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Faces and fatigue in myasthenia gravis

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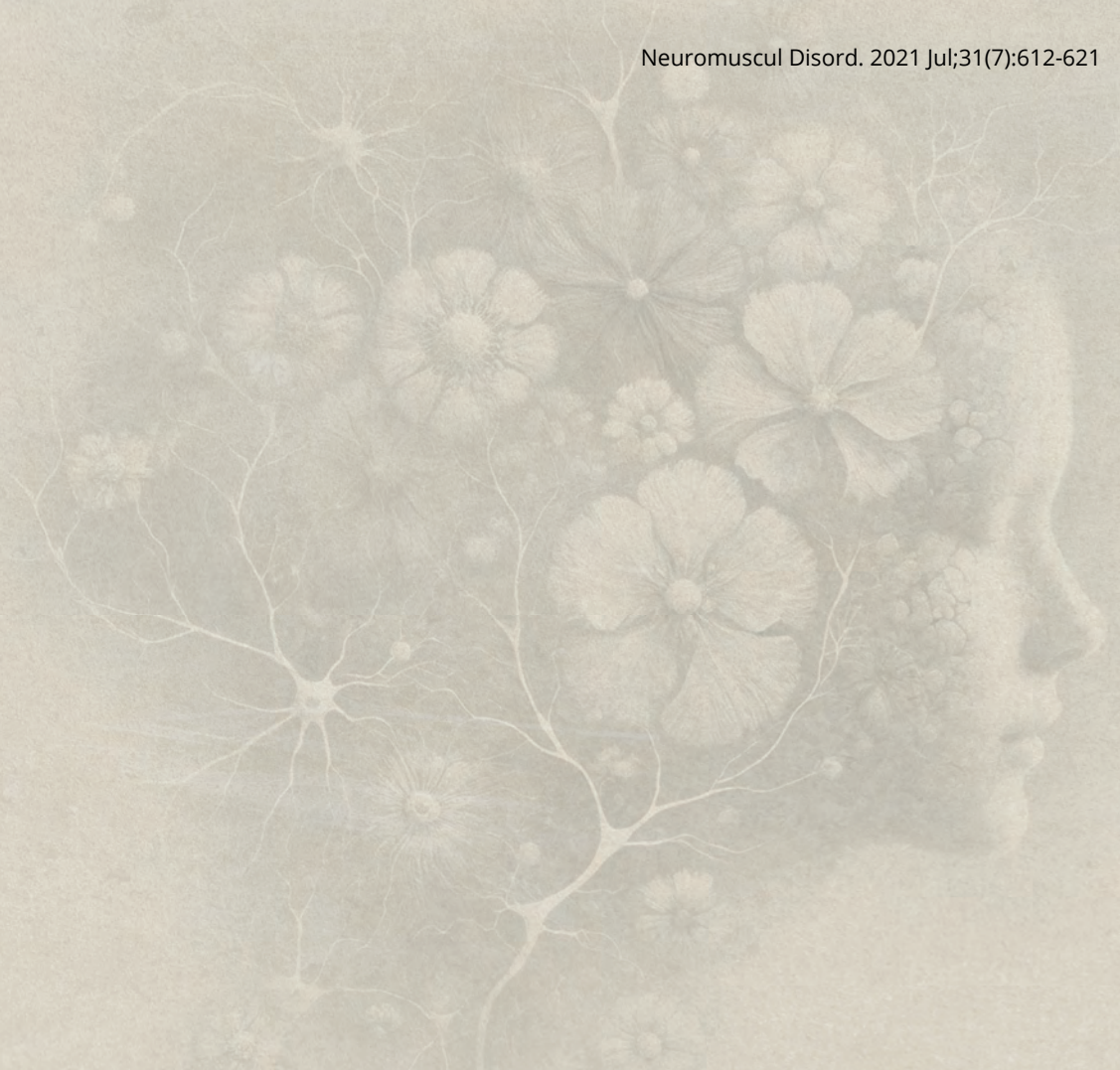
Chapter 4

Prevalence and associated factors of fatigue in autoimmune myasthenia gravis

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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.

Introduction

Abnormal or chronic fatigue is a symptom of many diseases, both somatic and psychiatric¹. Without an underlying disease, it can be diagnosed as an entity on its own: chronic fatigue syndrome². 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 activities³. 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 distribution⁶. 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 pathophysiology¹⁷. The prevalence 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.

