, 4-, and 5-response option scale. Scale “A” had 5 response options: “Not at all,” “A little bit,” “Somewhat,” “Quite a bit,” and “Very much.” Scale B had 4 options: “Not at all,” “A little bit,” “Somewhat,” and “Very much.” Scale C had 3 options: “Not at all,” “Somewhat,” and “Very much.” Patients were given 2 of these 3 scales to complete in clinic based on a predetermined schedule.

Results of the Prospective Phase II Study of the Revised MG-QOL15. A total of 1301 revised MG-QOL15 (MG-QOL15r) scales (Fig. 2) were

completed by 703 patients from Japan (230), the United States (363), Scotland (160), Iran (168), France (40), Canada (100), and China (240). Results were analyzed only for patients who completed 2 forms, including 3- (424 responses), 4- (441 responses), or 5-response (436 responses) option scales. Forms with any missing data were excluded from analysis. Demographic information was not collected during this phase of the study.

The 5-Response Option Scale. Overall, there were good item (8.6) and person (2.2) separation indices. The items “trouble grooming,” “trouble speaking,” and “trouble eating” differentiated between more severely affected patients and, therefore, were most appropriate for this group. On the other hand, “frustration,” “make plans around my MG,” and “trouble with vision” were more appropriate for less severely affected patients; this was similar to previous findings in other MG cohorts. Fit statistics revealed that “trouble with vision” was the most misfitting item when patients were given 5 choices (response options). Other items fit well, including the other 2 revised items. Response

Please indicate how true each statement has been (over the past few weeks).	Not at all 0	Somewhat 1	Very much 2
1. I am frustrated by my MG			
2. I have trouble with my eyes because of my MG (e.g. double vision)			
3. I have trouble eating because of MG			
4. I have limited my social activity because of my MG			
5. My MG limits my ability to enjoy hobbies and fun activities			
6. I have trouble meeting the needs of my family because of my MG			
7. I have to make plans around my MG			
8. I am bothered by limitations in performing my work (include work at home) because of my MG.			
9. I have difficulty speaking due to MG			
10. I have lost some personal independence because of my MG (e.g. driving, shopping, running errands)			
11. I am depressed about my MG			
12. I have trouble walking due to MG			
13. I have trouble getting around public places because of my MG			
14. I feel overwhelmed by my MG			
15. I have trouble performing my personal grooming needs due to MG			
Total MGOOL-R score			

FIGURE 4. The MG-QOL15r.

items). There was no major significant correlation between other items.

Differential item functioning of the 3-response option scale showed significant differences between population responses for items “trouble using my eyes,” “limited social activity,” “make plans around my MG,” “depressed about my MG,” “trouble walking due to my MG,” and “trouble performing my personal grooming” (items 2, 4, 7, 11, 12, 14, 15). The greatest discrepancies were seen

in “plans around my MG” in Iranian patients and “trouble walking” in Chinese patients. Otherwise the response patterns to all items were similar in all the clinics. These differences do not affect the validity of the scales in these languages and countries but do limit the use of the MG-QOL15r in direct population comparisons.

Overall, there was a modest and significant improvement in item-person stability and targeting in the 3-option scale. There was no significant

difference in sensitivity between the 3-option scale and the 4- and 5-option scales. While overall the items have a similar response pattern in different patient populations, there are some significant intergroup differences for some of items, as outlined above. Some differences may be related to differences in the proportion of patients with ocular versus generalized disease, other disease characteristics, or treatments in these different populations. It is also important to consider the roles of social and cultural differences and their psychodynamic role in HRQOL.

DISCUSSION

Rasch analysis demonstrates that the revised version of the MG-QOL15 (MG-QOL15r; Fig. 2) performs slightly better than the original MG-QOL15. However, this revision does not invalidate the original MG-QOL15, which has also undergone rigorous scrutiny and remains a valid tool for estimating disease-specific HRQOL in MG. This revision also does not invalidate any results and conclusions from studies that have used the MG-QOL15. Nevertheless, the MG-QOL15r is now recommended because of its slightly improved clinimetric properties and slightly improved face and content validity. Furthermore, the MG-QOL15r is slightly easier to interpret in the clinic setting.

Rasch analysis also supports our clinical experience that interpretation of the responses for each item is easier and more intuitive with the MG-QOL15r. For example, the difference between the options "very much" and "quite a bit" in the original MG-QOL15 was sometimes difficult to determine, whereas with the newer scale, the significance of a change from "very much" to "somewhat" is more obvious and interpretable to both the patient and the clinician. Thus, the revised scale performs more like an interval-level scale than the original scale (Fig. 4). However, a risk of having fewer response options is loss of sensitivity to change; fortunately, our analyses indicate there was no loss of sensitivity with fewer choices (e.g., no significant difference in the person separation index on Rasch analysis, on either the phase I or phase II analyses). The clinimetric properties were similar in the 3- versus 4-option scales, but the ocular item performed slightly better when there were 3 options rather than 4. With fewer options in the MG-QOL15r, the interpretation and meaningfulness of each response improves the clinical usefulness of the MG-QOL15r. This is important because an efficient, structured, consistent assessment of how the patient feels about 15 aspects of living with MG should be an essential clinical consideration for a symptomatic, chronic, treatable disease.

