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Fatigue is a common symptom in myelin oligodendrocyte glycoprotein antibody disease

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Abstract

Background: Unlike multiple sclerosis and neuromyelitis optica, the burden of fatigue in myelin oligo-dendrocyte glycoprotein antibody-associated disease (MOGAD) is unclear.

Objective: To compare fatigue levels between people with MOGAD and household controls (HC) and explore factors associated with fatigue severity.

Methods: In a cross-sectional survey, data were collected from people with MOGAD and HC by utilizing an online questionnaire. Data elements included demographics, sleep quality measures, comorbidities, MOGAD characteristics, and fatigue severity measured by the Modified Fatigue Impact Scale (MFIS). We compared fatigue severity between MOGAD participants and HC and assessed the associations between demographic and disease characteristics and fatigue severity.

Results: There were 180/283 MOGAD and 61/126 HC respondents. Compared to HC, people with MOGAD reported more severe fatigue, as measured by the MFIS total score (49.3 vs. 36.5; $p < 0.001$), and a larger proportion of MOGAD participants (75.6% vs. 44.3%; $p < 0.001$) were classified as fatigued. Among MOGAD participants, higher age ($p = 0.04$), history of bilateral optic neuritis ($p = 0.02$), and current use of acute treatment ($p = 0.04$) were independently associated with higher fatigue.

Conclusions: Fatigue is common in people with MOGAD, and a history of bilateral optic neuritis, comorbid conditions, and ongoing disease activity appear to contribute to fatigue severity.

Introduction

Fatigue, a subjective lack of physical or mental energy perceived by the individual with usual activities, is a common symptom of inflammatory and neurological disorders.[1,2] Fatigue is a well-known phenomenon in multiple sclerosis (MS) and one of the most common and disabling symptoms of the disease.[3,4] Even though the pathophysiology of fatigue is not fully understood, there is evidence that inflammatory cytokines, white matter and grey matter lesions, abnormal network recruitment, and the neuroendocrine system play a major role.[1,2,5]

Despite different pathophysiology and disease course and relative sparing of the brain, fatigue in aquaporin-4-IgG seropositive neuromyelitis optica spectrum disorder (NMOSD) is as common and severe as in MS.[6,7] Higher disability, number of attacks, and age have been associated with NMOSD fatigue.[8]

Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is another inflammatory, demyelinating disease of the CNS that has been recognized as a distinct entity.[9] MOGAD can be a monophasic disease or follow a relapsing course, but in contrast to MS, a slow and gradually progressive course does not appear to occur.[10] Common clinical manifestations include optic neuritis (ON) which is frequently bilateral, transverse myelitis (TM), acute disseminated encephalomyelitis (ADEM), and encephalitis.[9,11] Serum myelin

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oligodendrocyte glycoprotein IgG seropositivity, along with a compatible clinico-radiological presentation, confirms a diagnosis of MOGAD.[12,13]

Thus far, observational studies in MOGAD have focused mainly on MOGAD attacks and residual physical and visual disability. However, it is possible that similar to MS, chronic, less visible symptoms such as fatigue, cognitive dysfunction, and mood problems could be common and disabling in patients with this inflammatory demyelinating disease. Fatigue has previously been reported to be worse in people with NMOSD compared to MOGAD.[8] However, it is not clear whether fatigue in people with MOGAD is more common and/or severe than in healthy individuals and whether the site(s) of CNS involvement, clinical phenotype, or immune-based treatments affect fatigue severity.

In this cross-sectional study, we explored the severity of fatigue in people with MOGAD compared to household controls (HC) and examined its association with demographic and clinical characteristics.

Methods

Standard protocol approvals, registrations, and patient consent

Data collected were fully anonymous and the study analysis protocol was reviewed by the Johns Hopkins Institutional Review Board and determined to be exempt/non-human subjects research.

Study population

The link to a web-based survey was shared via the email distribution list and the social media outlets of The MOG Project (https://mogproject.org, an international advocacy group for people with MOGAD). People with MOGAD and healthy household members (people with no prior history of MOGAD or other demyelinating diseases who lived with a patient with MOGAD) self-identified through a screening set of questions. The controls were recruited from the household members of people with MOGAD to account for similar environmental and socioeconomic factors. The responses were collected and managed utilizing an electronic database.

