



Universiteit
Leiden
The Netherlands

Prevalence and associated factors of fatigue in autoimmune myasthenia gravis

Ruiter, A.M.; Verschuuren, J.J.G.M.; Tannemaat, M.R.

Citation

Ruiter, A. M., Verschuuren, J. J. G. M., & Tannemaat, M. R. (2021). Prevalence and associated factors of fatigue in autoimmune myasthenia gravis. *Neuromuscular Disorders*, 31(7), 612-621. doi:10.1016/j.nmd.2021.04.002

Version: Publisher's Version

License: [Creative Commons CC BY 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/3249522>

Note: To cite this publication please use the final published version (if applicable).



Prevalence and associated factors of fatigue in autoimmune myasthenia gravis

Annabel M. Ruiter*, Jan J.G.M. Verschuuren, Martijn R. Tannemaat

Department of Neurology, Leiden University Medical Center, the Netherlands

Received 24 February 2021; received in revised form 6 April 2021; accepted 11 April 2021

Abstract

Fatigue is usually defined as a subjective perception of lacking energy, mentally or physically, with a difficulty sustaining voluntary activities. It is a common symptom of many diseases and most likely has a multifactorial cause. In myasthenia gravis (MG), fatigue has a high prevalence and is correlated with female sex and disease severity. However, no large scale studies have been performed. Therefore, we aimed to evaluate fatigue in the Dutch participants ($n=420$) of the Dutch-Belgian Myasthenia Patient Registry using an online survey. Additional information was obtained on mood, sleep, coping, quality of life, disease severity, physical activities and medication. Severe fatigue was present in 62% with a mean score of 37.1 ± 13.2 points. Fatigue severity and prevalence increased significantly with disease severity. A positive correlation was found for female gender, BMI, disease severity and depressive symptoms. A negative correlation was found for strenuous physical activities and older age. The strong association with disease severity suggests that fatigue should be recognized as an element of the symptomatology of MG. The observed association between strenuous activity and fatigue and differences in coping style between fatigued and non-fatigued patients warrant future clinical trials on exercise and cognitive behavioral therapy.

© 2021 The Authors. Published by Elsevier B.V.

This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

Keywords: Autoimmune; Myasthenia gravis; Central fatigue; Cognitive fatigue.

1. Introduction

Abnormal or chronic fatigue is a symptom of many diseases, both somatic and psychiatric [1]. Without an underlying disease, it can be diagnosed as an entity on its own: chronic fatigue syndrome [2]. No exact definition of fatigue exists, but it is usually referred to as a subjective perception of lacking energy, mentally or physically, with a difficulty sustaining voluntary activities [3]. It is conceptually different from the muscle fatigability that is commonly observed in many neuromuscular disorders (NMDs). To approach these different types of fatigue, it has been proposed to distinguish peripheral and central fatigue [3,4]. Peripheral fatigue is related to muscle fatigue or fatigability and is the direct result of disorders of muscle, neuromuscular junction or nerve. Central fatigue is a perceived subjective lack of energy which can be both physical or mental but is not directly

related to muscle weakness or pain. This type of fatigue is also frequently referred to as cognitive or mental fatigue. It has been hypothesized that central fatigue is a physiological mechanism arising in the central nervous system with the aim of downregulating physical activities to protect the body from (further) damage [3,5]. In this paper, we will use the word ‘fatigue’ to describe central fatigue as defined above, unless specified otherwise.

Myasthenia Gravis (MG) is a chronic autoimmune disease with antibodies directed against the neuromuscular junction. The clinical hallmark of MG is fluctuating muscle weakness with an ocular, oculobulbar or generalized distribution [6]. Although MG is characterized by fluctuating skeletal muscle fatigue, central fatigue is a prevalent patient-reported symptom in Myasthenia Gravis (MG) [7–11]. Concomitant depressive disorders are frequent and it has a negative impact on quality of life in several studies [7–10,12–16]. Recently, a number of studies have addressed the problem of fatigue in MG, stressing the need for a better understanding of the underlying pathophysiology [17]. The prevalence

* Corresponding author.

E-mail address: a.m.ruiter@lumc.nl (A.M. Ruiter).

of fatigue ranges between 44 and 82% [7–11], with the lower limit containing only MG patients with mild to moderate disease (Myasthenia Gravis Foundation of America (MGFA) scale 0-II) [8]. Disease severity is strongly correlated with the prevalence and degree of fatigue. However, the high prevalence of fatigue in ocular MG or patients in pharmacological remission suggests that disease activity is not the only relevant factor [7–9,16,18,19].

In this study, we aimed to address fatigue in a representative cohort of the Dutch MG population, by studying fatigue and its relationship with disease severity, quality of life, sleep disturbances and mood. Additionally, we aimed to assess applied coping strategies, which have not been previously studied in fatigued MG patients. At last, we aimed to explore the influence of frequently used medication, comorbidity, body mass index (BMI) and physical activity.

2. Material and methods

2.1. Subjects

All MG patients from the Dutch – Belgian Myasthenia Patient Registry [20] were invited to participate in this study. Participation in the patient registry is voluntary, and all patients with a myasthenic syndrome can sign up. At the start of the current study, approximately 18–30% of Dutch MG patients were enrolled in the registry. Only Dutch MG patients were included because of the underrepresentation of Belgian patients in the registry at the time of this study ($n=8$). The study protocol was reviewed by the medical ethical committee of the Leiden University Medical Center.

2.2. Procedures

A personal link with a study invitation and an information letter were sent out by email. Digital informed consent was obtained before entering the study. Participants were asked to fill out a set of digital questionnaires, which they could complete at home. Printed questionnaires were available upon request. A reminder was sent in case of no response within 2 weeks; a second reminder was sent 4 weeks after the initial invitation. Participants completed self-report questionnaires on fatigue, depression, sleep, coping, quality of life and disease severity. In addition, participants were asked which medication they used now or during the past three months and to provide information on weight, height and level of physical activity. Physical activities were divided in moderate (walking, cycling or swimming at a regular pace, etc.) and strenuous activities (running, tennis, cycling at an increased pace, etc.). Data provided by the patient registry contained information on antibody status, disease duration and autoimmune comorbidity. Data on non-autoimmune comorbidity in the registry was not collected systematically.