Material and Methods

Subjects

All MG patients from the Dutch – Belgian Myasthenia Patient Registry²⁰ 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.

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.

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 8-56 points with ≥ 35 indicating severe or clinically relevant fatigue. After a review of different fatigue questionnaires²², this fatigue questionnaire was selected based on its use in previous research in other NMD's, including clinical trials²³⁻²⁵ and its focus on central fatigue. The CIS has been validated in the general population, chronic fatigue syndrome, rheumatoid arthritis, cancer survivors and multiple sclerosis²⁶⁻²⁸. 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 3, no scores on item 5 or 6), generalized MG (positive scores on item(s) 5 and/or 6).

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).

Results

Clinical characteristics

Out of 558 invited patients, 420 (75.3%) completed the survey. The mean age was 62.4 ± 13.9 years. Disease duration was 12.2 ± 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.

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 ± 13.9	66.6 ± 10.5	58.7 ± 15.4	<0.001
Disease duration in years, mean $\pm$ SD	12.2 ± 11.2	9.8 ± 8.9	14.3 ± 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 ± 5.0	27.8 ± 4.5	26.5 ± 5.3	0.007

Questionnaires. Table 2 shows the results of all questionnaires. The mean fatigue score (CIS-f) was 37.1 ± 13.2 points. Severe fatigue (CIS-f ≥ 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 ± 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 (figure 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 ± 13.7 , compared to 41.7 ± 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 ± 15.2 vs. 19.3 ± 12.1 ($p = 0.012$); only ocular symptoms 37.6 ± 12.6 vs. 28.7 ± 11.5 ($p = 0.015$); generalized symptoms 43.7 ± 9.3 vs. 38.7 ± 11.0 ($p < 0.001$).

Table 2. Results of questionnaires

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

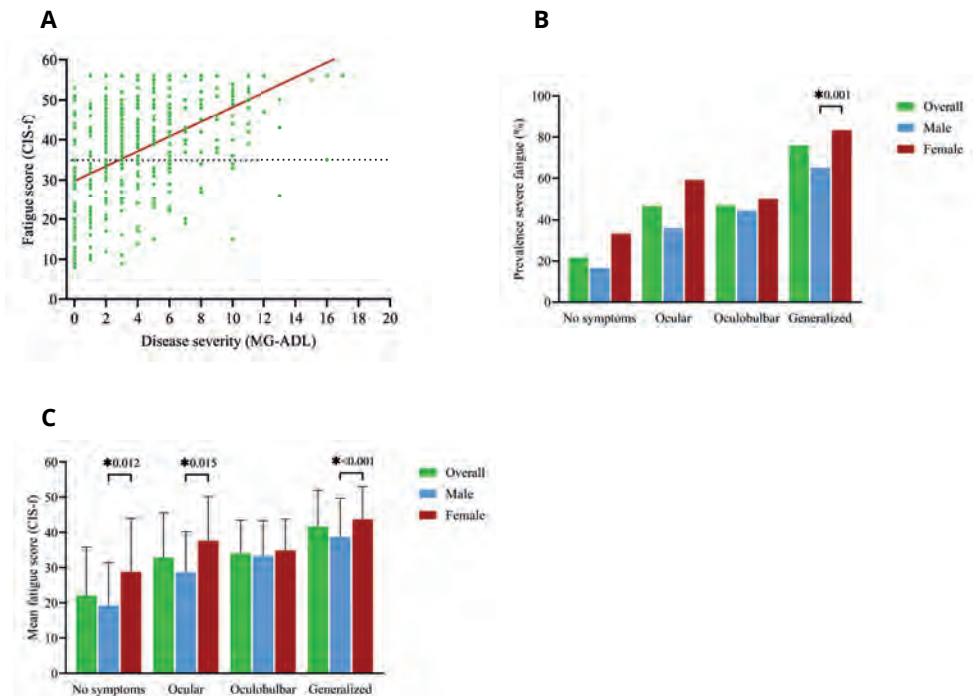


Figure 1. A) Correlation between fatigue (CIS-f) and disease severity (MG-ADL). Horizontal line indicates the cut-off for clinically relevant fatigue (≥ 35). B) Prevalence of severe fatigue (CIS-f ≥ 35) per MG-ADL subgroup. C) Mean fatigue (CIS-f) score per MG-ADL subgroup.