Survey

Survey questionnaires collected information regarding demographics, fatigue levels, present comorbidities, and sleeping habits. Comorbidities that were characterized as fatigue-inducing included cancer, depression, fibromyalgia, heart disease, hypothyroidism, iron-deficiency anemia, myalgic encephalomyelitis/chronic fatigue syndrome, rheumatoid arthritis, systemic lupus erythematosus, sleep apnea, and Sjogren's syndrome. In addition, information about years since MOGAD diagnosis, history of different MOGAD presentations, and current acute and/or chronic treatment use was collected in MOGAD participants. A caregiver or a family member could fill out the questionnaire on behalf of a person with MOGAD.

Fatigue impact was assessed utilizing the Modified Fatigue Impact Scale (MFIS), a validated questionnaire for MS[14] and NMOSD.[15] MFIS consists of 21 items – each one scored on a scale of 0 to 4 – which are summed to yield a total score (ranging from 0 to 84). Items can also be aggregated into three subscales assessing different aspects of fatigue, including physical (nine items; ranging from 0 to 36), cognitive (10 items; ranging from 0 to 40), and psychosocial (two items; ranging from 0 to 8), with each item included in only one of these subscales. Higher scores denote more severe fatigue. The cut-off value of 38, which is the value that distinguishes fatigued MS patients,[16] was used to differentiate fatigued from non-fatigued individuals.

Information on sleep quality was queried using a series of questions pertaining to frequency of difficulties sleeping with responses ranging from never to almost nightly, frequency of nighttime awakenings with responses ranging from 0 to ≥ 5, and the average number of hours of interrupted sleep per 24-h period with options for <5, 5–6, 7–8, and ≥ 9.

The majority of the survey's questions had predetermined answer options (multiple-choice), where the participant could only select single or multiple answers.

Although completed surveys were received from people with MOGAD and HC of the same household, we did not have the information to link these pairs and account for this in the analysis, due to the anonymous nature of the survey.

Statistical methods

Continuous and categorical variables were compared between HC and people with MOGAD utilizing two-sample *t*-test and chi-square test, respectively. Subsequently, we utilized univariable and multivariable linear regression models to assess associations of clinical and demographic characteristics with fatigue. The MFIS total score was treated as a dependent continuous variable. Age group and disease

duration were reported as categories (five levels for age and four levels for disease duration) and modeled as continuous variables. Since each age group (less than 24, 25–34, 35–44, 45–54, and over 55 years of age) approximately had a range of 10 years (with the exception of the youngest group, which contained 2 [5%] participants under the age of 5, and the oldest group which contained 7 [15%] participants over the age of 64), an increase of one point in the numeric variable was interpreted as an increase of 10 years in age. Ordinal sleeping variables were transformed into binomial variables, separating people with the two worst sleeping outcomes from the rest. A logistic regression model was utilized to examine the relationship between MOGAD disease and the proportion of fatigued people while adjusting for potential confounding factors. To assess the association of bilateral ON history with sleep quality, we used univariable and multivariable logistic regression models with the binomial sleeping variables as the outcome.

Statistical analysis was performed using the R software, version 4.1.2 (https://www.r-project.org/). Statistical significance was defined as $p < 0.05$.

Results
There were 283 participants with MOGAD and 126 HC, out of whom 180 (64%) and 61 (48%) completed the survey, respectively. Out of the 180 MOGAD surveys, 22 were completed by a caregiver on behalf of the participants, most of them (73%) being children. Demographics and clinical characteristics are shown in Table 1. Survey respondents were predominantly female (72%) and white (83%). Compared to the HC group, the MOGAD group consisted of a higher proportion of females, but demographics did not otherwise differ between groups. The majority of MOGAD participants had been diagnosed less than 5 years prior (90%), and were not on any acute treatment (defined as steroids [oral or intravenous], intravenous immunoglobulins, plasma exchange, or combination of the above) at the time of the survey (66%) and were receiving chronic immunomodulatory treatment (including oral immunosuppressive agents [mycophenolate mofetil, azathioprine, methotrexate], immunoglobulins [intravenous or subcutaneous], biological agents [rituximab, ocrelizumab, tocilizumab], oral steroids, or combination of the above) (77%).

