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ORIGINAL COMMUNICATION

Impact of autoimmune comorbidity on fatigue, sleepiness and mood in myasthenia gravis

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Abstract

Background Disease burden in myasthenia gravis (MG) and in other autoimmune disorders is often determined by common accompanying symptoms such as fatigue, sleepiness and mood disturbances. Many MG patients have a second autoimmune disease, but it is unclear whether autoimmune comorbidities add to the severity of fatigue, sleepiness and mood disturbances.

Methods We ascertained the presence of autoimmune comorbidities in 69 well-characterized MG patients. To assess fatigue, sleepiness and mood disturbances, we applied the Fatigue Severity Scale (FSS), the Fatigue Impact Scale (FIS), the Epworth Sleepiness Scale (ESS), as well as the Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory (STAI) to all patients.

Results Thirteen MG patients had concomitant autoimmune thyroid disease (AITD), including 1 patient with rheumatoid arthritis as third autoimmune disease. Fatigue (68.1%), excessive daytime sleepiness (14.5%), moderate-severe depression (20.3%) and anxiety (26.1%) were common, but MG patients with and without autoimmune comorbidities had similar FSS, FIS, ESS, BDI and STAI scores. The presence of autoimmune comorbidities was not associated with altered clinical and immunological MG characteristics, but MG patients with autoimmune comorbidities have more often been treated with corticosteroids than patients without autoimmune comorbidities (92.3% vs. 60.7%; $p=0.03$).

Conclusions While many MG patients were affected by fatigue, sleepiness, depression and anxiety, the present study does not suggest that coexisting autoimmune diseases substantially contribute to the magnitude of these cumbersome comorbid symptoms. However, the higher frequency of steroid treatment may have counterbalanced the effects of the autoimmune comorbidity.

Keywords Myasthenia gravis · Autoimmune comorbidity · Steroids · Fatigue · Sleepiness · Depression

Introduction

Myasthenia gravis (MG) is an autoimmune disease caused by antibodies that target distinct components of the post-synaptic muscle endplate. As a consequence, MG patients experience a fluctuating, exertion-dependent, and usually reversible muscle weakness [1]. A typical phenomenon throughout the spectrum of autoimmune diseases is that affected patients are more likely to develop a second autoimmune disease [2]. This is particularly true for MG, as it was exactly this observation that prompted Simpson in 1960 to speculate about an autoimmune origin in MG [3]. The prevalence of autoimmune overlap in MG ranges from 13 to 26% [4–8], with autoimmune thyroid disease (AITD), including Graves' disease and Hashimoto's disease [9–13], rheumatoid arthritis [14], systemic lupus erythematosus [15], and type 1

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diabetes [10, 16] being the most frequent among 23 reported autoimmune comorbidities [5, 17].

In addition to the clinical manifestations emerging from the attacked target tissue, autoimmune diseases share typical symptoms with strong impact on overall clinical burden—notably fatigue, sleepiness and mood disturbances. The high prevalence of these symptoms has been separately shown for most autoimmune diseases, including MG [18]. Immunologists consider pro-inflammatory cytokines as the main reason, why fatigue, sleepiness and mood disturbances are so common in autoimmune diseases. Cytokines are increasingly released by activated immune cells, interact with various brain structures and thereby represent an important factor for disturbed sleep–wake and emotional regulation [19–22]. In other words, these cumbersome symptoms in autoimmune diseases partly originate from this immune-neural link, and may thus be seen as a cytokine-mediated sickness behavior, as experienced during any infectious disease.

Surprisingly, the contributing role of autoimmune comorbidity to the magnitude of fatigue, sleepiness and mood disturbances has not yet been studied in MG. According to the above-mentioned considerations, however, it is conceivable to expect that patients affected by two autoimmune diseases at once carry an increased risk for these symptoms.

