Faces and fatigue in myasthenia gravis

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Chapter 3

Fatigue in patients with myasthenia gravis
A systematic review of the literature

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Abstract

Myasthenia Gravis (MG) is a chronic autoimmune disease affecting the neuromuscular junction. Although a hallmark of MG is muscle fatigability due to dysfunction of the neuromuscular junction (peripheral fatigue), a large number of MG patients also report symptoms of central fatigue, defined as an experienced lack of energy, physically and/or mentally. We systematically reviewed the literature on all aspects of central fatigue in MG. Results were categorized in 5 domains: prevalence, diagnosis, pathophysiology, treatment or impact.

The prevalence of patient-reported fatigue varies between 44 and 82%, which is significantly higher than in control subjects. Fatigue severity is usually assessed with standardized questionnaires, but the choice of questionnaire varies widely between studies. The pathophysiology of fatigue is unknown, but it is strongly associated with depressive symptoms, female gender and disease severity. Fatigue is also highly prevalent in ocular MG and patients in remission, suggesting a multifactorial origin. Fatigued MG patients have a lower quality of life. Pharmacological treatment of MG is associated with improvement of fatigue and promising results have been found with physical and psychological training programs.

Fatigue is a highly prevalent symptom of MG with a severe negative impact on quality of life. Physicians treating patients with MG should be aware of this symptom, as it may be treatable with physical or psychological training programs.

Introduction

Myasthenia Gravis (MG) is a chronic autoimmune disease (AID) with a prevalence of 1-2 per 10.000[1]. The clinical hallmark is fluctuating weakness of striated muscles with antibodies directly affecting the neuromuscular junction. In approximately 85% of patients, the initial presenting symptoms are asymmetric ptosis and/or diplopia. Approximately 80% of initially ocular MG patients will develop generalized MG within two years of disease onset[2].

Fatigue is a symptom of growing interest in many neuromuscular disorders[3-5]. A classification using two types of fatigue has been proposed in neuromuscular disorders: peripheral and central fatigue[5, 6]. Peripheral fatigue is a direct result of muscle fatigability due to disorders of the muscle or neuromuscular junction. This type of fatigue will not be discussed in this review. Central fatigue is an experienced lack of energy and feeling of tiredness not related to muscle weakness or pain, and interferes with mental or physical activities. Central fatigue is believed to be important in protecting muscles from further damage by down-regulating physical activities[5, 6]. In this review, we will use the word "fatigue" to describe central fatigue as defined above, unless specified otherwise.

In patients with MG, fatigue has been described as a common symptom[7-14], although its etiology is currently unknown. Due to its fluctuating and effort dependent nature, it may be difficult to distinguish from peripheral fatigue. However, even patients in remission frequently report feeling fatigued[9].

This review summarizes the literature on all aspects of fatigue in MG, with an emphasis on prevalence, diagnosis, pathophysiology, treatment and impact.

Methods

In this systematic review we adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and a pre-set review protocol (appendix A; prisma-statement.org).

Data sources and search strategy

PubMed, Embase, Web of Science, Cochrane Library, Emcare were systematically searched for potentially relevant studies up to June 1th, 2019 (date of search), using appropriate keywords (appendix B). We reviewed the bibliographies of the studies identified for additional data.

Study selection and data extraction

Eligibility was initially assessed through screening of titles and abstracts by two independent reviewers (A.M.R. and M.R.T.), based on the following inclusion criteria: (1) the subject of the article was autoimmune Myasthenia Gravis with or without antibodies against AChR or muscle specific kinase (MuSK); (2) the article described fatigue, and not only peripheral fatigue; (3) original research; (4) use of a quantitative fatigue questionnaire; (5) article in English, Dutch or German. Articles that did not meet all 5 inclusion criteria were excluded. Missing abstract was no reason for exclusion. Both reviewers (A.M.R and M.R.T.) decided independently on inclusion or exclusion after reading the full text of the paper, and Cohen's kappa coefficient for interrater reliability (κ) was calculated. Discrepancies were discussed until mutual agreement was reached. Articles identified for inclusion in this systematic review were broadly categorized in five domains based on their main subject: prevalence, diagnosis, potential modifiers in pathophysiology, treatment or impact.

Risk of bias assessment

Risk of bias was assessed using the Joanna Briggs Institute (JBI) checklist for case series or case control studies (appendix C). Minimum requirements for inclusion were set as follows: the quality threshold was set at five times "yes" or more in total. At least one positive response was obtained for items 1-3, at least two positive responses for items 4-8. Studies were classified as medium quality studies (JBI 6), high quality (JBI 7-8) or very high quality (JBI 9-10). In case of a randomized controlled trial (RCT) the JBI checklist for RCTs was used (appendix C). Requirements for inclusion of RCTs were as follows: the quality threshold was set at eight times "yes" or more, at least 4x "yes" for items 1-6, 2x "yes" for items 7-10. RCTs were classified as medium quality studies (JBI 8-9), as high quality (JBI 10-11) or as very high quality (JBI 12-13).