People with MOGAD are more fatigued compared to HC
People with MOGAD reported significantly higher MFIS scores compared to HC in both univariable and multivariable analyses adjusted for sex, age, presence of fatigue-inducing comorbidities, and the presence of nightly sleeping difficulties. This was observed for the total MFIS score (49.3 vs. 36.5; adjusted difference: 11.6 [95% CI: 6.6–16.6], $p < 0.001$) as well as the different subscales – physical (22.5 vs. 16.7; adjusted difference: 5.5 [95% CI: 3.1–7.9], $p < 0.001$), cognitive (22.0 vs. 16.6; adjusted difference: 4.6 [95% CI: 2.1–7.1], $p < 0.001$), and psychosocial (4.8 vs. 3.2; adjusted difference: 1.5 [95% CI: 0.91–2.1], $p < 0.001$) (Figure 1). Additionally, a larger proportion of MOGAD participants (75.6% vs. 44.3%; $p < 0.001$) were characterized as fatigued by the predetermined cutoff of 38 points in the MFIS total score. In the adjusted analysis, the odds of being fatigued for MOGAD participants were 4.7 times higher than HC (OR = 4.7 [95% CI: 2.3–9.6]; $p < 0.001$) (Table 2). After excluding people with MOGAD that were on acute treatment, we observed similar results for both the total MFIS score (47.0 vs. 36.5; adjusted difference: 10 [95% CI: 4.9–15.8], $p < 0.001$) and the proportion of fatigued people (71.4% vs. 44.3%, $p < 0.001$; adjusted analysis: OR = 4.0 [95% CI: 1.9–8.6], $p < 0.001$).

Factors predicting fatigue in HC
Univariable and multivariable analyses for HC are shown in Table 3. In both analyses, frequent sleeping difficulties (coefficient: 15.1 [95% CI: 6.2–23.9]; $p = 0.001$) were significantly associated with more fatigue.

Factors predicting fatigue in people with MOGAD
The results of univariable and multivariable analyses for MOGAD participants are shown in Table 4. Higher age (coefficient: 3.0 [95% CI: 1.1–5.0]; $p = 0.002$), presence of fatigue-inducing comorbidities (coefficient: 9.2 [95% CI: 3.9–14.6]; $p < 0.001$), frequent sleeping difficulties (coefficient: 14.1 [95% CI: 9.2–19.1]; $p < 0.001$), history of bilateral optic neuritis (ON) (coefficient: 7.4 [95% CI: 2.2–12.7]; $p = 0.006$), current acute treatment use (coefficient: 6.7 [95% CI: 1.2–12.3]; $p = 0.02$) and use of a combination of two regimens as an acute (coefficient: 11.7 [95% CI: 2.5–20.8]; $p = 0.01$) or chronic treatment (coefficient: 14.9 [95% CI: 4.2–25.6]; $p = 0.007$) compared to no treatment were all associated with more fatigue. Lack of chronic treatment demonstrated a trend (coefficient: −6.1 [95% CI: −12.4 to 0.26]; $p = 0.06$) towards decreased fatigue levels.

Utilizing a multivariable model, higher age (coefficient: 2.3 [95% CI: 0.17–4.5]; $p = 0.04$), presence of fatigue-inducing comorbidities (coefficient: 6.4 [95% CI: 0.82–11.9]; $p = 0.03$), history of bilateral ON (coefficient: 6.5 [95% CI: 1.3–11.8]; $p = 0.02$)

Table 1. Demographics and clinical characteristics.