In the present study, we, therefore, hypothesized that fatigue, sleepiness and mood disturbances would be more pronounced in MG patients with a concomitant autoimmune disease. To this goal, we ascertained the prevalence of autoimmune comorbidities in 69 well-characterized MG patients, and examined whether these comorbidities adversely affected the magnitude of the above-mentioned symptoms.

Materials and methods

In the present study, we included 69 MG patients from previous work that focused on the validation of fatigue scales in MG [18]. This previous study had been conducted between June 2014 and December 2017 at the Department of Neurology and Psychiatry of the Almazov National Medical Research Centre in St. Petersburg, Russia. The Ethics Committee of the Saint Petersburg State University approved the present study protocol (no. 44-2012), and written informed consent for study participation was obtained from all participants.

Study population

We described the demographic and clinical characteristics of our MG cohort ($n=69$) in a recent study [18]. Briefly, 65 MG patients were Russian natives, the remaining 4 were immigrants from Central Asia. We excluded patients if they were ≤ 18 years of age, and if they lacked the capacity to consent. For the present analysis, we excluded four MG patients with allergic comorbidities, including bronchial asthma ($n=3$) and allergic rhinitis ($n=1$), because allergic diseases represent an immune dysbalance and are known to influence the development of MG and other autoimmune diseases [23]. Demographic characteristics of the patients included age, sex, race, body mass index (BMI), marital status (single, married, or divorced) and highest education degree (primary school, college school, university). Diagnosis of MG was made on the presence of a typical history and at least one positive ancillary test, including repetitive nerve stimulation and MG-specific antibodies (anti-acetylcholine-receptor antibodies and striational antibodies, directed against intracellular proteins of striated muscles as titin, actin, myosin, ryanodine receptors) [24]. Disease severity was graded according to the Myasthenia Gravis Foundation of America (MGFA) classification [25]. We also ascertained the type of immunosuppressive treatment, including both current and past treatment (steroids, cytostatics, and plasmapheresis).

Autoimmune and other comorbidities

We evaluated the presence of autoimmune comorbidities in all MG patients. If patients exhibited any other symptoms than myasthenic, the routine diagnostic workup of MG was extended according to the clinical presentation. AITD, the most common autoimmune comorbidities, was diagnosed in the presence of typical clinical symptoms, thyroid ultrasonography, and blood parameters (thyroid-stimulating hormone, free and total thyroid hormones as well as anti-thyroid antibodies). In all patients, we also evaluated the presence of other general comorbidities, including metabolic, cardio- and cerebrovascular, gastrointestinal, urogenital, and musculoskeletal diseases.

Questionnaires

In all patients, we evaluated fatigue, daytime sleepiness and mood disturbance with the following questionnaires. The Fatigue Impact Scale (FIS) is a 40-item scale showing the consequences of fatigue on daily life; it includes cognitive, physical and psychosocial subscales [26]. The sum of the subscales ranges from 0 to 40 (physical and cognitive FIS) and 0–80 (psychosocial FIS), where the higher score indicates the more severe impact of fatigue on daily life. The Fatigue Severity Scale (FSS) evaluates the degree of mainly physical fatigue during the last week and contains nine items [27]. Patients have to indicate on a seven-point Likert scale for each item, how strongly they agree or disagree with the statements. FSS scores of ≥ 4.0 indicate clinically relevant fatigue. Daytime sleepiness was evaluated by the Epworth

Sleepiness Scale (ESS), with scores of ≥ 11 indicating excessive daytime sleepiness [28]. To evaluate depression and anxiety, we used the Beck Depression Inventory (BDI) [29] and the State-Trait Anxiety Inventory (STAI) [30]. BDI scores ≥ 19 indicate moderate-severe depression, and STAI scores ≥ 55 indicate significant anxiety.

Statistical analysis

For statistical analyses, we used SPSS (version 25; IBM, Armonk, New York, NY, USA). Group data were described by means and standard deviations. We used Student's *t* test to compare normally distributed data between two groups, and applied Chi-square test in case of nominal data. Significance was accepted at $p < 0.05$.