2.3. Questionnaires

Checklist Individual Strength (CIS-f) [21]. Fatigue severity was measured with the fatigue subscale of the CIS (appendix A). This is an 8-item self-assessment on experienced fatigue during the past two weeks and is scored on a 7-point Likert scale. The range is between 8 and 56 points with ≥ 35 indicating severe or clinically relevant fatigue. After a review of different fatigue questionnaires [22], this fatigue questionnaire was selected based on its use in previous research in other NMD's, including clinical trials [23–25] and its focus on central fatigue. The CIS has been validated in the general population, chronic fatigue syndrome, rheumatoid arthritis, cancer survivors and multiple sclerosis [26–28]. In contrast, several other scales include items that are likely to be influenced by peripheral fatigue. E.g. 'Do you make slips of the tongue when speaking?' (Chalder Fatigue Questionnaire), 'My muscles have felt weak' ((Modified) Fatigue Impact Scale).

Hospital Anxiety and Depression Scale (HADS) [29]. The HADS is a self-assessment consisting of an anxiety and depression subscale both containing seven items regarding symptoms over the past week. The answers are scored on a 4-point Likert scale. The maximum score for each subscale is 21 points; a cut-off score of ≥ 8 indicates a possible depression or anxiety disorder. This questionnaire does not contain items addressing symptoms of mood disorders which are also likely to be present in somatic diseases (e.g. questions on fatigue or insomnia).

Pittsburgh Sleep Quality Index (PSQI) [30]. Quality of sleep during the past month was assessed with the PSQI. The scale consists of 18 items with a maximum score of 21. A score > 5 indicates the presence of sleep disturbances.

The Utrecht Coping List (UCL) [31]. The UCL is a 47-item questionnaire that measures seven strategies of coping. An explanation of different strategies is provided in the UCL manual (appendix table B.1). Items are scored on 4-point Likert scale. Interpretation of results depends on gender and age. Reference ranges of representative samples are available in the UCL manual (for used reference group, see appendix B.2).

MG Quality of Life 15-items (MG-QoL-15) [32]. Health-related quality of life was measured with the MG-QoL15, an MG specific instrument. Questions cover the past couple of weeks. The scale contains 15-items on a 5-points Likert scale with a score ranging from 0 to 60. Higher scores indicate lower quality of life.

MG-Activities of Daily Living (MG-ADL) [33]. The MG-ADL is an eight item survey of symptom severity for estimating disease severity over the past week. Items are scored on a 4-point Likert scale and include questions on ocular, oropharyngeal, respiratory and motor function. The total score ranges from 0 to 24, with higher scores indicating more symptoms. For further analysis, subgroups were defined as following: no symptoms (MG-ADL of 0 points), ocular MG (positive scores on item(s) 7 and/or 8, no points on other items), oculobulbar MG (positive scores on item(s) 1, 2 and/or

Table 1
Clinical characteristics.

	Overall	Male	Female	Sig.
Total number of MG patients, n (%)	420	197 (46.9)	223 (53.1)	
Age, mean \pm SD	62.4 \pm 13.9	66.6 \pm 10.5	58.7 \pm 15.4	<0.001
Disease duration in years, mean \pm SD	12.2 \pm 11.2	9.8 \pm 8.9	14.3 \pm 12.5	<0.001
Antibodies (missing 19%)				
• AChR	80.0%			
• MuSK	4.1%			
• LRP4	0.3%			
• Seronegative	15.6%			
Thymectomy, n (%) (missing 4.8%)	149 (37.3)			
Body Mass Index (BMI), mean \pm SD	27.1 \pm 5.0	27.8 \pm 4.5	26.5 \pm 5.3	0.007

3, no scores on item 5 or 6), generalized MG (positive scores on item(s) 5 and/or 6).

2.4. Statistical analysis

For the descriptive analyses, mean and standard deviation (SD) of the variables were calculated. T-test, or Chi-square tests were used for comparison between subgroups. A multivariate linear regression analysis is used for independent association of variables with severe fatigue. The unstandardized beta (B) represents the slope of the line between the variable and fatigue: for every one unit increase in the variable, the fatigue score changes with B. Testing was performed with IBM SPSS Statistics software (version 25.0).

3. Results

3.1. Clinical characteristics

Out of 558 invited patients, 420 (75.3%) completed the survey. The mean age was 62.4 \pm 13.9 years. Disease duration was 12.2 \pm 11.2 years (table 1). Female patients were significantly younger ($p < 0.001$) and had a longer disease duration ($p < 0.001$). Medical information on antibody status was available in 81% of patients. Antibodies against the acetylcholine receptor (AChR) were present in 80% of the study population, muscle specific kinase (MuSK) antibodies in 4% and 16% was seronegative. Most patients (86%) used medication. Of those, 21% was on pyridostigmine monotherapy, 41% used corticosteroids and 25% a combination of corticosteroids with a non-steroid immunosuppressant. A second autoimmune disorder was reported by 24% of patients. Thyroid disease (9%) and rheumatoid arthritis (8%) were most frequently reported.

3.2. Questionnaires

Table 2 shows the results of all questionnaires. The mean fatigue score (CIS-f) was 37.1 \pm 13.2 points. Severe fatigue (CIS-f \geq 35) was present in 62%, with a higher prevalence in women compared to men: 74% vs. 49% ($p < 0.001$). The mean MG-ADL score for disease severity was 4.0 \pm 3.5 points. Most patients (66%) reported generalized symptoms during the past week. Only 15% reported no

clinical symptoms. The prevalence and mean score of fatigue increased with disease severity (Fig. 1). Severe fatigue was present in 22% of patients with no clinical symptoms compared to 76% of patients with generalized symptoms. In patients without clinical symptoms, the mean fatigue score was 22.2 \pm 13.7, compared to 41.7 \pm 10.3 in patients with generalized symptoms ($p < 0.001$). Women had significantly higher fatigue scores compared to men within all MG-ADL subgroups except oculobulbar symptoms: no clinical symptoms 28.8 \pm 15.2 vs. 19.3 \pm 12.1 ($p = 0.012$); only ocular symptoms 37.6 \pm 12.6 vs. 28.7 \pm 11.5 ($p = 0.015$); generalized symptoms 43.7 \pm 9.3 vs. 38.7 \pm 11.0 ($p < 0.001$).