Results

Search results

Our initial search produced 445 studies of which 45 were examined in further detail after screening of title and abstract. Twenty-one publications remained for final inclusion (Figure 1). Cohen's kappa coefficient for interrater reliability (κ) was 0.952.

The selected studies are detailed in table 1. A brief description of used questionnaires is provided in table 2.

Prevalence

In MG patients the prevalence of fatigue varies from 44 to 82% compared to 18-40% in control groups[7-9, 11, 13, 15, 16]. The prevalence increases with disease severity from 32% in patients in pharmacological remission to 72% in generalized MG (GMG)[9]. Chronic fatigue, defined as fatigue ≥6 months, occurred in 21 to 72%[8, 9].

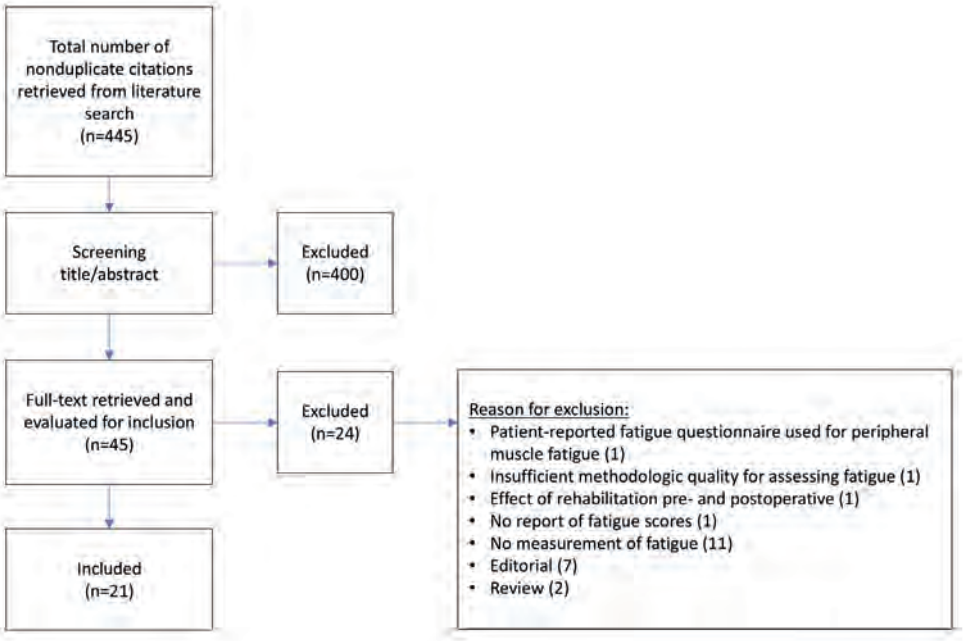

Figure 1. Flow diagram of selected studies

Table 1. Selected studies

Reference	MG, n	Fatigue intervention	Fatigue Questionnaire
Randomized controlled trials			
Andersen et al.[20]	125	Eculizumab	Neuro-QoL-F-SF
Rahbek et al.[28]	15	Physical training program (PRT vs AT)	MFIS
Case control studies			
Alekseeva et al.[7]	73	NA	FSS; FIS; VAS
Alekseeva et al.[15]	69	NA	FIS; FSS
Elsais et al.[8]	82	NA	CFQ
Elsais et al.[26]	10	NA	CFQ
Symonette et al.[19]	20	NA	MGFS; VAS
Jordan et al.[10]	32	NA	MGFS;
Westerberg et al.[16]	40	NA	FSS
Jordan et al.[11]	33	NA	FSMC; MGFS
Paul et al.[13]	28	Cognitive battery	MFI; FIS
Paul et al.[21]	28	Cognitive battery	MFI
Tascilar et al.[22]	19	NA	FSS
Case series			
Chen et al.[29]	29	plasmapheresis	ISS
Grohar-Murray et al.[23]	250	NA	FS; MGFS
Hoffman et al.[9]	200	NA	CFQ
Kittiwatanapaisan et al.[12]	67	NA	MGFS; CFQ
Tran et al.[14]	257	NA	Neuro-QoL-F-SF
Farrugia et al.[27]	10	Physical & psychological training program	FSS; MFIS; VAS
Kassardjian et al.[24]	8	NA	MFIS; VAS
Sabre et al.[25]	76	NA	FSS