Characteristic, n (%)	HC, N = 61	MOGAD, N = 180	p-value[a]
Sex, female	37 (61%)	136 (76%)	**0.025**
Age group			
<25	8 (13%)	30 (17%)	0.31
25–34	9 (15%)	40 (22%)	
35–44	11 (18%)	39 (22%)	
45–54	16 (26%)	40 (22%)	
>54	17 (28%)	31 (17%)	
Race, White/Caucasian[b]	50 (83%)	150 (84%)	0.93
Continent[e]			
Americas	45 (78%)	120 (70%)	0.29
Asia	1 (1.7%)	1 (0.6%)	
Europe	6 (10%)	33 (19%)	
Oceania	6 (10%)	17 (9.9%)	
Presence of fatigue-inducing comorbidities[d]	16 (26%)	67 (37%)	0.12
Presence of autoimmune disease	7 (11%)	39 (22%)	0.08
Sleep Quality			
Presence of frequent sleeping difficulties[e]	28 (47%)	96 (54%)	0.31
<6 h of sleep	42 (69%)	130 (72%)	0.61
≥4 awakenings	6 (9.8%)	34 (19%)	0.10
Years since MOGAD diagnosis[f]			
Less than 1 year		64 (36%)	
1–2 years		41 (23%)	
3–4 years		18 (10%)	
5 + years		56 (31%)	
MOGAD presentation history			
Unilateral ON		71 (39%)	
Bilateral ON		80 (44%)	
Transverse myelitis		67 (37%)	
Brainstem lesions		40 (22%)	
ADEM		34 (19%)	
Encephalitis		26 (14%)	
Other presentation		22 (12%)	
Unsure		5 (2.8%)	
≥2 Different presentations		93 (52%)	
Acute MOGAD treatment			
Steroids		24 (13%)	
IVIG		19 (11%)	
Plasma exchange		1 (0.6%)	
Combination of acute treatments		17 (9.4%)	
None		119 (66%)	
Chronic MOGAD treatment			
Oral immunosuppressants		36 (20%)	
Immunoglobulins		37 (21%)	
Biological agents		51 (28%)	
Combination of chronic treatments		15 (8.3%)	
Chronic oral steroids		1 (0.6%)	
None		40 (22%)	

[a]Chi-squared test; statistically significant values (<0.05) are bolded
[b]Missing data for one HC and one person with MOGAD
[c]Missing data for three HCs and nine people with MOGAD
[d]Fatigue-inducing comorbidities: Cancer, Depression, Fibromyalgia, Heart Disease, Hypothyroidism, Iron-deficiency anemia, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Rheumatoid Arthritis, Systemic Lupus Erythematosus, Sleep apnea, Sjogren's Syndrome
[e]Missing data for one HC and three people with MOGAD
[f]Missing data for one person
ADEM: acute disseminated encephalomyelitis; HC: household controls; IVIG: intravenous immunoglobulins; MOGAD: myelin oligodendrocyte glycoprotein antibody-associated disease; ON: optic neuritis; PLEX: plasma exchange.
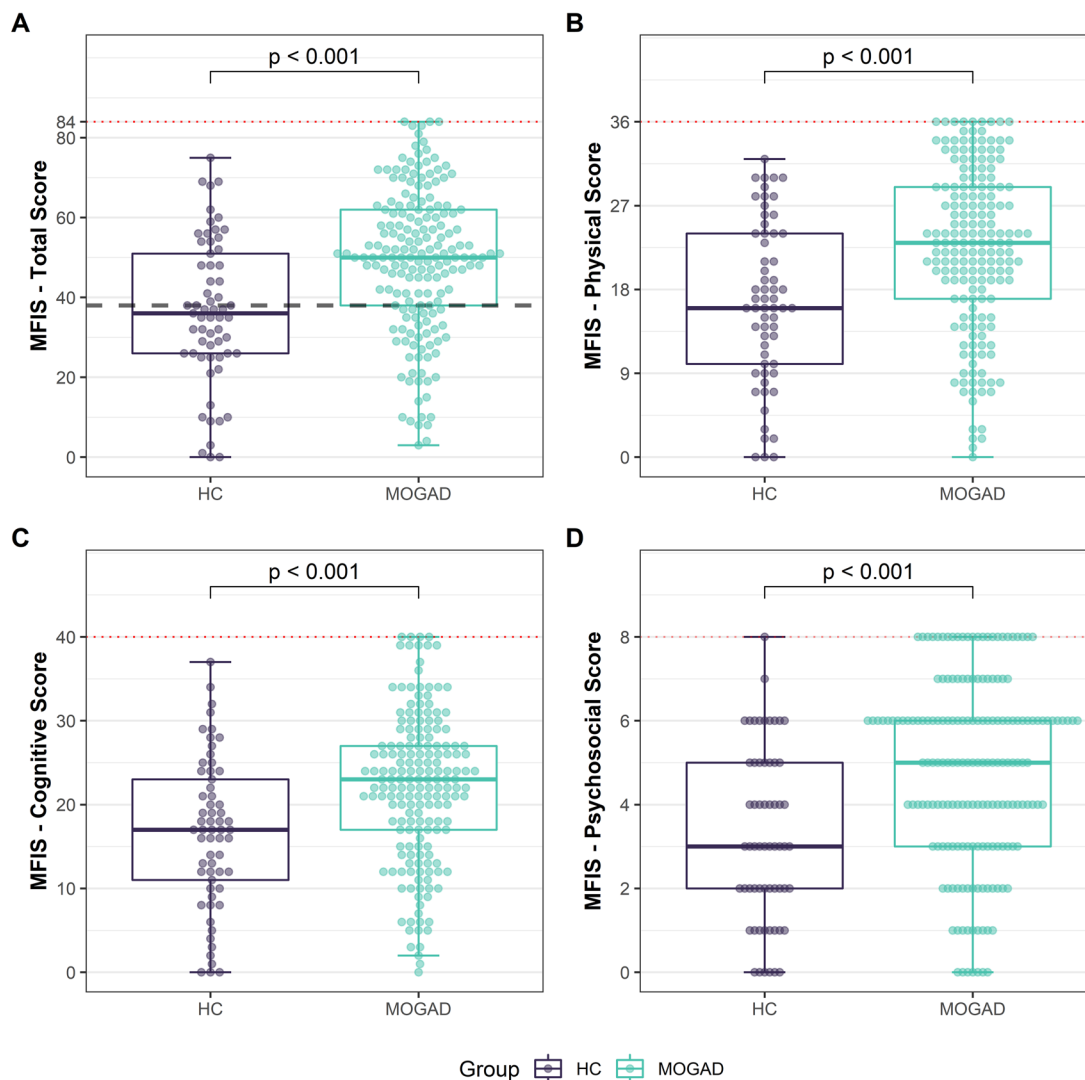
Figure 1. Fatigue in HC versus MOGAD participants. Box plots overlapped by swarm plots of total (A), physical (B), cognitive (C), and psychosocial (D) scores of MFIS in HC and MOGAD participants. Bounds of the box represent the interquartile range (IQR), while horizontal central lines denote the median and minimum and maximum whiskers correspond to the $Q1 - 1.5 \times IQR$ (or the minimum value, if larger) and $Q3 + 1.5 \times IQR$ (or the maximum value, if smaller), respectively. Dotted horizontal red lines indicate the maximum score for each MFIS subscale and the dashed horizontal line in plot A denotes the cut-off score (38) of total MFIS for defining fatigue. *P*-values derived from multivariable linear regression models adjusted for sex, age group, presence of fatigue-inducing comorbidities, and presence of increased sleeping difficulties.