The mean score on the HADS-d was 5.4 \pm 3.7 points. A possible depressive disorder (score 8–10) was present in 18% and a probable depressive disorder (score \geq 11) in 10%. Fatigued patients scored significantly higher than non-fatigued patients, 6.5 \pm 3.6 vs. 3.5 \pm 3.0 points ($p < 0.001$). Quality of life was significantly lower for fatigued patients with 25.9 \pm 10.7 points on the MG-QoL-15 compared to 13.0 \pm 10.9 for non-fatigued patients ($p < 0.001$, Fig. 2). The mean score for sleep quality, as measured with the PSQI, was 7.7 \pm 3.9 points. Fatigued patients had a lower sleep quality compared to non-fatigued patients: 8.5 \pm 3.8 vs. 6.3 \pm 3.5 ($p < 0.001$).

Fig. 3 shows coping strategies according to the UCL in comparison with values for the reference group. Fatigued male patients scored higher on avoiding and passive coping strategies compared to non-fatigued male patients ($p = 0.009$; $p < 0.001$). Fatigued female patients scored higher on passive coping strategies ($p = 0.047$). Avoiding and passive coping strategies are both associated with expressing mental and physical distress (appendix table B.1).

Significantly higher fatigue scores and MG-ADL scores were found for patients treated with pyridostigmine, intravenous immunoglobulins or plasma exchange therapy compared to patients not treated with this medication (Table 3). Fatigue was similar in patients with and without a previous thymectomy. The mean duration between thymectomy and participation in this study was 14.8 \pm 12.7 years. The mean score and prevalence of fatigue were significantly higher in patients with a concomitant autoimmune disorder compared to patients without: 41.6 \pm 11.4 vs. 35.8 \pm 13.3, $p < 0.001$ with a prevalence of 24% vs. 16%, $p = 0.003$.

Table 2
Results of questionnaires.

Questionnaire (mean ± SD)	Overall	Male	Female	Sig.
• MG-Activities of Daily Life (MG-ADL)	4.0 ± 3.5	3.1 ± 2.9	4.9 ± 3.7	<0.001
• Checklist Individual Strength-fatigue subscale (CIS-f)	37.1 ± 13.2	32.8 ± 13.6	40.9 ± 11.6	<0.001
• MG-Quality of Life (MG-QoL-15)	21.1 ± 12.4	18.2 ± 12.3	23.6 ± 12.0	<0.001
• Hospital Anxiety and Depression Scale-depression subscale (HADS-d)	5.4 ± 3.7	5.2 ± 3.7	5.6 ± 3.7	0.276
• Pittsburgh Sleep Quality Index (PSQI)	7.7 ± 3.9	6.5 ± 3.5	8.8 ± 3.9	<0.001

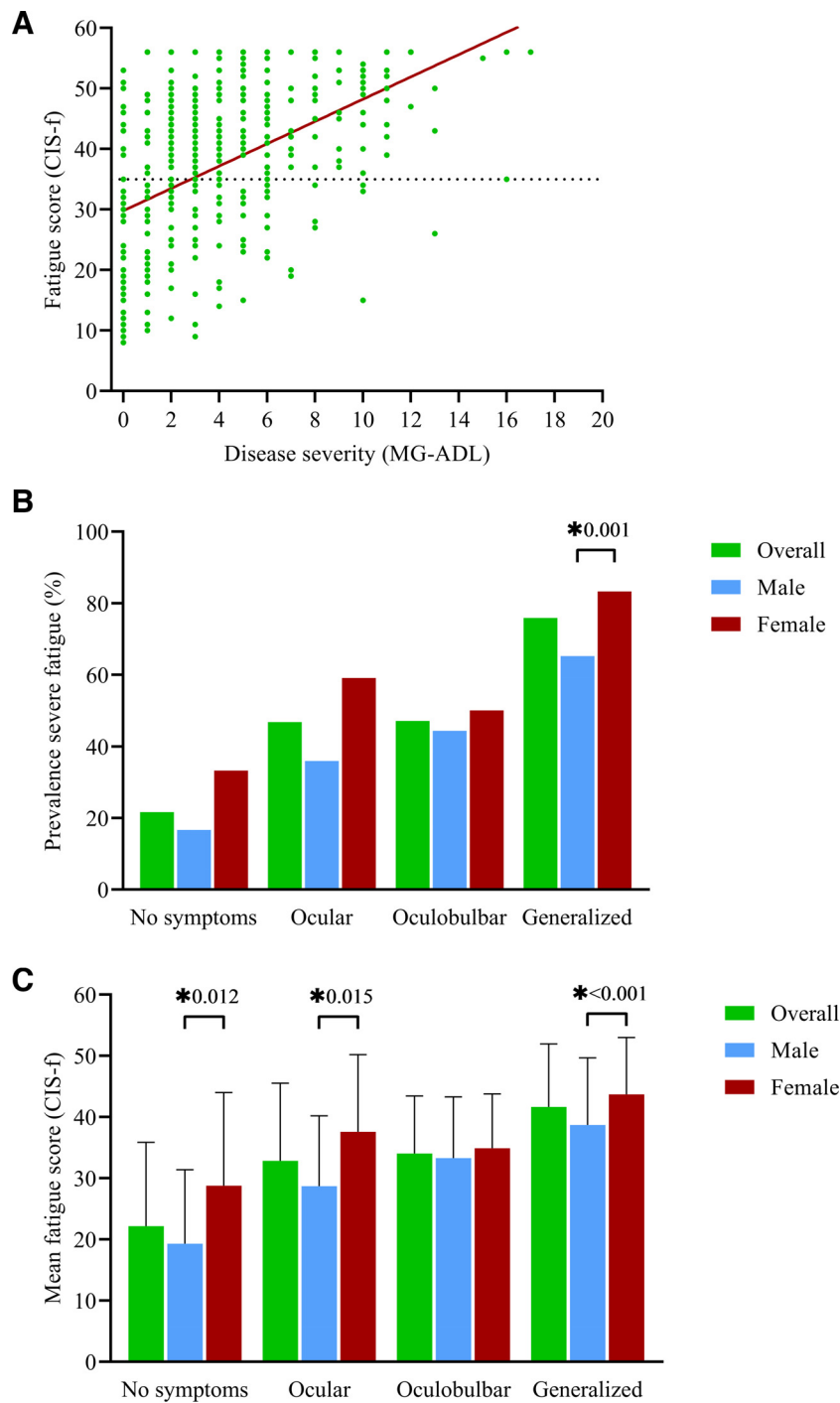


Fig. 1. a. Correlation between fatigue (CIS-f) and disease severity (MG-ADL). Horizontal line indicates the cut-off for clinically relevant fatigue (≥ 35). b. Prevalence of severe fatigue (CIS-f ≥ 35) per MG-ADL subgroup. c. Mean fatigue (CIS-f) score per MG-ADL subgroup.