Abbreviations: NA = not applicable; D= diagnosis; I = impact; Pa = pathophysiology; Pr = prevalence; T = treatment; a = JBI 6; b JBI 7–8; c JBI 9-10; b*JBI 10-11; c* JBI 12-13
6MWT = 6 minute walking test; AMT = arm movement test; ASP = autonomic symptom questionnaire; AT = aerobic training; B&B = box & block test; BDI = Beck depression inventory; CES-D = center for epidemiological studies depression scale short form; CFQ = Chalder fatigue questionnaire; CMDI = Chicago multiscale depression inventory; CPE=cardiopulmonary exercise; d2-R = attention and concentration test; EQ-5D = euroQoL 5 dimensions; ESS = Epworth sleepiness scale; FIS = fatigue impact scale; FS = fatigue survey; FSMC = fatigue scale for motor and cognitive function; FSS = fatigue severity scale; HADS = hospital anxiety and depression scale; HAM-A/D = Hamilton anxiety/ depression scales; IPQ = illness perception questionnaire; ISI = insomnia severity index; ISS = incapacity status scale; MDI = multiscale depression inventory; MFI = multicomponent fatigue index; MFIS = modified fatigue impact scale; MG-ADL = MG activities of daily living; MGC = MG composite score; MGFS = MG fatigue survey; MGII = MG impairment index; MGQ = MG questionnaire; MG-QoL15(r) = MG-quality of live 15 items (revised); MSLT = multiple sleep latency test; MWT = maintenance of wakefulness test; Neuro-QoL-F-SF = neuro-QoL-fatigue-short form; PASAT = paces auditory serial addition test; PRT = progressive resistance training; PSG = polysomnography; PSQI = Pittsburgh sleep quality index; QMG = quantitative MG; RNS = repetitive nerve stimulation; RWT = Regensburger verbal fluency test; SF-36 = 36-item short form health survey; SCT = stair climb test; STAI = State-Trait Anxiety Inventory; STS = 30-s sit to stand test, VAS visual analog scale.

Fatigue prevalence	Other assessments	Important exclusion criteria	Domain of subject	Quality
	QMG; MG-ADL; MG-QoL15		Pa; T	c*
	6MWT; B&B; MDI; MG-QoL15; SCT; STS		T	b*
69.9%	Data on sleep; BDI; ESS	Sleep-wake disorders	D; I; Pa; Pr; T	c
68.1%	BDI; ESS; STAI		Pa; Pr	b
44%	ASP; MGQ		Pa, Pr;	b
	CPE; MGQ; spirometry	Low CFQ score	Pa	b
	Dynamo; MG-ADL; RNS; QMG		Pa	c
	6MWT; AMT; CES-D; Dynamo; MG-ADL; MG-QoL15; PSQI; QMG; VAS	History of psychiatric illness	Pa; I	c
62-100%	MGC; MG-QoL15; RNS		Pa; Pr	b
57.5%	CES-D; D2-R; MG-ADL; MG-QoL15; QMG; PASAT; PSQI; RWT; timetap-task; VAS	History of psychiatric illness	Pa; Pr; I	b
82%	MDI	History of major psychiatric illness	Pr; I	b
	CMDI	History of psychiatric illness	I; Pa	b
	ESS; HAM-A/D; MG-QoL15; PSG; PSQI	History of psychiatric illness	I; Pa	c
	HADS; IPQ; SF-36		Pa; T	b
	NA		Pa; T	a
56.1%	HADS; ISI; MG-ADL; MG-QoL15; QMG		Pa; Pr; I	b
	CES-D; QMG		D; I; Pa	a
	EQ-5D; MGC; MG-ADL; MGII; MG-QoL15; QMG; SF-36		D; I; Pa; T	b
	HADS; MGC; MG-ADL; MG-QoL15r		T	b
	ESS; MSLT; MWT; PSG; MG-QoL15; QMG		I; Pa	b
NA	QMG; RNS		I; Pa	b

Diagnosis

All included studies used patient-reported questionnaires to assess fatigue; the choice of questionnaire varied widely (table 1). Three studies cross-validated fatigue questionnaires[7, 12, 14]. Fatigue Severity Scale (FSS) scores correlated significantly with all three subscales of the Fatigue Impact Scale (FIS) in both 73 MG patients and 230 controls[7]. Both scales had excellent internal consistencies. The Neuro-QoL-Fatigue short form (Neuro-QoL-Fatigue-SF) was validated by assessing responsiveness to treatment and by estimating the minimal important difference at group level and individual level[14]. At an individual level, sensitivity was 71% and specificity was 76%. The Myasthenia Gravis Fatigue Scale (MGFS) is a questionnaire developed especially for MG patients. Validation of its psychometric properties shows an excellent coefficient alpha scores for internal consistency (between .850 and .934). Its test-retest reliability is high (r = .872, p <.001)[12].

Potential modifiers in pathophysiology

Literature on the exact pathophysiology of fatigue is scarce and most publications report associations without providing evidence of causality. Publications in other neuromuscular disorders point towards a multidimensional cause[4, 17, 18]. In this review, we therefore classified studies reporting on factors associated with fatigue as potential modifiers in its pathophysiology.