Validation of the MG-QOL15r

Three items in the MG-QOL15 were slightly reworded to improve their clinimetric properties and face and content validity. The ocular item was revised to include the wording "e.g., double vision" in hopes of minimizing inclusion of nonspecific visual symptoms; the "work" item was broadened to include work at home, because many patients with MG are retired, unemployed for reasons other than MG, or students; and the "driving" item was broadened to include other limitations of personal independence.

The MG-QOL15 and MG-QOL15r are especially well-suited for MG, because the manifestations of MG fluctuate and are evident to the patient, often more than to the physician.^{2,3} The MG-QOL15 and MG-QOL15r should be useful in everyday clinical care, as an outcome measure in clinical trials, and as an instrument for studying the quality of life of patients with MG. The MG-QOL15 and MG-QOL15r both offer the following attributes in the everyday clinical setting: (1) The 15 items tend to respond to treatment (i.e., a major criterion for item selection was responsiveness to clinical change)⁴; (2) the items are meaningful to patients; (3) some of the items address meaningful consequences of MG that are not ascertained by a symptom-only appraisal (e.g., "limit social activities or hobbies," "make plans around," "frustrated," etc.); and (4) the scales provide an efficient, structured, consistent way to evaluate MG-QOL at each clinic visit. For clinical trials, both scales have shown excellent clinimetric properties and could be considered as a secondary outcome measure. It would be of interest to study the correlations between the MG-QOL15r and other measures, such as the MG-Activities of Daily Living, MG Composite, and Quantitative MG scales. We have learned from using the MGQOL that MG, even when mild, causes frustration, negatively impacts social life and the ability to enjoy hobbies and other pleasurable activities, and forces patients to constantly make plans around their disease.^{2,5,6,9-14} The HRQOL perspective provides a necessary step in understanding what "benefit" may be realized in any risk/benefit calculation.

In conclusion, Rasch analysis shows that the MG-QOL15r has slightly better clinimetric properties over the MG-QOL15. This does not invalidate previous use of the MG-QOL15, but the MG-QOL15r is now the preferred scale for the HRQOL evaluation of individuals and cohorts of patients with MG.

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MUSCLE & NERVE December 2016 1021

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6. Scientific communications

Oral Communications

Journée Ile-de-France, Groupe myasthénie de l'AFM. **Birnbaum, S.** « Activité physique et la myasthénie » 2017, Paris

Journées de l'INK, Muscle and cartilage, **Birnbaum, S.** Exercice physique et myasthénie, Paris, 2015.

Poster communications:

International Neurological Physiotherapy Association conference, **S. BIRNBAUM,** P. PORTERO, T. SHARSHAR, J.Y. HOGREL, and the MGEX Study Group. MGEX: Myasthenia Gravis and EXercise, a randomised, controlled trial protocol. London, 2016

5th international conference of myology, **S. BIRNBAUM,** P. PORTERO, T. SHARSHAR, J.Y. HOGREL in collaboration avec le MGEX Study Group. MGEX: Myasthenia Gravis and EXercise, a randomised, controlled trial protocol. Lyon, 2016

5th international conference of myology, **S. BIRNBAUM,** I. GHOUT, P. PORTERO, A. BEHIN, B. EYMARD, S. DEMERET, F. BOLGERT, T. SHARSHAR, JY. HOGREL. Translation, cross-cultural adaptation and validation of the French version of the Myasthenia Gravis Quality of Life Scale (MG-QOL 15). Lyon, 2016

World Muscle Society, **S. Birnbaum,** P. Portero, T. Sharshar, J.Y. Hogrel, and the MGEX Study Group MGEX: Myasthenia Gravis and EXercise, a randomised, controlled trial protocol. Granada, 2016

13emes journées de la société française de myologie, **S. BIRNBAUM,** P. PORTERO, T. SHARSHAR, J.Y. HOGREL en collaboration avec le MGEX Study Group. **MGEX** : La myasthénie auto-immune et l'exercice physique, étude randomisée et contrôlée (actuellement en cours). Lyon, 2015.

13emes journées de la société française de myologie, **S. BIRNBAUM,** I. GHOUT, P. PORTERO, A. BEHIN, B. EYMARD, S. DEMERET, F. BOLGERT, T. SHARSHAR, JY. HOGREL. Traduction, adaptation culturelle et validation de la version française de l'échelle MG-QOL 15 (15 item Myasthenia Gravis Quality of Life scale Translation and cross-cultural adaptation of a French version of the MG-QOL 15, Lyon, 2015.

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