Results

Prevalence and types of AC in MG

Thirteen MG patients (18.8%) had AITD as autoimmune comorbidity, and 1 of them had rheumatoid arthritis as third autoimmune disease (Table 1). During study execution, all patients with AITD were under specific treatment, and their thyroid parameters were within normal range. There was a 1.5:1 female predominance in our MG cohort, and female MG patients had an earlier disease onset than male patients (32.9 ± 15.6 years vs. 42.5 ± 16.1 years, $p = 0.02$).

Clinical and immunological correlates of autoimmune comorbidities in MG

The questionnaire findings revealed that a substantial proportion of MG patients had fatigue (68.1%), moderate-severe depression (20.3%), and significant anxiety (26.1%). Excessive daytime sleepiness was less common (14.5%). When comparing MG patients with and without autoimmune comorbidities, we did not find any differences in FSS, FIS, ESS, BDI and STAI scores (Table 2). However, MG patients with autoimmune comorbidities were more often under treatment with steroids than patients without autoimmune comorbidities (76.9% vs. 44.6%; $p = 0.035$). When including also steroid treatment in the past, the group difference was similarly significant (92.3% vs. 60.7%, $p = 0.026$). Otherwise, all demographic, clinical or immunological variables were similar between the groups (Table 2).

Compared to MG patients without autoimmune comorbidities, the group with comorbidities had double the number of striational antibodies, but this difference was not statistically significant (50% vs. 25.7%, $p = 0.10$). No MG patient was treated with antidepressants, only one MG

Table 1 Demographic, clinical and diagnostic characteristics of the MG patients with autoimmune comorbidities

Patient	Age/sex	Age at MG onset	MG duration	AC duration	Type of AC	Autoantibodies		Thymus histology	Fatigue (FSS ≥ 4.0)	Depression (BDI ≥ 19)	Anxiety (STAI ≥ 55)
						AChR	Striat				
1	70/M	62	8 years	1 year	AITD	n.d.	n.d.	–	+	–	–
2	61/M	60	1 year	> 1 year	AITD	+	–	–	+	–	+
3	62/F	15	47 years	16 years	AITD	n.d.	n.d.	n.d.	–	–	–
4	41/M	41	4 months	4 months	AITD	+	+	–	+	–	–
5	26/F	20	6 years	n.d.	AITD	+	–	–	+	+	–
6	57/F	51	6 years	2 years	AITD	–	–	–	+	–	–
7	27/F	26	9 months	2 months	AITD	+	–	B1, II	+	–	–
8	52/M	51	7 months	> 7 months	AITD*	+	+	–	–	–	+
9	59/F	53	6 years	39 years	AITD	+	+	–	+	+	+
10	41/F	23	18 years	21 years	AITD	+	–	Hyperplasia	+	–	–
11	27/F	21	5 years, 8 months	4 years, 6 months	AITD, RA	+	+	Hyperplasia	–	+	+
12	52/F	47	5 years	5 years	AITD	+	+	Hyperplasia	–	–	–
13	49/F	34	14 years, 9 months	3 months	AITD	+	–	–	+	+	–

AChR acetylcholine receptor antibodies, *n.d.* not determined, *with endocrine ophthalmopathy, *AITD* autoimmune thyroid disease, *RA* rheumatoid arthritis, *Striat* striational antibodies (titin, actin, myosin, ryanodine receptors)

Table 2 Comparison of myasthenia gravis (MG) patients with and without autoimmune comorbidities (AC)