HC: household controls; IQR: interquartile range; MOGAD: myelin oligodendrocyte glycoprotein antibody-associated disease; MFIS: Modified Fatigue Impact Scale.

and current use of any acute treatment (coefficient: 6.0 [95% CI: 0.18–11.9]; $p = 0.04$) remained significantly associated with higher MFIS. Since we speculate that having a history of bilateral ON might have an effect on sleep, we did not include any of the sleep quality measures in the pre-specified multivariable model (since sleep quality could conceivably mediate the relationship between history of bilateral ON and more fatigue), although these findings were consistent in sensitivity analyses including sleep quality measures. Being on combination chronic treatment showed a strong trend toward increased fatigue (coefficient: 10.6 [95% CI: −0.01 to 21.1]; $p = 0.05$).

History of bilateral ON and sleep quality
In order to assess whether a history of bilateral ON interferes with sleep quality, we used logistic regression models with a sleep quality variable as the

Table 2. HC versus MOGAD MFIS scores.

Characteristic	HC, mean (SD) N=61	MOGAD, mean (SD) N=180	Unadjusted Difference (95% CI) N=241	p-value[b]	Adjusted[a] Difference (95% CI) N=237[f]	p-value[c]
MFIS total	36.5 (18.3)	49.3 (18.1)	12.8 (7.5–18.0)	**<0.001**	11.6 (6.6–16.6)	**<0.001**
MFIS physical	16.7 (8.6)	22.5 (8.8)	5.8 (3.3–8.4)	**<0.001**	5.5 (3.1–7.9)	**<0.001**
MFIS cognitive	16.6 (8.9)	22.0 (8.9)	5.3 (2.7–7.9)	**<0.001**	4.6 (2.1–7.1)	**<0.001**
MFIS psychosocial	3.2 (2.1)	4.8 (2.2)	1.6 (1.0–2.2)	**<0.001**	1.5 (0.9–2.1)	**<0.001**
	HC, n (%)	MOGAD, n (%)		p-value[d]	Adjusted[a] OR (95% CI)	p-value[e]
MFIS ≥38	27 (44.3%)	136 (75.6%)		**<0.001**	4.7 (2.3–9.6)	**<0.001**