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

patients had a lower sleep quality compared to non-fatigued patients: 8.5 ± 3.8 vs. 6.3 ± 3.5 ($p < 0.001$).

Figure 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).

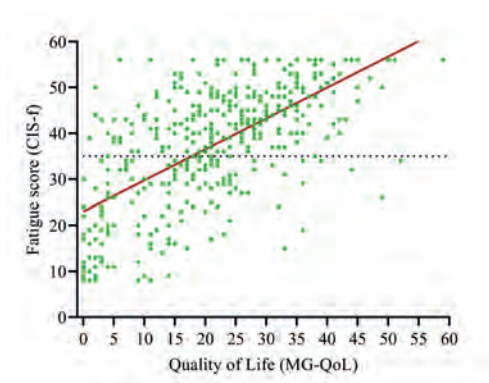


Figure 2. Correlation between fatigue and quality of life. Horizontal line indicates the cut-off for severe fatigue (CIS-f ≥ 35).

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 ± 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 ± 11.4 vs. 35.8 ± 13.3 , $p < 0.001$ with a prevalence of 24% vs. 16%, $p = 0.003$.

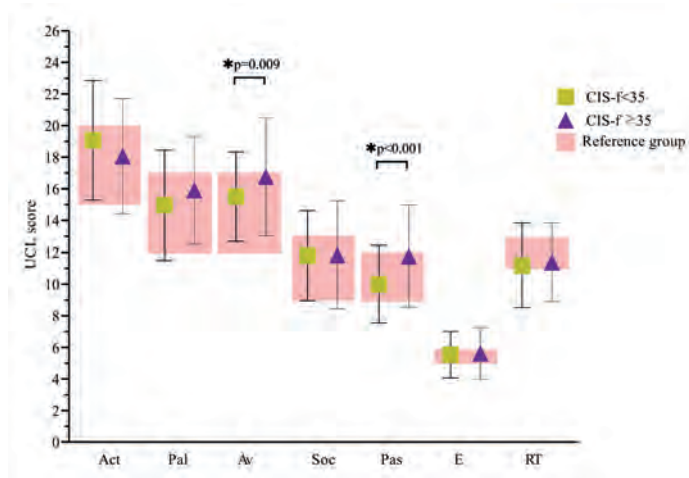


Figure 3A. Results Utrecht Coping List (UCL), males (n=197).

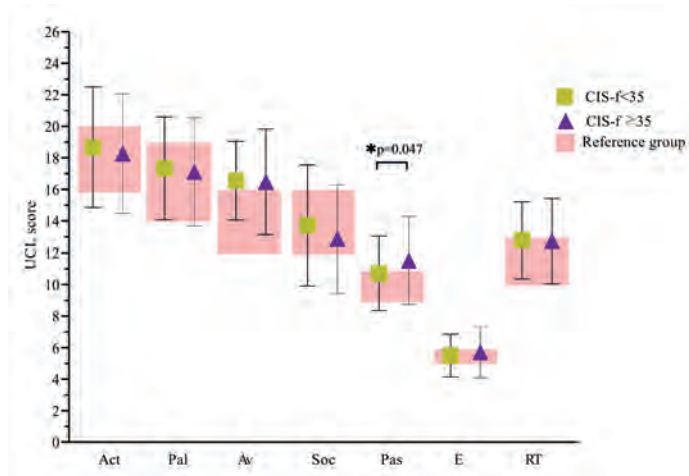


Figure 3B. Results Utrecht Coping List (UCL), females (n=218).

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 minutes every day (figure 4a).

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

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 , $p=0.012$) and >150 active minutes (32.9 ± 12.9 , $p<0.001$). Only a quarter of patients engaged in strenuous physical activities were (figure 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).

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.