	With AC ($n=13$)	Without AC ($n=56$)	p
Age (year)	48.0 ± 14.6	44.2 ± 15.1	0.41
Female sex	9 (69.2)	32 (57.1)	0.42
Body mass index	24.5 ± 3.8	28.0 ± 7.2	0.09
Duration of MG (y)	9.2 ± 12.5	7.9 ± 7.9	0.63
Age at MG onset (y)	38.8 ± 16.4	36.3 ± 16.5	0.63
ESS	5.9 ± 2.9	6.9 ± 3.7	0.36
EDS (ESS ≥ 11)	0	10 (17.9)	0.11
Unable to work	4 (30.8)	24 (42.9)	0.42
Marital state			0.14
Single	1 (7.7)	18/55 (32.7)	
Married	10 (76.9)	31/55 (56.4)	
Divorced	2 (15.4)	6/55 (10.9)	
Education			0.66
Primary school degree	4 (30.8)	21/54 (38.9)	
College school degree	2 (15.4)	4/54 (7.4)	
University degree	7(53.8)	29/54 (53.7)	
MGFA			0.21
I	2 (15.4)	9 (16.1)	
IIa	3 (23.1)	17 (30.4)	
IIb	1 (7.7)	9 (16.1)	
IIIa	6 (46.2)	16 (28.6)	
IIIb	0	5 (8.9)	
IVa	1 (7.7)	0	
Autoantibody profile			
Anti-AChR	10/11 (90.9)	34/39 (87.2)	0.73
Striational antibodies	5/11 (45.5)	9/35 (25.7)	0.23
Double negative	1/11 (9.1)	4/34 (11.8)	0.80
Decrement in RNS	10 (76.9)	41 (73.2)	0.78
Treatment			
Steroids (now)	10 (76.9)	25 (44.6)	**0.04**
Steroid (past or now)	12 (92.3)	34 (60.7)	**0.03**
Cytostatics[a]	4 (23.5)	13 (23.2)	0.72
Cytostatics (past or now)	4 (23.5)	15 (26.8)	0.51
Plasmapheresis (past or now)	7 (53.8)	19 (33.9)	0.10
Thymectomy	5 (38.5)	17 (30.4)	0.58
Thymic hyperplasia	3/12 (25)	11/55 (20)	0.70
Thymoma	1/12 (8.3)	5/55 (9.1)	0.93
Missing histology	1	1	
BDI	11.9 ± 7.0	11.8 ± 8.3	0.99
State anxiety (STAI)	42.5 ± 13.0	40.0 ± 9.9	0.46
Trait anxiety (STAI)	48.5 ± 10.1	48.4 ± 8.6	0.98
FSS	5.0 ± 1.6	4.6 ± 1.9	0.44
Fatigue (FSS ≥ 4.0)	9 (69.2)	38 (67.9)	0.92
FIS, cognitive	11.5 ± 5.0	12.3 ± 8.9	0.78
FIS, physical	25.2 ± 8.2	21.4 ± 9.6	0.20
FIS, psychosocial	33.3 ± 12.5	33.1 ± 17.3	0.96

Bold values indicate statistical significance

ESS Epworth Sleepiness Scale, *EDS* Excessive daytime sleepiness, *MGFA* Myasthenia Gravis Foundation of America, *Anti-AChR* acetylcholinesterase receptor antibodies, *RNS* repetitive nerve stimulation, *BDI* Beck Depression Inventory, *STAI* State-Trait Anxiety Inventory, *FSS* Fatigue Severity Scale, *FIS* Fatigue Impact Scale

[a]Azathioprine $n=15$, cyclophosphamide $n=1$, vincristine $n=1$

patient without autoimmune comorbidities was under anxiolytic treatment at the time of study participation.

We also assessed the frequency of other comorbidities, including metabolic, cardio- and cerebrovascular, urogenital, musculoskeletal, and gastrointestinal diseases. They were all somewhat higher in MG patients with than without autoimmune comorbidities, but the differences never reached statistical significance (Fig. 1). Two patients had cancer (breast and kidney), and both of them had no autoimmune comorbidity. The male patient with kidney cancer underwent thymectomy, and histology revealed thymic hyperplasia.

Autoimmune comorbidity occurred prior to MG onset in four patients, after MG onset in six patients, and in two patients, they were simultaneously diagnosed. In one patient, AITD onset could not be recalled. These groups did not differ in any of the tested variables.