The most frequently studied potential pathophysiological factor is MG disease severity[7-9, 12, 14, 16, 19, 20]. Fatigue scores showed a positive correlation with disease severity and in logistic regression analyses, higher disease severity is an independent associated factor for higher fatigue scores and more frequent fatigue[7-9, 14, 16]. There was no difference in fatigue scores between patients with bulbar or limb predominant MG[14]. In contrast, two smaller studies found no association between higher fatigue rates and increasing disease severity[12, 19]. One study (n=20) found no significant difference in fatigue scores between MG patients with and without a decrement upon repetitive nerve stimulation while patients with a typical decrementing response had significantly higher quantitative myasthenia gravis (QMG) scores[19]. Another study on 67 MG patients did not find a significant correlation between QMG scores and fatigue[12].

Higher scores on patient-reported depression scales significantly correlated with higher patient-reported fatigue rates[7, 10-12, 21]. Using the Hospital Anxiety and Depression Scale (HADS), the overall rate for depression among 200 MG patients was 20%[9]. Higher depression rates are found in GMG compared to OMG or patients in pharmacological remission: 25%, 15% and 10% respectively. In both univariate and multivariable logistic regression analyses, higher scores on the HADS were significantly associated with more fatigue. In one study

Table 2. Short overview of commonly used fatigue questionnaires and the domains queried

Questionnaire	Domains	No. items	Assessed by	Period
Chalder Fatigue Questionnaire (CFQ)[53]	Cognitive and physical.	11	Patient	Past week
Fatigue Impact Scale (FIS)[54]	Cognitive, physical and social.	40	Patient	Past week
Fatigue Scale for Motor and Cognitive function (FSMC)[55]	Cognitive and physical.	20	Patient	Unknown
Fatigue Severity Scale (FSS)[56]	Fatigue severity in different situations.	9	Patient	Past week
Fatigue Survey (FS)[23]	Demographic and medical information, fatigue characteristics, precipitating factors, interventions to reduce fatigue and rating of current functional state.	Unknown	Patient	Unknown
Incapacity Status Scale (ISS)[57]	Climbing, ambulation, transfers, bowel function, bladder function, bathing, dressing, grooming, feeding, vision, speech and hearing, medical problems, mood, thought disturbances, mentation, physical fatigue, and sexual function.	16	Patient	Unknown
Modified Fatigue Impact Scale (MFIS)	See Fatigue Impact Scale.			
Multicomponent Fatigue Index (MFI)[58]	Cognitive and physical. Developed to examine current levels and acute changes in fatigue.	15	Patient	Past 4 weeks
Myasthenia Gravis Fatigue Scale (MGFS)[23]	Perception, task avoidance, motor symptoms.	26	Patient	Unknown
Neuro-QoL-Fatigue short form (Neuro-QoL-F-SF)[44]	Physical, functional, social and mental activities.	8	Patient	Past week

(n=19), the difference in fatigue between patients and healthy controls disappeared when adjusting for depression and anxiety scores suggesting an association between depression and fatigue[22].

Most studies found that the female gender was independently associated with higher fatigue rates or higher fatigue-impact rates[7, 14, 23]. Only one study found no difference between genders[8].

Varying results have been published on sleep and fatigue[7-11, 24]. When comparing MG patients with and without fatigue, patients with fatigue scored significantly higher on the Epworth Sleepiness Scale (ESS)[7]. A significant correlation is found between the Pittsburgh Sleep Quality Index and fatigue and between sleep disturbances on the Autonomic Symptom

Profile and fatigue[8, 10, 11]. However, no significant association was found between fatigue and the Insomnia Severity Index[9]. In addition, a small study of eight MG patients with mild-to-moderate disease (QMG <20) found no correlation between patient-reported fatigue or results of the ESS and objective measurements of sleepiness using the Maintenance of Wakefulness Test and Multiple Sleep Latency Test[24].

Restriction of physical activity was the best predictor of fatigue severity after controlling for the effect of depression[12]. A cohort comparing 36 Estonian and 40 Swedish MG patients showed lower levels of physical activity and higher fatigue scores in Estonian patients, although QMG scores between the two groups did not differ[25].

The presence of both AChR and muscle-specific receptor tyrosine kinase (MuSK) antibodies was significantly associated with fatigue in a univariate analysis, but in a multivariate regression analysis only a strong association was found with the presence of MuSK antibodies[9]. In another study, the presence of AChR antibodies was significantly correlated with a decline in performance on one specific test of a cognitive assessment battery. However, this decline did not show a relationship with baseline fatigue scores[11].

The presence of a thymoma did not affect fatigue according to two small studies[10, 16]. One study found that 100% of patients in the thymoma subgroup (n=5) were fatigued, however fatigue was comparable among subgroups (early onset vs late onset vs thymoma)[16]. This study did not report on the current thymoma state. Another study concluded that a prior, successfully treated thymoma was not associated with fatigue[10] .