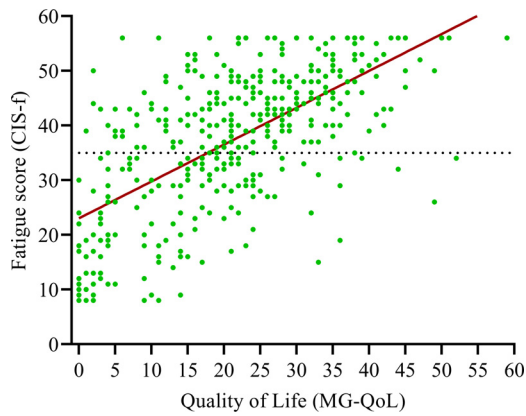


Fig. 2. Correlation between fatigue and quality of life. Horizontal line indicates the cut-off for severe fatigue (CIS-f ≥ 35).

3.3. Fatigue and physical condition

According to their BMI score, 1.7% of all participants were underweight (BMI <18.5), 41% were overweight (BMI 25–30) and 21% were obese (BMI >30). The mean BMI was 27.1 ± 1.0 points. There was no difference in BMI between patients with or without corticosteroids ($p=0.903$). Fatigue scores were significantly higher in obese patients compared to those with a healthy weight (BMI 18.5–25) and those who were overweight (BMI 25–30; $p < 0.001$; $p < 0.001$).

Most patients (78%) engaged in moderate physical activities >50 min every day (Fig. 4a).

The mean fatigue score was higher in patients with <50 active minutes every day (41.7 ± 11.3) compared to patients with 100–150 active minutes (36.8 ± 13.5 , $p=0.012$).

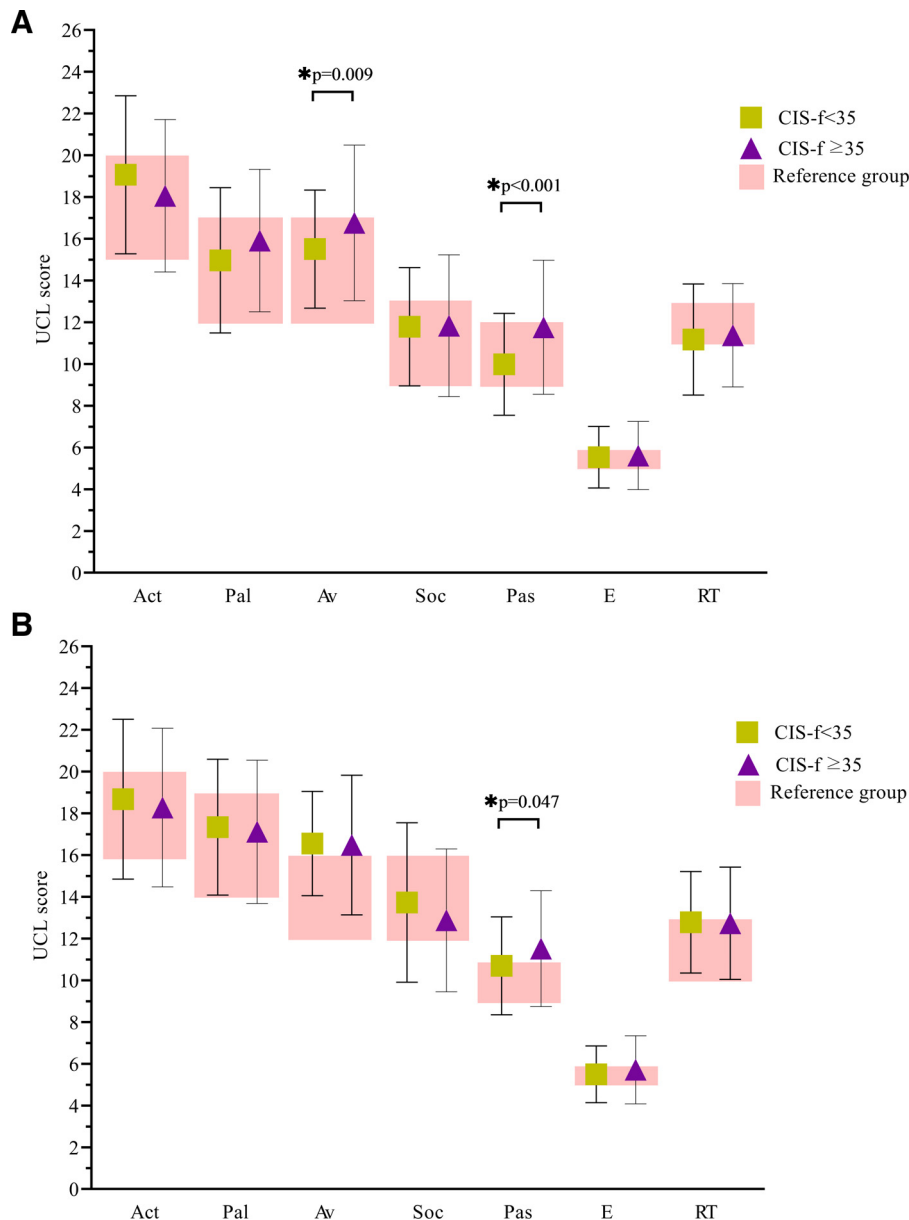


Fig. 3. a. Results Utrecht Coping List (UCL), males ($n=197$). b. Results Utrecht Coping List (UCL), females ($n=218$).