[a]Adjusted for sex, age category, presence of fatigue-inducing comorbidities, and presence of increased sleeping difficulties.
[b]Two-sample t-test; statistically significant values (<0.05) are bolded.
[c]Multivariable linear regression model; statistically significant values (<0.05) are bolded.
[d]Chi-squared test.
[e]Logistic regression model.
[f]Four people (one HC and three people with MOGAD) were excluded from the multivariable models due to missing data in sleeping difficulties.
CI: confidence intervals; HC: household controls; MOGAD: myelin oligodendrocyte glycoprotein antibody-associated disease; MFIS: Modified Fatigue Impact Scale; OR: odds ratio; SD: standard deviation.

Table 3. Univariable and multivariable regression analyses (MFIS total score as the dependent variable) for HC.

Linear regression model	Characteristic	Coefficient (95% CI)	*p*-value[a]
Univariable	Sex, male	0.5 (−9.1 to 10.2)	0.91
	Age group	−1.3 (−4.7 to 2.1)	0.44
	Race, non-White	−3.8 (−16.4 to 8.8)	0.55
	Fatigue-inducing comorbidities	4.6 (−6.1 to 15.2)	0.39
	Frequent sleeping difficulties	14.9 (6.2–23.6)	**0.001**
	<6 h of uninterrupted sleep	15.3 (6.0–24.7)	**0.002**
	≥4 arousals/night	15.9 (0.6–31.2)	**0.04**
Multivariable	Sex, male	2.3 (−7.5 to 12.0)	0.65
	Age group	−1.8 (−5.2 to 1.5)	0.27
	Fatigue-inducing comorbidities	3.4 (−7.1 to 13.9)	0.51
	Frequent sleeping difficulties	15.1 (6.2–23.9)	**0.001**

[a]Statistically significant values (<0.05) are bolded.
CI: confidence intervals; HC: household controls; MFIS: Modified Fatigue Impact Scale.

outcome variable and the presence of bilateral ON history and age as the independent variables. HCs were also included in the analysis resulting in three groups (HC, MOGAD without, and with a history of bilateral ON). MOGAD participants with a history of bilateral ON demonstrated a trend of poor sleep quality in terms of increased sleeping difficulties frequency compared to HC (OR = 1.8 [95% CI: 0.9–3.6]; *p* = 0.09). Furthermore, for MOGAD participants with a history of bilateral ON, the odds of having four or more arousals were 3.3 times that of HC (OR = 3.3 [95% CI: 1.3–9.7]; *p* = 0.02). On the other hand, these associations were not observed in MOGAD participants without a history of bilateral ON.

Discussion

In this observational study, we found that people with MOGAD were more frequently fatigued compared to HC. Fatigue was more severe in people with MOGAD in every dimension of the MFIS – total, physical, cognitive, and psychosocial. In people with MOGAD, increasing age, the presence of fatigue-inducing comorbidities, a history of bilateral ON, and the use of acute treatment were associated with higher fatigue levels.

Since direct information regarding relapse history was not collected, we interpreted the report of a current acute treatment – given that these medications are administered during a MOGAD attack and are not part of the conventional chronic treatment regimens[9] – as indirect evidence of a recent relapse. Furthermore, the survey's question explicitly stated

that the presence of a recent relapse is required in order for a treatment to be considered acute. Making this assumption, people with a probable recent MOGAD relapse were significantly more fatigued. MS relapses have been associated with increased fatigue.[17] In addition, CNS inflammation, and the consequent structural damage of white and gray matter have been associated with and are thought to play a major role in the pathophysiology of MS fatigue.[1,5,18,19] Similar features, including CNS inflammation and demyelination, have been described during MOGAD relapses,[9,20,21] which could explain the observation of more severe fatigue during a MOGAD relapse.