There was no difference in fatigue severity between 69 MG patients with and without autoimmune comorbidities[15]. In this study, 20% of the population had concomitant autoimmune thyroid disease and one patient had rheumatoid arthritis as a third AID.

In a small study of 10 MG patients assessing pulmonary function, stable MG patients with only mild ocular symptoms who scored high on fatigue appeared to have a minor degree of airway obstruction compared to healthy controls[26]. However, this study did not include a non-fatigued MG group.

One study reported on autonomic symptoms in 82 MG patients[8]. Higher fatigue scores were independently associated with higher scores on the Autonomic Symptom Profile (ASP), especially with the items sleep disturbance and sudomotor/ thermoregulation. A significant correlation between ASP and QMG scores indicated more autonomic symptoms with increasing disease severity.

Treatment

A ten-week physical and psychological training program in nine MG patients showed a small, temporary improvement mid-program and a non-significant trend towards improvement of fatigue at the end of the program, although scores had deteriorated again after three months[27]. Four out of nine patients did report that they had learned how to manage their MG symptoms and fatigue better, despite lacking a persistent improvement in fatigue. An eight-week exercise program comparing aerobic training (AT) versus progressive resistance training (PRT) showed a non-significant trend towards lower fatigue scores after the PRT program[28]. Remarkably, the AT group showed a non-significant trend towards higher fatigue scores. The QMG score in the latter study improved 1-2 points on average, not reaching statistical significance.

Reports on the effect of MG specific medication on fatigue are limited. Oral medication was assessed in only one study: fatigue scores did not differ between MG patients with and without oral corticosteroids[7]. Fatigue scores of a group of 95 MG patients who received a course of intravenous immunoglobulins (IVIG), plasma-exchange (PLEX) or prednisone improved significantly at their second visit 3-4 weeks later[14]. The improvement was similar for all three types of treatment. The effect of PLEX on fatigue was also confirmed in a different study[29], in which fatigue was the most reported symptom prior to treatment (n=29). One month after treatment, mean fatigue scores decreased and fatigue was no longer the most reported symptom, although this difference was not statistically significant.
In the phase 3 REGAIN study, the monoclonal antibody eculizumab was tested as a novel treatment for AChR positive generalized MG (GMG)[20]. Eculizumab was significantly correlated with greater improvement of fatigue than the placebo group; patients in the treatment group had a mean improvement from baseline of -16.3 points compared to -7.7 in the placebo group at week 26.

A majority of MG patients use self-care actions to manage fatigue (both physical and cognitive). In a large survey among 250 MG patients, mental interventions are reported by 76% of the respondents, 78% report applying physical interventions and 80% report resting or sleeping to manage fatigue[23]. However, no relationship or pattern was found between reported fatigue scores and self-care actions.

Impact

Fatigue is associated with more depressive symptoms (see pathophysiology)[7, 9-12, 21, 22]. None of the studies differentiated between depression as a cause or result of fatigue.

A patient-reported lower quality of life correlated with a higher prevalence and severity of fatigue[9, 11, 14, 24]. Improvement in fatigue scores correlated significantly with improvement in quality of life in both the treatment and placebo group in the REGAIN study[20]. In a study comparing 2 groups of MG patients from Estonia and Sweden, fatigue correlated strongly with self-perceived health status[25].

No relationship was found between cognitive performance and baseline fatigue[11, 21], but increased fatigue after completing a cognitive assessment is related with a poorer performance in MG patients[13, 21]. In contrast, controls did not have higher fatigue scores after completing the cognitive battery. In these studies there was no difference on the mood scale of the Multiscale Depression Inventory between MG patients and controls or depression was ruled out as an influencer by linear regression analysis. Outcomes of the Pittsburgh Sleep Quality Index were not of influence.

Discussion

The recent surge in studies on fatigue in MG indicates a growing awareness of the importance of the subject. The prevalence of fatigue in MG is comparable with fatigue in other neuromuscular diseases: a large study found fatigue rates between 61%-74% in facioscapulohumeral muscular dystrophy (FSHD), myotonic dystrophy and hereditary motor and sensory neuropathy type 1[3]. It has been hypothesized that muscle damage induces fatigue through a central nervous system mediated mechanism in order to temporarily down-regulate physical activities and protect muscles from further damage[5, 6, 30]. In patients with an ongoing neuromuscular disease, chronification of this feedback mechanism could induce continuous minimization of physical activity, although this remains speculative. This mechanism might also explain why patients with a neuromuscular disease appear to suffer from “central activation failure” during maximal voluntary muscle contraction[30]. Secondly, chronically decreased levels of physical activity have a negative effect on muscle mass and strength[31, 32], likely causing a vicious circle in patients with neuromuscular disorders. Indeed, restriction of physical activity is a good predictor for fatigue severity[12, 25]. Physical inactivity may lead to obesity. Due to a combination of inactivity and chronic steroid use, a large proportion of MG patients are overweight (BMI ≥25)[12]. In turn, obesity could contribute to fatigue, although a direct link between BMI and fatigue has never been established.