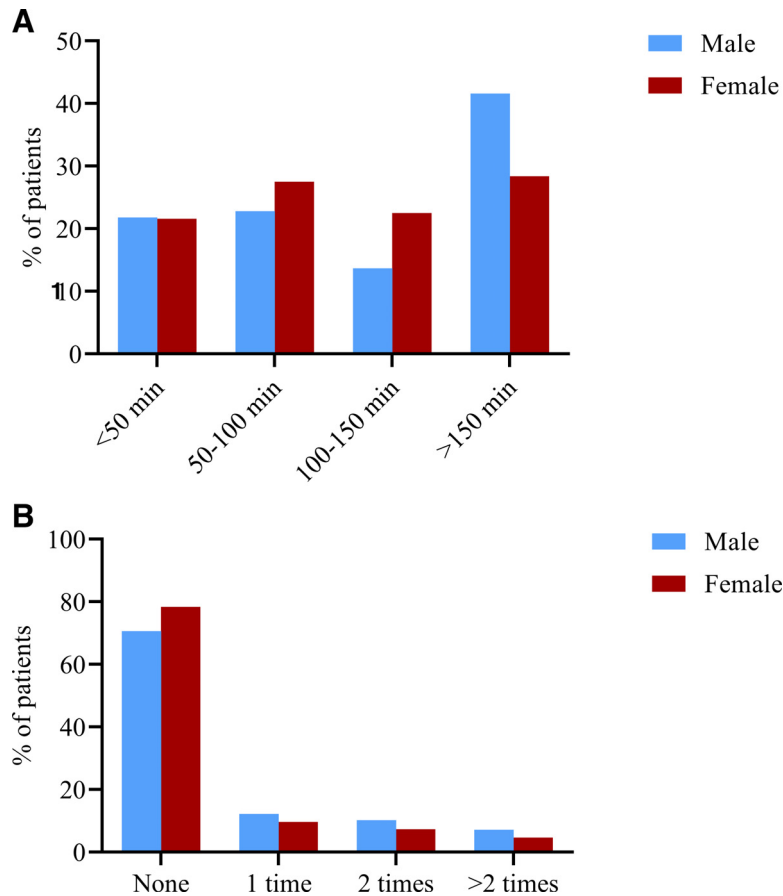


Fig. 4. a.Moderate physical activities (e.g. walking or cycling on regular pace), minutes per day. b. Strenuous physical activities (e.g. running, cycling at increased pace), times per week.

Table 3
Fatigue (CIS-f) and disease severity (MG-ADL) within different types of treatment.

	With treatment	Without treatment	Sig.
Pyridostigmine			
CIS-f (mean ± SD)	38.9 ± 11.7	34.4 ± 14.7	0.001
MG-ADL (mean ± SD)	4.7 ± 3.4	3.0 ± 3.3	<0.001
Corticosteroids			
CIS-f (mean ± SD)	37.4 ± 12.3	37.0 ± 13.7	0.732
MG-ADL (mean ± SD)	3.9 ± 3.4	4.2 ± 3.5	0.388
Non-steroid immunosuppressants			
CIS-f (mean ± SD)	38.2 ± 12.5	36.2 ± 13.6	0.110
MG-ADL (mean ± SD)	3.9 ± 3.4	4.1 ± 3.5	0.558
IVIG and/ or PLEX			
CIS-f (mean ± SD)	41.4 ± 12.2	36.4 ± 13.2	0.006
MG-ADL (mean ± SD)	5.4 ± 3.8	3.8 ± 3.3	0.002
Thymectomy			
Time (years) between study and thymectomy (mean ± SD)	14.8 ± 12.7	–	
CIS-f (mean ± SD)	37.2 ± 13.0	37.2 ± 13.2	0.984
MG-ADL (mean ± SD)	3.7 ± 3.1	4.1 ± 3.5	0.181

Abbreviations: CIS-f=Checklist Individual Strength – fatigue; IVIG=intravenous immunoglobulins; MG-ADL=MG – Activities of Daily Living; PLEX=plasma exchange therapy.

and >150 active minutes (32.9 ± 12.9, *p* < 0.001). Only a quarter of patients engaged in strenuous physical activities were (Fig. 4b). Fatigue scores were lower in all patients

with one or more periods of strenuous activity per week compared to those without these activities (39.7 ± 12.1 (none) vs. 30.6 ± 13.6 (1 time); 31.8 ± 13.1 (2 times); 26.3 ± 11.7 (>2 times), *p* < 0.001 for all frequencies).

3.4. Multivariate linear regression analysis

Table 4 shows the results of the multivariate linear regression analysis with CIS-f as dependent variable. Twenty-three (5.5%) patients were excluded from analysis because of missing data, mostly regarding medical history. An independent positive correlation for higher fatigue scores was found for female gender (*P* < 0.001), BMI (*p* = 0.001), MG-ADL (*p* < 0.001) and HADS-d (*p* < 0.001). Age was negatively correlated with fatigue scores (*p* = 0.001), older patients had lower fatigue scores. All frequencies of strenuous physical activities were negatively correlated with fatigue scores. This effect was strongest for a frequency of >2 times weekly, fatigue scores decreased with 7.9 points compared to those of subjects with no strenuous activities (*p* < 0.001) (total range CIS-f: 8–56 points). There was no correlation with moderate physical activity, sleep quality, concomitant autoimmune disorders, type of antibodies and disease duration.

Table 4
Multivariate linear regression analysis, $n = 397$.