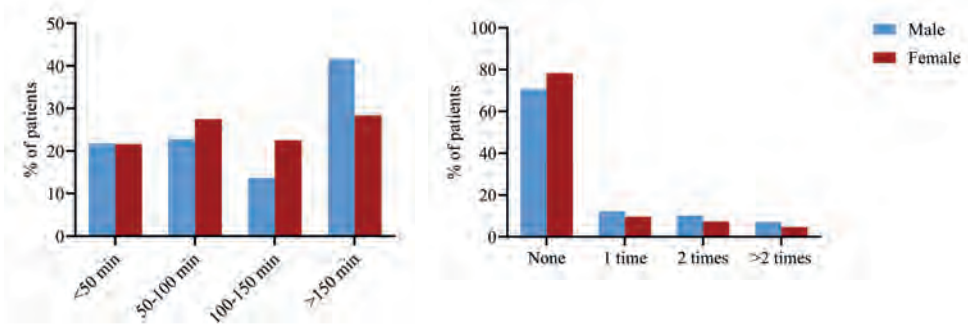


Figure 4. A) Moderate physical activities (e.g. walking or cycling on regular pace), minutes per day. B) Strenuous physical activities (e.g. running, cycling at increased pace), times per week.

Table 4. Multivariate linear regression analysis, n=397

Parameter	B	Std. Error	95% Wald Confidence Interval		Sig.
			Lower	Upper	
Female gender	4,648	1,0945	2,503	6,794	<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	-3,636	2,203	0,631
· MuSK	0,441	2,9151	-5,272	6,154	0,880
· Seronegative	0,716	1,4984	-2,203	3,636	0,631
Other AID	1,713	1,1123	-0,467	3,893	0,124
BMI	0,338	0,0975	0,147	0,529	0,001
MG-ADL	0,827	0,1650	0,503	1,150	<0,001
HADS-d	1,254	0,1454	0,969	1,539	<0,001
PSQI	0,256	0,1409	-0,020	0,533	0,069
Moderate physical activities					
· 50-100 minutes daily	1,310	1,3744	-1,384	4,004	0,340
· 100-150 minutes daily	0,458	1,5237	-2,528	3,444	0,764
· >150 minutes daily	-1,828	1,3476	-4,469	0,814	0,175
Strenuous physical activities					
· 1x/ week	-4,625	1,5584	-7,679	-1,570	0,003
· 2x/ week	-3,999	1,7453	-7,419	-0,578	0,022
· >2x/ week	-7,951	2,0982	-12,063	-3,838	<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

Discussion

With a prevalence of 1-2 per 10.000⁶, 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 Netherlands³⁴. 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 23²⁷. The prevalence of fatigue in the general population of Northern & Western Europe and United States varies between 18-38%^{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 study⁷ 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 with 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 MG⁴². 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 minutes cycling on an ergometer significantly improved fatigue compared to standard treatment²⁵. This effect was still present at 12 weeks follow-up. Similar results were found in post-Guillain Barre syndrome and chronic inflammatory demyelinating polyneuropathy patients⁴³. Fatigue severity reduced with 20% after a 12-week training program with 3 weekly cycling sessions on an ergometer. In myotonic dystrophy type 1, no additional improvement of fatigue was found after adding graded exercise to cognitive behavior therapy⁴¹, 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 responses⁴⁷, 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).

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 to 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 (figure 1a)

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.

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Appendix A

English translation of the Checklist Individual Strength – items of the fatigue subscale in bold

Instruction: On the next page you will find 20 statements. With these statements we aim to get an impression of how you have felt during the past two weeks. For example:

I feel relaxed

If you feel that this statement is completely true , place a cross in the left box; like this:

I feel relaxed

yes, that is true

☒ ☐ ☐ ☐ ☐ ☐ ☐

no, that is not true

If you feel that this statement is not true at all, place a cross in the right box; like this:

I feel relaxed

yes, that is true

☐ ☐ ☐ ☐ ☐ ☐ ☒

no, that is not true

If you feel that this statement in not “yes, that is true”, but also not “no, that is not true”, place a cross in the box that is most in accordance with how you have felt. For example, if you feel relaxed, but not very relaxed, place a cross in one of the boxes close to “yes, that is true”: like this:

I feel relaxed

yes, that is true

☐ ☐ ☒ ☐ ☐ ☐ ☐

no, that is not true

Do not skip any statement and place only one cross for each statement.