Patients with an AID are more likely to develop a second AID[34]. Having a second, possibly active, AID could contribute to the development of fatigue, but no difference was found between MG patients with and without concomitant autoimmune comorbidity[15]. Noteworthy

is the fact that autoimmune thyroid disease was the second most prevalent AID in all MG patients in this study, and fatigue is a main clinical feature of thyroid disease[35]. Furthermore, non-autoimmune comorbidity, including type 2 diabetes or non-allergic pulmonary disease, may also contribute to the development of fatigue[36, 37]. Active malignancy and subsequent treatment is likely to affect fatigue scores, as fatigue is a common symptom in patients with cancer and up to 80% experience fatigue during treatment[38].

Findings on the relation between fatigue and sleep disorders in MG vary widely. More objective sleep data is necessary to understand the role of sleep disorders in the context of fatigue.

People with a chronic disease have an increased risk for developing a depression[39]. The observed association between fatigue and depression in MG patients provides no evidence of causality, as depressive symptoms may be the cause or the result of fatigue[7, 9-12, 21, 22]. However, the observed correlation could also be caused by similarities between fatigue and depression questionnaires, e.g. the items 'Do you have problems starting things?' on the Chalder Fatigue Questionnaire and 'I could not get going' on the Center for Epidemiological Studies Depression Scale is likely to result in the same answer.

The reason for the observed higher prevalence of fatigue in women is not well understood. One hypothesis is that differences in hormonal and immunological homeostasis play a role[40].

For fatigue in general, evidence-based pharmacological treatment options are currently very sparse, but fatigue-specific programs with physical and psychological training have been proven to be effective in a range of neuromuscular diseases, including FSHD, Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy and myotonic dystrophy type 1[41-43]. So far, similar studies in MG have been far more limited in scope and size[27, 28]. This systematic review does not provide evidence that immunosuppressive treatment improves fatigue independently of improvement of neuromuscular weakness. Therefore, there is no evidence to support the initiation or intensification of immunosuppressive therapy to treat fatigue when there is no clear neuromuscular weakness.

All studies included used self-report questionnaires to assess fatigue with a known cut-off point for abnormal or clinically relevant fatigue. There are no other diagnostic tools for evaluating fatigue. Currently, there is no consensus on which questionnaire is most appropriate for assessing fatigue in MG.

Limitations of available studies

The most important limitation of included studies is the use of patient-reported questionnaires, not only for fatigue but also depression, sleep and autonomic symptoms. Self-assessments are inherently subject to external influences, mood and probably time of day, as daily fluctuations are a hallmark of MG. Secondly, the use of different questionnaires to measure fatigue and the absence of consensus on the most appropriate scale complicates comparing results of different studies. In a number of studies fatigue was a secondary outcome rather than its main subject, and conclusions on fatigue are therefore not always reported comprehensively. Another limitation is the absence of data on spontaneously reported fatigue rather than in response to questionnaires. Information on how often patients spontaneously report fatigue would provide some indication on its relevance and impact on quality of life.

Recommendations for future research

Future research on fatigue in MG would benefit from the use of one multidimensional assessment tool[45]. Despite its ability to detect change over time, the FSS provides little information on different aspects of fatigue. The multidimensional Checklist Individual Strength appears to be highly promising, as it detects change over time and is sensitive to treatment[45-47]. It consists of four subscales: subjective experience of fatigue, concentration, motivation and physical activity. The scale has been developed for chronic fatigue syndrome and although it has not been previously used in MG, it has been used in several other neuromuscular disorders[41, 48, 49], allowing a comparison between different diseases.

There is a surprising paucity of potential biomarkers for fatigue in MG. Previous studies in other diseases point towards inflammatory circulating proteins as potential causative factors, in particular cytokines such as IL-6 and TNFα[50]. In addition, thyroid function, antibody levels and complement activation could be of interest. Recently, circulating inflammatory proteins and micro-RNAs, in particular MMP-10, miR-150-5p and miR-21-5p, have emerged as a novel potential biomarkers for MG[51, 52].

Pilot data on an aerobic exercise program and cognitive behavioural therapy (CBT) in MG and their substantial benefits in other neuromuscular diseases warrant a large randomized clinical trial[41-43]. Exercise should be of sufficient duration and intensity and be performed under the supervision of an experienced physiotherapist. CBT modules for fatigue in other neuromuscular disorders are readily usable in MG patients[41, 43].

Conclusion

In this systematic review of the literature, we show that fatigue is a prevalent symptom in patients with MG. It is associated with higher disease severity, higher rates of depression and lower quality of life. Its pathophysiology is likely multifactorial in nature but fatigue may lead to a vicious cycle by reducing physical activity which in turn has negative effects on muscle strength and fatigue. Figure 2 represents a model summarizing the multifactorial nature of fatigue and the possible targets for therapy. There is no consensus on the most appropriate method to diagnose fatigue in MG. Encouraging results from physical and psychological training programs in MG and other neuromuscular diseases suggest that this vicious cycle can be reversed.