Another interesting observation in our study was that MOGAD participants who were on a combination of two different classes of chronic treatment regimens demonstrated a trend toward increased fatigue. Since there is no evidence-based consensus regarding chronic treatment, the choice of the agent is based on data from retrospective studies and clinical practice experience.[9] Based on an international survey of adult and pediatric neurologists, combination treatment was chosen as a second or third-line treatment option-if considered at all.[22] This may indicate that patients with MOGAD who do not respond to a single agent have a more severe and active disease course. Another potential explanation is that immunomodulating and immunosuppressive agents themselves could potentially worsen the fatigue,[5] although there was no such evidence when looking at individual treatment classes in our study.

Table 4. Univariable and multivariable regression analyses (MFIS total score as the dependent variable) for MOGAD patients.

Linear regression	Characteristic	Coefficient (95% CI)	*p*-value[a]
Univariable	Sex, male	−3.6 (−9.8 to 2.6)	0.25
	Age group	3.0 (1.1–5.0)	**0.002**
	Race, non-White	−7.0 (−14.2 to 0.2)	0.06
	Years from diagnosis	2.5 (−0.3 to 5.2)	0.08
	Fatigue-inducing comorbidities	9.2 (3.9–14.6)	**<0.001**
	Frequent sleeping difficulties	14.1 (9.2–19.1)	**<0.001**
	<6 h of uninterrupted sleep	10.3 (4.6–16.1)	**<0.001**
	≥4 arousals per night	9.9 (3.3–16.6)	**0.004**
	Hx of unilateral ON	0.6 (−4.9 to 6.1)	0.83
	Hx of bilateral ON	7.4 (2.2–12.7)	**0.006**
	Hx of any ON	5.0 (−1.0 to 10.9)	0.10
	Hx of transverse myelitis	3.7 (−1.8 to 9.2)	0.19
	Hx of brainstem lesions	3.8 (−2.6 to 10.2)	0.24
	Hx of ADEM	−2.8 (−9.6 to 4.0)	0.42
	Hx of encephalitis	−1.3 (−8.8 to 6.3)	0.74
	Hx of ADEM or encephalitis	−2.1 (−8.2 to 4.1)	0.51
	Hx of other presentation	11.7 (3.7–19.6)	**0.004**
	Hx of more than one different presentation	8.0 (2.8–13.2)	**0.003**
	Acute treatment		
	None	—	
	Steroids	4.0 (−3.9 to 11.9)	0.32
	IVIG	5.0 (−3.8 to 13.7)	0.26
	PLEX	22.0 (−13.4 to 57.4)	0.22
	Combination of acute treatments	11.7 (2.5–20.8)	**0.01**
	Any acute treatment	6.7 (1.2–12.3)	**0.02**
	Chronic treatment		
	None	—	
	Oral immunosuppressants	6.2 (−2.0 to 14.3)	0.14
	Immunoglobulins	6.2 (−1.9 to 14.3)	0.13
	Biological agents	3.4 (−4.1 to 10.8)	0.38
	Chronic oral steroids	7.5 (−28.3 to 43.3)	0.68
	Combination of chronic treatments	14.9 (4.2–25.6)	**0.007**
	No chronic treatment	−6.1 (−12.4 to 0.3)	0.06
Multivariable	Sex, male	−2.0 (−8.1 to 4.1)	0.52
	Age group	2.3 (0.2–4.5)	**0.04**
	Years from diagnosis	0.9 (−2.1 to 4.0)	0.55
	Fatigue-inducing comorbidities	6.4 (0.8–11.9)	**0.03**
	Hx of bilateral ON	6.5 (1.3–11.8)	**0.02**
	Hx of ADEM or encephalitis	0.8 (−5.5–7.1)	0.81
	On acute treatment	6.0 (0.2–11.9)	**0.04**
	Chronic treatment		
	None	—	
	Oral immunosuppressants	3.1 (−4.9 to 11.2)	0.44
	Immunoglobulins	1.2 (−7.0 to 9.4)	0.78
	Biological agents	3.0 (−4.2 to 10.2)	0.42
	Chronic oral steroids	6.3 (−28.3 to 40.9)	0.72
	Combination of chronic treatments	10.6 (−0.01 to 21.1)	0.05

[a]Statistically significant values (< 0.05) are bolded.
ADEM: acute disseminated encephalomyelitis; CI: confidence intervals; Hx: history; IVIG: intravenous immunoglobulins; MFIS: Modified Fatigue Impact Scale; MOGAD: myelin oligodendrocyte glycoprotein antibody-associated disease; ON: optic neuritis; PLEX: plasma exchange.