Parameter	B	Std. Error	95% Wald Confidence Interval		Sig.
			Lower	Upper	
Female gender	4648	1,0945	2503	6794	<0,001
Age	−0,124	0,0383	−0,199	−0,048	0,001
Disease duration	−0,049	0,0437	−0,134	0,037	0,267
Antibodies					
• AChR	−0,716	1,4894	−3636	2203	0,631
• MuSK	0,441	2,9151	−5272	6154	0,880
• Seronegative	0,716	1,4984	−2203	3636	0,631
Other AID	1713	1,1123	−0,467	3893	0,124
BMI	0,338	0,0975	0,147	0,529	0,001
MG-ADL	0,827	0,1650	0,503	1150	<0,001
HADS-d	1254	0,1454	0,969	1539	<0,001
PSQI	0,256	0,1409	−0,020	0,533	0,069
Moderate physical activities					
• 50–100 min daily	1310	1,3744	−1384	4004	0,340
• 100–150 min daily	0,458	1,5237	−2528	3444	0,764
• >150 min daily	−1828	1,3476	−4469	0,814	0,175
Strenuous physical activities					
• 1x/ week	−4625	1,5584	−7679	−1570	0,003
• 2x/ week	−3999	1,7453	−7419	−0,578	0,022
• >2x/ week	−7951	2,0982	−12,063	−3838	<0,001

Abbreviations: AChR = acetyl choline receptor; AID = autoimmune disorder; B = unstandardized beta; BMI = body mass index; HADS-d = Hospital Anxiety and Depression scale – depression subscale; MG-ADL = Myasthenia Gravis – Activities of Daily Living; MuSK = Muscle specific tyrosine kinase; PSQI = Pittsburgh Sleep Quality Index.

4. Discussion

With a prevalence of 1–2 per 10,000 [6], approximately a quarter of Dutch MG patients had signed up for the registry at the start of this study. We estimate that we have included 14–23% of all Dutch MG patients in this study. Baseline characteristics of our cohort were similar to the baseline characteristics of a previous cross-sectional study which included all ($n = 671$) MG patients in a predefined region in the Netherlands [34]. Therefore, we believe our cohort is a correct representation of the Dutch MG population. The high response rate of 75% indicates that this topic is highly important to MG patients. The high prevalence of severe fatigue (62%) was comparable with previous studies on fatigue in MG [7–11,19] but is not unique to MG. Many other medical (chronic) conditions are accompanied by severe fatigue with a similar prevalence [27,35,36].

The intensity and prevalence of fatigue in the general population is much lower. Among 1923 healthy Dutch representatives (age 16–88) the mean fatigue score, measured using the CIS-f, was 23 [27]. The prevalence of fatigue in the general population of Northern & Western Europe and United States varies between 18 and 38% [1,8,10,37–39]. Interestingly, the extent of fatigue among MG patients without clinical symptoms in our study (22%) was within this range. Unfortunately, because of the nature of questioning it was not possible to further distinguish between patients in pharmacological remission and patients in remission without medication. Similar findings have been demonstrated in one previous study [7] but two studies found opposite results with a higher prevalence of fatigue in MG patients

in (pharmacological) remission compared to the general population [8,9].

Fatigue increased with disease severity, in accordance to previous findings [7–11,19]. The current study does not provide longitudinal data to assess effects of MG-specific treatment on fatigue. However, our results suggest that chronic medication does not have a significant effect on fatigue, whereas short-acting medication does. However, the lack of information on dosage and duration precludes a definitive conclusion. Data from the literature on this subject is scarce. Three studies with sample sizes ranging from 29 to 257 participants, all demonstrated a decline in fatigue after successful treatment of clinical MG symptoms [16,18,40]. Our study does not provide additional answers to the question whether therapy should be initiated or intensified in fatigued patients.

A novel finding in this study is the difference in coping strategy between fatigued and non-fatigued patients. This finding could be a potential option for treatment of fatigue with cognitive behavior therapy. The identification of coping domains may form the basis of individualized, targeted therapy. Such an approach has been proven effective as treatment of fatigue in other NMD's [25,41] and limited pilot data is available in MG [42]. However, these studies did not provide information on differences in coping styles between fatigued and non-fatigued patients.

In addition, we gathered extensive information on physical activity. Strenuous physical activities showed a highly significant and strong negative association with fatigue. In facioscapulohumeral dystrophy, 3 weekly sessions of 30 min cycling on an ergometer significantly improved fatigue

compared to standard treatment [25]. This effect was still present at 12 weeks follow-up. Similar results were found in post-Guillain Barre syndrome and chronic inflammatory demyelinating polyneuropathy patients [43]. Fatigue severity reduced with 20% after a 12-week training program with 3 weekly cycling sessions on a ergometer. In myotonic dystrophy type 1, no additional improvement of fatigue was found after adding graded exercise to cognitive behavior therapy [41], although the group receiving exercise therapy in this study was relatively small (26% of participants). In MG, pilot data is available which demonstrates non-significant improvements of fatigue in small groups of patients [42,44]. These results, together with the strong negative association of strenuous activities with fatigue, suggest that a trial that tests the effect of an exercise program in MG, might provide interesting information. If successful, it could provide the basis for a therapy for fatigue that is relatively easy to apply and has few side-effects.

We found a negative correlation between increasing age and fatigue, although this effect was small ($B = -0.124$). Possible explanations could be that younger people have a more demanding lifestyle or that older people applied more effective coping strategies for fatigue. The observed association with female gender and depressive symptoms is consistent with previous research [7–10,12,14,16,19]. Gender differences in fatigue have been previously demonstrated in other medical conditions as well as in the working population [45,46]. The exact pathophysiology of these is unclear, but may be related to differences in the immune system and responses [47], or perhaps differences in social roles and activities contribute to the observed gender differences.

The association with depressive symptoms is not surprising, since fatigue is one of the symptoms of a depressive disorder according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) [48]. Therefore, this association does not provide any evidence of causality, since depressive symptoms may be the cause or result of fatigue. In addition, the observed association may have been caused by an overlap in fatigue and depression questionnaires, e.g. ‘I feel weak’ and ‘I feel fatigued’ (CIS-f) and ‘I feel like everything is going more difficult’ (HADS-d).

4.1. Limitations

This study has a number of limitations. First, the nature of this study, in which an invitation was sent out to all MG patients in the Dutch-Belgian MG registry, may have led to potential selection bias with an over-presentation of more fatigued MG patients. It is likely that fatigued patients are more willing to participate in a fatigue survey compared to non-fatigued patients. However, as 75% of all registry participants completed all questionnaires, this likely reduced the risk of selection bias. Selection bias may also affect participation in the MG registry itself: patients with more severe disease could be more willing to sign up for the registry compared to patients with no or only minimal symptoms. It is also possible that patients treated in university

hospitals are more likely be made aware of the existence of the registry compared to patients treated in smaller local hospitals.