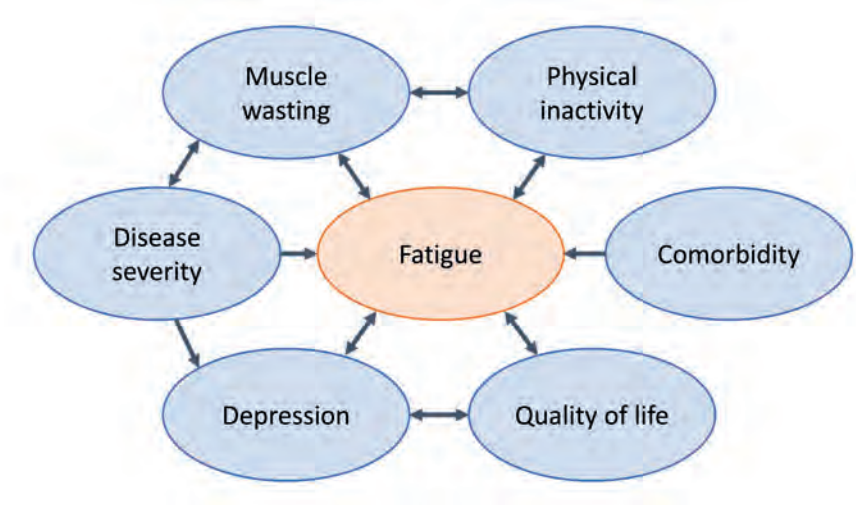

Figure 2. Model summarizing the multifactorial nature of fatigue and the possible targets for therapy

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Appendix A. PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6 Appendix 3
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8 Figure 3
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	20
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	20-22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

Appendix B. Full search strategy

Pubmed

((”Myasthenia Gravis”[Mesh] OR ”Myasthenia Gravis”[tw]) AND (”subjective fatigue”[tw] OR ”Mental Fatigue”[Mesh] OR ”Mental Fatigue”[tw] OR ”cognitive fatigue”[tw] OR ”central fatigue”[tw] OR ”perceived fatigue”[tw] OR (”Fatigue”[mesh] AND (”Cognition”[mesh] OR ”Perception”[mesh])) OR ”Fatigue”[Mesh] OR ((”Fatigue”[tw] OR Fatigue*[tw]) NOT (”muscle fatigue”[tw])))) NOT ((”Case Reports”[ptyp] OR ”case report”[ti]) NOT (”Review”[ptyp] OR ”review”[ti] OR ”Clinical Study”[ptyp])) NOT (”Animals”[mesh] NOT ”Humans”[mesh]))

Embase

((exp *”Myasthenia Gravis”/ OR ”Myasthenia Gravis”.ti,ab) AND (”subjective fatigue”.mp OR ”Mental Fatigue”.mp OR ”cognitive fatigue”.mp OR ”central fatigue”.mp OR ”perceived fatigue”.mp OR (”Fatigue”/ AND (exp ”Cognition”/ OR exp ”Perception”/)) OR *”Fatigue”/ OR ((”Fatigue”.mp OR Fatigue*.mp) NOT (”muscle fatigue”.mp))) NOT ((”Case Report”/ OR ”case report”.ti) NOT (exp ”Review”/ OR ”review”.ti OR ”Clinical Study”/ OR exp ”Clinical Trial”/)) AND exp ”Humans”/)

Web of science

(ts=(”Myasthenia Gravis” OR ”Myasthenia Gravis”) AND ts=(”subjective fatigue” OR ”Mental Fatigue” OR ”cognitive fatigue” OR ”central fatigue” OR ”perceived fatigue” OR (”Fatigue” AND (”Cognition” OR ”Perception”)) OR ((”Fatigue” OR Fatigue*) NOT (”muscle fatigue”))) NOT ti=(”case report” NOT (”Review” OR ”review” OR ”Clinical Study” OR ”Trial”)) NOT ti=(”veterinary” OR ”rabbit” OR ”rabbits” OR ”animal” OR ”animals” OR ”mouse” OR ”mice” OR ”rodent” OR ”rodents” OR ”rat” OR ”rats” OR ”pig” OR ”pigs” OR ”porcine” OR ”horse” OR ”horses” OR ”equine” OR ”cow” OR ”cows” OR ”bovine” OR ”goat” OR ”goats” OR ”sheep” OR ”ovine” OR ”canine” OR ”dog” OR ”dogs” OR ”feline” OR ”cat” OR ”cats”))