Discussion

The present study compared the magnitude of fatigue, sleepiness and mood disturbances between MG patients with and without autoimmune comorbidity. Contrary to our hypothesis, MG patients with coexisting autoimmune diseases did not exhibit higher levels of these cumbersome symptoms. However, MG patients with autoimmune comorbidity more often were under steroid treatment, and this might have counterbalanced the effects of the autoimmune comorbidity on fatigue, sleepiness and mood disturbances.

Several considerations and limitations may account for this unexpected finding. First, this single-center study was retrospective in design and, hence, did not follow well-defined diagnostic criteria for ascertainment of autoimmune comorbidities. Instead, detection of autoimmune comorbidities was usually triggered by salient symptoms, and patients without a suggestive clinical picture were not routinely screened for other autoantibodies. Therefore, we cannot exclude that we have missed certain subclinical autoimmune comorbidities, i.e., several MG patients may have erroneously been assigned to the mono-autoimmunity group. Still, the observed 18.8% frequency of autoimmune comorbidity in our MG cohort corresponds to numbers reported by other groups [4, 5, 7, 8], but these studies often had similar ascertainment methods. Moreover, the fact that all patients were recruited in one single center may have caused some local bias, and future studies should reassess this topic in a multicenter prospective fashion using a well-defined autoimmune screening. These studies may also want to include objective sleep studies, as insufficient sleep can worsen MG symptoms and our outcome parameters. However, the potentially