Second, this cross-sectional study does not provide information on causality of the observed significant observations. Third, we did not have sufficient information on type and dose of MG-specific medication used by participants to adequately investigate a potential influence of medication on fatigue. Finally, fatigue was assessed with a fatigue-specific questionnaire. We have no data on how frequently fatigue is reported spontaneously. The strong correlation of fatigue with disease severity suggests an overlap between the two types of fatigue. This is further demonstrated by the fact that the number of patients with a high MG-ADL who are not fatigued is extremely low (Fig. 1a)

5. Conclusion

Fatigue in Dutch MG patients is highly prevalent, consistent with previous findings in MG, other NMDs and non-neuromuscular chronic diseases. The strong association with disease severity suggests that fatigue should be recognized as an element of the symptomatology of MG, although it cannot be used to distinguish MG from other NMD's. The high response rate for this study demonstrated the importance of the topic for patients. Its high prevalence and strong negative effect on quality of life, suggest that fatigue should be systematically evaluated during consultations with MG patients. Unfortunately, literature on the effect of MG-specific treatment on fatigue is scarce and this study does not provide additional insights on this topic. This study however, demonstrates a strong negative association of strenuous physical activities with fatigue in a large group of MG patients. Our results suggest that increasing physical fitness could provide a potential treatment of fatigue. In addition, the observed differences in coping styles between fatigued and non-fatigued patients suggest that cognitive behavioral therapy or even targeted coaching may be effective as a treatment for treating fatigue in MG. Naturally, this would require randomized clinical trials to prove their effectiveness.

Study funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Financial disclosure statement

AMR reports no disclosures relevant to the manuscript. MRT has been involved in MG research sponsored by ArgenX, Alexion and NMD Pharma. All reimbursements were received by the LUMC, MRT had no personal financial benefit from these activities. JJGMV receives financial support from Target to B consortium, Prinses Beatrix Spierfonds, and has been involved in trials or consultancies for Argenx, Alexion,

Rapharma. He is coinventor on patent applications based on MuSK-related research. The LUMC received royalties from IBL and Argenx for MG research. All reimbursements were received by the LUMC. The authors are members of the European Reference Network for Rare Neuromuscular Diseases [ERN EURO–NMD].

Acknowledgements

The authors thank the Dutch patient support organization ‘Spierziekten Nederland’ for their support in the Dutch-Belgian patient registry. Second, the authors are grateful to neurologists encouraging patients to participate in the Dutch-Belgian patient registry.