Cochrane

((”Myasthenia Gravis” OR ”Myasthenia Gravis”) AND (”subjective fatigue” OR ”Mental Fatigue” OR ”cognitive fatigue” OR ”central fatigue” OR ”perceived fatigue” OR (”Fatigue” AND (”Cognition” OR ”Perception”)) OR ((”Fatigue” OR Fatigue*) NOT (”muscle fatigue”))):ti,ab,kw

Emcare

((exp *”Myasthenia Gravis”/ OR ”Myasthenia Gravis”.ti,ab) AND (”subjective fatigue”.mp OR ”Mental Fatigue”.mp OR ”cognitive fatigue”.mp OR ”central fatigue”.mp OR ”perceived fatigue”.mp OR (”Fatigue”/ AND (exp ”Cognition”/ OR exp ”Perception”/)) OR *”Fatigue”/ OR ((”Fatigue”.mp OR Fatigue*.mp) NOT (”muscle fatigue”.mp))) NOT ((”Case Report”/ OR ”case report”.ti) NOT (exp ”Review”/ OR ”review”.ti OR ”Clinical Study”/ OR exp ”Clinical Trial”/)) AND exp ”Humans”/

Appendix C. Risk of bias assessment

Risk of bias was assessed using the Joanna Briggs Institute (JBI) checklist for case series or case control studies. Minimum requirements for inclusion were set as follows: the quality threshold was set at five times “yes” or more in total. At least one positive response was obtained for items 1-3, at least two positive responses for items 4-8. Studies were classified as medium quality studies (JBI 6), high quality (JBI 7-8) or very high quality (JBI 9-10). In case of a randomized controlled trial (RCT) the JBI checklist for RCTs was used (online appendix 3). Requirements for inclusion of RCTs were as follows: the quality threshold was set at eight times “yes” or more, at least 4x “yes” for items 1-6, 2x “yes” for items 7-10. RCTs were classified as medium quality studies (JBI 8-9), as high quality (JBI 10-11) or as very high quality (JBI 12-13).

JBI Critical Appraisal Checklist for case control studies

Reviewer _____ Date_____

Author _____ Year _____Record Number_____

	Yes	No	Unclear	Not applicable
1. Were the groups comparable other than the presence of disease in cases or the absence of disease in controls?	☐	☐	☐	☐
2. Were cases and controls matched appropriately?	☐	☐	☐	☐
3. Were the same criteria used for identification of cases and controls?	☐	☐	☐	☐
4. Was exposure measured in a standard, valid and reliable way?	☐	☐	☐	☐
5. Was exposure measured in the same way for cases and controls?	☐	☐	☐	☐
6. Were confounding factors identified?	☐	☐	☐	☐
7. Were strategies to deal with confounding factors stated?	☐	☐	☐	☐
8. Were outcomes assessed in a standard, valid and reliable way for cases and controls?	☐	☐	☐	☐
9. Was the exposure period of interest long enough to be meaningful?	☐	☐	☐	☐
10. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Case Series

Reviewer _____ Date_____

Author _____ Year _____Record Number_____

		Yes	No	Unclear	Not applicable
1	Were there clear criteria for inclusion in the case series?	☐	☐	☐	☐
2	Was the condition measured in a standard, reliable way for all participants included in the case series?	☐	☐	☐	☐
3	Were valid methods used for identification of the condition for all participants included in the case series?	☐	☐	☐	☐
4	Did the case series have consecutive inclusion of participants?	☐	☐	☐	☐
5	Did the case series have complete inclusion of participants?	☐	☐	☐	☐
6	Was there clear reporting of the demographics of the participants in the study?	☐	☐	☐	☐
7	Was there clear reporting of clinical information of the participants?	☐	☐	☐	☐
8	Were the outcomes or follow up results of cases clearly reported?	☐	☐	☐	☐
9	Was there clear reporting of the presenting site(s)/clinic(s) demographic information?	☐	☐	☐	☐
10	Was statistical analysis appropriate?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for randomized Controlled trials

Reviewer _____ Date_____

Author _____ Year _____Record Number____

	Yes	No	Unclear	NA
1. Was true randomization used for assignment of participants to treatment groups?	☐	☐	☐	☐
2. Was allocation to treatment groups concealed?	☐	☐	☐	☐
3. Were treatment groups similar at the baseline?	☐	☐	☐	☐
4. Were participants blind to treatment assignment?	☐	☐	☐	☐
5. Were those delivering treatment blind to treatment assignment?	☐	☐	☐	☐
6. Were outcomes assessors blind to treatment assignment?	☐	☐	☐	☐
7. Were treatment groups treated identically other than the intervention of interest?	☐	☐	☐	☐
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	☐	☐	☐	☐
9. Were participants analyzed in the groups to which they were randomized?	☐	☐	☐	☐
10. Were outcomes measured in the same way for treatment groups?	☐	☐	☐	☐
11. Were outcomes measured in a reliable way?	☐	☐	☐	☐
12. Was appropriate statistical analysis used?	☐	☐	☐	☐
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)