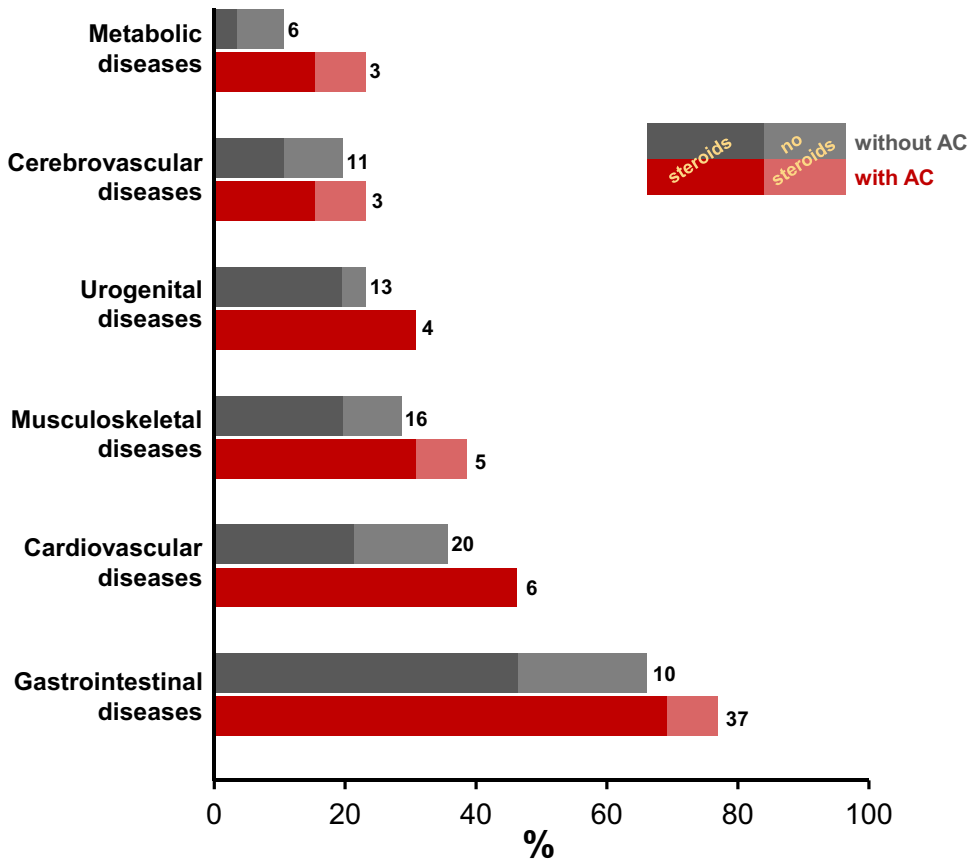

Fig. 1 General comorbidities in 69 myasthenia gravis patients with and without autoimmune comorbidities (AC). Metabolic diseases = type 2 diabetes, podagra. Urogenital diseases = acute and chronic pyelonephritis, urolithiasis, benign prostatic hyperplasia, kidney cyst, congenital hydronephrosis, chronic prostatitis. Musculoskeletal diseases = degenerative disc disease, arthritis, osteoporosis, osteoarthrosis. Cardiovascular diseases = arrhythmia, arterial hypertension, chronic heart failure, coronary artery disease. Gastrointestinal diseases = peptic ulcer disease, liver and biliary disease, gastritis, duodenitis, chronic pancreatitis, chronic hepatitis B, reflux esophagitis, axial gastric volvulus, sliding hiatus hernia, Gilbert's syndrome, irritable bowel syndrome. For each comorbidity in both groups, the percentage of patients with and without steroid treatment is additionally indicated

confounding role of obstructive sleep apnea (OSA) remains to be determined, since the specific contribution of OSA to daytime sleepiness was not significant in the largest study on this topic [31].

Second, with the exception of a patient with concomitant rheumatoid arthritis, AITD was the only autoimmune comorbidity detected in our MG cohort. This means that our results are not generalizable to autoimmune comorbidities other than AITD. In addition, all MG patients with comorbid AITD had already received specific treatment during questionnaires completion. Thus, while the adverse impact of both hyper- and hypothyroidism on fatigue, sleepiness, anxiety and depression cannot be denied [32–34], the lack of other autoimmune comorbidities with less favorable treatment response and more pronounced disability may partly explain why autoimmune comorbidity in our MG cohort had no significant impact on the magnitude of these symptoms. Moreover, several reports have suggested that comorbid AITD possibly implicates a milder clinical expression of MG [4, 11, 12], a finding not supported, however, by our data and those of a Mexican study [14]. Conversely, MG in association with autoimmune diseases other than AITD is more likely to have a poorer prognosis [35]. AITD is generally regarded as the most common autoimmune comorbidity in MG [4], but the 18.8% prevalence of comorbid AITD in our MG cohort is one of the highest reported so far, followed by numbers from Poland (13.4%) [13], Japan (11.9%) [17], Taiwan (8.2%) [12], and others [9]. According to a recent population-based screening study of 10,220 subjects, the prevalence of AITD in St. Petersburg was 14.9% [36], a higher number compared to reports from many other countries [37]. As is known, the prevalence of AITD may vary with race [37] but other explanations may account for the high AITD prevalence in our MG cohort. In 1999, after having established that up to 75% of the St. Petersburg population exhibited some degree in iodine deficiency, the government started a large-scale prevention with iodized salt supplies [38], a measure known to increase the risk of AITD development in susceptible subjects [39]. Moreover, as observed in neighboring Belarus following the Chernobyl disaster [40], we cannot exclude that local differences in radiation exposure also affected the AITD risk in St. Petersburg. Thus, both local and MG-related immunologic factors may have contributed to the high prevalence of comorbid AITD in our MG cohort.