References

- [1] Finsterer J, Mahjoub SZ. Fatigue in healthy and diseased individuals. *Am J Hosp Palliat Care* 2014;31(5):562–75.
- [2] Yancey JR, Thomas SM. Chronic fatigue syndrome: diagnosis and treatment. *Am Fam Physician* 2012;86(8):741–6.
- [3] Chaudhuri A, Behan PO. Fatigue in neurological disorders. *The Lancet* 2004;363(9413):978–88.
- [4] de Vries JM, Hagemans MLC, Bussmann JBJ, van der Ploeg AT, van Doorn PA. Fatigue in neuromuscular disorders: focus on Guillain–Barré syndrome and Pompe disease. *Cell Mole Life Sci* 2010;67(5):701–13.
- [5] de Vries JM, Hagemans ML, Bussmann JB, van der Ploeg AT, van Doorn PA. Fatigue in neuromuscular disorders: focus on Guillain–Barre syndrome and Pompe disease. *Cell Mol Life Sci* 2010;67(5):701–13.
- [6] Verschuuren JJ, Palace J, Gilhus NE. Clinical aspects of myasthenia explained. *Autoimmunity* 2010;43(5–6):344–52.
- [7] Alekseeva TM, Gavrilov YV, Kreis OA, Valko PO, Weber KP, Valko Y. Fatigue in patients with myasthenia gravis. *J Neurol* 2018;265(10):2312–21.
- [8] Elsaï A, Wyller VB, Loge JH, Kerty E. Fatigue in myasthenia gravis: is it more than muscular weakness? *BMC Neurol* 2013;13:132.
- [9] Hoffmann S, Ramm J, Grittner U, Kohler S, Siedler J, Meisel A. Fatigue in myasthenia gravis: risk factors and impact on quality of life. *Brain Behav* 2016;6(10):e00538.
- [10] Jordan B, Schweden TLK, Mehl T, Menge U, Zierz S. Cognitive fatigue in patients with myasthenia gravis. *Muscle Nerve* 2017;56(3):449–57.
- [11] Paul RH, Cohen RA, Goldstein JM, Gilchrist JM. Fatigue and its impact on patients with myasthenia gravis. *Muscle Nerve* 2000;23(9):1402–6.
- [12] Jordan B, Mehl T, Schweden TLK, Menge U, Zierz S. Assessment of physical fatigability and fatigue perception in myasthenia gravis. *Muscle Nerve* 2017;55(5):657–63.
- [13] Kassardjian CD, Kokokyi S, Barnett C, Jewell D, Bril V, Murray BJ, et al. Excessive daytime sleepiness in patients with myasthenia gravis. *J Neuromuscul Dis* 2015;2(1):93–7.
- [14] Kittiwatanapaisan W, Gauthier DK, Williams AM, Oh SJ. Fatigue in myasthenia gravis patients. *J Neurosci Nurs* 2003;35(2):87–93 106.
- [15] Paul RH, Cohen RA, Gilchrist JM. Ratings of subjective mental fatigue relate to cognitive performance in patients with myasthenia gravis. *J Clin Neurosci* 2002;9(3):243–6.
- [16] Tran C, Bril V, Katzberg HD, Barnett C. Fatigue is a relevant outcome in patients with myasthenia gravis. *Muscle Nerve* 2018;58(2):197–203.
- [17] Ruiter AM, Verschuuren J, Tannemaat MR. Fatigue in patients with myasthenia gravis. A systematic review of the literature. *Neuromuscul Disord* 2020;30(8):631–9.
- [18] Andersen H, Mantegazza R, Wang JJ, O’Brien F, Patra K, Howard JF Jr. Eculizumab improves fatigue in refractory generalized myasthenia gravis. *Qual Life Res* 2019.
- [19] Westerberg E, Landtblom AM, Punga AR. Lifestyle factors and disease-specific differences in subgroups of Swedish myasthenia gravis. *Acta Neurol Scand* 2018;138(6):557–65.
- [20] [Available from: 2020 <https://www.lumc.nl/org/neurologie/research/myasthenie-register/>].
- [21] Vercoulen JH, Swanink CM, Fennis JF, Galama JM, van der Meer JW, Bleijenberg G. Dimensional assessment of chronic fatigue syndrome. *J Psychosom Res* 1994;38(5):383–92.
- [22] Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue: a practical guide for clinicians and researchers. *J Psychosom Res* 2004;56(2):157–70.
- [23] Koopman FS, Voorn EL, Beelen A, Bleijenberg G, de Visser M, Brehm MA, et al. No reduction of severe fatigue in patients with postpolio syndrome by exercise therapy or cognitive behavioral therapy: results of an RCT. *Neurorehabil Neural Repair* 2016;30(5):402–10.
- [24] Panitz S, Kornhuber M, Hanisch F. The checklist individual strength (CIS20-R) in patients with amyotrophic lateral sclerosis - a longitudinal study. *Acta Neurol Scand* 2015;131(6):372–80.
- [25] Voet N, Bleijenberg G, Hendriks J, de Groot I, Padberg G, van Engelen B, et al. Both aerobic exercise and cognitive-behavioral therapy reduce chronic fatigue in FSHD: an RCT. *Neurology* 2014;83(21):1914–22.
- [26] Beurskens AJ, Bültmann U, Kant I, Vercoulen JH, Bleijenberg G, Swaen GM. Fatigue among working people: validity of a questionnaire measure. *Occup Environ Med* 2000;57(5):353–7.
- [27] Worm-Smeitink M, Gielissen M, Bloot L, van Laarhoven HWM, van Engelen BGM, van Riel P, et al. The assessment of fatigue: psychometric qualities and norms for the Checklist individual strength. *J Psychosom Res* 2017;98:40–6.
- [28] Hoogmoed Dv, Fransen J, Bleijenberg G, PLCMv Riel. How to assess fatigue in rheumatoid arthritis: validity and reliability of the checklist individual strength. *Arthritis Rheum*. 2008;58 S868 - S.
- [29] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67(6):361–70.
- [30] 3rd Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193–213.
- [31] Schreurs P.J.G., van de Willige, G., Tellegen, B., & Brosschot, J.F. *Herziene handleiding Utrechtse Coping Lijst (UCL)*. Lisse: swets & Zeitlinger BV. 1993.
- [32] Strijbos E, Gärtner FR, Verschuuren JJ. Translation and validation of the 15-item myasthenia gravis quality of life scale in Dutch. *Muscle Nerve* 2018;57(2):206–11.
- [33] Wolfe GI, Herbelin L, Nations SP, Foster B, Bryan WW, Barohn RJ. Myasthenia gravis activities of daily living profile. *Neurology* 1999;52(7):1487–9.
- [34] Boldingh MI, Maniaol AH, Brunborg C, Dekker L, Heldal AT, Lipka AF, et al. Geographical distribution of myasthenia gravis in Northern Europe—results from a population-based study from two countries. *Neuroepidemiology* 2015;44(4):221–31.
- [35] Kalkman JS, Schillings ML, van der Werf SP, Padberg GW, Zwarts MJ, van Engelen BG, et al. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. *J Neurol Neurosurg Psychiatry* 2005;76(10):1406–9.
- [36] Pope JE. Management of fatigue in rheumatoid arthritis. *RMD Open* 2020;6(1).
- [37] van’t Leven M, Zielhuis GA, van der Meer JW, Verbeek AL, Bleijenberg G. Fatigue and chronic fatigue syndrome-like complaints in the general population. *Eur J Public Health* 2010;20(3):251–7.
- [38] Galland-Decker C, Marques-Vidal P, Vollenweider P. Prevalence and factors associated with fatigue in the Lausanne middle-aged population: a population-based, cross-sectional survey. *BMJ Open* 2019;9(8):e027070.
- [39] Rose DM, Seidler A, Nübling M, Latza U, Brähler E, Klein EM, et al. Associations of fatigue to work-related stress, mental and physical health in an employed community sample. *BMC Psychiatry* 2017;17(1):167.
- [40] Chen Y-T, Chang Y, Chiu H-C, Yeh J-H. Psychosocial aspects in myasthenic patients treated by plasmapheresis. *J Neurol* 2011;258(7):1240–6.

- [41] Okkersen K, Jimenez-Moreno C, Wenninger S, Daidj F, Glennon J, Cumming S, et al. Cognitive behavioural therapy with optional graded exercise therapy in patients with severe fatigue with myotonic dystrophy type 1: a multicentre, single-blind, randomised trial. *Lancet Neurol* 2018;17(8):671–80.
- [42] Farrugia ME, Di MM, Kersel D, Carmichael C. A physical and psychological approach to managing fatigue in myasthenia gravis: a pilot study. *J Neuromuscul Dis* 2018;5(3):373–85.
- [43] Garssen MPJ, Bussmann JBJ, Schmitz PIM, Zandbergen A, Welter TG, Merkies ISJ, et al. Physical training and fatigue, fitness, and quality of life in Guillain–Barré syndrome and CIDP. *Natl Lib Med* 2004;63(12):2393–5.
- [44] Rahbek MA, Mikkelsen EE, Overgaard K, Vinge L, Andersen H, Dalgas U. Exercise in myasthenia gravis: a feasibility study of aerobic and resistance training. *Muscle Nerve* 2017;56(4):700–9.
- [45] Bensing JM, Hulsman RL, Schreurs KM. Gender differences in fatigue: biopsychosocial factors relating to fatigue in men and women. *Med Care* 1999;37(10):1078–83.
- [46] Erol K, Ertas SK, Ertas R. Fatigue is common and predicted by female gender and sleep disturbance in patients with chronic spontaneous urticaria. *J Allergy Clin Immunol Pract* 2020.
- [47] Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol* 2016;16(10):626–38.
- [48] Tolentino JC, Schmidt SL. DSM-5 criteria and depression severity: implications for clinical practice. *Front Psychiatry* 2018;9 450-.