Interestingly, we observed that people with MOGAD who had a history of bilateral ON reported greater fatigue than other participants. This was not true for unilateral ON or when clustering together patients with all episodes of ON. Furthermore, no other distinct MOGAD presentation was associated with fatigue (including a history of ADEM or encephalitis). Although bilateral ON is uncommon in MS,[23] we did not find a similar report of the association between MS fatigue and a history of bilateral ON. Total and physical fatigue were reported to be more severe in people with MS who had a history of ON or had worse binocular low-contrast visual acuity.[24,25] Although those findings could reflect more severe fatigue in people with generally more severe MS, the association of bilateral ON (and not transverse myelitis, encephalitis, or ADEM) with more severe fatigue may be due to the role that the retina plays in circadian rhythm, mood, and energy. Intrinsically photosensitive retinal ganglion cells (ipRGCs) that express melanopsin (a blue light-sensitive photopigment) are located in the ganglion cell and inner plexiform layer (GCIPL) of the retina and are mediators for light-induced non-image-forming visual functions.[26,27] ipRGCs have been shown to drive circadian photoentrainment via connections with the suprachiasmatic nucleus through the retinohypothalamic tract.[26,28,29] By controlling the circadian rhythm and sleep, ipRGCs can indirectly impact mood and energy levels, mediated by their effect on sleep.[30] In addition to this indirect pathway, these cells have been found to directly affect mood as well. Wild-type mouse models exposed to an aberrant light cycle demonstrated depression-related behaviors without changes in their circadian rhythm and sleep pattern. In contrast, in mice lacking ipRGCs, the aberrant light cycle did not impair mood.[31]

Studies employing optical coherence tomography (OCT) have demonstrated a profound decrease in the thickness of retinal layers (peripapillary retinal nerve fiber layer and GCIPL in particular) after ON episodes in patients with MOGAD,[32,33] which is notably more severe than that observed in MS. Furthermore, eyes with ON history in people with MS have been reported to have attenuated ipRGC-mediated response to blue light, and that thinning of the GCIPL was associated with this attenuation,[34] indicating that loss of these cells occurs as a sequela of ON. Bilateral involvement of the cells, as may occur with bilateral ON, can cause mood alteration and fatigue directly, and indirectly – via the dysregulation of circadian rhythm and sleep pattern. A study of people with glaucoma – a common cause of optic neuropathy – also demonstrated decreased ipRGC function and worse sleep quality.[35] Our findings of an association between a history of bilateral ON and increased fatigue and decreased sleep quality supports this hypothesis in people with MOGAD. Given the overlapping features of MS and NMOSD, ON-mediated destruction of ipRGCs could also be a contributing factor to fatigue in those conditions. There are other potential explanations for increased fatigue in people with a history of bilateral ON. For example, visual processing could become a high-effort activity that eventually leads to fatigue.[36]

To our knowledge, this is the first direct comparison of fatigue levels between people with MOGAD and controls. Furthermore, given the low prevalence and relatively recent discovery of MOGAD, our sample size is rather large. However, there are several limitations to our study. Firstly, this was a cross-sectional study that utilized surveys with all of the data (including the MOGAD diagnosis) being self-reported. Additionally, clinical factors that have been associated with fatigue in NMOSD[8] and might have been relevant in our analysis, such as the timing and number of relapses, the course of the disease (monophasic vs. relapsing), or the use of fatigue-inducing medications (including medications used for spasticity, neuropathic pain, or mood disorders), were not collected in this study. Although self-reported mood disorders were included in the fatigue-inducing comorbidities, we did not assess for the presence of depressive symptoms that could contribute to the fatigue. Another limitation is that a validated questionnaire was not used to evaluate the quality of sleep, which could have resulted in the misclassification of the participants. Furthermore, responses of HC participants were not linked to the specific household MOGAD participant, and therefore, we could not account for this in our analysis. Finally, ascertainment bias could conceivably have influenced our results.

In summary, our results demonstrate that fatigue is a highly prevalent symptom in people with MOGAD and suggest that optic nerve involvement may be an important contributor to it. Further studies with validated clinical information for MOGAD patients, more detailed history regarding ON episodes, and quantification of retinal layer thicknesses using OCT will be essential to validate and further explore these findings.

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