Third, steroid treatment was significantly more common in the group with autoimmune comorbidity, and may have weakened the assumed impact of autoimmune comorbidity on the severity of fatigue, sleepiness and mood disturbances. Indeed, corticosteroids are well known for their stimulating effects on alertness and mood, although impairment of sleep quality and worsening of mood disturbances are similarly common side effects. There are, however, additional reasons why the relationship between steroid treatment and autoimmune comorbidity could be of importance. Since many factors such as intercurrent infections, stress, and various drugs may deteriorate MG severity, it is conceivable that autoimmune comorbidity may aggravate the myasthenic process and thereby lead to a higher need of steroid treatment. Specifically, clinicians know that hyperthyroid AITD can worsen the myasthenic weakness [9]. On the other hand, the higher frequency of steroid treatment in MG patients with autoimmune comorbidity may also suggest that steroids increase the risk for a second autoimmune disease. While we are not aware of studies in autoimmune diseases that specifically investigated steroid treatment as potential trigger factor for autoimmune comorbidities, recent work showed that post-transplant immunosuppression (including steroids) involves an increased risk for secondary autoimmune diseases [41, 42]. Moreover, steroids can induce opportunistic infections, stress, and vitamin D deficiency—factors that all may predispose to secondary autoimmune diseases [43].

Fourth, co-occurrence of other autoimmune diseases in MG is typically associated with female sex, earlier disease onset, and certain immunogenetic factors [12, 13]. Specifically, the likelihood of autoimmune comorbidity appears to increase with thymic hyperplasia and positive AChR-antibodies, and to decrease with thymoma and positive MuSK-antibodies [7, 14]. In the present study, however, these observations were only partially confirmed. There were no sex-related differences regarding frequency of autoimmune comorbidities; age at disease onset as well as thymus histology was similar in MG patients with and without autoimmune comorbidity. Still, the doubled number of positive striational antibodies in MG patients with autoimmune comorbidities—though not statistically significant—suggests that in our MG cohort immunological features also had an impact on the frequency of autoimmune comorbidity. Indeed, striational antibodies are not very specific for MG and may also occur in other autoimmune diseases [24]. Nevertheless, the typical female predominance and earlier disease onset in female MG patients emphasizes that our patient cohort can be regarded as a representative MG sample.

Fifth, we must also consider the possibility that the rationales underlying our hypothesis were, at least in part, incorrect. The magnitude of fatigue, sleepiness and mood disturbance in MG with autoimmune comorbidity must not necessarily emerge from the summation of the specific clinical and immunological markers of both diseases. Instead, MG and the concomitant autoimmune disease may rather represent one single immunological disorder with two or multiple phenotypical manifestations. Moreover, the assumed immune-neural link might be less substantial in MG, a disorder affecting mostly the peripheral nervous system, without convincing evidence of an involvement of the central nervous system. In this line, MG patients and control

subjects differed only in physical fatigue, but not in cognitive fatigue or daytime sleepiness [18].

Finally, MG patients with and without autoimmune comorbidities not only had similar levels of fatigue, sleepiness and mood disturbance, but they also exhibited a similar number of other comorbidities (cardio- and cerebrovascular, gastrointestinal, urogenital, metabolic, musculoskeletal). However, it is noteworthy that all these comorbidities were slightly more prevalent in MG patients with autoimmune comorbidities. This might be a side effect of the steroid treatment, but the prevalence of metabolic disorders has been shown to be increased also in AITD patients without MG—even after successful treatment [44].

In conclusion, this is to our knowledge the first study examining the impact of autoimmune comorbidity on fatigue, daytime sleepiness, depression and anxiety in MG patients. We failed to verify our hypothesis—the level of these symptoms in MG patients did not appear to increase in the presence of a second autoimmune disease. Our results point to an intriguing association between steroid treatment and autoimmune comorbidity; while the higher frequency of steroid treatment in MG patients with autoimmune comorbidity might be primarily responsible for the lack of group-differences in fatigue, sleepiness and mood disturbances, it also provokes speculation about a causal relationship between steroid treatment and occurrence of secondary autoimmune diseases in MG. Due to the discussed limitations, we need larger prospective studies with comprehensive ascertainment of the most common autoimmune comorbidities to further explore our hypothesis, but also to elucidate the potentially far-reaching implications of steroid treatment in the development of secondary autoimmune diseases.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

Ethical standard The authors declare that the work documented in this-manuscript has been carried out in accordance with ethical standards.

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