1. I feel tired

yes, that is true

☐ ☐ ☐ ☐ ☐ ☐ ☐

no, that is not true

2. I feel very active

yes, that is true

☐ ☐ ☐ ☐ ☐ ☐ ☐

no, that is not true

3. Thinking requires effort

yes, that is true

☐ ☐ ☐ ☐ ☐ ☐ ☐

no, that is not true

4. Physically I feel exhausted

yes, that is true

☐ ☐ ☐ ☐ ☐ ☐ ☐

no, that is not true

5. I feel like doing all kinds of nice things

yes, that is true

☐ ☐ ☐ ☐ ☐ ☐ ☐

no, that is not true

6. I feel fit

yes, that is true

☐☐☐☐☐☐☐☐

no, that is not true

7. I do quite a lot within a day

yes, that is true

☐☐☐☐☐☐☐☐

no, that is not true

8. When I am doing something, I can concentrate quite well

yes, that is true

☐☐☐☐☐☐☐☐

no, that is not true

9. I feel weak

yes, that is true

☐☐☐☐☐☐☐☐

no, that is not true

10. I don't do much during the day

yes, that is true

☐☐☐☐☐☐☐☐

no, that is not true

11. I can concentrate well

yes, that is true

☐☐☐☐☐☐☐☐

no, that is not true

12. I feel rested

yes, that is true

☐☐☐☐☐☐☐☐

no, that is not true

13. I have trouble concentrating

yes, that is true

☐☐☐☐☐☐☐☐

no, that is not true

14. Physically I feel I am in a bad condition

yes, that is true

☐☐☐☐☐☐☐☐

no, that is not true

15. I am full of plans

yes, that is true

☐☐☐☐☐☐☐☐

no, that is not true

16. I get tired very quickly

yes, that is true

☐☐☐☐☐☐☐☐

no, that is not true

17. I have a low output

yes, that is true

☐☐☐☐☐☐☐☐

no, that is not true

18. I feel no desire to do anything

yes, that is true

☐☐☐☐☐☐☐☐

no, that is not true

19. My thoughts easily wander

yes, that is true

☐	☐	☐	☐	☐	☐	☐
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no, that is not true

20. Physically I feel in a good shape

yes, that is true

☐	☐	☐	☐	☐	☐	☐
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no, that is not true

Scoring of the Checklist Individual Strength

Subscales

- **subscale 1: Fatigue Severity** **items 1, 4, 6, 9, 12, 14, 16, 20**
- subscale 2: Concentration items 3, 8, 11, 13, 19
- subscale 3: Motivation items 2, 5, 15, 18
- subscale 4: Activity items 7, 10, 17

For the items: 2, 5, 6, 7, 8, 11, 12, 15, 20, scoring is as follows:

yes, that is true

1	2	3	4	5	6	7
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no, that is not true

For the items: 1, 3, 4, 9, 10, 13, 14, 16, 17, 18, 19, scoring is as follows:

yes, that is true

7	6	5	4	3	2	1
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no, that is not true

Appendix B

Appendix B.2. Reference groups UCL

Males: 19-65 years, a-select sample from Dutch population and Dutch railway personnel during periodic medical check-up.

Females: 18-65 years, a-select sample from Dutch population, Dutch railway personnel during periodic medical check-up and Dutch nurses.

Appendix table B.1. Explanation UCL coping domains

UCL strategy	Description	Associated characteristics
Active approach (Act)	Keeping an overview of the situation, being focused on the problem and confidently solving the situation	Positive correlation with high self-esteem and adequate functioning. Negative correlation with depressive symptoms, neuroticism and fear
Palliative reaction (Pal)	Looking for distraction, getting away from the situation/ problem	Positive correlation with fear, neuroticism, psychopathology and inadequacy
Avoidance (Av)	Avoiding difficult situations, waiting to see what will happen	Positive correlation with low self-esteem, fear, mental and physical distress
Seeking social support (Soc)	Discussing the problem with someone or getting someone to help	Positive correlation with internal locus of control
Passive reaction (Pas)	Being overwhelmed by the situation, incapable of action, worrying	Positive correlation with fear, depressive symptoms and inadequacy. Related to reporting health complaints
Expression of emotions (E)	Positive correlation with anger, fear and neuroticism	Positive correlation with fear, depressive symptoms and inadequacy. Related to reporting health complaints
Reassuring thoughts (RT)	Capable of seeing positive things when problems occur, putting the situation in perspective	Positive correlation with somatic complaints. Negative correlation with neuroticism. Matches with an active approach but also a palliative reaction